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Leprosy Review

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

LEPRA

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Wellesley Bailey Awards

The Leprosy Mission International (TLMI) welcomes nominations for the Wellesley Bailey Awards, to be presented at a special reception in England on 1 December 2001. They are for people who have experienced leprosy, who have made a significant contribution to their community or society, and have shown outstanding courage in overcoming challenging situations.

Four separate awards will be given; three to people who have had considerable influence at local level and one for a person who has had considerable experience at national or international level. The deadline for nominations with accompanying papers to reach TLMI is **25 June 2001.**

Further details about the awards and required documentation are obtainable from: Joyce Missing, The Leprosy Mission International Office, 80 Windmill Road, Brentford, Middlesex TW8 0QH, UK. Fax +44 20 8569 7808, email JoyceM@TLMInt.org.

The Epidemiology, Risk Factors and Response to Treatment by Corticosteroids of Acute Nerve Function Impairment in Leprosy is the title of my Doctoral Thesis. It describes the methodology and results of the Bangladesh Acute Nerve Damage Study (BANDS) as well as some related work along with an introduction, description of the study background and discussion. It is not too long, around 40,000 words! I have some copies available for interested readers of *Leprosy Review.* Please contact me, preferably by e-mail. Cost will be to cover postage only.

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Lepr Rev (2000) **71,** 246

Editor's Choice—September 2000

Many of you will be reading this issue of *Leprosy Review* at the Asian Leprosy Congress in Agra, India. To celebrate the congress we have published our largest issue ever of Leprosy Review with a record 11 papers. All the major leprosy endemic regions are represented. This is a tribute to all the work that is being done in our efforts to understand the disease and refine our management. We have papers ranging from the biochemical (looking at nitric oxide metabolites in reactions, p 355) through the epidemiological (the AMFES study, p 273) to the public health issue of predicting and understanding non-compliance (p 369). I hope that everyone will savour these articles. Many people have contributed in different ways to this issue and I would like to thank everyone who has worked so hard in the last few months bringing this issue to press.

The three editorials are all written from a global perspective. Maria Neira's article (p 247) outlines the World Health Organisation strategy, arguing that for some countries a more intensive strategy is needed. Terry Vasey's article (p 253) indicates how the Global Alliance can contribute to leprosy control. Leprosy research continues to be a priority at WHO and Paul Nunn (p 256) has outlined the thinking behind the Tropical Disease Research programme and I hope this will encourage people to apply for WHO funding.

Dominating this issue is a series of papers from the longitudinal AMFES study in Ethiopia. I decided to publish all these papers together to maximise their impact. This series represents a major success story for field workers, researchers and funders. Richard Croft (p 270) has written an overview highlighting the key points in the papers. This is the most comprehensive picture that we now have of the presentation and complications of leprosy in Africa.

I hope that the congress will generate more enthusiasm and that the post-congress papers will soon be reaching the *Leprosy Review* office.

DIANA N. J. LOCKWOOD

Leprosy Review has been informed of the death of Professor He Daxun, Vice President of the China Leprosy Association, on August 2, 2000 in Beijing after a short illness. He was 69 years old.

Leprosy Poster

Leprosy: Differential Diagnosis No. 2 Nodules. (McDougall/Patience). We would like to thank the Wellcome Tropical Medicine Resource for providing the images of onchocerciasis (Professor A. Bryceson). Kapos: Sarcoma (Dr M. Rolfe). Molluscum contagiosum (W.K. Jacyk), mycetoma (Dr M. Rolfe). Professor A. Bryceson provided the image of diffuse cutaneous leishmaniasis.

Lepr Rev (2000) **71,** 247–252

Editorial

REMAINING CHALLENGES TOWARDS ELIMINATION OF LEPROSY

Introduction

Among all communicable diseases, leprosy remains one of the leading causes of permanent physical disabilities worldwide. The disease and its visible deformities result in intense social stigma and in the discrimination of patients and their families. It commonly affects individuals in the most productive stage of their life and thus imposes a significant burden on the community. An intensified strategy focusing on the local level has recently been defined by WHO to make a fresh attempt at overcoming the remaining hurdles in the fight against leprosy. The key elements of WHO's intensified strategy to eliminate leprosy are early case-detection and treatment using multidrug therapy (MDT) – and the greatest challenge is to ensure its vigorous implementation. If elimination is to be achieved, it is imperative that MDT services become accessible to every community in all endemic countries.

The elimination strategy

The elimination of leprosy as a public health problem aims at reducing the prevalence, at national level, to less than one case per 10,000 population. The strategy initiated by WHO to achieve this aim, based on early case-detection and cure with MDT, assumes that:

- treatment with MDT, together with early case-detection, is highly effective;
- the reduction of prevalence to very low levels will lead, in time, to interruption of transmission of infection and reduce disease incidence to insignificant levels;
- having an insidious onset, a chronic course and a very strong self-healing character, it is not possible to measure the incidence of leprosy from routine surveillance systems;
- until a steady epidemiological state is reached, with no more 'hidden' cases and with MDT universally available, new cases will only reflect surveillance programme performance and not incidence;
- because of the lack of appropriate tools, elimination rather than eradication remains the objective.

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Main achievements over the last 15 years

- By the end of 1999, more than 10 million cases had been treated and cured.[1]
- All registered cases are today receiving MDT.[2]
- Less than one in 1000 patients (0·1%) suffer relapses.[3]
- No resistance to MDT has been reported.[4]
- The number of countries showing prevalence rates above one in 10 000 population has been reduced from 122, in 1985, to 24 at the end of 1999.[1]

Main limitations of the current strategy

Whilst, on the eve of the original elimination target date, which was set for the end of the year 2000, the global prevalence rate of registered cases stands at about 1·4 per 10,000, in the 12 most endemic countries the average prevalence rate remains 4·5 per 10,000. This demonstrates the limitations of the current strategy and indicates that additional efforts and new approaches are required if elimination is to be achieved. Some countries will need to pursue further and intensify their activities beyond the year 2000 in order to eliminate leprosy. The reasons why elimination will not be achieved in these countries by the end of the year 2000 are varied and include: high prevalence rates (Brazil, India and Nepal), intensity of disease transmission (Guinea, some states in India, and Madagascar), limited geographical coverage with MDT services and, in some countries, civil strife and poor health infrastructures (Angola, Democratic Republic of Congo, and Mozambique).

Basis of the intensified strategy for 2000-2005

Although most of the expectations of the global elimination programme were met during the period 1991–1997, there have been some setbacks since then. This is due, in part, to intensified activities in some parts of the world successfully revealing many epidemiological and operational situations that had not previously been well perceived and which needed to be analysed further. Whilst the 1991 World Health Assembly resolution on the elimination of leprosy clearly defined targets and achievements, it proved difficult to reach a consensus on the target as being one case per 10,000 population. The scientific community, governments and donor agencies all argued that elimination should relate to incidence reduction, claiming that a global target was meaningless, and pointing out that the strategy paid insufficient attention to people disabled by leprosy. The major concern today is the stability of the number of newly detected cases stagnating at some 500,000 cases per year. Obviously, leprosy has not yet been eliminated.

Experience shows that the number of health facilities able to provide MDT services is limited and that, even when available, MDT is only provided for a limited time during each month. Considered as a special disease, the diagnosis and treatment of leprosy are often considered beyond the capacity and responsibility of general health services and therefore the disease remains isolated.

In this context, WHO and its advisory bodies have developed technical and operational mechanisms to overcome these obstacles. Endemic countries are being provided with simplified guidelines for case management, training to strengthen local management

capacity, shortened treatment schedules, free supply of MDT drugs in blister calendar packs, and direct support, both financial and technical, in the form of leprosy elimination campaigns (LEC) and special action projects for the elimination of leprosy (SAPEL). All this is very useful but the impact on leprosy at local level remains questionable.

Elements of the intensified strategy

The delivery of MDT services within general health services is the single most critical element in the intensified elimination strategy. Without it, case-finding, diagnosis, classification and drug supply efforts are meaningless. Thus the revised strategy focuses on the coherence of these activities at district level.

IDENTIFICATION OF ENDEMIC DISTRICTS

Endemic countries exhibit regional differences in terms of disease burden, health service coverage and programme efficiency. In order to appropriately assess the epidemiological situation, and surveillance and control needs, countries in which leprosy remains endemic must implement a micro-information system providing data from as far down as the village level.

MDT SERVICES INTEGRATED INTO GENERAL HEALTH FACILITIES

MDT services must become available and accessible at all health centres so that patients can get treatment easily from their nearest centre. The integration of MDT services into general health services is currently regarded as the key to elimination. General health services are usually spread over a large area and often have close and frequent contact with the local community. Their participation would thus enhance case-finding and case-holding activities whilst improving the cost-effectiveness of programmes.

Successful integration can be achieved only if it is simple, practical, and if tasks assigned to health workers are clear and in line with their daily routine activities – including maintaining information systems. At the local level, integration will help in sustaining MDT services, especially in areas where prevalence is declining. Some national programmes already have integrated leprosy services, mainly because of the urgent need to expand MDT coverage; national co-ordination will, however, generally remain a central activity, providing technical guidance, monitoring activities and evaluating progress towards elimination. Training for surveillance, control and research will also remain the responsibility of a centralized service. National referral centres will be maintained or established to provide support to the general health services in diagnosing difficult cases and in the management of leprosy-related complications.

MONITORING ELIMINATION AT THE DISTRICT LEVEL

Most endemic countries are now using well-standardized information systems. The essential indicators have been identified as prevalence, case-detection, MDT coverage, cure rates, relapses and the number of newly detected cases with grade 2 disabilities and impairments. In the context of the improved strategy, however, these indicators are stored in an integrated district-level database and analysed at district level. Such monitoring approaches will allow

more pertinent assessment of performance of MDT services, particularly drug availability, cure rates and quality of patient care.

PROMOTING COMMUNITY ACTION

Increased participation of the community in elimination activities will reduce the fear of leprosy and the stigma attached to the disease. The main difficulty encountered currently is ignorance, and public awareness of the signs, symptoms and treatment of the disease needs to be improved. Elimination cannot depend upon health services alone; it is crucial that obstacles to community participation be identified in order to ensure enhanced contributions.

HISTORICAL HANGOVERS

Leprosy generates intense emotions probably owing to the historical stigma attached to it. The fight against leprosy has traditionally been undertaken by a relatively small group of people, highly dedicated with a strong humanitarian commitment. This phenomenon relates not only to programme managers, but also to groups of experts and charitable organizations. To some extent, this explains why achievements in leprosy control during the last half of the 20th century remained poorly recognized. Today, leprosy can be cured – but making the idea attractive to the public, the scientific community, decision-makers and politicians seems to be a difficult task. Awareness of the current reality that leprosy can be eliminated needs to be created through intensified information, education and communication efforts.

RE-MOTIVATING THE RESEARCH COMMUNITY

Estimating the exact enormity of the task ahead to achieve elimination, particularly in areas where high levels of new case-detection rates exist, is extremely difficult, owing mainly to the weakness of the tools currently available. New, more reliable and effective diagnostic, preventive and therapeutic tools are needed, and for this, research must be strongly promoted. Alternative drugs that are more effective and less toxic must be found for the management of adverse reactions; new methods for the early detection and treatment of lepra reactions and neuritis need to be developed and novel approaches to their prevention need to be explored; a common regimen for both multibacillary (MB) and paucibacillary (PB) leprosy would be a great advantage. Epidemiological and operational research is also required and should be encouraged and strengthened wherever possible. The research community needs to be motivated to find solutions.

PREVENTION OF DISABILITIES AND REHABILITATION

Simple disability prevention and management components need to be incorporated into leprosy elimination programmes. The most cost-effective approach to this would be to strengthen collaboration with other relevant services and non-governmental organizations.

The strategic plan and the role of WHO

WHO's role is to assist countries in developing more effective health systems. It remains the repository of knowledge on health issues, it sets global standards and pleads causes —

including that of eliminating leprosy. During the period 2000–2005, WHO and its partners will focus on eliminating leprosy in the countries where the disease remains a public health problem and on sustaining elimination in those countries which have recently achieved it. WHO hopes that new partnerships will develop more enthusiasm for leprosy elimination at all levels, both nationally and internationally. The implementation of an intensified strategy is expected to bring about the political commitment required to achieve elimination. There will undoubtedly be opportunities for creating a new image for leprosy through global and local advocacy, resulting in stronger partnerships and additional resources.

Focus at the country level

COUNTRIES THAT HAVE NOT YET REACHED ELIMINATION AT NATIONAL LEVEL

Several countries/areas have already been identified as having a greater leprosy problem than was previously believed. In some places, several years of intensified activities may be required to evaluate the real magnitude of the leprosy problem. In the new strategy, in-depth analysis of the leprosy situation in individual countries, in collaboration with WHO and other agencies, is foreseen in order to estimate the additional time likely to be required to achieve elimination at national and district levels, to decide on additional interventions to be introduced, to intensify ongoing ones or, when needed, to repeat them, and to estimate the cost of those interventions.

COUNTRIES THAT HAVE ALREADY REACHED THE ELIMINATION TARGET AT NATIONAL LEVEL

These countries must ensure that elimination is sustained at national level and must identify districts where the elimination target has not yet been reached. Intensive, time-limited activities should then be carried out as required. Certification or validation of elimination would be of little value and would not be cost-effective in the absence of reliable tools to ascertain absence of transmission.

Future challenges

Although significant progress has been made towards eliminating leprosy as a public health problem worldwide, it is clear that some countries will not reach the elimination target at national level by the end of the year 2000. In those countries where the target has been reached, there is still a need to achieve elimination at subnational levels and sustain elimination activities for several more years.

It is evident that owing to improved disease control activities, the detection rate of new cases has increased over the last few years. This does not mean that transmission is on the increase or that it has not been interrupted. This status simply reflects the inadequacy and inefficiency of some programmes in the past.

Leprosy is feared because of the disabilities it causes. Little has yet been done in this area and the issue would perhaps be better addressed through integrated services for all disabled people in the community, which until now has not been the case. Until then, early detection and treatment with MDT will remain the best strategy for the prevention of occurrence of

disabilities. The image of leprosy has remained unchanged for many thousands of years because of poor awareness of the impact of the disease. One of the big challenges now will be to accept that leprosy workers can hand over the job of promoting the necessary change we are so passionately trying to bring about to our colleagues in the primary health care services. In this long battle against leprosy, many excellent institutions have also contributed enormously towards the improvement of care through research and training. They will now be needed for activities such as simplifying case management, improving surveillance, strengthening socioeconomic rehabilitation services and remaining alert to counter any unforeseen challenges.

In the coming century, priorities and commitments are likely to change. Other diseases such as malaria, tuberculosis and AIDS, which are on the increase, will gradually absorb most of the resources available for health. Although this can easily be justified, it is the responsibility of each one of us to maintain leprosy high on the health agenda, not to lose momentum and, most importantly, not to lose this opportunity for its elimination.

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MARIA P. NEIRA*
D. DAUMERIE**

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Lepr Rev (2000) **71**, 253–255

Editorial

THE GLOBAL ALLIANCE FOR THE ELIMINATION OF LEPROSY (GAEL)

Introduction

Significant achievements in the control of the spread of leprosy have been made, particularly in the last 15 years, so much so that in 1991 the 44th World Health Assembly adopted a resolution to eliminate leprosy as a public health problem by the year 2000. The definition had as its target a prevalence of leprosy of less than 1 per 10,000 population. Obviously, the target will not now be reached. Based on the Assembly resolution, the Nippon Foundation pledged to support and strengthen the initiative through the Sasakawa Memorial Health Foundation (a member of ILEP) and to date have assisted the World Health Organisation with operational funding of over US$200 million which included a sufficient amount to enable the free supply of MDT drugs until 2000. In 1998/9 when it was clear that the target would not be reached, there was considerable debate about the future of leprosy control, and questions were raised about whom the principal players would be after the year 2000 (cf. Patrick J Brennan, ILA Forum 2nd Series Volume 7, No.1). It was feared that without alternative funding and without funds for drugs the leprosy unit of WHO may disappear. Fortunately, timely discussions with the Nippon Foundation of Japan, and with the pharmaceutical company Novartis, addressed both shortfalls and secured the status quo at WHO for a further 5 years.

GAEL

Following the concern about the ending of the contract between the Nippon Foundation of Japan and WHO, it was with some relief that we learned that a new funding contract between the two agencies was announced and that there would be a free supply of drugs from Novartis. These offers of support prompted Dr Maria P. Neira, Director. Department of Control, Prevention and Eradication, WHO, Geneva, to start discussions on a 'Global Alliance for the Elimination of Leprosy' with Novartis, the Nippon Foundation, governments of endemic countries DANIDA and ILEP members. The launch of the Alliance took place in Abidjan, Côte d'Ivoire last November and it is hoped that others will join.

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Of course, everyone involved in the fight against leprosy welcomed the new initiative to intensify efforts, particularly given that leprosy prevalence still stands around 4.5 per 10,000 in the 12 most endemic countries and that these countries represent about 90% of the global leprosy problem. Founding members of the Alliance were more than happy to sign up to the new elimination strategy.

The Director General of the World Health Organisation, Dr Gro Harlem Brundtland says that the reasons why the elimination goal is not likely to be met are varied: high prevalence (India, Brazil, Nepal), the intensity of disease transmission (some States in India, Guinea and Madagascar), limited geographical coverage with MDT services (all countries) and in a small number of countries facing civil strife and a damaged health infrastructure (Angola, Mozambique, DR Congo). She adds 'In these countries, elimination will be reached only if special action is taken. In countries having reached elimination recently, it is essential to ensure that core control activities are sustained, and the leprosy situation is closely monitored for a number of years before confirming that the disease has been eliminated' (see the GAEL website at: http://users.breathemail.net/steve.lyons/gael/index.htm).

The WHO elimination strategy is based on the widespread implementation of MDT and the Global Alliance is a partnership dedicated to ensuring that all leprosy patients, wherever they may live, and however poor, have free and equal access to the most modern treatment available. The robustness of this form of treatment enables paramedics, nurses and community leaders to treat the disease wherever it occurs – in the city or in the village.

The Director General notes that India, Indonesia and Myanmar account for 70% of all the cases in the world. In Africa, the second most affected area, the situation is more difficult for the moment. The AIDS epidemic, the resurgence of the major tropical diseases, weaknesses in health infrastructure, social unrest and armed conflict make leprosy elimination seem like a luxury, an impracticable one at that. The situation remains worrying in Latin America. Brazil is particularly badly affected, accounting for over 80% of cases in that continent. In Central and Eastern Europe, there are sporadic cases; it is impossible at present to tell how many such cases go unreported. WHO and its partners are dedicated to ensuring that all leprosy patients, wherever they may live, and however poor, have free and equal access to the most modern treatment available.

Since the launch of the Alliance, several meetings have taken place to discuss the intensified strategy and a Technical Advisory Team has been formed. Health Education and Training Materials have been designed and are being tested. Several countries have set up national and/or local Task Forces bringing together all those engaged in the fight against the disease and plans have been drawn up in many countries. The first global review of the Alliance is planned to take place in India (the first Chair of GAEL) in January 2001.

In India the five endemic states of Bihar, Madyha Pradesh, Orissa, Uttar Pradesh, and West Bengal contribute 70% of the total patient load of the country and so in coming years there will be increasing focus on these areas. The intensified strategy there is directly linked to the second phase of World Bank funding to the National Leprosy Elimination Programme. The plan is to consolidate achievements in leprosy elimination and will focus on integration of the (largely vertical) programme into the general health service. This integration is planned to take place within the 3-year period of the Bank's funding. It is likely that some states will not be in a position to effect integration until almost the end of the time period. An adequate surveillance system to prevent the resurgence of the disease is also extremely important to the success of the future strategy.

ILEP members, as part of GAEL, recognize the need to engage constructively in the

broadening of effective alliances. In the Indian context therefore it will be of vital importance over the next 3 years that we are proactively involved in the government's leprosy work being funded by the World Bank. The importance of the role of NGOs including ILEP members is already clearly recognized by the World Bank. To quote Mr Peter Heywood, Principal Public Health Specialist, World Bank, New Delhi, 'The project envisages a significant input from NGOs both international and local. The significant contribution of international and national partners in leprosy control is known. It is expected that NGOs contracted under the project would take up substantial proportions of the activities under each unit. The relationship between the government and non-government organizations would be clearly defined and would be assessed by an agreed set of performance criteria.''

