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Hypothesis: Possible idiotypic suppression of cell-mediated immunity in lepromatous leprosy

J FERLUGA,* V COLIZZI,† A FERRANTE,‡
M J COLSTON§ & E J HOLBOROW**
**Department of Immunology, London Hospital Medical College, London, UK; †Institute of Microbiology, University of Pisa, Pisa, Italy; ‡University Department of Paediatrics, The Adelaide Children's Hospital Inc., Adelaide, Australia; §Laboratory for Leprosy and Mycobacterial Research, National Institute for Medical Research, London, UK; **Bone and Joint Research Unit, London Hospital Medical College, London, UK*

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Summary It is suggested that lepromatous leprosy may develop as a result of chronic suppression of specific cellular immunity by anti-idiotypic (Id) antibodies and Id-restricted suppressor lymphocytes. This potential immuno-tolerizing mechanism would probably be initiated most effectively in early life. Auto-anti-Id responses may be induced by exposure to *Mycobacterium leprae* antigens, or maternal anti-Id antibodies may be acquired transplacentally. The anti-Id antibodies would be directed against a predominant self-antigenic idiotype located on immuno-recognition molecules for *M. leprae* antigens on lymphocyte membranes. Together with certain HLA-self-antigens such Id-anti-Id responses would determine the susceptibility to leprosy.

Introduction and hypothesis

Patients with tuberculoid leprosy develop granulomatous hypersensitivity, while in the lepromatous form of the disease cell-mediated immunity to *Mycobacterium leprae*, though not to other organisms, is deficient.[1] This probably allows the bacterium to replicate in macrophages and to disseminate, in spite of an elevated humoral immune response. It is not clear to what extent this defect is primary or secondary; most polar lepromatous patients present with evidence of having 'downgraded' from the borderline or tuberculoid end of the spectrum, whereas others present with evidence of having developed lepromatous disease *a priori*. In addition, whereas treatment of borderline patients might result in 'upgrading'

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reactions,[2] in which specific immunological parameters appear to increase, polar lepromatous patients retain complete anergy towards *M. leprae* in spite of effective chemotherapy. Several mechanisms of immuno-suppression arising during infections have been suggested.[3,4] Recently, it has been found that auto-anti-idiotypic (Id) antibodies induced during the immune response to various antigens, and in some infections, may temporarily or permanently suppress specific humoral or cellular immunity.[5–7]

Our hypothesis is that during infection with *M. leprae*, an anti-Id response against an idiotype predominant in determining immunity to *M. leprae* is induced. This anti-Id immune response may be responsible, at least in part, for the anergic lepromatous form of the disease.

Experiment and clinical data

Idiotypes are self-antigenic epitopes located on lymphocyte receptors and antibody molecules.[8] The combination of an anti-Id antibody with an idiotypic receptor stimulates the Id-bearing lymphocyte. This is equivalent to, but independent of the stimulation that results from the combination of the nominal antigen with the specific recognition site located on the same cell receptor. Hence anti-Id antibody may by itself induce or prime for an immune response in a positive or negative way, to an associated nominal antigen, and vice versa.[9,10] According to the network theory proposed by Jerne,[11] antigen, by expanding the specific clone, also augments the associated idiotype. The latter then as antigen induces a feedback anti-Id response in the form of anti-Id antibodies and anti-Id receptor-bearing cells which regulates immunity to nominal antigen by stimulating Id-bearing helper and suppressor T cells. A given idiotype specificity may be shared by a set of immunoglobulin molecules and B and T cells, thus linking different cell components in their response to nominal antigen.[8] Inheritable predominant Id specificities can occur on the majority of antibodies against particular antigens, such as the Id-T15 in Balb/c mice immunized with phosphorylcholine or with pneumococcal polysaccharide which has the same antigenic determinant and the Id-A5A in A/J mice immunized with a streptococcal A antigen. It has been suggested that predominant Id-restricted responses depend on the functioning of two types of helper cells—one restricted by the major histocompatibility gene complex (MHC) (ie, by Ia molecules expressed on the surface of antigen-presenting macrophage-like cells), the other restricted by the Id genes which code for the variable region of the heavy chains of immunoglobulin molecules and possibly also for T cell receptors.[12,13] In this way the Id-genes would function in concert with MHC genes to determine and direct the immune response to a particular antigen. Interactions between genes determining Gm allotype and HLA locus antigens have been demonstrated for

antibody responses to a *Salmonella* flagellin antigen,[14] and in the rat there is evidence of linkage between idiotypes and heavy chain allotypes.[15]

It has been shown that anti-Id-T15 antibodies, which are otherwise stimulatory, when injected into neonatal Balb/c mice suppress chronically and possibly for life the appearance of T and B cell functions related to this idiotype.[16] In adult A/J mice, combined treatment with anti-Id-A5A antibodies and streptococcal antigen produces chronic suppression of most of the anti-streptococcus antibody response.[8] Feedback suppression by anti-Id antibodies of autoantibodies against acetylcholine receptors in myasthenia gravis [17] and of antibodies to DNA in systemic lupus erythematosus patients[18] has also been inferred. Furthermore, transient anti-Id antibodies reacting with anti-tetanus toxoid immunoglobulins have been found in individuals receiving booster inoculations.[5] These anti-Id antibodies inhibit the *in vitro* production of anti-toxoid antibodies by B lymphocytes.

Auto-anti-Id antibodies have also been shown to react with the receptors expressed on T cells involved in delayed type hypersensitivity responses. Both T effector cells and T suppressor cells, which regulate contact sensitivity, may be blocked by anti-Id antibodies.[19] Auto-anti-Id antibodies are also induced in the course of *M. bovis* (BCG) infection in mice.[6] Their presence in the serum is responsible for the inhibition of passive transfer of delayed type hypersensitivity to PPD of tuberculin in heavily BCG-infected animals and for the specific anergy they display. In another study, immune serum from mice infected with *Nocardia brasiliensis*, probably containing anti-idiotypic antibodies, promoted infection with this organism in mice.[20]

Relevance of anti-Id response to leprosy

In lepromatous leprosy one defect in cellular immunity apparently lies in specific helper T cells and their ability to produce interleukin-2.[21] Although some authors have been able to demonstrate suppressor factors in lepromatous leprosy associated both with macrophages [22,23] and with T-cells,[24] others have been unable to demonstrate the presence of antigen-specific suppressor T-cells.[25] It is possible that in the extreme (polar) form of lepromatous leprosy in which the immunodeficiency is not drug reversible, the function of both subsets of specific T cells is abolished or their development is prevented by anti-Id antibodies in the same way as anti-Id-T15 produces its effects in neonatal mice.[16] Alternatively, the suppression of helper cells for cell-mediated immunity may be perpetuated by a long-lived, Id-restricted suppressor cell population similar to that in the A/J mice,[8] which may have remained undetected in leprosy studies as has been suggested previously.[26] This type of suppressor cell bearing either the Id or the anti-Id receptor, may be distinct from the HLA (MHC) restricted cells described elsewhere.[24] Inheritance of the appropriate HLA genes and of the genes

responsible for the putative predominant Id associated with immunity to *M. leprae*, perhaps combined with exposure to anti-Id antibody from immune or infected mothers during embryonic life, may lead to a chronic specific defect of immunity. In mice it has been shown that mothers suppressed for the expression of Id-T15 confer the unresponsiveness to their offspring via anti-Id antibodies.[16] In later life, auto-anti-Id antibodies may be induced and boosted by prolonged exposure to *M. leprae* antigens. The Id-bearing anti-*M. leprae* antibodies, alone or complexed to antigen, would be especially effective in restimulating both anti-Id antibodies and anti-Id receptor bearing suppressor cells.[27,28]

In lepromatous leprosy humoral immunity may be also suppressed initially if associated with a predominant (inherited germline) idiotype. However the suppression of the latter may be bypassed by recruitment of alternative, individual Id-specificities which are also associated with anti-*M. leprae* antibodies, as has been shown in mice in relation to other antigens.[16,28] This would not be expected with cellular immunity which appears to be more restricted in idiotype than humoral.[10,28]

An important relevant finding from family studies in man is that idiotypes shared between rheumatoid factors in different individuals are inherited independently of HLA genes.[29] Such non-HLA linked inheritance of the presumptive *M. leprae* associated predominant Id may explain the lack of correlation between and incidence of lepromatous leprosy and HLA product frequencies.[30–32] In Indian familial studies, a correlation with HLA–DR2 containing haplotypes has been found in siblings suffering from tuberculoid leprosy, but only in families where the parents were healthy,[30] whereas in a study carried out in South America HLA–DR3 appeared to be associated with the immunological response to infection with leprosy.[32] Where similar studies were carried out on affected children of affected parents, no significant associations with HLA tissue haplotypes were found. In such families, the children may have passively acquired maternal anti-Id antibodies or have been exposed to *M. leprae* antigens and thus produced auto-anti-Id antibodies. In either case, the anti-Id antibodies may have induced transient suppression, allowing the infection to establish itself. Such anti-Id responses, whether or not of predominant type, might well swamp susceptibility effects due to HLA type. In experiments on congenic mouse strains it has been shown that the Balb non-H-2 (MHC) background in combination with H-2^k haplotype genes, ie in Balb/K mice, favours dissemination of *M. leprae murium* infection.[33] A possible predominant Id which would be coded by V_H genes of the immunoglobulin (Ig 1) region on chromosome 12, may be encompassed in the genetic non-MHC background. The influence of Id genes would thus be distinct from that of the susceptibility genes to various intracellular parasites, which are known to be present on chromosome 1 and which are non-specific.[33] These latter genes probably determine the activation and bactericidal capacity of macrophages in the early, innate resistance phase of infection. In the acquired, immunological phase of resistance or susceptibility, macrophages

are recruited and activated further, in concert with the early mechanisms, by lymphokines from stimulated T lymphocytes, which are in turn regulated by genes of the MHC (on chromosome 17 in the mouse), and possibly also by Id-genes.

This general explanation is in harmony with the accepted view that multiple genetic factors control susceptibility to leprosy.[34]

Immunosuppression by an anti-Id response or by maternally transmitted anti-Id antibody, especially in early life, which has been suggested as one mechanism of immunological tolerance,[35] may thus also be important for the development of lepromatous leprosy. Compatible with this view is the finding that some persons free of the clinical disease but having contact with it develop a specific humoral response to *M. leprae*, but unlike other contacts, do not develop a delayed hypersensitivity skin reaction to lepromin.[1,36] Exposure to a particular environmental antigen may play a critical role in the development and expression of a predominant Id.[13] Thus, a given infection may develop owing to a secondary immune response generating presumptive long-lived Id-restricted antigen-specific suppressor memory cells. Perhaps more often, a protective primary or an anamnestic response of helper memory cells, also associated with a predominant Id, may occur and the infection may pass subclinically. It has been suggested that among transplacentally transmitted protective anti-malaria antibodies there may be anti-Id antibodies which prevent infants in endemic areas from mounting immunity to malaria during natural exposure.[37] Suppressive priming for leprosy by anti-Id antibodies may not be as readily apparent owing to the long incubation period, low infectivity and unequal exposure to *M. leprae*. Nevertheless, foetal exposure to maternal anti-*M. leprae* antibodies and mycobacterial antigens has been demonstrated.[38] Similar considerations may apply to other infections in which cellular immunity appears deficient, such as disseminated cutaneous and visceral (kala azar) leishmaniasis, chronic mucocutaneous candidiasis, fulminating tuberculosis and hepatic and extrahepatic infection with hepatitis B virus.[1,39] Such antigen driven specific tolerizing conditions are distinct from primary immunodeficiencies due to inborn defects in the development of an entire lymphocyte set or subsets.

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Lepr Rev (1984) **55,** 229–237

A survey of the eye complications of leprosy in South Korea

P COURTRIGHT,* R GREEN, R PILARSKI & J SMUCNY
7113 San Fernando Drive, Boise, Idaho 83704, USA

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Summary A survey on the ocular complications of leprosy has been carried out in South Korea by members of the American Peace Corps. The results in 2925 patients examined in resettlement villages show the high incidence of ocular damage caused by the disease with over 40% of the sample having some form of eye problem. As many as 11% of the patients had visual levels of less than 20/200 in both eyes, and extrapolation of these and other figures emphasizes the magnitude of the problem in the country. The setting up of regional clinics to deal with eye complications of leprosy is recommended.

Introduction

Leprosy has been present in South Korea for many centuries and although sulphones were made generally available 35 years ago the number of affected cases has shown little sign of diminishing. The origins of the disease in the Korean peninsula are uncertain: it may have spread from China in the eighth century AD, or have derived from Japanese invasions in the thirteenth century, but whatever its history, leprosy rapidly became endemic in Korea in the Middle Ages and has remained so ever since.

At present, out of a total South Korean population of about 40 million there are over 28,000 registered patients[1] and estimates from the Korean Ministry of Health and Social Affairs Department put the figures in the region of 50,000. Field workers in leprosy suggest that numbers may be far higher, perhaps reaching as many as 100–150,000 cases,[2] but however accurate the estimates they portray a situation with important and increasing health problems.

A policy of resettlement of leprosy cases has been carried out since 1961 by the

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South Korean government and the distribution of the patients can be divided on the basis of their location (Figure 1). About 5000 patients (17%) live in leprosaria some of which are government-sponsored, such as the National Leprosy Hospital on Sorok Island which was started by the Japanese in 1916 and still accommodated over 6000 patients at the end of the Second World War. In addition there are several smaller leprosaria sponsored by Christian churches, such as the Wilson Leprosy Centre—an internationally famous American Presbyterian mission at Suncheon, the St Lazarus Hospital at Shi Hueng and the Sacred Heart Clinic at San Chung. Patients in these leprosaria are generally the chronic severely affected cases, many of whom prefer to remain in these institutions rather than venture out into the community. A high proportion of these patients are disabled and many have advanced eye disease.[3] The second group of leprosy patients live in resettlement villages of which there are now officially 98 (Figure 2). These

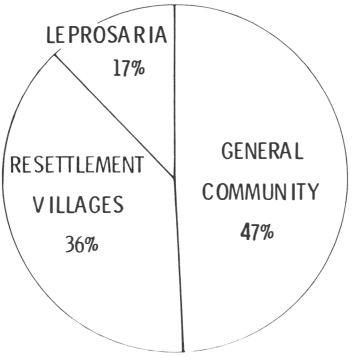

Figure 1. The distribution of registered leprosy patients (28,298) in South Korea, 1981.

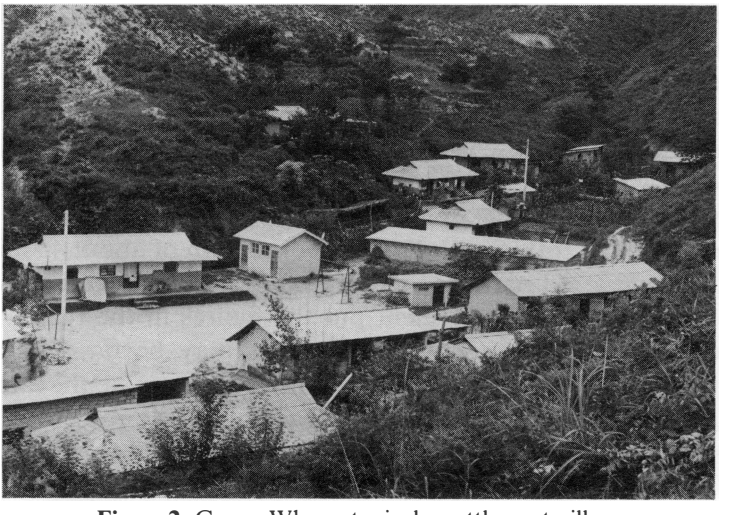

Figure 2. Geang Wha, a typical resettlement village.

villages are scattered throughout the 8 mainland provinces of South Korea, but are more concentrated in the south of the peninsula (Figure 3). Approximately 10,000 registered leprosy patients (36%) live in these villages. The remaining 13,250 registered patients (47%) live in the community as do the large numbers not registered with the Health Authority on whom little information is available.

An analysis of the 28,158 registered patients was undertaken in 1979 by the Korean Ministry of Health and Social Affairs and showed that 61% were male—a male: female ratio of 1·5: 1. The age incidence of these patients is shown in Figure 4 and the type of leprosy was found to be lepromatous in 57%, tuberculoid in 35·6%, borderline in 3·9% and indeterminate in 3·5%.

Figure 3. The distribution of 98 resettlement villages in South Korea.

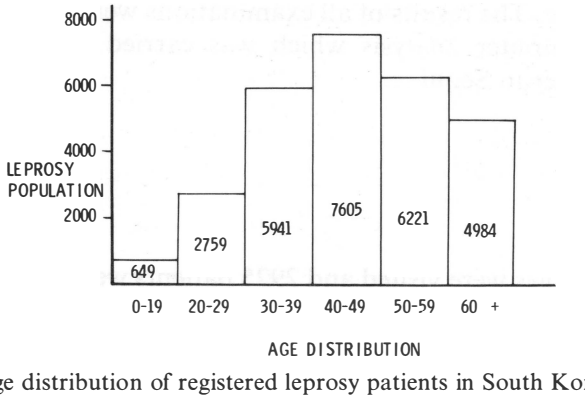

Figure 4. Age distribution of registered leprosy patients in South Korea, 1979.

Present study

In 1980 a project on the eye changes associated with leprosy was set up by a group of American Peace Corps workers. The primary objective of this project was to study the eyes of a large number of leprosy patients in the resettlement villages regardless of whether they were experiencing ocular symptoms or not. It was hoped that this would provide statistical information on the prevalence of various types of ocular complication related to leprosy in a country where the disease was common, and by this to identify those patients who were at risk of blindness and who might be helped by surgery that could be carried out at certain hospitals such as the Wilson Leprosy Centre. Prior to the start of the survey the 4 participants in the project had received instructions on methods of eye examination and assessment by members of the staff of the Wilson Leprosy Centre and by visiting ophthalmic surgeons from England.

Procedure

The selected villages were visited in rotation by members of the survey team working singly or in pairs. Initial information about the villages was obtained from regional health centres. Considerable help was provided by local leprosy workers who accompanied the participants and arranged introductions to village leaders. The name, age and sex of each patient were recorded together with the date of the examination and the name and location of the village. Information on the type, duration and status of leprosy was obtained from the medical records or from the patients themselves. (This data was inadequate in many instances, particularly the details regarding the status of the disease, in which case all patients not definitely known to be positive were recorded as negative.) The basic survey equipment consisted of a Snellen's E test type, a pinhole aperture, a pen torch and in some studies an illuminated loupe for examining the anterior segment of the eye. The results of all examinations were recorded on a proforma designed for computer analysis which was carried out using the American Embassy computer in Seoul.

Results

A total of 69 villages were visited and 2925 patients were entered into the survey. This represents over two thirds of the resettlement villages in South Korea, with examination of approximately one third of affected individuals. 51% of the patients were male and the age distribution of both sexes is shown on Figure 5.

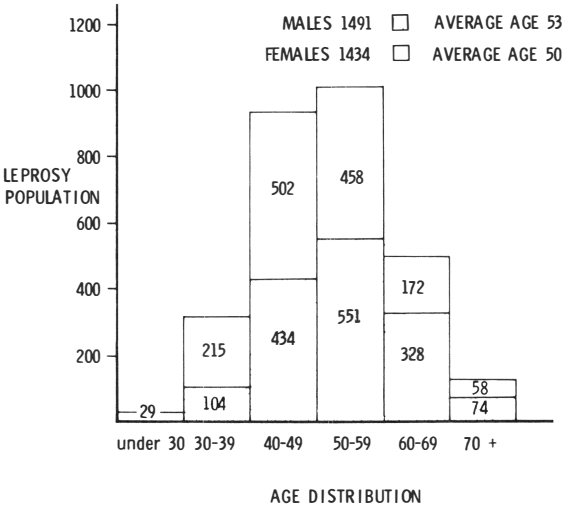

Figure 5. Age distribution of leprosy patients examined.

The type of leprosy was recorded as:

	Male (%)	Female (%)
lepromatous	64	58
tuberculoid	24	26
borderline	3	2
indeterminate	—	1
unknown	9	13

The duration of the disease and the therapy were difficult to assess as information was often unreliable, but most patients had started therapy more than 15 years previously. In only 3% of the sample was the bacterial index known to be positive.

VISUAL ACUITY

Ophthalmic examination commenced with measurement of visual acuity with the E test at 20 feet with distance glasses if worn, and patients with vision of less than 20/20 were tested with a pinhole. The results of these measurements are shown on Figure 6 for males and females; of the 5850 eyes examined no significant difference in visual acuity was observed between the right and left eyes. Visual levels of less than 20/200 are considered to represent functional blindness by Western standards and this occurred in 18% of eyes in male leprosy patients and in 11·5% of affected females. In 11% of patients both eyes had vision of less than 20/200, and a total of 251 eyes (4·3%) in the survey were either absent or had no perception of light (male:female ratio 2·5:1).

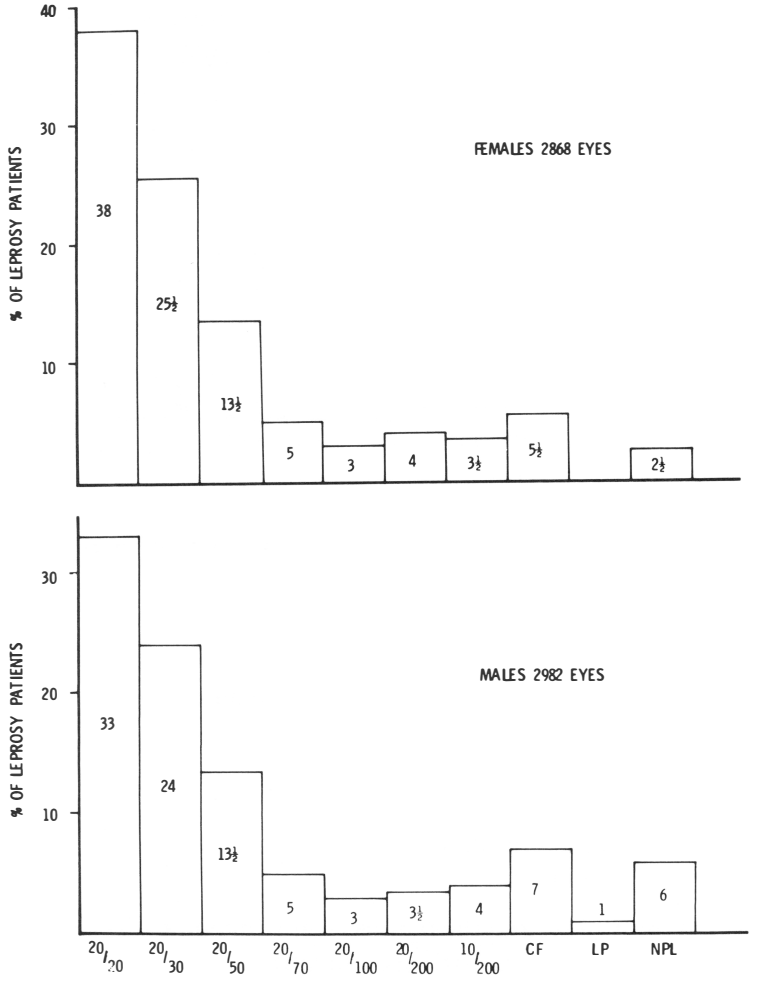

Figure 6. Visual acuity in 2925 leprosy patients examined.

