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Leprosy Review

A journal contributing to the better understanding of leprosy and its control

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Leprosy Review is published by the British Leprosy Relief Association (LEPRA) with the main objective of contributing towards the better understanding of leprosy and its control. Original papers on all aspects of leprosy, including research, are welcomed. In addition, *Leprosy Review* seeks to publish information of educational value which is of direct benefit to the control of leprosy under field conditions, and hence to the individual patient. The Journal aims to interpret what is being done in other disciplines, particularly for field workers.

From time to time the Editorial Board invites special articles or editorials from experts in various parts of the world, and gives consideration to the production of a supplement or special number devoted to a particular subject or theme of major importance.

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Editorial

PRIORITIES IN LEPROSY CONTROL

In the recently published Sixth Report of the World Health Organization Expert Committee of Leprosy (1988), the world prevalence is estimated to be between 10 and 12 million cases.[1] About one third have significant deformities. More than 1·6 billion people live in countries where the estimated prevalence is above 1 per 1000 of the population and who are therefore at risk of infection. But in recent years, leprosy has been recognized as a major health problem in many endemic countries and the recommendations of the World Health Organization (WHO) in 1982 on regimens of multiple drug therapy (MDT) of relatively short duration[2] opened new and unprecedented perspectives for leprosy control. Today leprosy can be seen not as 'an historic fatality but as a problem with a solution'.[3] The implementation of MDT as standard treatment has become a prime strategic priority for leprosy control programmes. The objectives of leprosy control have been clearly stated, the methods well defined and the most important 'essential' or 'key' activities needed for an effective leprosy control programme described in considerable detail.[4–6] In the context of the global policy of 'health for all' it is now generally accepted that leprosy control should be implemented into general health services, using the primary health care approach. The problem, as usual with the control of any major disease, is bridging the gap between words and action.

At the recent 13th International Leprosy Congress in The Hague, many words were spoken on virtually all aspects of leprosy but with notably few contributions on operational aspects, as opposed to laboratory-based research. Opinion is still divided not only on the total list of priorities in leprosy but also on their relative importance or ranking. Experts are bound to differ. Immunologists may emphasize the importance of the development of a vaccine and serological tests for susceptibility, subclinical infection, clinical disease and leprosy reactions—and few would question the need for continued support of such research. Clinicians may highlight diagnosis, classification, chemotherapy and management. Epidemiologists may call for the collection and detailed analysis of more data on incidence, prevalence, disability and relapse rates, while sociologists will underline the importance of remembering that there is much more to leprosy than a mere bacterial infection. Pharmacologists, whilst acknowledging the efficacy of the drugs actually available, may (with considerable justification) call for research on new compounds, and finally, microbiologists may return to the long-standing problem of achieving *in vitro* growth of the bacillus. Many of these claims are valid, but the resources are limited and a choice often has to be made between what needs to be resolved now and what could be developed, perhaps with great benefit, for use in the future.

The priorities are not easy to define and are even more difficult to place in order of importance. For the purpose of this paper we propose to discuss the subject under two headings—'Strategic' and 'Operational'—but recognizing that in reality they are interwoven.

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Strategic priorities

IMPLEMENTATION OF MDT

The Third Coordinating Meeting on Implementation of Multidrug Therapy in Leprosy Control, held recently in The Hague, recorded significant progress in leprosy control activities and the coverage of leprosy patients with MDT. Over the past few years some leprosy endemic countries have increased their budget for MDT leprosy control and substantial contributions have been made by members of the International Federation of Antileprosy Associations (ILEP) and the Japan Shipbuilding Industry Foundation (JSIF).

The number of registered cases in 1985 was 5·4 millions, a figure which represents an increase of 90% over that of 1966.[1] In 1987 the registered total was 5·1 millions, a reduction which has been related[7] to the drug treatment and release of large numbers of patients, thus supporting the efficiency of multiple drug therapy as recommended by WHO in 1982. From these figures, it can be seen that only about half of the estimated total are registered. About one third are receiving regular treatment. Although progress is indeed being made in the implementation of MDT, with recent indications of an upward trend in the graph, the fact is that a full 6 years after the publication of the WHO recommendations, the total number of patients who have so far received MDT is only just over 2 million (of whom over a quarter have completed treatment and are no longer considered to have the disease). Despite the efforts which are being made, often in the face of considerable odds, it is thus probable[3] that between 8 and 10 million patients with leprosy are not benefiting from a form of treatment which is available and manifestly effective. It is particularly worrying that in Africa with 600,000 registered patients only about 50,000 (8·2%) are on MDT. Nigeria, which harbours more than 160,000 registered patients has only 3·2% on MDT and other countries (Zaire and Uganda) have not yet introduced it.[7]

It is obvious that a priority of the utmost importance globally is the more rapid expansion of MDT, and that the achievement of such a task depends on the understanding and full commitment of national governments, non-governmental organizations and international contributing agencies, as well as effective coordination between them for the utilization of resources.

ACCEPTANCE OF *WHO-RECOMMENDED* MDT REGIMENS

Another important aspect of MDT centres on the global acceptance and implementation of WHO-recommended regimens for multibacillary (MB) and paucibacillary (PB) leprosy. In the late 1970s, mainly because of the increasing problems of dapsone resistance, various regimes of multiple drug therapy were proposed and applied quite widely. The Fifth Report of the WHO Expert Committee on Leprosy in 1977[8] strongly recommended further investigation into multiple drug regimens. However, in the following years, and even after the publication by WHO in 1982 of recommendations for the treatment of all cases with MDT, other regimens, or significant modifications of the WHO regimens, have been used. Whilst some of these appear to have been successful, none, to our knowledge, has been shown to be superior in terms of clinical and bacteriological cure, acceptability by patients and staff, toxicity, or relapse rates to those so clearly recommended by WHO in 1982. The use of multiple drug regimens other than those recommended by WHO significantly complicates the whole process of the training of staff, education of patients, drug ordering and dispensing. Unless definite advantages for *non*-WHO regimens can be established, there is surely a case for encouraging government and non-government agencies to use the WHO regimens whenever possible.

INTEGRATION

The policy of implementing MDT leprosy control as an integral part of the primary health care

system has received increasing acceptance in recent years. The rationale for this concept, elegantly reviewed by Feenstra and Tadele Tedla,[9] is that comprehensive and continuous leprosy services, with the widest possible availability, can be best delivered through a decentralized health care system. The strategy and method of procedure for integration have however not yet been well defined. Where leprosy endemicity is high and the development of health services inadequate to meet the demands of MDT control, a specialized national programme would be the rational approach. However the strategy of such programmes should, from the outset, be to progressively change from vertical to horizontal, i.e. from specialized to general health care, involving primary health care staff in leprosy control activities and preparing the general services to take full responsibility in future. On the other hand, integrated leprosy control services cannot function efficiently without the element of specialized technical support. There are striking examples of specialized, national leprosy control programmes (India), as well as integrated programmes (Indonesia).

Regrettably, there are already indications that in either of these situations the system is not working satisfactorily. One of us (GDG) recently visited seven countries in west and south-east Africa as part of a feasibility study on the teaching of leprosy[10] and this included discussion with people in ministries of health, leprosy control programmes and other relevant organizations. One of the disconcerting findings was that some programmes, although officially integrated and under ministry of health direction, in fact retain to a great extent the attitudes of 'vertical' control projects. This has the effect of isolating leprosy programmes from health care development in general and in many areas, the participation of medical and health staff at district level has been minimal and their training in leprosy non-existent. In some programmes, the coverage of patients for MDT, even after 6 years, was only 10–30%, case detection rates remained low and disability rates unacceptably high. The lesson to be learned is that the entire process of integrating leprosy control into general health services, whether *ab initio*, or from a previous specialized service, has to be planned in detail, including the creation of positive attitudes for close cooperation between non-government organizations and ministries of health.

TRAINING OF MEDICAL AND HEALTH STAFF

The importance of relevant, adequate and proper training of all medical and health staff in leprosy has been repeatedly stressed in a number of WHO and ILEP documents and re-emphasized during the 13th International Leprosy Congress. The methodology of task-orientated teaching of leprosy has been excellently described and abundant teaching and learning materials and aids, including slides, films and video recordings have been developed in recent years.[11] However, it is common knowledge that very little has been done to improve leprosy teaching in medical and paramedical schools. During the study for the promotion of leprosy teaching referred to above,[10] with a few notable exceptions, the findings were more disconcerting than might have been predicted. It has for many years been generally known (and for the most part not denied by schools in various parts of the world) that the teaching of medical and paramedical students about leprosy, and particularly leprosy control, is inadequate, and this was amply confirmed in the above study. In brief, it was found that there is an urgent need for the introduction of basic leprosy teaching into the curricula, as well as in continuing and distance education systems, not only for medical students (who have often been singled out), but for virtually all cadres of the health staff. A systematic approach and sustained efforts for relevant and adequate training in leprosy cannot be over emphasized, if integrated leprosy control, depending on the safe and effective implementation of MDT is to succeed. This experience from a continent in which only 8·2% of all registered cases have so far been treated with MDT[7] points to the subject of information distribution, teaching and training as one of the highest priority.

If this conclusion is correct and it is agreed that it calls for action, we may be facing a problem of considerable size and complexity, the implications of which have not yet been fully appreciated. The

educational and training effort has to be directed at literally hundreds of thousands of the health staff, including teachers. Has the master plan of action been outlined? Should it be pursued by WHO, ILEP, the World Federation for Medical Education,[12] the International Foundation for Dermatology[13] or perhaps in a special programme, supported by all of these agencies? Do the teaching modules exist? Are they available in English, French, Spanish and Portuguese? Where are the courses for training the teachers? Are tuberculosis and common tropical skin conditions to be taught at the same time? Is the money available? Despite the size of this challenge and its complexity and cost, it appears however, to be an almost over-riding priority which, if properly planned and executed, could be a valuable pattern for the teaching of the control of malaria, venereal disease, AIDS, tuberculosis and other major diseases. We hazard the opinion that any progress which can be made in leprosy control in the next 5–10 years will depend mainly on the extent to which the teaching and training of general health service staff in leprosy is turned from words into action. Is there in fact a viable alternative?

Operational research

The potential benefits of current scientific research, notably on possible vaccines and serological tests, have yet to be declared in terms which are of practical use in control programmes. It is difficult to avoid the comment that the amount of time, money and effort allocated, on an apparently increasing scale, to laboratory-based research in leprosy is perhaps somewhat out of control. At the recent 13th International Leprosy Congress in The Hague, an examination of the published Abstracts[14] shows that most of the contributions were on immunology, molecular biology or closely related topics; extremely few dealt directly with the operational aspects of leprosy and fewer still were of high quality. If this reflects the availability of funds and a positive selection of subjects for research, then surely the priorities should be revised to acknowledge the pressing needs of operational research in leprosy control and MDT implementation.

It has already been proven beyond any doubt that MDT is an effective tool for leprosy control. What is still not well known and remains controversial, is how best and most efficiently this tool can be used in the national leprosy control programmes. This will include all operational aspects of effective early case finding, prevention of disability, motivation of health workers, patient treatment compliance, family support, community awareness and participation and many others. The evaluation of present operational strategy and methods, and the testing of new technology are other important fields for research.

Relevant operational field-based research requires multidisciplinary involvement of epidemiologists, health economists, social anthropologist and those involved in management on a wide basis. This includes not only those working in specialized leprosy projects but the resources and potential of the universities and research institutions in endemic countries.[10] Encouragement of operational research and active recruitment of suitable professionals of various specialities and their adequate remuneration, together with at least medium-term career prospects, is essential. In this context, an important invitation has recently been published from the Office of the Special Programme for Research and Training in Tropical Diseases (TDR)[15] calling for applications from scientists with a capability in field research in leprosy. The main objective is to promote leprosy-related field research and the list of topics offered for consideration includes 'Operational studies aimed at measuring and improving the effectiveness of leprosy control programmes'.

OPERATIONAL PRIORITIES

Management

Although the importance of management in health care at both middle and other levels, has been

recognized in a number of publications, the messages have for the most part still to be translated into action. The word 'management' covers a lot (possibly too much), but if it is understood to include day-to-day administration and decison making; the teaching and supervision of junior staff; the ordering, receipt, storage, dispensing and use of drugs, or equipment; the collection of basic data and maintenance of records; monitoring, assessment and evaluation of health care activities, then it is almost impossible to overstate its importance. The finest plan of action for leprosy control and all the drugs in the world will be useless if the syringes do not fit the needles, inner tubes for the bicycles are 'unobtainable' and the junior staff are poorly taught, badly supervised and underpaid at irregular intervals. Within management and administration, the matter of logistic support in leprosy control calls for study equal in terms of financial backing and professional ability to that which is given to, for instance, immunology. Although it is easier to say this than to devise teaching or learning activities which will bring about the necessary changes in attitude and performance, it is our belief that significant improvement could be brought about by (a) analysing the day-to-day problems on the spot, at the scene of work (rather than in a 'training centre'), and (b) enlisting the cooperation of locally based, indigenous workers in the development of procedures or 'devices' which solve at least some of the problems. For example, has any good study ever been carried out to determine the *minimum* number of forms and monthly reports needed for good health care management at peripheral level?

Training of health staff at district level

This subject has already been referred to above in the context of strategic priorities, with emphasis on the need to improve training in leprosy for virtually all categories of health staff. For operational purposes there is new evidence to suggest that the main thrust should be at district hospital level, using continuing education and modules which are based on the real health needs in leprosy and other subjects, including primary health care.[10,16,17] As already stated, a wide range of health teaching–learning materials on leprosy, for both teachers and students are already available,[11] but this should be backed up, and eventually perhaps replaced by the production of similar material locally, using indigenous (not expatriate) expertise. It is also essential to ensure that staff see that their education is backed by constant logistic support, as described above, for the work they are expected to perform.

New strategies and technology

It is doubtful if the proposals above can be realized in the foreseeable future without the development of new, dynamic and flexible strategies.[18] Some of the old ones (for example, the relentless survey of vast numbers of people in populations where it is known that the prevalence is not more than 0·1%), are completely inappropriate if the main objective is the faster and wider implementation of MDT. Prominent amongst the outstanding needs is a way (or perhaps several ways) of making a rapid assessment of the leprosy situation in any given region or country and the recent WHO paper on this subject[19] is thus extremely welcome. In the opening paragraphs, Dr S K Noordeen, WHO Chief Medical Officer, Leprosy, draws attention to the difficulties of arriving at a figure for the estimated total of cases in the world and also to the fact that the current, cumbersome methodology, using expensive and difficult sample surveys, may have actually impeded the implementation of MDT, notably in Africa. Elsewhere in this important document, attention is drawn to the value of a systematic clinical and bacteriological examination of all registered cases at the outset of any MDT programme. In some parts of Africa, it was found '. . . that only one third of them required treatment with MDT: this results in a dramatic drop in the leprosy prevalence rate when the numerator is made of all cases eligible for treatment'.

As still in tuberculosis,[20] case-finding in leprosy remains a somewhat neglected subject; the methodology for achieving the diagnosis of a larger number of cases, either by self-presentation or

case-finding has not yet been adequately defined. Apart from the likelihood that integrated programmes, using the entire general health service, will result in the detection of larger numbers of cases,[9] the use of cured patients, as 'publicity agents' in the community calls for investigation. The potential role of the family in compliance to domicilary treatment, prevention of disability and the social and economic rehabilitation of patients calls for research.[21] New strategies are also needed to ensure that all patients have a constant supply of all the drugs needed, in adult and child doses, throughout their period of treatment. The use of blister calendar packs for this purpose has recently been described in some detail.[22–24] Despite the formidable range of teaching–learning materials which has been available for various grades of health staff working in leprosy for many years, suitably written and illustrated material for patients and their families still needs development. Patients are not fools; many of them are keenly interested in taking medication properly and being cured of their disease; literacy rates in many countries are surprisingly high. Using local expertise we should produce, pre-test, modify and finalize such material not only for treatment, but also for early case detection.[25]

Conclusion

This paper deals with one aspect of a complex disease, namely its control, with emphasis on field work and operational aspects. We have attempted to address the matter of priorities under the headings 'strategic' and 'operational', giving considerable emphasis to case detection and multiple drug therapy. But success will only be achieved if attention is given, persistently, to a package of activities aimed at control. Writing of tuberculosis, Fox recently commented: 'Short-course chemotherapy is not a panacea, although it offers major benefits for the service, the supervisory staff, the patients and the community. To make an impact many other deficiencies must be tackled successfully. . . . The challenge is largely to eliminate them all, leaving only the inevitable minor lapses, and to be able to detect and so rectify, even these.'[20]

We put the question before,[18] and repeat it here; why is it that so much money and effort is put into laboratory-based research, and so little into the study of the operational aspects of this disease, for which treatment is available and effective? Should we try harder to define and agree the priorities so that available manpower, money and effort are used to the greatest possible advantage?

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Evaluation of *Mycobacterium leprae* antigens in the serological monitoring of a clofazimine-based chemotherapeutic study of dapsone resistant lepromatous leprosy patients in Cebu, Philippines

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Summary Thirty-one dapsone resistant lepromatous leprosy patients receiving clofazimine based therapy were serologically monitored throughout their 5-year period of treatment. Sequentially collected sera were used to examine 4 *Mycobacterium leprae* antigens to evaluate their usefulness in ELISA's for monitoring the progress of their therapy. The ELISA results were compared with decline in bacterial load over the treatment period and with duration of treatment. In addition the ELISA's were compared with each other. The ELISA's based on the measurement of IgM antibodies to the two neoglycoproteins (NDO and NTO) representing the phenolic glycolipid antigen of *M. leprae* were found to be the most effective with regard to monitoring treatment. A whole *M. leprae* based ELISA was less efficient in monitoring treatment because it failed to measure antibodies in 5 out of 31 patients. The ELISA-inhibition test based on the detection of antibodies to a species-specific epitope on the 36 K antigen of *M. leprae* was less suitable because of persistent reactivity during therapy.

Introduction

The emergence of dapsone resistant *Mycobacterium leprae* has become an increasing concern in recent years.[1] As a result the World Health Organization has developed a multidrug therapy (MDT)

§Deceased 8 January 1988.

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protocol using a 3-drug regimen for lepromatous leprosy patients.[1] A difficulty in treating these patients is in monitoring the effectiveness of therapy. Currently, effective treatment is monitored by clinical evaluation and bacterial index. Both of these methods are liable to subjective interpetation. Serological monitoring could provide a needed additional quantitative test.

One of the components of MDT is clofazimine. Recently, at the Leonard Wood Memorial Research Center, Cebu, Philippines, we were given the opportunity to test sequentially collected sera from 31 patients harbouring dapsone resistant *M. leprae*. These patients received a clofazimine-based therapy regimen for a period of 5 years. The sera were collected sequentially over a 5-year period, permitting the monitoring of individual patients over the course of therapy.

In this article we describe the results of 4 serological tests measuring antibody reactivity to different *M. leprae* antigens throughout the course of a clofazimine-based treatment. Three tests measured IgM antibodies, 2 to neoglycoprotein antigens representing the phenolic glycolipid I of *M. leprae*, one of which was a disaccharide antigen (NDO-ELISA) and the other was a trisaccharide antigen (NTO-ELISA)[2–6]. A third antigen tested was whole irradiated *M. leprae* (MLEP-ELISA).[7] The fourth test (ELISA-INH) was based on the inhibition of monoclonal antibody binding by human sera to a species-specific epitope on the 36 K protein antigen of *M. leprae*.[8–10]

The test results were correlated with duration of treatment and bacterial index (BI). Furthermore the usefulness of the antigens represented by the 4 tests were analysed in relation to each other and in monitoring the clofazimine-based therapy of these lepromatous leprosy patients.

Methods

CASE DATA

Sera for this study were collected from patients with dapsone resistant *M. leprae* who participated in the Joint Chemotherapy Trial (JCT) conducted by Leonard Wood Memorial Center for Leprosy Research in Cebu, Philippines in collaboration with the Sasakawa Health Foundation, Tokyo, Japan. Sera of patients from 2 chemotherapeutic protocols ('IIa' and 'IIc') of the Joint Chemotherapy study were used. Regimen 'IIa' received clofazimine, 100 mg, 3 times a week for 5 years and rifampicin, 600 mg/day for 4 weeks. Regimen 'IIc' received clofazimine, 100 mg, 3 times a week for 5 years and rifampicin, 1·2 g once a month for 24 weeks (6 doses). Medication was administered under the supervision of a nurse. The patients were relapsed, previously treated lepromatous, with proven DDS resistant organism (by mouse footpad inoculation as described by Shepard),[11] free of any serious intercurrent disease and screened by chest X-ray to be free of tuberculosis on admission to the trial. A total of 32 patients were sequentially admitted and randomly allocated to either regimen 'IIa' or 'IIc'. A total of 16 patients, 13 males, ranging from 19 years to 47 years (average age, 35·5 years), and 3 females, ranging from 36 years to 44 years (average age 40·0 years), were admitted to the therapy group 'IIa'. All were clinically and histologically LL[12] with an average bacterial index of $4{\cdot}7 \pm 0{\cdot}7$. A total of 16 patients, 10 males, ranging from 18 years to 57 years (average age, 36·1 years) and 6 females, ranging from 12 years to 48 years (average age, 24·2 years), with an average bacterial index of $4{\cdot}2 \pm 0{\cdot}8$, were admitted to the therapy group 'IIc'. Three patients in group 'IIa' and 4 patients in group 'IIc', absconded during the course of the trial.

Preliminary evaluation did not show any significant differences between the 2 regimens in terms of clinical improvement and reduction in the average bacterial index in the smears. However, some reduction in the occurrence of moderate to severe ENL was noted among patients on "IIc' regimen.

SERA

The sera from each patient were collected on admission and sequentially every 12 months during the 5-year period of therapy.

INDIRECT ELISA

The ELISA used in this report was an indirect assay with a 0·05-ml suspension of antigen dried onto 'U' bottom microtitre plates. Antigen coated wells were blocked to prevent nonspecific binding by adding 0·075 ml of 5·0% goat serum or 5·0% BSA (bovine serum albumin) in phosphate buffered saline, pH 7·2 (PBS) and incubating overnight at 4°C or for 2 h at 37°C. Serum was diluted 1:500. An antihuman IgM conjugate was used with these antigens. None of the sera were found to exhibit non-specific binding to uncoated and BSA-coated plates. Positive and negative control sera were used on each plate to adjust for plate-to-plate and day-to-day variation. The remainder of the assay was carried out as previously described.[13–15]

INDIRECT ELISA ANTIGENS

Three antigens were tested: whole armadillo derived irradiated *M. leprae* and 2 neoglycoprotein antigens one of which mimics the 2 terminal sugars and the other mimicking the 3 terminal sugars of the phenolic glycolipid I (PG-1) of *M. leprae*.[6] These semi-synthetic antigens are: ND-O-BSA (natural disaccharide) with octyl linkage to bovine serum albumin; and NT-O-BSA (natural trisaccharide) with an octyl linker arm attached to BSA.[16] The octyl-linked neoglycoprotein antigens, ND-O-BSA and NT-O-BSA, and whole *M. leprae* were provided under NIH contract (NO1 AI-52582) by Dr P. Brennan, Colorado State University. The ELISA in which ND-O-BSA was used as antigen is referred to as NDO-ELISA, the ELISA with NT-O-BSA as NTO-ELISA and the ELISA with *M. leprae* as MLEP-ELISA.

INDIRECT ELISA ANTIGEN PREPARATION

Immulon II plates (Dynatech Laboratories, Alexandria, VA, 22314) were coated with antigen in a volatile buffer. The whole cells, *M. leprae* used as ELISA antigen, were suspended in a volatile coating buffer at a concentration of 0·04 absorbance units at 420 mn. The volatile coating buffer used was 0·01 M, ammonium acetate/carbonate, pH 8·2. The ND-O-BSA and NT-O-BSA were diluted from a concentrated solution of 100 μg/ml to 0·3 μg/ml and mixed thoroughly. Each of the 3 antigens was coated on microtitre plates by adding 0·05 ml of antigen suspension to each well. The plates were then incubated overnight at 37°C to dry the antigen onto the plate. Each well was examined for uniform coating and any unevenly coated wells were eliminated from use. The antigen coated plates could then be stored for several months at room temperature.[13]

ELISA INHIBITION TEST

Polystyrene ELISA microtitre plates (Dynatech, Alexandria, VA, USA) were coated with 100 μl per well of a soluble *M. leprae* preparation (0·5 μg/ml) in 0·05 M sodium bicarbonate buffer, pH 9·6, for 18 h at 37°C. The plates were washed 3 times with phosphate buffered saline (PBS), containing 0·05% Tween 20. Simultaneously to each well was added 20 μl of serum and 80 μl of peroxidase-labelled monoclonal antibody F47-9[9] diluted 1:1000 in PBS containing 0·1% Tween 20 and 0·6% BSA and the plates were incubated for 3 h at 37°C. Sera were tested in duplicate. After washing with PBS containing 0·05% Tween 20, wells were incubated with 100 μl TMB-substrate solution (12 mg of 3,3′, 5·5′-tetramethylbenzidine (TMB) in 5 ml of ethanol was added to 15 ml of 0·1 M citrate/phosphate buffer, pH 5·0; H_2O_2 was added to a final concentration of 0·015%). Reactions were stopped after 15 min by the addition of 50 μl 2 M H_2SO_4. Resulting absorbances were measured at 450 nm. Each test plate contained negative (OD = 1·5) and positive control sera on each plate to adjust for plate-to-plate and day-to-day variation. The percentage inhibition of the sera was calculated as [(1-OD/OD neg) × 100%].[9] The ELISA-inhibition test is referred to as ELISA-INH.

STATISTICAL ANALYSIS

As previously stated, preliminary evaluation did not detect significant differences in the 2 treatment regimens according to clinical improvement and reduction in average BIs; however, some reduction in the occurrence of moderate to severe ENL was noted in patients of the IIc regimen. Statistical analyses of MLEP-ELISA, NDO-ELISA, NTO-ELISA, INH-ELISA and BI values were not significantly different between the 2 treatment regimens. Because of these similarities between the 2 treatment groups, data were combined for analysis of test values and how these values changed over the duration of treatment.

Because of the long follow-up period all sera samples could not be obtained for all patients. Sera were collected on only 9 out of 31 cases for all collection periods; most had 1 serum sample missing at one of the collection periods. Consequently, matched analysis over the entire 5-year period was not possible for all 31 cases.

After preliminary evaluation of the data, it was apparent that the greatest declines in test values were during the first 3 years of treatment. For this period of treatment there were 17 cases for which sera were collected at all sample times, from 0 to 36 months of treatment, thus allowing for matched analysis of each of these cases throughout the first 3 years of treatment.