Further, at a state level he goes on to say 'all inputs for leprosy control by all organizations would have to come together in a cohesive manner for best results to be achieved, and be reflected in the state and central government's plans for elimination of leprosy (by 2003!).'

Keeping in mind that the GoI is the chair of GAEL and that the bulk of our (ILEP's) work is there, the need to actively engage in such broader alliances is crucial if our work is to continue to be effective in ensuring every person affected by leprosy receives the effective treatment and care they require.

Conclusion

We have set ourselves a tough target and if we are to be successful we must ensure that all involved keep leprosy near the top of the agenda and wherever possible attract the involvement of new partners. What is imperative is that we all recognise the contribution of each other and avoid duplication. We must ensure that resources are used in the most efficient manner whilst recognizing that for members of the Alliance, the elimination target is not our only concern. WHO provides technical assistance on many diseases and conditions, Health Ministers are concerned with the general health of their population, donors may support other causes and for ILEP members, elimination is only part of our overall goal. Even after the target is reached, there will continue to be new cases of leprosy, and the number of people who have been affected by the disease continues to grow. ILEP is pledged to fight for a world without leprosy and members will continue to strive for this after the target date is reached as many who are affected by the disease will still be with us.

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Editorial

LEPROSY RESEARCH IN THE NEW MILLENNIUM IN THE SPECIAL PROGRAMME FOR RESEARCH AND TRAINING IN TROPICAL DISEASES (TDR)

Change is afoot in TDR. During its silver jubilee, the new Director, Dr Carlos Morel has instituted a strategic review to come up with a long-term vision and a strategic plan. We have attempted to address the long-standing tension in relations between the research and control communities; the need for a more productive, strategic approach to research capacity strengthening; and the need for a stronger, more dynamic disease focus. The entry of more resources and more players into the field of health research means that TDR cannot expect to remain at the centre of things unless it carefully defines its comparative advantages, works in partnership with the private and not-for-profit sectors and makes far more use of the possibilities in the new information and communications technologies.

Too often in the past, TDR had stopped at the point of 'proof of principle' in its development work, leaving the demonstration of how the tool should be used, and assessments of feasibility and cost-effectiveness, to others. Too many times this meant the work was left undone. It is now TDR's intention to expand its implementation research with obvious implications for the involvement of control programmes both at the conception phase, when work begins on a potential product, and at the evaluation stage.

The dynamic disease portfolio has already meant the addition of tuberculosis and dengue fever. However, it also means that diseases will not simply be phased out when TDR's traditional role has been fulfilled (tools developed for disease control). Rather, the research will shift to fields that are appropriate for the stage of the disease. With respect to leprosy, this means a shift of the research priorities to ensure that research contributes maximally to the elimination of the disease.

The strengthening of the 'disease function' signifies the intention to put more effort into analysing the needs for research, taking into account the epidemiological stage of the disease, and identifying opportunities and potential partners. TDR is unlikely to fund areas of research that are felt to be adequately resourced by other agencies.

Research for 'the final push' in leprosy elimination

The strategic review is still working its way into the planning of TDR so that the leprosy research agenda (like those of the other TDR diseases) is actively under discussion, and no final decisions have yet been made as to what new activities will be undertaken, or what old activities might be concluded. However, a first pass at a likely strategy has suggested that the overall objective should be the reduction in the burden of leprosy, with specific objectives to

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include the efficient integration of leprosy control into the general health services, the simplification of diagnosis and treatment and the determination of the magnitude of rifampicin resistance. The opportunity to exploit the new information from the genome of *M. leprae* should not be missed, especially in the development of the tools necessary for eradication, such as a test for infection.

More specifically in relation to control of leprosy, health systems and services research aimed at design and testing of leprosy control components within the general health services is likely to be a priority. Innovative ways to improve the quality of services will be explored, such as the expansion of coverage using private practitioners and not-for-profit voluntary organizations in the 'mopping up' of high prevalence districts. Recent concerns about the loss of national research expertise in high prevalence countries are likely to be addressed by the Research Capacity Strengthening (RCS) Team and may involve strengthening country-specific health systems and services research units attached to leprosy control programmes.

As leprosy moves towards elimination, the need for accurate epidemiological information about the extent of the disease and changes brought about by the control programmes becomes paramount. Mathematical modelling of the epidemiology of leprosy will probably be supported to aid decision making in both control issues and the setting of research priorities.

Researchers in the more basic sciences will be able to submit proposals to the Basic and Strategic Research (STR) Team committees for pathogenesis and functional genomics that will continue in the new system. Workers in vaccine development will probably be able to approach the Inter-cluster Vaccine Research Initiative (IVR) and the mechanisms to do this will soon be established. Social, economic and behavioural research will be considered by a committee of the same name that will begin work in September 2000. All grants will be reviewed by these committees on a competitive basis.

The Product Research and Development Team will be responsible for any new drug discovery activities and for work aimed at development of new diagnostics. Clinical trials aimed at development of new regimens to reduce duration of treatment, enhance its simplicity, or create regimens for the treatment of all forms of leprosy will be addressed by some development of the existing THEMYC (Therapy of Mycobacterial Diseases Committee) group.

Finally, one of TDR's comparative advantages is the ability to bring the world's best experts together to consider the best approaches to the problems of research, and one important need of the research community is to meet together at intervals to exchange ideas and stimulate each other. TDR will work with the organizers of the highly successful meeting in Paris in June 2000, hosted by the Association Raoul Follereau, to consider the most appropriate series of meetings that will answer the intellectual needs of the community as well as the responsibilities of TDR to formulate the global needs for research to make a difference to control.

Communicable Diseases Research & Development (CRD)
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REVIEW

Monitoring motor nerve function in leprosy patients

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Accepted for publication 1 August 2000

Summary Manual muscle strength testing has an important function in the management of leprosy patients. Its importance was first recognized in the 1960s, especially when following patients who were started on steroid treatment to monitor the nerve function and the effect of treatment. In those days, and still in many centres today, many or all muscles were tested that are innervated by the nerves that can be at risk in leprosy. The author argues that not all muscles innervated by the nerves at risk need to be tested and also that many muscles cannot be tested in isolation. A muscle charting form is presented which is suitable for screening purposes, and that also allows for more detail when motor function is impaired.

Introduction

Assessment and evaluation of motor function is very important in the detection of early motor nerve function impairment. When nerve function impairment is detected early it is often reversible. Changes in nerve function impairment are often taken into account when deciding on doses and duration of corticosteroid treatment. In addition, the (changing) status of motor nerve function is taken into consideration when deciding on tendon transfer surgery. For these reasons it is important to have a muscle charting form that lists muscles/movements that can be tested and graded and that will give reliable information for decision making. It should be realized that manual muscle strength testing, and also sensory testing, is a 'proxy' for nerve function evaluation which can only be done with electroneurophysiological equipment. In other words, by grading muscle strength we indirectly obtain information about the primary function of the nerve, which is conduction of electrical impulses.

Goodwin was the first to write about the importance of muscle charting in leprosy neuritis.[1] The charting was elaborate. All muscles supplied by the nerves that could be affected in leprosy were listed and the naming and listing of the individual muscles implied that they could all be graded. It has been shown that in most movements often more than one muscle contributes to the movement and the strength when testing for resistance.[2,3] In a later

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paper, only those movements were listed that could be graded and would allow for easy evaluating and monitoring of motor function changes in leprosy patients.[4] The purpose of this paper is to discuss the tests that should and could be done. For details about the testing itself, the reader is referred to the aforementioned publication. A form is presented that is suitable for screening purposes or for 'follow-up' with more detail for subjects with established motor function impairment to evaluate and monitor changes over time. This paper will not discuss muscle tests that may be relevant from a (reconstructive) surgical point of view. Specific surgery forms should be used for subjects that are considered for reconstructive surgery.

Detail of grading

The Medical Research Council 6-point scale (0–5) is nowadays the most commonly used to assess and evaluate muscle strength.[5] The grades are defined by range of motion, degree of resistance that can be overcome and whether or not the limb (segment) moves against gravity (Table 1). The grading is very useful in the evaluation of patients who are treated for recent nerve function impairment to monitor the effect of instituted treatment(s). The grading of muscle strength needs a certain level of understanding of anatomy, standardization of testing procedures and experience. Some authors felt that this was not always present in 'field' leprosy control work and they proposed tests that could be easily performed by the fieldworker or copied by the subjects.[6–8] The distinct disadvantage of these tests is that minor degrees of weakness will not be detected. Patients with 'minor' degrees of weakness will still be able to perform these tests. In other words, most of these tests will first become 'positive' when there is considerable weakness of the muscles present. If early detection of nerve function loss improves prognosis for preservation of nerve function tests should be used that test for resistance. Such tests will more likely reveal early motor function impairment.

Facial nerve

The facial nerve innervates all muscles of facial expression. Most commonly, the upper branch is affected which will result in weakness or paralysis of the muscle that closes the eye. Grading with the MRC scale will be possible except maybe for grade 1. In my experience, the testers find it difficult to agree on a grade 1. There is good agreement between the testers on a

Table 1. Medical Research Council (MRC) muscle grading scale

Medical Research Council (MRC) scale[a] (6 grades)	Modifications (9 grades)
5 Full range of motion; full resistance	1+ moderate resistance
4 Full range of motion; some resistance	3+ minimal resistance
3 Full range of motion; no resistance	2+ nearly full range
2 Decreased range of motion	
1 Muscle flicker	
0 Complete paralysis	

[a]The MRC scale originally grades 4–5 against gravity and 0–3 with gravity eliminated. For muscle grading of small muscles the effect of gravity is negligible.

grade 0 (inability to close the eye) and grade 2, partial closure. For this reason it is now being considered not to use grade 1 for eye closure.

In light eye closure the subject is asked to close his eye as if falling asleep. An eyelid gap, if present, is then measured. This measurement is indicated for subjects with strength less then grade 3. It is another way of evaluating changes in strength avoiding the compensatory movements that subjects often use by pulling up their cheeks to achieve full closure.

The 'empty' rows on the muscle charting form (Figure 1) can be used to list and grade one or two additional muscles in case there is a total facial palsy. Weakness or paralysis of the frontalis muscle, responsible for raising the eyebrow, does occasionally occur in leprosy patients. This could also be indicated in the empty row. Using the MRC grades for strength evaluation of this muscle, however, is not practical.

Ulnar nerve

In a separate paper, the author has discussed in more detail the testing and grading of the intrinsic muscles of the hand.[9] With six tests the motor function of the ulnar nerve can be evaluated and monitored: abduction of the little and index fingers and intrinsic position of the four fingers.

The main contributing muscle towards abduction of the little finger is possibly the abductor digiti minimi. With respect to its function, it could be considered a dorsal interosseus (flexion and abduction of the (fifth) metacarpophalangeal joint). The hypothenar muscle mass is easily palpable to be able to give a grade 1 or 2. This is also the case for abduction of the index finger for which the muscle mass (first dorsal interosseus) is easily palpable in the first webspace. When in doubt about the presence of a very weak first dorsal interosseus (grade 1–2), the examiner could ask the patient to strongly pinch against the index finger preferably in a pulp to pulp pinch with the thumb in opposition. The first dorsal interosseus muscle may then become palpable.

The interossei are the muscles responsible for MCP stabilization and they are tested in the so-called 'lumbrical' position/test. This has been discussed more extensively elsewhere by the author but the main evidence will be summarized here.[9]

In an isolated ulnar palsy there is always 'latent', sometimes called 'hidden', clawing of the index and middle finger. Only in the presence of a Martin–Gruber anastomosis or localized damage of the ulnar nerve at the level of the wrist may near normal strength still be present in the intrinsic position (MCP flexion, IP extension) of the index and to a lesser degree of the middle finger.[10–14] In long standing ulnar palsy 'overt' four finger clawing will become evident. Secondly, the author has never seen cases of low median palsy in which clawing of the index and middle fingers was present. Thirdly, the so-called lumbrical function is restored by 'reactivating' the interossei by direct insertion of tendon grafts into the interossei tendons. 'Clawing' is also corrected by restoring primary flexion of the MCP joint in the so-called Zancolli Lasso operation. No leprosy surgeon, I would hope, would do only a two-finger (ring and small fingers) 'claw' correction in an ulnar palsy. The author has seen cases in which, in the early days of tendon transfer surgery, only the ring and little fingers were corrected. When reviewing these patients years later the index and middle fingers showed clawing!

It can be very misleading in a muscle charting form to have the 'lumbrical' test for the index and middle fingers under the 'heading' median nerve. An isolated palsy of the ulnar nerve will show weakness and, often at a much later stage, paralysis of the 'lumbricals' of the

Green Pastures Hospital
Voluntary Muscle Testing

Name Hosp. No:

	YEAR
	Day/Month
	TRIGEMINAL
	Blink Y / N
	Corneal sens. Y / N
	FACIAL
	Eye closure (grade)
	Lid gap (mm)
	ULNAR
	Abduction little finger
	Abduction index finger
	Intrinsic position R-S
	Intrinsic position I-M
	FDP(R) - FCU
	MEDIAN
	Abduction thumb
	Opposition thumb
	FPL
	RADIAL
	Wrist extension
	C. PERONEAL
	Dorsiflexion (L.A.)
	Eversion
	EH (EDL)
	Signature

First assessment weakness/paralysis in red; following assessments only deterioration in red.
Always note duration of (new) muscle weakness/paralysis

Date:	Comments:

MRC scale: 5= normal range of motion (ROM) and strength; 4= normal ROM reduced strength; 3= normal ROM no resistance; 2= partial ROM no resistance; 1= muscle flicker only; 0=paralysed JWB version 5/2000

Figure 1. Muscle charting form.

index and middle finger. Most therapists and medical doctors alike will attribute this to anomalous innervation or, worse still, to partial median nerve involvement. It seems therefore justified to include this test for the interossei (preferred term 'intrinsic test') for all four fingers listed with the ulnar nerve.

There are no clinically reliable tests by which the strength of the lumbricals can be graded on the MRC scale.

Differences in grades between ulnar innervated muscles on the radial side of the hand versus the ulnar side may be explained on account of a Martin–Gruber anastomosis or localized damage at near or at the ulnar carpal tunnel (Guyon's canal).

Two extrinsic muscles are innervated by the ulnar nerve: the flexor digitorum profundus to the ring and small finger and the flexor carpi ulnaris. Testing of these muscles could be of interest from a prognostic point of view. Do patients with a 'low' ulnar palsy have a better chance for recovery?

The empty rows on the form could be used to record the outcome of any alternative 'tests' (see Discussion). For screening purposes, we advise testing abduction of the little finger. When weakness or paralysis is detected, the other movements are also tested.

Median nerve

The median nerve is most commonly affected at the level of the wrist, rarely in the cubital fossa (level of the elbow). When the nerve is affected at the wrist there will be weakness or paralysis of the muscles that oppose the thumb: abductor pollicis, opponens pollicis and to a variable degree, depending on its pattern of innervation, the flexor pollicis brevis. In addition, the median nerve innervates the lumbrical muscles to the index and middle fingers. As argued above, the interossei are the muscles tested in the so-called 'lumbrical' test.

The only two tests to evaluate the motor function of the median nerve are abduction and opposition of the thumb. Neither movement can be attributed to the action of one muscle only.

For screening purposes, we advise to test abduction of the thumb. Other tests should also be done if this test reveals weakness. It could then also be of interest to check if there is weakness of the extrinsic muscles that are innervated by the median nerve. For this, we suggest that thumb IP flexion is tested (flexor pollicis longus) and/or the flexor digitorum superficialis of the index finger.

Radial nerve

The radial nerve is rarely involved in leprous neuropathy. In leprosy, when there is motor function impairment of the radial nerve, there often will be associated motor function impairment of the ulnar and median nerves. This is often referred to as a triple (=3) palsy. However, isolated motor function impairment of the radial nerve does occur. If a patient is making use of crutches a 'crutch palsy' (neuropraxia), because of the wrong use of crutches, should be ruled out!

For screening purposes, it is sufficient to test the combined wrist extensors in extension of the wrist. Only when weakness or paralysis is detected in this movement, one or two other muscles/movements could be tested. These can be included in the 'empty' row. The common

finger extensors are appropriate for this. The subject is asked to extend the fingers at the mcp joints keeping the fingers flexed at the IP joints. The examiner can test simultaneously all four fingers for resistance with four fingers of his hand.

It should be noted that the intrinsic thumb muscles contribute to thumb IP extension. In isolated radial nerve damage thumb IP extension may therefore still be possible and strong. This if often mistaken as an action of the extensor pollicis longus!

Common peroneal nerve

The common peroneal or lateral popliteal nerve 'branches' at the site where it winds around the head of the fibula. Depending on the exact site of branching and extent of damage one or both of the branches may be impaired. The *d*eep branch innervates the *d*orsiflexors, tibialis anterior, and the two toe extensors; the superficial branch, the evertors. It is common to talk about a total footdrop when both branches are not functioning and an incomplete footdrop when only one of the two is affected, most commonly the deep branch. An irregular 'footdrop' (better irregular pattern of paralysis) would be one in which only one or two muscles are functioning or are weak, e.g. isolated weakness of toe extension or normal strength for great toe extension only.

For screening purposes, we recommend that dorsiflexion of the foot is tested. Only when weakness or paralysis of dorsiflexion is evident may further detailed testing be indicated.

Posterior tibial nerve

The posterior tibial nerve is commonly affected behind and above the medial malleolus, in or above the tarsal tunnel. For many people it is difficult to isolate a specific movement by which the strength of the intrinsic muscles can be graded. In Karigiri the technicians for many years have tested the 'toe-grip'. The subject was asked to try to keep a piece of paper between the great toe and the second toe. The examiner then tried to pull the piece of paper from between the toes. This test has now been discarded because the technicians found this test not to be very practical and stated that many times in unaffected feet with normal sensation and in control subjects the test was (false) 'positive'. Likewise, toe-fanning, the spreading of toes, is a qualitative test which is likely to be positive in many non-affected subjects!

'High' posterior tibial (medial popliteal) nerve damage very rarely occurs, some even deny its occurrence.[15] High posterior tibial motor function impairment would result in weakness or paralysis of the muscles of the calf. In Karigiri, we have included a test for high posterior motor function impairment for research purposes. What is the incidence of 'high' posterior nerve impairment and is it associated with motor function impairment of the lateral popliteal nerve?

Reliability

Only a few reliability studies have been conducted on manual muscle strength testing with leprosy patients as subjects.[16–19] Overall, the studies report acceptable reliability and support

the use of manual muscle strength testing. A notable exception is the study by Lewis, which was methodologically and conceptually flawed.

In the most recent reported study, however, it has been shown that reliability coefficients to a great extent are influenced by the high proportion of completely normal or completely paralysed muscles.[17] In this study intertester reliability was assessed from data obtained from 72 leprosy affected persons using an extended 9-point MRC scale. When omitting the normal scores and the completely paralysed muscle scores from the analysis, the direct agreement percentage dropped considerably. On the basis of the results of this study, the hospital in which the study was conducted decided not to 'value' the 'in-between grades' as they are sometimes reported by the physiotherapist or technician.

Basic form and lay-out

Figure 1 shows the muscle charting form with the tests recommended to screen subjects for possible motor function impairment and to monitor subjects with confirmed motor function impairment. First, the facial nerve is listed, followed by the nerves in the upper extremity and finally, the lower extremity. For the upper extremity the nerves are listed in the order of most commonly to least often affected. For each nerve, when applicable, first the intrinsic tests are listed and then the test for extrinsic muscles.

The nerves and muscles/movements are listed in the central column. On the left side of the form, the tests for the right side of the body are graded and on the right side, those for the left side. Normally, the subject is facing the examiner and so the side that is examined corresponds with the same side of the form. The results of the first assessment could be recorded starting from the centre of the form and then working towards the right and left side for subsequent assessments. Alternatively, in some programs the grades are recorded from left to right; the results of the first assessment for the right side are recorded in the first column.

The proposed form allows for seven muscle assessments. In Green Pastures Hospital, this matches the number of sensory assessments that can be recorded on the reverse side of the form.

There is a provision for comments that should be used to record the presence of pain on testing that will influence the muscle score. This should also be used to make note of irregular pattern of paralysis, duration of palsy, lack of co-operation of patient in testing etc.

The tests for screening purposes area shaded on the muscle charting form. If practical, and when expertise is available, it is recommended that 'detailed' testing is done for those nerves for which the screening test showed weakness/paralysis.