LIDS

The lids were examined to assess ectropion, lagophthalmos or entropion, and an estimation of lid function was made by asking the patient to close the eyes forcibly against resistance. Severe lagophthalmos, defined as more than 5 mm, was observed in 7% of eyes and in a further 15% it was considered to be mild (less than 5 mm). Severe ectropion was noted in 2·5% and in a milder form in 10%, entropion was much less common, affecting only 3% of eyes examined and associated with trichiasis in 1%. Lid function was therefore found to be affected in at least 25% of the eyes examined in the sample.

LACRIMAL APPARATUS

Assessment of the lacrimal function and drainage was not easy to determine but it was possible to identify 14 eyes with inflammation in the region of the lacrimal sac accompanied by symptoms of watering and discharge.

CORNEA

The cornea was examined with a torch or illuminated loupe. Opacities were graded according to their probable influence on sight and were observed in 11% of all eyes examined. In half of these cases the opacities were considered to be sufficient to cause significant visual impairment. Blinding opacities were seen more commonly in male patients with a male:female ratio of 2·5:1. Pterygium was noted in 14% of eyes with the sexes equally affected. Corneal sensation was tested with cotton wool and in 14% of males and in 9·5% of females it was considered to be reduced; in a further 9·5% of males and 7% of females sensation was totally absent. Approximately 20% of the total sample of patients therefore were found to have some impairment of corneal sensation and blinding corneal opacities were seen in over 5%.

IRIS

Examination of the pupils was carried out as much as possible under standard conditions and pupil reactions were tested with a pen torch. By this method an assessment could be made of the size and shape of the pupil and abnormalities of position were noted. Synechiae were seen in some eyes but if small were often difficult to detect. In many cases with advanced corneal disease the pupil abnormalities could not be determined and in several patients previous intra-ocular surgery had altered the pupil shape. In 19·5% of all eyes in which examination was possible the pupil size was noted to be less than 2 mm (male:female ratio 1·4:1) and non-surgical irregularities of pupil shape or position were observed in 8%. The pupil reactions to light were completely absent in 12·5% of eyes (male:female ratio 1·6:1) and sluggish in a further 17·5%. Synechiae were positively identified in 7% and 88 eyes had had iridectomies. Pupil abnormalities of some sort were therefore observed in at least 20% of the total sample, and since in many cases advanced corneal disease prevented observations of the pupil or iris, the proportion of cases with pupil abnormalities is likely to be nearer 25%.

CATARACT

A slit-lamp or an ophthalmoscope were not available so that it was not easy to determine the presence of lens opacities, especially in eyes with very small pupils.

Advanced cataract was observed in approximately 5% of eyes although it is realized clearly that this figure is likely to underestimate the true incidence.

Discussion

It is evident, both from personal experience and from discussion with leprosy workers in South Korea, that ocular problems make up a high proportion of the out-patient complaints of leprosy sufferers. This survey was designed to give some indication of the incidence of eye complications throughout the leprosy population of South Korea by examining a large number of patients in resettlement villages regardless of whether or not they had ocular symptoms.

The results confirm the suspicion of the high incidence of ocular complications of leprosy—out of a total of 2925 cases examined in the survey at least 40% had some form of ocular disturbance attributable to the disease. More important was the observation that serious eye complications occurred in a significant percentage of cases—abnormalities of lid function in 25%, impaired corneal sensation in 20%, corneal opacities in 11% and iris changes in 25%, and in that most of these might be considered to predispose to blindness. Most important of all was the finding that visual acuity measurements showed that 11% of all patients had vision of less than 20/200 in both eyes and were therefore registerable as blind by Western standards, and that 4·3% of eyes examined were absent or had no perception of light.

The implications of these findings must be considered in relationship to the total leprosy population in South Korea. If the figures were repeated throughout the country with its 28,000 registered patients at least 3000 of these would be expected to be blind and the numbers are probably considerably higher since they do not take into account the large proportion of unregistered patients, and also because it is known that the cases living in leprosaria (about 5000) have a much higher incidence of advanced eye disease and these were not included in this present survey. Allowing for these factors it is estimated that there are at least 5000 blind leprosy patients living in South Korea and this represents a considerable socio-economic problem.

The difficulties faced by leprosy sufferers because of their loss of sensation and limb deformities are severe enough; if loss or impairment of vision is added to these, the problems become magnified and the implications for the individual and for the social services are obvious. The present care of the ocular problems of leprosy patients in South Korea is limited, with much of the burden being borne by Church missions whose resources are low and already stretched by their work in other fields of leprosy, such as general health care, orthopaedic surgery and dermatology. Many advanced cases need surgery to restore sight or to prevent the onset of blindness, and procedures such as tarsorrhaphy, iridectomy and cataract extraction, although carried out on an intermittent basis at certain centres,[4] are not generally available.

The main problems which predispose to the more severe ocular complications need routine supervision, relatively simple therapy, and the setting up of out-patient centres equipped for eye examination, situated in easily accessible areas with an ophthalmologist in attendance. Such clinics could be available for regular eye checks on leprosy patients, with instructions being given on basic eye care and preventive measures, and those cases requiring more sophisticated forms of therapy or surgery could be referred to the appropriate centres.

It is hoped that this survey will stimulate further improvement in the care of these patients.

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The American Peace Corps Survey of the ocular complications of leprosy in South Korea: an evaluation and appraisal

T J FFYTCHE
St Thomas's Hospital, London

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Summary The results of the American Peace Corps Survey of the ocular complications of leprosy in South Korea have been evaluated and compared with other surveys. Defective vision remains an important aspect of leprosy with 11% of the total number of 2925 patients examined having a visual acuity in both eyes of less than 6/60. It is hoped that the presentation of these figures will stimulate a more organized and rational approach to this difficult problem.

Introduction

In 1980 four American Peace Corps workers undertook an extensive survey of the ocular complications of leprosy in resettlement villages in South Korea. A total of 69 villages were visited and altogether 2925 patients were examined. The data collected was sorted and analysed with the aid of computer facilities at the American Embassy in Seoul.[1] None of the participants in this survey had any formal medical training although all had received basic instruction in methods of examination of the eye. They were not therefore in a position to interpret the results of their survey from a medical standpoint, and it is my pleasure to undertake an evaluation and assessment of their study in this companion paper.

Importance of the Survey

The Peace Corps Survey is unique for three reasons: firstly for the number of patients in the study, secondly for the sample of the leprosy population, and lastly for the nature of the eye complications that occur in leprosy in South Korea. The conception of the survey itself and its success, despite the relative ophthalmic

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inexperience of the participants, makes this an important model for future projects.[2]

The present survey is the second largest to be reported on ocular leprosy, being exceeded in numbers only by the Malawi study in which 8325 patients were examined.[3] A less detailed study was carried out in India in 1978 when 2731 patients in mining areas were seen,[4] but apart from this only 2 other surveys contain over a thousand patients—1279 in Brazil,[5] and 1212 in Tanganyika.[6] The largest survey previously reported in north-east Asia, where racial and environmental factors could be considered similar, is the study on 750 patients in Japan.[7]

Unlike many other surveys an attempt has been made to avoid bias in the selection of cases. Most studies in the past have been carried out in leprosaria where the majority of patients are the chronic sick and disabled, many of whom have advanced eye disease. Such reports are not representational of the leprosy population in general, and often concentrate only on those patients with overt ocular complications. By examining patients living in resettlement villages, regardless of whether they had ocular symptoms or not, the Peace Corps Survey has obtained information on a cross-section of the leprosy population, and the size of the sample—10·4% of the total number of registered leprosy patients in South Korea—allows extrapolation of some of the results in terms of the disease in the whole country.

In carrying out the survey in South Korea the authors have selected a leprosy population particularly at risk from ocular damage, without the manifestations of eye involvement being influenced by other blinding diseases. The temperate climate combined with the high incidence of lepromatous leprosy in the Korean race are factors known to be associated with ocular complications.[8] The economic status of the country has eliminated malnutrition and xerophthalmia as a cause of visual impairment, and the major blinding diseases of trachoma and onchocerciasis are not endemic in this area. As a result, eye symptoms and signs that develop in leprosy patients in South Korea are usually related to the disease itself, and can therefore be studied in the 'pure' form.

Another unique feature of the Peace Corps Survey is that the participants had received no formal medical training; but by the intelligent use of knowledge gained from instruction in the techniques of ocular examination, they were able to carry out a number of standardized subjective and objective tests on the patients in the study and thus provide data for analysis.

This achievement demonstrates that valuable information on ocular leprosy can be obtained by informed paramedical workers or medical students. It is of course admitted that some of the findings need more skilled medical interpretation, particularly those concerning the iris and lens, and that data on posterior segment involvement and non-leprotic disease is even less reliable. Even so, information produced by such a survey can be analysed with a fair degree of accuracy and the results compared with other studies carried out under similar conditions.[2]

Results

A number of ophthalmic parameters were recorded in the survey and need individual assessment, although not all have an effect on visual function. The results are deficient in one aspect in that it is not possible to interrelate these parameters to derive information on the different causes of blindness, nor can the relationship between the various types of ocular complication be established. Despite this, much of the information is valuable and an attempt will be made to extract the data that is important and try to compare it with other studies. In many instances this is not possible because of the fundamental differences in the types of survey carried out and in the way the data is presented.

TYPE OF LEPROSY

Lepromatous leprosy occurred in 61% of the patients examined and tuberculoid in 25%. This distribution of the type of leprosy conforms with the statistics provided by the Korean Ministry of Health and Social Affairs for the whole country—lepromatous 59% and tuberculoid 35·6%, with the discrepancy in the tuberculoid figures accounted for by the relatively high proportion of cases whose status was unknown (11%). These findings emphasize the preponderance of lepromatous leprosy in Asiatic races and are important since ocular complications are commoner in this form of the disease. In the Malawi survey, by comparison, tuberculoid leprosy was more frequent, occurring in 70% whereas the incidence of lepromatous leprosy was only 23%,[3] and similar ratios are seen throughout Africa. In India there is also a high frequency of tuberculoid leprosy—being seen in 53% in a survey in 1976[9] with the lepromatous form occurring in only 16%, and the interpretation of ocular complications in different countries should take these racial characteristics into account.

AGE AND SEX DISTRIBUTION

The age distribution of the patients in the survey is similar to that found in leprosy for the whole country with the majority of cases aged between 40 and 60.

An interesting feature was the almost equal number of males and females examined. In most studies leprosy has been reported as commoner in males,[10] and this is supported by the national statistics for South Korea where there is a male:female ratio of leprosy patients of 1·5:1. The explanation for this discrepancy may lie in the composition of the resettlement villages which tend to be comprised of family units with the healthier and more able-bodied males remaining. Once an individual becomes severely affected by the disease a move to a leprosarium usually takes place and the distribution of male and female patients is more likely to reflect the general trend. Hobbs & Choyce, for example, found a male:female ratio of 1·5:1 in 507 patients in the Sunjei Buloh leprosarium in

Malaysia.[11] and a ratio of 2:1 was observed in over 500 patients in the Htauk–Kyant Hospital in Burma.[12]

The sample therefore represents a broad cross-section of the leprosy population in South Korea rather than the institutionalized cases, and since these patients are the ones who contribute to the daily running of the community, the effect of the disease on visual function and efficiency has a real importance both from an economic and social point of view.

VISUAL ACUITY

The most alarming finding in the survey was the high proportion of patients with severely impaired vision. 11% of the 2925 patients had a combined visual acuity of less than 6/60 and were therefore functionally blind by Western standards. Blindness was commoner in males suggesting the higher susceptibility of the male patient to trauma because of working conditions. Resettlement villages are generally agricultural and male patients with defective lid closure or impaired corneal sensation who work outdoors are at greater risk from ocular trauma than similarly affected females who tend to stay indoors. Occupational hazards to the eyes of leprosy patients are therefore an important aspect of medical care and preventative measures to reduce them should be one of the prime objectives of medical and paramedical services.

It is not possible to analyse the different causes of blindness although experience from other studies on ocular leprosy in South Korea shows that the major complications result from corneal damage secondary to defective lid closure or from the late effects of chronic iritis.[13] Figures for blindness elsewhere in the world vary considerably but present equally disturbing statistics: 13% in Ceylon,[14] 7·1% in Malaysia,[11] whereas in Africa the overall incidence of blindness in leprosy is greatly reduced—1·3% in Uganda[15] and 0·3% in Malawi.[3] A straight comparison of these figures is difficult because of the differences in the way blindness is defined and in the sample of leprosy patients examined and analysed, most studies taking place in leprosaria.

LID ABNORMALITIES

Lid function was found to be affected in 25% of the eyes examined mostly in the form of ectropion or lagophthalmos. In an unpublished survey carried out in the Wilson Leprosy Centre in South Korea lid abnormalities were found even more frequently, with 37% of the patients having lagophthalmos with or without ectropion.[16]

Lid involvement in leprosy usually implies the presence of a VIIth nerve palsy which occurs in all forms of the disease. These figures are high compared with other studies and the incidence of lid changes are reported as much less in Africa, with only 3% of the patients in the Malawi survey affected[3] and 6% in Uganda.[15]

Elsewhere in the world the figures for facial nerve palsy vary considerably, being as high as 27% in Vietnam,[17] 21% in Israel,[18] 13% in Brazil,[19] and 7% in Turkey.[20]

CORNEAL DISEASE

Corneal involvement is also a major complication of ocular leprosy in all forms of the disease. It results either from primary infection, although the changes from the superficial stromal keratitis that occurs in lepromatous leprosy seldom cause severe visual symptoms,[21] or more commonly the cornea develops scarring secondary to impaired sensation and defective lid closure. In many tropical countries corneal disease arising from non-leprosy causes is added to the damage from leprosy. As expected, blinding corneal lesions were commoner in males and occurred in over 5% of the patients examined. 11% of all eyes in the survey had some sort of corneal opacity and in at least 20% the corneal sensation was either absent or impaired. No statement can be made on the relationship between corneal opacification and loss of sensation, nor on the relative incidence of the different forms of the disease, but similar studies elsewhere have shown a variable degree of corneal involvement with 23% affected in the Wilson Leprosy Centre Survey,[16] 17% in Malawi,[3] whereas only 8% of 750 patients in Japan were affected[7] and in Tanganyika the incidence of corneal damage was reduced to 5%.[6] Again this regional difference is difficult to explain and suggests that a number of factors are responsible.

IRIS ABNORMALITIES

The cause of blindness in all forms of leprosy is shared equally between corneal scarring and the results of intraocular disease affecting the iris and lens. Acute iritis may occur in patients with all forms of leprosy, often accompanying a change in polarity either spontaneous or related to treatment as part of the lepra reaction.[11] Chronic iritis occurs in lepromatous leprosy and is responsible for progressive atrophy of the iris and increasing miosis which reduces visual acuity especially in the presence of corneal or lenticular changes.[22]

The early signs of chronic iritis are often difficult to diagnose without the aid of a slit-lamp and are frequently missed since they may not be accompanied by any symptoms. As the condition progresses clinical signs become more evident and these include a decrease in the size of the pupil and, if synechiae are present, a distortion of its shape. There is a corresponding reduction in the amplitude of the light reflex and the end-result is a small unreacting pupil through which very little light can be transmitted. The Peace Corps Survey was not equipped to distinguish or differentiate the early changes of chronic iritis, but the measurement of pupil size, shape and reactions gives some indication of iris involvement and at least 20% of all eyes examined showed some abnormality. Figures derived from other studies show a considerable variation with 76% of lepromatous patients in a study

in Iran showing iris involvement,[23] and 47% of the Wilson Leprosy Centre Survey were similarly affected;[16] by contrast only 7% of lepromatous cases in Malawi had iris disease,[3] 6% in Japan[7] and 3% of all cases in the Uganda survey.[15]

LENS CHANGES

In the more posterior parts of the eye examination techniques become difficult unless sophisticated instruments are available. For this reason the assessment of cataract by the Peace Corps Survey was inaccurate, partly because of the lack of experience of the participants but also because in a large number of patients the pupil aperture was too small to allow an adequate assessment of the state of the lens. This problem cannot be easily resolved even with access to the slit-lamp and ophthalmoscope as it is not usually possible to dilate pupils affected by chronic iritis.[24] No firm conclusions can therefore be drawn on the presence or absence of lens opacities except to note that cataract has been reported as a common secondary complication of chronic iritis in lepromatous leprosy.[25,19,26]

Discussion

The results of the American Peace Corps Survey in South Korea throw an important light on the nature of eye complications in a country where leprosy is still endemic and where racial and environmental factors combine to encourage the development of ocular involvement. Eyes that are affected are in addition unlikely to be subjected to other major causes of blindness so that the Korean leprosy population presents a 'pure' form of ocular disease. The results confirm that ophthalmic complications are a fundamental aspect of the condition and that therapy directed towards their prevention and treatment is of paramount importance.

The figures of vision less than 6/60 in both eyes in 11% of this cross-section of the leprosy community are alarmingly high by any standards and need urgent attention. Preventive measures to protect the eyes particularly with reference to occupation should form a basic aspect of leprosy health care and education. Such measures would go a long way towards reducing the amount of corneal damage and preventing opacification. The treatment of chronic iritis presents a greater problem since it is often very difficult to diagnose in the early stages as it is usually asymptomatic. It requires supervision of leprosy patients, particularly those with the lepromatous form of the disease, by ophthalmologists equipped with the slit-lamp; and although conventional therapy may not always be effective, secondary complications could be detected early and the necessary surgical procedures instituted. Most patients with chronic iritis eventually require surgery, either for optical iridectomy or lens extraction, and this can be carried out as a non-urgent procedure at selected centres. The simple creation of eye

clinics in regional centres which could be attended on a regular basis by qualified ophthalmologists would therefore be a valuable development in the management of eye complications in a country such as South Korea where the problem of leprosy is so extensive.

The comparison of findings in this survey with studies undertaken elsewhere in the world demonstrates the variable incidence and nature of ocular complications and stresses the importance of epidemiological studies in the detection of those factors which predispose to ocular damage.

The significance of the American Peace Corps Survey is that by its simple conception it can act as a model for future surveys in different countries to identify those areas where there is a need for ophthalmic supervision both for the individual leprosy patient and for the leprosy community as a whole.

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Lepr Rev (1984) **55,** 247–253

A follow-up investigation of the Malta-Project

W H JOPLING,* MARIAN J RIDLEY,†
E BONNICI‡ & G DEPASQUALE‡
**WHO short-term consultant; †Hospital for Tropical Diseases, London; ‡St Luke's Hospital, G'Mangia, Malta*

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Summary A report is presented of a follow-up examination of 116 multibacillary leprosy patients who had received multidrug therapy (MDT) as part of a leprosy eradication programme known as the Malta-Project, inaugurated in 1972. Length of treatment varied between 5 and 89 months, and side-effects were mostly mild. No signs of clinical relapse were found at follow-up, and 36 patients had positive skin smears; 26 had granular bacilli alone, and 10 had scanty 'solids'. It is proposed that these 'solids' are 'persisters', and their significance will be known after long-term follow-up of these 10 patients.

Introduction

The objective of this follow-up investigation, carried out in April 1983, was to examine the bacilliferous patients who had been given multidrug therapy (MDT) in Malta since 1972. The particular objectives were the following: 1, to look for signs of clinical relapse; 2, to discover if any leprosy bacilli, whether granular or solid-staining, were present in skin smears; and 3, to study the incidence of side-effects.

Professor E Freerksen's design of the Malta-Project[1] was to treat by MDT all leprosy patients whose names appeared on the registration lists of the Ministry of Health, and similarly to treat all new patients diagnosed in subsequent years, with the objective of eradicating leprosy from Malta by rapidly rendering the patients non-infectious. It should be noted that he never intended that this should be looked upon as therapeutic research:

> 'The Malta-Project is not meant to be a trial with the objective to assess anti-leprosy drugs, but an eradication programme which is exclusively based on antimycobacterial chemotherapy.'[1]

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Two-hundred-and-six patients began MDT in June or July 1972 when the Malta-Project was launched, and included paucibacillary and multibacillary cases. The majority had received monotherapy with dapsone for varying periods measured in years. Chemotherapy in all cases consisted of 4 drugs: rifampicin, dapsone, prothionamide, and isoniazid, the last 3 being incorporated in a tablet named Isoprodian. Patients weighing 50 kg or more received 600 mg of rifampicin and 2 tablets of Isoprodian daily for 6 days/week, each tablet consisting of 50 mg of dapsone, 175 mg of prothionamide, and 175 mg of isoniazid, and a reduction in dosage was made for those weighing less than 50 kg. The majority of patients began MDT in June or July 1972, the minority subsequently. Length of MDT depended on the original clinical, bacterial, and histological assessment of each patient, taken in conjunction with response to treatment; the shortest course was 5 months (a BL patient who had previously been treated with dapsone for 6 years), and the longest was 89 months (a new and hyperactive LL patient).

Materials and methods

There were 128 patients listed as multibacillary who were available for examination in April 1983, 75 males and 53 females, their ages ranging from 20 to 82 years, with a mean of 55 years. Because of the limited time available, clinical examinations were shared as follows: 83 patients were examined by WHJ, and examination of the remaining 45 was shared between EB and GD. Six skin smears were taken by WHJ from each of the 128 patients, and the following system was strictly followed:

Smear no.1 from the right earlobe.
Smear no.2 from the left earlobe.
Smear no.3 from the right mid-finger (dorsum of 1st phalanx).
Smear no.4 from the left mid-finger (dorsum of 1st phalanx).
Smear no.5 from the right upper arm (just above elbow).
Smear no.6 from the left upper arm (just above elbow).

The urine of every patient was examined for protein and sugar, and a small sample was sent to Dr H. Huikeshoven, Amsterdam, to be tested for the presence of dapsone by his ELISA method.[2] Medical records were studied and side-effects of treatment were noted.

Results

Findings in 6 of the 128 patients were excluded from this report because a study of case records showed that they were originally classified as BT cases. This left a

total of 122 multibacillary patients, and from this number a further 6 were excluded as 2 had not completed MDT at the time of the investigation, and 4 because Dr Huikeshoven could not give an unequivocal assurance regarding absence of dapsone in their urine samples. Urine specimens from the 2 patients who had not completed MDT were found to be strongly positive. All other specimens were negative for dapsone.

This left 116 multibacillary patients for clinical and bacterial follow-up. The group consisted of 70 males and 46 females, their ages ranging from 22 to 82 years with a mean of 56. At the time of diagnosis 88 patients had been classified as LL,

Table 1. Details of 26 multibacillary leprosy patients with only granular bacilli in follow-up skin smears in April 1983

Patient	DDS prior to MDT (years)	MDT began	MDT (months)	Months since beginning MDT	Months since ending MDT
1 LL	3	June 1972	56*	130	74
2 BL	7	June 1972	33	130	97
3 LL	24	June 1972	30*	130	100
4 LL	19	June 1972	29*	130	101
5 LL	11	June 1972	23*	130	107
6 LL	19	June 1972	23*	130	107
7 LL	17	June 1972	22	130	108
8 LL	5	June 1972	22*	130	108
9 LL	29	June 1972	21	130	109
10 LL	20	June 1972	21	130	109
11 BL	5	June 1972	20*	130	110
12 LL	19	June 1972	20*	130	110
13 LL	5	June 1972	20*	130	110
14 LL	26	July 1972	80*	129	49
15 LL	21	July 1972	26	129	103
16 LL	14	July 1972	26*	129	103
17 LL	23	Sept. 1972	12	127	115
18 LL	17	Nov. 1972	17*	125	108
19 LL	15	Apr. 1973	71*	120	49
20 LL	1	Feb. 1974	48*	110	62
21 BL	0	July 1974	16*	105	89
22 LL	2	Mar. 1978	26*	61	35
23 LL	3	Aug. 1978	21*	56	35
24 LL	0	June 1979	11*	46	35
25 LL	0	Mar. 1980	32*	37	5
26 LL	0	May 1982	8 (interrupted)	11	3

LL = Lepromatous. BL = Borderline-lepromatous. *Granular bacilli present at end of MDT.