Whenever ELISA or BI values were compared for a time or between each other within a given time period, homogeneity of variance was first evaluated. If homogeneity of variance was fulfilled, then parametric matched analyses were performed, e.g. repeated measures analysis of variance (ANOVA) and paired *t* test. If homogeneity of variance was in question or if the data was in a form for which a nonparametric analysis was better, then a Kruskal–Wallis ANOVA[17] was used when comparing 3 or more variables and a Wilcoxon sign rank analysis[18] for paired values. Since median values for BIs are better central values at any given sample time, BI values also were evaluated by median analyses.

Both Pearson and Spearman correlation coefficients[19,20] were calculated between ELISA results and in combination with BI or INH results. Coefficients of determination (i.e. r^2) were calculated from linear regression analysis as: (regression sum of squares/total sum of squares) $\times$ 100%. These values were calculated to provide an indication of the amount of the total variation which could be explained by the regression of the two variables under consideration.

All probabilities presented in the results are two-tailed values.

To provide an overall evaluation of how the indirect ELISAs, the INH-ELISA and BIs changed over time, another set of calculations were prepared. Each initial value for an individual was scored as 100%. For subsequent samples test results were calculated as a percentage of the individual's original test value. These percentage values were then analysed independently by either a parametric or nonparametric ANOVA.

Results

ELISA AND BI VALUES DURING THERAPY

Overall mean ELISA and BI values for the 31 cases and the standard deviations at 1-year intervals during the course of treatment are presented in Table 1. Five patients who gave negative values in the MLEP-ELISA throughout the study period had high OD values in the NDO- and NTO-ELISA's. Four of these 5 patients had high inhibition values in ELISA-1NH. Sera from 3 patients which gave negative inhibition values throughout the study period had high OD values in the other 3 ELISA tests. One patient was negative in all 4 tests throughout the study period.

Since the greatest declines were observed during the first 3 years of treatment, all cases during this period from whom sera were collected at every sampling period were selected to allow for matched analysis of test values over time. Means and standard deviations for this group are

Table 1. Overall mean ELISA and BI values by treatment duration

Test	Therapy/months					
	0	12	24	36	48	60
NDO-ELISA	1·13* ±0·87 (31)	0·67 ±0·81 (26)	0·43 ±0·64 (26)	0·4 ±0·64 (28)	0·38 ±0·61 (24)	0·37 ±0·55 (19)
NTO-ELISA	1·08 ±0·76 (31)	0·67 ±0·8 (26)	0·47 ±0·66 (26)	0·46 ±0·69 (23)	0·32 ±0·46 (15)	0·29 ±0·31 (7)
MLEP-ELISA	0·73 ±0·7 (31)	0·42 ±0·51 (26)	0·3 ±0·38 (26)	0·15 ±0·15 (23)	0·12 ±0·12 (15)	0·08 ±0·05 (7)
INH-ELISA	43·27 ±29·31 (31)	26·86 ±27·59 (26)	26·09 ±26·53 (26)	20·62 ±23·89 (28)	19·7 ±25·84 (24)	23·97 ±23·7 (19)
BI	4·42 ±0·85 (31)	3·00 ±1·1 (26)	1·35 ±0·94 (26)	0·81 ±0·79 (27)	0·35 ±0·71 (23)	0·11 ±0·47 (18)

*Results are expressed as the mean value ± standard deviation. The number of samples tested is given in parentheses.

Table 2. Mean ELISA and BI values of cases matched over treatment duration

Test	Therapy (months)			
	0	12	24	36
NDO-ELISA	1·02 ± 0·96*	0·64 ± 0·81	0·49 ± 0·77	0·43 ± 0·8
NTO-ELISA	0·97 ± 0·77	0·64 ± 0·85	0·52 ± 0·79	0·45 ± 0·78
MLEP-ELISA	0·78 ± 0·73	0·36 ± 0·39	0·28 ± 0·44	0·17 ± 0·17
INH-ELISA	36·32 ± 32·06	25·61 ± 28·32	19·95 ± 26·22	19·81 ± 26·5
BI:				
Mean ± s	4·53 ± 0·72	3·06 ± 1·14	1·35 ± 0·86	0·82 ± 0·73
Median	5	3	1	1

$n = 17$.

*Values expressed as mean ± standard deviation, except for BI values where both mean and median values are provided.

presented in Table 2. Year-to-year decreases for each of these 17 cases could then be averaged according to mean declines in OD values for indirect ELISA values (Table 3) and mean declines in percent inhibition or BI values (Table 4).

As presented in Table 3, from 0 to 12 months of treatment, the average decline in OD values for NDO-ELISA was 0·384 units (p 0·001), for NTO-ELISA was 0·328 units (p 0·01), and for MLEP-ELISA was 0·424 units (p 0·01). For the next year (12–24 months of treatment), the average decline for NDO-ELISA was another 0·153 units (p 0·001) and for NTO-ELISA another 0·125 units (p 0·001); the average decline of 0·076 units for MLEP-ELISA was not significant. After 24 months of treatment, the year-to-year declines in any of the OD values were not significant.

Table 4 illustrates that for INH-ELISA the average year-to-year decline in percent inhibition for

Table 3. Average decreases of paired OD values by antigen and by duration of treatment

Treatment period (months)	ELISA OD value decreases by antigen		
	NDO	NTO	MLEP
0–12	−0·384‡	−0·328†	−0·424†
12–24	−0·153‡	−0·125‡	−0·076
24–36	−0·064	−0·064	−0·112

$n = 17$ (persons for which all measurements were taken for each of the above four sampling periods, i.e. 0, 12, 24 and 36 months of treatment).

*$p < 0{\cdot}05$; †$p < 0{\cdot}01$; ‡$p < 0{\cdot}001$; All others: no significant decrease in OD value.

Table 4. Decreases in INH-ELISA values and BI values by treatment duration

Treatment period (months)	INH-ELISA (% inhibition)§	BI††
0–12	10·71*	−1·47‡
12–24	−5·66*	−1·71‡
24–36	−0·14	−0·53*

$n = 17$.

* $p < 0{\cdot}05$; †$p < 0{\cdot}01$; ‡$p < 0{\cdot}001$.

§Average decreases were calculated from paired t test analysis; p values were similar whether calculated from both paired t test or Wilcoxon sign rank analyses.

††Average decreases in BI values were calculated using paired t analysis; p values represent both paired t results and Wilcoxon sign rank analysis. Results from median analysis similarly agree.

Table 5. Frequency of cases by BI and by treatment duration

Treatment duration	BI values						
(months)	6	5	4	3	2	1	0
0 ($n=31$)	1	16	10	3	1		
12 ($n=26$)		1	8	11	2	4	
24 ($n=26$)				2	11	7	6
36 ($n=27$)					6	10	11
48 ($n=23$)				1		5	17
60 ($n=18$)					1		17

For each treatment duration category one of the cells has been underscored. This cell represents the location of the median value for that category.

0–12 months of treatment was 10·71 (p 0·05), for 12–24 months of treatment was another 5·66 (p 0·05), and further declines after 24 months were not significant. BI values presented are average year-to-year declines of 1·47 BI during 0–12 months of treatment, another 1·71 BI during 12–24 months of treatment (p 0·001), and another 0·53 BI during 24–36 months of treatment (p 0·05). After 36 months of treatment year-to-year BI declines were no longer significant. Since BI values are actually ranks, median values also were analysed in year-to-year declines. The results of median analyses similarly compare to the parametric analyses presented in Table 4. Refer also to Table 5 for a frequency distribution of cases, by BI values, at each treatment duration sampling period.

CORRELATIONS BETWEEN TESTS AND BI

For any given treatment duration sample, both Pearson and Spearman correlation coefficients were calculated for indirect ELISA values, INH-ELISA values and BI values. Spearman probabilities were similar to Pearson values so Pearson values were used, allowing calculation of r^2 from linear regression analysis. These correlations are presented in Table 6. The OD values of the indirect ELISA's or INH-ELISA were not significantly correlated with BI values.

NDO-, NTO- and MLEP-ELISA values were significantly correlated with each other. NDO-ELISA and NTO-ELISA correlations were excellent, ranging from 0·963 to 0·998 (p0·001) with coefficients of determination (i.e. r2) ranging from about 92·7% to about 99·6%, respectively. MLEP-ELISA values were significantly correlated with either NDO-ELISA or NTO-ELISA, with correlations ranging from 0·631 (p 0·01) to 0·887 (p 0·001). These latter correlations, however, translate to r^2 values of 39·8% to 78·7%, respectively. This indicates that the agreement between

Table 6. Correlation coefficients by test and treatment duration

Months	NDO	NTO	MLP	INH	BI
NDO:					
0	—	0·963‡	0·631†	0·593*	−0·192
12	—	0·993‡	0·887‡	0·421	0·109
24	—	0·997‡	0·878‡	0·438	0·06
36	—	0·998‡	0·795‡	0·339	0·126
NTO:					
0		—	0·701†	0·569*	−0·163
12		—	0·881‡	0·392	0·104
24		—	0·855‡	0·397	0·033
36		—	0·789‡	0·325	0·11
MLP:					
0			—	0·396	−0·044
12			—	0·551*	0·357
24			—	0·654†	0·126
36			—	0·646†	0·309
INH:					
0				—	−0·379
12				—	0·147
24				—	−0·035
36				—	0·082
BI:					—

All probabilities are based on 15 df $p < 0·001$.
*$p < 0·05$; †$p < 0·01$; ‡$p < 0·001$.

Table 7. Mean paired differences in OD values at given treatment duration periods

	Treatment Duration (months)	Antigen NDO	NTO	MLEP
NDO:	0 (30 df)	—	0·045	0·391†
	12(25df)	—	0·002	0·246*
	24 (25df)	—	−0·041	0·132
	36 (16df)	—	−0·028	0·256
NTO:	0 (30df)			0·346†
	12 (25df)		—	0·244*
	24 (25df)		—	0·173*
	36 (16df)		—	0·284
MLP				—

*$p < 0{\cdot}05$; †$p < 0{\cdot}01$.

MLEP-ELISA with either NDO-ELISA or NTO-ELISA is not as high as the agreement between NDO-ELISA and NTO-ELISA.

At the initial sample (i.e. 0 months of treatment) NDO-ELISA and NTO-ELISA were significantly correlated with INH-ELISA ($r = 0{\cdot}593$, p 0·05; $r = 0{\cdot}569$, p 0·05, respectively). These translate to r^2 values of 35·2% and 32·4%, respectively. At subsequent sample periods INH-ELISA was not significantly correlated with either NDO-ELISA or NTO-ELISA.

MLEP-ELISA was significantly correlated with INH-ELISA at 12, 24 and 36 months of treatment ($r = 0{\cdot}551$, p 0·05; $r = 0{\cdot}654$, p 0·01; $r = 0{\cdot}646$, p 0·01, respectively). Coefficients of

Table 8. ELISA and BI percentage units over the course of treatment

Test	Therapy (months) 0	12	24	36	48	60
NDO-ELISA	100* (31)	52·8 ± 22·1† (26)	35·8 ± 20·7 (26)	31·6 ± 22·2 (28)	29·8 ± 18·2 (24)	28·5 ± 18·4 (19)
NTO-ELISA	100 (31)	54·0 ± 27·2† (26)	41·2 ± 22·2 (26)	37·6 ± 24·1 (23)	29·3 ± 20·9 (15)	NT‡
MLEP-ELISA	100 (31)	55·9 ± 34·9† (26)	41·8 ± 27·9 (26)	38·3 ± 35·5 (23)	27·3 ± 25·4 (15)	NT‡
ELISA-INH	100 (31)	57·2 ± 45·9† (26)	49·2 ± 32·7 (26)	40·0 ± 31·7 (28)	38·1 ± 35·4 (24)	48·8 ± 33·0 (19)
BI	100 (31)	69·3 ± 23·3† (26)	29·0 ± 19·4 (26)	18·0 ± 17·2 (28)	8·0 ± 16·9 (24)	2·2 ± 9·2 (19)

* The data from each assay were standardized by assigning the initial value at the start of therapy for each patient at 100%. The subsequent values for each patient over the course of treatment was calculated as a percentage of the initial values. Results are expressed as mean value ± standard deviation thereof. The number of samples tested is given in brackets.

† Mean values throughout the therapy period are significantly lower than the initial values at the start of therapy (Kruskal–Wallis test, $p < 0{\cdot}01$).

‡ Not tested.

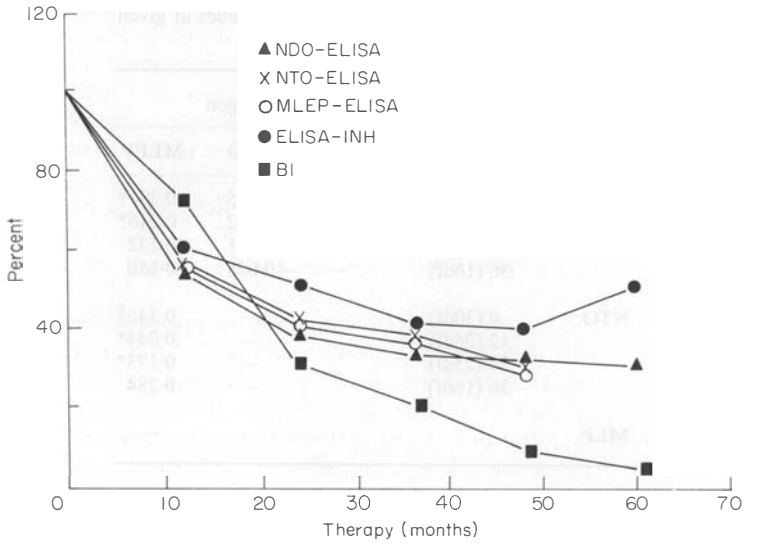

Figure 1. ELISA and BI declines over the course of clofazimine treatment in dapsone resistant lepromatous patients. Graphic representation of the mean values presented in Table 8.

determination were about 30·3%, 42·8% and 41·7%, respectively, thus indicating relatively poor agreement between MLEP-ELISA and INH-ELISA values.

Paired *t* test analysis was applied to the indirect ELISA values to determine if there were significant differences in OD values depending upon whether NDO, NTO or whole *M. leprae* (MLEP) were used (Table 7). As presented in Table 7 no significant differences were detected in OD values between NDO-ELISA or NTO-ELISA. Both NDO-ELISA and NTO-ELISA, however, provided consistently higher OD values than did MLEP.

ELISA AND BI VALUES BY PERCENTAGE OF ORIGINAL VALUES

The data from each assay were standardized by assigning the initial value (i.e. at the start of treatment) for each patient as 100%. The subsequent values for each patient over the course of treatment were calculated as a percentage of the initial values. The averages and standard deviations of these percentages are presented in Table 8 and Figure 1. All 3 indirect ELISAs showed a decline to approximately 30% of the initial values after 4–5 years of therapy. The INH-ELISA showed a much slower decline to 40–50% of the initial values after 4–5 years of therapy. The BI values showed a sharp decline to 30% of starting values after 2 years of therapy.

Discussion

Our results indicate a marked decline in ELISA reactivity over the duration of clofazimine-based treatment which parallel the decline in BI. All patients were proven dapsone resistant lepromatous cases by mouse footpad inoculations[11] and received 2 different chemotherapeutic protocols, which differed only in the duration of rifampicin administration at the beginning of the therapy period (JCTII-A for 4 weeks and JCTII-C for 24 weeks); thereafter, clofazimine monotherapy was given for at least 4·5 years until the end of the 5-year therapy period. Clinical and serological evaluation did not indicate any significant differences between the 2 treatment regimens (JCTII-A and JCTII-C). The data, therefore, were combined from patients of 2 therapy regimens.

The ELISA's measuring IgM antibodies to the NDO, NTO and whole *M. leprae* antigens showed a significant paired decline in OD values over treatment duration, particularly during the 0–12 month treatment period. During this first year of treatment the average paired declines in OD units for NDO-ELISA was 0·384 units (p 0·001), for NTO-ELISA was 0·328 units (p 0·001), and for MLEP-ELISA was 0·424 units (p 0·01). The decline in antibody levels to phenolic glycolipid I is not surprising, since the antigen itself, when detected, disappears more rapidly from the circulation as a consequence of effective treatment.[29] The rapid disappearance of the antigen is most likely due to its low molecular weight and its solubility in body fluids. Using different antigens, ELISA conjugates and therapy protocols, we and others have noted declines of antibody levels during treatment.[21–26,31] However, here we report the monitoring of dapsone-resistant patients during their secondary course of dapsone-free therapy.

Sequential sera of 5 patients were negative throughout the therapy period using MLEP-ELISA. These patients' sera, however, were positive by NDO- and NTO-ELISAs. The antigens used in these latter ELISAs represent the sugar epitope of the phenolic glycolipid of *M. leprae*, indicating that the MLEP-ELISA does not detect antibody reactivity to this phenolic glycolipid. Given the excellent correlation between NDO-ELISA and NTO-ELISA OD values and the fact that there is no significant difference in these values, it appears that either NDO or NTO can be used and either would provide similar OD results. Although the correlations between NDO-ELISA or NTO-ELISA with MLEP-ELISA are significant, the r^2 values are not particularly high. This, combined with the fact that either NDO-ELISA or NTO-ELISA provide significantly higher OD values than MLEP-ELISA and that MLEP-ELISA did not detect 5 cases, indicates that using either NDO or NTO provides better results.

Although all of the indirect ELISA values, the INH-ELISA and the BIs declined significantly over the duration of the treatment period, none of the indirect ELISA values nor the INH-ELISA were significantly correlated with BI values. This, therefore, indicates poor agreement between ELISA values and BI. One explanation could be that whereas BI reflects bacterial load at individual sites, the ELISA could be interpreted as a reflection of systemic bacillary load. Another explanation could be the subjective determination of the BI, such as the selection of sites and interpretation of observations.[30] This is in contrast to the quantitative, objective findings by ELISA. This suggests that the phenolic glycolipid I based ELISA's using synthetic antigens may be a better method for monitoring patients progress during chemotherapy.

In comparing the correlations between the indirect ELISA's the NDO-ELISA and NTO-ELISA showed excellent correlations (Table 6). This high correlation is not surprising, since the antigens used in these ELISA's mimic phenolic glycolipid I's terminal oligosaccharide, differing only in the third sugar. These results are in agreement with previously published data.[6] A lower correlation was found when these antigens were compared to whole *M. leprae*. This was not unexpected since 5 patients did not show any detectable reactivity in the MLEP-ELISA but did with NDO-ELISA and NTO-ELISA and since MLEP-ELISA consistently provided lower OD values than NDO-ELISA or NTO-ELISA.

Year-to-year paired comparisons of INH-ELISA values showed a significant average decline of 10·71 units (p 0·05) during the first year of treatment and another 5·66 units (p 0·05) during the second year of treatment. Thereafter, the year-to-year declines in INH-ELISA values were not significant. As previously stated, INH-ELISA values were not significantly correlated with BI values. This is in accordance with the finding that 'burned-out' lepromatous and tuberculoid patients frequently have high ELISA-INH values (P. Klatser, unpublished data). Some patients (7 out of 19), however, do decline to negative reactivity, comparable to the values found with uninfected controls and tuberculosis patients.[28] Similar findings have been reported measuring the persistence of antibodies to the lipoarabinomannan antigen during and up to 10 years of treatment of lepromatous patients.[6,27] The reasons for and implications of the persistence of antibody production to the 36 K antigen of *M. leprae* are not clear.

For the monitoring of chemotherapy of lepromatous leprosy patients of the indirect ELISA's

investigated, NDO-ELISA or NTO-ELISA were found to be the most effective with respect to duration of treatment. It is possible that in some cases the NDO- or NTO-ELISA reactivity may be more accurate reflections of bacterial load. The ELISA-INH is less suitable for monitoring patients on chemotherapy because of persistent reactivity throughout the therapy period. Whether these persistent INH-ELISA reactivities play any role as to relapses requires further investigation.

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A comparison of sensory loss tests and histopathology in the diagnosis of leprosy

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Summary Three different sensory loss tests, for anaesthesia to light touch, for diminished pain sensation and for loss of thermosensation, were compared with histopathological examination results in the diagnosis of suspected tuberculoid leprosy in 120 individuals with 126 lesions. Though none of the 3 tests used in this study was found to be strikingly superior to any of the others, the results indicate potentially important differences in their usefulness in different subgroups of suspected patients. The methodological problems inherent in such studies are discussed.

Introduction

Different forms of peripheral sensory loss are well recognized consequences of infection with *Mycobacterium leprae*. Anaesthesia is generally cited as one of the cardinal signs of leprosy, and its assessment—in particular anaesthesia to light touch—is part of the routine clinical examination for the disease. In addition some workers have recommended the use of tests for diminished pain sensation and for loss of thermal sensation in the diagnosis of leprosy.[2,3]

Testing for sensory loss is often difficult, in particular under field conditions. The individuals being tested must both understand and co-operate in the procedure. If the sensory loss is not extensive, considerable time, patience and scepticism may be required of the tester. Given the importance and difficulty of such tests in leprosy work, it is of interest to assess their usefulness in practice. In particular we wish to know their validity in terms of sensitivity (the proportion of 'true' leprosy lesions which are correctly identified as showing sensory loss), specificity (the proportion of lesions not due to *M. leprae* which do not show sensory loss), and their repeatability in the hands of different workers.

There is little literature assessing these tests. The only relevant publication known to us is a study comparing the repeatability of 4 different sensory loss (light touch, static 2-point discrimination, tuning fork and pinprick tests) and voluntary muscle tests in a group of 20 tuberculoid leprosy patients with established nerve lesions.[4] The author suggested that the light touch test was more sensitive than the other 3 sensory loss tests. She reported no significant difference between sensory tests performed by the same observer at intervals of 2 weeks. No values for the sensitivity of the sensory tests were given.

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This lack of literature on this subject is attributable in part to a problem which confronts all studies of diagnostic tools in leprosy—the absence of an appropriate reference test. The sensitivity and specificity of any diagnostic tool should in theory be calculated with reference to a series of individuals whose true diagnostic status is known with reasonable certainty on the basis of some alternative diagnostic tests.[5] Such reference information is difficult to obtain in leprosy, in particular for those 'early' paucibacillary lesions for which the field diagnosis is difficult and for which improvements in diagnostic methods are most needed.

Recognition of the problems of sensory loss testing has led to interest in a portable thermal sensation tester (Speyside Electronics, St Aethans, Burghead, Moray, UK). Such a device might prove useful in leprosy diagnosis for two reasons. First, it can provide a fixed standarized stimulus. Second, in so far as thermal and pain sensations are dependent upon non-myelinated fibres, whereas touch sensations are dependent largely upon myelinated fibres, the ability to discriminate temperature might be lost before the touch sensation is impaired.[6]

This paper reports findings in assessing standard measures of anaesthesia to light touch, of diminished pain sensation and of diminished thermal sensation in the diagnosis of leprosy in the LEPRA Evaluation Project in Northern Malaŵi.

Methods

Three different sensory losses were applied to 120 individuals identified by paramedical workers as leprosy suspects in the course of a total population survey in Karonga District, Northern Malaŵi.[7] All 120 individuals were suspected to have paucibacillary leprosy, usually with unknown time of onset and presumably in an early stage of the evolution of tuberculoid disease. Only 1 individual already had typical peripheral nerve damage of very recent onset, but 6 individuals were suspected relapses (or re-infections?) as they had received antileprosy treatment before. The 120 individuals do not represent a selected group but were found consecutively during the population survey. The following 3 tests for sensory loss were carried out by the medical officer (JMP):

1 Loss of appreciation of light touch: The individuals were shown cotton wool which was rolled to a point, and the threshhold was tested at which they could just still feel the wool's touch on normal skin in the vicinity of the lesion and in particular on normal skin in an area on the body opposite to the suspected lesion. After the test had been explained, the individual's eyes were shielded so that he or she could not see the examiner's hand. Care was always taken to compare the lesion with an area of similar basic sensitivity to light touch.[8] After repeatedly touching the suspected lesion and comparable normal skin it was concluded that there was anaesthesia to light touch if the individuals always noticed the touch and pointed to it on the normal skin but repeatedly missed touches on the lesion. Misreference, a failure to indicate the exact location touched by the cotton wool, was not interpreted as a sign of anaesthesia to light touch.

2 Loss of thermosensation: The hand-held penlight battery-powered device,[9] which has a 'cold' (=environmental temperature) end and a 'hot' (=40°C) end, was demonstrated on normal skin until it was clear that the individual understood the procedure. Early in the investigation it was recognized that the thermosensation test had to be carried out in the shade. Otherwise the 'cold' end would get just as warm as the 'hot' end and it became impossible to discriminate between the two. Loss of thermosensation was recorded as present if individuals could not discriminate between hot and cold within the lesions but did so on normal skin in the vicinity of the lesion and on normal skin in an area on the opposite part of the body.

3 Diminished pain sensation: This was tested by pricking lightly with the sharp end of a 26-gauge needle. It involved explanation of the concept of 'more' and 'less' painful, a concept which is very difficult to translate into the local languages (Kyangonde and Chitumbuka, e.g. a 'faster' runner has to be translated as 'the first to arrive'). On a few occasions it was not possible to perform this test

despite patient efforts by the paramedical worker (Leprosy Control Assistant) to explain it. Once understood, pain sensation was compared by pricking the lesion and normal skin in random order. A marked reduction of pain sensation was sometimes indicated by the absence of a withdrawal reflex. However, in recording results, such visible evidence was not distinguished from diminished pain sensation according to the individual's answers as to whether there was 'less' pain sensation in the lesion.

All tests were performed with the suspects closing their eyes or having eyes shielded with a pad of paper. Suspects and observer were always seated during the testing unless the site of the lesion(s) made that impractical. In general the test for diminished pain sensation was performed last because it was the most unpleasant and difficult to understand of the three.

The results of all 3 tests were recorded as: Y, Yes, loss of . . .; N. No, loss of . . .; D, doubtful loss of . . .; and U/T, procedure not understood or technically unsatisfactory.

After performing these tests 1 or more 4-mm punch biopsies were taken under local anaesthesia and processed as described elsewhere.[10] The size and site[11] of each lesion which was tested and from which a biopsy was taken were entered into an examination form (LEP Detailed Examination Form).[7] The histopathologist was not aware of this study while it was in progress and the biopsy specimens were thus processed and examined in the routine fashion established for the LEP as described elsewhere.[10]

For the purpose of this study the histopathology results are taken as the reference diagnosis against which the sensitivity and specificity of the sensory testing are measured. We are aware that this method is not entirely satisfactory in so far as the histopathological diagnosis cannot be assumed to be invariably correct.[12] On the other hand, the histopathological results may reasonably be considered more accurate than sensory testing results, in particular if the result of only 1 test is compared with the histopathology result. The methodology becomes more questionable if the results of 2 or 3 tests contrast with the histopathology result. We shall discuss this issue further after presenting our data.