The lay-out of the form allows for easy recognition and visualization of the problem nerve(s). The row in line with the nerve headings 'separates' the nerves. This row could for example be used to indicate start and finish of prednisolone treatment. Visualization of problem nerves and changes can be further enhanced by using a red pen to record the grades for tests that score less than grade 5 on the first assessment. For subsequent assessment 'red' should only be used when there is new or increased motor function impairment.

Discussion

A notable feature of the form is the avoidance of Latin names for muscles. This will make it easier to teach muscle testing to the 'paramedical' leprosy workers. The point has been made

that most muscles cannot be tested in isolation. Also in other patient populations in which muscle scores are an outcome measure, the researchers test and grade movements rather then individual muscles.[20–22] This author proposed already in 1981 a simplification of muscle charting for leprosy patients but in many projects detailed testing is still practised.[4] Goodwin already recognized in the first paper on muscle testing in leprosy that some muscles may be easy to test and that others are difficult to grade.[1]

The intrinsic muscles do contribute to grip and pinch strength. Some studies are underway to see if dynamometry is more sensitive in detecting and monitoring changes in the motor function of the ulnar nerve. This would be especially useful in the 3–5 MRC range. Dynamometry for the evaluation of motor function in leprosy patients was already suggested in 1963 by Harris, who gives credit for this to Dr P. Brand.[23] In a case report dynamometry values and MRC scores were obtained and compared in a case of bilateral low ulnar neuropraxia.[13] The empty rows on the form could be used to record grip and/or pinch strength values. Some studies look into the possible value of testing for endurance, the number of contractions with some predetermined amount of resistance, to evaluate the motor function of especially the ulnar nerve. This could be valuable to quantitate muscle strength in patients with a grade of more than 3. These studies seek to develop a test which may be more sensitive to detect changes in motor function of the ulnar nerve.

Contraction of the interossei in the so-called lumbrical test can be easily demonstrated on the index and little fingers. When giving resistance towards flexion in the intrinsic position of these fingers, palpation of the first dorsal interosseus and abductor digiti minimi (which could be considered a dorsal interosseus) reveals a strong contraction of these muscles. These muscles are not only abductors of those fingers but they are also the primary flexors. In leprous neuropathy it is not really necessary to test all the dorsal and palmar interossei in abduction and adduction of the fingers. Besides the fact that they are already graded in the intrinsic test, abduction and adduction would be difficult to grade using the MRC grading, except, of course, in abduction of the index finger.

High median nerve function impairment (cubital fossa) does occur in leprosy patients, but is relatively rare. If present, it will be associated with weakness or paralysis of the intrinsic muscles. Weakness or paralysis of only the extrinsic muscles may occur when there is entrapment of the anterior interosseus nerve as it passes through the pronator teres but this is distal to the site where the nerve may become affected in leprosy. Nothing is known about the prevalence of high median involvement, but when present, it is usually associated with radial nerve motor function impairment. Isolated radial nerve damage does occur but a crutch palsy should be excluded. More commonly, when there is paralysis of the radial innervated muscles, there will be motor function impairment of the ulnar and median nerve as well (triple palsy).

It is advisable to test the extrinsic muscles/movements when the screening test for the nerve reveals weakness or paralysis. When the extrinsic muscle tests are normal they can then be excluded from follow up assessments. It is unlikely to find weakness or even paralysis of extrinsic muscles innervated by the ulnar or median nerve in the presence of normal intrinsic muscle strength. For the ulnar and median nerves the extrinsic muscle strength tests are in italics.

For research purposes it may be interesting to include grading of the strength of extensor hallucis (EH) muscle to establish the prevalence of isolated EH weakness/paralysis in the presence of normal strength for dorsiflexion. It has been noticed that there may be isolated weakness and even paralysis of EH.[17]

It would be good to include in some centres in the muscle charting form a test for the motor function of the posterior tibial nerve ('high' – not shown in the muscle chart) in addition to a test for the motor function of high median nerve. This is for research purposes only, in order to be able to say something about the prevalence of high posterior tibial and high median nerve motor function impairment and its possible association with lateral popliteal and radial nerve motor impairment, respectively.

Sometimes paralysis of the m. frontalis is noticed. This is the muscle responsible for wrinkling the skin above the eye, the forehead. The muscle is innervated by a branch of the facial nerve. The nerve that is sometimes palpable across the forehead is a branch of the ophthalmic branch of the trigeminal nerve (supra-orbital nerve). Grading of the m. frontalis on the MRC scale is not practical. Would a count of wrinkles be useful?

Manual muscle testing is often considered to be 'subjective', implying unreliability. Whereas there is an element of subjectivity in the muscle testing, several studies have shown that muscle strength can be reliably graded. Pain, the ultimate subjective phenomenon, can be very reliably assessed. The nature of the phenomena to be tested and the reliability of a test are often confused. Objective phenomena may be measured unreliability; subjective phenomena when measured with adequate instruments can show high inter- or intratester reliability.[24]

Further studies on the reliability of manual muscle strength testing in leprosy are encouraged, both field and hospital based. A cautionary note: it is not correct to assume that when acceptable reliability has been reported in one or more studies, reliability will also be good in your own setting. Only a replicate study will confirm this.

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Lepr Rev (2000) **71**, 268–269

SCIENCE COMMENTARY

Are cytokines our key to immunity against mycobacterial diseases?

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A current dynamic area of mycobacterial research is the identification of correlates of protective immunity to mycobacteria. Such a correlate (either *in vivo* or *in vitro*) would greatly enhance our understanding of the pathogenesis of both leprosy and tuberculosis; would assist in the identification and evaluation of promising vaccine candidates; and may provide a more accurate marker of exposure than do the current skin tests. In this context, there are an increasing number of studies being conducted, such as that recently reported by Lima *et al.*,[1] that are measuring *in vitro* cytokine responses—from blood cells stimulated with mycobacterial proteins—as the 'read out' of the immune response in an individual. Findings to date from these studies indicate that cytokine responses—most prominently the interferon-gamma (IFNγ) response—may indeed provide useful markers of immune response that could be employed as correlates of protective immunity, although further evaluation is required. IFNγ production by T-cells is a key component of the protective response against mycobacteria, as it activates infected macrophages to kill intracellular *M. leprae* or *M. tuberculosis*.

It has been recognized that current basic laboratory research on leprosy can benefit from the intense efforts underway to define the protective immune response against tuberculosis, and—given our experience with BCG—it may be that a new more effective tuberculosis vaccine could also be effective against leprosy. BCG vaccines have shown widely varying protective efficacy against pulmonary tuberculosis depending on the area of the world in which they have been used.[2] In the course of TB protection studies, it emerged that BCG is also highly protective against leprosy[3] although this may also vary according to location.[4]

The development of the human immune response to BCG vaccination is being studied by several groups. Ravn *et al.*[5] found that in 20 healthy Danish donors vaccinated with BCG (Copenhagen strain), *in vitro* peripheral blood mononuclear cell (PBMC) proliferative responses to tuberculin PPD and fractions/secreted proteins of *M. tuberculosis* increased more rapidly during the year following vaccination in those subjects who had responded to *M. tuberculosis* PPD by *in vitro* assay prior to BCG vaccination. They interpreted this observation as evidence that prior exposure to mycobacteria in these subjects may have played a role in priming the immune system. Interestingly, some of these 'primed' donors had 'negative' tuberculin skin test results. The IFNγ response to secreted proteins was increased 2 months after vaccination in all donors, as was the cytotoxic response to PPD-pulsed macrophages, and tuberculin skin test sensitivity increased in the majority of

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donors. BCG vaccination has been shown to be highly protective against TB in Denmark.[2] In contrast, a study of PBMC responses to tuberculin PPD and heat killed *M. tuberculosis* in a group of 20 tuberculin negative BCG vaccinees in South India found no increase in IFNγ responses to PPD or heat-killed *M. tuberculosis* 2 months after BCG vaccination (Copenhagen strain), although tuberculin skin test sensitivity had increased.[6] BCG vaccination has been shown to provide no protection against tuberculosis in South India.[7] This suggests that the *in vitro* IFNγ response may be a better correlate of BCG-induced protection against tuberculosis than the tuberculin skin test response. Lima *et al.*[1] in Brazil have extended this work to analyse the BCG-induced protective response against leprosy. Their study of BCG vaccination (Moreau strain) in seven healthy household contacts of multibacillary leprosy patients (five of whom had previously received BCG in infancy) found that the IFNγ responses to whole *M. leprae* in some of these subjects was increased 15 days and 1 year after vaccination with BCG. This was accompanied by a clear shift in the profile of the innate inflammatory response in all subjects—a decrease in the ratio of tumour necrosis factor α to interleukin 10 production. Although only small groups were investigated in each of these studies, they provide an indication of changes in cytokine response that result from BCG vaccination, which may reveal the mechanism behind development of a protective response against leprosy and/or tuberculosis, and therefore provide a tool to examine why BCG may not work in some populations. It is hoped that future larger scale studies of the immune response to BCG vaccination, such as the parallel studies currently underway in Malawi and the UK (Black, Weir *et al.*, manuscript in preparation), may further illuminate the important role of cytokines in mycobacterial infections.

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Lepr Rev (2000) **71**, 270–272

COMMENTARY

A PROSPECTIVE COHORT STUDY COMES OF AGE

The current issue of *Leprosy Review* contains a record seven papers from the same study group which together present the findings of the ALERT MDT Field Evaluation Study (AMFES), ripe fruit harvested 12 years after its planting in 1988. In the published literature, there are only three longitudinal, prospective cohort studies which report the outcome of leprosy patients treated with MDT. They are: Schreuder's cohort from Thailand,[1–3] the Bangladesh Acute Nerve Damage Study (BANDS),[4–7] and AMFES from Ethiopia. Each study reports on a different study population: AMFES from Africa, and the other two from ethnically distinct Asian countries. AMFES and the Thailand study are of similar size (AMFES 650, and Thailand 640 patients) while BANDS is rather larger with a cohort of 2,664. The BANDS papers present findings after 2 years of follow-up; the Thailand publications after 8 years; but the AMFES corpus published with this commentary reports findings 11 years from the time of first recruitment. This, combined with the breadth of the published material, gives the AMFES series a unique position in this trinity of cohort studies.

Four earlier papers have been published using the AMFES cohort. In 1994 De Rijk *et al.* wrote about the study organisation and methodology, giving preliminary reports after 5 years on MDT completion and the occurrence of reactions and neuritis on just 286 patients.[8,9] As an offshoot, De Rijk and Byass used the same group to compare 10 g and 1 g monofilaments for the sensory testing of hands, concluding that the 1 g filament was a more sensitive tool;[10] and Meima *et al.* used a larger group (592 patients) in their study, which found that age and delay in presentation were associated with the presence of impairments in new leprosy patients.[11]

The first paper sets out the methodology and objectives of the study. The objectives were to determine the incidence of relapse, reactions and nerve dysfunction amongst the cohort patients: the subsequent papers show how far this has been achieved. A single line from this paper is a poignant reminder of the very human element involved in leprosy: *'There were far fewer pregnancies in the AMFES women after the diagnosis of leprosy'*.

The second paper provides us with the real meat of the study by detailing the pattern of leprosy-related neuritis in the cohort. At a single sitting, the incidence, risk factors and outcome of neuritis are presented. There is much important material here that needs careful consideration. The finding that over 80% of all nerve damage had occurred before diagnosis emphasises the priority of public health education in control programmes. Recovery from acute neuritis using prednisolone treatment was excellent at 88%, a figure higher than that reported from other studies, including BANDS. A significant proportion of the recovery occurred *late* – well after a year – underlining the importance of 'the long view'. Interestingly, spontaneous recovery of nerve damage was found in up to a third of nerves,

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confirming a similar finding from Bangladesh.[7] Chronic and recurrent neuritis were identified as very important risk factors for poor outcome. Surprisingly, multibacillary leprosy was *not* identified as a significant risk factor for the development of neuritis. This probably reflects the classification system in use at the time which assigned all smear-negative BT patients as paucibacillary; the current WHO system would have assigned patients with six or more skin patches to the MB group. The AMFES PB group was thus 'more multibacillary' than comparable PB cohorts.

The subject of relapse after fixed-duration MDT is very topical, and it is reassuring that there were *no* relapses diagnosed in the AMFES cohort, even amongst the 57 cases with an average bacteriological index (BI) of ≥ 4. This is an interesting counter-balance to some papers telling an opposite story.[12,13] However, the number of high-BI patients who have had follow-up for more than 5 years (20) is small compared with 260 in the Indian study reported by Girdhar.[13] It is important that the small AMFES group are followed up – and this is planned for a further 5 years. A further interesting point is that, as has been stated, the AMFES PB leprosy group included a number of multi-lesional (smear negative) BT patients who would have received MB-MDT today. There was no relapse amongst them either, despite only receiving PB-MDT.

Related to the relapse topic is a further paper reporting the pattern on decline in the BI after MDT. The study group found that a delay of less than 3 years to presentation and more severe impairment at start of MDT were both significantly associated with a faster drop in the BI – why this should be so, is not clear! The occurrence of reversal reactions did not increase the speed of clearance of bacilli.

The incidence and risk of reversal reactions in the skin are the subject of another paper. Not surprisingly, borderline leprosy emerges as the major risk factor while the initiation of MDT was also (importantly) found to be an important risk factor for up to 12 months after the start of treatment. HIV infection, pregnancy and lactation at the time of diagnosis and female gender (independent of pregnancy and lactation) were all also found to be more weakly associated with a greater risk of reversal reaction. A similar study on the incidence and risk factors for ENL reactions found that co-infection with HIV was strongly associated, not surprisingly, that LL leprosy and a BI of 6. However, the numbers were small: only 16/300 MB patients (5%) developed ENL.

Finally, the effect of HIV status on the clinical picture of leprosy was examined. The total number of HIV-positive individuals was small, 22 amongst 581 patients tested (4%). Not surprisingly, there was an excess of deaths among the HIV-positive group (27%) compared with the HIV-negative group (6%). There was a higher risk of developing ENL, and a weaker association with reversal reactions; but no association with developing MB rather than PB disease, or with the development of impairment.

It should be clear to the reader what a wealth of important material has resulted from this long-term study. Prospective studies have a very important place in enhancing our understanding of the interaction between *Homo sapiens* and *Mycobacterium leprae.*

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The ALERT MDT Field Evaluation Study (AMFES): a descriptive study of leprosy in Ethiopia. Patients, methods and baseline characteristics

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Summary The ALERT MDT Field Evaluation Study (AMFES) is a long-term prospective study of 650 patients (594 new cases and 56 relapses after dapsone monotherapy), treated with fixed-duration multiple-drug therapy (MDT), as recommended by WHO. Follow-up has continued for up to 11 years from the start of treatment. This paper presents the methodology of the study and the baseline characteristics of the cohort, while accompanying papers examine the incidence of, and possible risk factors for, the various complications of leprosy, including relapse, reactions and nerve function impairment. The methods of diagnosis, classification and treatment with MDT are described; nerve function was assessed at every visit to the clinic using a standardized methodology, so that reactions and new impairment could be detected early and treated. Eighty-four per cent of new case had at least one thickened nerve, with the ulnar nerve most commonly involved. Seventy-seven per cent of cases completed treatment and only one adverse reaction to the MDT drugs was noted. Twenty-eight per cent of all patients were given steroids at one time or another, almost always for new nerve function impairment, and 3% of these developed significant complications of steroid treatment. Twenty-nine patients (5%) received hospital care, including 14 patients who underwent major surgery. Sixty-one per cent of the women over 19 years of age had at least one pregnancy, but pregnancies were much less common after leprosy was diagnosed.

Introduction

The WHO-recommended multi-drug therapy (MDT) for leprosy has proved to be remarkably effective in curing the disease, with very low reported rates of relapse. The complications of

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leprosy (in particular, reactions and nerve damage) remain, however, as important causes of impairment and disability. Most previous reports of these complications of leprosy have been retrospective studies, so a long-term, prospective study was planned at the All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre (ALERT) in Ethiopia, to characterize more accurately the incidence of, and risk factors for, reactions and nerve function impairment.

The ALERT MDT Field Evaluation Study (AMFES) was started in 1988 with three main objectives. These were to assess:

1. The incidence of relapse and factors associated with the occurrence of relapse after fixed-duration MDT: 6 months treatment for paucibacillary (PB) cases and 24 months for multibacillary (MB) cases;
2. The incidence of leprosy reactions and factors associated with the occurrence of reactions, both during and after MDT; and
3. The incidence of new or increased nerve dysfunction and its progression to permanent nerve function impairment.

In all, 660 patients were enrolled between 1988 and 1993. After release from treatment, active surveillance was carried out. PB patients were followed for 5 years after release from treatment and then discharged, while MB patients have remained on active surveillance. The AMFES project will close at the end of 1999, but it is hoped that a group of 180 MB patients who are still on surveillance, will be reviewed annually for at least a further 5 years to look for late relapses.

The enrolment procedures and the administration of treatment have been described in detail.[1] In the absence of active case finding, practically all patients enter the control programme as self-reporting new cases. All new, untreated leprosy patients were eligible for enrolment. While that initial paper reported on the first 286 patients enrolled, this paper now reports on the complete cohort of 660 patients. Accompanying papers report the findings in relation to the original objectives of AMFES, building on the interim results reported by de Rijk *et al.*[1,2]

Materials and methods

BACKGROUND

The ALERT leprosy control programme covers an area of 85,000 km^2 in central Ethiopia, an area which used to be one province (Shoa) but which is now divided between several new administrative regions. The population has grown from under 11 million in 1988, to over 13 million in 1998. The programme includes the capital city, Addis Ababa, but is otherwise predominantly rural. Travel in more remote parts of the programme area is difficult. AMFES was started in only certain parts of the programme area, because of the difficulty of travel and communication.

The former government of Ethiopia was overthrown in May, 1991, with much civil unrest and insecurity in the period before that date and some disruption of routine services in the period afterwards. Thus it is to the great credit of the field staff of the programme and the patients themselves, that case-holding during those difficult times was maintained at a reasonable level, although the greatest number of losses to follow-up occurred at that time. The staff working in the AMFES project number about 12–15 experienced health assistants and there have been remarkably few staff changes, so that most patients have been reviewed by either one or two individuals throughout the period of treatment and surveillance.

The ALERT leprosy control programme functioned as a vertical programme throughout the AMFES study period, but is now in the process of being decentralized and integrated into the general health services. As a vertical programme attached to the Training Centre at ALERT, however, it was a useful testing ground for a number of initiatives which have since become standard practice for field programmes; for example, the regular assessment of nerve function and the treatment of neuritis with steroids.[3,4] More recent initiatives have looked at ways of preventing further disability with protective footwear[5] and methods of empowering former patients to take responsibility for their own care. The issue of delay in presentation of new leprosy cases has also been investigated in the field programme[6] and has been reported for the AMFES cohort also.[7]

DIAGNOSIS

The methods of diagnosis, administration of fixed-duration MDT and case-holding in AMFES have been previously reported[1] and were essentially the same as in the routine leprosy control programme run by ALERT. The finding of at least one of the three classical cardinal signs of leprosy (loss of sensation in a typical skin patch, thickening of a peripheral nerve or a positive skin smear) was the basis of the diagnosis. Skin smears were done routinely and the bacillary index (BI) and morphological index (MI) were recorded for each of four sites. The patient's BI was taken as the highest of the four readings. Case-finding was generally by voluntary self-reporting and treatment was given through a series of monthly clinics run as a vertical programme.

HISTOLOGY

Histological services were available at ALERT. Biopsies were taken from 30% of patients, either because of uncertainty in diagnosis or classification (16%), or as a random sample to check the clinical diagnosis and classification (14%).

CLASSIFICATION

Patients were classified according to the Ridley/Jopling method on clinical grounds, with BB cases being grouped together with BL cases. For the WHO treatment categories, the following definitions were used:

- Paucibacillary (PB) cases are those clinically or histopathologically classified as tuberculoid (TT), borderline tuberculoid (BT) or indeterminate (I), whose highest BI at any site is no more than 1.
- Multibacillary (MB) cases are those clinically or histopathologically classified as borderline lepromatous (BL) or lepromatous (LL) and any others who had a BI of more than 1 at any site.

Soon after the start of the project these definitions were altered so that any patient with a positive skin smear at any site was treated as an MB case. Three cases with a BI of 1 were treated with the PB regimen under the earlier rules; they were not reclassified or re-treated. The number of skin lesions and number of nerves involved were not used to classify patients as is currently the case in many programmes, following recent recommendations by WHO.[8] A large number of the PB cases in this study would have been

classified as MB, if the main indicator for being MB were the presence of more than five lesions.