22 as BL, and 6 as BB. However, all 122 patients are included in the study of side-effects of treatment.

Clinical findings in 116 patients

No signs of clinical relapse were found.

Bacterial findings in 116 patients

Examination of skin smears was carried out by MJR at the Hospital for Tropical Diseases, and 36 were found to have positive smears (31%); 26 had only granular bacilli (Table 1), 3 had a combination of scanty solid-staining and granular

Table 2. Details of 10 multibacillary leprosy patients with solid-staining bacilli in follow-up skin smears in April 1983

Patient	DDS prior to MDT (years)	MDT (months)	Months since beginning MDT	Months since ending MDT	Findings in skin smears, April 1983
1 LL	2	74*	130	56	Scanty 'solids' in left upper arm. The other 5 smears are negative.
2 LL	0	72*	121	49	One 'solid' in right mid-finger. The other 5 smears are negative.
3 LL	0	42*	83	41	Scanty 'solids' in left mid-finger, and a few granular bacilli in right upper arm. The other 4 smears are negative.
4 LL	19	41*	130	89	Scanty 'solids' and granular bacilli in right mid-finger and in right earlobe. The other 4 smears are negative.
5 BL	16	24*	130	106	One 'solid' in right mid-finger. The other 5 smears are negative.
6 LL	3	23*	130	107	One 'solid' in right mid-finger. The other 5 smears are negative.
7 BL	0	21*	56	35	Scanty 'solids' in left mid-finger. The other 5 smears are negative.
8 BL	12	20	130	110	Scanty 'solids' in left mid-finger. The other 5 smears are negative.
9 BL	0	20	94	74	One 'solid' in left mid-finger. The other 5 smears are negative.
10 LL	0	14*	45	31	Scanty 'solids' in right upper arm, and granular bacilli in all 6 smears.

Notes. LL = lepromatous. BL = borderline-lepromatous. *Granular bacilli present at end of MDT.

bacilli, and 7 had only scanty solid-staining bacilli (Table 2). In the 10 patients with solid-staining bacilli, one or other finger was positive in 8, and in 7 the fingers were the only sites containing solid-staining organisms (Table 2).

Side-effects of MDT in 122 patients

Although a number of patients had died since the launching of the Project in 1972, no deaths were attributable to treatment. One patient developed clinical jaundice 8 months after beginning treatment, but was able to continue after an interval of 4 months. Other effects were mild and included gastro-intestinal upset in 31, glossitis in 16, dizziness in 9, nerve pain in 3, joint pain in 1, and abnormal liver function tests were noted in a patient who had begun MDT in May 1982, causing treatment to be interrupted; but it should be noted that LFT's were not routinely recorded prior to 1978. ENL occurred in 52 patients (42.6%). Bouts of ENL were usually of short duration, and more prolonged bouts were satisfactorily controlled by thalidomide so that treatment was not interrupted. Necrotic ENL was not encountered. Upgrading (reversal) reactions were seen in 2 patients.

Other findings in 122 patients

Routine urine tests revealed protein in 7 and sugar in 8. In addition, one specimen contained protein and sugar. The finding of glycosuria in 9 patients reflects the high incidence of diabetes in Malta, and the majority of these 9 patients were known diabetics.

Discussion

Clinicians who are instituting MDT for the first time, and are anxious about possible serious side-effects, will be encouraged by these findings, especially as 4 drugs were used in the Malta-Project as against 3 recommended in 1982 by the WHO Study Group.[3] These 3 drugs are rifampicin, dapsone, and clofazimine, with rifampicin given on a monthly regimen (supervised), with the possible alternative of substituting prothionamide (or ethionamide) for clofazimine in patients with light skins who find skin pigmentation intolerable. Freerksen included isoniazid in his multidrug regimen for 2 reasons: firstly, because he credits it with a potentiating effect on the other 3 drugs, and secondly to have a combination of drugs suitable for treating tuberculosis as well as leprosy.[4] This combination was well tolerated in the group under consideration; although ENL was observed in 42.6%, and gastro-intestinal upset in 25.4%, these and rarer side-effects did not cause any interruption of treatment except for the 2 patients who showed signs of liver toxicity.

No signs of clinical relapse were noted, and examination of skin smears

showed that granular bacilli alone (i.e. without solid-staining bacilli) were found in 26 patients (22·4%); 19 of these 26 patients had granular bacilli even though 10 years or more had elapsed since the time of beginning MDT, 4 or more years had elapsed since stopping, and 2 patients had received treatment for 6–7 years (Table 1). This finding raises doubts about the practicality of the recommendation of the WHO Study Group that, where possible, MDT should be continued up to bacterial negativity, namely, up to the time when the last granular bacillus has disappeared from follow-up skin smears, for this may necessitate continuing treatment for up to 10 years. After all, removing dead bacilli from the tissues is not a function of chemotherapy but is a function of macrophages, and macrophages in lepromatous leprosy are peculiarly ineffective at this task.

Table 2 shows that scanty 'solids' were found in 10 patients out of 116 (8·6%), yet 2 of them had been treated for 6 years (72 and 74 months respectively); in 3 there were granular forms in addition, but in 7 the solid-staining forms were the only ones found. It is of special interest that one or other finger was positive for 'solids' in 8 of these 10 patients, and in 7 of them the fingers were the *only* positive sites. This finding gives strong support to the original work at the Hospital for Tropical Diseases which showed that in long-treated LL patients the fingers are the most likely sites in which to find them,[5,6] and confirms that follow-up skin smears in multibacillary leprosy should always include two from fingers. We suggest that these 'solids' represent 'persisters' (drug-sensitive, dormant bacilli), and that the generous supply of dermal nerves in fingers increases the likelihood that bacilli sheltering within them may be extracted by the tip of the scalpel blade. Freerksen has decided that these 10 patients will not be retreated but will be closely observed over future years to see if any multiplication and dissemination of leprosy bacilli takes place, and this will prove an important piece of clinical research.

It is important that an answer is found to the question of how long MDT should be continued. The expense of continuing up to bacterial negativity could be justified if it could be shown that the likelihood of eliminating 'persisters' would thereby be increased, and it is to be hoped that future clinical research will provide an answer to this question. The findings in this follow-up investigation suggest that in many cases it is unnecessary to continue MDT up to bacterial negativity, and stopping treatment at a stage when granular bacilli are still present in skin smears can be justified, for out of 116 patients there were 67 (57·7%) who had granular bacilli when MDT ceased, yet no 'solids' were found in April 1983; 48 of these 67 patients had completely negative skin smears at follow-up, and 19 had only granular bacilli. Length of treatment in these 67 patients averaged 30 months. Further experience with MDT may show that if 'persisters' are not killed after 2–3 years of treatment, no useful purpose will be served by continuing up to bacterial negativity. The important proviso is, however, that a programme of follow-up examinations must be strictly followed.

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Lepr Rev (1984) **55,** 255–264

Leprosy treatment in Nepal with multidrug regimens

MAUREEN C BIRCH
Patawalonga, Orchard Field, Avening, Tetbury, Glos GL8 8PE

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Summary New multidrug treatment regimens have recently been recommended for use in Leprosy Control Programmes by the World Health Organization. This study was performed at Green Pastures Leprosy Hospital, Pokhara, Nepal where multidrug regimens have been in use for seven months. It was aimed at detecting problems resulting from the introduction of the new treatment.

No major difficulties with the use of multidrug regimens for leprosy treatment have been encountered, although several initial practical problems have arisen which may easily be remedied.

This study has failed to detect any significant side-effects associated with the use of multidrug regimens. Furthermore, few leprosy 'reactions' during multidrug treatment regimens have been reported.

Introduction

In the last 5 years it has become apparent that there are several problems with chemotherapy for leprosy control. An increasing number of cases of primary and secondary dapsone resistance have been reported in addition to problems with bacterial persistence after long periods of treatment.[1]

In order to resolve these problems, the World Health Organization (WHO) convened a Study Group in Geneva in October 1981. As a result of the meeting, a report on the 'Chemotherapy of Leprosy for Control Programmes' was produced in early 1982.[2] The report recommends multidrug regimens (MDR) for the treatment of all types of leprosy.

In November 1981 the 'Second National Workshop on Leprosy Control' was initiated by Dr Adigia (Chief of Leprosy Services in Nepal). Multidrug regimens were devised for The National Leprosy Control Project based on the WHO recommendations.[3] Introduction of the new regimens was begun in 1982 with the intention of extending MDR treatment to all areas within 2 years. The aims are: to eradicate leprosy as soon as possible; to limit the time of treatment and infectivity; and to avoid the dangers of drug resistance.

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This is a vast undertaking. Nepal has an estimated 100,000 leprosy patients with relatively high prevalence rates of primary and secondary dapsone resistance.[4]

The first phase of the introduction in the Western region of Nepal began at Green Pastures Leprosy Hospital, Pokhara in April 1982. This hospital acts as a major regional referral centre for Western Nepal and undertakes outpatient treatment of leprosy patients who choose Green Pastures Leprosy Hospital as their treatment centre. It is run by the International Nepal Fellowship, which has been involved in the National Leprosy Control Project in Western Nepal since 1975.[5]

Three months after the MDR was introduced at Green Pastures Leprosy Hospital a standing order containing a well-defined protocol was produced for use under field conditions. This is available in both English and Nepali.[6] Details of multidrug regimens used in Nepal are given in Table 1.

Table 1. Details of multidrug regimens used in Nepal

Multibacillary			
First choice	Adults	Daily	100 mg dapsone
			50 mg clofazimine
		Monthly	600 mg rifampicin
			300 mg clofazimine
	Children and adults		< 35 kg
		Daily	50 mg dapsone
			50 mg clofazimine
		Monthly	300 mg rifampicin
Second choice	Adults	Daily	2 tablets isoprodian
		Monthly	600 mg rifampicin
Paucibacillary			
First choice	Adults	Daily	100 mg dapsone
		Monthly	600 mg rifampicin
	Children and adults	< 35 kg	
		Daily	50 mg dapsone
		Monthly	300 mg rifampicin

The WHO report encourages continuous measurement of progress and periodic assessment by independent teams. As an elective Medical Student based at Green Pastures Leprosy Hospital from October to December 1982, I was able to perform this study as an outside observer during my daily work in the hospital. At this time the MDR had been in operation for 7 months at the hospital and had also been recently introduced in 4 other districts, 2 in the Western region and 2 in the Mid-western region of Nepal.

Materials and methods

The study was carried out at Green Pastures Leprosy Hospital, Pokhara, Nepal on all patients from the Kaski District (the area immediately surrounding the hospital) who attend the Outpatients Department for their leprosy treatment. Information was gathered from the following 3 sources:

A DATA-FORMS

All the notes of leprosy patients in Kaski registered at Green Pastures Leprosy Hospital were reviewed. A data-form was filled in for each patient to extract relevant information about their past leprosy history and current MDR treatment.

B COMPLIANCE STUDY

A study was carried out on those patients taking multibacillary MDR treatment who attended Green Pastures Leprosy Hospital outpatients department during a 6-week period. This regimen includes the drug clofazimine (lamprene) which causes skin coloration. A form was completed for each patient indicating whether clofazimine skin coloration was present or not. This was assessed by Nepali paramedical workers who are experienced in observing skin colour.

C OBSERVATIONS

During my 8 weeks at Green Pastures Leprosy Hospital I was able to observe the management of inpatients and outpatients who were receiving MDR treatment.

Results

The data-forms, results of the compliance study and observations were evaluated, enabling the following results to be extracted.

A GENERAL STATISTICS (Table 2)

In Kaski, 73% of patients attending Green Pastures Leprosy Hospital are now receiving MDR treatment. Of those who are not, the majority were given more than 6-month supplies of dapsone treatment (according to the old regimen[7]) in the 6 months preceding the introduction of MDR. (In Nepal it is sometimes necessary to give large supplies of drugs to patients who live many days walking distance from the hospital.) These patients will eventually be started on MDR treatment. There are a number of patients who have not been started on the MDR

because they have defaulted. Four patients (2 paucibacillary and 2 multibacillary cases) have refused to start the MDR. Three of these patients were very old, infirm and unable to walk well, so would have had difficulty in attending for their supplies of drugs. The fourth patient had a history of poor compliance and at the same time refused admission for an infected ulcer because of a 'bad home situation'. These 4 patients were all continued on the old treatment regimens and given 6- or 12-month supplies of dapsone to take away.

Only 4 patients were unable to start the MDR because they had one of the conditions listed in the standing order exempting them from starting. They were all suffering from tuberculosis.

Table 2. General analysis of patients in the study

	Male	Female	Total
No. of patients registered in Kaski	239	111	350
No. of patients on MDR	172	83	255
No. of patients on multibacillary MDR	95	34	129
No. of patients on paucibacillary MDR	77	49	126

B PAST LEPROSY HISTORY (Table 3)

The majority of patients started on the MDR are old cases previously treated on the old regimens. Forty-four per cent of multibacillary cases and 36% of paucibacillary cases have been registered for more than ten years. It seems likely that among the paucibacillary cases on treatment for over 10 years there may be some patients who should have been released from control and never started on

Table 3. Past leprosy history of patients on the multidrug regimen

No. of years registered	Multibacillary	Paucibacillary
New cases	5	16
1–5	37	43
6–10	28	19
11–15	33	21
16–20	15	23
21+	9	1
?	2	3

the MDR. Unfortunately, at the time of the study no data was collected on the length of inactivity before starting MDR treatment.

C CHOICE OF MULTIDRUG REGIMEN (Table 4)

All the patients on the MDR are on the first choice regimens. In the standing order it is emphasized that the second choice multibacillary MDR regimen should only be used for those who refuse to take clofazimine. When MDR treatment was commenced in Western Nepal a second choice regimen without clofazimine was included because no data was available on the acceptability of clofazimine skin coloration to Nepali leprosy patients. However, the first choice regimen is

Table 4. Numbers of patients for each choice of multidrug regimen

	Multibacillary		Paucibacillary
	First choice regimen	Second choice regimen	First choice regimen
Adults	126	0	125
Children	3	0	1
Adults < 35 kg	0	0	0

preferable. In fact, 5 patients in this study refused to continue taking clofazimine. They had been taking clofazimine for 2–4 months as part of the MDR. One patient had been on the MDR for 3 months, but was noted not to show clofazimine skin coloration. In the case of 3 of these patients MDR treatment was stopped and dapsone treatment according to the old regimen was started. The other 2 patients were transferred to the paucibacillary regimen as their disease had been inactive for over 10 years. It was decided not to offer these patients the second choice regimen. If it became public knowledge that alternative treatment without clofazimine was available, an unacceptably large number of patients might demand to be put on the second choice regimen.

D DURATION OF MULTIDRUG REGIMEN TREATMENT (Table 5)

A total of 35 patients have been released from the paucibacillary MDR after completing the full course of treatment (twenty-eight per cent of the total number

Table 5. Details of duration of multidrug regimen treatment

Number of months on MDR	Multibacillary	Paucibacillary
1	3	11
2	2	14
3	9	12
4	19	13
5	22	25
6	23	16
7	46	
8	4	35
9	—	(released from treatment)
10	1	

number on the paucibacillary regimen.) Of these, 26 were released at least a month before this study took place. Eight patients had been released from treatment on the date of their last supervised dose of rifampicin when they were given a further month's supply of daily dapsone. It states clearly in the standing order that patients should be released only on completion of the full course of daily drugs. No smears or examinations were performed on release from treatment, as demanded by the standing order. These will take place at the time of the patient's next annual examination.

E COMPLIANCE (Table 6)

The data on compliance extracted from the data-forms suggests that attendance may be slightly better for MDR treatment compared to the old regimens. Unfortunately the numbers are too small to draw any definite conclusions; however the figures obtained indicate that of those who were poor attenders for the old regimen, 54% continue to be so for the MDR.

The most common reason for missed once-monthly doses of MDR treatment is illness, in particular foot ulcers, which may make travel difficult. Some patients were unable to attend because of social problems or a 'bad home situation'. Others could not attend as they had to travel out of the area.

In addition it was noted that 10 patients were late for treatment because they said they were still taking their daily dapsone and did not need further supplies. Some admitted obtaining dapsone from other sources (often a friend or relative) but it seems likely that many of these patients had not taken their dapsone daily. Conversely, patients returned early to collect their MDR treatment because they

Table 6. Comparison between regularity of monthly attendance for treatment in patients changed from old regimen to MDR

	Old regimen	MDR
No. of patients with > 75% regularity	178	192
No. of patients with < 75% regularity	37	23

$$\text{Regularity} = \frac{\text{No. of months attended for treatment}}{\text{Total No. of months treatment possible}} \times 100\%$$

Total number of patients (215) excludes new cases, those with incomplete notes and those who withdrew from MDR because of clofazimine skin coloration.

had 'lost' their medicine. One patient returned early for this reason in 3 consecutive months. He was probably an unreliable character but the possibility does exist that he was selling his supplies.

The compliance study for patients on the multibacillary MDR attending outpatients showed that 98% of patients had clofazimine skin coloration and were therefore assumed to be taking their medicine regularly. This is a subjective method of measuring compliance, but these results do indicate that no major problems with poor compliance may be expected.

F UNSUPERVISED DOSES (Table 7)

In the standing order it states that at least half of the once-monthly drugs should be given under supervision. (This is not in accordance with the WHO report which recommends full supervision. However, the inaccessibility of many regions in Nepal renders it necessary to allow unsupervised doses to be given under field conditions where patients may have to walk for many days to collect treatment.) At any one clinic attendance no more than 2 doses of monthly drugs should be given, one as a supervised dose then, and another unsupervised dose for the following month. No more than one unsupervised dose should be given consecutively—if a patient cannot attend once every 2 months, then he should be continued on daily drugs only and the treatment period prolonged until he is able to attend for the required number of once-monthly supervised doses.

Many patients were given one dose of unsupervised once-monthly drugs and this was occasionally collected by a proxy (usually a close relative). However 9

Table 7. Supervision of once-monthly drugs

Number of unsupervised doses during 7 months of MDR treatment	Multibacillary	Paucibacillary
1	54	49
2	21	18
3	4	9
4	6	1
5	3	2
6	—	—

patients on the multibacillary MDR and 3 patients on the paucibacillary MDR were given more than 3 of their requisite 6 monthly doses unsupervised.

G LEPROSY 'REACTIONS' DURING MDR TREATMENT (Table 8)

No leprosy 'reactions' occurred in patients on the paucibacillary MDR. Six patients on the multibacillary MDR (5% of those receiving multibacillary treatment) suffered reactions; 4 were reversal reactions and 2 were ENL reactions. Four of these patients had had previous reactions on the old regimen, one had had none on the old regimen and another patient was a new case.

From these initial observations it appears that very few patients have suffered 'reactions' during MDR treatment.

Table 8. Occurrence of leprosy 'reactions' during MDR treatment

	Type of leprosy	Type of reaction	Month of MDR treatment reaction occurred	Previous reactions on old regimen
1	BL	Reversal reaction	1	Reversal reaction and ENLs. (Possibly dapsone resistant.)
2	BL	Reversal reaction	4–6	Reversal reaction
3	L	Mild ENL	1–2	Recurrent ENLs
4	L	Reversal reaction	3–4	Recurrent ENLs
5	BL	Reversal reaction	1–2	New case
6	L	Severe ENL	1–3	None previously

ENL = erythema nodosum leprosum

H SIDE-EFFECTS OF MDR TREATMENT (Table 9)

During the 7 months since the introduction of the MDR no major side-effects have been reported and no patients have had their MDR treatment halted because of side-effects. There have been 7 cases of 'flu syndrome possibly attributed to rifampicin treatment. However several of these cases coincided with a 'flu epidemic in the area and it is impossible to directly attribute such symptoms to MDR treatment. Eight patients complained of non-specific abdominal symptoms for which no obvious cause was detected on examination or investigation. It must again be stated that this is a common complaint in Nepal and impossible to attribute directly to MDR treatment. One patient complained that dapsone made him 'feel bad'. In all of these patients their problems were relieved with symptomatic treatment.

Table 9. Side-effects of MDR treatment

	Multibacillary	Paucibacillary
? 'Flu syndrome		
First month of treatment	3	3
Second month of treatment	—	1
Unexplained abdominal symptoms		
First month of treatment	3	1
Second month of treatment	3	1
Third month of treatment	1	—
Others		
Dapsone made him 'feel bad'	—	1

Discussion

It must be emphasized that this study had many limitations. Most of the data was collected from patients' notes which may not be complete, although the standard of note keeping appeared to be very high. The study was conducted over a limited time period by someone inexperienced in leprosy and unable to speak Nepali. It was performed in addition to daily responsibilities in the hospital, which was without a resident doctor during this time.

The overall findings of the study are that the introduction of the WHO MDR at Green Pastures Leprosy Hospital for patients in the Kaski District has been a well planned and executed undertaking. There have been very few problems so far with the operation of the new regimens. I was very impressed with how efficiently MDR treatment is carried out, especially since the MDR is complex compared to

the old regimens, with a far more demanding workload on medical and paramedical staff.

The problems that have arisen are mostly related to the uncertainties associated with the introduction of the regimens before the standing order was produced. The standing order was designed for use under field conditions and not specifically for use at Green Pastures Leprosy Hospital. In addition there have been several changeovers of Nepali paramedical staff and expatriate medical staff during the introductory period. They are all relatively minor problems and may be overcome with ease as the paramedical and medical workers involved become more familiar and experienced with using the MDR.

This study was not aimed at evaluating the effectiveness of MDR treatment in the control of leprosy. This is a task which will have to be performed later when the MDR has been running for a longer period of time. However, it is significant that in the seven months the MDR has been in operation, no major side-effects have occurred. In addition, very few leprosy 'reactions' have been seen in patients on the MDR. It is hoped that the introduction of the MDR to all treatment areas over the next 2 years will continue, subject to availability of the necessary drugs and trained personnel.

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Multidrug treatment of leprosy—practical application in Nepal

N M SAMUEL, SUSIE SAMUEL, N NAKAMI, & R MURMU
Anandaban Leprosy Hospital, PO Box 151, Kathmandu, Nepal

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Summary In June 1981, 25 years after its first involvement in the treatment and control of leprosy, the Anandaban Hospital in Nepal introduced multiple drug therapy. The main objectives were: 1, to treat all newly diagnosed patients, both pauci- and multibacillary; 2, to give multiple drug therapy to all active multibacillary cases, irrespective of previous treatment; and 3, to document the regularity of attendance of patients, including those living at great distances from the hospital clinic. Preliminary results are reported in a group of 348 patients.