Biopsy results were graded as follows: 1a, 'leprosy confirmed beyond reasonable doubt'; 2b, 'pathological and possibly due to leprosy but lacking specific diagnostic criteria'; and 3a, 3b or 4, no evidence of leprosy (3a, 'definitely pathological but completely nonspecific'; 3b, 'normal or near normal tissue'; and 4, 'pathological but indicative of a specific disease other than leprosy').[10,12]

Results

During the course of this study a total of 126 lesions were tested and biopsied in 120 individuals with suspected tuberculoid leprosy. The results of testing for anaesthesia to light touch are shown in Table 1. All individuals understood the procedure and there were no technically unsatisfactory results. The results were considered doubtful in 5 lesions.

The sensitivity of testing for anaesthesia to light touch is calculated as the percentage of histopathologically confirmed tuberculoid leprosy lesions (biopsy grading 1a) which were found to be anaesthetic. These were 32 out of 66, and thus the sensitivity of testing for anaesthesia to light touch in this series was 48·5%. The relative specificity of testing for anaesthesia to light touch is calculated as the percentage of 'lesions considered not due to leprosy' (biopsy grading 3a–4) in which no anaesthesia to light touch was found on single testing (at the time of taking the biopsy). There were 18 out of 25, giving a relative specificity of testing for anaesthesia to light touch in this series of 72%.

Table 1 also shows the results of testing for loss of thermosensation. Data on only 125 lesions are included, as one result was lost. The sensitivity of testing for loss of thermosensation can be calculated as 49·2% (32/65). The relative specificity of the test in this series is 68% (17/25).

Table 1 further shows the results of testing for diminished pain sensation. Results are available for only 100 lesions because this test was added to the protocol only after the first 26 lesions had been

Table 1. Anaesthesia to light touch, loss of thermosensation and diminished pain sensation test results in 120 individuals with suspected tuberculoid leprosy. Sensory loss results are recorded as Y (yes), N (no), D (doubtful) or U/T (not understood or technically unsatisfactory)

Biopsy results	Y	N	D	U/T	Total number of lesions	χ^2 value excluding D and U/T results
Anaesthesia to light touch						
Leprosy certain	32	31	3	0	66	
Possibly leprosy	13	21	1	0	35	
No evidence of leprosy	6	18	1	0	25	
Total	51	70	5	0	126	4·98 ($p > 0·05$) NS
Loss of thermosensation						
Leprosy certain	32	26	0	7	65	
Possibly leprosy	10	24	1	0	35	
No evidence of leprosy	6	17	1	1	25	
Total	48	67	2	8	125	8·76 ($p < 0·05$)
Diminished pain sensation						
Leprosy certain	30	11	1	9	51	
Possibly leprosy	8	16	0	1	25	
No evidence of leprosy	7	12	1	4	24	
Total	45	39	2	14	100	12·47 ($p < 0·01$)

tested for loss of appreciation of light touch and loss of thermosensation. The sensitivity and relative specificity of testing for diminished pain sensation were 58·8% and 50% respectively. The test was considered technically unsatisfactory or was not understood for 14 individuals.

The association between sensory tests giving a result of Y or N and biopsy result were analysed using a χ^2 test (2 degrees of freedom).[13] The χ^2 and p values are shown in Table 1. This analysis reveals no statistically significant association between anaesthesia to light touch and biopsy result, some association between loss of thermosensation and biopsy status, and a highly significant association between diminished pain sensation and biopsy result.

The results are subdivided by age (< 25 versus $=$ or > 25 years), sex and lesion site (face versus rest of body) in Table 2. The most interesting finding in this analysis is that both the sensitivity and the relative specificity of all 3 tests were higher in individuals less than 25 years of age than in older individuals. Though they are consistent for all 3 tests, these differences in sensitivities and relative specificities between young and older individuals cannot be considered independent, and thus they fail to reach statistical significance at the 5% level.

In addition, it appears that for lesions on the 'rest of the body' the sensitivity and relative specificity may be slightly higher by testing for anaesthesia to light touch than by the other 2 tests.

For males testing for anaesthesia to light touch appeared slightly preferable while in females testing for loss of thermosensation seems the superior test. However neither of these differences is statistically significant.

Thus far the analysis has addressed the question whether any of the 3 tests had an advantage over the others. A further question is how useful it is for the clinician to use more than 1 test in order to arrive at a diagnosis in suspected tuberculoid lesions. To answer this we have analysed the results

Table 2. Sensitivity and relative specificity of testing for anaesthesia to light touch, loss of thermosensation and diminished pain sensation by subgroup. The actual numbers of lesions are given in brackets.

Subgroup	Sensitivity	Relative specificity
	Anaesthesia to light touch	
< 25 years of age	59·1% (13/22)	90·1% (10/11)
= or > 25 years of age	43·2% (19/44)	57·1% (8/14)
Face	15·4% (2/13)	100% (8/8)
Rest of the body	61·2% (30/49)	66·7% (10/15)
Males	58·3% (14/24)	80% (12/15)
Females	46·2% (18/39)	66·7% (6/9)
Total	48·5% (32/66)	72% (18/25)
	Loss of thermosensation	
< 25 years of age	59·1% (13/22)	90·1% (10/11)
= or > 25 years of age	44·2% (19/43)	50% (7/14)
Face	46·2% (6/13)	87·5% (7/8)
Rest of the body	50·1% (26/51)	56·2% (9/16)
Males	41·7% (10/24)	66·7% (10/15)
Females	53·7% (22/41)	70% (7/10)
Total	49·2% (32/65)	68% (17/25)
	Diminished pain sensation	
< 25 years of age	72·2% (13/18)	60% (6/10)
= or > 25 years of age	51·6% (17/33)	42·9% (6/14)
Face	80% (8/10)	42·9% (3/7)
Rest of the body	55% (22/40)	56·2% (9/16)
Males	72·2% (13/18)	50% (7/14)
Females	51·6% (17/33)	50% (5/10)
Total	58·8% (30/51)	50% (12/24)

Table 3. Sensory test results for 75 lesions in which all results were either Y, 'loss of . . .' or No, 'no loss of . . .' (excluding all lesions in which any sensory test result was U/T or D).

Test	Result				Result				Total
Anaesthesia to light touch	Yes				No				
Loss of thermosensation	Yes		No		Yes		No		
Diminished pain sensation	Yes	No	Yes	No	Yes	No	Yes	No	
Biopsy result									
Leprosy certain	8	1	5	3	9	2	4	3	35
Possibly leprosy	1	1	5	3	2	2	0	9	23
No evidence of leprosy	2	1	1	0	0	1	3	9	17
Total	11	3	11	6	11	5	7	21	75

Table 4. Sensitivity and relative specificity results for 17 individuals with at least one lesions in whom all three sensory test results were either 'Y' or 'N'

Number of tests indicating a sensory loss	Sensitivity	Relative specificity
3	22·2% (8/35)	88·2% (15/17)
At least 2	65·7% (23/35)	76·4% (13/17)
At least 1	91·4% (32/35)	52·9% (9/17)

in those individuals who understood all 3 tests and in whom there were no technically unsatisfactory or doubtful results. The test results of 75 lesions are included (Table 3). Two points deserve note in Table 3: (a), in 3 (14%) out of 21 individuals who showed no evidence of sensory loss by any of the 3 tests the histopathologist found definite evidence of leprosy. In 2 of these 3 individuals the biopsy was taken from the face; and (b), in 2 (18%) out of 11 individuals in whom the clinician found evidence of sensory loss with all 3 tests the histopathologist found no evidence of leprosy. While it would seem possible that the clinician was deceived, or deceived himself, in these two instances, they may represent false negative biopsy results. Since both individuals were started on antileprosy treatment because of the clinical findings, the question can not be resolved by repeat examination or biopsies.

The sensitivity and relative specificity of at least 1 recorded loss, of at least 2 recorded losses and of all 3 tests showing loss of appreciation of light touch, loss of thermosensation and diminished pain sensation respectively are presented in Table 4. This reveals how requiring progressively more stringent criteria decreases the sensitivity but increases the specificity of the diagnostic procedure.

Discussion

Ideally, to examine the validity of a test, one needs to compare its results with those of a test which is both 100% sensitive and 100% specific. However, no such test is available in 'early' paucibacillary leprosy. The clinical certainty scale we developed includes anaesthesia to light touch as one of the findings to be considered and is therefore not suitable for reference purposes.[14] We have therefore used histopathology as the reference criterion in this study. Though the true sensitivity of the histopathological diagnoses is unknown, we may reasonably assume that there were fewer false positive than false negative biopsies. This means that the sensitivity measures calculated in this study, which were based upon the histopathologically confirmed cases, are likely to be more accurate than are the specificity measures (given that we expect some 'true' leprosy cases to have escaped biopsy confirmation). For this reason we have used the phrase 'relative specificity' throughout this paper, to emphasize that the several tests are being measured with reference to biopsy information.

For an ideal study lesions should have been included in the study which were definitely not due to leprosy. However, no such lesions were available for both sensory testing and biopsy. Indeed, such a study would be difficult to arrange in so far as the clinician would be influenced by his perception of the lesion and his knowledge that sensory loss is associated with very few lesions except those due to leprosy.

The histopathologist was blind as far as the diminished pain sensation and thermosensation testing results were concerned, but information on the anaesthesia to light touch was occasionally communicated to him as part of the routine description of the lesions (which also usually contained a reference to the age and sex of the suspect and the site from which the biopsy was taken).[10] There is

however no evidence that the histopathologist was appreciably influenced by the clinical notes in assigning his biopsy certainty grade.[12] The clinician did not know the biopsy results at the time of performing the sensory tests. On the other hand, the clinician was aware of the previous test's result when performing the second and third tests. This could have influenced him slightly, when in doubt. The only way to avoid this potential bias would be either to randomize the order of testing in different suspects or else to have each test performed independently by different clinicians.

In spite of these shortcomings in the design of this study we conclude that an observed sensory loss of some kind has to be treated with considerable caution in the diagnosis of 'early' tuberculoid leprosy.

The sensitivity and relative specificity of each of the tests as used in this study was approximately 60%. None was found to be strikingly superior to any of the others. One might argue that the results indicate that testing anaesthesia to light touch is the least reliable of the three, since the association with the histopathological results is weakest for this test (Table 1). However, this is due to the fact that the χ^2 test results are based on positive and negative results only, and exclude doubtful and technically unsatisfactory results. As the percentage of such results was highest for diminished pain sensation testing, the sensitivity and specificity figures are better indicators of the tests' overall usefulness than are the χ^2 values.

In theory, the application of multiple tests can raise the sensitivity of the procedure. More than 91% of the histopathologically confirmed lesions showed sensory loss with at least one of the tests (Table 4). On the other hand, such a multiple test criterion was associated with a fall in relative specificity to only 53%. We have discussed the relative importance of sensitivity and specificity in leprosy diagnoses in another publication.[15]

The tests may differ in their usefulness between certain subgroups. In particular, all 3 tests appeared to be more valid in younger than in older individuals (Table 2). One important consequence of such a result is that whenever the sensitivity and specificity of sensory tests are compared, for example between different investigators or centres, the results should be related to the age of the individuals tested.

While the results of this study indicate potentially important differences in the usefulness of the test in different subgroups, a large investigation and more detailed analysis will be required to confirm these findings. We thus plan to expand this investigation in the future. In the short term we believe these preliminary results will be of interest to leprologists grappling with the difficult problem of diagnosing 'early' tuberculoid leprosy in the field.

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The role of nerve biopsies in the diagnosis and management of leprosy

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Summary Skin and nerve biopsies from 81 patients clinically suspected to have leprosy were studied. Histologically 54% of the patients showed leprosy. Both nerve and skin biopsies were histologically diagnostic of leprosy in 64% of these cases while 32% were diagnostic in the nerve but not skin biopsy. In the 11 patients with multibacillary leprosy (BI ≥ 2) a multibacillary picture was seen in all nerve biopsies while 8 patients exhibited a paucibacillary leprosy of the skin and a multibacillary leprosy in the nerve. The present results emphasize that leprosy is a disease of peripheral nerves and that diagnostic criteria other than skin parameters is important to reach a proper diagnosis. The evident possibility of having patients with a multibacillary leprosy in peripheral nerves and paucibacillary in skin emphasize the need of clinical studies to clarify the criteria for the diagnosis of paucibacillary leprosy and the drug regimen for this group of patients.

Introduction

Leprosy of peripheral nerves is the most common cause of peripheral neuropathy world wide.[5] Although lesions in nerves and other tissues have been known since the earliest writings on this disease, it is the external, visible cutaneous lesions which have held the interest of the leprologists.[6] Histological examinations for diagnostic purposes have mainly been performed on skin. The nerve damages, however, may start before, during or after leprosy treatment and are often associated with reactional episodes, namely reversal reaction and erythema nodosum leprosy.[4,10] Clinical assessment of the nerves to identify the normal variations as well as the pathology of the nerves requires a lot of practical experience and may not yet be sufficient to document the status of nerve involvement.[7] Although the main criteria for diagnosis of leprosy are related to skin parameters, leprosy is primarily a disease of peripheral nerves.[9] Three studies have shown discrepancies in histopathological findings including the bacterial load between different tissues in leprosy patients.[3,12,13] Antia & Pandya have found a higher load of bacteria in biopsies from the peripheral nerves than from skin and lymph nodes.[3]

This study was undertaken to compare the histopathological results of the nerve biopsies with a classification based on a parallel skin biopsy. Emphasis was put on the role of nerve biopsies in detection of patients with multibacillary leprosy.

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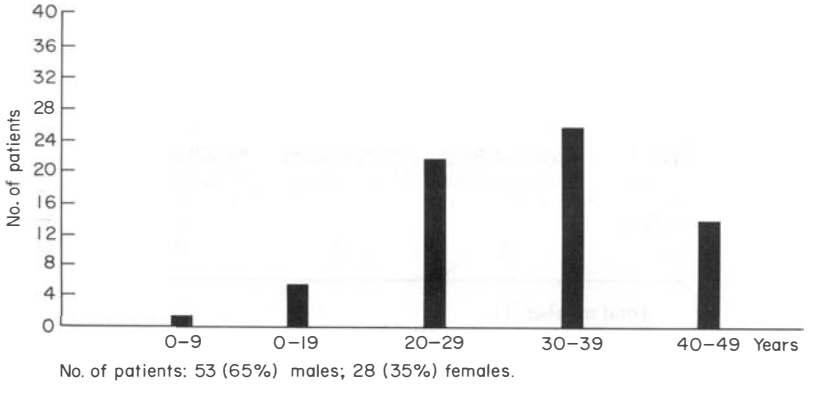

Figure 1. Age and sex distribution of patients for nerve biopsies.

Material and methods

In 1985, 237 leprosy patients were referred for nerve biopsies at All African Leprosy and Training Rehabilitation Centre, ALERT, Addis Ababa, Ethiopia. In 81 of these cases a parallel skin and nerve biopsy was obtained. The age and sex distribution are shown in Figure 1.

Nerve biopsies were mainly taken from the radial cutaneous nerve ($n=66$), but also from the sural ($n=11$), peroneal ($n=3$) and ulnar ($n=1$) nerves. Biopsies were made under local anaesthesia. Skin punch biopsies were taken from the skin lesions and not from skin overlying the nerve biopsy site. Nerve biopsies were taken from the same areas in all patients. Parts of the biopsies were taken from clinically thickened nerves, while the rest were taken from clinically normal nerves. The specimens were immediately fixed in 4% buffered formaldehyde or FMA fixative, dehydrated and embedded in paraffin by routine methods.[11] Sections, 4-μm thick, were cut, processed and stained with a modified Fite stain and the TRIFF stain both suitable for the demonstration of acid-fast bacilli.[11]

Skin biopsies were classified histopathologically according to the Ridley–Jopling and Ackerman classifications for dermatitis.[1,9,11] In addition, the respective bacterial index (BI) was recorded. Nerve biopsies with a $BI \geq 2$ were classified as multibacillary (MB), biopsies with a $BI \leq 1$ as paucibacillary (PB) leprosy.

The tentative clinical diagnosis obtained was extracted from the biopsy request form and the clinical cards at the hospital.

Table 1 Diagnosis of leprosy in parallel skin and nerve biopsies

	Combinations of skin and nerve histology		
Skin	+	−	−
Nerve	+	+	−
Number	28	14	2
%	63·6	31·8	4·5

Total number: 44.
+, histologically diagnostic for leprosy.
−, not histologically diagnostic for leprosy.

Table 2 Multibacillary leprosy: comparison of skin and nerve biopsies

Combinations of nerve and skin			
Skin Nerve	Paucibacillary Multibacillary	Multibacillary Multibacillary	Multibacillary Paucibacillary
Number	8	3	0
%	73	27	0

Total number: 11.
Paucibacillary means a BI ≤ 2.
Multibacillary means a BI ≥ 2.

Results

In 44 (55%) of the 81 patients studied a histological diagnosis of leprosy was given (Table 1). Twenty-eight (64%) of these patients demonstrated skin and nerve biopsies diagnostic of leprosy, while 14 of the 44 patients (32%) had histologically diagnostic leprosy in the peripheral nerve biopsy without corresponding positive skin biopsy (Table 1). In 2 patients a diagnostic skin biopsy and a non-diagnostic nerve biopsy were found.

In 11 (25%) of the patients with histologically diagnostic leprosy of multibacillary leprosy (BI ≥ 2) was found in either nerve or skin (Table 2). Eight (73%) of these 11 multibacillary patients revealed multibacillary leprosy in the nerve biopsy and paucibacillary leprosy in the skin biopsy while 3 showed multibacillary leprosy in both skin and nerve biopsies.

In 37 (45%) of the 81 patients there were no histological diagnostic findings of leprosy in the nerve or the skin biopsies. In 18 (32%) of these patients (Table 3) normal histology of both the skin and the nerve biopsies were found. However, of these 18 patients, 7 had been given a clinical diagnosis of probable leprosy while 11 had received a diagnosis of leprosy.

In 5 (9%) of the patients without diagnostic leprosy a fibrotic nerve lesion and a normal skin were found. Although the fibrosis might well be a consequence of leprosy no diagnostic indications of leprosy were found in these lesions. Five (9%) of the patients showed chronic inflammation in the nerve biopsies, but without any other histological or bacteriological criteria for leprosy.

Table 3 Histology of skin and nerve biopsies from patients not diagnostic of leprosy

Combinations of skin and nerve histology					
Skin Nerve	Norm* Norm	CI† Norm	Norm Fibr‡	Norm CI	CI CI
Number	18	9	5	2	3
%	31·5	15·7	8·8	3·5	5·2

Total number: 37.
* Norm, normal findings histologically.
† CI, chronic inflammation.
‡ Fibr., fibrosis and hyalinization histologically.

Discussion

The present study showed that there was a marked discrepancy in the histological and bacteriological picture between nerve and skin lesions of a significant group of the leprosy patients studied. The exact magnitude of this difference in the whole leprosy group is difficult to anticipate from the present study due to the fact that the biopsies were taken from a rather unselected group of patients. Many of the patients were referred for biopsies due to uncertain clinical diagnosis and doubtful skin symptoms.

The data obtained from the group of patients with a histological diagnosis of leprosy present three main patterns (Table 1). One third (32%) of the patients exhibited a diagnostic nerve biopsy and a non-diagnostic skin biopsy. These results from Ethiopia correspond to findings from India where 19 of the 36 leprosy patients had a higher bacillary load and a more lepromatous picture in nerves than in skin.[13] The reliability of using nerve biopsies to disclose the status of the disease also corresponds with the findings of Antia *et al.* who have found nerve involvement prior to any clinical manifestations.[2,3] Our results are in contradiction to those of a study from the People's Republic of China where they have found the same histological findings in skin and nerve lesions from 92 autopsies.[14] They had, however, a comment that bacilli were more easily found in TT nerves than TT skin. In spite of a high number of bacteria being found in nerve than skin lesions, Ridley & Ridley have suggested from morphological studies of patients from Nepal that skin lesions represented the general tissue response of the patients.[12] In the present study, 8 of the 44 patients with diagnostic leprosy demonstrated a multibacillary leprosy in the nerve while the parallel skin biopsy showed paucibacillary leprosy. Immunological studies of both nerve and skin biopsies in these patients revealed that nerve lesions may have an immunological picture of a non-responsive leprosy in contrast to skin lesions.[8] This can explain the results from studies in India where one study[13] shows that 7 of the 8 patients with relapses displayed relapses only in the nerve. An immunologically non-responsive form of leprosy can thus reside in nerve lesions and a responsive form in skin lesions. These results, however, are in contrast to the conclusions made by Ridley & Ridley claiming that the skin tissue response demonstrates the general tissue response towards *Mycobacterium leprae*.[12]

This discrepancy in both the bacteriological and immunological status of the nerves compared to the skin should be considered when establishing treatment programmes for leprosy. The patients studied were given a treatment according to the WHO's regimen of multidrug therapy (MDT) for leprosy. With only a skin smear or a skin biopsy these patients would have been treated as paucibacillary cases with possible relapse as a consequence.

The criteria used for classification at present are mainly based on the status of skin lesions and thus not reflecting the nerve lesions. From the present results it might therefore be reasonable to question if the same drug regimen should be used for patients with paucibacillary as for multibacillary leprosy. To evaluate the treatment regimen, however, a well organized and randomized trial should be conducted.

Although nerve biopsies have been proven to be important, the need for a good histology laboratory and a pathologist makes this not applicable for the leprosy problems of the developing world. However, hospitals and research centres having these possibilities should work further to establish better clinical criteria and simple test methods suited for the actual needs of leprosy control programmes.

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Eye lesions in leprosy

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Summary Out of 742 out-patients screened for ocular disease, 177 (24%) had eye lesions due to leprosy. These were more in the lepromatous spectrum of the disease and showed increasing trend with age of patient and duration of the disease. Madarosis was the commonest lesion (76%). The serious and sight threatening lesions like lagophthalmos, corneal anaesthesia, corneal opacities and ulcers, iritis and complicated cataracts constituted 8·22% of the lesions. Blindness due to corneal opacity and complicated cataract developed in 6 patients, constituting 3·4% of eye lesions with a prevalence rate of 0·8% among all the leprosy patients. Although the blinding lesions occurred in a very small percentage of patients, most of these are preventable through early recognition and institution of appropriate treatment. The simple techniques of examination to detect protentially sight threatening lesions should be taught to all leprosy workers to prevent blindness among leprosy patients.

Introduction

Estimates from India on the magnitude of ocular complications in leprosy vary from 5 to 80%.[1,2] Such wide variations may be due to the differences in methodology of assessment, populations studied, sampling designs and definitions adopted. Without a scientifically designed study, it is difficult to establish the role of clinical or epidemiological factors in ocular lesions of leprosy.

A study was carried out on an unselected sample of patients seeking care for leprosy and not just for eye problems. The eyes of these patients were carefully examined using standardized techniques. This paper presents the types and extent of ocular lesions in leprosy and discusses the ocular disease from the point of view of disability and morbidity.

Materials and methods

Seven hundred and forty-two consecutive leprosy patients seen at the general out-patient clinic of the Schieffelin Leprosy Research and Training Centre, Karigiri, were included in this study.

Each patient was examined carefully and the findings on age, sex, occupation, type of leprosy,

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duration of leprosy, skin smears, details of treatment, regularity of treatment and eye findings were recorded on a modified proforma adapted from the one proposed by ffytche.[3]

Visual acuity was tested with Snellen's chart and only corrected visual acuity (with a pinhole or with glasses) was recorded. Patients with visual acuity not more than 3/60 in the better eye were recorded as blind. Corneal sensation was tested with a wisp of cotton. A torch and corneal loupe were used to examine all patients. All the patients in the lepromatous spectrum and any other patient with serious eye lesions were examined with a slit lamp microscope. Tension was assessed digitally. Shiotz tonometer was used to check tension if the digital tension was found to be high. Examination of the posterior segment of the eye was not attempted since it is affected very rarely.[4]

Findings

Out of 742 (537 males and 205 females) leprosy patients 177 or 23·9% had eye lesions due to leprosy. The prevalence of these lesions by age and sex are given in Table 1.

The prevalence of eye lesions increased significantly with age ($p < 0{\cdot}01$). Males are affected more than females ($p < 0{\cdot}01$).

The prevalence of eye lesions by types of leprosy is given in Table 2.

Eye lesions were significantly more in lepromatous and borderline lepromatous leprosy ($p < 0{\cdot}01$). Within each type of leprosy there was no significant difference by sex.

Table 1 Prevalence of eye lesions by age and sex

	Male			Female		
		Eye lesions			Eye lesions	
Age (years)	No. observed	No.	%	No. observed	No.	%
0–14	29	—	0·0	18	1	5·5
15–34	219	34	15·5	85	15	17·6
35–64	271	99	36·5	101	19	18·8
65 and over	18	9	50·0	1	—	0·0
Total	537	142	26·4	205	35	17·1

Table 2 Eye lesions by type of leprosy

		Eye lesions	
Types of leprosy	No. observed	No.	%
Lepromatous (LL)	163	92	56·4
Borderline lepromatous (BL)	155	48	31·0
Borderline borderline (BB)	36	3	8·3
Borderline tuberculoid (BT)	328	32	9·8
Tuberculoid T)	22	1	4·5
Indeterminate (I)	24	1	4·2
Neuritic (N)	14	—	—
Total	742	177	23·9

Table 3 Eye lesions by duration of leprosy

Duration (years)	No. observed	Eye lesions	
		No.	%
< 5	392	64	16·3
≥ 5	350	113	32·3
Total	742	177	23·9

Table 4 Eye lesions in relation to bacterial index (BI)

Skin smears	No. observed	Eye lesions	
		No.	%
Negative	412	52	12·6
BI < 2·0	118	26	22·0
BI ≥ 2·0	185	94	50·8
Not available	27	5	18·5

The prevalence of eye lesions in relation to duration of the disease is shown in Table 3.

Those having leprosy for more than 5 years had a significantly higher prevalence of eye lesions than those who had leprosy for less than 5 years ($p < 0{\cdot}001$).

The prevalence of eye lesions by skin smear results at the time of initial visit to the hospital are shown in Table 4.

Frequency of eye involvement is directly proportional to the severity of disease as judged by bacterial index ($p < 0{\cdot}01$).

The various eye lesions and their relationship to the types of leprosy are shown in Table 5.

Madarosis was the most frequent eye lesion and was seen in lepromatous and borderline leprosy. Among the lid lesions, lagophthalmos was the commonest and was seen in 30 patients. Two of these in addition had ectropion, 1 patient had entropion with trichiasis. Lagophthalmos was higher in BT cases as compared to LL or BL cases, but the difference was not statistically significant. Lagophthalmos was associated with diminished corneal sensation in 15 patients. Among the other 15 patients, 5 had a history of type I or type II reaction. Of those with lagophthalmos the cornea was exposed in 13 patients only and 8 of these had developed corneal opacity.