The term neural leprosy was used for patients with nerve involvement only, indicated by undoubted nerve enlargement, with or without nerve function impairment, but with negative skin smears and no skin lesions. Patients in this group with only one nerve involved were treated with the PB regimen, while all others received the MB regimen.

SURVEILLANCE AND REVIEW

During the period of surveillance after treatment, patients were given 6-monthly appointments and were traced by various methods if they failed to attend. These methods included sending a message with other patients, the use of a scout to visit the patient, or a home visit by the health worker. The period of surveillance for PB patients was 5 years, but has been extended for MB patients because of the possibility of relapse in the second 5-year period after release from treatment. There was no active surveillance of non-AMFES patients during this period.

The assessment of patients every month (every 6 months after release from treatment) has also been described in detail[2] and consisted of a brief history and examination, followed by a standardized nerve function assessment: this included voluntary muscle testing (VMT) and sensory testing (ST) of nerves supplying the eyes, hands and feet. This procedure was also standard practice throughout the ALERT leprosy control programme area. Four muscles were tested for muscle strength: eye closure (facial nerve), abduction of the fifth finger (ulnar nerve), abduction of the thumb (median nerve) and dorsiflexion of the foot (peroneal nerve); a three-point scale was used to record the results, each muscle being graded as strong (S), weak (W) or paralysed (P). Sensory testing involved testing 10 sites on the palm of each hand and the sole of each foot with a 10 g nylon monofilament; at each of the 40 points the monofilament was recorded as either 'felt' or 'not felt'.

IMPAIRMENT AND DISABILITY

The details of the examination were recorded each time on the patient's record card. The WHO Disability Grades, more correctly referred to as Impairment Grades,[9] were also recorded for each examination. For the purpose of analysis they have been tabulated at the start of treatment, at release from treatment and 5 years after release from treatment. De Rijk *et al.* proposed a simple summation score of WHO grades[1] and this has been refined into the 'EHF' score, which is becoming more widely used to monitor groups of patients over time.[9] The EHF score (the Eye-Hand-Foot score, which is the sum of all six WHO Grades) can be calculated from the Impairment Grades and these scores have been tabulated at the same stages of the disease as the WHO Grades.

EVENTS

At each review, the main outcome was the presence or absence of an event. Four categories of event are recognized:

1. Reversal or type 1 reaction.
2. Erythema nodosum leprosum (ENL) or type 2 reaction.
3. Neuritis and new nerve function impairment (grouped together as neuropathy).
4. Relapse.

Reactions were diagnosed according to the history and clinical examination of the skin. Reversal reactions were diagnosed when there were symptoms and signs of inflammation in the leprosy skin lesions; no distinction was made between upgrading and downgrading reactions. Erythema nodosum leprosum was diagnosed when the typical red and painful nodules of the condition were seen.

New nerve function impairment and neuritis were recorded as one category (neuropathy), as they were considered to reflect different degrees of the same pathological process and were managed in the same way. Neuritis, or inflammation of a nerve, is indicated by pain or tenderness in the nerve, with or without loss of function. New nerve function impairment is indicated by a deterioration in the results of voluntary muscle testing and/or sensory testing: any recent loss of muscle strength (a change from 'S' to 'W' or from 'W' to 'P' or from 'S' to 'P' in any muscle) shows new impairment, and a recent loss of at least two points of sensation also shows new impairment; if the symptoms and signs of nerve involvement are of less than 6 months duration, the event is referred to as an episode of acute neuropathy. Neuritis and new nerve function impairment often occur with reactions, but may also occur alone; new nerve function impairment without accompanying symptoms of a reaction and without nerve pain, is referred to as silent neuropathy.[10]

Many patients have repeated events. There are as yet no strict definitions of the terms 'chronic' and 'recurrent' as applied to reactions and neuropathy in leprosy, although the terms are used. For this series of reports on the AMFES cohort, an event is said to be chronic if it recurs within 3 months of stopping treatment (usually steroids), or if the standard course of steroids has to be prolonged because of continuing signs and symptoms. Recurrent events are those events that recur after a gap of at least 3 months, during which the patient has no symptoms of reaction or neuritis and is not being treated with any anti-reaction medication.

MANAGEMENT OF EVENTS

Mild reactions of both types are defined as those involving only the skin, without any neuritis or nerve function impairment; they are treated symptomatically with aspirin. Severe reversal reactions have skin signs and new nerve function impairment and are treated with a course of steroids – prednisolone can be prescribed in the leprosy clinic, according to clear guidelines and with appropriate safeguards.[4,11] If new nerve function impairment is detected within 6 months, there is a strong possibility of reversing some or all of the damage with steroids.[12] Patients who require steroids but who have a contraindication to steroid treatment should be referred to ALERT hospital.

Severe ENL reactions are those with new nerve function impairment and/or involvement of other organs, such as the eyes (irido-cyclitis), testes (orchitis) or fingers (dactylitis), with fever and general malaise. These cases should be referred to ALERT hospital, because of the chronic and debilitating nature of the condition, the need for further investigations and the need for prolonged treatment (perhaps including admission) in many cases.

Suspected relapses require thorough investigation and should be referred to ALERT. The results of such investigations carried out to date are reported elsewhere.

RECORDS

Data management and analysis has been carried out throughout the study period. Patient record cards were regularly submitted to the statistical unit for data entry. Quality control

Table 1. The classification of AMFES patients

R/J classification	New cases			Relapse cases			Grand
	PB	MB	Total	PB	MB	Total	total
TT	6	–	6	–	–	–	6
BT	287	12	299	3	1	4	303
BL	–	202	202	–	41	41	243
LL	–	84	84	–	11	11	95
Neural leprosy	1	2	3	–	–	–	3
Total	294	300	594	3	53	56	650

took place at various levels: medical officers checked the patient records for consistency and a number of manoeuvres to check the internal consistency of the database were carried out; finally, unresolved inconsistencies and missing data were discussed and checked by reference to the original record card or by asking the patient directly, if possible.

Data entry and management used dBase software, while analysis has largely been done using EpiInfo v6, Excel v5 and Egret software.

Results

DIAGNOSIS

A total of 660 patients were enrolled and there were 10 exclusions. The reasons for exclusion were: incorrect enrolment procedures (five cases) and incorrect diagnosis (five cases). The five cases with an incorrect diagnosis included cases of granuloma annulare, chronic non-specific dermatitis, secondary syphilis and onchodermatitis, all diagnosed histologically; one case was not biopsied but the diagnosis of leprosy was ruled out by the medical officer on clinical grounds. On reviewing the record card, it was concluded that the case with onchodermatitis may have had leprosy as well, but he had completed PB-MDT before being discharged.

Of the remaining 650 cases, 594 were new cases and 56 were patients previously treated with dapsone monotherapy, presenting as relapses. The new cases had sometimes had a few doses of dapsone prior to starting MDT, but this was less than 8 weeks treatment for PB cases and less than 16 weeks for MB cases.

The new patients included in the AMFES cohort have been compared with the other new cases started on MDT during the same period in the routine programme of ALERT, with regard to age, sex, classification and impairment status at diagnosis. No important differences were observed and the AMFES patients are thus regarded as representative of all new cases detected in the area during the same period.[7]

Table 2. Number of skin lesions in new PB cases

	N	Number with 1–5 lesions	Number with 6–19 lesions	Number with 20 or more lesions	Unknown
TT cases	6	6	–	–	–
BT cases	287	81	150	50	6
Total	293	87	150	50	6

Table 3. Impairment of individual nerves at diagnosis

Nerve	Modality	Patients with 1–5 lesions (n = 87)		All PB patients (n = 294)		MB patients (n = 300)	
		Number	Percent	Number	Percent	Number	Percent
Ulnar	Sensory	11	13	68	23	71	24
	Motor	8	9	66	22	84	28
	Both	6	7	51	17	49	16
Median	Sensory	9	10	66	22	64	21
	Motor	3	3	29	10	24	8
	Both	3	3	25	9	19	6
Facial	Motor	2	2	20	7	22	7
Post. Tib	Sensory	28	32	131	45	164	55
Peroneal	Motor	0	0	15	5	10	3

CLASSIFICATION

The classification of the AMFES patients is shown in Table 1. There were no indeterminate cases. Table 2 shows the number of skin lesions seen in PB cases and thus how they may be classified according to current recommendations.

NERVE INVOLVEMENT AT DIAGNOSIS

Thickened nerves are one of the cardinal signs of leprosy. Of 594 new cases, 496 (84%) had thickened nerves. The ulnar nerve was most commonly involved (403 cases), followed by the radial cutaneous nerve.

Impairment at diagnosis is examined more fully in a separate report[7] where it is shown that delay in diagnosis is strongly associated with impairment. Impairment related to individual nerves is shown in Table 3.

TREATMENT

Table 4 shows the results of treatment for all 650 cases. Seventy-seven per cent of all patients completed treatment (83% for PB cases and 73% for MB cases). There were five additional deaths after completion of 5 years surveillance that are known of.

Table 4. Results of treatment of AMFES patients

Status	New cases			Relapse cases			Grand total
	PB	MB	Total	PB	MB	Total	
Enrolled	294	300	594	3	53	56	650
Transferred out	–	1	1	–	–	–	1
Died during treatment	1	12	13	–	2	2	15
Treatment not completed	50	75	125	–	7	7	132
Released from treatment	243	212	455	3	44	47	502
Died during follow-up	11	7	18	–	–	–	18
Incomplete follow-up	109	22	131	–	–	–	131
Discharged after 5 years	123	46	169	3	1	4	173
Continuing follow-up	–	137	137	–	43	43	180

Table 5. Baseline characteristics of patients in relation to treatment completion

	Variables	Number (%) of enrolled patients	Number (%) who completed treatment	Number (%) who did not complete treatment	Number (%) who died during treatment
Number	(*n*)	650 (100)	502 (77)	132 (21)	15 (2)
Sex:	Male	415 (64)	322 (78)	81 (19)	11 (3)
	Female	235 (36)	180 (76)	51 (22)	4 (2)
Age	up to 19 years	177 (27)	146 (82)	30 (17)	–
	20–49 years	361 (56)	275 (76)	77 (21)	9 (3)
	50 and over	112 (17)	81 (72)	25 (22)	6 (6)
Classification	TT	6 (1)	5 (83)	1 (17)	–
	BT	303 (46.5)	251 (83)	50 (19)	2 (1)
	BL	243 (37.5)	171 (71)	61 (25)	10 (4)
	LL	95 (14.5)	73 (77)	19 (20)	3 (3)
	Neural	3 (0.5)	2 (67)	1 (33)	–
Impairment	WHO grade 0	272 (42)	211 (78)	57 (21)	4 (1)
at start	WHO grade 1	200 (31)	153 (77)	44 (22)	3 (1)
	WHO grade 2	178 (27)	138 (78)	31 (17)	8 (5)
EHF score	<2	316 (48.5)	244 (77)	68 (22)	4 (1)
at start	2–4	245 (37.5)	185 (76)	52 (21)	7 (3)
	>4	89 (13)	73 (82)	12 (15)	4 (5)

Table 6. The prescription of steroids in relation to classification.

R/J Classification	Number of cases	Number given steroids at any time	Percent
TT	6	0	0
BT	303	60	20
BL	243	94	39
LL	95	30	32
Neural leprosy	3	1	33
Total	650	185	28

The drugs used to treat leprosy were very well tolerated. Only one drug-related problem arose: a 15-year-old female, HIV-negative patient with BL leprosy developed an allergy to dapsone, which was confirmed in hospital with a later challenge dose. The allergy took the form of an exfoliative dermatitis and started during the second month of MDT. The patient continued treatment with two drugs, rifampicin and clofazimine, for 2 years.

Table 5 shows baseline data for all 650 AMFES patients and compares the baseline characteristics of those who completed treatment with those who did not.

Of the 50 PB patients who did not complete MDT, 31 (62%) received more than two doses of MDT and of the 82 MB patients not completing treatment, 35 (43%) received 12 or more doses of MDT.

USE OF STEROIDS

In all, 185 (28%) of the 650 patients in AMFES were treated with steroids at one time or another, almost always for new nerve function impairment. Table 6 shows the need for steroids according to classification.

Steroids were generally well tolerated, but 5 (3%) of the 185 patients did have serious complications; all five were multibacillary cases. One had an acute fever possibly due to typhoid after a short course of steroids. The other four had all had prolonged courses of steroids for chronic events and developed foot sepsis/osteomyelitis (two cases), tuberculosis (one case) or pre-senile cataracts (one case).

HOSPITAL RECORDS AND SURGERY

Fifty-seven (9%) of the 650 AMFES patients have ALERT hospital records, but half of these (28 cases) were seen only for diagnosis and did not require admission or further specialist attention. Twenty-nine cases (4.5%) have been followed up more intensively by the hospital, with regular outpatient reviews and/or periods of in-patient care. Fourteen cases had major surgery (excluding basic septic surgery): this included 13 (2.2%) of the 594 new cases in the study and one further patient refused surgery (an ulnar nerve release). Nerve release surgery was carried out on four patients and reconstructive surgery on six patients.

PREGNANCY

The timing of deliveries was recorded in order to assess the status of pregnancy as a risk factor for events in female patients. Of the 235 women enrolled, 156 (67%) were over 19

years at diagnosis. Ninety-five (61% of those over 19 years) had had at least one pregnancy. There were 14 deliveries in the 6 months before leprosy was diagnosed, giving an incidence of 23 per 100 person-years-at-risk (14 deliveries in 124 women currently of child-bearing age, observed for 6 months). No control group was studied but this is a typical figure for women in the region at that time.[13] There were far fewer pregnancies in the AMFES women after the diagnosis of leprosy.

Discussion

AMFES has provided an unusual opportunity to follow a large cohort of leprosy patients over a long period. The main objectives are to establish the relapse rate after fixed-duration MDT and to elucidate the natural history of reactions and nerve damage, especially in the period after the completion of MDT, when medical care may be much less accessible for many patients.

Ethiopia is a large country with a prevalence of leprosy of around 1 per 10,000 population, putting it amongst the 10 countries with the most leprosy, in terms of case numbers. MDT is well established but stigma remains a major obstacle to good leprosy control.[6]

There is wide variation in the characteristics of new cases of leprosy around the world, in terms of disease classification and impairment status at diagnosis. In South Asia there tends to be a predominance of PB disease: for example, 83% of cases in Bangladesh[14] and 66% of cases in Thailand.[15] In other countries, such as Indonesia, the Philippines and Brazil there tends to be a much higher percentage of MB cases.[16] The mix of cases in Africa is perhaps more variable, reflecting greater variation in case-finding activities, but the AMFES cohort with 50% of cases being MB may be regarded as fairly typical. The AMFES patients have a generally higher rate of disability at diagnosis than is reported elsewhere. There are several possible explanations for this, including the length of delay in being diagnosed and the routine use of the 10 g monofilament for sensory testing; this is a sensitive instrument and may allow the finding of more loss of sensation than other routine methods, such as the ballpoint pen. There has been considerable debate over the normal thresholds for sensation in the hand and foot, and what the implications are for the diagnosis of impairment in leprosy.[17,18] The 10 g monofilament may be too sensitive for the foot in many situations and may have led to the overdiagnosis of sensory loss in some cases. Some referral centres use graded monofilaments to determine the level of sensory loss, but as almost all the nerve function assessments in this study were done under field conditions, this more sophisticated method was not used.

The commonest impairment in the AMFES cohort was loss of sensation in the sole of the foot, found in about half of all patients. About one-quarter of all patients had ulnar nerve function impairment, with sensation and muscle strength affected equally. With the median nerve, sensory loss is more common than loss of muscle strength. These findings are similar those reported from Bangladesh, although the overall rate of impairment in that study is much less.[14]

MDT is very well tolerated and only one adverse reaction was noted in the AMFES cohort, namely an allergic reaction to dapsone. Steroids were used in over a quarter of all cases at one time or another. Complications of steroid use were almost entirely confined to those patients given prolonged courses, although this could be related to better

record-keeping: patients given prolonged courses of steroids would be under a hospital consultant and have more detailed hospital records.

There is very little literature on the effect of pregnancy on leprosy and its complications, although some studies suggest that new leprosy cases present more commonly either during pregnancy or soon afterwards.[19] The results reported here show that pregnancy and delivery were much more common in the 6 months before diagnosis than in the years after diagnosis. There are many possible confounding factors, but a comparison with figures for women without leprosy in the region suggests that a reduced incidence of pregnancy after the diagnosis has been made, is the more significant finding. A number of possible social factors could be proposed to account for this, such as divorce or a reduced possibility of marriage.

In conclusion, the AMFES project involves a cohort of leprosy patients with severe disease, manifested by a high MB rate, a high rate of smear positivity and a high degree of nerve involvement. The incidence of and risk factors for further nerve damage and disability, as well as leprosy relapses, will be examined in subsequent papers.

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Lepr Rev (2000) **71,** 285–308

The pattern of leprosy-related neuropathy in the AMFES patients in Ethiopia: definitions, incidence, risk factors and outcome

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Summary The ALERT MDT Field Evaluation Study (AMFES) began in 1988 and followed patients prospectively for up to 10 years after release from treatment (RFT). This paper presents the findings from this cohort with regard to neuropathy and nerve damage. Five hundred and ninety-four new cases of leprosy are included in the study, 300 multibacillary (MB) and 294 paucibacillary (PB) cases. Fifty-five percent of patients had some degree of impairment at diagnosis and a further 73 (12%) developed new nerve function impairment (NFI) after starting multiple drug therapy (MDT). The overall incidence rate for neuropathy was 39 episodes per 100 PYAR in the first year after diagnosis, gradually declining to 12 episodes per 100 PYAR in the sixth year. In those patients without impairment at diagnosis, the incidence rate of neuropathy was 25 episodes per 100 PYAR for MB cases and 11 per 100 PYAR for PB cases in the first year; in 33% of MB cases whose first episode of neuropathy occurred after diagnosis, that first episode took place after the first year, or after the normal period of treatment with MDT. Seventy-three patients with neuropathy developing after diagnosis are reported more fully: 34 (47%) had only one nerve involved and of these 25 (73%) had a single, acute episode of neuropathy. Nine (27%) had further episodes. Thirty-nine (53%) had more than one nerve involved and of these 16 (41%) had a single, acute episode, while 23 (59%) had further episodes. The terms 'chronic' and 'recurrent' neuropathy are defined and used to describe the pattern of neuropathy in those with repeated attacks. In patients with no impairment at the start of the study, treatment with steroids resulted in full recovery in 88% of nerves with acute neuropathy but only 51% of those with chronic or recurrent neuropathy. The median time to full recovery from acute neuropathy was approximately 6 months, but in a few cases recovery occurred gradually over 2–3 years.

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Severe neuropathy was less likely to be followed by a complete recovery than mild or moderate neuropathy. Forty-two percent of nerves with acute neuropathy that were not treated with steroids also fully recovered. In the group of patients who were thought to have old, permanent impairments at diagnosis, full recovery of nerve function occurred in 87/374 (23%) of the nerves involved. The overall outcome is illustrated by examining the average EHF score for groups of patients. Patients with no new neuropathy after diagnosis show a gradual improvement in their EHF score, while those with any episodes of neuropathy after diagnosis show a gradual deterioration after completion of MDT. Possible explanations for these findings are discussed. Risk factors for neuropathy, for chronic and recurrent neuropathy, and for a poor outcome 5 years after release from treatment, are examined. Impairment at diagnosis was the main risk factor for a poor outcome, accompanied by the occurrence of chronic/recurrent neuropathy or a reversal reaction.

Introduction

Nerve damage is the most serious consequence of leprosy and it is generally assumed to occur as part of a reactive process, even in the absence of a clinically apparent reaction. Acute inflammation of one or more nerves (acute neuropathy) is frequently associated with a reversal reaction (RR), in which there is an increase in cell-mediated immunity to antigen in dermal macrophages and Schwann cells,[1] with inflammation. Acute neuropathy can also occur with erythema nodosum leprosum (ENL) reactions, in which antigen-antibody complexes are deposited in the tissues, with the activation of complement and local inflammation.[2] Silent neuropathy is damage occurring without any accompanying reaction or nerve pain/tenderness, but the underlying pathology remains unclear.[3]

Small nerve fibres in the leprosy skin lesions are frequently damaged, but the more important and crippling damage occurs in peripheral nerve trunks, especially when they are near the surface of the skin or in fibro-osseous tunnels. In these situations inflammatory oedema leads to raised intra-neural pressure with nerve compression and ischaemia.[4]

Nerve damage may occur at any time throughout the course of the disease. It may already be present at the time of diagnosis and can occur during and after correct and successful treatment of the infection with multiple drug therapy (MDT).[5] Richardus found that in Bangladesh 26% of new patients had nerve function impairment,[6] while in Nepal the figure was 34%.[7] During treatment in Thailand, the incidence rate for new nerve damage in those cases without impairment at diagnosis was 1·7 per 100 person years at risk (PYAR) for paucibacillary (PB) patients and 12 per 100 PYAR for multibacillary (MB) patients.[8] Figures from a recent prospective study in Bangladesh are 1·3 and 24 per 100 PYAR for PB and MB cases, respectively, although these figures are for all cases, not just those with no impairment at diagnosis; for the latter group, an overall figure of 1·7 episodes of new nerve function impairment per 100 PYAR, is given.[9] Few studies have followed a large cohort after completion of MDT, so the incidence of nerve damage at that stage has not been quantified.