Introduction

Many people in third world countries are affected by leprosy and this may perhaps be due to marginal living conditions and ineffective health care systems. In countries like Nepal, where leprosy is a major problem, it is estimated that there are twice as many unreported cases suffering from leprosy.[1] The achievement of control is far distant or unattainable by current DDS-based practices and methods used for the control of the disease. In 1976,[2] a WHO expert committee on leprosy emphasized the need for preventing the development of dapsone resistance and in its report recommended that all active bacteriologically-positive multibacillary patients be treated with at least two anti-leprosy drugs. The increase in emergence of dapsone-resistant leprosy is well known. The rapidly increasing prevalence in Nepal of multibacillary patients with mouse footpad proven secondary and primary dapsone resistance has been reported.[3,4]

The Anandaban Leprosy Hospital has been involved in treatment and control of leprosy for the past 25 years in Nepal. In June 1981, a clinical and bacteriological evaluation of patients (Tables 1 and 2) showed that 514 (49%) of multibacillary patients were still clinically active and smear positive. This justified the immediate introduction of multidrug treatment at the Skin Clinic, Shantha Bhawan Hospital (10 km from Anandaban), with the following objectives: (1) To

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administer multidrug treatment regimens to all newly-diagnosed patients, both paucibacillary and multibacillary leprosy patients; (2) to administer multidrug treatment regimens to all active multibacillary patients irrespective of previous treatment; and (3) to document the regularity of patients when regular home follow up may not be feasible as patients attend the clinic from all over the country. Shantha Bhawan Hospital was the first unit in Nepal to introduce multidrug therapy.

Patients and methods

1 A large proportion of the patients who attend the Skin Clinic at Shantha Bhawan Hospital present voluntarily and a further significant number are 'referred' by patients under treatment.

2 A total of 348 patients have been entered in the study, of these 199 (57%) were newly diagnosed and had no previous treatment. 149 (43%) patients, irrespective of past treatment and who were clinically active and bacteriologically positive for AFB were initiated on combined chemotherapy.

3 Retraining of all medical staff. We were aware of the urgent need to retrain the paramedical workers, nurses and laboratory technicians before patients could be administered the combined drugs at the Skin Clinic in Shantha Bhawan Hospital.

4 Premultidrug therapy education of patients. Paramedical workers and other medical staff including nurses, attending the weekly clinic explained to and discussed with patients what combined treatment for leprosy meant, the importance of regular attendance at the clinic, and of notifying side-effects and reactions. If the medical staff were not satisfied that the patient was ready to be included in the study, then with the patient's consent they were admitted to Anandaban Leprosy Hospital for intensive health education and to impress upon them that a shorter course of treatment would be effective.

5 Medical records. Medical records were designed to facilitate the recording of: identification of the patient (including the name of parent or spouse, address, sex, age and black and white photograph); dates of initial diagnosis, start of treatment; smear record; body charts; dates of supervised treatment given; drug side-effects; and reactions and treatment.

6 After obtaining the patient's consent and necessary information the doctor and the senior paramedical worker performed the clinical examination for leprosy and recorded their findings on a body chart. The patients were given a Ridley–Jopling classification, the following investigations were undertaken: (a) skin smears from 4 sites bacteriological and morphological indices; (b) pretreatment skin biopsy; (c) liver function tests and serum proteins; (d) chest X-ray; (e) sputum for AFB; (f) ESR, WBC, Hb; (g) urine-sugar/albumin; and (h) Mitsuda lepromin; leprosin A and tuberculin skin tests. Skin smears were repeated every 3

months. Skin biopsies and liver function tests were repeated during the treatment period and after withdrawal of the drugs.

7 Drug regimen.

(A) Multibacillary patients:

Dapsone 100 mg od	Unsupervised.
Clofazimine 100 mg od	Unsupervised.
Rifampicin 600 mg	One dose supervised at the clinic.
Two doses in a month	Second dose supervised by the patient.

Duration. Till skin smears for AFB become negative.

(B) Paucibacillary patients:

Dapsone 100 mg od	Unsupervised.
Rifampicin 600 mg	One dose supervised at the clinic.
Two doses in a month	Second dose supervised by the patient.

Duration. Six months.

8 Monthly clinic visits. At monthly visits the patient was identified, and complaints and side-effects, if any, were recorded. During the monsoon season a significant number of patients were given treatment for more than a month, up to 3 months maximum. Rifampicin is not given by proxy.

9 Post-multidrug therapy follow up.

A (i) Paucibacillary patients (Patients whose initial smears were positive): when 3 consecutive smears for AFB are negative and no sign of activity remains, these patients are requested to come for a follow-up examination every 6 months. (ii) Paucibacillary patients (Patients whose initial smears were negative): after 6 months of multidrug treatment these patients are kept under surveillance and requested to come for a follow-up examination every 6 months.

B Multibacillary patients: when 3 consecutive smears for AFB are negative and no active sign remains, patients are kept under surveillance and asked to report for follow-up examination every 6 months.

Results

Table 1 shows that 1057 multibacillary patients were registered in previous years at the Skin Clinic. 543 (51%) were inactive and 514 (49%) were active and bacteriologically positive. Out of 514 active patients only 108 (21%) were taken for immediate administration of combined chemotherapy due to financial

Table 1. Showing the clinical and bacteriological status of multibacillary patients attending the clinic and the year of registration of active patients

	No. of multibacillary patients attending clinic	No. inactive	No. active and bacteriologically positive		
	1057	543 (51%)	514 (49%)		
	Active multibacillary patients year of registration				
	1950–60	1961–70	1971–80	1981	Total
No.	19 (4%)	102 (20%)	192 (37%)	201 (39%)	514 (100%)

constraints and non-availability of drugs. 108 patients are among those who received dapsone monotherapy for varying periods (Table 4).

Table 2 shows that a total of 348 patients form the multidrug treatment study. Of this, 255 (73%) are male and 93 (27%) are female. 90 patients are in the age group, 31–40 years.

From Table 3, it is seen that 199 newly-diagnosed leprosy patients are entered in the study. Newly-diagnosed patients form 57% of the study subjects. 142 (71%) are male and 57 (29%) are female. It is interesting to note that 77 (39%) are BT and 12 (6%) are TT type of patients.

Table 4 shows that 149 leprosy patients entered in the MDT study, received

Table 2. Shows 348 patients in the multidrug therapy study according to age and sex distribution

Age group	Male	Female	Total
0–10	5	4	9 (25%)
11–20	21	18	39 (11%)
21–30	54	24	78 (22%)
31–40	70	20	90 (26%)
41–50	55	14	69 (20%)
51–60	33	11	44 (13%)
60>	17	2	19 (5%)
Total	255 (73%)	93 (27%)	348 (100%)

Ratio of 2·7 male: 1·0 female.

Table 3. Showing the number of newly diagnosed leprosy patients in the multidrug therapy study according to sex and type of leprosy

	TT	BT	BB	BL	LL	PN	IND	Total
Male	5	57	2	38	35	3	2	142
Female	7	20	1	13	15	1	0	57
Total	12 (6%)	77 (39%)	3 (2%)	51 (26%)	50 (25%)	4 (2%)	2 (1%)	199 (100%)

Table 4. Distribution of leprosy patients entered in the multidrug therapy study irrespective of the previous treatment

	BT	BL	LL	Total
Male	28	28	58	114
Female	13	4	18	35
Total	41 (28%)	32 (21%)	76 (51%)	149 (100%)

dapsone monotherapy for varying periods and are still active and bacteriologically positive. 43% of the study subjects are those who had previously received dapsone. 108 patients were from the old registered patients (Table 1) and 41 patients were referred from other clinics for management.

Figure 1 shows the distribution of 348 leprosy patients in Nepal receiving multidrug treatment at the Shantha Bhawan Hospital.

In Table 5 the results of post-MDT (6 months) follow up of borderline tuberculoid patients is shown. Of 77 newly-diagnosed BT patients (Table 3) 56 (73%) patients have completed 6 months of combined treatment. The post-MDT follow up period varied from 3 to 16 months.

The observations of post-MDT follow up of 56 newly-diagnosed borderline tuberculoid patients are:

1 Initial lesions: that the lesions were unchanged up to 3 months on follow up. By 6 months we could observe the positive change in sensation. By 12 months onwards the original lesions were becoming vague and wrinkled in appearance. 2 New lesions: in all 56 BT patients no new lesions appeared. 3 Nerve damage: 2 patients developed ulnar neuritis at 10 months post-MDT follow up. One patient who on initial examination presented with type I reaction continued up to 12 months and was treated with cortico steroids. A total of 3 (5%) BT patients suffered from neuritis during the follow up. 4 Smears for AFB: patients whose

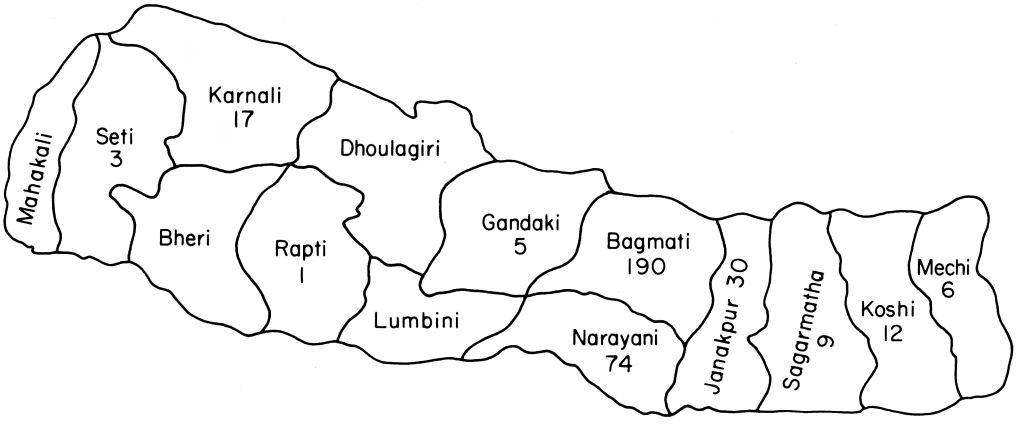

Figure 1. The distribution of 348 leprosy patients in Nepal receiving multidrug treatment at the Skin Clinic, Shanta Bhawan Hospital.

Table 5. Results of clinical observations on post MDT (6 months) follow up in 56 borderline tuberculoid patients

Duration of follow up in months after completing 6 months of MDT	No. of patients	New lesions observed	Neuritis detected	Changes observed in the initial lesions
1–3	8	Nil	Nil	Lesion unchanged
4–6	11	Nil	Nil	Lesion unchanged sensation +
7–10	11	Nil	2 patients ulnar neuritis	Lesion unchanged sensation +
11–13	13	Nil	1 patient type I reaction	Lesions vague
14–16	13	Nil	Nil	Lesions vague wrinkling of skin observed

smears were negative for AFB at cessation of treatment continued to be negative on follow up. 5 Histology of post-MDT follow up: this will be reported in another communication.

Discussion

Because of the disturbing, mouse foot pad proven primary and secondary dapsone-resistant leprosy in Nepal, the Leprosy Mission with the co-operation of

His Majesty's Government of Nepal took the initiative to administer supervised multidrug treatment from a centralized clinic set up when 'defaulter retrieval' is impossible. As mentioned earlier, the patients come from very long 'walking distances' however, this has not deterred them from attending the clinic regularly. Of 348, 13 (4%) patients failed to visit the clinic regularly. In our experience the key to the successful implementation of multidrug therapy is the 'first contact' between the medical team and the patients and the enthusiasm of the multidrug therapy medical team.

A proportion of the multibacillary patients are receiving the 24th dose of intermittent therapy. Among 13 defaulters, 4 (30%) are multibacillary patients (from Table 3). Efforts are being made to trace them with the co-operation of the local panchayat leaders. The bacterial clearance of BL/LL patients may take more than 24 months as the immune mechanisms in these patients are inadequate to eliminate the dead *Mycobacterium leprae*. Therefore, studies are in progress in active multibacillary patients to administer in addition to effective chemotherapy, a mixture of BCG/*M. leprae* in multiple doses.[5]

It is reported that in administering rifampicin to BT patients there is a potential danger of nerve damage.[6] With the exception of 3 BT patients on follow up, no further damage was observed in others.

Due to limited resources, priorities have to be drawn up for administration of combined chemotherapy for leprosy patients in a control programme. As shown in this study, our opinion is that multibacillary relapsing patients should have priority over paucibacillary patients. From an administrative and managerial point of view the latter group is important.[7] The WHO study group recommendations are practical and can be applied in the field for control of leprosy.[8] In our experience, it improves patients' compliance and permits frequent interaction between patient and multidrug therapy medical team.

Acknowledgments

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Lepr Rev (1984) **55,** 273–281

A further investigation of skin-test responsiveness and suppression in leprosy patients and healthy school children in Nepal

ALISON MORTON,* PAMELA NYE,†§
G A W ROOK,† N SAMUEL‡ & J L STANFORD†
** Middlesex Hospital Medical School, London; † School of Pathology, Middlesex Hospital Medical School, London W1P 7LD; ‡ Anandaban Leprosy Hospital, P.O. Box 151, Kathmandu, Nepal*

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Summary This paper confirms and extends our previous studies of skin-test responsiveness and suppression in Nepal. The ability of leprosy patients to make positive responses to group i and group ii (common mycobacterial, and slow grower associated) antigens is markedly impaired in comparison with healthy school children. Of the 2 suppressor mechanisms associated with mixtures of reagents prepared from fast and slow growers which were demonstrated in Bombay, only the phenomenon of local suppression previously seen in Nepal was found. Although originally thought to be associated with group iv (species specific) antigens of fast growers, the phenomenon occurred whichever reagent of 9 fast growing species was mixed with the slow grower reagent. Thus our present view is that the phenomenon demonstrable in both Bombay and Nepal is related to the presence of antigen common to any fast growing species. The observation of this suppressor mechanism in leprosy patients, leprosarium staff and healthy school children shows that it is unlikely to be related to the disease, although it may be related to susceptibility to it.

Our inability to demonstrate in Nepal the distant suppressor mechanism found in Bombay suggests that this may be due to geographical differences, probably in the amount of oral contact with environmental mycobacteria, and perhaps in the species that are present.

Introduction

A system of quadruple skin-testing employing 3 mixtures of new tuberculins[1] and Burulin,[2] prepared from *Mycobacterium ulcerans*, was designed for the investiga-

§ Address for reprints: School of Pathology, Middlesex Hospital Medical School, London.

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tion of responsiveness of leprosy patients to different groups of mycobacterial antigens. Burulin was used since *M. ulcerans* is not known to occur in Nepal and positive responses to it must be to the group i or ii antigens shared with other species. Preliminary studies[3] showed marked impairment of the ability to respond to groups i and ii[4] antigens and uncovered an unexpected suppressor mechanism. This was local suppression of response to the antigens of slowly growing mycobacteria when these were injected as a mixture with the antigens of fast growing species. Further investigation of this with modified reagents[5] in Bombay confirmed this type of suppression and showed it to be associated with the species *M. duvalii*, *M. fortuitum*, *M. flavescens*, *M. gilvum*, *M. neoaurum* and *M. nonchromogenicum*. A second suppressor phenomenon was observed in Bombay, when antigens of the fast growing species *M. chitae*, *M. diernhoferi*, *M. rhodesiae* and *M. vaccae* were injected with the mixed antigens of slowly growing species. In this phenomenon the suppression was not expressed locally, but distantly on the other arm where the mixed antigens of slowly growing species had been injected on their own.

In addition to the above, previous studies[3,5,6] have shown that a system of quadruple skin-testing with individual new tuberculins distinguishes 3 categories of responders dependent upon whether the person tested responds to all 4 reagents (category 1), none of the reagents (category 2), or some but not all of the reagents (category 3). That these differences have significance is shown by categories 1 and 2 including more individuals than would be expected by chance and by the observation that category 2 individuals lack the HLA-DR3 determinant.[7] Previous studies (largely unpublished) have shown that category 1 is reduced in the course of tuberculosis and leprosy and that category 2 is expanded in parts of the leprosy spectrum.[6]

This student elective study was carried out to further investigate responsiveness to antigen groups and to try to relate suppressor mechanisms operative in Nepal to particular mycobacterial species.

Materials and methods

The persons tested were 95 children aged 5–17 years (mean age 12·5 years), of which 53 were male, attending the Himalayan Middle School, Banepa, and 69 leprosy patients with a mean age of 37·2 years (56 were male) at Anandaban Leprosy Hospital. Sixteen of the patients had lepromatous disease, 19 had borderline lepromatous disease, 29 had borderline tuberculoid disease and 5 had tuberculoid disease. All the leprosy patients were receiving chemotherapy, which in the case of multibacillary disease included rifampicin.

The reagents were the same as those used in our previous studies[3,5] except that the mixed reagent prepared from 12 fast growers and 12 slow growers (F/S) was not used at all, and the combinations of the mixed slow grower reagent (SG) with

Duvalin and Nonchromogenicin used in Bombay were replaced with combinations of SG with R877S (a reagent prepared from the smooth variant of *M. vaccae* strain R877), and with Smegmatin (prepared from *M. smegmatis*). These reagents are listed in Table 1.

Each individual was tested with SG and the mixed fast grower reagent (FG) on one arm and with Burulin and the variable 4th reagent on the other arm. So far as possible an equal number of school children received each of the different fourth reagents. Only 6 of the SG and fast grower mixes were tested on the leprosy patients because of the small number available. As usual responses were recorded as diameters of induration 72 h after injection.

Results

The distribution of the categories of responders according to the reagents they received are shown in Table 2 and these data are also incorporated in the figure. Twenty-five of the 95 school children and one of the 69 leprosy patients (a BT case) were category 1 responders reacting to all 4 reagents. Fifteen school children and 32 leprosy patients (2 TT, 8 BT, 13 BL and 9 LL) were of category 2, failing to respond to any of the reagents with which they were tested.

The responses of individual category 3 school children are given in Table 3a

Table 1. Reagents tested on everyone

FG	Contains antigens of 12 different fast growing mycobacteria	
SG	Contains antigens of 12 different slow growing mycobacteria	
B	Burulin prepared from *M. ulcerans*	

Fourth reagents consisting of equal volumes of reagent SG with the following reagents prepared from fast growing species

SG/Chi	SG + Chitin	(*M. chitae*)
SG/Dh	SG + Diernhoferin	(*M. diernhoferi*)
SG/F	SG + Flavescin	(*M. flavescens*)
SG/Gi*	SG + Gilvin	(*M. gilvum*)
SG/Ne*	SG + Neoaurumin	(*M. neoaurum*)
SG/R	SG + Ranin	(*M. fortuitum*)
SG/Rh*	SG + Rhodesin	(*M. rhodesiae*)
SG/Sm*	SG + Smegmatin	(*M. smegmatis*)
SG/R877R	SG + Vaccin R	(*M. vaccae* strain R877 rough)
SG/R877S	SG + Vaccin S	(*M. vaccae* strain R877 smooth)

* Only tested on school children.

Table 2. Distribution of the categories of responders

4th reagent	Responder categories 1	2	3
School children			
SG/Chi	5	1	3(1)*
SG/Dh	1	1	7
SG/F	3	2	4
SG/Gi	1(1)	2	6(2)
SG/Ne	1	3	6(1)
SG/R	2	2	6(2)
SG/Rh	2	1	7(2)
SG/Sm	4	1	5(2)
SG/R877R	5	1	4(1)
SG/R877S	1	1	7
Totals	25	15	55
Leprosy patients			
SG/Chi	0	10	10(5)
SG/Dh	0	0	4(3)
SG/F	0	7	6(4)
SG/R	0	5	6
SG/R877R	1	4	6(3)
SG/R877S	0	6	4(3)
Totals	1	32	36

* Numbers in parentheses are those showing local suppression at the 4th reagent site.

and those of the category 3 leprosy patients in Table 3b. Ten of the 55 category 3 children (18%) and 18 of the 36 category 3 patients (50%) showed suppression of response to the SG/fast grower mixtures, but this did not seem to be associated with any particular fast growing species. A reduction to half or less of the diameter of induration to SG alone is taken as evidence of suppression. One school child and 1 BT leprosy patient (marked ** in the tables) may show suppression of response to SG of the kind seen in Bombay. Fifteen category 3 school children and 5 category 3 patients responded to Burulin; presumably to its group ii[4] antigens.

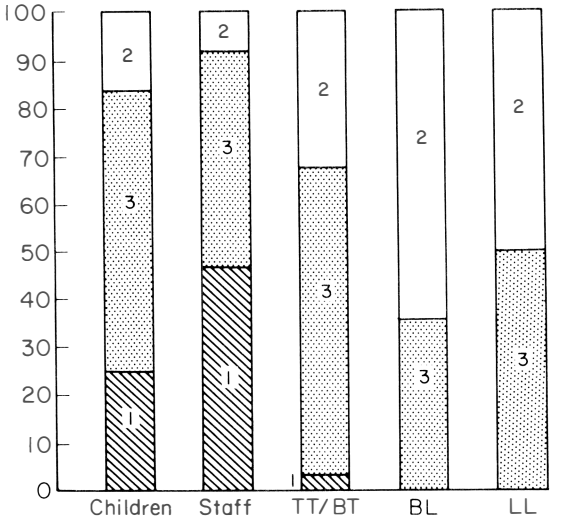

Figure 1. Division of the study groups into the categories of skin-test responsiveness. This figure includes data from the present study and an earlier study in Nepal.[3]

Discussion

This second study in Nepal confirms remarkably well the observation of our preliminary investigation.[3] Only 2 out of the combined total of 133 leprosy patients tested in the 2 studies were category 1 responders possibly reacting to group i (common mycobacterial) antigens. Both were borderline tuberculoid patients. Responses to group ii (slow grower associated) antigens were restricted to 5 out of 33 patients of category 3 in the first study and to 5 out of 36 such patients in this second study. In comparison, 10 out of 12 category 3 staff members and 15 out of 55 category 3 school children produced positive responses to Burulin. Thus the results of this second study strongly support our earlier contention that leprosy patients do not produce positive skin-test responses to group i antigens and have an impaired ability to respond to group ii antigens. Recently published data on HLA-DR typing of leprosy patients[8] and healthy persons in relation to their skin-test response categories[7] suggests that perhaps there is a genetic basis for these observations.

None of the individuals included in the study had recently received other skin-tests, but most of the leprosy patients had been tested with other reagents in the past. However, there is no available evidence that this would have influenced our results. The patients with multibacillary disease were receiving drug regimens including rifampicin, and although this may have had some effect the distribution of responder categories in the present study was little different from that found in

Table 3.
(a) Individual skin-test responses (mm) in category 3 school children

FG	SG	SG/Chi	B	FG	SG	SG/Dh	B
0	9	8	0	8	15	13	0
6	20	8	0	0	25	27	0
0	11	9	0	0	9	10	0
				0	15	15	10
		SG/877R		10	15	11	0
				6	24	23	0
0	13	0	0	0	7	8	6
10	15	10	0				
0	3	3	0			SG/Gi	
0	13	9	5				
				0	5	9	5
		SG/R		0	12	7	0
				0	0	7	5**
0	8	0	5	0	8	0	0
0	16	10	15	0	13	11	6
0	17	15	10	0	17	14	9
0	10	10	0				
0	10	0	0			SG/Rh	
0	7	5	0				
				0	15	0	0
		SG/F		3	5	3	0
				0	5	0	0
0	18	19	0	0	10	16	0
0	4	4	0	0	3	5	0
0	14	11	0	0	10	10	0
9	14	16	0	0	8	11	0
		SG/R877S				SG/Ne	
0	14	19	0	0	17	12	0
0	16	23	8	0	11	0	0
0	23	16	10	0	10	14	6
0	9	7	0	0	5	5	0
9	0	0	0	0	15	14	0
0	20	20	0	0	3	3	0
0	11	20	3				
		SG/Sm					
0	8	0	0				
0	12	12	0				
0	11	17	0				
0	12	12	6				
0	5	0	0				

Table 3—(*cont.*)
(b) Individual skin-test responses (mm) in category 3 leprosy patients

	FG	SG	SG/Chi	B		FG	SG	SG/Chi	B
TT	7	5	0	8	BL	0	10	6	6
	8	8	6	0		0	11	0	0
						0	10	10	0
			SG/F1			0	9	0	0
						0	6	7	0
	0	9	0	0					
								SG/R	
			SG/Chi						
						0	8	5	0
BT	0	6	0	0					
	7	7	10	0				SG/Chi	
			SG/R877R		LL	0	14	0	5
	0	7	7	0				SG/R877R	
	0	10	0	0					
	0	10	0	0		0	8	9	0
	0	10	11	0		0	10	0	0
			SG/R					SG/R	
	0	6	9	0		0	18	13	0
	0	7	9	0					
	0	8	8	0				SG/F	
	0	6	5	5					
						0	7	0	0
			SG/F						
								SG/R877S	
	0	10	5	0					
	0	12	0	0		0	6	0	0
	0	0	7	0**		10	6	0	0
	0	10	7	0					
			SG/R877S						
	0	6	0	0					
	0	0	0	2					
			SG/Dh						
	0	9	9	0					
	0	11	0	0					
	4	9	4	0					
	0	4	0	0					

other populations of leprosy patients receiving dapsone alone (unpublished observations).