Out of 24 patients with corneal hypoaesthesia, 3 had developed corneal ulcers. Among 21 patients with corneal opacity, diminished corneal sensation could be detected in 16 patients.

Iris lesions, mostly atrophy, were confined to patients in the lepromatous spectrum of the disease. Iris pearls were seen in 2 patients out of 177 examined (1·23%). Of the 7 cases with acute iritis, 5 were positive for lepra bacilli on routine skin smears from 4 sites. Among the 10 with chronic iridocyclitis, 5 had positive skin smears. Five patients with chronic iritis had a history of erythema nodosum leprosum reactions lasting for more than 6 months, and had been treated with both steroidal and non-steroidal anti-inflammatory drugs. The sequelae to iridocyclitis were occlusio pupillae, posterior synechiae and complicated cataract.

Table 5 Eye lesions in relation to types of leprosy

Eye lesions	Types of leprosy					
	All types	LL	BL	BB	BT	T&I
Madarosis	135	87	38	1	9	—
Nasolacrimal duct blockage	1	—	—	—	1	—
Lagophthalmos	30	5	5	2	17	2*
Scleral and conjunctival lesions	16	11	4	—	1	—
Corneal lesions:						
hypoaesthesia	24	10	3	2	8	—
opacities	21	10	5	—	6	—
ulcers	3	2	1	—	—	—
Iris lesions:						
iritis—acute	7	5	2	—	—	—
chronic	10	9	1	—	—	—
iris atrophy	19	15	4	—	—	—
iris pearls	2	2	—	—	—	—
Synechiae:						
posterior	10	7	1	—	—	—
anterior	—	2	—	—	—	—
Lens lesions complicated cataract (secondary to iridocyclitis)	2	2	—	—	—	—

* There was 1 each in tuberculoid leprosy and indeterminate leprosy.

Discussion

To lose one's eyesight when the sense of touch is also gone is a real disaster. The purpose of the present study was to determine the magnitude of the eye problem in those who had visited the hospital for general leprosy care and not necessarily for the eye. It was noted that a vast majority of patients in the study group were ignorant of their eye problems even though a significant number among them required eye care.

Males seemed to be affected more than females, as observed by others.[5,6] It is possible that more males seek medical attention or are more prone to injury by virtue of their outdoor work; however, the frequency is the same in each sex by type of leprosy, and the overall sex difference might therefore be due to the larger number of male patients seen with lepromatous leprosy.

Eye lesions were more common and severe in the lepromatous spectrum of the disease and with increased duration of the disease. There is thus a need for close monitoring of this group for early recognition of potentially sight threatening lesions.

To explain facial palsy in leprosy, one study[7] postulated that leprous infections entered the malar skin through sensory fibres of the trigeminal nerve and ingressed into the cutaneous branches of the facial nerve with which they are in close proximity. In our series, among the 30 patients with lagophthalmos only 15 had corneal anaesthesia, indicating that facial nerve can be affected independent of trigeminal nerve involvement. Five patients with lagophthalmos but no corneal anaesthesia, had a history of reactions in the past which may account for the development of the facial palsy.

Corneal opacity was present with and without lagophthalmos. In the absence of lagophthalmos this could have developed as a sequelae to degenerative changes to which hypoaesthetic corneas are

particularly prone. In the 5 patients who had corneal opacity without either lagophthalmos or demonstrable corneal hypoaesthesia it may have been due to healed corneal ulcers of unrecalled trauma.

Two out of 7 patients with acute iritis and 5 out of 10 patients with chronic iritis showed neither clinical nor bacteriological evidence of active disease. Reactions which frequently have acute iritis as one of their commonest features were also absent in these patients. It may be that the 2 patients with acute iritis were in a state of reaction, with iritis as the earliest single or more obvious feature. Such isolated tissue involvement in reaction is not uncommon as for instance in the case of neuritis. An alternative explanation is that the acute iritis represented an early reactivation of the disease which could not be detected at that time by routine skin smears from 4 sites.[8] An iris which is derived of its nerve supply as a result of leprosy, tends to disintegrate. ffytche[9] has suggested that such disintegrated muscle fibres can evoke inflammatory response leading to chronic iritis. This may explain the chronic iritis in 5 of the patients in our series in whom no active evidence of leprosy could be detected.

Glaucoma has been reported to be rare in leprosy because of atrophy and hyalinization of the ciliary body with diminished aqueous humour production.[10,11] Also glaucoma was not detected in any of our patients. This however may not reflect the true incidence of glaucoma in leprosy, because our patients were screened on the basis of digital assessment of tension and tonometer assessment was made only where digital tension indicated increased pressure. Further, all patients were examined at a single point in time. With follow-up examination during episodes of iridocyclitis, perhaps more cases of glaucoma might have been picked up.

There is need for a practical scheme of classification and grading of eye lesions, for clear understanding and effective management. One study[12] based their classification on pathogenesis, whereas WHO classification is on the basis of disability grading.[13] A simple but useful classification was suggested by Lamba[14] wherein he divided the ocular lesions into 2 main categories: a, cosmetically disfiguring, e.g. madarosis; and b, potentially sight threatening. While Lamba's classification enables one to project the levels of ocular morbidity it does not adequately stress the importance of lesions like madarosis which can be significant from the patient's dehabilitation point of view. In our study 61 patients (8·22%) had potentially sight threatening lesions and 6 patients had become blind. The emphasis should be towards early detection and care for these.

While cross-sectional studies are useful to gauge the extent of eye morbidity, follow-up studies of those at high risk are necessary to determine incidence of this morbidity. Patients in the lepromatous spectrum of the disease, those with lagophthalmos and those with corneal lesions are particularly prone to silent but progressive eye lesions even after release from treatment. Follow-up studies will help in the further understanding of the pathogenesis and epidemiology of eye lesions due to leprosy.

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The current state of leprosy control activities in Sri Lanka

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Summary In Sri Lanka the overall prevalence of leprosy was 0·14 per 1000 population and the incidence 0·07 per 1000 population at the end of 1987. Although the endemicity is low in the island, disease transmission has not yet been achieved as the annual detection of new cases and the child rate has been gradually rising. The major activities of the leprosy control programme are case-finding, treatment and defaulter retrieval, health education, rehabilitation and training. The field programme is implemented through 15 specially trained paramedical workers. In addition there are 5 medical officers attached to the Anti-leprosy Campaign. The Director of the Anti-leprosy Campaign is in overall charge of the National Leprosy Programme and is also project manager for the Sri Lanka Emmaus Leprosy Control Project.

Introduction

Sri Lanka, a small island in the Indian Ocean close to South India, has an area of 65,610 square kilometres. Its length is 445 kilometres, breadth 225·3 kilometres, and it has a population of 16·34 million.

There is a belt of high prevalence of leprosy ranging from 0·3 per 1000 population to 0·13 per 1000 in the Western and Southern Provinces extending to the Eastern Province along the coast, with endemic foci in certain districts. The Northern Province is moderately endemic. The rest of the country has a very low endemicity with prevalence rates below 0·07 per 1000 population.

Though leprosy has a low degree of endemicity in the country, interruption of disease transmission has not yet been achieved. This observation is based on the following indicators:
New cases detected annually have risen gradually from 329 in 1947 to 1194 in 1986, but there was a decrease to 1074 in 1987 probably because the case-finding programme, planned was not fully implemented.
Child rate which was only 5·4% in 1959 has increased to 20·4% in 1987.

Situation analysis

The statistics at the end of 1987 showed that the overall prevalence in the island was 0·14 per 1000 population and the incidence 0·07 per 1000 population. During the first half of 1987 on the recommendation of a WHO Consultant (who was in Sri Lanka to review the National Leprosy Control Programme) updating of patients' registers were done and many cases were taken out of the

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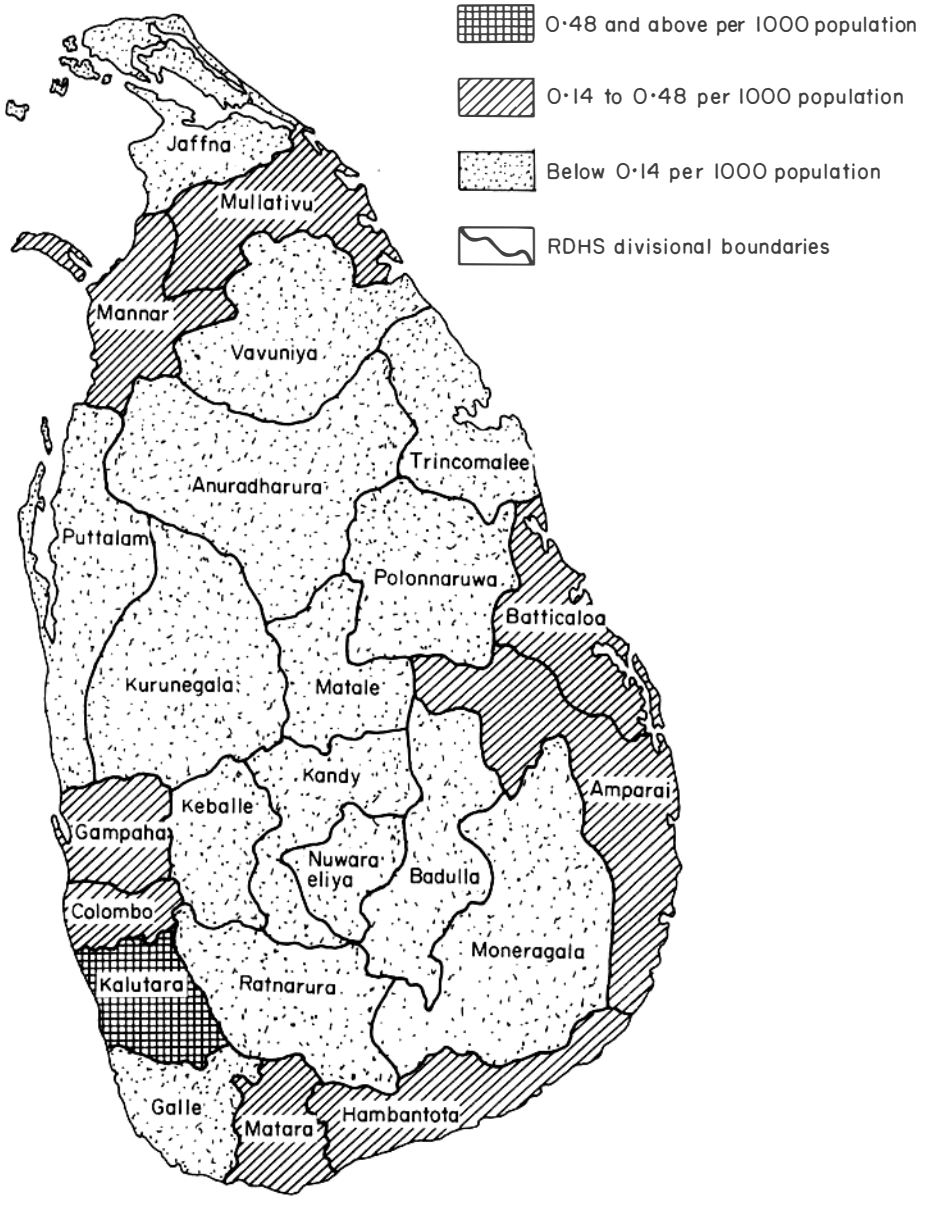

Figure 1. Endemicity of leprosy in Sri Lanka by Regional Director of Health Services Divisions on 31.12.87.

Table 1. Registered cases and new cases by Provinces as on 31.12.87

Regions	Population 1987	Registered 1987	New cases 1987
Western	4,238,000	4879	537
Southern	2,115,000	1102	124
Eastern	1,148,000	355	109
Sabaragamuwa	1,608,000	297	50
North Western	1,910,000	437	99
Northern	1,249,000	441	38
Central	2,095,000	208	45
North Central	952,000	228	41
UVA	1,007,000	147	31
Total	16,322,000	8094*	1074

*This has been made up as follows:

Active cases	2305
Cases under surveillance	4531
Cases for care only	1258
	8094

Table 2. Prevalence rates and incidence rates by Provinces as on 31.12.87

Province	Total no. of cases*	Prevalence rate	Incidence rate
Western	4879	0·30	0·13
Southern	1102	0·13	0·06
Eastern	355	0·17	0·09
Northern	441	0·12	0·03
North Central	228	0·07	0·04
North Western	437	0·07	0·05
UVA	147	0·05	0·03
Sabaragamuwa	297	0·05	0·03
Central	208	0·04	0·02

*Registered cases, 8094.

Table 3. Total number of active cases by ethnic groups as on 31.12.87

Race	Multibacillary			Paucibacillary			Total
	M	F	Total	M	F	Total	
Sinhalese	466	163	629	602	464	1066	1695
Cey. Tamil	96	55	151	198	227	425	576
Cey. Moors	09	04	13	10	9	19	32
Malays	—	—	—	—	—	—	—
Burghers	—	—	—	—	—	—	—
Ind. Tamil	—	—	—	—	—	—	—
Ind. Moors	—	—	—	—	—	—	—
Total	571	222	793	811	701	1512	2305

Table 4. Total number of active cases by age groups as on 31.12.87

Age group (years)	Multibacillary			Paucibacillary			Total
	M	F	Total	M	F	Total	
0–4	—	—	—	12	07	19	19
5–9	02	02	04	54	52	106	110
10–14	13	09	22	90	86	176	198
15–24	67	16	83	154	146	300	383
25–39	144	58	202	174	148	322	524
40–49	108	43	151	130	122	252	403
50–59	103	39	142	86	63	149	291
60–69	70	41	111	71	53	124	235
70+	64	14	78	40	24	64	142
Total	571	222	793	811	701	1512	2305

Table 5. Total number of new cases detected in 1987 by age groups

Age group (years)	Multibacillary			Paucibacillary			Total
	M	F	Total	M	F	Total	
0–4	—	—	—	06	03	09	09
5–9	—	01	01	38	45	83	84
10–14	02	—	02	69	55	124	126
15–24	08	09	17	61	79	140	157
25–39	32	15	47	123	98	221	268
40–49	16	06	22	52	62	114	136
50–59	23	05	28	57	61	118	146
60–69	15	07	22	44	37	81	103
70+	06	01	07	27	11	38	45
Total:	102	44	146	477	451	928	1074

'active' cases register, hence there was a drop in prevalence rate of 0·6 per 1000 population in 1986 to 0·14 per 1000 population in 1987. The incidence was the same in 1986 and 1987 respectively.

Statistics of all the island as at 31.12.87:

Total number of active cases	2305
Total number of surveillance cases	4531
Total number of 'care' cases	1258
Of active cases:	
Multibacillary	34·5%
Paucibacillary	65·5%
Among active cases:	
Males	59·9%
Females	40·1%
Children below 15 years of age	14·2%
New cases were detected mainly by:	
Referrals	54·5%
Surveys	31·4%
Contact examination	10·7%
Self-reporting	3·4%
Among new cases detected during 1987:	
Multibacillary	13·6%
Paucibacillary	86·4%
Children below 15 years of age	20·4%

97·96% of new cases detected were without Grade II and III deformities.

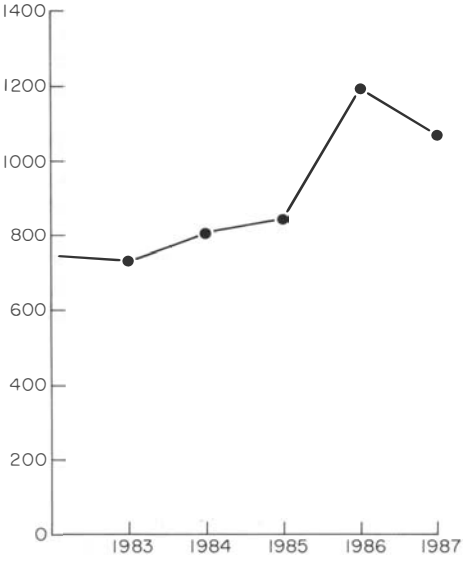

Figure 2. New cases detected since 1983.

Table 6. Total number of new cases detected in 1987 below and above 15 years of age

	Multibacillary			Paucibacillary			
Age	M	F	Total	M	F	Total	Total
−15	02	01	03	113	103	216	219
+15	100	43	143	364	348	712	855
Total	102	44	146	477	451	928	1074

The major activities of the Leprosy Control Programme are:

Case finding:
  Active methods
  Passive methods
Treatment and defaulter retrieval
Health education
Rehabilitation
Training

All cases on the Active Case Register are on multidrug therapy. The treatment regimen advocated by the WHO is being adhered to and carried out at 81 treatment centres throughout the country. Multidrug therapy commenced in 1982.

The field programme is implemented through 15 specially trained public health inspectors (paramedical workers). These public health inspectors are responsible for the above activities in their control areas (the country being divided into fifteen control areas). They integrate at the periphery with the primary health care workers and with voluntary workers. In addition to the 15 public health inspectors there are 5 medical officers attached to the leprosy campaign: 2 in Colombo at the Central Leprosy Clinic which is the headquarters of the Leprosy Control Programme, 1 as the Regional Medical Officer of the Southern province, and the other 2 are in charge of the 2 leprosy hospitals situated in the Western and Eastern Provinces. The former was constructed in 1706 during the period of Dutch occupation and the latter in 1921 during the period of British occupation of the country.

As government policy no new admissions have been made to the 2 hospitals since 1977 except those needing temporary hospitalization for reactions and ulcers.

The Director of the Leprosy Control Programme is in overall charge and is the National Programme Manager.

Emmaus Suisse a private voluntary organization assists and augments the National Leprosy Control Programme, in addition (since 1981) a model pilot project to intensify case detection was implemented in 1 district in the Western Province. This is being extended to 4 other districts in the Western and Southern Provinces now.

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Relapses after multidrug therapy for leprosy: a preliminary report of 22 cases in West Nepal

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Summary. The WHO recommended multidrug therapy regimens for leprosy patients were implemented in Nepal from 1982. Therefore a considerable number of both paucibacillary (PB) and multibacillary (MB) patients have been on observation after release from MDT, for as long as 4–5 years. A retrospective study was done considering the patients who relapsed during this period and who were registered at the Out-patients Department of Green Pastures Hospital in Pokhara, Nepal. A total of 22 patients relapsed out of 927 who were released from MDT.

Introduction

Very little has been published on relapse after MDT, because the WHO–MDT regimens have only recently been implemented in most leprosy control projects. The WHO recommendations for the multidrug treatment of leprosy were published in 1982[1]— paucibacillary patients (PB): I, TT, BT leprosy in the Ridley & Jopling classification, with Bacteriological Index (BI) less than 2 at any one site, were to be treated with a 6-month course of DDS and rifampicin; and multibacillary patients (MB): classified as BB, BL and LL, with a BI of $\geqslant 2$ at any one site, are to be treated with the combination of DDS, clofazimine and rifampicin for a minimum of 24 months. These recommendations were implemented in Nepal from 1982. The only differences being that:

1 Because of the huge logistical problems in Nepal, patients who live too far away from the health post to come monthly, but who can attend bi-monthly, are given 1 monthly doses of rifampicin, or rifampicin and clofazimine to take unsupervised at home, in between their clinic visits.
2 All smear positive patients have been treated with MB–MDT.

Patients, materials and methods

Green Pastures Hospital in Pokhara is a referral centre for leprosy patients in the west of Nepal and has 1465 out-patients on register. Of these, 927 patients are on observation after release from MDT (555 PB and 372 MB). Of the 538 patients still on treatment, 334 are on MDT and 204 are on monotherapy (MT).

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TREATMENT REGIMENS (according to WHO)

PB patients: DDS 100 mg once daily and rifampicin 600 mg monthly for 6 months. After this, a patient is released from treatment (RFT) and put on observation (yearly) for another 4 years.
2 MB patients: DDS 100 mg and clofazimine 50 mg daily, and rifampicin 600 mg and clofazimine 300 mg monthly for a minimum of 24 months.

CRITERIA FOR RELEASE FROM MB–MDT

Clinically inactive and at least 2 sets of negative skin-smears (routine sites: (R) earlobe, (R) elbow, (R) knee and a nasal smear. Additional smears from lesions where indicated), 4 or more months apart. After release a patient is put on observation for 8 years.[2]

Since the introduction of MDT in our hospital, 40 patients were registered as having relapsed after release from either PB or MB MDT. After careful examination of the clinical records, 18 patients were excluded from this study, either because of initial misclassification, or failing to meet the criteria for release from MDT (see above) or the criteria for relapse (see below).

RELAPSE IS DEFINED AS

'A return of active disease in a patient who has apparently completed a prescribed course of treatment and whose treatment was therefore stopped by an authorized member of the health services.'

'Active disease' in leprosy can either indicate bacteriological activity, due to viable, multiplying *Mycobacterium leprae* or immunological activity due to the presence of (residual) *M. leprae*-antigen in the tissues; the latter is of course not a true relapse.

FEATURES OF RELAPSE/ACTIVE DISEASE

Time:	Slow in onset
Clinical features:	New signs of activity appear:
	a New lesions
	b Extension of existing lesions
	c Erythema
	d Neuritis
	e New nerve function loss (without clinical signs of neuritis)
	f Eye symptoms, e.g. iritis
Bacteriology:	A previously negative BI becomes positive $\geqslant 2+$.
	A single $1+$ finding is not sufficient.
Histology:	Signs of active leprosy in a skin/nerve biopsy.

We realize that quite a few of the symptoms and signs of 'active disease' also could fit the diagnosis 'reversal reaction'. The decision is usually based on clinical judgement. It is very much a diagnosis made under field conditions.

Results

Table 1. Number of relapses according to sex

Type	No. of relapses	M	F
BT	16	10	6
BL	4	4	—
LL	2	2	—

Table 2. Time of relapse (relapse interval)

	No. of patients			
	1 yr	1–2 yr	2–3 yr	3–4 yr
BT	3	2	9	2
BL	—	3	1	—
LL	—	1	1	—
Total	3 (14%)	6 (27%)	11 (50%)	2 (9%)

Table 3. Signs of relapse

Class	Positive BI	Lesions*	Neuritis	NFL	Reaction	Iritis	Paresthesia
BT	2	10	3	3	1	—	4
BL	2	—	1	1	—	1	—
LL	1	1	—	—	—	—	—
Total	5 (23%)	11 (50%)	4 (18%)	4 (18%)	1 (4·5%)	1 (4·5%)	4 (18%)

* No histoid nodules were found in any of these patients, but usually hypopigmented, hypaesthetic, or anaesthetic macules.

NFL, nerve function loss.

PAUCIBACILLARY GROUP

In the paucibacillary group 16 relapses were found. All of these patients were clinically classified as BT and all had 3 or more areas of the body* involved at the initial examination. 'Involved' means: signs of skin or nerve lesions present, therefore, e.g. dryness, ulcers, clawing and absorption are also counted as 'involvement'. All but one patient received PB–MDT. The clinic attendance was very satisfactory in all cases (minimum 75%). The project average regularity is 77% over the whole control area.[3]

One of the patients received 12 doses of MB–MDT, possibly because his smear was initially 1+. Except for this patient, all patients were smear negative at their initial examination. Five patients received MT for a considerable length of time (15–52 months) before starting PB–MDT. However, this did not make any difference on the relapse interval. Only 2 patients were smear positive (1+) at the time of relapse.

In our study all relapses occurred within 4 years after release from treatment (RFT) and 92% even occurred within 3 years. But since the first patients were only released from (PB) MDT $4\frac{1}{2}$ years ago, there may still be a group of 'late' relapses, which so far have not been discovered.

* Body area is defined as follows: 1 area is the head, or 1 arm or 1 leg, or half of the front or back of the trunk, when divided in halves sagittally. The total number of body areas is therefore 9.

Table 4. Body areas involved

Type	<3	3–4	5–6	⩾7	Total
BT	—	3	4	9	16
BL	—	—	1	3	4
LL	—	—	1	1	2

Table 5. Relapse percentages

Classification	No. of patients RFT	No. of relapses	Relapse (%)	Annual (%)
PB	555	16	2·9	0·73
MB	372	6	1·6	0·4
Total	927	22	2·4	0·6

MULTIBACILLARY GROUP

In this group there were 6 relapses, 4 were classified 'BL' and 2 'LL' at their initial examination. All were smear positive, (2+–5+). All but one received DDS or Isoprodian therapy before starting MB–MDT. Again this, though shortening the length of MDT, did not affect the relapse interval.

Clinic attendance was again very satisfactory, though overall slightly less regular than in the PB group. The lowest percentage was 86%. The WHO standard is a minimum of 67%. Three patients were smear positive as a first sign of relapse. These were all found during routine annual follow-up examinations.

Discussion

We are aware of the difficulty in distinguishing relapse in PB patients from late reversal reaction. Waters *et al.*[4] discuss the problems in differentiating between the two, clinically, bacteriologically and histologically. Even the latter, '. . . may fail to distinguish between relapse and reversal reaction.' In practice, however, the great majority of diagnosis are made based on clinical judgement under field conditions. So we look for clinical criteria on which the diagnosis 'relapse' can be made with reasonable certainty. In only 1 out of our 22 patients did the lesions at the time of relapse look like reversal reaction.

We reckoned that this was not 'a late reaction,' but a relapse presenting as RR, because it occurred 41 months after RFT. It is possible for reactions to occur after RFT. This nearly always happens within the first year after starting chemotherapy, but occasionally can occur up to 3 years after the beginning of effective chemotherapy.[4] Some of our patients, who presented with symptoms of neuritis only, may have been reversal reactions, who showed no 'reactional skin lesions,' because they had no active skin lesions.

Among our 22 patients 6 had nerve problems only; the rest had either new skin lesions (usually hypopigmented macules) or they had a positive skin smear.

Relapse can have the following causes:

Original misclassification (leading to wrong treatment).

2 Inadequate chemotherapy due to: (a) low dose treatment; (b) treatment mistakes; (c) irregularity and non-compliance of the patient; and (d) inadequate treatment protocols.
3 Drug resistance.
4 *M. leprae* persisters.
5 Re-infection (only likely in lepromatous patients).

Causes 1–2(b) were excluded from our study, so cannot account for any of the relapses. Noncompliance is a widely recognized phenomenon. However, looking at the clinic attendance regularity, there is no reason to think that these 22 patients would be less compliant than nonrelapsing patients, Pandian *et al.* write:[5] 'This relapse rate does not appear to be related to the regularity of treatment.' The reason for this, they argue, is that the sulphone levels in the blood remain above the MIC for as long as 10 days after the last (100 mg) dose. Therefore even very irregular self-administration should still lead to adequate therapy. This is even more so if monthly supervised rifampicin is added to the treatment regimen.