The assessment of nerve function has received considerable attention in the literature in recent years. Measuring autonomic function is only possible in a laboratory setting at present,[10] but voluntary muscle testing (VMT) and sensory testing (ST) can be carried out routinely in the clinic setting.[11–15] The use of slightly different techniques in different programmes, however, makes the detailed comparison of results difficult.

In the literature it is often difficult to distinguish risk factors for neuropathy from those for reversal (or type 1) reactions. However, several risk factors have been documented, including: bactericidal drug regimens,[16] attending as a self-reporting case,[17] having a facial patch, as a risk for lagophthalmos,[18,19] the presence of anti PGL-1 antibodies and a positive lepromin test,[19,20] during MDT and the subsequent 6 months,[21,22] extensive disease, indicated by the number of body areas involved,[19,22] borderline classification,[22] BCG vaccination,[23] pregnancy,[24] enlarged ulnar nerves at diagnosis,[19] a positive BI[19] and impairment present at diagnosis.[25]

The mainstay of treatment of acute neuropathy is a prolonged course of corticosteroids,[1] although there is not yet agreement on the starting dose and the length of treatment needed. Treatment on an ambulatory basis, prescribed by leprosy control supervisors according to fixed guidelines, was first used in the ALERT control programme in Ethiopia.[26] Reported results of treatment vary from 11% to 88%, depending on the nerves involved, the type of neuropathy and length of time that impairment had been present.[4]

A long-term prospective study of new leprosy patients was set up at the All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre (ALERT) in 1988, with the primary task of determining the rate of relapse after MDT. The ALERT MDT Field Evaluation Study (AMFES) as it is known, had the subsidiary objective of determining the incidence of new nerve function impairment and possible risk factors for nerve damage. The findings in relation to this objective are now reported.

Materials and methods

Six hundred and sixty patients were enrolled in AMFES between March 1988 and March 1993. Ten patients were excluded, either because the diagnosis was changed or the enrolment procedures were incorrectly followed. A further 56 patients, who were relapses after dapsone monotherapy, were not included in this review. Thus 594 new cases were reviewed.

Cases were classified as MB if they were classified clinically as BB, BL or LL in the Ridley–Jopling classification. In addition, BT patients were classified as MB if they had a positive skin smear at any site, although three BT patients with a bacillary index (BI) of 1 were treated as paucibacillary cases in the first year of the study, under earlier guidelines. BT patients with many skin lesions were classified as PB if their smears were negative.

The AMFES patients were examined regularly whilst on MDT (usually monthly) and then at 6-monthly intervals thereafter. These regular reviews consisted of a general examination of the skin and the leprosy lesions, palpation of the peripheral nerve trunks, voluntary muscle testing (VMT) and sensory testing (ST). For the VMT, four muscles were tested (eye closure—facial nerve, little finger out—ulnar nerve, thumb up—median nerve, foot up—peroneal nerve), with the result being 'Strong,' 'Weak' or 'Paralysed.' For the ST, a 10 g nylon monofilament was used at 10 points on each hand and foot; in the hand, four points were in the distribution of the ulnar nerve and six points in the distribution of the median nerve; all 10 points in the foot are innervated by the posterior tibial nerve.

In AMFES, a clinical definition for neuropathy was used, the most important components being the development of new nerve function impairment (NFI),[27] nerve pain or tenderness in a nerve trunk. It is assumed that in most cases nerve pain or tenderness alone and nerve function impairment have similar underlying pathologies, and that one will lead on to the other, if not treated. New neuropathy (nerve tenderness and/or new NFI) was managed with steroids, according to a fixed protocol, 'new' meaning that the signs and

symptoms had been present for less than 6 months. Two steroid regimens were used, both starting with 40 mg of prednisolone daily and decreasing regularly: for multibacillary patients, the regimen was for 24 weeks with 4 weeks at each of the following six doses (40 mg, 30 mg, 20 mg, 15 mg, 10 mg, 5 mg); for paucibacillary patients, the regimen lasted for 12 weeks only, with 2 weeks at each dosage level. Some patients could be given tailor-made regimens prescribed by physicians, but in general this only occurred when patients were admitted to the ALERT teaching hospital. In the peripheral clinics, further standard courses of steroids could be prescribed for patients developing further episodes of neuropathy, although failure to respond to steroids was an indication for referral to hospital.

The timing of episodes of neuropathy in individual patients was classified retrospectively as follows:

Acute neuropathy:	new (<6 months duration) neuropathy (nerve tenderness and/or new NFI), presenting with symptoms of reaction (RR or ENL) or nerve tenderness.
Silent neuropathy:	new NFI without accompanying symptoms of reaction (RR or ENL) or nerve tenderness.
Recurrent neuropathy:	a subsequent episode of acute neuropathy at least 3 months after cessation of steroids during which time no signs or symptoms of acute neuropathy have been evident.
Chronic neuropathy:	further signs of active neuropathy (nerve pain or tenderness or new NFI) within 3 months of cessation of steroids.

The pattern of recurrent neuropathy has not been previously described in the literature. The decision to use a 3-month cut-off for the definition of chronic neuropathy is arbitrary, but, based on the clinical experience of the authors, it appears to be quite a practical cut-off point, in that under this definition there are similar numbers of 'recurrent' and 'chronic' cases.

In many cases, new nerve function impairment occurring after the start of treatment was noted within 6 months of onset and could be treated with steroids. If patients missed follow-up appointments various methods of tracing and contacting them were used. Some patients, despite these measures, were not examined for a period of longer than 6 months and some of these developed new NFI which would not be treated if apparently present for more than 6 months.

New nerve function impairment is defined as a new loss of two or more points of sensation in the distribution of any one nerve trunk, or a decrease in voluntary muscle strength of one or more steps (in the scale Strong-Weak-Paralysed) for any muscle. A potential source of inconsistency lies in the fact that two points of loss of sensation are needed for the diagnosis of neuropathy, while only one point of LOS is required to move from WHO Impairment Grade 0 to Grade 1. Those cases who had loss of sensation at one point only, either at the start of treatment or later, are not deemed to have had neuropathy for the purposes of this study, even though they will have had a WHO Impairment Grade of 1 at the times when the loss of sensation is recorded.

For this analysis, the severity of new nerve function impairment was graded on a three-point scale for each nerve trunk: mild, moderate and severe. Tenderness alone was always graded as mild; two points of loss of sensation in the ulnar or median nerves and three points in the posterior tibial nerve were also graded as mild. Moderate new nerve function impairment implied loss of muscle strength from 'Strong' to 'Weak' and/or loss of sensation

of 3 points in the ulnar nerve, 3–4 points in the median nerve and 4–7 points in the posterior tibial nerve. Severe new nerve function impairment implied complete loss of muscle strength ('Paralysis') and/or loss of sensation of 4 points in the ulnar nerve, 5–6 points in the median nerve and 8–10 points in the posterior tibial nerve.

The outcome has been assessed by examining the number (or proportion) of nerves which fully recover from neuropathy. Full recovery means that the nerve in question has returned to normal function as measured by the routine VMT/ST test. For each patient, normal function includes both sides for each particular nerve; thus if there is full recovery of the ulnar nerve, both ulnar nerves have normal function (either or both may have been affected by neuropathy).

Outcome has also been assessed more generally by examining the EHF score over time for groups of patients. This is a summary score of the individual WHO Impairment Grades for the Eyes, Hands and Feet.[25,28,29] It has the advantages of simplicity and widespread usage and, while inappropriate for following up individual patients, it gives a very helpful overview of the experience of groups of patients.

Longitudinal patient records within this prospective cohort study were managed throughout using dBase software. Analysis used Epi-Info software and logistic regression modelling of multiplicative relative risks was performed using Egret. The possibility of using Cox or Poisson regression was considered: these methods give a lower weight to those cases with a shorter follow-up. We did not consider this to be necessary, as the risk for events is generally highest at the start of treatment; the risks for outcome are, however, only calculated for those with 5-year follow-up data.

Results

PREVALENCE OF NEUROPATHY AT DIAGNOSIS

Table 1 shows how the 594 new cases enrolled in the study can be grouped according to their initial impairment status and subsequent experience of neuropathy.

Of the group with no impairment at the start and no subsequent neuropathy (195 patients), four patients had steroids for reversal reactions and one had mild erythema nodosum leprosum (ENL), not requiring steroids. This group by definition never had nerve function impairment. In the group with acute neuropathy at the start (47 patients), 21 (45%) had no further neuropathy while 16 (34%) had recurrent episodes and 10 (21%) had chronic neuropathy.

Table 1. The initial impairment status of new AMFES patients and their subsequent experience of neuropathy

Group	PB (%)	MB (%)	Total (%)
1) No impairment at start; never developed neuropathy	124 (43)	71 (24)	195 (33)
2) No impairment at start; developed neuropathy later	16 (5)	57 (19)	73 (12)
3) Recent impairment at start; treated immediately	23 (8)	24 (8)	47 (8)
4) Old impairment at start not treated immediately, but active neuropathy occurred later	51 (17)	87 (29)	138 (23)
5) Old impairment at start; no further neuropathy	80 (27)	61 (20)	141 (24)
Total enrolled	294 (100)	300 (100)	594 (100)

INCIDENCE OF NEUROPATHY DURING THE COURSE OF THE DISEASE

Episodes of neuropathy are most common at the start of treatment and decrease in frequency thereafter. Significant numbers of episodes occur, however, up to 8 or 9 years after the start of treatment. Figure 1 shows the actual number of episodes of new nerve function impairment by year after the start of treatment, while Figure 2 shows the incidence of new neuropathy by year in episodes per 100 PYAR. Follow-up involved 460 PYAR for the first year of follow-up reducing to 124 PYAR for the seventh year of follow-up. No incidence figures are given for years 8 and 9, as the number of patients followed is too low to give meaningful results.

In order to allow some comparison with other published data, Figure 3 shows the incidence rate of neuropathy by year in those 268 patients who had no impairment at diagnosis (namely, groups 1 and 2 in Table 1). The highest incidence is 25 episodes per 100 PYAR in MB patients during the first year of treatment. The difference between Figures 2 and 3 is incidence of neuropathy in those with impairment at the start (not shown).

CLASSIFICATION OF NEUROPATHY

The patients who had no impairment at the start but who subsequently developed neuropathy are perhaps the most interesting group to examine closely, as the full history of their nerve involvement is documented. Table 2 shows the timing of the first episode of neuropathy in this group; one third of MB patients in this group had their first episode after the current end of MDT.

Table 3 shows which nerves were involved in this group of 73 patients and how the neuropathy was classified. The ulnar and posterior tibial nerves—each involved in 52 (71%)

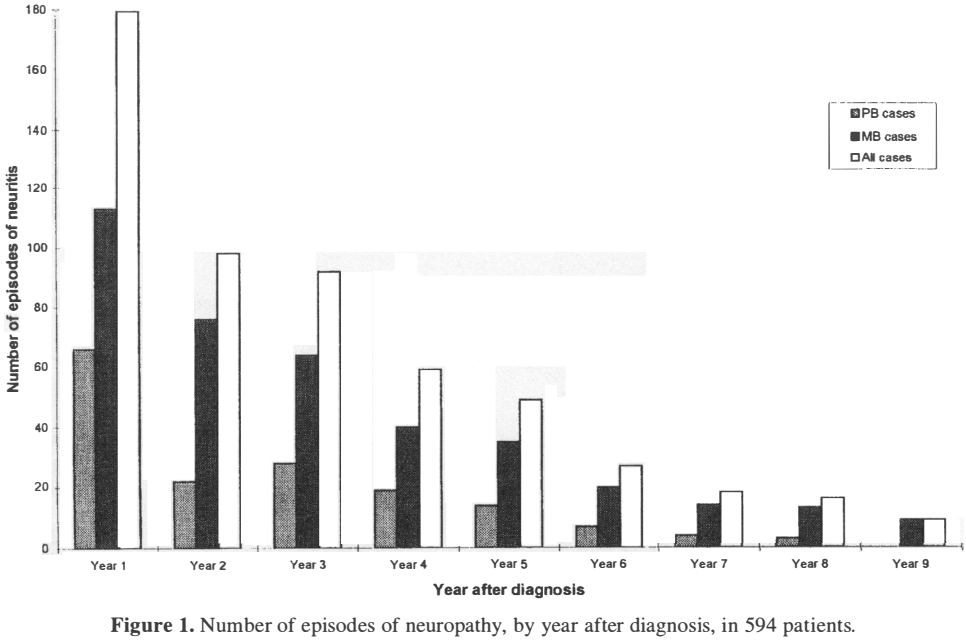

Figure 1. Number of episodes of neuropathy, by year after diagnosis, in 594 patients.

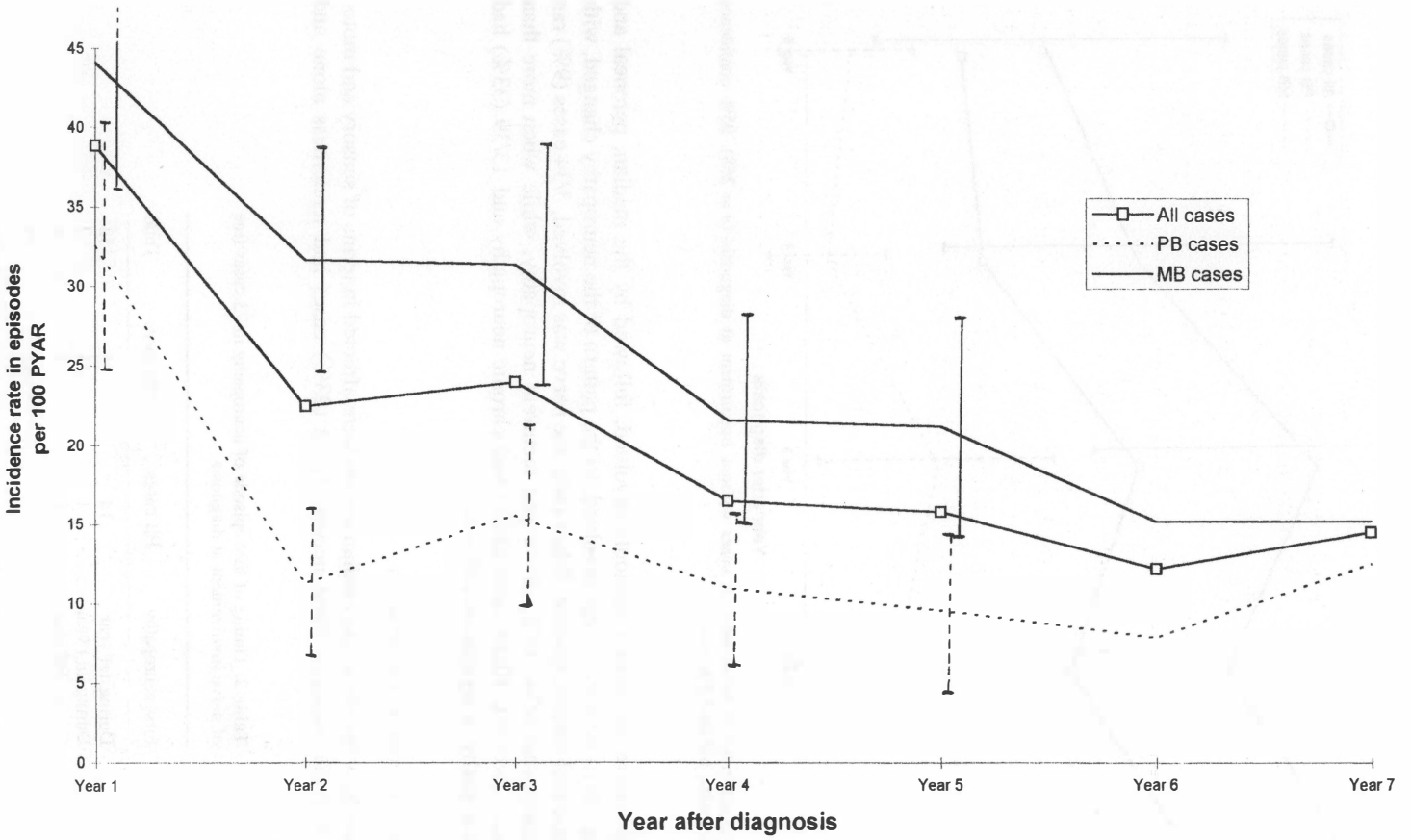

Figure 2. Incidence rates of episodes of neuropathy, by year after diagnosis (n = 594). 95% confidence intervals are given for MB and PB cases.

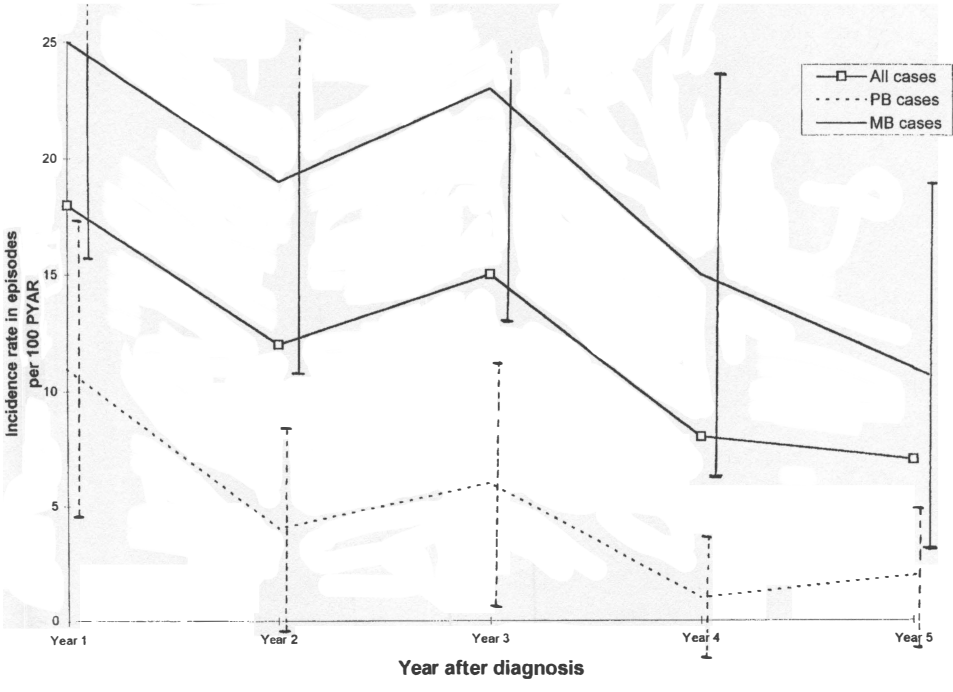

Figure 3. Incidence rates of neuropathy in cases without impairment at diagnosis ($n = 268$). 95% confidence intervals are given for MB and PB cases.

of the cases—were the most commonly involved, followed by the median, peroneal and facial nerves. As more nerves were involved, so the pattern of the neuropathy changed, with more recurrent and chronic disease. When only one nerve was involved, 3/34 cases (9%) ran a chronic course and 6/34 (18%) developed recurrent neuropathy, while when more than one nerve was involved, 10/39 cases (26%) had chronic neuropathy and 13/39 (33%) had recurrent neuropathy, a significant difference.