The immunosuppression expressed as a relative failure to respond to the combinations of reagents prepared from slow and fast growing mycobacteria when injected together was observed in 10 of the category 3 and 1 of the category 1 school children and in 18 of the 36 category 3 leprosy patients. In the previous Nepal study[3] this phenomenon was observed in 3 of 12 category 3 staff members and 21 of 33 category 3 leprosy patients.

Since the combined study shows that the phenomenon occurs in school children without known close contact with leprosy, staff members of the leprosarium and leprosy patients of all parts of the immunopathological spectrum, it is difficult to see how it can be directly related to development of the disease. Nevertheless, suppression of this kind is twice as common amongst category 3 responders at all parts of the disease spectrum (TTBT: 51%, BL: 69%, LL: 53%) than it is amongst school children (18%) or staff members (25%).

Although our failure to attribute the phenomenon to the inclusion of any particular fast growing species is not absolute proof that further investigations with other species would fail to do so, the evidence now available suggests that the phenomenon is either due to changes in proportions of the different groups of antigens present or to a suppressor activity associated with the group i antigens of fast growers. The involvement of group iii (fast grower associated) antigens would seem to be ruled out since *M. vaccae* has not been shown to contain them.[9]

The most striking difference between the Nepal results and those obtained previously in Bombay[5] is the almost complete absence of the suppressor phenomenon in which the addition of reagents prepared from *M. chitae*, *M. diernhoferi*, *M. rhodesiae* and *M. vaccae* to SG administered on one arm, suppressed the response to SG alone on the other arm. Whereas in Bombay 14 of 21 (67%) contacts of leprosy patients and 30 of 51 (59%) leprosy patients themselves showed this phenomenon, only 2 individuals in the present study, 1 school child and 1 BT patient might show the phenomenon even though 21 school children and 24 leprosy patients of category 3 received reagents expected to exhibit the effect. Similarly in the earlier Nepal study only 2 people, a staff member and a lepromatous patient may have demonstrated the phenomenon. Thus this type of suppression associated apparently with species specific antigens of certain fast growing species appears to be geographically determined. Possible geographical factors are racial genetics and different patterns of immunologically effective contact with freeliving mycobacteria. Of these the latter would seem most likely and recent unpublished work on experimental animals might relate the phenomenon to a large oral intake of mycobacteria with food and water. Our study groups in both Nepal and Bombay were of very mixed ethnic origin, but obviously there was a bigger Mongolian influence on those in Nepal. Although we cannot exclude the possibility that differences in the ethnic mixtures have influenced our results, experience in other places makes this unlikely.

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We should like to thank the children of the Himalayan Middle School, Banepa and the patients and staff of Anandaban Leprosy Hospital for their assistance and participation in this study. Our thanks are also due to LEPRA and the Leprosy Mission, respectively for financial support and hospitality, without which this study could not have been carried out.

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Lepr Rev (1984) **55,** 283–289

Hepatotoxicity of combined therapy with rifampicin and daily prothionamide for leprosy

JI BAOHONG,* CHEN JIAKUN,* WANG CHENMIN† & XIA GUANG†
**Zeng Yi Hospital, Shanghai, and †Hai-an Leprosy Hospital, Jiangsu Province, People's Republic of China*

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Summary Liver injury was observed in 56% of 39 leprosy patients treated with combinations of dapsone, prothionamide (PTH), and *iso*piperazinylrifamycin SV in Hai-an, and in 22% of 50 patients treated with a combination of dapsone, rifampicin (RMP), PTH and clofazimine in Shanghai. Fatalities occurred among both groups of patients after 3 or 4 months of combined chemotherapy. The drug responsible for liver injury was probably PTH, although RMP administered simultaneously may have been a contributing factor. It appears necessary to examine liver function monthly during the first 6 months of treatment by a combined drug regimen that includes PTH.

Introduction

In its fifth report,[1] the WHO Expert Committee on Leprosy emphasized the need to prevent the development of drug resistance, and recommended that all active cases of multibacillary leprosy be treated with at least 2 effective anti-leprosy drugs. Subsequently, because the prevalence of dapsone resistance, both primary and secondary, had been steadily increasing in many leprosy-endemic countries, the WHO Study Group on Chemotherapy of Leprosy for Control Programmes further recommended,[2] that at least 2 additional drugs be combined with dapsone for treatment of multibacillary leprosy, and that one of these drugs be rifampicin. Following these recommendations, we embarked on a clinical trial of combined chemotherapy in Hai-an County, Jiangsu Province, and in Shanghai. A high incidence of liver injury was observed after 1–3 months of treatment, accompanied by several deaths.

Hai-an

Thirty-nine patients were treated, 29 males and 10 females, whose ages ranged

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from 26 to 88 years (median age 47 years), and who included 18 patients with LL leprosy, 18 with BL, and 3 with BB leprosy. The duration of disease ranged from 1 to 35 years (median duration 16 years); only 2 were 'new' patients, the remaining 37 having been treated with dapsone as monotherapy for from 3 to 227 months (median duration 57 months). The general condition of the patients was fair; body weights ranged from 45 to 70 kg (median weight 62 kg); liver and renal function were normal before the initiation of combined therapy.

The patients were divided into 3 groups. Those of Group A, 22 in number, were treated with dapsone 100 mg and prothionamide (PTH) 300 mg, each administered daily, together with R-76-1 (*iso*piperazinylrifamycin SV[3]) 300 mg, on each of the first 2 days of treatment and once monthly thereafter. The 13 patients of Group B were treated with dapsone 100 mg and PTH 300 mg daily, together with R-76-1 300 mg on each of the first 14 days and 600 mg once monthly thereafter. The 4 patients of Group C were treated with PTH, either 300 mg (3 patients) or 500 mg (1 patient) daily as monotherapy for the first 90 days of treatment, in order to measure the initial rate of killing of *Mycobacterium leprae* by PTH; thereafter, their treatment was supplemented with dapsone 100 mg daily together with R-76-1 300 mg daily on 2 consecutive days every month. Administration of all of the drugs was supervised. The duration of combined therapy varied somewhat among individual patients; the median duration was 97 days among Group A patients, 99 days among the patients of Group B, and 105 days among those of Group C. The median total dosages of dapsone, PTH and R-76-1 per patient were, respectively, 9700 mg, 28,800 mg, and 1500 mg for Group A patients, 9900 mg, 29,100 mg, and 5400 mg for Group B patients, and for the patients of Group C, dapsone 1500 mg, PTH 31,200 mg (3 patients) and 52,000 mg (1 patient), and R-76-1 600 mg.

Gastrointestinal side-effects, among them anorexia, nausea and vomiting, occurred in 17 (44%) patients. In fact, almost all patients complained of loss of appetite in some degree. The nausea and vomiting usually occurred about 30 minutes after ingesting the drugs, and endured 1–5 h. Because these side-effects also occurred in 2 of the 4 patients of Group C, they appear to have been caused mainly by PTH. The gastrointestinal side-effects subsided during continued therapy in only 1 patient, and became progressively worse in 11 patients, all of whom were found to have evidence of liver damage. Thus, it appears that the gradual worsening of the gastrointestinal side-effects resulted from liver damage as well as from local irritation of the gastrointestinal tract.

Fifteen (39%) patients became jaundiced between 24 and 120 days (median 96 days) after initiation of combined therapy. In 5 patients, jaundice appeared only 5–20 days after therapy had been suspended.

Because urobilirubin or urobilinogen was found in the urine of 28 (72%) patients about 90 days after initiation of therapy, liver and renal function were examined in all patients. Renal function was entirely normal. However, serum glutamic-pyruvic transaminase (SGPT) levels were found to be elevated in 19

patients: 7 in the range 41–100 units; 6 in the range 101–200 units; 3 in the range 201–300 units, and 3 in the range 301–384 units. Fourteen patients—all except for 5 of the 7 whose elevation of the SGPT was in the lowest range—developed jaundice, either before SGPT levels were measured or subsequently. In 3 additional patients, elevations of icterus index or serum bilirubin or a positive flocculation reaction were detected, accompanied in all by urobilirubin or urobilinogen in the urine. Thus, a total of 22 (56%) patients showed laboratory evidence of liver damage—12 from Group A, 7 from Group B and 3 from Group C. The frequency of liver damage among the 3 treatment groups was, for Group A 55%, for Group B 54%, and for Group C 75%; the differences among the treatment groups are not significant ($P > 0{\cdot}05$). Such a high frequency of liver damage was unexpected.

Combined therapy was immediately suspended in all cases. In all but 2 patients, the liver function tests returned to normal within 60 days. One patient, No. 977, died during convalescence from liver damage, the cause of death apparently acute haemorrhagic necrotic enteritis. A second patient, No. 166, showed progressive jaundice despite suspension of therapy, became comatose and died. A brief history of this patient's illness is given.

This 63-year-old male with LL leprosy began combined therapy (Group A) on 23 March 1982. On 4 May 1982, 42 days after beginning treatment, he complained of anorexia and gastric discomfort. On 27 June 1982, jaundice was recognized, and the patient complained of profound anorexia accompanied by nausea and vomiting. Laboratory studies at this time revealed: icterus index 120, serum bilirubin 13·6 mg%, SGPT 306 units, HBsAg negative. His jaundice progressed, and his liver rapidly became smaller, as shown by physical and ultrasound examinations. On 1 July 1982, petaechial haemorrhages and haematemesis occurred, and the patient became comatose. Two days later, 102 days after initiation of combined therapy and 6 days after the onset of jaundice, the patient died in hepatic insufficiency. An autopsy was not performed.

Shanghai

Fifty patients, 31 males and 19 females ranging in age from 22 to 69 years (median age 44 years), were treated in Shanghai. Forty-one were classified as LL, 8 as BL, and 1 as BB. Duration of disease ranged from 5 to 48 years (median duration 26 years). All had been treated with dapsone as monotherapy for periods ranging from 48 to 324 months (median duration 288 months). Their general condition was fair, and body weights ranged from 52 to 76 kg (median weight 59 kg); liver function tests were normal before beginning combined chemotherapy.

The single combined regimen consisted of dapsone 100 mg and PTH 300 mg, each self-administered daily, together with rifampicin (RMP) 900 mg, PTH 500 mg, and clofazimine (CLO) 300 mg, each administered monthly under super-

vision. The duration of combined therapy was 30 days for 24 patients, and 31–50 days for the remaining 26 patients. The median total dosages of RMP and CLO per patient were, respectively, 900 and 300 mg for the first group, and 1800 mg and 600 mg for the second.

Gastrointestinal side-effects were encountered in 32 (64%) of the patients—primarily anorexia, nausea and vomiting. These side-effects became more striking immediately after the monthly supplemental doses had been administered. One patient became jaundiced about 30 days after initiation of combined therapy, whereupon liver function was examined in all patients between 30 and 50 days after beginning therapy. Liver damage was detected in 11 (22%) patients, 8 of whom showed elevations of the SGPT—5 in the range 41–100 units, and 3 in the range 101–200 units. Three additional patients demonstrated elevation of the icterus index and serum bilirubin. Combined therapy was suspended in all patients, and liver function tests were repeated. Among the 11 patients with evidence of liver damage, 9 had recovered by 30 days after the suspension of therapy, but the remaining 2 patients revealed elevations of the SGPT—to 80 and 168 units—60 days after therapy had been suspended.

The frequency and severity of liver damage were less among the Shanghai than among the Hai-an patients, perhaps because of the shorter duration of combined therapy administered to the former group. However, acute hepatic insufficiency occurred in another patient after treatment for 4 months with PTH 300 mg daily and RMP 900 mg monthly. A brief history of this patient's illness is the following.

This 62-year-old male, with leprosy classified as LL and with dapsone resistance demonstrated by mouse foot-pad inoculation, began combined chemotherapy on 19 March 1982. On 23 July 1982, 126 days later, he complained of anorexia and nausea and was noted to be slightly jaundiced. Therapy was immediately suspended. Laboratory study revealed icterus index 72, serum bilirubin 7·0 mg%, and SGPT >400 units. In spite of treatment, jaundice progressed, and on 1 August 1982, the patient became comatose; at this time, his blood ammonia was measured at 200 μg%. Three days later, 138 days after beginning combined therapy and 12 days after the onset of jaundice, the patient died in hepatic insufficiency. At autopsy, acute hepatic necrosis was discovered.

Discussion

The prevalence of secondary dapsone resistance among patients with multibacillary leprosy in the Shanghai area was recently shown to be greater than 8/100 patients at risk,[4] and primary resistance to dapsone has recently been detected both in Shanghai and in the Hai-an area (Ji Baohong *et al.*, unpublished data). Thus, the need to adopt combined therapy for leprosy is urgent. However, there has been some uncertainty with respect to the choice of appropriate combined

drug regimens, based on considerations of safety, efficiency and operational feasibility, as evidenced by the many multidrug regimens that have been recommended since 1976. The regimens selected for the present study comply with the basic requirement laid down by the WHO Study Group,[2] *i.e.* they include at least 2 effective drugs in addition to dapsone, one of which is RMP. Because many Chinese patients do not accept CLO, PTH was also employed in these regimens.

The liver damage observed in the course of the present study had the following characteristics: (1) it appeared almost simultaneously among the patients under treatment, and did not occur among patients treated with dapsone as monotherapy during the same period; (2) most patients recovered within 30–60 days after the therapy was suspended; and (3) of 15 patients from the Hai-an area and 9 from Shanghai examined for evidence of HBsAg and HBcAg, only one of the first group was positive for HBsAg. Thus, viral hepatitis, at least that caused by the hepatitis B virus, may be excluded as an important cause of the liver damage encountered in the present study. On the other hand, toxic hepatitis, caused by the combined therapy employed in this study, appears to be the only explanation for the liver damage observed.

There is very little information in the literature with respect to the hepatotoxicity of combined regimens containing both PTH and RMP. In the treatment of tuberculosis, PTH had been largely abandoned at the time that RMP became available. However, one study has been reported. It has been reported[5] that among 23 patients treated with daily RMP together with PTH in a daily dose of at least 500 mg, 4 developed jaundice, and 3 manifested abnormalities of liver function without clinically evident jaundice.

Among leprosy patients treated at the Institut Marchoux, Bamako, Mali, with a regimen consisting of dapsone 100 mg, RMP 600 mg and PTH 500 mg, each administered daily,[6] 4 of 12 patients became jaundiced and 1 of the 4 died.[7] One study[8] has found 7 cases of hepatitis, 5 of them clinically jaundiced, among 54 patients treated with daily RMP together with 500 mg daily of either PTH or ethionamide. After the dosage of the thioamide had been reduced to 5 mg/kg body weight, no additional cases of jaundice occurred, although elevated serum transaminase levels were noted in a few patients.

The dosages of RMP and R-76-1 were rather low in the present study, as these drugs were usually administered by a monthly schedule. No toxic effects of monthly RMP have been reported.[9] A number of patients with multibacillary leprosy have been treated with R-76-1 as monotherapy in a daily dosage of 150 mg for 6–18 months, or in a monthly dosage of 1200 mg, with negligible hepatotoxicity.[3] Because there has been no controlled clinical trial with combined regimens of prothionamide and either RMP or R-76-1, we cannot confirm or deny the possibility that R-76-1 may predispose to more serious hepatotoxicity than does RMP when combined with daily prothionamide. However, although the total dosage of R-76-1 was highest in Hai-an Group B patients, there was no

difference of the frequency of liver injury among the 3 groups of Hai-an patients. Therefore, the liver injury reported in this present study cannot be attributed to the hepatotoxicity of RMP or R-76-1.

Thus, it appears that, among the drugs administered in the present study, the drug responsible for the liver injury is PTH. However, it is uncertain whether the hepatotoxicity was simply a toxic effect of PTH, or whether it represented a summation of the effect of PTH combined with that of RMP or R-76-1, even though the latter 2 drugs were administered only in low dosage.

We cannot exclude the possibility that, despite normal liver function tests at the onset of treatment, some pre-existing liver damage was present among the patients of this study. All of the patients were active (i.e. skin-smear-positive) multibacillary cases. From the literature, leprous granulomata as well as acid-fast bacilli have frequently been demonstrated in the livers of leprosy patients.[11,12] The leprous granulomata were found in 21% of patients with tuberculoid leprosy and in 62% of patients with lepromatous leprosy; further, granulomata were also discovered in the livers of 22 of 101 leprosy patients who had no acid-fast bacilli in skin smears.[11] The liver lesions in some patients were characterized by early cirrhosis.[12] In addition, a rise of transaminase activity, although not as serious as that in our patients, has also been reported in patients under dapsone treatment.[13] Therefore, pre-existing liver damage may have been an important predisposing factor to hepatotoxicity with prothionamide. Liver damage is rare among patients with tuberculosis, except in cases of miliary tuberculosis.[14] This could be one of the explanations of why the hepatotoxicity of prothionamide appears to be less serious in tuberculosis patients than in leprosy patients.

To be safe, we have temporarily suspended treatment by all of the regimens employed in this study. On the other hand, PTH exerts powerful bactericidal activity against *M. leprae* (10; Ji Baohong *et al.*, unpublished data). Considering that a significant proportion of Chinese patients will not accept CLO, it does not appear justified to abandon PTH as a component of combined drug regimens. In fact, PTH may still be used with safety, provided the patients are carefully supervised and followed up. We are planning additional controlled trials, to evaluate further the hepatotoxicity of PTH alone and in combination with RMP. In order to detect toxicity as early as possible, tests of liver function will be performed monthly during the first 6 months of the combined treatment.

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Different mode of circulating immune complexes and anti-ssDNA antibodies in sera of lepromatous leprosy and systemic lupus erythematosus

FUKUMI FURUKAWA,*‡ HARUYOSHI YOSHIDA,* KENICHI SEKITA,* MOTOAKI OZAKI,† SADAO IMAMURA† & YOSHIHIRO HAMASHIMA*

From the Department of Pathology and Dermatology†, Faculty of Medicine, Kyoto University, Sakyo, Kyoto 606, Japan*

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Summary Circulating immune complexes (CIC) and anti-ssDNA antibody were detected in sera of the patients with lepromatous leprosy (LL) and systemic lupus erythematosus (SLE). There was a markedly quantitative difference in the level of CIC and anti-ssDNA antibody between LL and SLE. Quantitative correlation study showed a lack of association between these 2 serological tests in LL but a significant association in SLE. In addition, ssDNA was not demonstrable in CIC of LL.

These findings suggest that the mode of the appearance of these serological abnormalities in LL was completely different from that in autoimmune disease like SLE and might be the result of polyclonal B cell activation, whose causative factors seemed to be different from those of SLE.

Introduction

It is well known that circulating immune complexes (CIC) and some auto-antibodies are demonstrated in sera of patients with lepromatous leprosy (LL).[1,2] These serological abnormalities are also frequently found in systemic lupus erythematosus (SLE) and have diagnostic value. We have reported the presence of CIC and anti single-stranded (ss)DNA antibody in sera of patients with LL.[3,4] Of special interest is whether or not LL belongs to the spectrum of autoimmune disease and another interesting point is what kinds of antigen are involved in CIC of LL and SLE.

‡ Correspondence: Fukumi Furukawa, Department of Pathology, Faculty of Medicine, Kyoto University, Sakyo, Kyoto 606, Japan.

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In this report we designed the comparative analysis of mode of the appearance of CIC and anti-ssDNA antibody in patients with LL and discussed the difference of serological abnormalities in LL compared with SLE.

Material and method

Serum samples obtained from 53 patients with LL, which was diagnosed according to the criteria of Ridley–Jopling classification,[5] were studied. Their age ranged from 20 to 76 years. Clinical stage was divided into 2 groups, that is, active stage and inactive stage according to the criteria of Japanese leprosy committee.[6] The patient number of each group was 21 and 32 respectively. All patients were under the treatment of anti-leprosy agents but without corticosteroids. Patients with systemic infectious disease, cancer, liver disease and autoimmune disease were excluded from the protocol.

Serum sample was collected from 61 patients with SLE who visited the Departments of Internal Medicine and Dermatology, Kyoto University Hospital. These patients satisfied the diagnostic criteria of the American Rheumatism Association for SLE.[7] Their age ranged from 8 to 45 years. Activity of SLE was judged by the presence of at least 2 of the following items: (1) facial erythema; (2) arthralgia; (3) Raynaud's phenomenon; (4) unexplained fever; (5) central nerve abnormalities; (6) serositis; (7) onset of edema; (8) hypertension; (9) LE cells; (10) leukopenia; and (11) proteinuria. Twenty-five serum samples as control were obtained from healthy individuals whose age ranged from 25 to 79 years. All sera were stored at $-80°C$ until use.

CIC were detected by C1q solid phase assay which was performed as a modification of the method of Hay, Nineham & Roitt.[8] Briefly, removal microtiter wells (Cooke, USA) were coated with 100 μl of C1q solution at a concentration of 10 μg/ml at 4°C for 20 h, and further incubated with 1% BSA-PBS. Twenty μl of test sample was incubated with 80 μl 0·2M-EDTA-2Na (pH 7·4) at 37°C for 30 min. To these mixtures, 500 μl of 0·05%-Tween 20-PBS was added; 100 μl of this mixture was transferred to the C1q coated well in duplicate, and incubated at 37°C for 1 h and 4°C for 30 min. After washing 3 times, each well was incubated with 100 μl of ^{125}I-protein A at 37°C for 2 h. After washing 3 times, radioactivity was counted. According to our previous report,[3] levels and cut-off point were determined and statistical analysis was made.

When the effects of ssDNA on CIC were determined, 100 μl of ssDNA solution was added before incubation with ^{125}I-protein A. The ssDNA was prepared by heating calf thymus DNA (Worthington Diagnostics, USA) at 100°C for 10 min, then immediately cooling in an ice bath. The ssDNA was diluted with 1 mM EDTA-PBS (pH 7·4) at varying concentrations (10

μg/ml–1mg/ml). The results of inhibition were expressed as per cent inhibition of C1q binding activity, calculated as follows:

$$\% \text{ inhibition} = \left(1 - \frac{\text{cpm in the presence of ssDNA} - \text{background}}{\text{cpm in the absence of ssDNA} - \text{background}}\right) \times 100$$

The background represents the cpm of the wells without C1q solution.

Modified Farr assay[9] was employed for the detection of anti-ssDNA antibody in sera, which was described recently.[4] Briefly, the reaction mixture (200 μl) contained 5 μl of heat-inactivated test serum and 5 ng of heat-denatured ^{125}I-ssDNA (calf thymus) in borate buffer. The mixture was incubated at 37°C for 1 h and then at 4°C for 16 h. Precipitation was made by saturated ammonium sulfate. The amount of anti-ssDNA titers higher than 2 standard deviation values from the mean level of healthy subjects were regarded as positive (> 15%).