Non-compliance with treatment is also more likely to lead to 'failure to cure' or relapse during treatment, than to relapse after RFT. All our relapse patients had previously responded favourably to MDT, indicating sufficient compliance. Since only the WHO–MDT protocols were used, we assumed that they had been given 'adequate treatment'. However, 'the ultimate and significant test of chemotherapeutic effectiveness is and will be the relapse rate'.[4]

Drug resistance as a cause for these relapses is very unlikely after a course of MDT, combining 3 effective antileprosy drugs. Re-infection remains a possible cause of relapse in lepromatous patients, because of their lasting defect in their cell-mediated immunity. Almeida *et al*, write:[6] 'In a leprosy-endemic area, it is argued that beyond the first 3 years of smear negativity in a LL or BL patient, sources of *M. leprae* outside the patient may be more responsible for relapse, than a patient's own bacilli. Since all our relapses in the MB group occurred within $2\frac{1}{2}$ years after RFT, re-infection is not likely to play a major role here.

The most likely explanation of the relapses in the MB group is persistence of *M. leprae* bacilli in the tissues. This has been reported by several investigators. These persisters are usually fully sensitive to the drugs used before. Therefore Toman[7] writes: 'There is little reason to believe that in the near future a new drug or combination of drugs will be found that is capable of eradicating persisting *M. leprae*.' Jopling[8] found that MDT is unable to eradicate persisters in about 7% of MB patients.

Concerning the 'relapse interval' or 'incubation time for relapse', our findings are in agreement with those of Bourland *et al.*[9] They found that 50% of the relapses occurred within 3 years after RFT. In our study this was even as much as 92%. The overall relapse percentage is 2·6%. The annual exam rate among 'RFT patients' is only $\pm 50\%$. But since most patients presented themselves with symptoms in between the annual exam dates, the relapse percentage found is assumed to be close to the actual percentage in the whole group of RFT patients.

An overall relapse percentage of 2·6% seems to indicate that the MDT regimens as recommended by WHO offer very acceptable and adequate treatment for the great majority of patients. However, we hope to find that by treating BT patients with more than 2 body areas involved with MB–MDT, that the relapse rate in this group will be even further reduced.

We would like to emphasize again the following points:

1 The need for regular, annual follow-up, in order to detect relapses as early as possible (in our programme: PB 4 years, MB 8 years).
2 The need to include skin smears as a routine procedure in the follow-up examination (especially in the case of MB patients).

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SPECIAL ARTICLE

Prostaglandins and leprosy. A role for aspirin?

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Summary Prostaglandins not only have a role in inflammation, but may also be involved as mediators in the immune response. Drugs which affect prostaglandin synthesis may therefore be potential tools with which to modulate disturbed immunity. These possibilities are discussed with reference to immunity in leprosy, and in particular reversal reactions.

Introduction

All clinicians are aware of the role of prostaglandins as inflammatory mediators; non-steroidal anti-inflammatory agents are crucial drugs in every formulary. Now, too, we are getting used to the idea of aspirin as a powerful antiplatelet agent, with significant effects on mortality from coronary heart disease and stroke. However, there may yet be another role for these drugs, for as the arachidonic acid metabolites are ubiquitous and multifaceted, so their inhibition may have widespread effects. It has been known for over 15 years that prostaglandins (PGs) may modulate the immune response—although how important this role is, is not yet clear. In this essay I would like to examine the potential effects of PGs on one disease, leprosy, and suggest that aspirin and its fellows may yet have a part to play in its therapy.

Prostaglandin synthesis

PGs are derived from arachidonic acid and its analogues, via an oxidative process. Arachidonic acid is present in the membranes of all cells, normally bound to phospholipid. The first step in PG synthesis therefore is release from the cell membrane through the action of the enzyme phospholipase A2. This enzyme is inhibited by steroids, which therefore present the synthesis of all arachidonic acid metabolites.[1]

Arachidonic acid available within the cell may then go down two pathways, the lipoxygenase pathway, to form leukotrienes, and the cyclo-oxygenase pathway. Action of the latter enzyme creates an intermediate PGG_2 from which three main groups are derived, prostacyclin, thromboxane and the PGE and PGF series. Aspirin, indomethacin and the non-steroidal anti-inflammatory agents (NSAIA's) act on cyclo-oxygenase to inhibit the production of all these metabolites. They are thought to have little action on lipoxygenase synthesis (perhaps even causing an increase in flux through this pathway as a 'diversion' for arachidonic acid), although recently it has been shown that there may be some inhibition *in vitro*.[2]

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The biological functions of the PGs are numerous and beyond the scope of this essay. Prostacyclin and thromboxane have opposing effects on platelet aggregation and vasoconstriction, the former acting as an antagonist. PGs of the E and F series are pro-inflammatory agents, causing local vasodilatation, increased vascular permeability, and potentiating the action of histamine and bradykinin in causing pain and accumulating oedema.[1] They are implicated in a number of other body systems, for example as endogenous pyrogen within the hypothalamus, and in renal homeostasis—however, in this essay, it is their involvement in immune regulation which is to be considered.

Prostaglandins in normal immunity

IN VITRO STUDIES

The first report directly suggesting that PGs may act as immunoregulatory agents came in 1971, when Smith and his colleagues noted that PGE_2 inhibited incorporation of radiolabelled metabolites into human lymphocytes stimulated by mitogens. These results were then followed by those of a number of other investigators who showed that PGE could suppress *in vitro* markers of lymphocyte activity, e.g. antibody and lymphokine secretion.[3] However, these results do not prove that PGE is an endogenous mediator of immunosuppression; any cell poison would have the same effect. The following observations argue in its favour:

1 Prostaglandins are produced *in vitro* in the proliferative response to mitogens.
2 Inhibition of PG synthesis by indomethacin causes a reduction in PG concentration and a rise in *in vitro* immune reponsiveness.
3 Addition of PG to these systems negates the effect of indomethacin. Importantly this effect is seen at physiological concentrations (10^{-8} to 10^{-6}M).

One study[3] further narrowed down this role as an immunosuppressant to PGs of the E series. Physiological concentrations of these agents inhibit not only the lymphocyte proliferative response but also E rosetting, cytotoxic T cell and NK cell activity. There is evidence, however, that PGE_1 may act as an immunostimulant in certain *in vitro* systems,[4] e.g. response to BCG. Thus while the overwhelming balance of evidence is in favour of a suppressive role in most *in vitro* systems, this experiment reminds us that it is dangerous to extrapolate from one such system to the next, let alone to the whole animal. A related point is that the action of prostaglandins and antiprostaglandins in these studies is commonly restricted to a narrow time window at the beginning of the reaction,[3] with minimal effects beyond 24–48 h.

IN VIVO STUDIES

PGs may be present and active in the test-tube, but does this have any relevance to the whole animal? There have been few *in vivo* studies of PGs in the normal human immune response, although the continuous uncontrolled experiment with the thousands of individuals already taking antiprostaglandin agents would suggest that such effects are likely to be small. This does not mean, however, that they are either (a) insignificant, or (b) irrelevant to the disease state where there may already be a disorder of immune regulation.

There have been a number of experiments in mice which demonstrate enhanced antibody response to antigen challenge *in vivo*.[3] Indeed, as long ago as 1968, Robinson and colleagues demonstrated that mice pretreated with indomethacin had an enhanced ability to resist infections. However, perhaps most relevant of these animal experiments was the observation of one study[5] that simultaneous oral administration of indomethacin resulted in a marked increase in skin thickness of the delayed type hypersensitivity (DTH) response to intradermal *Mycobacterium tuberculosis*. This

startling result emphasizes just how carefully we must tread in this field, for most clinicians, trained with the idea of indomethacin as an anti-inflammatory agent, would have predicted exactly the opposite effect.

In normal humans, there has been no observed equivalent effect of indomethacin on skin test responses to mumps, candida and trychophyton.[6] However, responses to an Influenza A vaccine were enhanced by pretreatment with indomethacin in normal volunteers. This only occurred in strains to which the individual had been previously sensitized, suggesting that PG synthetase inhibitors may act to stimulate the secondary rather than the primary repsonse.[13]

How might prostaglandins act?

While it is clear from the above experiments that PGs may have effects, whether major or minor, on *in vitro* and *in vivo* measures of immunity, there are a number of issues raised, perhaps the most important of which is how they might act.

The major PG producing cell amongst the mononuclear class is glass-adherent, and it is generally thought that the most important of these is the macrophage.[7] This, by secreting PGE, may either directly suppress T cells or activate a non-glass adherent T suppressor subset (which does not act through prostaglandins). The exact mechanism involved in this immunosuppression is not clear, but is thought to involve both reduced IL2 secretion and IL2 responsiveness.[8] PGs exert their effect through cyclic AMP within the cell[9] and it is of note that indomethacin may have effects on levels of this metabolite directly via phosphodiesterase inhibition and may also act on cyclic AMP-dependent protein kinase. In other words, indomethacin may have immunomodulatory effects independently of PG inhibition and this should be borne in mind in interpretation of *in vitro* and *in vivo* work.

Another complicating issue in understanding PG action is that of the effects of leukotrienes on the immune response. There is *in vitro* evidence that leukotrienes, notably LTB_4, have antagonistic effects to PGs in immunity: lipoxygenase products stimulate mitogen-induced proliferation, which is inhibited by lipoxygenase pathway inhibitors. One effect of PG synthetase inhibitors may be, therefore, to channel more arachidonic acid into the lipoxygenase pathway, as has been proposed in aspirin-induced asthma.[1]

This mechanistic approach takes us away from the problem of the biological function of PGs in immunity. While we are used to the idea of positive feedback in the inflammatory response, if tissue damage is to be limited there must also be negative feedback between the inflammatory and immune cells. Within the immune system, T suppressor cells and idiotypic networks have been proposed to fill such a role. Perhaps PGs, while enhancing the local inflammatory response act to damp the escalation of the developing immune reaction, by feedback inhibition. If this model is true, two predictions can be made. Firstly, we will only be able to fully understand the role of PGs if we consider the immune and inflammatory responses together, not in isolation. Secondly, there may be disease states in which over- or under-damping occurs, leading to hypo- or hyper-responsiveness.

Prostaglandins and abnormal immunity

There is evidence that PGs may play a part in various disease states with disordered immunity. In patients with Hodgkin's Disease, for example, where there is reduced cell-mediated immunity, T suppressor cells are found to produce four times the normal quantity of PGE. *In vitro*, this suppressive effect can be overcome with indomethacin.[11] In tumour-bearing mice, tumour-induced immunosuppression may be reversed with indomethacin both *in vitro* and *in vivo*. Indomethacin not only reduces the rate of tumour growth, but also enhances the therapeutic effect of BCG.[12]

Perhaps the most fascinating experiment in this area has been that concerning the effects of indomethacin on 2 patients with common variable immunodeficiency, a disease associated with abnormal T suppressor function.[13] These patients were previously anergic to skin testing with antigens including PPD (purified protein derivative from TB), but showed a return to skin test responsiveness and restoration of *in vitro* markers of cellular immunity upon drug therapy (disappearing on stopping the drug). This result, although on a small scale, suggests that such immunomodulation may be of clinical significance in situations where the immune system is 'overdamped'. A similar experiment in AIDS patients would be obviously worthwhile, although the underlying pathology is different.

While there is no such profound immunodeficiency disorder in leprosy, there is a precedent for PG-mediated specific immune unresponsiveness in infectious disease. PGs have been implicated in chronic fungal infections, TB, and brucella.[3] Treatment of mice infected with *Schistosoma mansoni* with synthetic PGE led to a significant reduction in the development of egg-induced granulomas.[15] These granulomas result from an immune-mediated hypersensitivity response—PGE had no effect on the development of non-immunological foreign body granulomas. Lymphocyte unresponsiveness in Q fever (caused by the organism *Coxiella burneti*) has been shown to be mediated by PGE_1. Here, antigen-specific T suppressor cells appear to secrete an unidentified factor enhancing PGE production by monocytes.[16] Interestingly, antigen-specific T suppressor activity has also been implicated in leprosy.[17]

Prostaglandins in leprosy

Leprosy is a spectrum of diseases caused by a single organism. The position in the spectrum, from the lepromatous pole to the tuberculoid pole, depends on the host immune response. *In vitro* tests of lymphocyte responsiveness mirror clinical and histopathological indicators of the disease state.[18] The role of immune suppression in determining this response has been studied in some depth, although exactly which cells are involved and how they act is not yet clear.

Nath and colleagues in India have been searching for a monocyte derived suppressor factor; although this has not yet been isolated, its production does not appear to be inhibited by indomethacin, and its physical characteristics make it unlikely to be a PG.[19,20] Such a factor may act directly to inhibit IL2 production in T cells of lepromatous patients, although alternative (and more complex) models exist.[8,21] One study,[22] for example, found that the ability of lepromin to induce suppression of *in vitro* mitogen responsiveness was mediated by two groups of cells, an adherent cell (assumed to be a macrophage) and a non-adherent T cell.

Other groups have attempted to answer directly the question of whether PGs are involved in the immune response of leprosy. One study[23] looked at the effect of PG synthetase inhibition on responsiveness of T cells from normals and leprosy patients from the lepromatous and tuberculoid poles. They found that the unresponsiveness of BL/LL patients was not affected by indomethacin, whereas there was an approximate doubling of *in vitro* immune reactivity in TT/BT patients. This suggests that PGs are unlikely to be involved *in vitro* in the hyporesponsiveness of BL/LL patients. Similarly, it also provokes the idea that it might be possible to enhance further the immune responsiveness of BT/TT patients using indomethacin. Interestingly, one study[3] noted that cells become more responsive to PG-induced immunosuppression in the presence of low concentrations of antigen, which would be the case in BT/TT individuals.

One study,[24] using a guinea-pig *M. leprae* granuloma model and cell sorter found no detectable PGE in the supernatant of cultures of stimulated granuloma cells. This suggests that the demonstrated inability of these granuloma macrophages to act as accessory cells in immune responses[25] is not due to excess PG production.

Thus *in vitro* evidence would point against an important role for PGs in the immunosuppression

of leprosy. While a study of *in vivo* effects of PG synthetase inhibitors in leprosy has not been found, there may be circumstantial evidence from a study of the effects of other drugs.

Anti-leprosy drugs and prostaglandins

Drugs involved in the treatment of leprosy may have immunopharmacological effects over and above their antimicrobial action. This may occur either indirectly, through changes in antigen load, or directly via intrinsic immunomodulatory activity.[26] As it stands, none of these mechanisms have been proven *in vivo*, but there is some *in vitro* evidence in the cases of dapsone and clofazimine.

Dapsone has known anti-oxidant properties and may be a weak inhibitor of PG synthesis.[27] It has been suggested[26] that it may act as an immunostimulant through its inhibition of autoregulatory PGs, e.g. there may be an increase in lepromin reaction with dapsone therapy. This is currently a matter for debate, for while it is known that reversal reactions, flare-ups of hypersensitivity in patients with borderline disease, may be precipitated by treatment, one study[28] has provided evidence that dapsone in high doses may have a protective effect. However, so little is known about the aetiology of reversal reactions that to draw any conclusions as to the potential role of PGs from these observations is rather difficult.

Clofazimine (or Lamprene), on the other hand, has been claimed to act as an immunosuppressant, inhibiting reversal reactions, and inhibiting *in vitro* markers of lymphocyte reactivity.[29] Anderson has suggested that clofazimine and dapsone are mutually antagonistic with respect to PG production, the former having pro-oxidant effect, and therefore enhancing PG production. An interesting example of clofazimine-induced oxidation is the deposition of ceroid, a substance thought to result from lipid peroxidation and condensation, in a patient on such therapy.[30] While these arguments are attractive, they provide only indirect evidence for a role for PGs in leprosy, since these drugs have many other actions.

Lipids and leprosy

Another intriguing insight into the potential effect of drugs on immunity comes from experiments[31] with Chaulmoogra and other oils. Chaulmoogra oil had been used for many years in the treatment of leprosy, taken 'internally, externally and eternally'. Its mode of action is unknown, but is thought to be due to the action of fatty acids of high melting point (hydnocarpic, and chaulmoogric). His account of the effect of such oil on a patient is interesting: 'There was . . . thickening of the tissues, febrile reaction . . . swelling up and softening with subsequent more rapid resorption of the lesions.'

This sounds very much like an 'upgrading reversal reaction' using modern terminology. This could, of course, be explained through a release of antigen as a result of antimicrobial activity, but Rogers then went on to perform similar experiments with fish oils (cod-liver oil). He reports 51 cases treated with cod-liver oil alone, of whom 80% improved or cleared, and 65% cleared completely over the course of 1 year. Rogers notes that the oil appears to have no direct effect on the mycobacteria themselves.

How might these oils be acting? I propose that it may be via an inhibitory action on PG synthesis. It is known that eicosapentenoic acid (EPA) found in fish oils inhibits the synthesis of and is poorly synthesized to PGs.[32,33] Indeed, increase of EPA in the diet may lead to an increase in mitogen-induced lymphocyte responsiveness via PG depletion. EPA derived from fish oil is one example of an 'n–3' fatty acid—and it is suggested that all lipids in this group may be inhibitors of PG synthesis.[34] Linolenic acid, for example, may have a 'restraining' effect on PGE metabolism.[35]

Inhibition of PG synthesis by EPA in fish oil may cause immunostimulation, therefore through release of suppressor activity and promote resolution of leprosy lesions. Hydnocarpic acid itself may also have a weak antioxidant effect by virtue of its resonance hybrid forms (Carpenter K., pers.

comm.). It would be of great interest to know the effects of this and other oils on PG synthesis in normals and leprosy patients. The original experiments may be over 60 years old, but we may still have something to learn from them.

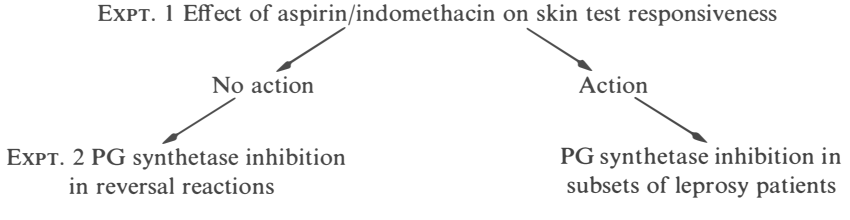
Prostaglandins in leprosy: a synthesis

There is good evidence that PGs are involved in regulation of the normal immune response, and that they may play a part in various disease states. There is little evidence as yet, however, that they are important in leprosy. This question is not purely academic. We have cheap and reliable antiprostaglandin agents available which could be of use in this disease. I would like to consider two possible situations.

1 PGs are relevant to the immune defect in leprosy. In this case, there is a chance that PG synthetase inhibitors may accelerate a cure in concert with current antileprosy drugs. This may be restricted to certain areas of the leprosy spectrum, or certain stages of the disease. The effect on reversal reactions is also unpredictable, since we do not understand their basis. Immunotherapy for leprosy of this kind is not such a far-fetched idea, for this is effectively what is being attempted with the BCG vaccine.

2 PGs are irrelevant to the immune defect in leprosy. In this case, our hopes of immunomodulation with simple drugs such as aspirin are dashed. There may, however, be an important role for antiprostaglandins as anti-inflammatory agents. In reversal reactions, this is a sudden flare-up of hypersensitivity, as discussed, and this is accompanied by oedema formation within the lesions. Such oedema within a nerve sheath may lead to irreversible ischaemic damage. Currently, emergency treatment for these reactions relies on steroids, which are powerful but dangerous drugs, particularly in the hands of those with little experience in their use. Simple anti-inflammatory agents may be very useful in these situations to counteract the critical oedema, and if indeed it does turn out that these drugs have few immunostimulant properties (which might provoke or potentiate the reaction), a trial of their use may be warranted.

A scheme for the further investigation of the role of PGs in leprosy is set out below:



PGs may be relevant or irrelevant to leprosy. In either case, PG synthetase inhibitors may have a role in the future therapy of the disease. The drugs are cheap, and while the side-effects (notably gastrointestinal bleeding) are not insignificant, they compare favourably to those of steroids. Essentially, there is little to lose by trying—and a great deal to gain. In this essay I hope to have demonstrated that we have at least a rational basis for such an attempt.

Acknowledgments

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SPECIAL ARTICLE

An evaluation of 35 years of leprosy control in Northern Nigeria as demonstrated in the original pilot project Katsina

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Leprosy control is nothing more and nothing less than trying to interrupt transmission of the disease by first diagnosing and then treating all the active leprosy patients with a sufficient amount of drugs for a sufficiently long time.

Though this seems very easy in theory, it proves to be extremely difficult in practice, and almost none or only very few of the leprosy control projects have achieved this goal.

In Northern Nigeria leprosy control was started in 1952 by Dr C M Ross with the then Katsina Emirate as a pilot project, and by 1960 it belonged to the largest leprosy control projects in the world.

But what it had and still has in quantity, it missed and still misses in quality. Already in 1960 the WHO–LAT survey in Katsina Emirate noted that the recording was very poor and 'absolutely unsuitable for even the most elementary statistics', and it recommended improvement of the recording and that only the leprosy supervisors should make the diagnosis and authorize the registration.

Though an enormous amount of work has been done over the years, basically the same situation exists or it has even become worse. From October 1984 until March 1987 we reviewed all the 185 leprosy clinics in all the 7 local governments of now Katsina State. We found only 2323 real leprosy patients (8·4%) among the 27,675 persons registered: no reliable diagnosis, no proper recording, no discipline, no supervision in the field, irregular and insufficient drug supply to patients and clinics and no uniform guidelines. During the 450 clinic visits made we struck 25,352 persons (91·6%) off the leprosy registers, as we could not detect any sign of leprosy or because they did not attend (some 20% had fake names?) the visits involved a total drive of 110,000 km.

The total disintegration of the leprosy control and leprosy field work is to be blamed mainly on the non-existence of recording and the complete lack of supervision.

But the strange thing is, there seems to be a tremendous decline in the prevalence of leprosy in Katsina State by at least a factor of 20, in 1951 Dr C M Ross found a prevalence of 39 per thousand, in 1960 the WHO–LAT survey showed a prevalence of 28·7 per thousand, in 1977 the NSL survey noted a prevalence of 3·4 per thousand and in 1987 we come to a calculated prevalence of 1·5–2 per thousand, all in the same area.

In my opinion this decline is due to the natural course of the leprosy epidemic and to a change in the sociohygienoeconomic conditions in Northern Nigeria, as has occurred in other parts of the world in the past, and is certainly not due to leprosy control, because the quality is too poor.

So, is leprosy in Northern Nigeria under control? Nobody knows, and this question still has to be solved.

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Table 1

Local government	Number of leprosy clinics	Number of registered persons			Number of leprosy patients		
		Males	Females	Total	Males	Females	Total
Daura	18	656	1235	1891	96	61	157
Dutsin-Ma	34	1517	5094	6611	144	155	299
Funtua	27	701	1328	2029	234	176	410
Kankiya	30	999	3356	4355	193	138	331
Katsina	24	936	3114	4050	302	310	612
Malumfashi	27	587	2046	2633	142	160	302
Mani	25	1276	4830	6106	110	102	212
Total Katsina State except hospital clinic	185	6672	21003	27675	1221	1102	2323

But even with a prevalence rate of 1·5–2 per thousand there are 100,000 to 150,000 leprosy patients in Northern Nigeria, who need some kind of help.

What should be done is the following: First of all we have to review our whole programme and make an inventory of what we have, so that we come to baseline data. Secondly we have to upgrade and improve all the aspects of our project, namely diagnosis, recording, registration, discipline, supervision, administration, transport etc. Last of all, we should think about introducing multiple drug treatment, but only if we have a well organized and well disciplined project.

I would like to stress that MDT in itself is no solution for a disorderly and bad leprosy control project and will do more harm than good.

As leprosy control cannot be done sitting in an easy chair behind a desk, it means that we have to go into the field where the patients and work are to be found. There is nothing heroic about leprosy

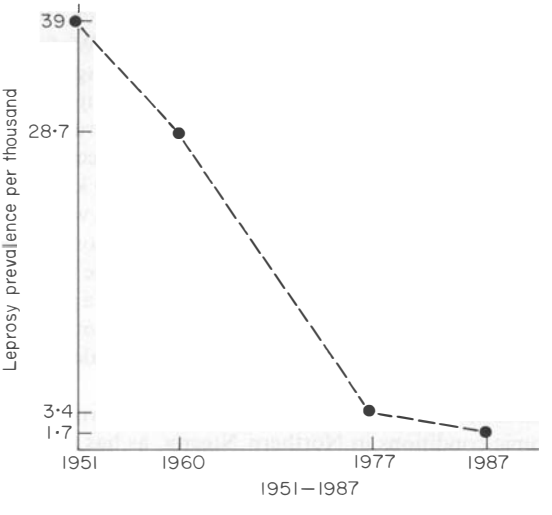

Figure 1

control, but it can be: tiresome, frustrating, sitting for hours in a car, travelling for kilometers on dangerous and rough roads, suffocating from the heat, sweating profusely, eating sand, inhaling dust, feeling thirsty, seeing sometimes no patient at all and occasionally very boring. However, there is no way out and we have to do it, as only by a continuous effort it just might be possible to control and eradicate leprosy.

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SPECIAL ARTICLE

The leprosy control programme in the People's Republic of China

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At an International Leprosy Symposium in 1985[1] in the People's Republic of China, China pledged to eradicate its leprosy problem by the year 2000. For any other leprosy-endemic country this statement might be dismissed as a hopeless political dream; but for China, with a declining number of leprosy cases,[2,3] and a well-structured health system since 1949, this dream is already coming true.

For my final year elective project I decided to take advantage of China's 'Open Policy' to examine how well the eradication programme is working. Dr A C McDougall of the Slade Hospital, Oxford, contacted the Ministry of Health, Beijing, and I was then invited to stay at China's Leprosy Centre (CLC) in Guangdong Province from March to June 1988. The welcome I received surpassed any elective students expectations: I was greeted by the Director, Professor Zheng Ti-Sheng, and applauded during welcoming speeches at a special meeting the next day. I soon learnt that I was the first Western medical student to work in this Centre. I visited the various departments: Rehabilitation, In-patients, Pathology, Microbiology and Epidemiology.

The Rehabilitation Department consists of 6 doctors who performed over 150 reconstructive operations from 1985 to 1987. Unfortunately, the patients on whom they operated while I was there had not used protective gloves, shoes or glasses, and had not had regular physiotherapy before they came to the Centre for repair of their damaged limbs. The Epidemiology Department is the 'power house' of China's Control Programme. Here, on computer, are available the data of all provinces, autonomous regions and municipalities. Incidence and prevalence rates since 1957 are recorded but, alas, there is little data on disability and deformity rates.

I also managed to visit county, township and village hospitals where I soon realized that the most important parts of the leprosy control programme have not changed since the 1950s: the Provincial Centre organizes manpower; the County Centre trains workers; the Township Hospital will see most of the patients monthly at its outpatient clinic or village clinics; and severe cases or socially uprooted patients, stay at the leprosy village.