SENSORY AND MOTOR INVOLVEMENT

Table 4 shows how the ulnar and median nerves were affected in terms of sensory and motor modalities. For the posterior tibial nerves, 12/52 (23%) cases had tenderness alone and

Table 2. Timing of first episode of neuropathy in 73 cases free of nerve involvement at diagnosis

First neuropathy	PB cases	MB cases	Total
During 1st year	14	38	52
During 2nd year	1	11	12
During 3rd year	1	8	9
	16	57	73

Table 3. The pattern of later neuropathy in 73 cases with no impairment at diagnosis. Fifty-seven (78%) of these cases are MB patients; of the 16 PB patients, 10 had acute, three had recurrent and three had chronic neuropathy

	Predominant pattern of neuritis			
Nerve	Acute	Recurrent	Chronic	Total
Facial alone	1	–	–	1
Ulnar alone	11	2	1	14
Median alone	–	–	–	0
Posterior tibial alone	13	4	1	18
Peroneal alone	–	–	1	1
Sub-total	25	6	3	34 (47%)
Ulnar & median	3	–	2	5
Ulnar & post. tibial	7	5	4	16
Median & post. tibial	–	1	–	1
Ulnar, median & post. tibial	6	6	3	15
Ulnar, median, peroneal & post. tibial	–	1	1	2
Sub-total	16	13	10	39 (53%)
Total	41 (56%)	19 (26%)	13 (18%)	73 (100%)

40/52 cases had sensory loss on the sole of the foot. The results of treatment by modality are shown, although the small numbers make interpretation difficult.

SEVERITY OF NEUROPATHY

Tenderness alone was always given a grading of mild. For the ulnar nerves with sensory or motor involvement, 19% were graded severe, 79% were graded moderate and 2% were graded mild. For the median nerves, 36% were graded severe, 40% moderate and 24% mild. For the posterior tibial nerves, 27% were graded severe, 38% moderate and 35% mild.

Table 4. The involvement of different modalities of the ulnar and median nerves, in 73 cases with no impairment at diagnosis

	Ulnar nerves		Median nerves	
Modality	Number (%) of nerves affected	Number (%) achieving full recovery	Number (%) of nerves affected	Number (%) achieving full recovery
Tenderness only	11 (21)		5 (22)	
Sensory only	3 (6)	3 (100)	10 (43)	7 (70)
Motor only	28 (54)	24 (86)	5 (22)	5 (100)
Mixed motor & sensory	10 (19)	4 (40)	3 (13)	2 (67)
Total	52		23	

N.B. The categories 'sensory only,' 'motor only' and 'mixed motor and sensory' do not exclude the presence of nerve pain or tenderness.

SILENT NEUROPATHY

Silent neuropathy occurred at one time or another in 43 (59%) of the 73 cases whose only neuropathy occurred after diagnosis. Not every episode was silent in that 19 of these 43 cases also had a reversal reaction at some time and four had an ENL reaction at some time.

PROGNOSIS AND TIMING OF RECOVERY

Steroids were given to 167 (28%) of the 594 cases being examined. Twenty-nine (17%) patients also received steroids in the ALERT hospital. Fifty-four (32%) of all those receiving steroids had more than the standard course: 33 had additional standard courses in a rural clinic and 21 of the 29 patients receiving steroids at ALERT had prolonged or repeated courses. Some patients did not receive steroids even though there was an indication in terms of NFI; the reasons for this are not available, but could include contraindications such as a plantar ulcer, logistic problems (for example, prednisolone not available), an impression that the NFI was insignificant, or simply something overlooked in the middle of a busy clinic.

Table 5 indicates the outcome of the various patterns of neuropathy and the time taken to reach full recovery in those that achieved this outcome. The time to recovery for recurrent and chronic neuropathy is the time between the first episode of neuropathy and first date after which there is no further NFI; there may have been times in between these dates when the nerve had normal function, but the neuropathy flared up again later. Some patients with recurrent neuropathy may recover fully from the initial episode, but be left with residual damage after a subsequent episode—these are excluded from the group with full recovery. Some patients experienced a partial recovery of nerve function, with or without steroids, while others developed progressive nerve damage despite treatment with steroids.

Seventeen patients were not given steroids but had 35 episodes of neuropathy noted. Usually the neuropathy was mild. Seven patients fully recovered and of these, two had nerve tenderness without loss of function, one had mild sensory loss and four had muscle weakness (always involving the ulnar nerve, in two cases involving the facial nerve and once the median nerve), which is moderate neuropathy as defined here. Muscle weakness may be difficult to assess, depending as it does on the full co-operation of the patient and it may be that the health worker was not fully convinced of the evidence for neuropathy and therefore withheld steroids at that time.

It may be expected that recovery depends, amongst other factors, on the severity of the neuropathy. Table 6 shows the recovery rates for neuropathy according to pattern and severity. While the numbers are quite small, those with severe neuropathy tend to have a worse prognosis.

NEUROPATHY IN THOSE WITH PRE-EXISTING IMPAIRMENTS

Table 7 shows the experience of those 47 cases who had NFI at diagnosis (namely, group 3 in Table 1) and were considered to have some hope of recovery, in that at least some of the damage was thought to have occurred within the previous 6 months. They were all treated with steroids at the start of MDT. The median time to full recovery for all 36 episodes of acute neuropathy that recovered was 7 months (range 1–60 months). The median time to full recovery for the 12 cases with recurrent or chronic neuropathy in this group was 35·5 months (range 20–98 months).

Table 5. The prognosis and timing of recovery in different nerves according to the pattern of neuropathy, in 73 cases with no impairment at diagnosis. The times to recovery are in months

Nerve	No. of cases	Steroids	Full recovery from acute neuropathy	Median time to recovery (range)	Full recovery from recurrent neuropathy	Median time to recovery (range)	Full recovery from chronic neuropathy	Median time to recovery (range)
Ulnar	52	Yes 38	21/22 (95%)	6·5 (1–33)	6/9 (89%)	30 (22–57)	3/7 (43%)	14 (10–15)
		No 14	5/10 (50%)	6 (5–45)	2/2 (100%)	43 (18–69)	0/2 (0%)	–
Median	23	Yes 18	12/12 (100%)	5 (3–14)	3/5 (60%)	26 (18–49)	0/1 (0%)	–
		No 5	1/4 (25%)	27	1/1 (100%)	32	–	–
Post. tibial	52	Yes 36	15/20 (75%)	9·5 (2–41)	4/12 (33%)	29 (13–58)	3/4 (75%)	27 (8–54)
		No 16	4/10 (40%)	10 (7–18)	1/6 (17%)	64	–	–
Peroneal	3	Yes 3	2/2 (100%)	6 (1–11)	–	–	1/1 (100%)	32
Facial	1	Yes 1	0/1	–	–	–	–	–
All nerves	131	Yes 96	50/57 (88%)		13/26 (50%)		7/13 (54%)	
		No 35	10/24 (42%)		4/9 (44%)		0/2 (0%)	

Table 6. The rates of full recovery in various nerves according to pattern and severity of neuropathy, in 73 cases with no impairment at diagnosis

Pattern of neuropathy	Severity	Ulnar no.	%	Median no.	%	Post. tib. no.	%	Peroneal	Facial	Total no.	%
Acute	Mild	2/4	50	7/7	100	11/14	79	–	–	20/25	80
	Moderate	21/23	91	4/4	100	4/9	44	2/2	–	31/38	82
	Severe	3/5	60	2/5	60	4/7	57	–	0/1	9/18	50
Recurrent	Mild	4/5	80	2/2	100	1/8	13	–	–	7/15	47
	Moderate	3/5	60	1/3	33	2/5	40	–	–	6/13	46
	Severe	1/1	100	1/1	100	2/5	40	–	–	4/7	57
Chronic	Mild	1/2	50	–	–	2/2	100	–	–	3/4	75
	Moderate	2/5	40	0/1	0	0/1	0	1/1	–	3/8	38
	Severe	0/2	0	–	–	1/1	100	–	–	1/3	33
Total		37/52	71	17/23	74	27/52	52	3/3	0/1	84/131	64

A further group (group 4 in Table 1), with 138 patients, had NFI at the start which was considered too old to be treated with steroids. This group had subsequent episodes of neuropathy, however, as shown in Table 8. The median time to full recovery for all 52 episodes of acute neuropathy that recovered was 10 months (range 1–57 months). The median time to full recovery for those 37 patients with recurrent or chronic neuropathy or old damage who recovered, was 35 months (range 5–94 months). The overall prognosis in this group was poor, with only 27% of nerves showing full recovery.

OLD NERVE DAMAGE

One hundred and forty-one patients had nerve function impairment at diagnosis, which was considered of longer duration than 6 months and was therefore not treated with steroids. This group of patients did not develop any new nerve function impairment over the course of treatment and surveillance. They were therefore never treated with steroids, except for two patients who received steroids for reversal reactions not involving the nerves. It is assumed that these patients have old, stable and more or less permanent nerve damage.

Surprisingly perhaps, a proportion of patients in this category experienced full recovery of some nerves, as indicated in Table 9. Between one-quarter and one-third of

Table 7. The results of treatment with steroids in 47 cases with presumed new nerve function impairment at diagnosis. Numbers and percentages are those that experienced full recovery of that nerve

Pattern of neuropathy	Ulnar No.	%	Median No.	%	Posterior tibial No.	%	Peroneal No.	%	Facial	Total No.	%
Acute	11/15	73	10/15	67	11/12	92	3/3	100	1/1	36/46	78
Recurrent	1/7	14	1/7	14	2/9	22	–	–	0/1	4/24	17
Chronic	2/11	18	3/6	50	2/10	20	1/1	100	–	8/28	29
Total	14/33	42	14/28	50	15/31	48	4/4	100	1/2	48/98	49

Table 8. The pattern and outcome of neuropathy in those patients with old nerve damage at diagnosis, who subsequently developed new episodes of neuropathy. The numbers and percentages indicate those experiencing full recovery in specific nerves. ($n = 138$)

Pattern of neuropathy	Ulnar No.	%	Median No.	%	Posterior tibial No.	%	Peroneal No.	%	Facial	Total No.	%
Acute	24/36	67	18/27	67	6/14	43	2/3	67	2/2	52/82	63
Recurrent	2/13	15	11/27	41	11/48	23	1/8	13	1/3	26/99	26
Chronic	1/24	4	1/7	14	2/8	25	–	–	–	4/39	10
Old damage only*	1/30	3	0/17	–	1/55	2	4/7	57	1/1	7/110	6
Total	28/103	27	30/78	38	20/125	16	7/18	39	4/6	89/330	27

*Certain nerves had old damage without any further neuropathy, the patient experiencing new neuropathy in other nerve trunks.

nerves with presumed permanent nerve damage showed full recovery over a long period of follow-up.

MEASUREMENT OF OUTCOME

Outcome was examined by means of the average EHF score for different groups of patients over time. Figure 4 shows the average EHF score at diagnosis, at RFT and 5 years after RFT for four of the groups of patients given in Table 1; group 1, in which neuropathy never occurred and in which the EHF score remained at zero throughout, is not shown.

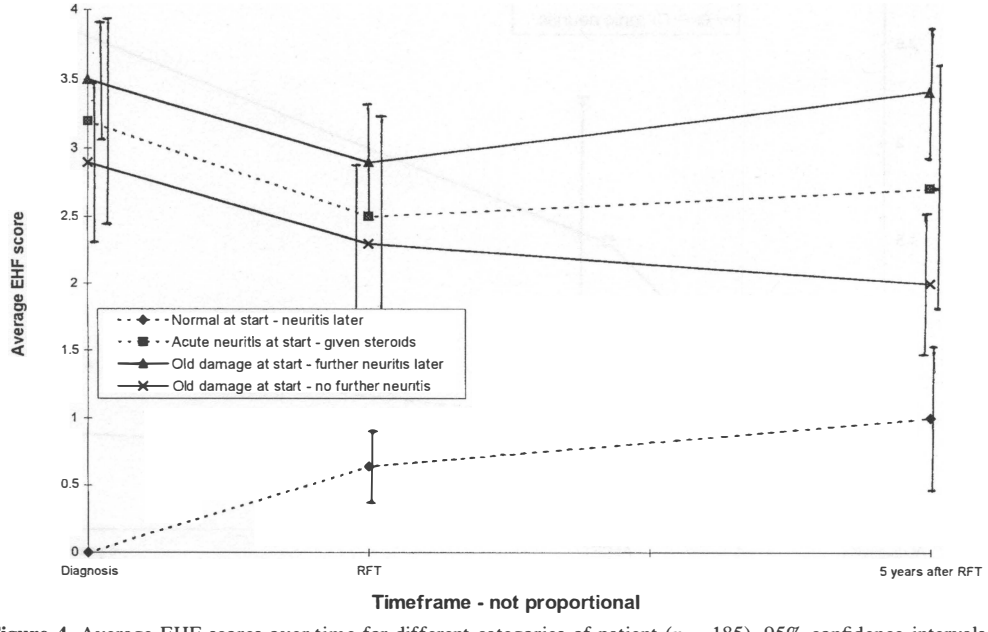

Figure 4. Average EHF scores over time for different categories of patient ($n = 185$). 95% confidence intervals are given.

Table 9. Patients with old nerve function impairment experiencing full recovery in specific nerves over time, without steroid treatment ($n = 141$)

Nerve	Right side	Left side	Both sides normal at latest review
Ulnar	12/39 (31%)	13/43 (30%)	15/56 (27%)
Median	10/31 (32%)	7/30 (23%)	9/40 (23%)
Peroneal	0/4 (0%)	2/4 (50%)	2/6 (33%)
Posterior tibial	21/113 (19%)	22/110 (20%)	22/124 (18%)

Groups 3, 4 and 5 all had nerve damage at the start and all improved slightly on average whilst on MDT. Groups 2, 3 and 4 all had active neuropathy at some point after diagnosis and all showed some deterioration on average, in the 5 years after RFT when contact with the health workers was reduced; this may be due to poor self-care or to an on-going low level of neuropathy. Group 5 had old nerve damage at the start and this group continued to improve slowly after RFT. This may indicate better self-care or it may reflect axonal regeneration and spontaneous recovery of some impairments over a long period.

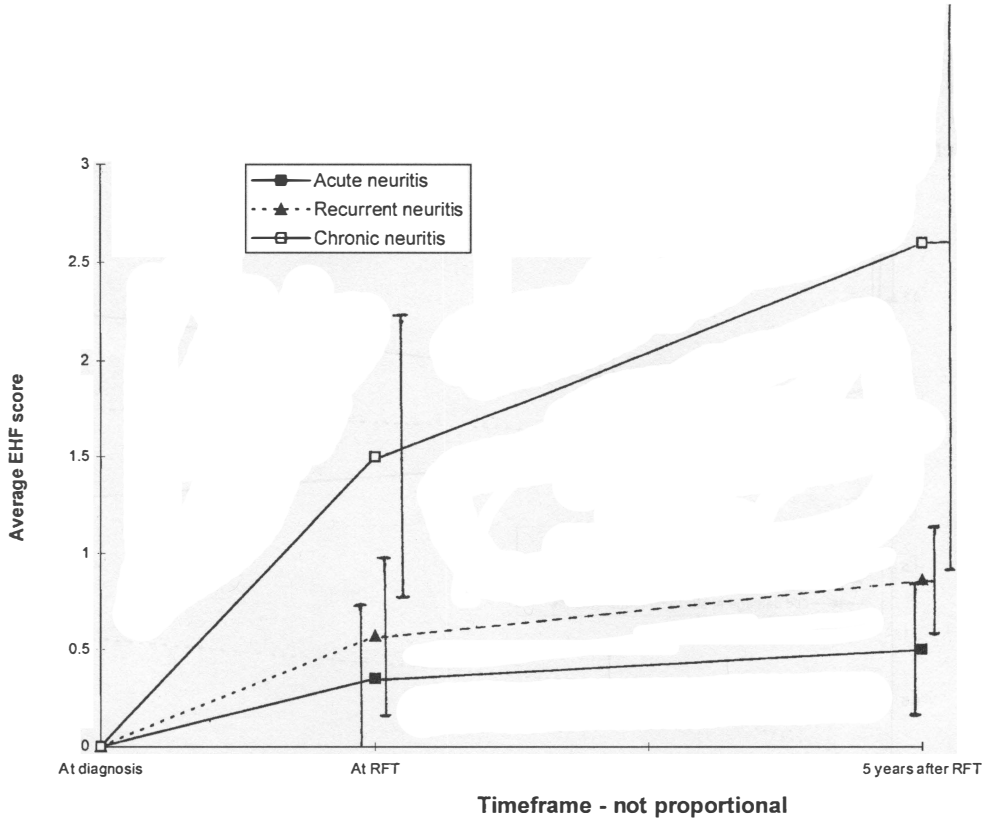

Figure 5. Average EHF scores over time for different types of neuropathy in those cases without impairment at diagnosis ($n = 42$). 95% confidence intervals are given.

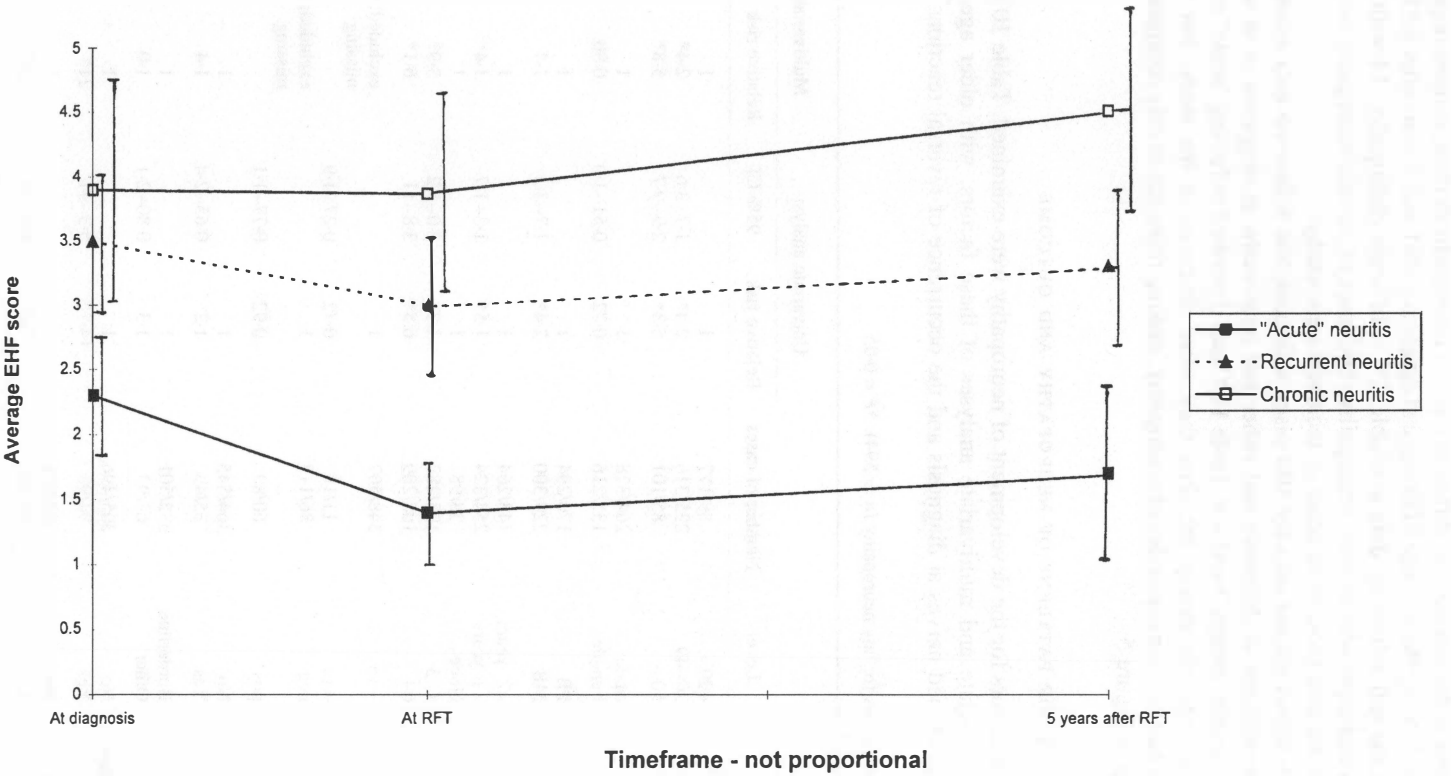

Figure 6. Average EHF scores over time for different types of neuropathy in those with impairment at diagnosis ($n = 106$). 95% confidence intervals are given.

Figure 5 looks at the outcome for different types of neuropathy in those without impairment at diagnosis, also using the average EHF score at diagnosis, RFT and 5 years after RFT. Only 42 cases have the full follow-up data available: 20 with acute neuropathy, 14 with recurrent neuropathy and eight with chronic neuropathy. The cases of chronic neuropathy have a much worse outcome than those with acute or recurrent neuropathy.