Statistically, student's *t*-test, Chi-square test and Spearman rank correlation analysis were used in this study. A *P* value of more than 0·05 was considered not significant.

Results

Table 1 shows the incidence and mean level of CIC in patients with LL and SLE. CIC were demonstrated in 14 patients (66·7%) with active LL, in 12 patients (38·7%) with inactive LL, in 26 patients (83·9%) with active SLE and in 10 patients (33·3%) with inactive SLE. The mean level of CIC is 11·2 μg/ml, 6·4 μg/ml, 62·1 μg/ml and 14·6 μg/ml respectively. Mean level of active SLE and LL is significantly high, compared with the control values described in Table 1. There is a significant difference between active LL and inactive LL ($0{\cdot}02 < P < 0{\cdot}05$). Active SLE has significantly high level of CIC, compared with the level in active LL ($P < 0{\cdot}001$). However, statistical analysis shows no difference between inactive LL and inactive SLE.

Table 1. CIC in patients with LL and SLE

Patients	Stage	No. case	No. positive (%)	Mean level (SD)* of CIC (μg/ml)	*P* value†
LL	Active	21	14 (66·7)	11·2 (8·3)	$P < 0{\cdot}001$
	Inactive	31	12 (38·7)	6·4 (6·1)	not significant
SLE	Active	31	26 (83·9)	62·1 (60·8)	$P < 0{\cdot}001$
	Inactive	30	10 (33·3)	14·6 (26·9)	not significant
Control		25	1 (4·0)	4·6 (2·6)	

* SD means standard deviation.

† Results of student's *t*-test, compared with the CIC level of control.

Table 2 shows the incidence and mean level of anti-ssDNA antibody in patients with LL and SLE. Anti-ssDNA antibody was demonstrated in 4 patients (19·0%) with active LL, in 7 patients (20·6%) with inactive LL, in 30 patients (100%) with active SLE and in 22 patients (73·3%) with inactive SLE. The mean binding activity is 11·8%, 12·2%, 69·2% and 29·5% respectively. As shown in Table 2, there is no significant difference between active LL and control but significantly high activity of binding is demonstrated in inactive LL, active SLE and inactive SLE. In both active and inactive stage, SLE has significantly high activity of binding compared with LL ($P < 0{\cdot}001$).

We examined whether the amount of CIC was correlated with the levels of anti-ssDNA antibodies in sera with positive CIC. As shown in Figure 1, there is

Table 2. Anti-ssDNA antibody in LL and SLE

Patients	Stage	No. case	No. positive (%)	Mean level (SD)* of ssDNA Ab (%)	*P* value†
LL	Active	21	4 (19·0)	11·8 (7·6)	not significant
	Inactive	32	7 (20·6)	12·2 (6·4)	$0{\cdot}02 < P < 0{\cdot}05$
SLE	Active	30	30 (100·0)	69·2 (12·6)	$P < 0{\cdot}001$
	Inactive	30	22 (73·3)	29·5 (19·9)	$P < 0{\cdot}001$
Control		25	4 (16·0)	9·1 (2·9)	

* SD means standard deviation.
† Results of student's *t*-test, compared with the normal control.

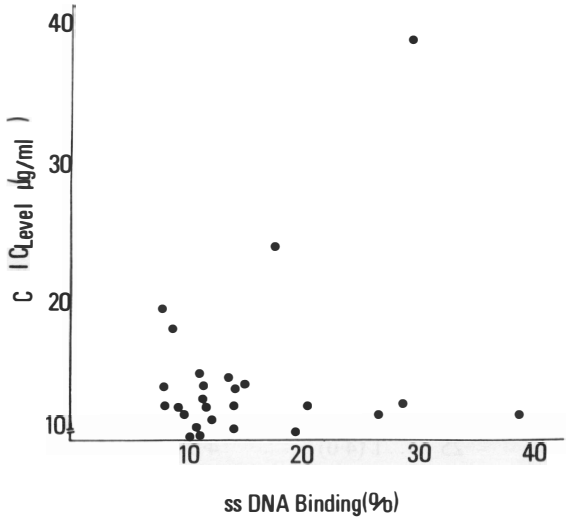

Figure 1. A lack of quantitative association between CIC and anti-ssDNA antibody in patients with LL ($r_s = -0{\cdot}023$, *P* not significant).

no significant association between these two serological abnormalities in LL by Spearman rank correlation analysis ($r_s = -0{\cdot}023$, P: not significant). However, the significant association was found between them in SLE ($r_s = 0{\cdot}56$, $P < 0{\cdot}01$) (Fig. 2).

For the next step, we examined the effects of ssDNA on the levels of C1q binding activity. Preliminary, the pooled sera were obtained from LL, SLE and

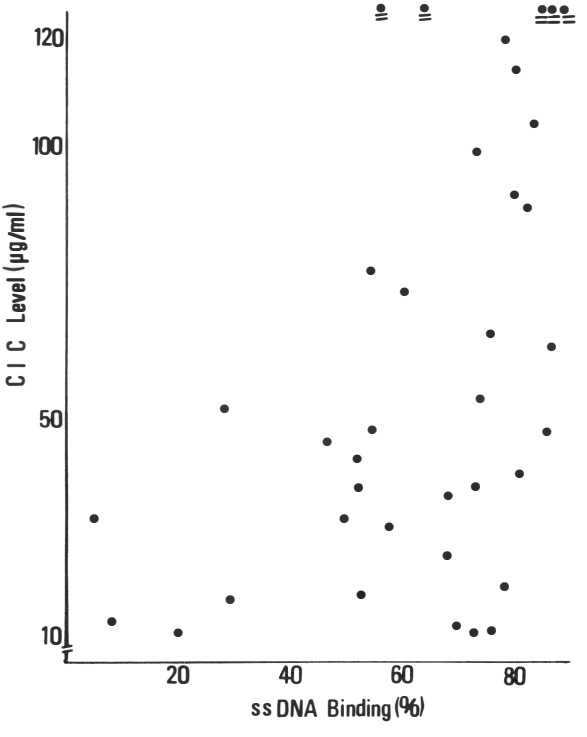

Figure 2. Significant association between CIC and anti-ssDNA antibody in patients with SLE ($r_s = 0{\cdot}56$, $P < 0{\cdot}01$).

normal healthy (NHS) control and the inhibition tests were made. Fig. 3 showed that the reduction of C1q binding activity was demonstrated by addition of ssDNA solution. In healthy control, per cent inhibition at any concentration of ssDNA solution showed similar ratio but, in SLE and LL, it increased with the concentration and reached the maximum at the concentration of 100 μg/ml. Therefore, 100 μg/ml was the optimal dose for this inhibition assay. We selected 8 serum samples from LL who showed positive level of CIC and also selected randomly 10 and 20 serum samples from SLE and healthy controls, respectively. The results of inhibition tests were shown in Fig. 4. Inhibition ratio was similarly low in LL and healthy controls ($0{\cdot}2 < P < 0{\cdot}3$; not significant) but inhibition ratio of SLE was significantly high compared with the results of LL ($P < 0{\cdot}001$).

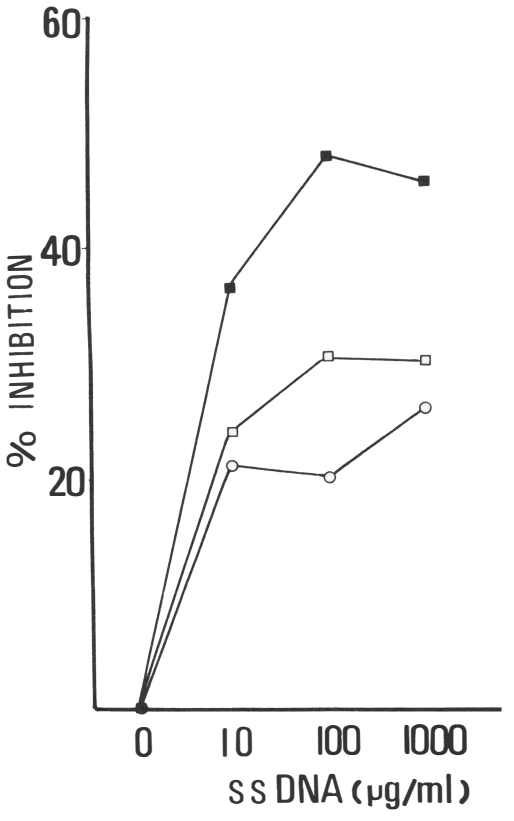

Figure 3. Dissociation of CIC in pooled sera by ssDNA solution. (■) systemic lupus erythematosus, (□) lepromatous leprosy, (○) normal human serum (NHS).

Discussion

Patients with LL show abnormalities of humoral immunity and cellular immunity.[10] The disturbance of humoral immunity in LL is characterized by the appearance of CIC,[11] autoantibodies[12] and variations in the levels of serum immunoglobulins.[13] Recently we investigated the incidence of CIC and anti-DNA antibodies in sera of patients with LL and demonstrated the presence of CIC and anti-ssDNA antibody and relative absence of anti double-stranded DNA antibody.[4] Similar immunological disorders are also found in sera of patients with SLE.

Of special interest is whether or not the serological mode of the appearance of CIC and autoantibodies in LL has the similarity to those found in SLE. In 1981 Nuti *et al.*[1] examined CIC and autoantibodies in sera of patients with LL and found the significant correlations between CIC level and the appearance of autoantibodies. However, Malaviya *et al.*[14] studied the immunoglobulin levels,

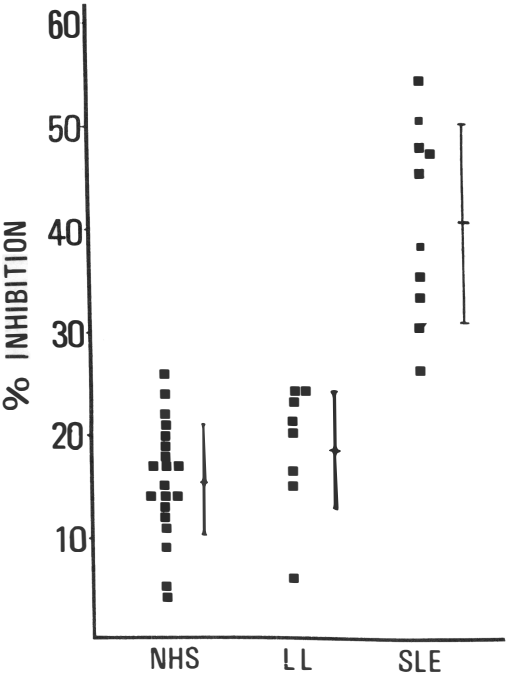

Figure 4. Reduction of C1q binding activity by ssDNA solution. NHS; normal human serum (control), LL; lepromatous leprosy, SLE; systemic lupus erythematosus. Bar represents the mean level ± one standard deviation.

autoantibodies, hepatitis-associated antigens and C-reactive protein in sera of patients with LL and concluded that the presence of autoantibodies in leprosy was only a paraphenomenon, suggesting that leprosy is not an autoimmune disease.

CIC in LL and SLE are well known to correlate significantly with clinical features.[15,16] Although anti-ssDNA antibody in SLE is one of clinical indicators, this antibody in LL does not reflect the clinical features because the incidence and the mean level of anti-ssDNA antibody were higher in inactive stage than active stage. However, the statistical analysis revealed that the appearance of anti-ssDNA antibody in LL had the significance and, therefore, we evaluated the anti-ssDNA antibody as a parameter of polyclonal B cell activation. Taking account of these findings, we selected 2 serological tests, CIC and anti-ssDNA antibody, in order to verify the values and the mode of serological abnormalities in LL.

The incidence of CIC in each stage of LL was almost similar to that of SLE but CIC level in active SLE was significantly high compared with active LL. The incidence of anti-ssDNA antibody in LL was lower than in SLE and there was a significant difference in the amount of this antibody between LL and SLE in each

stage. A markedly quantitative difference was present in the appearance of CIC and anti-ssDNA antibody between LL and SLE. Quantitative correlation studies revealed that there was a significant association between CIC and anti-ssDNA antibodies in SLE but not in LL. This result in SLE was compatible with other reports.[15,16] Based on these results, we could clearly discriminate the mode of CIC and anti-ssDNA antibody in LL from that in SLE.

A few important questions raised by these data are as follows: (1) the identification of antigen involved in CIC of LL and SLE; and (2) the mechanisms of abnormal production of CIC and anti-ss DNA antibody.

Firstly, inhibition study suggested that CIC in LL did not contain the ssDNA as antigen but CIC in SLE had in part ssDNA or related substances. Similar inhibition studies were tried using phenolic glycolipid-I but in vain because this was not soluble in the medium or buffer solution used in this study. However, we have already showed the significant association between CIC and bacteriological index, which suggested the possibility that CIC contained *M. leprae* related substances as antigen.[3]

Secondly, the mechanism of abnormal production of CIC and anti-ssDNA antibody could result from polyclonal B cell activation. The causative factors responsible for polyclonal B cell activation are still unknown.

Regardless of the cause of polyclonal B cell activation, special attention should be given to the fact that the mode of serological abnormalities or polyclonal B cell activation in LL was different from that in SLE. In a few recent publications from our laboratory, it was reported that natural thymocytotoxic autoantibodies (NTA) and anti-DNA antibodies in New Zealand mice did not correlate with anti-dinitrophenyl (DNP) IgM antibodies, which was one of the parameters of polyclonal B cell activation.[17,18] The same results were demonstrated in sera of SLE.[19] However, there were significant associations among NTA, anti-DNA antibodies and CIC in SLE. In contrast, such significant relationships were not found in LL. Polyclonal B cell activation is not considered to appear in the same pattern. It is important to clarify the polyclonal B cell activator, disease by disease. The animal studies using the administration of phenolic glycolipid-I are now under investigation.

Acknowledgment

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Lepr Rev (1984) **55,** 301–308

Normal numbers of T_6 positive epidermal Langerhans cells across the leprosy spectrum

R B NARAYANAN,*§ L K BHUTANI,†
A K SHARMA‡ & INDIRA NATH*
**Departments of Pathology and †Dermatology, All-India Institute of Medical Sciences; ‡Department of Dermatology, Safdarjung Hospital, New Delhi-110029, India*

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Summary Langerhans cells (LC) in the skin lesions of 25 untreated leprosy patients were defined by indirect immunofluorescence using monoclonal antibodies against phenotypic markers T_6 and Ia like antigens. Normal numbers of epidermal LC were seen in leprosy lesions. No differences were observed in the intensity of fluorescence or in the numbers of T_6+Ia+LC across the leprosy spectrum. However, the dermal granulomas of tuberculoid leprosy (TT/BT) showed a high proportion of T_6+cells in the mononuclear infiltrate surrounding the epithelioid cells. Smaller numbers of these cells were seen in borderline leprosy (BB, BL) with a virtual absence in polar lepromatous leprosy (LL). Ia like antigens were associated with the macrophages in BL and LL granulomas and with the lymphocytes in tuberculoid lesions. B cells were conspicuously absent in all leprosy lesions.

Introduction

Leprosy is a polymorphic granulomatous disease with a spectrum of lesions ranging from the paucibacillary epithelioid cell granulomas surrounded by abundant lymphocytes in the tuberculoid forms of leprosy to the lymphopenic lesions with bacilli laden foamy macrophages in lepromatous leprosy (LL).[1] These lesions are thought to reflect the host resistance to *Mycobacterium leprae*. The mechanisms leading to good cellular immunity in tuberculoid leprosy and the lowered T cell functions in the lepromatous form of the disease are still under investigation.[2] The immunological phenomena in leprosy have been extensively

Correspondence: Dr Indira Nath, Department of Pathology, All India Institute of Medical Sciences, New Delhi-110029, India.

§ R B Narayanan's present address: Central JALMA Institute for Leprosy, Taj Gunj, Agra, India.

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investigated in the past by means of *in vitro* systems using peripheral blood lymphocytes and monocytes. The *in situ* analysis of cells in leprosy lesions has been recently possible with the availability of monoclonal antibodies to phenotypic markers present on subsets of lymphocytes and monocytes.[3–5]

Accessory cells other than macrophages have been shown to play an important part in the presentation of antigen to T cells.[6,7] Langerhans cells (LC) present in the epidermis of skin have been shown to participate in experimental allergic contact dermatitis and delayed hypersensitivity reactions.[6–8] These cells bear immunological markers, in common with other macrophages, namely Fc (IgG) receptor, C_3b receptor, Ia antigens and possess small amounts of acid phosphatase and abundant ATPase enzymes.[9] They can be distinguished from morphologically similar dendritic macrophages by the presence of T_6 marker[10] which is also seen on early and activated T cells.[10,11] Scant information is available on the role of LC in the presentation of antigen in a predominantly dermal disease such as leprosy. Electron microscopic[12] and histochemical studies[13,14] indicated morphological and numerical alterations in LL. With a view to understanding the *in situ* cellular interactions in leprosy, we had earlier used indirect immunofluorescence with monoclonal antibodies directed against subsets of T cells and monocytes. Using antibodies to T_6 and Ia like antigens, we report here the results obtained on the status of Langerhans and other T_6 positive cells in the skin lesions across the leprosy spectrum.

Materials and methods

PATIENTS AND TISSUE MATERIALS

Three to five mm skin biopsies were removed from 25 untreated leprosy patients attending the Dermatology Departments of the All India Institute of Medical Sciences and Safdarjang Hospital, New Delhi. The patients were graded on the clinicopathological criteria of Ridley & Jopling.[1] Each biopsy was bisected on removal, one half was fixed in 10% buffered formalin and processed by conventional paraffin embedded blocks. The other half of the skin was quick frozen, and stored at $-20°C$. Cryostat sections were cut within 24 hours and serial sections were stained with hematoxylin and eosin (H&E), Ziehl Neelsen and monoclonal antibodies. Only those results are reported where H&E stains of formalin fixed and cryostat sections had shown typical histopathological features.[15]

IMMUNOFLUORESCENCE

Five micron thick cryostat sections (IEC, USA) were cut at $-20°C$, air dried for 5 minutes, fixed in 1:1 acetone-chloroform mixture and stained by indirect

immunofluorescence technique. Four to five serial sections were used for the antibody tested. After dipping in 50 mM phosphate buffered saline (PBS), pH 7·4, the sections were covered with 1 : 10 dilution of OKT_6 or 1 : 20 dilution of OKIa antibodies (Ortho Pharmaceutical Co., USA), and left at room temperature for 30 minutes. Control sections were covered with PBS only. Subsequently, the sections were washed in PBS for 30 minutes and layered with 1 : 60 dilution of sheep FITC conjugated antimouse $F(ab)_2$ (New England Nuclear, Boston, USA) mixed with 1 : 100 dilution of pontachrome violet for 30 minutes at room temperature. After washing as above, the sections were mounted in 90% PBS-glycerol containing paraphenylene diamine and viewed under a Carl Zeiss microscope with epillumination and HBO 50 mercury lamp. Sections of normal skin removed during surgery were used as controls.

The degrees of infiltration by lymphocytes, epithelioid cells and foamy macrophages were graded arbitrarily on serial sections stained with H&E according to the criteria of Ridley.[15] Quantitation of positive cells in: (a) typical well-formed granulomas was done by assessing the percentage of cells showing fluorescence as compared to total cells in the same field; and (b) the number of T_6 positive epidermal Langerhan cells were quantitated per 100 keratinocyte as well as per high power field.

IDENTIFICATION OF B CELLS

B cells were identified by the presence of surface IgM using direct immunofluorescence. Cryostat sections of skin were incubated with 1 : 5 dilution of normal rabbit serum for 45 minutes at 4°C and washed in 50 mM PBS pH 7·4 for another 15 minutes. They were then layered with 1 : 120 dilution of fluorescein conjugated rabbit anti-human IgM antibodies (Dakopatts A/S, Denmark) and incubated at 4°C for 30 minutes. Subsequently, the sections were washed in PBS for 45 minutes, mounted, and viewed as described above. Controls consisted of sections from human tonsils treated in a similar manner.

Results

EPIDERMIS

The number of T_6 positive epidermal dendritic cells suggestive of LC were within normal limits in the leprosy patients (Table 1). Though the lesional skin of tuberculoid patients showed an apparent increase in LC, this was not found to be statistically significant. LC enumerated per high power field or per hundred keratinocytes showed no significant differences. The intensity of fluorescence also showed no variation across the leprosy spectrum (Fig. 1). Monoclonal antibodies against T_6 identified relatively more LC than anti-Ia like antibodies (data not cited).

Table 1. Numbers of LC in the skin lesions of untreated leprosy patients

Diagnosis	Epidermis OKT$_6$ +ve cells/high power field Mean ± SE (range)
Control (Normal skin) 5*	16·0 ± 2·0 (9–21)
Tuberculoid leprosy (BT/TT) 11*	20·0 ± 2·0 (11–30)
Borderline leprosy (BB/BL) 6*	16·0 ± 2·0 (6–21)
Polar lepromatous leprosy (LL)	15·0 ± 2·0 (5–22)

Statistical analysis was done by Students 't' test.
TT, LL and BB/BL vs Control, P = not significant.
TT vs LL, P = not significant.
* Number of individuals studied.

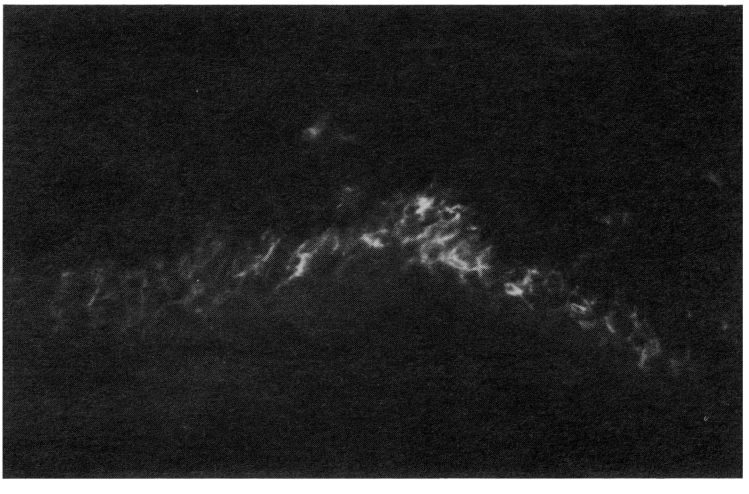

Figure 1. LC in the epidermis overlying a lepromatous lesion, showing intense immunofluorescent staining for T_6 antigen on the cell bodies and dendritic processes. (Cryostat Section; counterstained with pontochrome violet × 220.)