The effectiveness of China's leprosy programme

China's control methods of repeated case-finding surveys, replacing Missionary hospitals with Government hospitals staffed by Chinese doctors, and financial assistance from the Government for all leprosy patients since 1950, have produced laudable results. Of the accumulated 500,000 leprosy patients from 1957 to 1988, only 14% are now classified as active cases. Since 1957, 10 provinces (one-third) in the North and North-East of China have achieved the goal of 'basic eradication', i.e. a prevalence rate of less than 0·01 per 1,000, and an incidence rate of less than 0·02 per 100,000. The prevalence of leprosy in children under 15 years of age has fallen from 16% of all

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leprosy patients in 1957 to 0·06% of all patients in 1986. Virtually all this has been accomplished using dapsone monotherapy.

Despite the remarkable effectiveness of incidence and prevalence control measures, the effectiveness of *continuing care*, including the prevention of deformities among the accumulated half a million patients, provides a marked contrast. While the 50 patients with disabilities that I examined came from leprosy villages or the Centre's clinical department and were mostly of the more severe forms of leprosy, they were also the only patients who could be supervised every day. On average, disability or deformity occurred 6 years after the diagnosis of leprosy and 70% of the disabilities were Grade 3, using the WHO scale.[4] On direct questioning, only half the patients said they inspected their anaesthetic areas daily, while only a third exercised their nerve-damaged eyes, hands or feet. None of the patients had special shoes, protective gloves or glasses for their anaesthetic and unprotected disabilities, although 10 patients had had reconstructive operations or amputations.

The worrying aspect of the above is that while China's Leprosy Centre and the leprosy service generally have the organizational skills, manpower, and the Government backing to reduce incidence and prevalence of leprosy, they seem to be lacking in the incentive to prevent and treat deformity among 'cured' patients. This is all the more regrettable since the technology to do so is in fact available.[5,6]

Lessons to be learnt

The disability data in the People's Republic of China, if eventually collected, will show a sad trend. Rehabilitation as a specialty in China began only in the 1980s—decades after America—but, even today, it attracts little enthusiasm as a medical subject among the younger doctors.

The current plan is to build 10 rehabilitation centres; 2 by 1990, which will: 1, research into rehabilitation; 2, retrain 2000 doctors in rehabilitation; and 3, educate patients with Grade 2 disability every 3–6 months. There are, however, grounds for questioning the need for special centres and even the need for doctors in teaching 'self-care'. Workers drawn from leprosy patients themselves, and medical workers like 'community physiotherapists' may be better suited to the job of visiting patients every month (or seeing the patients in clinics), and perhaps organizing a County 'Self-Care' day every 6 months for all patients. Motivation could be enhanced by financial bonuses to workers whose patients' deformities have not worsened during the preceding 6 months.

Perhaps the above is impractical but, either as a result of steady improvement in socioeconomic conditions and/or the application of medical measures (essentially dapsone monotherapy), highly significant reductions in incidence and prevalence have been achieved in the People's Republic of China. It is to be hoped that disability control will make similar progress. The basic organization already exists and in a country with such able and highly motivated people, where so much has been achieved in 'bacillus control', it should be possible to tackle 'disability control' with equal success.

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Obituary

GEORGE HATEM (DR MA HAIDE)
1910–1988

George Hatem was an American physician in the Chinese Communist Army during the revolution and the founder of public health in the People's Republic. The first foreigner to become a Chinese citizen under the Communist regime, Hatem was described by Mao's biographer, Edward Snow, as 'knowing more about Red China and its leaders than any foreigner alive'.

Hatem will be remembered in China as one of its handful of best 'old foreign friends', second only to Edgar Snow himself and Norman Bethune, the Canadian doctor who died during the revolutionary war. He devised, mounted and oversaw the campaigns which virtually eliminated venereal diseases (they have only recently begun to reappear), leprosy, smallpox and other endemic diseases which afflicted millions of Chinese. He was universally known in China as Ma Haide, the Virtuous Foreigner.

Born in the USA of immigrant Lebanese parents, Hatem grew up in Buffalo, New York, and after pre-medical training at the University of North Carolina he studied medicine at the American University of Beirut and then in Geneva, to which he travelled from the Lebanon on a bicycle.

In 1933 Hatem and two other young Americans decided to try doctoring in Shanghai where they set up a venereal disease practice. Before long Hatem became the staff doctor for the police in the Shanghai International Settlement. Years later he remembered 'examining girls from the brothels and cleaning them up until the next dose. A lot of cops were in the same clinic. They wanted *their* whores clean.'

It was Agnes Smedley, the radical American journalist, then writing in Shanghai, who brought Hatem into contact with the Communist underground. Although planning to return to the USA in 1936 he and Edgar Snow travelled secretly to Siam in Central China, then into the 'red areas'. Years later it emerged that Mao Tse-tung had brought Snow to the guerrilla area to tell the Communist story to the world and Hatem to save the lives of the wounded.

It was a great turning point for Hatem who was to devote the next 52 years to the Chinese Communists and the people of China. Snow wrote, 'Dr Hatem was acting on his own conscience alone. He was not a Communist, he spoke no Chinese, he really knew nothing of what faced him and for a young doctor just beginning life he seemed to be burning a lot of bridges behind him.' Snow described Hatem as the only American missionary who volunteered for service with the Communists—'on the other side of the river'.

He soon became invaluable to the Reds, whom he had first taken to be a new sort of bandit. After Norman Bethune's death, Hatem was one of only two Western-trained doctors in the army (the other was a Chinese) and he travelled by mule throughout the 'liberated areas' in danger from both the Japanese forces and those of Chiang Kaishek. In Yanan, Mao's guerrilla capital, he met his Chinese wife, who had refused him until she saw him deliver a baby; 'I didn't think any foreigner could be that gentle,' she recalled.

Hatem witnessed the tumultuous meeting between the two streams of the guerrilla armies at the

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end of the Long March. 'What a reunion. Men threw their arms about each other laughing and weeping at the same time or walking arm in arm and pouring out questions about other comrades.' He saw the legendary commander Chu Teh, who, with Mao, had led the March. 'Thin as a ghost, but strong and tough with a full growth of beard and clad in a lousy skin coat. He looks like the father of the Red Army.' Hatem himself attracted much attention among the guerrilla soldiers who at first assumed he was Stalin's representative.

Almost 50 years later when asked whether he had known the young commissar Deng Xiaoping at the guerrilla headquarters, and whether he thought that some day he would lead China, Hatem replied, 'Never. But I never thought Mao would either. We weren't thinking of the revolution coming in our lifetime. We thought it would be in the next generation—the one after Mao.'

Once the new People's Republic had come to power in 1949 Hatem returned to Shanghai and set about conquering venereal diseases, which in some areas afflicted up to 10% of the population. His medical teams fanned out across the country, his propagandists urged people to seek treatment and brothels were closed. Ninety per cent of all disease carriers were identified and by 1966 Hatem could write, 'syphilis is now under full control through the country'. Not a single new case was found until about 5 years ago. Using the same methods, Hatem claimed, smallpox was eradicated in China 25 years before the World Health Organization stated it was no longer a global problem.

All his life Hatem believed that many diseases arose from political and social origins. After traditionally dying off in their late twenties, Chinese now live into their seventies, a tribute to Hatem's view that 'the old axiom of public health depending on affluence and income and gross national product is not the only road to a healthy population.'

JONATHAN MIRSKY

Reproduced with full permission from *The Independent*, 7 October 1988.

I cannot recall the exact dates, but it must have been either late 1980 or early 1981 that Dr Huan-Ying Li of the Beijing Tropical Medicine Research Institute, Friendship Hospital, Beijing, visited Oxford. She encouraged me to contact George Hatem and to correspond with him about leprosy control and research in China. Late in 1981, my wife Josephine and I had the opportunity to visit the People's Republic in China. She planned to travel with some friends on the Trans-Siberian Railway; I would fly out to Beijing after completing some work in Africa. These were difficult days for 'individual' tourists and we would never have obtained permission to enter without George Hatem's help and influence. On arrival in Beijing, we seemed to become firm friends almost at once. In the quiet of his courtyard house, once the formalities were over, he made it clear that there was work for me to do (although I had intended the whole trip as a holiday) and after some brief but memorable sight-seeing in Beijing, he sent me to Shanghai, where I had the pleasure of meeting Dr Ji Baohong and talking, with Dr Li Futian as interpreter, to many groups of people interested in leprosy control. In May 1982, George Hatem came to Oxford with Dr Ye Ganyun and Dr Su Junrui, as part of a world trip to contact people who might be able to help with their plan of 'basic eradication by the year 2000'. Later still, on his way home from one of his trips to the USA, he came to stay with us in Lower Radley and I have a vivid memory of him talking at length to our daughters, Alice and Hannah, over a breakfast which lasted 2 hours. Children delighted him. He met many people in Oxford working in dermatology, venereal disease and epidemiology and he impressed them all—as he did me—with his quiet confidence and professional knowledge, so obviously based on great experience. From time-to-time, he was kind enough to ask for my advice on the training of doctors and the control of leprosy in China, but in fact he himself saw the most important aspects of these (and many other) subjects with exceptional clarity, and he combined this with ability, determination and compassion, the like of which I have never known.

A COLIN McDOUGALL

It was indeed very shocking to learn that Dr Ma Haide passed away on 3 October 1988 at the age of 78. His passing has been a tremendous loss to the national efforts to eradicate leprosy in the People's Republic of China, and also a personal loss to numerous leprologist and leprosy workers the world over.

Dr Ma Haide obtained his medical degree from the University of Geneva and went to China in 1933 on a short visit which was extended to a period of 55 years of dedicated service to that nation.

Years of service, in medical and health fields in China were recognized by the award of the 'Pioneer in medical and health service of New China' by the Central Government in 1983. A year earlier (1982), he received the Damien–Dutton Award. This was followed with recognition by the 'K W Kellog Foundation for outstanding international contribution to the field of Public Health' (1985), 'Order de Order—Commander' from the President of the Lebanon (USA, 1986). His last award was the International Gandhi Award (GMLF, India, 1988).

Dr Ma Haide had a special relationship with India and had worked with Dr Dwarkanath Kotnis, leader of a 5-member team of doctors deputed by India to China during the years of China's war with Japan. His visit to India to receive the International Gandhi Award was probably his last trip abroad. Accompanied by his wife, Mrs Su Fei, he visited the GMLF headquarters and endeared himself to everyone by his politeness, soft-spoken manners, sharp understanding and his grasp and fresh perspective on all aspects of leprosy.

Friends, colleagues and admirers of Dr Ma Haide will miss him during the XV International Leprosy Congress which is scheduled to be held in Beijing in 1996—the date by which they hope to eradicate leprosy in China. But, nevertheless, he will be remembered for his sweetness of disposition, dedication and determination as a scientist and politeness as a humanitarian.

S P TARE

Lepr Rev (1989) **60,** 67–75

Letters to the Editor

THE USE OF XYLENE (XYLOL) IN MEDICAL LABORATORIES

Sir,

Coincidentally I have recently received two items of information concerning xylene (xylol) which may be of interest to laboratory workers, especially when large volumes are used for histopathology processing or other purposes.

1 *The use of xylene to remove (clean) immersion oil from microscope slides after examination for acid-fast bacilli*

Some months ago a medical student in Oxford asked me if the use of xylene for this purpose, especially if repeated, could impair the red (carbol fuchsin) staining of mycobacteria. I have never noted such an effect, nor heard of it from those with experience over many years in the examination and re-examination of slit-skin smears for leprosy bacilli. With regard to the use of xylene for cleaning microscope slides in tuberculosis, Dr B W Allen (Royal Postgraduate Medical School, Hammersmith Hospital, Ducane Road, London W12 0NN) has written to say that he has never noticed deterioration in acid-fastness, even after several cleanings. Nevertheless the question remains somewhat disconcerting, since slides in both leprosy and tuberculosis are often re-examined, sometimes several times, by supervisors or reference laboratories. I would be most interested to know if any of your readers have carried out a systematic study to see if there is in fact any recordable deterioration, especially after repeated use of xylene.

2 *A xylene substitute*

Xylene (xylol) is classified by the Health and Safety Factory Inspectorate of the United Kingdom as a material of 'medium' danger in laboratory, commercial or industrial situations. Apart from its hazard to health from inhalation or accidental ingestion, it is also highly flammable. It may be helpful to know that a substitute has been produced (Shandon Southern Products Ltd, 93–96 Chadwick Road, Astmoor, Runcorn, Cheshire WA7 1PR, England) which is non-flammable; readily distillable for re-cycling; not harmful to plastic parts of processors, etc; non-sensitizing to normal skin. It also has an airborne exposure limit three times safer than xylene (TLV is 300 ppm). Price: UK £27.00 for 4 litres.

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SUGAR AS AN AID TO WOUND HEALING AND THE TREATMENT OF ULCERS IN LEPROSY

Sir,

In the 7 December 1985 issue of *The Pharmaceutical Journal*, Drs Middleton and Seal, writing from the Departments of Pharmacy and Microbiology at Northwick Park Hospital, Watford

Road, Harrow, Middlesex, HA1 3UJ, England, describe the use of sugar paste in the treatment of abscess cavities and pressure sores with good results. The formula they use for sugar paste is as follows:

	Thin	Thick
Castor sugar	1200 g	1200 g
Icing sugar (additive free)	1800 g	1800 g
Polyethylene glycol 400	1416 ml	686 ml
Hydrogen peroxide 30%	23·1 ml	19·0 ml

The consistency of thin honey is suitable for installation via a syringe and fine plastic tubing into abscess cavities and small openings.

One of our nursing sisters encountered the above article recently and developed a thick paste composed of simple white sugar and 'Betadine' (providone–iodine 10% in a water-miscible base; UK cost is £1.85 for 80 g). This avoids the use of polyethylene glycol 400 in the above formulation, which unfortunately costs UK £62.00 per litre. Our paste has been tried out on leprosy patients with ulcers in our programmes in KwaZulu, Swaziland and Ciskei, and the results so far are extremely encouraging. Where there is no underlying bone or tissue damage, the healing period for ulcers has been reduced from 6 to 3 months. Patients can apply the ointment daily, which has helped to improve many patients' attitudes in self-care. We have also had an outstandingly good result in one seriously ill patient who developed ulcers on buttocks and thighs following septicaemia.

In view of the high cost and frequent difficulty of obtaining plaster of Paris and other materials for the treatment of ulcers in leprosy, we consider that the above approach merits serious consideration and further trial. We record these preliminary impressions and look forward to hearing from readers of *Leprosy Review* who have to care for large numbers of patients with ulcers and who may be encouraged to try this inexpensive method of treatment. We would be happy to supply a sample of this paste on request.

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L A WISEMAN

BLOCKING OF HAEMOLYTIC COMPLEMENT BY HETEROGENEOUS FACTORS PRESENT IN LEPROMATOUS LEPROSY

Sir,

Patients with lepromatous leprosy have characteristically high levels of circulating immune complexes (CIC).[1] In another study, it has been reported that CIC vary in size when sera of systemic lupus erythematosus patients were separated on a gel column.[2] Of special interest is the study of whether or not the anticomplement activity (ACA) formed in sera of patients with lepromatous leprosy are homogeneous or heterogeneous substances which can be separated from other sera proteins. The present investigation has studied the possible use of gel filtration for removing ACA of lepromatous leprosy sera.

Fresh serum was obtained from patients presenting Hansen's bacillus infection and used immediately. Nine pooled lepromatous leprosy sera (4 ml) were chromatographed on a G-200 Sephadex column measuring 4 × 90 cm and the fractions were tested for complement haemolytic activity consumption.[3] Briefly, the protocol for each one of the intervals of the three peaks filtered through the column consisted of incubation of 100 μl of triethanolamine buffer, 100 μl of optimal dilution (1:30–1:50) of guinea-pig sera (complement source) and 50–100 μl of elution fractions for 10 min at 37°C. The sensitized sheep erythrocytes (EA, 25 μl) were then added. After incubation, 20 ml of ice-cold buffer was added; the tubes were centrifuged and the haemoglobin was determined

and recorded with the absorbance at 420 nm. For controls, buffer or fractions from normal sera were used instead of sera fractions from patients. The outlined method indicates that ACA was more evident in certain eluted fractions. Indeed, ACA was excluded from G-200 Sephadex resin just before the first peak, with only a small amount retarded in its elution (Figure 1). Thus: (a) the material (only 10 μg in protein) in the void volume peak inhibited 100% of EA lysis. It was further observed that heating this active material at 56°C for 30 min caused removal of most of ACA from the chromatographic fraction; (b) no ACA was detected in the top of the second peak even at a higher protein concentration (300–500 μg) (this is contrary to the pattern of separation of ACA in

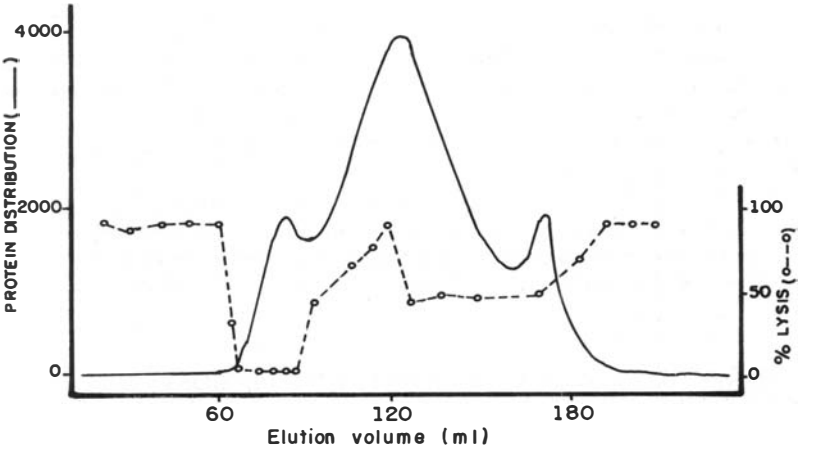

Figure 1. Protein distribution (280 nm) and haemolysis-inhibiting activity (420 nm) following G-200 Sephadex gel filtration of lepromatous leprosy serum.

patients with Chagas' disease or schistosomiasis mansoni)[3,4] and (c) the region between the descendent fraction of the second peak and the third peak showed 30–55% EA lysis inhibition at a higher protein concentration (200–300 μg). Chromatographic effluents from control individuals were negative for ACA (results not included). The relatively large size of the second peak compared to the other two peaks may be due to the hypergammaglobulinemia which is known to occur in the sera of lepers. However, this point was not pursued.

Although these experiments have not established the exact size of the proteins eluted from G-200 Sephadex and also have not defined the factors at the molecular level responsible for ACA, the anti-haemolytic action formed by lepromatous leprosy vary in size as can be seen by a heterogenous elution pattern of a G-200 Sephadex column.

Since ACA are often identified by the affinity for complement, a more widely used method for their demonstration is based on the decrease of complement haemolytic activity.[5] However, it has been reported that various inhibitors are not easily distinguished from circulating immune complexes[5,6] when one is using the haemolytic evaluation of the anticomplementary activity.[5] In this respect it is difficult to ascribe the ACA detected in the third fraction due to the presence of classical antigen antibody complexes. It is known that immune complexes can not be observed in the low molecular weight (third peak) of Sephadex G-200. Furthermore, the G-200 Sephadex column and the haemolytic techniques have made it possible to detect heterogenous material in fractions from sera of patients with lepromatous leprosy which inhibit the lytic effect of complement system, *in vitro*, so that their nature may be more precisely determined. The significance of the ACA in

lepromatous leprosy is uncertain. In fact, little is known about the role as yet played by the complement system in human parasitism.

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B C NASCIMENTO, E O CISALPINO & M CHAMONE

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REPLY: NONSEPTIC TARSAL DISINTEGRATION IN LEPROSY

Sir.

We have done a study on more than 50 cases of tarsal disintegration (TD). The research work comprised studying various biomechanical and other factors involved in the aetiopathology of this neuropathic entity.

To date we have a record of 28 cases having the nonseptic variety of TD. None of them had a history of ulcers. Out of 28 cases (2 bilateral) the majority were of the borderline–tuberculoid variety. All of them were under regular antileprosy treatment and had negative skin smears. Twenty-two patients had medial pillar involvement, 6 patients had posterior pillar involvement and in 2 patients all pillars were involved.

Among 28 there were 5 cases who underwent tibialis posterior transfer surgery for foot drop. These patients were treated with ordinary MCR footwear with arch support and follow-up showed stable lesion.

The rest of the patients were treated successfully by Fixed Ankle Brace (FAB) Walkers and a period of 2 years of follow-up showed stable results.

Superficial and deep sensory testing could be performed only in 8 patients. All of them had total loss of superficial sensation. There was a loss of joint position sense in all. All of them had higher vibratory threshold values when compared with the other leg.

Superficial sensory testing has direct correlation with the process of disintegration: however, loss of deep sensation does not seem to have predictive value as observed from our experience.

All the cases who had TD had significantly higher vibratory threshold values, but all cases having higher vibratory threshold need not have TD. This was observed in a separate study where in 40% of the patients who had no ulcers and no signs of TD had abnormal vibratory threshold values.

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V N KULKARNI

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Mr Kulkarni has thrown interesting light on this subject. It is particularly valuable that they have demonstrated a correct approach to early prevention of further damage, once the loss of proprioceptors is a fact. If, as the preliminary evidence indicates, early diagnosis of loss of joint position sense is of predictive value, then there really is hope that we may be able to prevent at least many of the late, unfortunate and disastrous results that too often leads to ablative surgery with all its unhappy effects.

J G ANDERSEN

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REPLY: NONSEPTIC TARSAL DISINTEGRATION IN LEPROSY

Sir,

Dr J G Andersen has written about 'Nonseptic tarsal bone disintegration in leprosy' and asks about other cases (*Lepr Rev*, 1988, **59:** 187). What he describes is not unusual in the Eastern half of Asia.

In the first patient that he speaks of he states '. . . some new bone formation of a hazy nature' was seen along with the lysis of other bones. This statement provides the clue to management.

A large proportion of tarsal bone disintegrations is nonseptic and the remnants of bone are still in the foot—though virtually invisible because of the degree of osteoporosis. If the foot is completely immobilized in a functional position in a contact walking plaster cast the bones will return. That is, recalcification to occupy the shape as moulded in the cast, will recur and eventually (9–12 months) the bones will be hard enough and sufficiently sclerosed for the patient to walk again without braces or moulded footwear. Healing should be carefully tested clinically, by a trial of walking—starting with a few minutes a couple of times daily and increasing the duration daily, provided there is no heat or swelling (hot spots). The occurrence of hot spots that persist or rapidly recur suggests that the contact cast needs to be replaced for a further 2–3 months.

These patients can be detected early by teaching the patient to look for 'hot spots'. Although there is usually no direct history of trauma, the initial lesion is usually a fracture, which may be very mild and go unnoticed because of no pain. Osteoporosis develops around any fractured bone and the weakened bone is then fragmented as the two edges rub together during use. Biopsy has shown that osteoclastosis and osteoblastosis are normal but continued movement prevents the formation of solid bone. So it is not unusual to find evidence of 'new bone' in radiographs.

Unfortunately, there is no satisfactory way of neurological testing that will prewarn of the possibility of a degeneration occurring. Any patient with a sensory neuropathy may be affected, but some patients have developed marked neuropathy in the presence of apparently normal motor and sensory function. Obviously, deep sensation can be affected without superficial neural deficit.

Prevention lies in teaching daily self-care, which these patients apparently did, together with checking for hot spots. The patient can be taught to check and institute therapy early, if needed, before marked deformity has occurred. He needs to know the significance of a hot spot.

The reconstructed bones will last many years (I have follow-ups of over 20 years now) provided the shape achieved in the plaster is compatible with use. Feet that are grossly deformed can be reshaped surgically and bone healing will occur. It is probably easier to wait 3–6 months in plaster before starting reconstructive surgery, so that the bones have somewhat reconstructed and one can see better what one has to work with. Sometimes the bones are soft enough to cut with a knife!

There is no place for surgical decompression in the swelling phase—the swelling will subside when movement is stopped.

Early diagnosis carries a good prognosis if adequately treated.

The Leprosy Mission GRACE WARREN
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Dr Warren rightly underlines that nonseptic tarsal disintegration is not uncommon. I am in full agreement with the outline of treatment and prevention that she employs. Certainly it is a major tragedy to come across patients with tarsal nonseptic disintegration that require major ablative surgery. This must at all costs remain the very last resort.

Unfortunately the correct treatment requires not only a good understanding and cooperation from the patient, but also social and economic conditions that well may prevent the patient from accepting the correct treatment. Less than perfect peripheral services may often mean that these patients simply come too late for correct treatment.

I am puzzled by her statement that there is no satisfactory way of neurological testing that will prewarn the possibility of a degeneration occurring.

My own experiences indicate that absence of joint and position sense, as distinct from sensory loss, is an eliciting factor, although not all people with loss of proprioceptor sensation do develop nonseptic tarsal disintegration. The remark that surgical decompression has no place in the management of this condition must be underlined. 'Where there is pus, evacuate. Where there is no pus, for goodness sake don't evacuate.'

Braineparken 85 J G ANDERSEN
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Denmark

REPLY: NONSEPTIC TARSAL DISINTEGRATION IN LEPROSY

Sir,

I want to respond to the letter on this subject by Dr J G Andersen. In reading over Dr Andersen's letter he talks of doing major ablative surgery in patients who have had tarsal disintegration. I'm not clear as to what he means, I think the implication is amputation.

In my experience it is rarely necessary to amputate for tarsal disintegration, even when there is marked destruction of bone. It is usually possible to arthrodese what bone there remains by cutting flat opposing surfaces and bringing them together by the use of a Charnley clamp applied to Steinman pins for opposition and fixation.

In instances where there are inadequate bony surfaces to provide solid fixation with a Charnley clamp a 3 pin procedure can be used. Thus, when there are 3 bones that can be brought into apposition, the opposing surfaces are prepared and fixed with 3 pins. In order to hold the Steinman pins they are encircled at either end with long strips of rubber which are cut from an inner tube of a tyre. The duration of fixation in such cases is necessarily somewhat longer than for a normal extremity in which there is sensation. In nearly every instance a good functioning extremity will result. If protective footwear is supplied this can provide a practical and functional foot.

I recall one patient who had a completely flail ankle joint and approximately 4 inches of shortening of the distal end of the tibia. Even in this extreme situation it was possible to obtain a solid bony fixation and provide adequate function for ambulation after this type of surgery, plus footwear with ankle support.

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R E PFALTZGRAFF

Drs Pfaltzgraff and Warren have responded with an excellent description of the correct treatment of such conditions. With this I am in full agreement. Nor should ablative surgery be necessary. That it unfortunately may become so, is probably to some extent due to problems in the field management of the disease. I wanted to mention that I have consistently found absence of response to vibration test, indicating loss of proprioceptor sensation. In my present situation I am unable to follow up this observation. I therefore ask workers with the potential for such studies to do so. None of us has mentioned that the differential diagnosis of nonseptic tarsal disintegration against deep septic infection or oedema of other aetiology may be difficult. Neither antibiotics nor corticosteroids have any place in the management of this condition.