Figure 6 shows similar data for 106 cases with complete follow-up data amongst those who had impairment at diagnosis and either had neuropathy at diagnosis or at some time thereafter (namely, groups 3 and 4 in Table 1). Cases described as having 'acute' neuropathy had only one episode during the time they were observed in the study, but most had presumably had previous episodes of neuropathy, making them not strictly comparable to the acute group in Figure 5.

RISK FACTORS FOR PATTERNS OF NEUROPATHY AND OUTCOME

Possible risk factors for the development of neuropathy were examined. Table 10 shows the results of univariate and multivariate analyses of these factors, with older age, delay in diagnosis, thickened nerves at diagnosis and the occurrence of reversal reactions being the

Table 10. Risk factors for any neuropathy ($n = 594$). $^*P < 0{\cdot}05$

			Univariate analysis		Multivariate analysis	
Factor	Level	Number of cases	Relative risk	95% CI	Relative risk	95% CI
Age group	<20	89/177	1		1	
	20–49	225/316	2·4*	1·7–3·6	2·4*	1·5–3·7
	50+	85/101	5·3*	2·9–9·7	5·8*	2·9–11·5
Sex	Male	264/378	1		1	
	Female	135/216	0·72	0·51–1·0	0·90	0·56–1·4
Leprosy type	PB	170/294	1		1	
	MB	229/300	2·4*	1·7–3·3	1·4	0·88–2·2
Delay	<2 years	143/264	1		1	
(6 missing)	2+ years	254/324	1·5*	1·3–1·7	1·4*	1·2–1·7
Thickened nerves	None	38/98	1		1	
	1–5	193/287	3·2*	2·0–5·2	3·9*	2·2–6·9
	6+	168/209	6·5*	3·8–11	6·1*	3·2–11·7
HIV	−ve	348/507	1		excluded; 69 cases missing	
(69 missing)	+ve	11/18	0·72	0·27–1·9		
Lepromin	neg	86/117	1		excluded; 388 cases missing	
(388 missing)	pos	60/89	0·92	0·77–1·1		
Pregnancy	No	364/545	1		1	
	Yes	35/49	1·2	0·65–2·4	1·4	0·60–3·3
Class	Borderline	332/501	1		1	
	Other	67/93	1·3	0·80–2·1	1·0	0·55–1·9
Reversal reaction	No	305/496	1		1	
	Yes	94/98	14·7*	5·3–41	21*	7·2–62
ENL reaction	No	384/578	1		1	
	Yes	15/16	7·6*	1·0–58	3·7	0·43–31

Table 11. Risk factors for chronic or recurrent neuropathy ($n = 594$). *$P < 0.05$

			Univariate analysis		Multivariate analysis	
Factor	Level	Number of cases	Relative risk	95% CI	Relative risk	95% CI
Age group	<20	38/177	1		1	
	20–49	73/316	1·1	0·70–1·7	0·71	0·40–1·3
	50+	28/101	1·4	0·80–2·5	0·88	0·44–1·8
Sex	Male	92/378	1		1	
	Female	47/216	0·86	0·58–1·3	0·81	0·47–1·4
Leprosy type	Pb	43/294	1		1	
	Mb	96/300	2·8*	1·8–4·2	1·7*	1·0–2·9
Delay	<2 years	50/264	1		1	
(6 missing)	2+ years	89/324	1·6*	1·1–2·3	1·1	0·91–1·3
Thickened nerves	None	10/98	1		1	
	1–5	65/287	2·6*	1·3–5·2	2·0	0·85–4·5
	6+	64/209	3·9*	1·9–8·0	1·7	0·71–4·0
HIV	−ve	123/507	1		Excluded; 69 cases missing	
(69 missing)	+ve	3/18	0·6	0·18–2·2		
Lepromin	Neg	42/117	1		Excluded; 388 cases missing	
(388 missing)	Pos	23/89	0·6	0·32–1·2		
EHF on diagnosis	0	32/268	1		1	
	1–2	43/157	2·8*	1·7–4·6	2·8*	1·5–5·2
	3+	64/169	4·5*	2·8–7·3	6·4*	3·4–12
WHO score	0	32/268	1		Excluded; too closely correlated with EHF score	
	1	55/185	3·1*	1·9–5·1		
	2	52/141	4·3*	2·6–7·1		
Class	Borderline	109/501	1		1	
	Other	30/93	1·7*	1·1–2·8	1·9*	1·0–3·6
Pregnancy	No	127/545	1		1	
	Yes	12/49	1·1	0·54–2·1	1·2	0·47–3·1
Reversal reaction	No	80/496	1		1	
	Yes	59/98	7·9*	4·9–12·6	10·6*	6·0–19
ENL reaction	No	127/578	1		1	
	Yes	12/16	10·7*	3·4–33	11·6*	3·1–43

significant factors in the multivariate model. It is not surprising that reversal reactions are a risk factor for neuropathy, as the underlying pathology is thought to be the same in many cases, but this study shows no such relationship for ENL reactions. The fact that being classified as MB is not a significant risk factor in this study, may relate to the way patients were classified: almost all BT patients with negative smears were classified as PB, making this a larger group than in other studies. Pregnancy does not appear to be an important risk factor, and while neither HIV nor lepromin status was included in the multivariate model, there is no indication from the univariate analysis that they are significant factors.

Table 11 shows the risk factors for the development of chronic or recurrent neuropathy. In this case leprosy type and the borderline classification were barely significant risk factors,

Table 12. Risk factors for poor outcome, defined as an EHF score of >0 at 5 years after release from treatment ($n = 262$). *$P < 0.05$

			Univariate analysis		Multivariate analysis	
Factor	Level	Number of cases	Relative risk	95% CI	Relative risk	95% CI
Age group	<20	32/89	1		1	
	20–49	73/131	2·2*	1·3–3·9	1·6	0·69–3·6
	50+	29/42	4·0*	1·8–8·7	1·6	0·49–5·1
Sex	Male	91/173	1		1	
	Female	43/89	0·84	0·50–1·4	1·3	0·53–3·0
Leprosy type	Pb	57/123	1		1	
	Mb	77/139	1·4	0·88–2·3	1·1	0·47–2·4
Delay	<2 years	47/120	1		1	
	2+ years	87/142	2·5*	1·5–4·0	1·1	0·83–1·4
Thickened nerves	None	12/47	1		1	
	1–5	62/116	3·3*	1·6–7·1	1·3	0·47–3·8
	6+	60/99	4·5*	2·1–9·7	2·5	0·82–7·8
EHF on diagnosis	0	17/116	1		1	
	1–2	46/71	10·7*	5·3–22	9·1*	4·2–20
	3+	71/75	103*	33–320	65*	18–225
Class	Bt/bl	115/219	1		1	
	Other	29/43	0·72	0·37–1·4	0·64	0·21–1·9
Pregnancy	No	124/244	1		1	
	Yes	10/18	1·2	0·46–3·2	0·81	0·16–4·1
Reversal reaction	No	97/203	1		1	
	Yes	37/59	1·8*	1·0–3·3	1·3	0·49–3·7
ENL	No	129/252	1		1	
	Yes	5/10	0·95	0·27–3·4	0·76	0·16–3·8
Any chronic or recurrent neur.	No	62/169	1		1	
	Yes	72/93	5·9*	3·3–10·6	3·7*	1·5–9·2

while level of impairment at diagnosis and the occurrence of either type of reaction were important factors. It is not at all surprising that impairment at diagnosis is associated with chronic or recurrent neuropathy, in that by definition any further episode of neuropathy is a repeated event. ENL is a chronic condition, so while no link with neuropathy as such was demonstrated, it is not surprising that it is associated with the development of chronic or recurrent neuropathy. In several cases, the chronic neuropathy associated with ENL consisted of prolonged pain and tenderness, with little or no impairment.

Poor outcome was indicated by an EHF score of more than zero, 5 years after release from treatment. Table 12 shows the risk factors for a poor outcome and indicates the importance of impairment at diagnosis and the occurrence of chronic or recurrent neuropathy for the long-term prognosis.

Discussion

A unique feature of this study is the long period of follow-up for a large cohort of leprosy patients, with regular, detailed reviews of nerve function. The limitations of the study include

the loss to follow-up of about 30% of the cohort after completion of treatment. The setting of the study, within the routine services of a vertical leprosy control programme, is both an advantage and a disadvantage. The quality of care and surveillance in a specialised vertical programme means that the data are quite reliable, but the same standard of long-term patient care cannot be expected in an integrated setting. The wider context of the study in Ethiopia, with a high rate of multibacillary patients, a significant delay between the onset of symptoms and diagnosis (on average)[30,31] and a high rate of impairment at diagnosis, means that the application of these findings in other contexts must be done with caution.

Nerve function assessment was carried out with a methodology suitable for use in the field,[15] but which is less sensitive than that used in some other studies. In particular, sensory testing was done with a 10 g monofilament, while other programmes may use a number of graded monofilaments and take insensitivity to a 2 g monofilament as indicative of impairment.[14,32] This must be borne in mind when comparing data from different studies, as it affects both the diagnosis of new nerve function impairment and the results of treatment. Thus the results of this study may not be so good if a 2 g monofilament were used to test for sensation. We suggest, however, that the 10 g monofilament is a reasonable instrument for field use, probably indicating protective sensation.[15]

Some other studies have used the 6-point MRC scale for voluntary muscle testing,[33] which may have a similar effect in the determination of full recovery of muscle strength.

The reliability of both sensory testing and voluntary muscle testing is an important consideration. The best methods of testing are still being discussed, but this study used what were thought to be appropriate methods at the time, giving reasonably reliable results in experienced hands.[11] Nevertheless, it remains the case that a certain proportion of new impairment diagnosed in the field will be due to observer variability, rather than a true change in nerve function and this has to be borne in mind when considering the figures for spontaneous recovery of nerve function.

Fifty-five percent of the AMFES cohort had some impairment at diagnosis, while only 12% developed neuropathy for the first time after diagnosis (Table 1). Impairment at diagnosis was the major risk factor for permanent nerve damage as indicated by the EHF score 5 years after release from treatment. If the initial score was three or more, the relative risk for a poor outcome was 65 (Table 12). The recent prospective study in Bangladesh found long-standing impairment at diagnosis to be a major risk factor for further neuropathy.[9] This supports previous findings that early case-finding is the most worthwhile intervention in preventing disability in future leprosy patients.[6]

The incidence of neuropathy in this study is high compared with other published results. There is a gradual decline in incidence rate from a high of 39 episodes per 100 PYAR in the first year after diagnosis to 15 episodes per 100 PYAR in the sixth year (Figure 2). In their comprehensive review of the subject, Lienhardt and Fine found similar figures reported previously from Ethiopia, but generally lower figures reported elsewhere.[23] Recent figures from Bangladesh are much closer to those found here, with an incidence rate of 34 per 100 PYAR amongst MB patients in the first 6 months after diagnosis, decreasing to 18 per 100 PYAR in the period 18–24 months after diagnosis.[9] Figures from Thailand show an incidence rate of new nerve function impairment of 1·7 per 100 PYAR in PB cases and 12 per 100 PYAR in MB cases, in those with no impairment at diagnosis.[8] This compares with figures in this study of 11 per 100 PYAR in PB patients and 25 per 100 PYAR in MB patients in the first year, in those without impairment at diagnosis (Figure 3). Comparisons for PB patients are difficult because of differing definitions of PB cases: in the study in Thailand

any BT patient with 10 or more lesions was classified as MB,[34] while in our study BT patients with negative smears were classified as PB, irrespective of the number of lesions.[31]

The timing of neuropathy, shown in Figures 1–3 and Table 2, is by no means limited to the period of MDT when patients are more closely observed by health staff. New neuropathy, even in those who have never had any impairment before, occurred after the 12-month period of MDT in 19 of 57 MB cases (33%), exactly the same figure being found in Bangladesh.[9] New neuropathy occurred in both the second and the third years after diagnosis, while further episodes continued to occur throughout the period of follow-up, with a gradually declining incidence. It is therefore imperative that patients are taught to recognise for themselves the signs of new nerve damage and what is available to them in terms of treatment. The only group that could possibly be excluded from this requirement are those PB patients with no impairment at any time before release from treatment, especially if the PB group is more narrowly defined than in this study.

In those who developed neuropathy after diagnosis, the involvement of more than one nerve led to an increased risk of developing chronic or recurrent neuropathy (Table 3). In those who developed a chronic or recurrent pattern of neuropathy, the prognosis was worse and the time taken to recover was greatly prolonged (Table 5).

Silent neuropathy was common, occurring at some point in 59% of cases without impairment at diagnosis in this study. Van Brakel found it in 13% of new patients at some point,[3] while Croft *et al.* found 86% of all new episodes of neuropathy were silent.[9]

The results of treatment with steroids depend on various factors. If the impairment has been present for longer than 6 months, the results are poor[35] and more severe impairments have a worse outcome than moderate cases.[36] In this study, very high rates of full recovery (88%) were achieved in those cases with acute neuropathy treated with steroids (Table 5). In the Bangladesh study already quoted, the overall rate of full recovery from acute neuropathy treated with prednisolone was 37%, with some improvement in 67%.[37] Various reasons as to why these rates are higher than in other reported studies can be advanced. Firstly, this is a very selective group with no impairment at diagnosis, being carefully watched for the first signs of neuropathy—in many studies, including the Bangladesh study, all cases of new or acute neuropathy are grouped together. It is clear that a patient with impairment at diagnosis has already had neuropathy and therefore a subsequent episode should, according to the definitions used here, be termed recurrent or chronic. Secondly, the use of the 10 g monofilament as the assessment tool for sensation, and the 3-point scale for voluntary muscle testing, may be less sensitive than the tools used in other studies, especially hospital-based studies. Thus someone with full recovery in our study could have a mild residual impairment if a more sensitive test were used.

A third possible reason relates to the period of follow-up. In our study follow-up was for up to 10 years after completion of MDT, with many cases of neuropathy achieving recovery more than a year after treatment with prednisolone. In the Bangladesh study, results are so far only reported up to 12 months after the start of prednisolone for neuropathy.[37] Interestingly in Bangladesh, it was noted that sensory recovery at 12 months was less in those with a short history of impairment, than in those with a longer history; if the natural history of the condition is long in some cases, say 12–18 months, those that started later may recover later and perhaps those with a short history will show further recovery with further follow-up.

If the neuropathy was recurrent or chronic the results were less good. Table 6 shows that severity of impairment was an important factor, with only 50% of severe acute neuropathy

cases recovering fully. Table 5 also indicates that the time taken to reach full recovery may be rather long, certainly longer than the standard course of steroids. Studies that assess the results of treatment immediately such a standardised course is completed will underestimate the amount of recovery.

Forty-two percent of episodes of acute neuropathy recovered fully without steroids. Surprisingly, this also applies to between a quarter and one-third of those nerves in which the damage was assumed to be permanent because of its long-standing nature. Schreuder noted partial improvement in 14% of his cases in Thailand with impairment at diagnosis but no further neuropathy and no treatment with steroids,[8] while Croft *et al.* found full recovery in 17% of untreated cases, with some improvement in 62%.[37] This suggests that studies looking at the effectiveness of steroids, or other forms of treatment for neuropathy, must not assume that all improvement is the result of a specific intervention.

The number of cases examined in detail here makes it difficult to show a difference in prognosis between motor and sensory impairment, but more severe neuropathy has a worse outcome. Croft *et al.* found no association between outcome and type of nerve damage, nor its duration or severity.[37]

Studies are being developed to look for new treatments for neuropathy.[4] This study has shown that certain groups of patients do very well with steroids, but that others do not. The development of chronic or recurrent neuropathy incurs a much worse prognosis and any new treatment could be targeted to that group. After treatment for neuropathy with a standard course of steroids, patients may continue to improve over several more months (Table 5), but any further deterioration in nerve function by definition indicates some form of chronic or recurrent neuropathy and demands more aggressive treatment.

Figures 4–6 show the long-term trends in EHF score for different groups of patients. The gradual improvement in those with old, permanent damage is clearly shown in Figure 4. Similarly, a continued deterioration in those who have had any neuropathy at or after diagnosis is apparent. Effective self-care in the former group and poor self-care in the latter group, seems a contradictory and unlikely explanation for these findings. It seems more likely that there is ongoing neuropathy in those showing deterioration and axonal regeneration in some of those with permanent damage.

In Figure 5, the small group without impairment at diagnosis are illustrated. The much worse prognosis in those with chronic neuropathy is demonstrated. Figure 6, however, shows that those with impairment at diagnosis generally remain with much the same level of impairment over the course of the disease.

Risk factors are examined in Tables 10–12. Not all known risk factors could be examined in this study, but some clinical risk factors have been confirmed and quantified, while others are shown to be less important. Both univariate and multivariate analyses were carried out. The multivariate analysis looks at all the factors together for the best combined explanation of risk and therefore reduces the error from confounding of factors. The univariate analysis is quick to do, so is a useful start, but is more subject to error. The factors significantly associated with the development of neuropathy (including neuropathy occurring before diagnosis, as evidenced by impairment when first seen) were: older age, a delay in diagnosis, a higher number of nerves noted to be thickened at diagnosis and the occurrence of reversal reactions. Classification and the occurrence of ENL reactions were not risk factors in this study, nor were pregnancy, HIV positivity and lepromin positivity.

Risk factors for developing chronic or recurrent neuropathy were also examined (Table 11) with classification, impairment at diagnosis and the occurrence of either reversal

or ENL reactions being significant. Neither HIV positivity nor pregnancy was a significant risk factor.

Poor outcome is examined in Table 12, which indicates how important impairment at diagnosis and chronic or recurrent neuropathy are for the long-term prognosis. The fact that pregnancy has not been found to be a risk factor for either neuropathy in any form, or a poor outcome, means that female patients can be reassured about the safety of becoming pregnant at any stage of the disease. Since a good long-term outcome in people who get leprosy is one of the main goals of all leprosy control work, these results suggest that health promotion for early diagnosis, and the diagnosis, management and prevention of chronic and recurrent neuropathy, are the main challenges for those currently working in leprosy control programmes.

Conclusions and recommendations

1. The vast majority of all nerve damage occurs before diagnosis: 82% of all patients who eventually get nerve damage have some damage at diagnosis and an EHF score of 3 or more at diagnosis gives a 65-fold risk of a poor outcome. Therefore, public education for early diagnosis should be the highest priority in leprosy control programmes.
2. Management of acute neuropathy with steroids can achieve very good results: 88% of acute neuropathy episodes in those without previous impairment recover fully when treated with a standardized steroid regimen; training of health workers to do this effectively in peripheral clinics is a worthwhile development.
3. Chronic and recurrent neuropathy need to be identified: chronic and recurrent neuropathy are risk factors for a poor outcome. Patients who show any deterioration after treatment with a standard regimen should be referred for more intensive treatment with steroids, or newer types of treatment that may become available. Guidelines for managing these cases need to be developed.
4. Neuropathy can occur for the first time after MDT has been completed: 33% of MB cases with no impairment at diagnosis who eventually get neuropathy, do so after the 1-year period of MDT and many others continue to get episodes of neuropathy for years after completing MDT; patient awareness, self-examination and self-referral must be fostered. Provision for the assessment and management of these cases must be made.
5. Recovery of apparently permanent nerve damage may occur: up to one-third of nerves with long-standing damage may spontaneously recover over a period of several years; prevention of further damage and disability during that process is important.
6. Risk factors identified in this study include: for *neuropathy*, older age, delay in diagnosis, thickened nerves at diagnosis and reversal reactions; for *chronic or recurrent neuropathy*, classification, impairment at diagnosis, reversal and ENL reactions; and for a *poor outcome*: impairment at diagnosis and chronic or recurrent neuropathy.