DERMIS

The dermal granulomas of leprosy showed cells positive for Ia like and T_6 antigens (Table 2). Ia positivity was associated predominantly with the lymphocytes surrounding epithelioid cells in tuberculoid and with foamy macrophages in lepromatous lesions as described earlier.[4] Interestingly, T_6 positive cells lacking dendritic processes reminiscent of LC were found in the lymphocyte mantle of

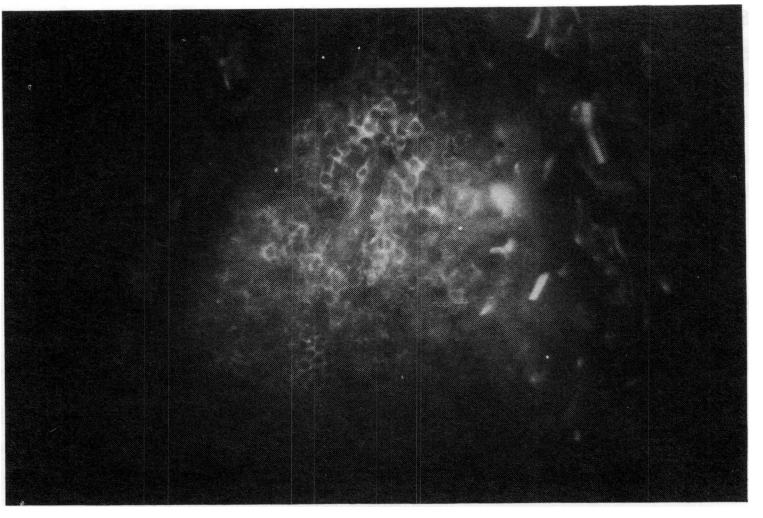

Figure 2. Dermal granuloma of tuberculoid leprosy showing immunofluorescent staining for T_6 antigen on small round nondendritic cells in the lymphocyte mantle surrounding small collections of epithelioid cells. (Cryostat Section; counterstained with pontochrome violet $\times 220$.)

Table 2. Numbers of OKT_6 and OK Ia positive cells in the dermal lesions of patients with tuberculoid leprosy

	Histopathology			Infiltrating cells in the dermal granuloma (range percentage positive cells)		
Diagnosis	Lymphocytes	Epithelioid cells	AFB	T_6	Ia	B cells (surface IgM)
BT	++	++	—	50–60	80–90	ND
BT	+	+	—	30–40	80	ND
BT	+	+	—	5–10	70–80	ND
BT	+	+	—	5–10	80	±
BT	+	+	—	5–10	70–80	±
BT	+	+	—	5–10	90	ND
BT	++	++	—	ND	80–90	ND
BT	+	+	—	ND	80–90	ND
TT	++	++	—	70–80	80–90	ND
TT	++	++	—	40–50	90	ND
TT	++	++	—	30–55	90–95	ND

± = occasional; ND = not detectable.

TT/BT lesions (Fig. 2). Smaller numbers of such cells were also observed in borderline leprosy (Table 3). Lesions of lepromatous leprosy showed a conspicuous lack of T_6 positive cells but had abundant Ia + T_6 − macrophages (Table 4).

No detectable staining was observed with anti-human IgM antibodies in leprosy granulomas indicating the absence of B cells. These antibodies had shown intense staining for B cells in the human tonsils and lymphnodes.

Table 3. Numbers of OKT_6 and OK Ia positive cells in the dermal lesions of patients with borderline leprosy

	Histopathology			Infiltrating cells in the dermal granuloma (range percentage positive cells)		
Diagnosis	Lymphocytes	Macrophages	AFB	T_6	Ia	B cells (surface IgM)
BB	±	+	1+	5–10	100	ND
BB	+	+	2+	5–10	100	ND
BB	+	+	1+	ND	100	ND
BL	+	+	3+	5–10	100	not done
BL	+	+	3+	5–10	100	ND
BL	±	+	3+	ND	100	ND

± = occasional; ND = not detectable.

Table 4. Numbers of OKT_6 and OK Ia positive cells in the dermal lesions of patients with polar LL

	Histopathology			Infiltrating cells in the dermal granuloma (range percentage positive cells)		
No.	Lymphocytes	Macrophages	AFB	T_6	Ia	B cells (surface IgM)
1	±	++	$5\frac{1}{2}$+	ND	100	ND
2	±	++	$5\frac{1}{2}$+	ND	100	ND
3	−	++	6 +	ND	100	ND
4	±	++	6 +	ND	100	ND
5	±	++	$5\frac{1}{2}$+	ND	100	not done
6	−	++	6 +	ND	100	ND
7	±	++	6 +	ND	100	ND
8	±	++	6 +	ND	100	ND

ND = not detectable.

Discussion

Functional studies involving cells from the lesional tissues face operational problems. Thus attempts were made in the present study to evaluate the status of antigen presenting cells by means of monoclonal antibodies directed against functional phenotypic markers. No significant differences were found in the numbers of LC in the lesional skin across the leprosy spectrum though an apparent increase was observed in TT/BT. In particular, LL patients known to have depressed T cell responses showed normal levels of these cells. However, these studies do not rule out qualitative and degradative changes in LC as reported by previous workers using other methodologies.[13,14] Where ATPase has been used as a marker of LC, it is possible that differences in the content of this enzyme may explain the reported apparent reduction of these cells in LL.

The dermal granulomas of many leprosy patients showed both Ia+ and T_6+ cells. In TT/BT lesions T_6+ cells appeared to be nondendritic small cells scattered amongst the lymphocytes surrounding the epithelioid cells. Though it is likely that LC have migrated from the epidermis to the dermal granuloma, the T_6 marker occurs on the immature T cells in the thymus.[11] Therefore, it is possible that the T_6 positive cells in the dermis are of T cell lineage. Our earlier studies[4] had shown these areas to have lymphocytes which were predominantly Ia+T_3+(pan T cell) with a large proportion of T_4+ (helper/inducer) and to a lesser extent T_8+(suppressor/cytotoxic) cells.

The presence of normal numbers of LC and the abundance of Ia like antigens on macrophages of LL would suggest that the antigen presenting capacity of these 2 accessory cells may not be significantly defective. It would seem therefore that the paucity of T cells in the granulomas may be the major cellular defect leading to non-killing of bacilli within the macrophages.

Acknowledgment

The financial support of British Leprosy Relief Association (LEPRA) and the technical assistance of Mr Maheshanand is gratefully acknowledged. Dr Narayanan was a Pool Officer of CSIR.

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Lepr Rev (1984) **55,** 309–310

Domiciliary and Field Work

The dosage of anti-leprosy drugs for children

We are indebted to the Chairman of the Medical Advisory Board of LEPRA, Dr R J W Rees, for the submission of the following tables, which set out the dosages of various anti-leprosy drugs which are currently recommended by LEPRA to those who apply to the Children's Fund for financial support.

Recommended dosage of anti-leprosy drugs in milligrams (mg) based on age of children

Paucibacillary leprosy (2 drugs—dapsone and rifampicin)

Age groups	Dapsone: daily dose, unsupervised	Rifampicin: monthly dose, supervised
Up to 5 years	25	150–300
6–14 years	50–100	300–450
15 years and above*	100	600

Multibacillary leprosy (3 drugs—dapsone, rifampicin and clofazimine)

			Clofazimine	
Age groups	Dapsone: daily dose, unsupervised	Rifampicin: monthly dose, supervised	Unsupervised dose	Monthly dose supervised
Up to 5 years	25	150–300	100 once weekly	100
6–14 years	50–100	300–450	150 once weekly	150–200
15 years and above*	100	600	50 daily	300

The MDT is as recommended by WHO; it is assumed that clofazimine is acceptable for your children and therefore no children will require ethionamide/prothionamide.

Where a range of doses is given this relates to age range of the children; those near the lower age range receive the lower dose and those near the upper age range receive the higher dose.

* i.e. use adult doses.

Voluntary Health Association of India (VHAI), 1983 *Catalogue of Educational Material*

Many who attended the recent International Congress in Delhi will have had the pleasure of visiting this well-known centre for educational material and communication. The Centre's description of the catalogue runs as follows:

"This is a catalogue of the health education materials available from Voluntary Health Association of India. VHAI provides these as an educational and information service. We try to collect the best available and most appropriate items, giving technical information which is helpful for those who are in rural health and development programmes and those working in hospitals. These materials are aimed at helping those who are working in remote areas to keep themselves up to date with the latest information and developments. We collate information from many sources, including societies and agencies who do not advertise.

This is our eighth catalogue and our mail order service is now 9 years old. We run this service on a no profit/no loss basis. This catalogue has a circulation of 10,000. It goes to a wide cross-section of society including voluntary hospitals, Govt. departments and official agencies, various developmental programmes, etc. Still a surprising number of people have not seen our catalogue. We ask you to share it with your friends and others who are interested in health. If we should send this catalogue to a friend or colleague, do please write to us."

We welcome suggestions and sample items for consideration for inclusion in our next catalogue. Intending authors are welcome to share their plans with us.

Please visit us at our office opposite IIT main gate on the Palam Road. We are open from Monday to Friday, 9 am to 5.30 pm. Our phone numbers are 668071 and 668072.

Voluntary Health Association of India, C-14 Community Centre, Opp. IIT Main Gate, SDA, New Delhi 110 016, India.

Maintaining motorcycles: a fieldworker's manual. World Neighbours, USA

This is a 26 pp booklet, A4 size, clearly written and extremely well illustrated. The author is Russel Henning and the address of *World Neighbours* is 5116 N. Portland Avenue, Oklahoma City, Oklahoma 73112, USA. The date of publication is not recorded, but the information is still very much up to date and this manual should be of great practical value to many in leprosy control and other forms of fieldwork.

Ethiopia, *Manual for multiple drug therapy*, December 1983

We are grateful to Dr Ad de Rijk, Leprosy Documentation Service, Amsterdam, for sending us a copy of this excellent manual (20 pp, 13 appendices), which was devised in order to interpret and give additional instruction on the WHO recommendations for multiple drug therapy. The authors considered that the resultant manual, essentially for use in Ethiopia, might be of value to those implementing MDT in other parts of the world. We congratulate all concerned on a most valuable and carefully thought out manual; it is in fact the most comprehensive and detailed we have so far received and may well serve as a useful model for other countries.

OXFAM-LEPRA, Oxford, UK. A mini-pack of teaching materials on leprosy

Following the development and distribution of a larger pack of teaching–training materials on leprosy during the past 2 or 3 years, OXFAM in cooperation with LEPRA have assembled 100 packs containing only 8 items, as follows:

1 *Chemotherapy of Leprosy for Control Programmes* (1983). Technical Report Series 675, 1211 Geneva 27, Switzerland.
2 *OXFAM Memorandum on the Implementation of Multiple Drug Therapy (MDT) for Leprosy* (1984). The Health Unit, OXFAM, 274 Banbury Road, Oxford OX2 7DZ, UK.
3 *Leprosy* (1979) by Bryceson and Pfaltzgraff. Published by Churchill Livingstone, Edinburgh, UK.
4 *The Diagnosis and Management of Early Leprosy* (1983) by Browne. Published by the Leprosy Mission International, London, UK.
5 *Better Care in Leprosy* (1978). Published by the Voluntary Health Association of India, New Delhi, India.
6 *Insensitive Feet* (1981) by Paul Brand. Published by the Leprosy Mission International, London, UK.
7 *Technical Guide for Smear Examination for Leprosy by Direct Microscopy* (1983) by Leiker and McDougall. Published by the Leprosy Documentation Service (INFOLEP), Amsterdam, the Netherlands.
8 *Atlas of Leprosy* (1983). Published by the Sasakawa Memorial Health Foundation, Tokyo, Japan.

Intended mainly for: Medical students, medical officers (with or without experience of leprosy), leprosy control officers, nurses, tutors and other potential teachers.

In view of the high cost of postage by air or surface mail, OXFAM strongly recommends 'personal' delivery. Copies may be obtained by calling at OXFAM in Oxford during normal working hours. Delivery, especially for bulk orders, may also be possible through embassies and consulates in London and by liaison with ILEP, the International Federation of Anti-Leprosy Associations, 234 Blythe Road, London W14 (Tel. 01-602 6925) which holds twice-yearly meetings, often abroad. Cost £10 (USA $15).

S G Browne honoured by Order of St Lazarus of Jerusalem

At an Investiture at All Saints Church, Northampton on 20 June 1984, Dr S G Browne, a Vice-President of LEPRA and formerly Secretary of the International Leprosy Association, was made a Knight of the Military and Hospitaller Order of Saint Lazarus of Jerusalem in recognition of his worldwide activities on behalf of leprosy sufferers.

Lepr Rev (1984) **55,** 311–314

Reports, News and Notes

LEPRA: Sixth Clayton Memorial Lecture; April 1984: 'Leprosy and the Eye'

The Clayton Memorial Lecture was established by LEPRA in 1973 as a tribute to the late Reverend P B Clayton, CH, MD, DD, Founder Padre of Toc H. In this decision, LEPRA was mindful of the fact that it was Dr Clayton's personal inspiration which was responsible in 1933 for the establishment of the Overseas Staff of this Association, and that he maintained a life-long interest in the control of this disease. Through the years the speakers have been as follows:

1974, Dr R J W Rees, 'Science and leprosy—progress and problems in "applied" research'; 1975, Dr A C McDougall, 'Leprosy; a continuing challenge to clinical medicine and research'; 1976, Dr T W Meade, 'How effective is the treatment of leprosy?'; 1978, Dr Tore Godal, 'Is immunoprophylaxis in leprosy feasible?'; 1980, Dr Noshir Antia, 'Clinical and experimental studies on the causation of nerve paralysis in leprosy'.

The 1984 lecture was given by Mr Timothy ffytche, Consultant Ophthalmologist at St Thomas's Hospital and Moorfields Hospital, London and his subject was 'Leprosy and the Eye'. Under the chairmanship of Sir John Wilson of the Royal Commonwealth Society for the Blind, Mr ffytche spoke to an audience of over 120 people, including doctors and research workers from various units in London and elsewhere. He described the clinical manifestations of leprosy with particular reference to the eye and gave emphasis to the importance of the epidemiology of eye complications in this disease and to the data which has already been collected by Peace Corps and other volunteers. Much of this work has been supported by grants from LEPRA and results have already been published in *Leprosy Review* and other journals.

Leprosy by S G Browne; *Acta Clinica*; Documenta Geigy, Switzerland

Many who have used the previous edition of this booklet will be delighted to know that it has now been brought up-to-date and issued as a revised edition, 1984. As before, it is extremely well produced and the illustrations in colour (over 100) are of high quality. All aspects of leprosy are covered. We congratulate Dr Browne and the Medical Department of this company on the renewed production of one of the most valuable booklets of its kind currently available.

Leprosy in India changes its name to *Indian Journal of Leprosy*

We are grateful to the Assistant Editor for the following information:

The name of this journal *Leprosy in India* has been changed to *Indian Journal of Leprosy* beginning from Volume 56 (1984), and its volume number will be continuous with the present one i.e. Volume 55 (1983). For reference purpose, the new name of the journal shall be abbreviated as *Indian J. Lepr* (*Indian* in full in order to avoid any confusion with *Int.* or *Inter.* standing for *International*).

Leprosy in India was started in 1929 in the nature of 'Notes' for circulation amongst workers in India with Dr Ernest Muir as its first Editor. The journal made tremendous progress under the Editorship of Dr Dharmendra who has been editing the journal from 1943 with a brief break of 5 years in the 50s (1955–60) and of 2 years in the 70s (1970–72). Of late it has grown up tremendously owing to increased research activities going on all over the world including India in the field of leprosy and reported in this journal. Therefore it is now considered to be one of the foremost International Journals on Leprosy. In view of its present status, it was strongly felt that there was a need to change the title of the journal suitably in order to ensure that the title reflects the nature and contents of the journal. Suggestions for a suitable title were invited from several Leprologists, and the majority of the opinion was that the title *Indian Journal of Leprosy* (*Indian J. Lepr.*) would be most appropriate. This suggestion was unanimously approved by the Governing Body of the Hind Kusht Nivaran Sangh.

Sasakawa Memorial Health Foundation, Japan

We acknowledge with thanks receipt of the following:

1 *Symposium on Immunotherapy and Immunoprophylaxis of Leprosy*. This is a 55 pp booklet describing a Symposium held in Tokyo in November 1982, with Dr Convit, Dr Zuniga and Dr Ulrich from Caracas as the main speakers. The main headings are: 'Immunotherapy and Immunoprophylaxis of Leprosy' (Convit); 'Epidemiological Orientation in the Immunoprophylaxis in Leprosy' (Zuniga); 'Studies of Antibodies in Leprosy and Healthy Contacts by Enzymatic Immunoassay' (Ulrich).

2 *The Proceedings of the Workshop on Serological Tests for Detecting Subclinical Infection in Leprosy*, Tokyo, Japan, May 1982. The keynote lectures were entitled 'Fundamental and Practical Requirements of Serological Test for Drafting Subclinical Infection in Leprosy' (Mashide Abe) and 'The Phenolic Glycolipid from *Mycobacterium leprae*; Use in Serological Tests' (Douglas B. Young *et al.*). Further information: The Sasakawa Hall 6F, 3-12-12 Mita, Minato-ku, Tokyo 108, Japan.

Centre for Medical Education, University of New South Wales; Workshop Forum on Evaluation of Training programmes for Primary Health Care, 1983

This is one of a regular series of publications from this centre and it records the proceedings of the intercountry workshop sponsored by WHO in February 1983. The subject headings covered the nature of evaluation, steps in evaluation, the role of the evaluator, analysis and presentation of data. Apply to the above Centre at the University of New South Wales, P.O. Box 1, Kensington, NSW, Australia 2033.

Excerpta Medica Section 51; change in title—*Mycobacterial Diseases; Leprosy, Tuberculosis and Related Subjects, 1984*

With Volume 6, Issue 1, the publishers draw attention to this change which '. . . reflects research and application trends in these areas and has been instituted following the suggestions of authorities in this field.' This section is published on behalf of the Leprosy Documentation Service, Royal Tropical Institute, Mauritskade 63, 1092 AD Amsterdam, The Netherlands, and subsidized by The Netherlands Leprosy Relief Association, Amsterdam.

Courses and Training in Pathology in the UK

We are grateful to the National Advice Centre for Postgraduate Medical and Dental Education and Training, 7 Marylebone Road, London NW1 5HH for detailed information on courses and training in pathology in the UK. Information is also available on bacteriology, biochemistry, haematology, neurological science, neurochemistry and physiology, including details of the awarding body for degrees, qualification required before entry, other requirements, timing of the examinations and fees.

'Lamprene' (clofazimine, B663) on leprosy; basic information; CIBA–GEIGY, 1984

This booklet, which was distributed at the recent Delhi Congress, has been completely revised and contains a great deal of information on this valuable drug under the following headings—composition, presentation, absorption, tissue distribution, metabolism and excretion, therapeutic effect, indications, dose schedules, toxicity, tolerability, precautions and references. It was compiled by S J Yawalkar and W A Vischer and is available from Pharma Division, CIBA–GEIGY Ltd., Basle, Switzerland, free of charge.

WHO; *Weekly Epidemiological Record*, 1983, 58, 109–116, Tuberculosis and leprosy

The opening pages of this issue describe the deliberations of a consultative group of epidemiologists who met in Geneva in November 1982 to identify the main problems of immediate importance for tuberculosis and leprosy control, and to indicate areas for research. The text is in English and French. The account will be of great interest to those attempting to control leprosy or tuberculosis—or the 2 diseases together.

WEMOS; Stichting Werkgroep Mediese Ontwikkelingssamenwerking

Mrs Janita Janssen has kindly sent the following information from Amsterdam:

WEMOS, Workgroup for Medical Cooperation in Developing Countries was founded in 1979 by a group of medical students who wanted to gather information about Western aid to developing countries. The group is subsidized by the Dutch ministry for work in developing countries and its purpose is to stimulate a critical way of thinking about development matters. One of our main themes is: underdevelopment is not caused by illness or poverty, but illness and poverty come about because of economic and political factors. Our means are: publishing books and articles; gathering all kinds of documents and books; organizing conferences (1981 on Dutch Aids, Health and Politics; May 1983 on Pharmaceuticals and The Third World; 1984 Policies of Dutch Private and Governmental aid programmes); give readings, and organize workgroups. Our main subjects at the moment are: Position of women in developing countries; Pharmaceuticals and the third world; The big drug companies; Contents of the Dutch aid programmes; and Information to schools.

At the moment WEMOS has about 600 members in Holland, and regional groups have been set up in 6 other big cities. Members come from all kinds of disciplines, mainly concerned with health and anthropology. Address: WEMOS, Minahassastraat 1, Amsterdam-Oost, The Netherlands.

NOVIB; Netherlands Organization for International Development Cooperation

We are grateful to Miss Ingrid Kalf in INFOLEP, Amsterdam for contacting this organization in the Netherlands, who have sent the following information: In 1954, the action group Plein 1954 and the National Hugenholz Committee took an initiative in establishing a 'Netherlands Organization for International Assistance' (Novib). Plein 1954 strove to break through ecclesiastical, societal, and political isolation. The Hugenholz Committee drew attention to needs in less-developed countries. Both wanted to bind together as many Dutch institutions as possible as members in the new Novib. In this way, virtually everyone in the Netherlands would have the chance to get in touch with Novib, at least indirectly. It took 2 years to get 70 Dutch organizations together. On 23 March 1956, the founding of Novib became a fact: the first, and for the time being, only, non-ecclesiastical, non-political Dutch foundation created to respond to problems in developing countries.

An excellent brochure is available with further details, including brief descriptions of the work of this organization in Cape Verde, Sri Lanka and Bolivia, from Novib, 7 Amaliastraat, 2514 JC, The Hague, Netherlands.

Graves Medical Audiovisual Library; Catalogue of Tape and Slide Programmes, 1983

Fay Fontana, Administrator/Marketing Manager of this Library, Holly House, 220 New London Road, Chelmsford, Essex CM2 9BJ, United Kingdom (Tel: 0245-83351) has written to confirm that there are in fact over 1000 titles listed in the current catalogue. New items are constantly being added. The material includes tape–slide and video-tape programmes. The catalogue runs to well over 100 pages and almost every imaginable aspect of medicine in the broadest sense is covered. [But it is highly regrettable that there is nothing on leprosy, all previous material having fallen out-of-date. For an organization with such remarkable national and international influence, surely this defect should be corrected without delay. *Editor*]

BWINO from Zambia; Special Position Paper Number 4, on Leprosy Control

A few months ago we received this dynamic publication from Lusaka, Zambia. Previous position papers in this series have been on nutrition and diarrhoea, the energy/protein issue and infant feeding. This one on leprosy has been prepared with the objective of providing a manual to keep health workers in leprosy up to date with leprosy in general and with some of the problems which are of particular relevance in Zambia. Leprosy control policy for the country is described in full. Then follow sections on diagnosis, classification, skin smears, treatment complications and their treatment, shoemaking, assessment, discharge and release from control. We congratulate Dr Richard de Soldenhoff on this initiative; the whole presentation is extremely clear, easily read and of just the right length. Others would do well to copy this example and may consider contacting the Leprosy Specialist, P.O. Box 30205, The Ministry of Health, Lusaka, Zambia, Africa.

University of Dundee; Centre for Medical Education

For over 8 years this teaching centre has run courses for medical teachers on a variety of topics, including assessment teaching methods and curriculum planning. Those in 1984 include 'Effective Teaching in Medical Education', 'Assessment in Medical Education' and 'Curriculum Planning in Medical Education'. The duration of each is for a few days only and accommodation can be arranged; fees are moderate. Apply (for 1985) to The Centre for Medical Education, The University, Dundee DD1 4HN (Tel: 0382-23181).

Learn about leprosy: Leprosy Mission International, London

This is a strongly produced paperback of 20 pages, illustrated in black and white and colour, giving a simple account of leprosy in terms which are understandable to the layman. The headings are: Leprosy Today; The Cause; Nerve Damage; The Feet; The Face; Isolation; Treatment; Surgery; and Control. The text and design are by David Huggett, originally produced in 1979. This is a first-rate booklet which must surely be of great value for non-medical people in the UK and elsewhere who want to learn the facts from a reasonably short text. Apply: TLMI, 50 Portland Place, London W1N 3DG, United Kingdom.