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J G ANDERSEN

REPLY: NONSPECIFIC TARSAL DISINTEGRATION IN LEPROSY

Sir,

In recent travels in Africa this year, I saw 2 cases, reminiscent of that described by Dr Andersen, hospitalized in 2 different countries. In neither case were the team aware of the need to detect and prevent this distressing complication of leprosy.

In one case, a heavy man who had been on bed rest after an amputation of one leg walked with crutches too much and too soon after immobilization, and in the absence of adequate pain protection pounded the osteoporotic talus of the 'good leg' to fragments. Radiologically the talus was fragmented and the tarsal architecture disintegrated.

The other case (clinically diagnosed as early disintegration) was a woman with a hot swollen ankle, walking too early and too much just after ulcer healing by immobilization, started her on the slippery path towards total disintegration. Hopefully if the precautions given were observed her foot will be saved.

There is no way a sprained ankle can stand uninhibited walking in the absence of pain protection without disintegrating, especially if the tarsal bones are already weakened either by disuse, osteoporosis or infection.

Although the degree of anaesthesia is scientifically interesting and may be predictive, all patients with anaesthetic feet should be aware of the dangers of diminished (if not absent) protection of their ankles by pain, and appropriate deformity prevention measures observed.

J R HARRIS

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Reference

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REPLY: CORTICOSTEROID-INDUCED ACTIVATION OF CHRONIC ULCERATION IN LEPROSY

Sir,

In response to the letter by Dr J G Andersen (*Lepr Rev*, 1988, **59,** 185) I would like to comment as follows: Certainly one wants to prevent ablative surgery in every instance where there is damage to an extremity but I do not think it is necessary to recommend that steroids not be used when indicated for control of reaction. This, the control of reaction, is so extremely important in order to prevent progressive nerve damage and destruction to limbs that it is essential to implement it in every instance.

For this reason any person with plantar or other ulceration should be given an antibiotic to control secondary infection when it is necessary to suppress reaction. Destructive surgery is almost never necessary and the use of antibiotic coverage is vital to attain that goal. It was my practice to use penicillin for any patient with any ulceration in which there was a possibility of a secondary infection. When that did not obviously begin to control the infection rather promptly, it was augmented by the addition of streptomycin.

In this way when a patient has plantar ulceration and also an active reactive state it is possible to treat both of these problems at the same time. This approach to the management of reactions in a patient with ulcerated extremities is entirely satisfactory—it was used repeatedly.

R E PFALTZGRAFF

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Dr Pfaltzgraff rightly underlines that we should not omit treatment of reaction with corticosteroids if they are indicated. Neither should ablative surgery be necessary. My communication was prompted by several unhappy experiences where deep, septic infection in the foot was overlooked with disastrous results. I wanted to emphasise two points: even deep purulent infection does not respond with such activation, provided there is free, open drainage from the focus. And secondly that antibiotics have little if any effect on such closed purulent infection.

I notice that Dr Pfaltzgraff recommends the use of penicillin and streptomycin. My own preference would be sulphadiazin/trimethoprim, occasionally supplemented with metronidazol.

Thus we avoid the use of questionable syringes and make the medication easier to administer in the field.

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J G ANDERSEN

A 7-GROUP CLASSIFICATION OF LEPROSY FOR INSTITUTIONAL AND FIELD WORK

Sir,

For most of this century a dialogue has gone on to evolve a consensus classification which could meet the requirements of both institutions and field workers. The terminology used in this dialogue has been a source of confusion to many workers.[1] An important element in all systems of classification has been the use of clinical criteria for delineating the disease and since this is a subjective activity, likely to differ from one individual to another, it has undoubtedly fuelled the controversy. Many of the systems in use today are not reproducible from one centre to another and this is a major handicap between various international and Indian classifications.

It is important to recognize that the five groups, namely TT, BT, BB, BL and LL,[2] not only take cognizance of clinical features, but also of bacteriological, immunological and histopathological characteristics. Indeterminate leprosy does not find a place in the spectrum, but in fact, it is an important entity. Furthermore, leprosy manifesting in the form of thick and tender nerves without any evidence of lesions over the skin surface is another important clinical entity, particularly in some parts of the world, and provision should be made for its inclusion, notably in India. I do not wish to confound the issue by proposing yet another system of classification, but rather to suggest that 7 groups would indeed be valuable in both institutions and some control programmes. These could be tuberculoid, borderline—tuberculoid, mid-borderline, borderline—lepromatous, lepromatous, indeterminate and polyneuritic. Finally, I would greatly favour classification based mainly on *clinical* findings in situations where histopathology, immunology and slit-skin smear services are either not available or unreliable.

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Reference

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Lepr Rev (1989) **60,** 76–77

Leprosy Control and Field Work

Directions: PATH

Directions, Volume 8, No. 2 draws our attention to 2 useful publications: Practical suggestions for community involvement in programme evaluation are contained in *Partners in evaluation: evaluating development and community programmes with participants* by Marie-Thèrése Feuerstein. To obtain a copy write to: Teaching Aids at Low Cost (TALC), PO Box 49, St Albans, Hertfordshire AL1 4AX (cost £1.50).

On being in charge: a guide for middle-level management in primary health care is an excellent resource book with practical techniques and suggestions for improved management. It is available to developing countries at reduced rates from WHO Regional Offices or WHO, Distribution and Sales Service, 1211 Geneva 27, Switzerland.

The copy book—free of copyright!

The copy book published by Intermediate Technology Publications Ltd aims to be understood world-wide 'because it is a picture book with a difference'. Extracts from the press release read as follows:

'*The copy book* is jammed full of illustrations on food, health, work and shelter for use by field workers in developing countries. All the pictures have been donated by members of the Association of Illustrators and are free of copyright.

The project arose out of an article in *Illustrators*, the Association of Illustrators magazine. The article challenged commercial illustrators in the developed world to use their powerful marketing techniques to get across more helpful messages than those they had put out when working for international corporations.

A meeting of interested illustrators, publishers and development workers followed and 2 men, Bob Linney and Bruce Wilson, were inspired to take up the challenge. *The copy book*, is the result.

In the poorest rural and urban areas of many developing countries there is a severe shortage of posters and aids for health and development. Most of the materials produced are not understood by poor rural people because their level of visual literacy is low.

Posters need to show objects and figures that people can easily recognize from everyday life. *The copy book* aims to encourage local workers to make their own drawings and adapt the book's illustrations for their own use.

Through the book, Linney and Wilson have also tried to introduce British illustrators to 'development communications' in order to introduce to schools the idea as an aid in classes on art, development and health.

The book is available from Intermediate Technology Publications Ltd, at Unit 25, Longmead Industrial Estate, Dorset, SP7 8PL, for £9.95 plus £2 postage and packing or from the IT Bookshop, 103–105 Southampton Row, London WC1B 4HH.

Britain–Nepal Medical Trust

The 1987 report of the Trust describes a period of consolidation after the expansion in eastern Nepal in the previous year. Many patients were treated in the new Khotang clinic—121 patients with pulmonary tuberculosis were diagnosed in the first year. The other main aims of the Trust at present are leprosy control, drug supply and distribution, and community health leader training programmes. Six of the 8 clinics are now run by Nepalis, and the Trust has a staff of 80 Nepalis and 9 expatriates. In the hill districts, which might have only 1 doctor for 150,000 people, the Trust provides an important community service. The chairman, Dr John Cunningham, notes that 1988 marks the 20th anniversary of the founding of the Trust; discussions with the Nepal government will take place to decide future plans, which may include an expansion of the tuberculosis support programme in further districts in the Terai.

Address: BNMT, Stafford House, 16 East Street, Tonbridge, Kent TN9 1HG.

Supplies of medicines in developing countries

From the *Lancet*, 7 May 1988, page 1063:

Many patients in developing countries are denied access to life-saving medicines not only because of limited health-care budgets but also because of inappropriate government legislation, inefficient means of distributing supplies, and irrational prescription practices. In India, for example, drug overproduction co-exists with shortage of essential drugs for treating and preventing widespread diseases such as tuberculosis, vitamin A deficiency, and iodine deficiency goitre. One reason for this paradox was legislation in force until recently which restricted the manufacturer's profit margin on essential drugs. In Kenya, when drugs for primary health care units were distributed from hospital stores, 25–30% of the supplies used to be stolen for sale privately; centralization of distribution centres and regular issue of drugs in ration kits have cut down on this waste.

A report from the British Medical Association's Board of Science and Education examines these and other factors that influence the availability of medicines in developing countries and makes recommendations on what governments can do. In the case of imported drugs, a simple means of quality control is participation in the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, backed up by national licensing and registration systems for companies and products. However, since many developing countries lack the necessary infrastructure for regulating the quality of drugs, international standards are needed, and here the booklet urges prompt implementation of the Bannotti report, adopted by the European Parliament two years ago, on the export of pharmaceutical products to the Third World. Drug marketing practices also need to be controlled. The International Federation of Pharmaceutical Manufacturing Associations has a code of marketing practice; but, as the booklet points out, there is no provision for penalty when the code is breached, and the code does not apply to the over-the-counter drugs.

The British Medical Association's address is: Tavistock Square, London WC1H 9JR.

Arogya Agam, India

John Dalton has very kindly supplied the following account of this voluntary organization working under the National Leprosy Eradication Programme in India:

Arogya Agam which means 'place of health' in Tamil, was started 25 years ago by an English woman named Dora Scarlett. The area of operation is Aundipatty Taluk of Tamil Nadu, whose plains area rises into the remote Varusanadu valley which is still feared for its reputation for lawlessness. The upper slopes give way to thick forest interspersed with tea, coffee and cardamon plantations. The total, population is around 200,000 spread over an area of more than 1000 km^2.

In 1963 the first 7 patients were treated under a tree and the team travelled by bullock cart. It was only in 1982 that the unit had the 8 paramedical workers and other staff and infrastructure needed to cover the entire area. A temporary admission ward with 40 beds was constructed and the set pattern established under the National Leprosy Eradication Programme of the Government of India. These developments were all made possible with the help and encouragement of The Damien Foundation.

MDT was introduced in stages from 1983 and for all patients by late 1986. By 1988 MDT coverage had reached 95% of all known active cases with an annual drop-out rate of less than 10%. This was achieved by increasing the number of both treatment circuits and stopping points, increased responsibility given to the PMWs also gave good results. The caseload fell from a maximum of 2400 in 1984 to between 500 and 600, where it seems to have levelled off in 1988. Similarly, active prevalence fell from around 15 to an estimated 6 per thousand. The faster turnover of cases under treatment is now balanced by the increased case finding made possible by the availability of time previously used for case holding. Various methods, such as 'enquiry' and 'rapid' survey have been tried out, but it is found that systematic total population survey is the most efficient way of detecting the very early cases, it is more efficient still when done as a team. Annual school and healthy contact surveys are also carried out.

Given the importance of health education 2 extra staff, skilled in communication, were engaged and education was given in the villages on other vital health topics also, especially mother and child health.

A number of methods for imparting health education are in use as no one method can fill all needs.

The falling caseload followed by fewer patients requiring surveillance will allow further diversification of the work. A community health project has already been started and there is a need for the rehabilitation of those who are disabled. Other potentially suitable areas of work include the control of tuberculosis and perhaps of AIDS, the future spread of this disease seems inevitable.

Contact: Arogya Agam, Aundipatti 626512, Madurai District, South India.

Special supplement on experimental leprosy chemotherapy

From the *TDR Newsletter*, No. 25, Winter/Spring 1988:

Papers presented at a workshop cosponsored by TDR and the Sasakawa Memorial Health Foundation were published as a supplement to the *International Journal of Leprosy*, Vol. **55,** No. 4 (December 1987). A limited number of copies are still available free of charge. Work covered includes the latest progress in research on experimental leprosy chemotherapy and the application of mouse footpad techniques in monitoring clinical trials. Interested scientists should write to: Dr Ji Baohong, Secretary, Steering Committee on the Chemotherapy of Leprosy, World Health Organization, 1211 Geneva 27, Switzerland.

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Teaching Materials and Services

Health teaching made easier: How to create a manual. *Contact*

The October 1988 issue of *Contact* No. 105 contains a very useful and extensive item on 'Health teaching made easier: How to create a manual' by Birgitta Rubenson, RN, MPH. Suggestions are given on how simple learning materials can be produced by teachers and health care supervisors to help health workers. The ideas, directions and examples given can also be easily adapted for use when producing other kinds of learning materials. Some points from the main headings are:

Objective of the manual. The questions: 'Who are the readers going to be? What is the message of the manual?' are asked. Health workers should be able to identify with the content in the manual. The better defined the group of readers are, the more useful the manual will be. In a good manual the health worker can recognize him or herself and the working situation.

Structure and style. Here guidelines for writing simply are given, for example, use simple, short common words, explain technical words. The language has to be simple, so that the health worker can understand and learn. The manual should be written for the reader to understand and learn, not for the writer to show his knowledge of profession and language.

Illustrations. Several examples of illustrations are displayed and the author states that: 'Illustrations can make explanations clearer and more easily understood, but they can also cause confusion. It is important to use clear, simple illustrations in the right way. They serve to: make the text more inviting to read: highlight important issues; explain difficult concepts; and increase understanding.'

Layout. Layout is the way you arrange the text and illustrations on the pages of the manual. You need to decide on: the size of the pages; the margins; the type of headings and sub-headings; and the type of letters.

Conclusion. We have given you some help on how to prepare simple learning materials for students and staff. There is a great need for these materials using local languages and customs. If you have some information to share, we encourage you to try and then let us know how you get on. In case of great need, CMC has a small fund to support printing of locally produced materials. If you have questions or concerns in relation to preparing materials you are invited to write to *Contact*. This issue also gives details of other publications which could prove useful:

Helping Health Workers Learn, by David Werner and Bill Bower, 1982, 632 pages. This book, by the authors of the village health care handbook, 'Where There Is No Doctor', is a collection of methods, aids and 'triggers to the imagination'. It is based on 16 years of experience with a villager-run health programme in the mountains of western Mexico. Written in clear, basic English with hundreds of drawings and photographs to emphasize the key points, its focus is educational rather than medical.

The book is aimed at instructors and health workers who identify with the working people and who feel that their first responsibility is to the poor. This community-based approach tries to help people analyse and improve their situation. For more information write to: *The Hesperian Foundation, PO Box 1692, Palo Alto, CA, 94302 USA.*

Teaching Health-care Workers, A Practical Guide, by Fred Abbatt and Rosemary McMahon. MacMillan, 1985, 249 pages. This book is very useful for teachers who train health care workers, especially in developing countries. Specific guidance is given on decisions about what students should learn, how to teach, and planning training programmes. *For more information write to: TALC, Box 49, St Albans, Herts, AL1 4AX, UK.*

Teaching for Better Learning—a guide for teachers of primary health care staff, by F R Abbatt, funded by the Government of the United Kingdom Overseas Development Administration, 1980, 137 pages. What should your students learn? How can you help your students learn? How do you know whether your students have learnt? How do you prepare teaching materials? These are essential questions to ask before starting to teach others. And this book answers these questions with the help of many other experienced people. *For more information write to: TALC at the above address.*

To obtain a copy of issue No. 105 of *Contact* write to: CMC/WCC, PO Box 66, CH-1211 Geneva 20, Switzerland. Cost including postage is SF2.50 (US$1.50).

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News and Notes

World Leprosy Reports

World Leprosy Reports is a new publication presented in brochure style and is prepared by the staff of the Gillis W Long Hansen's Disease Center, Carville, Louisiana, USA. It summarizes current educational, treatment and research activities world-wide. John C Duffy, the Editor writes:

'Information reported on here is not always available at our Center. Whenever possible, we will include ordering information. This is a limited distribution publication, duplication is encouraged.

Intended as a resource list and information exchange, *WLR* strives to disseminate recent and relevant information about all aspects of the disease (prevention, control, treatment, research, rehabilitation, training and education) and other areas with direct or indirect application.

We plan on a quarterly publication schedule. Colleagues in all fields are encouraged to communicate with us about new or innovative programmes or publications so that current developments in the field can be reported quickly. Please understand. Our intention is not to produce a Carville publication. *WLR* is a place to share information for all. This first issue was made possible by a grant from the Hansen's Disease Foundation. Future support will depend upon the degree of interest.

Your letters and comments are always welcomed and appreciated. The Center has language capabilities in Spanish, French, German, Portuguese, Hindi, Punjabi, Tamil, Farsi, Estonian, Amharic, Chinese and Japanese. While we are unable to publish articles in those languages at present, we can translate your letters and respond.

Only you can tell us if you find "Reports" helpful. Without your interest, this initiative will fail. We look forward to hearing from you.'

If you wish to receive *WLR* send your name, address and profession to: Gillis W Long Hansen's Disease Center, Training and Education Branch, Carville, Louisiana 70721, USA, requesting to be added to the mailing list.

TDR: Field research in leprosy. H D Engers and Ji Baohong

The following is taken from *TDR Newsletter* No. 26, Summer 1988.

The TDR Components on the Chemotherapy (THELEP) and Immunology (IMMLEP) of Leprosy have established a new joint subcommittee on field research in leprosy. The objective of the first meeting, held in Geneva in April 1988, was to promote leprosy-related field research in the following areas: field-testing of new tools—drug regimens, vaccines and diagnostic assays—for leprosy control; development and evaluation of the delivery of leprosy control measures in endemic countries.

The subcommittee's role will be to identify and promote promising areas for field research in leprosy and to support areas of research which need to be strengthened, including the role of social and economic factors in leprosy, studies of effectiveness (including cost-effectiveness) of current control programmes, and the management and, more importantly, prevention of disabilities.

The subcommittee identified specific field research topics for the short to medium term, which fell under 5 broad headings: methodological research concerned with diagnosis and related problems; aetiological studies on the epidemiology and natural history of leprosy; studies on secondary prevention and the efficacy of such treatment(s); and operational studies aimed at measuring and improving the effectiveness of leprosy control programmes.

Scientists wishing further information, including indications of possible study methods and protocols, and/or research proposal forms should write, as appropriate, to Dr Ji Baohong, Secretary, THELEP Steering Committee, or to Dr H D Engers, Secretary, IMMLEP Steering Committee, at the following address: World Health Organization, 1211 Geneva 27, Switzerland.

Netherlands Leprosy Relief Association (NSL)

The following is a profile of the Netherlands Leprosy Relief Association:

Objective and policy: the NSL is the national Dutch organization for the campaign against leprosy. It assists its partners in developing countries, generally speaking the local governments, in their activities to control the poverty disease leprosy and does so irrespective of race, politics or religion. The aim of the NSL is to integrate

leprosy control activities into the general health system; it operates as an organization of medical development cooperation.

Education and training of local personnel are important aims of the organization, which cooperates closely with leprologists of the Royal Tropical Institute, who play an advisory role in NSL projects. NSL promotes and finances leprosy research. This includes medical laboratory research in the Netherlands and in developing countries as well as sociomedical field research. Health education in the supported projects is also included.

Organization and finance: the Association is a private foundation with a Board and a Supervisory and Advisory Council. The members of these bodies are appointed on the basis of their functional qualities. It cooperates with 23 sister organizations in the International Federation of Anti-Leprosy Associations (ILEP) and maintans contact with the WHO and makes use of WHO-guidelines. The NSL cooperates with the Dutch government, which has contributed to the funding of certain NSL projects since 1978.

The NSL sends out experts. In 1987 there were 32 (mainly doctors and physiotherapists, and 2 NSL-representatives in Nigeria and Kenya) working for the NSL in developing countries. The NSL supports projects in Africa, South America and Asia. Most of these experts work in Africa, e.g. Tanzania, Kenya, Nigeria and Ethiopia). Recently the Association has increased its activities in Asia, e.g. in Nepal, Indonesia, Thailand, Vietnam and China. The NSL is responsible for the organizing of the World Leprosy Day in the Netherlands (the last Sunday of January).

The NSL publicly accounts for the execution of its activities and the expenditure of its funds. The income of the NSL mainly consists of private donations, legacies and interest.

Projects: in 1987, the NSL supported 55 leprosy control projects in South America, Asia and Africa as well as several scientific research projects. Nearly 8 million Dutch guilders a year are spent on these projects.

Leprosy histopathology

At the recent XIIIth International Leprosy Congress in The Hague, Dr J M Broekman kindly indicated that he would be glad to receive biopsies of skin and other tissues from leprosy patients (or from patients with other conditions if there is diagnostic difficulty), and to send out a written report. Specimens should be full depth in the case of skin, of adequate size and without evidence of squeezing (for instance by forceps during removal). The fixative preferred is 10% buffered formalin, which should be prepared at fairly frequent intervals, so that batches are fresh. Please send specimens, with full clinical details, including any treatment given to: Dr J M Broekman, Department of Pathology, Grootziekengasthuis, Nieuwstraat 34, 5211NL, 's-Hertogenbosch, Netherlands.

2nd Asian Dermatological Congress, Singapore, November 1989

The Dermatological Society of Singapore, in conjunction with the Asian Dermatological Association, is organizing the 2nd Asian Dermatological Congress to be held in Singapore from 23–26 November 1989. The Congress will serve as a forum for scientists, research workers and clinicians, involved or interested in the latest advances in dermatology. The topics to be covered include: new strategies in management; microbiology, including AIDS; immunology and allergy; update in psoriasis; contact and industrial dermatitis; pigmentary disorders; cosmetic surgery; skin cancers; and dermatopathology. There will also be plenary lectures, symposia, pre- and post-Congress workshops.

For further information write to: 2nd Asian Dermatological Congress, c/o Communication Consultants, 20 Kramat Lane, #03-07 United House, Singapore 0922.

Mycobacterial disease: developments in serodiagnosis and therapy

This volume of approximately 100 pp is the Proceedings of a symposium of the same title and is No. 313 in the series *Bulletins of the Royal Tropical Institute*. The Institute's press release states:

The Proceedings are of interest to lung physicians, specialists in infectious diseases, dermatologists, medical microbiologists, and newcomers to the research field of mycobacterial diseases.

The first chapter is an introduction to the epidemiology of tuberculosis, leprosy and diseases caused by atypical (opportunistic) mycobacteria. The increase in tuberculosis and atypical mycobacterial disease in AIDS patients and the increase of atypical mycobacterial disease in the general population are detailed here.

The laboratory contribution (Chapters 2 and 3) deals with new developments in the detection of mycobacteria, questions such as the antigens relevant to protective immunity, the use of recombinant DNA clones for serodiagnosis and skin tests and the prospects for vaccines obtained by recombinant DNA techniques.

The manifestation and treatment of tuberculosis in AIDS patients are discussed in Chapter 4.

Diseases caused by *M. avium, M. intercellulare* and *M. scrofulaceum* (MAIS) complex, the various manifestations and the treatment of these infections are outlined in Chapter 5.

An extensive review of the treatment of leprosy from the late 19th century to modern multidrug treatment, immunotherapy and immunoprophylaxis is presented in the last chapter.

Orders together with Dfl. 17.50 should be sent to: Royal Tropical Institute, Publications Department, Mauritskade 63, 1092 AD Amsterdam, The Netherlands.

Dr Wayne Meyers, Presidential Closing Address to the 13th International Leprosy Association Congress, The Hague, 17 September 1988

President Lechat, Mrs Veder-Smit, Distinguished colleagues and friends. It is a great honour for me to accept the position of President of the International Leprosy Association. This is indeed a humbling experience, especially when we consider the renowned men who brought the ILA into existence on the occasion of the Leonard Wood Memorial Conference on Leprosy in Manila in January 1931. One year later, the first General Council of the organization was named, and representatives were included from the following countries: Argentina, Brazil, China, France, Germany, Great Britain, Holland, Japan, Norway, the Philippines, Switzerland and the United States of America.

The initial objectives of the ILA were:

1 To encourage and facilitate mutual acquaintance between persons of all nationalities who are concerned with leprosy work and to coordinate these efforts;
2 to facilitate the dissemination of knowledge of the disease of leprosy, and its control;
3 to aid in any other practical way the antileprosy campaign throughout the world; and
4 to this end, to publish a scientific journal, known as the *International Journal of Leprosy*.

These objectives have been realized and continue to be developed in the work of the organization.

Professor Lechat, I pay tribute to you for your untiring efforts during the past 10 years of dedicated service as President, carrying the spirit and objectives of the organization into new geographic, social, and scientific realms. Michel, we thank you; we depend on your counsel during the challenging days ahead.

I also most gratefully acknowledge the dedicated service given by the other officers of the ILA to an almost unending number of details: Dr Thangaraj as Secretary, Dr Ross as Treasurer, Dr Hastings as Editor of the Journal, and to the entire body of councillors. To those of you officers who are leaving this governing body, I give you my heartfelt thanks, and know that you will not forget us, nor the great cause which we serve.

I look forward with keen anticipation to working together with the Council established today. It is good to know that Dr Bob Hastings will continue as Editor of the Journal and Dr Felton Ross as Treasurer, and we welcome as General Secretary, Dr Yo Yuasa, who brings to this work his global experience as a physician and administrator.

This 13th International Congress has revealed the great strides that have been made in the understanding of leprosy and appreciating the situation of the leprosy patient. Pathogenesis and the immunologic responses are better understood. Dissection of the leprosy bacillus continues. Multidrug therapy is being fine-tuned. Training of physicians and para-medical workers, and the education of the public have helped to advance the effectiveness of control programmes. The plight of many leprosy patients has greatly improved since the last Congress, and in some geographic areas there is a marked reduction in the risk of leprosy in the general population. For this, that great body of dedicated leprosy workers can take some pleasure—the para-medics, primary care physicians, national government officials, administrators, personnel in the network of voluntary agencies, research scientists and laboratory technicians, and finally the granting agencies that support them. Many of these efforts are being effectively enabled and coordinated by WHO programmes and ILEP.

But, there is no place for complacency. Less than one-third of all leprosy patients and as few as one in ten in some major endemic areas, receive multidrug therapy. One in every four patients has disabling deformities. The diagnostic methods of leprosy, although continually being refined, remain unchanged from those dating back to the era of Armauer Hansen, i.e. clinical and histopathologic findings. Worldwide, the public understanding of leprosy and the social stigma of the disease has only fractionally improved. Socio-economic factors contributing to the transmission and ineffective control of leprosy prevail in vast populations at risk.

There is every hope that by the 14th international Congress, in Florida, the redoubtable leprosy bacillus will be nearer to surrendering its more important secrets for survival, that modes of transmission will be firmly established, that mechanisms of nerve damage will be better understood and more effectively prevented, that shorter term and less expensive chemotherapy will be available, and that the early reports on an effective much needed vaccine will prove promising.

What is the ILA's role in serving these causes? There are a few points that may be emphasized:

1 We must strive to increase our membership. The membership of the ILA in 1932 was 394. Today it is only between 500 and 600. This is astonishing. Remember that membership is open not only to physicians and laboratory scientists but 'to persons who are or have been actively connected with leprosy work'.
2 We must improve our attempts, through the *International Journal of Leprosy* and other means, to provide continuing education in the medical and social aspects of leprosy, while not neglecting the reporting of original basic scientific findings.
3 We must enhance the collaboration of the ILA with national governments, the World Health Organization and its regional offices, ILEP, and all other bodies of goodwill, while maintaining the integrity and identity of the ILA.
4 We must ensure that the Council be sensitive to the desires of the membership, so that an atmosphere of cooperation and collegiality may be effected.

And so, as we leave The Hague, let us be encouraged by the breadth and depth of the developments reported here, and challenged by the great task before us.

Ladies and gentlemen, with profound appreciation to all who have organized and participated in this great meeting, I hereby and finally declare the 13th International Leprosy Congress officially closed.

Conference on Dermatology in the Developing World, Oxford 1988

The combined Conference of the International Society of Dermatology with the International Society of Dermatopathology was held in Oxford on 4–8 September 1988. The purpose of this Conference was to sensitize dermatologists to the needs of the developing world. Apart from concentrating on subject matter such as leprosy, leishmaniasis, schistosomiasis and AIDS, there were also review lectures on the problems of pyoderma and the epidemiology of fungus infections. This was a conference full of ideas, introducing debates on the needs of immigrants in the Western Community, a discussion on dermatology in a besieged community based on experiences in Lebanon; there were important symposia on the management of elephantiasis, nutrition and hair, and a symposium on the management of blistering diseases world-wide. Two breakfast sessions were given by audiovisual aids' expert Bob Linney and chaired by Colin McDougall, the sessions being devoted to the content and production of posters for an illiterate community. Lunch-time sessions included workshops on the pathology of leprosy in which the lucky participants were able to take away a complete set of histology slides, illustrating the spectrum of pathology in leprosy.

Following the Conference, the feedback suggests that it has indeed been a success and the slides are being used for teaching. The International Society of Dermatopathology has appointed Gerald Pierard from the Department of Dermatology, University of Liege, Belgium to facilitate the Society's interest in the developing world. Much of the content of the Conference will be published in the *Journal of the International Society of Dermatology*. A few copies of the book of abstracts are still available and can be obtained from the Department of Dermatology, Slade Hospital, Oxford, England.

One of the main social events where there were presentations of awards by the two Societies was at Blenheim Palace. The recipients were: The Merck Foundation for their benevolence with respect to river blindness; George Hatem for his life-long contribution to the elimination of disease in China, and the Wellcome Trust for their continued support of tropical medicine.

International Foundation of Dermatology

The aims of the International League of Dermatological Societies, according to its rules and regulations, is to encourage the advancement of Dermatology; the promote personal relations among the Dermatologists of the world; to represent dermatological interests in other international organizations and to hold international congresses on Dermatology. For several decades the International Congress of Dermatology has occupied most of the attention of the members of the International Committee, and it has been an anxiety for successive members of the committee to realize that they are perhaps doing too little for the developing world. Stimulated by Dr Darrell Wilkinson, UK, the idea of an International Foundation for Dermatology, came to its fruition when the International League of Dermatological Societies at their International Congress in Berlin in May 1987 agreed that there should be such a Foundation to further and develop Dermatology throughout the world. The Foundation is a subsidiary of the International League of Dermatological Societies, and knowing of its existence, several national societies and many individuals have already contributed finance to support its objectives. All such donations will be used for the furtherance of its aims. The cost of setting up the Foundation will be covered by donations from a sum donated specifically for that purpose by the members of the International Committee of Dermatology. The Board of Directors of the Foundation, chaired by Dr Alfred W Kopf, USA, and supported by regular members of the International Committee, Dr Terence Ryan, Great Britain, Dr Ramon Ruiz-Maldonada, Mexico, Dr Jean Thivolet, Lyons, France together with the President of the International League of Dermatological Societies, Professor Klaus Wolff, Vienna, and the Secretary General, Professor Stuart Maddin, Vancouver, Canada, and two co-opted members, Dr Henning Grossman, Berlin, and Professor Francisco Kerdel-Vegas, Venezuela, agreed at a meeting in December 1988 on the following primary aims and missions for the International Foundation for Dermatology.

Primary Aims

The International Foundation for Dermatology, which serves under the aegis of the International Committee of Dermatology of the International League of Dermatological Societies, has as its primary aim to: *Improve Dermatologic Health in Developing Counties Through the Promotion of Service, Training and Science.* These aims are to be carried out on all levels with emphasis on primary health care by assisting in preventive, curative, and rehabilitative activities.

Mission 1. Facilitate dermatologic education and training at all health-care levels.
Mission 2. Assist in the establishment and continued support of Regional Dermatology Training Centres.
Mission 3. Aid in the delivery of dermatologic care in developing countries.
Mission 4. Develop a cadre of experienced dermato-venereologists willing to serve on a short-term or long-term basis as visiting teachers, lecturers, advisers, or practitioners of dermatology.
Mission 5. Document the burden of dermatologic disease and the current status and future needs of dermatologic manpower and technical resources.
Mission 6. Promulgate collaborative programmes between institutions from developed and developing countries of the world.
Mission 7. Promote dermatologic education and communication needs in the developing countries at national and international meetings.

Mission 8. Support the establishment of fully-fledged Departments of Dermatology in at least one medical school in each developing country.
Mission 9. Assist in the development of model lists of essential dermatologic therapeutic agents for all health care levels.
Mission 10. Strengthen research orientated to the dermatologic priority.

Since its inception, bye-laws have been written and approved and incorporation was accomplished in the State of Illinois, USA. Bank accounts have been established in Sweden and the USA. The priority mission to establish Regional Dermatology Training Centres in Africa has been identified and the magnitude of dermatologic diseases in developing countries, particularly in rural areas, has been reported on. A delegation has met with the Directors or their representatives of various Divisions of the World Health Organisation in Geneva, Switezerland. The IFD was encouraged to proceed along its lines of taking steps to improve dermatology and dermatologic care in developing countries.

Errata: Leprosy Review, 59, No. 4 – Pre-congress workshops

p. 289, penultimate line: *for* 'prevention of management' *read* 'management of prevention'.
p. 303, lines 6 and 15: *for* 'ILA' *read* 'ILEP'.

Back issues of *International Journal of Leprosy*: wanted and for sale

Dr T J Ryan of the Department of Dermatology, The Slade Hospital, Oxford OX3 7JH, England wishes to purchase the following issues of the *International Journal of Leprosy* 1962: Volume 30, Nos 1–3; 1963: Volume 31, Nos 1–3, 1964; Volume 32, Nos 1–3, 1965: Volume 33, Nos 1–4; 1966: Volume 34, No. 4; 1974: Volume 42, Nos 2–4; 1975: Volume 43, Nos 3 and 4; 1976–1982: Volumes 44–50, all issues are required. 1983: Volume 51, Nos 1, 3, 4; 1984–88; Volumes 52–6, all issues are required.

The following issues of the *International Journal of Leprosy* are available from: Assistant Editor, LEPRA, c/o 94 Church Road, Wheatley, Oxon OX9 1LZ, England. Please send payment to cover postage and packing. 1962: Volume 30, No 3; 1967: Volume 35, No 1, No 2, Part 1 and 2, No 3, No 4, Part 1 and 2; 1968: Volume 36, Nos 1–3, No 4, Part 2; 1969: Volume 37, No 1; 1970: Volume 38, Nos 1–3; 1971: Volume 39, No. 2 Part 1, No. 3; 1972: Volume 40, Nos 1 and 2; 1974: Volume 42, No. 1.

Back issues of *Leprosy Review*: wanted and for sale

Dr T J Ryan of the Department of Dermatology, The Slade Hospital, Oxford OX3 7JH, England would very much like to complete his library of *Leprosy Review*. If you have any of the following issues available Dr Ryan would be delighted to reimburse you.
1951: Volume XXII, Nos 3–4, 1952 Volume XXIII, No. 2; 1954: XXV, Nos 2–4; 1955 Volume XXVI, Nos 1, 3; 1956 Volume XXVII, No 4; 1957: Volume XXVIII, Nos 1, 2; 1958; Volume XXIX Nos 1 and 2; 1959: Volume XXX, No 3; 1960: Volume XXXI, No. 3; 1971: Volume 42, No 3; 1974: Volume 45, No. 2; 1977: Volume 48, No 2; 1979: Volume 50, No 2; 1980: Volume 51 Nos 1 and 2.

The following issues of *Leprosy Review* are available from: Assistant Editor, LEPRA, c/o 94 Church Road, Wheatley, Oxon OX9 1L2, England. Please send payment to cover postage and packing. 1953: Volume XXIV, Nos 1–3; 1954: Volume XXV, No 1; 1955: Volume XXVI, No 4; 1956: Volume XXVII, No 1; 1959: Volume XXX, No 4; 1961: Volume XXXII, Nos 1, 3, 4; 1962: Volume XXXIII, Nos 1–4; 1963: Volume XXXIV, Nos 1–4; 1964: Volume XXXV, Nos 1–4; 1965: Volume XXXVI, Nos 1–3; 1966: Volume XXXVII, Nos 1–4; 1967: Volume XXXVIII, Nos 1–4; 1968: Volume XXXIX, Nos 2–4; 1969: Volume 40, No 1; 1970: Volume 41, Nos 1–4; 1971: Volume 42, No. 1; 1972: Volume 43, No 3 and 4; 1973: Volume 44, No 1; 1974: Volume 45, Nos 3 and 4; 1975: Volume 46, No 2; 1976: Volume 47, Nos 1–4; 1977: Volume 48, No 1; 1981: Volume 52, No 4.

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Book Reviews

The pathogenesis of leprosy and related diseases. **D S Ridley**

Leprosy, tuberculosis and leishmaniasis are granulomatous diseases which continue to pose a very serious health problem in the world. They are caused by slow-growing intracellular parasites which reside chiefly in host macrophages. Each is a disease with a spectrum of clinical, histological and microbial manifestations determined by the immunological status of the host. So, although leishmaniasis is due to a group of protozoa, whereas leprosy and tuberculosis are each caused by a species of mycobacteria, there is obvious merit in considering the three together when dissecting out the factors determining the course of such infections.

By adopting such an approach in this book, Dr Ridley emphasizes recurring themes in the pathogenesis of these granulomatous diseases, such as the role played by the host's innate and acquired resistance, the antigenic load, the site of antigen and the immunogenicity and cytotoxicity of the aetiological agent.

At the same time as being a very interesting discourse on comparative pathology, Ridley's book offers an extremely thorough account of the histological diagnosis and classification of leprosy. This is to be expected, since he is undoubtedly the world's greatest authority on this aspect of leprosy and, together with Jopling, defined the five-group classification upon which all subsequent advances in leprosy research have been based.

Although, regrettably, the numerous histological pictures are in black and white, the book is well presented and logically subdivided, making it easy to follow. Ridley is careful to familiarize the reader with, for example, the nature of the immune response and of normal skin and nerve, before launching into detailed histopathological descriptions.

This book is not intended to be, and should not be approached as, an exhaustive account of all aspects of leprosy and related diseases, but it has to be the definitive text on its chosen subject area. As such, it should be read by all those interested in granulomatous diseases.

Sally A Cowley

Published by Wright (Butterworth Scientific) London, 1988. Price: £60, 250 pp.

Tuberculosis and leprosy. **Editor: R J W Rees**

With an estimated 12 million leprosy patients in the world and an annual incidence of 10 million cases of tuberculosis, these mycobacterial infections remain very high on the list of communicable diseases.

The fields of tuberculosis and leprosy research have always been closely linked, but today more than ever, our understanding and management of these diseases are progressing hand-in-hand. New technologies have been applied to mycobacterial research with interesting and far-reaching results and applications. Most notable among these are the production of antimycobacterial monoclonal antibodies; the development of immunodiagnostic assays; the production of recombinant mycobacterial proteins; and the establishment of antigen-specific T cell clones.

Chemotherapy employs some of the same drugs in leprosy as in tuberculosis and, with increasing problems with resistance, the push for new drugs is relevant to both diseases. The efficacy of BCG as a protection against both tuberculosis and leprosy is being carefully evaluated as efforts to develop new vaccines proceed.

This volume is, therefore, a very timely review of the state of the art of these various paths of research. With chapters written by recognized experts in the fields it offers up-to-date information and well-referenced accounts of recent research developments. It covers the broad subject areas of molecular biology, microbiology, immunology and epidemiology very thoroughly. There are also chapters on pathology and disease management which, of necessity, consider the diseases separately.

The volume concludes with a chapter on mycobacterial infections and AIDS. This is a subject of obvious growing importance where much of our present knowledge of the mycobacteria involved in opportunistic infections in AIDS has been an offshoot of research into leprosy and tuberculosis.

Some subject areas are conspicuous by their absence—not least is any contribution on nerve damage in

leprosy—though whether this was an oversight, or deliberate because of the lack of progress in research, only the planning committee of this volume will know.

Every mycobacterial research worker should regard this book as an invaluable review of the most interesting developments in the subject. For those new to the field, including those working with mycobacteria in association with AIDS, it will serve as an excellent general introduction to a diverse and often rather paradoxical branch of research.

Sally A Cowley

Published by Churchill Livingstone, Edinburgh, 1988. Price: £22·50.

The Global Impact of AIDS. Editors: A F Fleming, M Carballo, D W FitzSimons, M R Bailey and J Mann

This publication reports the proceedings of the first International Conference on the Global Impact of AIDS held in London in March 1988. There have been many publications on the virological and immunological aspects of AIDS. This volume faces up to the epidemiological and sociological aspects of the problem. As such, it is important reading for all leprosy field workers in AIDS endemic areas, particularly in Africa, although it may be but a short time before leprosy workers in other continents will be equally in need of the information conveyed in this book.

The book contains 52 individual contributions. An indication of its pointer towards leprosy is the fact that the fourth chapter is entitled, 'The effects of the AIDS epidemic on the tuberculosis problem and tuberculosis programmes' and states in summary 'There is now evidence of an increased rate of progression from asymptomatic to overt tuberculosis for persons co-infected with HIV. There are early trends suggesting an increased number of cases in some regions where both infections are common.' It also expresses concern about possible altered safety or efficacy factors in the current anti-Tb practices.

A few chapter headings will give an idea of the scope of this book: 'HIV and international travel'; 'AIDS and family planning programmes'; 'The direct and indirect cost of HIV infection in developing countries'; 'The cases of Zaire and Tanzania'; 'The impact of human immunodeficiency virus and AIDS on a primary industry: Mining (a case study of Zambia)'. There is a whole section on the impact of HIV infection on family life including the burden in Africa particularly on the aged grandmother who has to become the wage earner or food producer.

Then there is a section on the response of different countries to the problem. This includes public health organization and new legislation. The role of education is emphasized as an important public health measure.

A problem familiar to leprosy workers is that of stigma. Here at least the disease is not on the surface for everyone to see, but the ethical problems associated with HIV testing have a familiar ring. As well as the direct effect of HIV on the surrounding population in a leprosy endemic area, many of the problems that the HIV worker is facing or about to face are the same as, or similar to, those that have been faced by leprosy workers for many years, decades, even centuries.

J L Turk

Published by Alan R. Liss Inc., New York, 1988. Price: $29.50.

Leprosy—a learning package. The Wellcome Tropical Institute

The learning package consistes of a handbook and set of 10 posters. The posters are elaborately produced on thick glossy paper that can be rolled up and easily transported. They are highly coloured.

The handbook reproduces the photographic material of the posters with considerable up-to-date written material. It is also a highly glossy production. The material is well explained and easy to understand and will be particularly useful to those teaching medical students and paramedicals. The tables and diagrams are good as are the clinical photographs. The sections on MDT, vaccines and immunopathology are well covered, as also is disability control and rehabilitation.

This package will be found particularly useful in educating medical students from the developed countries and in making them aware of the problems of leprosy. It is to be hoped that funds will be made available for its distribution to medical schools, and centres for the training of paramedicals in leprosy endemic areas.

J L Turk

Published by The Wellcome Tropical Institute, London, 1988. Price: £55.

The All Africa Leprosy and Rehabilitation Training Centre (ALERT) has the following vacancies:

CLINICAL RESEARCH CO-ORDINATOR

Requirements:

1 Medically qualified.
2 Experience in clinical leprosy and clinical research preferably a Post-graduate training in epidemiology.
3 Publications of relevant articles in recognized international journals.

Date of employment: As soon as possible.
Contract period: 2 years.
Salary: Negotiable.

Address application with copies of testimonials and job certificates in English to: Executive Director, ALERT, PO Box 165, Addis Ababa, Ethiopia.

The deadline for submitting application is 1 month after the publication of this vacancy.

★ ★ ★

CHIEF PHYSIOTHERAPIST

Requirements:

1 Should have an internationally recognized degree in physiotherapy.
2 Advantageous to have experience in teaching.
3 Should have training or experience in management.
4 Should have practical work experience of a minimum of 4 years in physiotherapy or in a rehabilitation centre and preferably overseas experience.
5 Should have good leadership qualities.
6 Should have good command of the English language.
7 Should be innovative and be able to adapt or modify existing situations.

Date of employment: As soon as possible.
Contract period: 2 years.
Salary: Negotiable.

Address application with copies of testimonials and job certificates in English to: Executive Director, ALERT, PO Box 165, Addis Ababa, Ethiopia.

The deadline for submitting application is 45 days after the publication of this vacancy.

★ ★ ★

ORTHOPAEDIC SHOEMAKER

Requirements:

1 Basic qualifications as an orthopaedic shoemaker.
2 Should have a good command of the English language.
3 Should have a good knowledge of assessment and management of the insensitive and often deformed foot.
4 Should be a good communicator and be able to establish rapport with his co-workers.
5 Should have a minimum of 5 years working experience, preferably with overseas experience.
6 Should be innovative and be able to adopt, modify and develop footwear.

Date of employment: As soon as possible.
Contract period: 2 years.
Salary: Negotiable.

Address application with copies of testimonials and job certificates in English to: Executive Director, ALERT, PO Box 165, Addis Ababa, Ethiopia.

The deadline for submitting application is 45 days after the publication of this vacancy.

ORTHOPAEDIC WORKSHOP SUPERVISOR

Requirements:

1 Basic qualifications as an orthopaedic appliance maker, orthotics and prosthetics or orthopaedic shoemaker. Preferably both.
2 Should have a good knowledge of assessment and management of the insensitive and often deformed foot.
3 Should have a good command of the English language.
4 Should be a good communicator and be able to establish rapport with his co-workers.
5 Should have a minimum of 5 years working experience, preferably with overseas experience.
6 Should be innovative.
7 Should be able to adapt, modify and develop footwear.

Date of employment: As soon as possible.
Contract period: 2 years.
Salary: Negotiable.

Address application with copies of testimonials and job certificates in English to: Executive Director, ALERT, PO Box 165, Addis Ababa, Ethiopia.

The deadline for submitting application is 45 days after the publication of this vacancy.

★ ★ ★

PROSTHETIST

Requirements:

1 Basic qualifications as prosthetist
2 Should have a good command of the English language.
3 Should have a good knowledge of assessment and management of the insensitive and often deformed foot.
4 Should be a good communicator and be able to establish rapport with his co-workers.
5 Should have a minimum of 5 years working experience, preferably with overseas experience.
6 Should be innovative and be able to adopt, modify and develop footwear.

Date of employment: As soon as possible.
Contract period: 2 years.
Salary: Negotiable.

Address application with copies of testimonials and job certificates in English to: Executive Director, ALERT, PO Box 165, Addis Ababa, Ethiopia.

The deadline for submitting application is 45 days after the publication of this vacancy.

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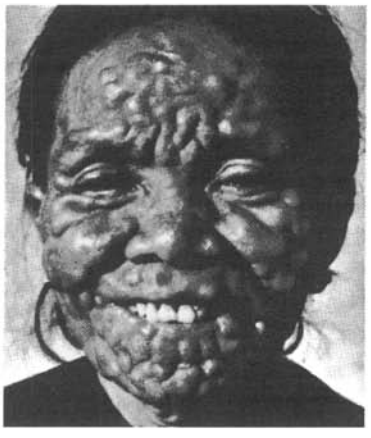

Two highly effective drugs for use in the treatment of leprosy

Lamprene
Capsules of 50 mg and 100 mg

Composition: Clofazimine. *Capsules* of 50 mg and 100 mg. Indications: Lamprene, employed in combination with dapsone and rifampicin (Rimactane), serves as treatment for multibacillary forms of leprosy, such as lepromatous (LL), borderline lepromatous (BL), and mid-borderline (BB) leprosy, as well as erythema nodosum leprosum (ENL). Combined chemotherapy is necessary in order to prevent the emergence of resistant strains of *M. leprae*. Dosage: *Adults* (of approx. 60 kg body weight): for the treatment of multibacillary leprosy (LL, BL, BB) the WHO (World Health Organisation) recommends the following dosage schedule: Lamprene: 300 mg once a month under surveillance + 50 mg once a day as self-medication. Rifampicin: 600 mg once a month under surveillance. Dapsone: 100 mg once a day as self-medication. This threefold combination should be administered for at least 2 years and, whenever possible, until such time as the skin smears become negative. If the patient develops ENL, the treatment with dapsone and rifampicin should be continued as before, whereas the dosage of Lamprene should be raised to at the most 300 mg per day. These high daily doses must not be given for longer than 3 months. *Children:* Children should receive lower doses adapted to their body weight. Administration: The capsules should be taken at mealtimes or together with milk. Contra-indication: Known hypersensitivity to clofazimine. Precautions: Leprosy patients suffering repeatedly from abdominal pains and diarrhoea, as well as those with liver or kidney damage, should if possible not be treated with Lamprene. Treatment with daily doses of Lamprene exceeding 100 mg should not be continued for longer than 3 months, and during this time the patient should be kept under medical supervision. If gastro-intestinal symptoms develop during the treatment, the dosage should be reduced or the interval between doses prolonged. In the event of persistent diarrhoea or vomiting, the patient should be hospitalised. Pregnancy and lactation: As in the case of any form of drug therapy, Lamprene should be employed with caution during pregnancy, especially in the first 3 months. Clofazimine crosses the placental barrier and causes temporary discoloration of newborn infants. The active substance also passes into the breast milk. Unwanted effects: The following side effects have been observed: Reddish to dark-brown discoloration of the skin and of the leprous lesions, particularly in pale-skinned patients at sites exposed to light. Discoloration of the hair, conjunctiva, cornea, and lacrimal fluid, as well as of sweat, sputum, urine, and faeces. This discoloration is reversible, although in the case of the skin it often does not disappear completely until some months after the cessation of treatment. Dryness of the skin, ichthyosis, pruritus, photosensitivity, acneform eruptions, and non-specific skin rashes. Nausea, vomiting, abdominal pains, diarrhoea, anorexia, loss of weight, and eosinophilic enteropathy. Storage: Protect from heat and moisture. Packages: 100 capsules of 50 mg or 100 mg. Further information is available on request.

Rimactane
Capsules of 150 mg and 300 mg

Composition: Rifampicin. *Capsules* of 150 mg and 300 mg. Indications: *Leprosy:* in combination with other antileprosy drugs as treatment for lepromatous and dimorphous (borderline) forms of leprosy, as well as in patients with other forms of leprosy, in whom intolerance of, or resistance to, other antileprosy drugs is encountered. Administration: At least ½ hour before a meal on an empty stomach according to WHO recommendations. Contra-indications: Hypersensitivity to rifamycins. Jaundice associated with reduced bilirubin excretion. Note: Daily treatment with Rimactane is generally better tolerated than intermittent therapy. Resumption of treatment with Rimactane after termination of a course of long-term therapy with the drug involves risks and should therefore, if possible, be avoided. In patients with *liver diseases,* as well as in *severely undernourished patients,* treatment with Rimactane entails a higher risk and its therapeutic benefits should therefore be weighed against the possibility of its causing further damage. If such treatment is necessary, the dosage must be correspondingly reduced. During pregnancy the use of Rimactane should, if possible, be avoided. Rimactane passes into the breast milk. Mothers in whom its use proves unavoidable should refrain from breast-feeding their infants. Unwanted effects: Gastro-intestinal disturbances; disorders of hepatic function, e.g. mild transient elevation of the transaminase values, may occur – chiefly at the start of treatment – but do not generally necessitate discontinuation of the medication; isolated occurrences of jaundice, leucopenia, and eosinophilia; particularly in patients taking Rimactane intermittently or in patients in whom daily treatment is resumed after a temporary interruption, side effects – possibly of immunopathological origin – may take the form of influenza-like symptoms ('flu syndrome) and, in rare instances, of cutaneous manifestations, thrombocytopenia, purpura, and fever, as well as of acute renal failure, dyspnoea, or haemolytic anaemia. If serious complications occur, such as thrombocytopenia, purpura, renal failure, or haemolytic anaemia, treatment with Rimactane should be stopped at once and not reinstituted at a later date. Packages: 8, 16, and 80 capsules of 150 mg; 8 and 40 capsules of 300 mg. Further information is available on request.

1. Chemotherapy of leprosy for control programmes, Report of a WHO Study Group, WHO Technical Report Series 675, WHO, Geneva 1982.
2. S. J. Yawalkar, J. Languillon, S. K. Hajra, A. C. McDougall, S. Gosh, D. V. A. Opromolla, C. J. S. Tonello. Once-monthly rifampicin plus daily dapsone in initial treatment of lepromatous leprosy. Lancet 1199, 29 May 1982.

Instructions to Authors

Papers submitted for publication in *Leprosy Review* should be sent to the Editor, Professor J. L. Turk, LEPRA, Fairfax House, Causton Road, Colchester CO1 1PU, England. The name(s) of the author(s) and the place where the work was done should be clearly indicated below the title of the paper. Degrees and diplomas are not to be included.

It is understood that the paper is offered to *Leprosy Review* alone, that it will be subject to editorial revision, and that its copyright becomes the property of the British Leprosy Relief Association. Manuscripts should be typewritten, in double spacing, on one side of A4 (297 × 210 mm) paper, with wide margins (4 cm all round). Contributors must send three complete copies of the text, tables and figures. On a separate sheet give the title, short title, name and postal address of the author, together with the name of the institution where the work was done. Abbreviations of titles of journals should follow the list of journals indexed in *Index Medicus*. References to books should include the editor(s), publisher and place of publication.

Units and Abbreviations. The Journal recognizes the adoption of the Système International d'Unitès (SI Units) proposed in *Units, Symbols and Abbreviations* (1972) published by the Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. Abbreviations should only be used for unwieldy names, and only when they occur frequently.

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