The Journal of Audiovisual Media in Medicine

The publishers have kindly supplied the following information: In 1978 the Institute of Medical and Biological Illustration launched *The Journal of Audiovisual Media in Medicine* to replace *Medical and Biological Illustration* as the official journal of the Institute. *The Journal of Audiovisual Media in Medicine* is designed to appeal to those involved in the production of audiovisual media be they photographers, artists, graphic designers, cinematographers, television personnel, audiovisual specialists, educational technologists, or manufacturers of audiovisual hardware and software. *Editor:* K P Duguid, Department of Medical Photography and Illustration, Westminster Hospital Medical School, 17 Page Street, London SW1P 2AP, UK.

INTRAH; International Training in Health, University of North Carolina, USA

The Coordinator, Catherine Murphy, has kindly brought us up to date on this organization and the following is an extract from her letter: '. . . Let me first explain that the African Health Training Institutions Project ended several years ago. Dr James Lea is currently the director of the Program for International Training in Health (INTRAH). INTRAH, funded by the Agency for International Development, Washington, DC, conducts training of paramedical and auxiliary health personnel in Africa and the Middle East. The primary training topics are Maternal and Child Health Care and Family Planning.

The INTRAH Program has developed and is developing educational material to supplement training in the Africa/Middle East regions. For example, Ms Elizabeth M Edmands, INTRAH's Public Health Nurse Educator, has written a manual, *Concepts and Issues in Family Planning: Guidelines for Nurses, Midwives, and Other Health Personnel*, and the Educational Materials Unit of INTRAH is currently developing an *Audio-Visual Aids Training Manual*.' Further information is obtainable from Educational Materials Unit, Program for International Training in Health, The University of North Carolina at Chapel Hill, 208 North Columbia Street, (344A), Chapel Hill, North Carolina 27514, USA.

Bureau for Overseas Medical Service (BOMS), London

BOMS has recently moved to a permanent office in the Africa Centre, a cultural and educational centre, in Covent Garden. This growing charity runs a register for doctors and health workers who are interested in working in the Third World. There are currently 543 doctors and 157 paramedical workers on the register.

Recent placements include sending an orthopaedic surgeon to work with the *Malawi Against Polio* project and a physiotherapist to South Lebanon to work on a joint Oxfam–Middle East Council of Churches project in the Ain El Hilweh Refugee Camp. The constant demand for medical personnel to fill vacancies like these shows the need for an efficient register. The *Bureau* acts as clearing house rather than recruiting agency and it aims to eliminate the problems and costs of communication for those who can least afford them in terms of time and money.

For further information please contact the Secretary, Jane Lethbridge, Bureau for Overseas Medical Service, Africa Centre, 38 King Street, London WC2E 8JT, UK. Tel: 01-836 5833.

The Heiser Program for Research in Leprosy

Beginning postdoctoral research fellowships, research grants, and visiting research awards available in amounts up to $18,000 per year, plus other allowances. Applicants should have MD, PhD, or equivalent degree. Applications by February 1 1985, for awards to be activated June–December, 1985. For information write: The Heiser Program, 450 East 63rd Street, New York, New York 10021, USA.

LEPRA Prize Essay Competitions for Medical Students in the UK and India

United Kingdom. Following the tradition of previous years (started in 1972) LEPRA offered prize money for an essay on a leprosy subject in 1983, and the first prize was awarded to Nicola Strickland (Green College, Oxford) for her entry on the subject of '*The influence of immunosuppression and immunodeficiency on infections with leprosy and tuberculosis*'. Her essay will be published in the medical press in 1985. Second prize was awarded to Roderick MacRorie (Green College, Oxford) for his essay on '*Factors influencing the compliance of patients to prescribed drugs in chronic diseases, with particular reference to leprosy*' and third prize to Amyn Kadri (Balliol College, Oxford) for his entry on the immunological subject above. The subjects for 1984 are '*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, specialised programmes*' OR '*Leprosy will be most expediently controlled by the use of fully-integrated programmes which make use of the primary health care approach.*'

India. A LEPRA prize essay competition was first offered to St John's Medical College, Bangalore, South India, in 1981 on the subject of '*Leprosy control in South India*'. In 1982 the subject was '*Factors influencing compliance to drug treatment in leprosy in South India*' and in 1983 '*Leprosy and the eye*'. For the latter subject, the first prize was awarded to Mr Rajeev Thomas Thachil: two equal second prizes were awarded to Miss Mabel Cordeiro and Mr V J Joseph. The subject for the current year, 1984, is '*Leprosy and primary health care*'.

XVth General Assembly of ILEP, Venice, June 1984

This Assembly took place in the Giorgio Cini Foundation in Venice. The Plenary Meeting included the following items: biennial reports of Ad Hoc Working Group No. 2 on health education and information, AHWG No. 3 on social aspects, AHWG No. 5 on training, AHWG No. 6 on primary health care, AHWG No. 7 on leprosy and tuberculosis and AHWG No. 8 on leprosy in Europe. Dr Cap, Chairman of the Medical Commission, gave a biennial report of its activities. The Medical Commission met on 12 June and considered: the role of the Medical Commission and the position of its Secretary; monitoring by computer of MDT programmes; priorities in research; the ILEP meeting in Delhi on MDT; the WHO meeting on MDT in Delhi; up-dating the ILEP booklet on the '*Introduction of Multidrug Therapy for Leprosy*'; a report by Dr S G Browne on the *International Leprosy Congress* in New Delhi, 1984. The next meeting is to be in Paris, December 1984.

National Workshop on Laboratory Techniques for Leprosy Control, Shanghai

Under an agreement between WHO Headquarters, Western Pacific Regional Office of WHO (WRPO) and the Ministry of Public Health of the People's Republic of China, a workshop, funded by WRPO, was held 5–23 March 1984 at the Zeng Yi Hospital, Shanghai. Twenty-six participants, representing 19 institutes in 14 provinces (or autonomous regions) were trained in the mouse foot-pad technique for cultivation of *M. leprae* or the Ridley–Jopling technique for classification of leprosy. In addition, an intensive course of lectures on the two techniques and on the principles of multidrug therapy was presented. Workshop facilitators included five foreign experts (Dr S K Noordeen, Prof. L Levy, Dr D S Ridley, Prof. S R Pattyn and Mrs L P Murray) and seven Chinese scientists.

Medical Laboratory Manual for Tropical Countries; Monica Cheesbrough, 1984

Volume 2 on Microbiology has now been published and is available from Monica Cheesbrough at Tropical Health Technology Ltd, 14 Bevills Close, Doddington, Cambridgeshire PE15 OTT, England. It has been produced with the object of assisting those working in regional and district hospital laboratories and medical and nursing students in developing countries. Special features include:

Emphasis on the laboratory diagnosis of major communicable diseases; more than 50 colour plates illustrating pathogens that cause Campylobacter enteritis, Salmonella and Shigella infections, cholera, amoebic dysentery, meningitis, tuberculosis, leprosy, gonorrhoea, pneumonia, staphylococcal and Group A streptococcal infections, donovanosis, diphtheria, clostridial infections, anthrax, trachoma, and relapsing fever; free kit with each manual to make condenser stops, to examine specimens by dark-field microscopy; special subsidized low price to developing countries.

The total cost of this new volume, including packaging and posting in the UK is only £9.95 (unbelievable value for the 488 pages and illustrations); and the cost to developing countries is even lower: £6.40 by surface mail and £12.10 by airmail postage.

Lepr Rev (1984) **55,** 315–317

Letters to the Editor

EXPERIENCES WITH A PHENAZINE DYE, B628, IN THE TREATMENT OF LEPROSY IN CHINA

Sir,

Dr Levy reported (*Lepr Rev* 1981; **52:** 23–6) his studies on 4 analogues of clofazimine in experimental leprosy and summarized ' The results suggest the importance of the 2 *p*-chlorosubstituents that are a structural feature of clofazimine'. This conclusion is of considerable interest in relation to B628, one of the series of phenazine dyes[1] with the *p*-chlorosubstituents on the 2 benzene rings (Figure 1), and which has been synthesized by Sin Yi Pharmaceutical Factory of Shanghai in small quantity. Dr Ji Baohong has shown that B628 is similar to clofazimine in its activity against both *Mycobacterium leprae* and *M. lepraemurium* in animal models.[2–4] As a clinical pilot study, I treated 3 cases with lepromatous leprosy in South-west China with B628 as monotherapy for 5 months, from October 1974 to March 1975, at a dosage of 150 mg daily for the first month and 100 mg daily thereafter. Simultaneously, another group of 6 patients with LL or BL were treated with the same regimen in Shanghai for 6 months.[5,6] A dramatic clinical improvement was observed in 2 months, including the subsidence of nodular and diffuse

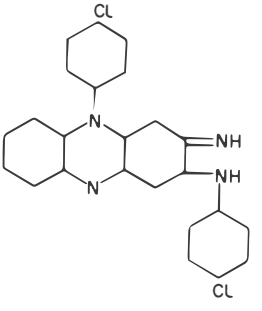

Figure 1. Structure of B628. [3-(*p*-chloroanilino)-10-(*p*-chlorophenyl)-2,10-dihydro-2-iminophenazine].

infiltrated skin lesions and the clearance of purulent nose discharge and nose blockage. The protracted ENL eruptions and neuralgia were under control after ½–3 months of therapy. Bacterial Index of skin smears showed no change after 5 or 6 months therapy, but the percentage of morphologically intact bacilli (MI) decreased sharply from an average of 24% to 2%. Although it had been expected that the skin pigmentation would be the main side-effect of this drug, the quality of colouring produced by it was less marked and more acceptable than the brick-red or chocolate colour developed by B663 (clofazimine) in Chinese patients. However, the following toxic effects had been noticed; elevated SGPT level occurred in 3 cases and gynacomastia in 2 out of 7 male cases. Because of the shortage of drug supply, the clinical use of this drug was discontinued, and all patients in these 2 groups were changed to dapsone therapy later on.

LI FUTIAN

Shanghai Zun Yi Hospital
Gong He Xin Lu
Shanghai, China

(Dr Li Futian has kindly translated the main parts of references 5 and 6 from Chinese to English and copies are available from this office. *Editor.*)

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REPLY TO 'IS THE LEPROMIN TEST RELIABLE IN CHILDREN?'

Sir,

Dr Stanley Browne's letter[1] on this subject is of considerable interest, especially as he recommends the institution of investigations into this problem which is equally applicable to adults.

In 1957–8 I was fortunate to have under my care 2 very co-operative patients who let me carry out extensive clinical examinations, slit smears, Mitsuda tests and biopsies on small areas of dimorphous skin lesions all within a short space of time.[2]

My conclusions about the Mitsuda tests closely parallel those of Dr Browne. They were that: 'The presence of a poorly developed lepromatous infiltrate did not appear to exclude a positive lepromin reaction in a clinically similar part of the lesion neither did the prior development of epithelioid and giant cells exclude lepromin negativity of the lesion very close to where they were found.'

Perhaps the repetition of this type of investigation using larger numbers of willing patients would help to solve the problem posed by Dr Browne, and at the same time tell us more about the nature of the interactions between different cell types and live and denatured Hansen's bacilli.

M G CORCOS

Coombe Wood
6 Eastcombe Road
Weston-Super-Mare
Avon BS23 2TQ

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DAPSONE COMPLIANCE USING ISONIAZID-MARKED FORMULATION

Sir,

In *Lepr Rev*, 1983; **54:** 317–25, Stanley *et al.*[1] describe their investigation of dapsone compliance using an isoniazid-marked formulation in conjunction with the determination of dapsone/creatinine (D/C) ratios in urine. Their basic idea is to determine the mean D/C ratios in the urines of individual patients under conditions of full compliance which—in their procedure—is not established by a period of supervised dapsone intake, but by the detection of 2 isoniazid metabolites in the urines. Once an estimate of the individual's mean 'compliant' D/C ratio has been obtained, his compliance can be followed by comparing the D/C ratios in further urine samples with this estimated mean. The paper gives an example of such comparisons in which numbers of missed doses are calculated based on a fall in D/C ratios by about 50% every 27 h.

I have considerable doubts about the validity of this procedure because of the following:

1 The urine of a patient who would have missed yesterday's dapsone dose, but would have taken today's dose correctly, would be equally positive in the marker test for compliance as the urine of a fully compliant patient.

2 The 'compliant' D/C ratios of individuals in this study had on average a variation about the mean of 'only' ±12%, but in more than a quarter of the individuals the lowest D/C 'compliant' ratio was less than 73% of the highest one, the percentage that is used to discriminate between full compliance and one missed dose.

3 Because of the 'small' variability in the 'compliant' D/C ratios all marker-positive urines were considered to be due to dapsone intake that same morning. However, at least the lower D/C 'compliant' ratios referred to under point 2 could quite well be interpreted as being due to dapsone intake on the previous day.

4 Previous studies of half-lives of dapsone in man have reported considerable variation, with ranges from 11–53 h and means varying from 18–38 h.[2–4] Calculations in individuals should therefore be based on individual half-lives and not on a mean value.

In view of the points raised above, such calculations of numbers of missed doses as presented in the paper are of little value. But even if it could lead to valid calculations, to introduce an isoniazid-marked formulation would seem equally far-fetched as hospitalization for the purpose of establishing full compliance when estimating the 'compliant' D/C ratios of individual patients. A few days of supervised intake of dapsone at home combined with health-education could be a simple and productive alternative.

I would certainly not envisage the isoniazid-marked formulation in conjunction with the determination of D/C ratios as a 'much improved standard approach to monitoring the dapsone compliance of out-patients', as is suggested by the authors. A standard approach should be simple and cheap, but none the less valid. In my current experience, the urine spot test employing filterpaper impregnated with a modified Ehrlich's reagent, which was recommended by the WHO Expert Committee on Leprosy as early as 1966,[5] fully qualifies for this purpose. A slightly revised account of this test is published in the April 1984 issue of *Tropical Doctor*.[6]

H HUIKESHOVEN

Department of Tropical Hygiene
Royal Tropical Institute
Mauritskade 63
1092 AD Amsterdam
The Netherlands

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REPLY TO 'DAPSONE COMPLIANCE USING ISONIAZID-MARKED FORMULATION'

Sir,

In his analysis of the data set out in our paper[1] Dr Huikeshoven should have compared the dapsone/creatinine (D/C) ratios of individual urine samples giving positive isonicotinic acid tests with the *means* of such 'compliant' ratios—and not with the highest individual values. This would have revealed that in only one instance (patient 12) did the lowest value fall below 73% of the mean value—and in this case it was actually 72% of the mean! If these lowest compliant D/C ratios had been due to isoniazid-marked capsules having been ingested on the previous day, they might have been expected to have been only about half of the mean compliant values. We therefore believe that the mean compliant D/C ratios were probably not unreasonable estimates of the true values that ideally should be determined after giving courses of daily supervized doses.

Dr Huikeshoven suggests that a simpler approach would be to give daily supervised dapsone doses to the patients in their homes. However, in the city of Hyderabad where our study was conducted (and probably most cities in developing countries) home visits are far from simple. At least half our patients refuse permission for their homes to be visited for fear that it might reveal to their neighbours that they had leprosy. When patients are willing, their homes are often very hard to find, even when addresses have been taken carefully by staff who know the area well. During working hours patients are often working far from home. Furthermore, daily home visits, in our experience, can embarrass even patients who agree to once a month visits. We consider Dr Huikeshoven's suggestion impracticable except for small numbers of carefully selected patients.

We do nevertheless accept Dr Huikeshoven's criticism that our method for monitoring dapsone compliance, though more precise than simply measuring D/C ratios, is still limited by variability in the rates at which dapsone is eliminated from the body by different individuals. The same limitations would apply to interpreting the results obtained by any procedure for monitoring dapsone compliance whether it be quantitative or qualitative.

The great attraction of using qualitative urine tests for monitoring dapsone compliance, including the spot-test procedure advocated by Dr Huikeshoven, is their potential simplicity. Their major disadvantage is that the positivity of urine samples is inevitably markedly affected by diuresis.[2] The problems posed by the effects of diuresis are virtually overcome in the quantitative D/C ratio method,[3] but it is inevitably a more complicated procedure. In the end the choice concerning which type of method to use is clear, precision *or* simplicity. It is impossible to have both.

J N A STANLEY & J M H PEARSON

Dhoolpet Leprosy Research Centre
Karwan
Hyderabad, 500 006
India

G A ELLARD

National Institute for Medical Research
The Ridgeway
Mill Hill
London NW7 1AA

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THE USE OF COLCHICINE IN THE MANAGEMENT OF TYPE 2 LEPRA REACTION (ERYTHEMA NODOSUM LEPROSUM)

Sir,

Patients with mild or intermittent Type 2 lepra reaction can be adequately and safely managed using analgesics, chloroquine, antimonials, and short courses of steroids. But of the drugs available to manage severe reaction, clofazimine causes disfiguring discolouration, thalidomide is teratogenic, and long-term continuous corticosteroid treatment causes multiple toxic side-effects. There is clearly need for an acceptable and safe drug to treat severe Type 2 lepra reactions. Sarojini & Mshana[1] have described the rationale for the use of colchicine for this purpose, and report its use in a trial which included 10 patients; their study, however, was uncontrolled.

We have carried out an internally controlled outpatient trial of the use of colchicine to treat patients with severe Type 2 lepra reaction. Five patients, all adult Indian men, were included; all had suffered from recurrent and often almost continuous reaction for at least 2 years prior to the trial. All were receiving dapsone 50–100 mg daily together with clofazimine 100 mg daily, and all required corticosteroids, in short repeated courses and sometimes almost continuously. One patient had received a course of thalidomide a year prior to the study. The diagnosis of Type 2 lepra reaction was confirmed in all cases by biopsy of an active skin nodule during the course of the trial.

The trial covered a period of 6 months, during which dapsone and clofazimine were continued in unchanged dosage. Each patient received colchicine 2 mg daily during months 3 and 4; the first and last 2 months were control periods. Prednisolone was prescribed according to need, using the usual criteria of this centre, and patients were (almost) always seen by the same physician (JNAS). The effect of the colchicine was determined by its impact on the steroid requirement.

The results of the study, showing the number of mgms of prednisolone prescribed for each patient month by month, are shown in Table 1. It is clear that colchicine had little or no effect on the steroid requirement of these patients, individually or as a

Table 1. Total dosage of prednisolone (mg) prescribed monthly to trial patients

Case no.	Bacterial index	Monthly total dosage of prednisolone (mg)					
		1	2	3	4	5	6
1	3·6	220	310	245	130	280	85
2	4·2	355	55	255	310	405	270
3	0·7	100	150	100	130	105	135
4	2·3	220	140	235	95	180	205
5	4·5	370	305	315	155	80	100
Total		1265	960	1150	820	1050	795

group. Diarrhoea was a common side-effect, being severe enough to compel 3 patients (cases 2, 4 and 5) to reduce their colchicine dosage to 1 mg daily for part of the trial period. Nevertheless, 2 patients (cases 2 and 4) have reported an increased sense of well being during the period of colchicine treatment, and one of them has requested that it be prescribed for him again.

This study has the usual limitations of outpatient trials in which the drug intake is unsupervised. Nevertheless the results indicate that colchicine is not a 'wonder drug' for more severe Type 2 lepra reaction, though it may have mild activity, equivalent possibly to that of the antimonials. It will probably be unacceptable for patients to whom loose stools are unwelcome.

The results of this study differ considerably from those reported by Sarojini and Mshana. The reasons for this are uncertain. It is likely that the patients in our study had more severe reaction, and any effect of the colchicine may have been masked by the concurrent administration of clofazimine and corticosteroids. Another difference is that Sarojini's patients appear to have been hospitalized; that study may therefore have demonstrated the improvement that commonly occurs without specific medication when patients with Type 2 lepra reaction are admitted to hospital. Our study indicates that colchicine does not answer the need for a safe and acceptable drug to manage severe Type 2 lepra reaction.

Acknowledgment

Dhoolpet Leprosy Research Centre is the 'city centre clinic' of Victoria Hospital Dichpalli, and is managed in collaboration with the Medical Research Council (of Great Britain).

J N A STANLEY, K U KIRAN & J M H PEARSON

Dhoolpet Leprosy Research Centre
Hyderabad 500 006
India

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TRACHOMA PREVALENCE IN LEPROSY AND NON-LEPROSY POPULATION OF BICHENA DISTRICT, GOJJAM ADMINISTRATION REGION, ETHIOPIA

Sir,

Between February 1 and May 14 1981 a mass survey was carried out in the Bichena District of the Gojjam Administrative Region of Ethiopia to investigate the magnitude of leprosy and trachoma in the population. The regional medical officer of health, government officials, chairman of farming groups, youth and women's associations, community leaders and health workers were all briefed about the operation well in advance. Extensive health education, especially on trachoma, was organized, using filmstrips, loudspeakers and posters. Each peasant and Kebele association contributed to the survey by assigning one or two of their own men to assist our surveyors in guiding and mobilizing people for physical examination. Three members of the trachoma project were assigned and they worked in close association with our leprosy control personnel throughout. During the above period, no fewer than 223,402 people were examined. Our findings are shown in the accompanying tables. It has to be acknowledged that there are many difficulties in obtaining accurate information from patients under these circumstances. It is, for instance, possible that some of the 814 leprosy cases regarded as 'new' may in fact have been previously registered, or received treatment elsewhere. We believe that such difficulties do not, however, detract from the value of the figures overall, which show that trachoma affected 82·2% of patients with leprosy, compared with 45·5% of patients in the general population. The high incidence of trachoma in this part of Ethiopia may be attributable to lack of personal hygiene, inadequate community sanitation, high density of flies, scarcity of water and limited access, often at great distance, to health services. As regards the even higher incidence of trachoma in leprosy patients, it is presumably possible that immunological or genetic factors may play a part, and it may also be that one disease predisposes the development of the other. Our data give no indication, however, of which disease came first, though the high figures and wide age-spread in the general population suggest that any patient acquiring leprosy would have had a high chance of being already infected with trachoma. On the other hand, patients with anaesthesia of the cornea or defects in lid closure (due to leprosy) may be unusually vulnerable to infection with trachoma. Finally, it should be kept in mind that the environmental and socio-economic factors listed above may be even more important in patients with leprosy whose social status may be lower than average.

We are encouraged to present these preliminary findings by the recent publication of data in Egypt on 'Leprosy in a Trachomatous Population'[1]—which reviews the relevant literature and draws attention to the disastrous effects of the association of these two diseases in the eye.

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TADELE TEDLA

National Leprosy Control Programme
P.O. Box 5033
Addis Ababa
Ethiopia

Reference

[1] Schwab IR, Nasser E, Malaty R, Zarifa A, Korra A, Chandler R, Dawson R. Leprosy in a trachomatous population. *Arch Ophthalmol*, 1984; **102:** 240–44.

Table 1. Active Trachoma cases, percentage distributions and prevalence rate per thousand population in four sub-districts of Bichena District

Sub-district	Population examined	No. of cases	Percentage (%)	Prevalence rate per 1000 pop.
Deboy Tilatgin	42,404	19,653	46·3	463·5
Enarje Enawga	71,225	32,174	45·2	451·7
Enemoy	68,932	28,916	41·9	419·5
Shebd Berenta	40,841	21,004	51·4	514·3
Total	223,402	101,747	45·5	455·4

Table 2. Active trachoma cases in leprosy patients percentage distribution by sub-districts of Bichena District

Sub-district	No. of leprosy cases	No. of leprosy cases with trachoma	Percentage (%)
Deboy Tilatgen	235	168	71·4
Enarje Enawga	248	199	80·2
Enemay	182	171	93·9
Shebel Bereta	149	136	91·3
Total	814	674	82·8

CONTENTS

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