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Reversal reactions in the skin lesions of AMFES patients: incidence and risk factors

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Summary Reversal reactions affect the skin and/or nerves of leprosy patients. This paper looks at reversal reactions involving the skin in 594 new patients in central Ethiopia, followed for between 6 and 11 years after the start of treatment. The incidence of reversal reaction declines steadily after the start of treatment, but the first episode may occur as long as 5 years after diagnosis in both paucibacillary (PB) and multibacillary (MB) patients. Recurrent episodes occurred up to 6 years after diagnosis. PB patients were at greatest risk for reversal reaction in the first year after diagnosis and MB patients in the first 4 years. The highest incidence rate was 18 episodes per 100 person years in MB patients during the first year after diagnosis. The ratio of the incidence rates for the first 3 years in MB versus PB patients is 2.4 (95% CI 1.6–3.8). This study confirms that starting effective treatment and borderline classification are risk factors for reversal reactions. Pregnancy/delivery in the 6 months prior to diagnosis was a significant risk factor for presenting with a reversal reaction [relative risk (RR) 5.9 (95% CI 2.1–16.5)], but later pregnancies were not associated with an increased risk. Being female was a significant risk factor for the late appearance of the first episode of reversal reaction. Having a reversal reaction in the first year after diagnosis was a highly significant risk factor for the development of later reactions [RR in PB cases 11.9 (95% CI 3.4–41.7); in MB cases 6.4 (95% CI 3.8–10.6)]. Being HIV positive was a risk factor for developing recurrent reversal reactions, although only three out of 29 recurrent cases were HIV positive [RR 2.7 (95% CI 1.4–5.1)].

Introduction

With the success of multi-drug therapy in the treatment of leprosy, attention has focused on the problem of leprosy reactions, which are now the most significant issue in the management

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of the individual patient.[1] Much is known of the epidemiology of reactions, but their incidence after the period of MDT is less well documented because of the lack of long-term, prospective studies.[2] The range of clinical presentations and their management has been well documented, especially for reversal, or type 1, reactions.[3]

Clinically, in reversal reactions the leprosy lesions become erythematous, raised oedematous and infiltrated; there may be oedema of the hands and/or feet. Lesions occasionally ulcerate and new lesions may appear, presumably due to inflammation around inapparent foci of bacilli.[3] Corticosteroids are the drug of choice in severe reversal reactions with nerve involvement, while simple analgesics are effective in mild reactions.

Reversal reactions are characterized by episodes of increased inflammatory activity in skin and/or nerves of patients with borderline leprosy.[2] In practice, there are two main clinical presentations, in which either skin signs or neurological signs predominate. Reversal reactions often present with typical signs and symptoms of inflammation in the skin lesions. There may or may not be associated nerve damage, but the pain in the skin lesions causes the patient to seek help or the inflamed lesions may be noticed by the health worker at a routine clinic visit. In a second group of patients, skin signs are less obvious or are even absent, and nerve function impairment is the sign that inflammation is present in the nerves.[4] The patient may complain of nerve tenderness or loss of function, but often the damage occurs insidiously and is only noted by the health worker through routine nerve function tests.

Risk factors for reversal reactions have been looked at in a number of contexts, but as yet there is no method of confidently predicting which patients are at risk.[2,5] In the literature it is often difficult to distinguish risk factors for neuritis from those for reversal (or type 1) reactions. However, several risk factors have been documented, including bactericidal drug regimens,[6] attending as a self-reporting case,[7] having a facial patch, as a risk for lagophthalmos,[5,8] the presence of anti PGL-1 antibodies and a positive lepromin test,[5,9] during MDT and the subsequent 6 months,[10,11] extensive disease, indicated by the number of body areas involved,[5,11] borderline classification,[11] BCG vaccination[2] and a positive BI.[5]

This paper examines the incidence of, and risk factors for, reversal reactions affecting the skin, following van Brakel,[11] while an accompanying paper looks at the much more complex issue of nerve involvement in some detail. In this paper, therefore, the term reversal reaction implies signs of inflammation in leprosy skin lesions, although nerve involvement may also be present.

Materials and methods

A prospective cohort study of leprosy patients treated with fixed-duration MDT, was set up at the All Africa Leprosy, Tuberculosis and Rehabilitation Centre (ALERT) in central Ethiopia in 1988, with the objectives of determining the incidence rates of relapse, reactions and nerve damage, and the risk factors for these events. In all, 660 patients were enrolled in this ALERT MDT Field Evaluation Study, known as AMFES, between March 1988 and March 1993.[12,13] Ten patients were excluded soon after diagnosis, either because the diagnosis was changed or the enrolment procedures were incorrectly followed. A further 56 patients, who were relapses after dapsone monotherapy, were not included in this review of reversal reactions; this group includes four of the 22 HIV-positive individuals in the cohort. Five hundred and ninety-four new cases are reviewed. After completion of treatment, the following proportions attended

for follow-up: 92% attended for the first year, 87% the second, 76% the third, 71% the forth and 62% the fifth.

Cases were classified as MB if they were classified clinically as BB, BL or LL in the Ridley–Jopling classification. In addition, BT patients were classified as MB if they had a positive skin smear at any site, although three BT patients with a bacillary index (BI) of 1 were treated as paucibacillary cases in the first year of the study, under earlier guidelines. BT patients with many skin lesions were classified as PB if their smears were negative.

A reversal reaction could be diagnosed by field staff on the basis of the clinical finding of signs of inflammation in leprosy skin lesions.[13] Findings may include complaints by the patient of pain and/or tenderness in the skin lesions, swelling and warmth of the lesions, and sometimes erythema. Nerve function impairment was assessed and recorded separately. Recurrent reversal reactions were defined as further episodes occurring more than 3 months after the start of a previous episode, whatever treatment may have been given. The term therefore includes those whose reaction flared up again immediately steroids were stopped, and those in whom a subsequent reaction occurred months or years later. Episodes of reaction may have been observed at a routine follow-up examination, or the patient could easily attend as a self-reporting case.

While type 1 or reversal reactions can occur years after the start of treatment, they are much more common at the start of treatment and in the first year thereafter. The experience of patients is therefore analysed by year after diagnosis. This allows the quantification of the change in incidence over time. Risk factors are analysed in a similar way, allowing the characterization of specific risk factors for late reactions.

Longitudinal patient records within this prospective cohort study were managed throughout using dBase software. Analysis used Epi-Info software and logistic regression modelling of multiplicative relative risks was performed using Egret.

Results

PREVALENCE AT DIAGNOSIS

Table 1 indicates the prevalence of various events at the time of diagnosis. Reversal reactions were present in 5% of new cases (4.3% of MB cases and 5.8% of PB cases).

The following possible risk factors were examined for association with the presence of reversal reaction at diagnosis: age, sex, classification, BI, contact status, HIV status, lepromin status, pregnancy (either pregnant at the time of diagnosis, delivery in the previous 6 months

Table 1. The frequency of various complications present at diagnosis. Numbers of cases and (percentages)

	Number of cases	Reversal reaction alone	Reversal reaction + acute neuritis
MB cases	300	1 (0.3%)	12 (4%)
PB cases	294	2 (0.7%)	15 (5%)
Totals	594	3 (0.5%)	27 (4.5%)

or in the previous 3 years) and delay in presentation. The only factor significantly associated with an increased risk of reversal reaction at diagnosis was the delivery of a baby in the 6 months prior to diagnosis: relative risk (RR) 5.9 (95% CI 2.1–16.5). These results were essentially the same in both univariate and multivariate analyses.

RISK FACTORS FOR, AND TIMING OF, THE FIRST REVERSAL REACTION AFTER DIAGNOSIS

Ninety-eight of the 594 cases (16.5%) under review developed a reversal reaction at some time, including those with a reaction at presentation. This represents 11% of PB cases and 22% of MB cases. Twenty-nine of the 98 cases (29%) had more than one episode of reversal reaction.

Table 2 shows the risk factors for developing a reversal reaction, while Figure 1 shows the

Table 2. Risk factors for the development of a reversal reaction. (reaction cases = 98; study population = 594; cases included in the multivariate analysis = 509, with 86 reaction cases). Note: the stepwise multivariate analysis only includes those factors whose association with the dependant variable approaches significance

Factor	Number of cases with reversal reaction	Univariate analysis of relative risk (95% CI)	Stepwise multivariate analysis of relative risk (95% CI)
PB	32/294	1.0	
MB	66/300	2.3 (1.5–3.7)	–
Classification: other	8/93	1.0	
Classification: borderline	90/501	2.3 (1.1–5.0)	4.2 (1.8–9.8) $P < 0.001$
Negative skin smear	34/312	1.0	
Positive skin smear	61/268	2.4 (1.5–3.9)	3.6 (2.2–6.1) $P < 0.001$
Male	55/378	1.0	
Female	43/216	1.5 (0.9–2.3)	1.6 (1.0–2.7) $P = 0.51$
No pregnancy	85/545	1.0	
Any pregnancy since 3	13/49	1.9 (1.0–3.8)	–
Age <20	32/177	1.0	
Age 20–49	49/316	0.8 (0.5–1.4)	–
Age 50+	17/101	0.9 (0.5–1.7)	–
HIV negative	85/507	1.0	
HIV positive	4/18	1.4 (0.4–4.8)	–
Lepromin negative	29/117	1.0	–
Lepromin positive	20/89	0.9 (0.4–1.8)	–
No history of contact	71/434	1.0	
Contact history positive	27/160	1.0 (0.6–1.7)	–
Delay <4 years	80/464	1.0	
Delay >4 years	18/124	0.8 (0.5–1.2)	–

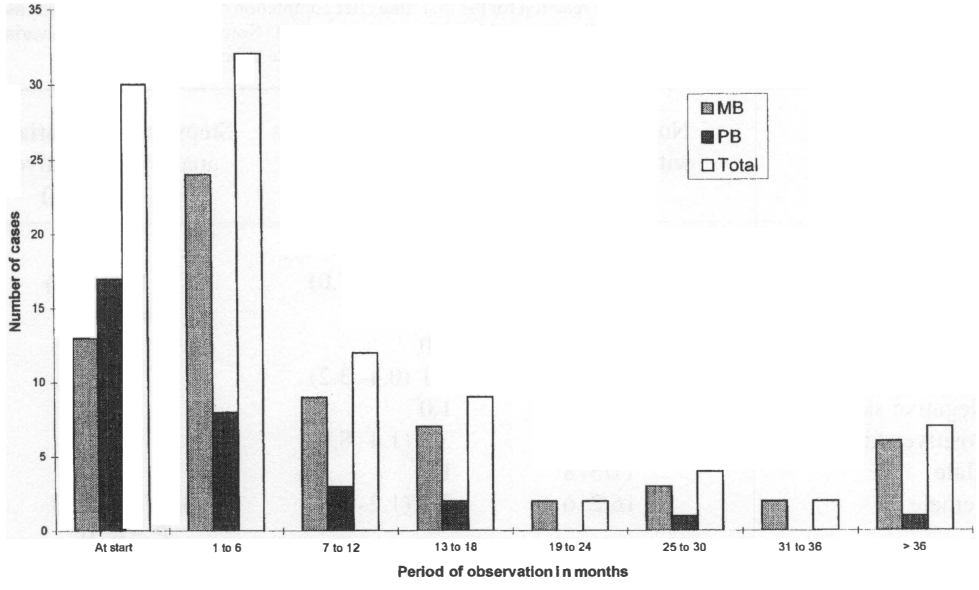

Figure 1. Timing of first episode of reversal reaction (n = 98).

timing of the first episode of reversal reaction in 98 cases. Borderline classification and a positive skin smear at diagnosis were significant risk factors for reversal reactions, while being female approached significance as a risk factor.

While reversal reactions can occasionally occur for the first time more than 5 years after the start of treatment (this occurred in two MB patients in this cohort), the majority of first episodes occur in the first year. Twenty-eight of 32 PB patients (88%) and 46 of 66 MB patients (70%) had their first episode within the first year after starting treatment. Twenty-five of the PB patients had their first episode within the first 6 months.

Possible risk factors for being amongst the seven PB patients whose first reversal reaction occurred after the 6-month period of MDT, were examined. No association was found with any of the following factors: sex, age, HIV status, delay in presentation, pregnancy, contact status and lepromin status. Patients with WHO Impairment Grade 2 at diagnosis had an increased risk of developing their first reversal reaction after the end of MDT (RR 2.34; 95% CI 1.2–4.6), although the fact that they already have impairment strongly suggests that they have had a reactional episode prior to diagnosis.

The same risk factors were examined for the 20 MB patients whose first reversal reaction occurred later than 1 year after the start of treatment, i.e. after the currently recommended period of MDT. There was no association with any of these factors (including the WHO Impairment Grade at diagnosis), except being female (RR 4.01; 95% CI 1.65–9.72), but this was not associated with later pregnancies. The BI at diagnosis was not associated with late reversal reaction in MB patients.

Table 3 gives the risk factors for developing a reversal reaction after the end of MDT for PB and MB cases together. Being female and being multibacillary are the only statistically significant risk factors, while pregnancy is not an important factor in this cohort. The multivariate analysis was repeated for females alone, but pregnancy did not become an important risk factor in that regression model either (RR 1.3).

Table 3. Risk factors for developing a reversal reaction for the first time after completion of MDT. (late reaction cases = 27; study population = 594; cases included in the multivariate analysis = 509). Note: the stepwise multivariate analysis only includes those factors whose association with the dependant variable approaches significance

Factor	Number of cases with late reversal reaction	Univariate analysis of relative risk (95% CI)	Stepwise multivariate analysis of relative risk (95% CI)
PB	7/294	1.0	
MB	20/300	2.9 (1.2–7.0)	3.7 (1.4–10.4) $P = 0.006$
Classification: other	4/93	1.0	
Classification: borderline	23/501	1.1 (0.4–3.2)	–
Negative skin smear	7/312	1.0	
Positive skin smear	19/268	3.3 (1.4–8.0)	–
Male	11/378	1.0	
Female	16/216	2.7 (1.2–5.9)	3.4 (1.4–8.2) $P = 0.01$
No pregnancy	23/545	1.0	
Any pregnancy since 3 years before diagnosis	4/49	2.0 (0.7–6.1)	–
Age <20	11/177	1.0	
Age 20–49	12/316	0.6 (0.3–1.4)	–
Age 50+	4/101	0.6 (0.2–2.0)	–
HIV negative	22/507	1.0	
HIV positive	2/18	2.8 (0.6–12)	–
Lepromin negative	12/117	1.0	–
Lepromin positive	4/89	0.4 (0.1–1.3)	–
No leprosy contact	17/434	1.0	
Contact history positive	10/160	1.6 (0.7–3.7)	–
Delay <4 years	21/464	1.0	
Delay >4 years	6/124	0.9 (0.5–1.6)	–

INCIDENCE OF REVERSAL REACTIONS BY YEAR

Figure 2 shows the incidence rate of reversal reactions by year for both MB and PB cases. Seventeen patients (nine PB and eight MB) had reversal reactions only at the start, so are not included here. Eighty-one patients (23 PB and 58 MB) had 130 episodes of reversal reaction (36 in PB cases and 94 in MB cases) after starting treatment.

For the first 3 years taken together, the overall incidence of reversal reactions is 7.8 per 100 person-years-at-risk (PYAR) (95% CI 6.2–9.3). For MB cases the figures are 10.6 PYAR (95% CI 8.2–13.0) and for PB cases the figures are 4.3 PYAR (95% CI 2.6–6.0). The rate ratio is 2.4 (95% CI 1.6–3.8).

RECURRENT REVERSAL REACTIONS

For PB cases there were nine episodes after the first year and of these four were first episodes

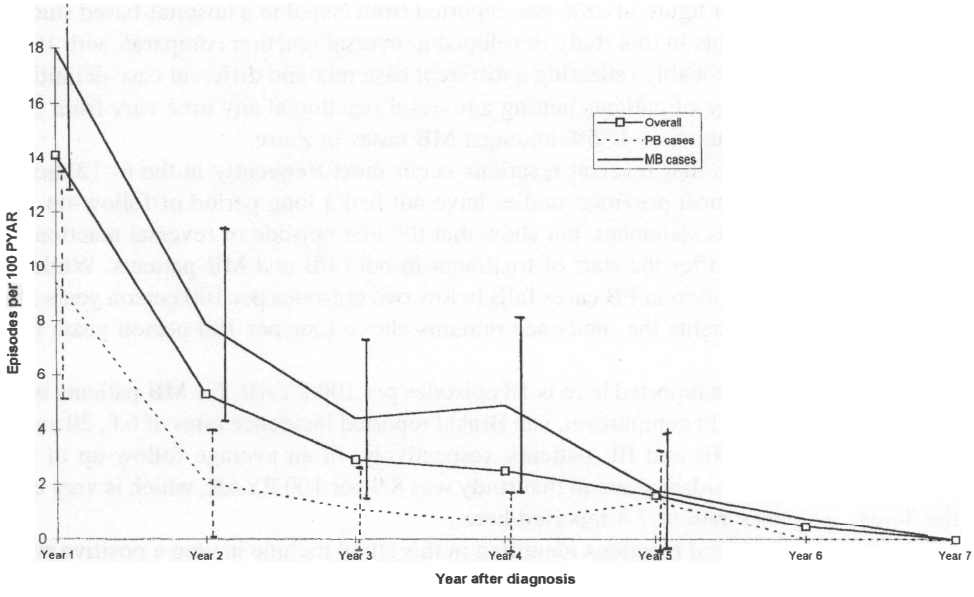

Figure 2. Incidence rate of reversal reactions after diagnosis, by year (130 episodes in 98 patients). 95% confidence intervals are given for MB and PB cases.

and five were repeat episodes. Having a reversal reaction at the start or during the first year is associated with an increased risk of having another episode later than 1 year after diagnosis (RR 11.9; 95% CI 3.4–41.7).

For MB cases there were 43 episodes after the first year, including 20 first episodes and 23 repeat episodes. There is an increased risk of a late reversal reaction if an episode occurred at the start or during the first year (RR 6.35; 95% CI 3.8–10.6).

Other risk factors for recurrent reversal reaction were looked for. There was no association with age, sex, classification, BI, contact status, lepromin status, pregnancy, impairment status at start or at RFT, or delay in presentation. Being HIV positive was associated with an increased risk of having more than one episode of reversal reaction in the new cases examined here (RR: 2.7; 95% CI 1.4–5.1), although the number of cases involved is small – of the 29 patients with recurrent reversal reactions, two had no HIV test result, three were positive and 24 were negative; of the four HIV-positive patients who had any reversal reaction, however, three had recurrent episodes.

Discussion

The definition of reversal reaction still remains a problem and different studies use different definitions; some include episodes of neuritis or nerve function impairment (NFI) within a broad definition of reversal reaction.[2] In this report, reversal reaction refers only to the clinical syndrome in which leprosy skin lesions show signs of inflammation, whether or not there was accompanying NFI. A separate report examines the data for NFI.

Previous reports indicate a prevalence of reversal reaction at the time of diagnosis of between 2.6% and 6.4%, and the findings presented here are compatible with those figures,[2]

although the much higher figure of 28% was reported from Nepal in a hospital-based study.[11] In all, 16.5% of all patients in this study developed a reversal reaction compared with 10.9% in Hyderabad, India,[14] probably reflecting a different case mix and different case definitions. Figures for the percentage of patients getting a reversal reaction at any time vary from 3.5% amongst PB cases in Malawi to 47.5% amongst MB cases in Zaire.[2]

Although it is known that reversal reactions occur most frequently in the 6–12 months after starting MDT,[3,10] most previous studies have not had a long period of follow-up. The AMFES data confirm this statement, but show that the first episode of reversal reaction can occur as late as 5 years after the start of treatment in both PB and MB patients. While the incidence of reversal reaction in PB cases falls below two episodes per 100 person years after the first year, in MB patients the incidence remains above four per 100 person years for 4 years.

The highest incidence reported here is 18 episodes per 100 PYAR, for MB patients in the first year after diagnosis. In comparison, van Brakel reported incidence rates of 6.8, 20 and 15 per 100 PYAR in BT, BB and BL patients, respectively, in an average follow-up of 20.7 months.[11] The overall incidence rate in that study was 8.9 per 100 PYAR, which is very close to the 3-year incidence rate of 7.8 reported here.

Risk factors for reversal reactions identified in this study include having a positive smear at diagnosis and borderline classification. Unfortunately, information about which patches developed a reaction was not recorded, so it is not possible to examine the importance of a reacting face patch as a risk factor for other complications. Female sex as a possible risk factor, independently of pregnancy, just fails to reach significance. Interestingly, the previously quoted study in Nepal found that amongst BT cases, females had a significantly greater risk of developing a reversal reaction, although data for pregnancies were not available.[11]

Pregnancy and lactation are reported to be risk factors for reversal reactions, but the association has not been quantified and remains unclear.[2,15] Amongst the AMFES women, delivery of a baby in the 6 months before the diagnosis of leprosy was made, was associated with an increased risk of reversal reaction at diagnosis. Later pregnancies were fewer in number and were not associated with reversal reactions, but being female was associated with the late appearance of the first reversal reaction.

Recurrent episodes of reversal reaction are an important phenomenon, as they may be associated with continuing nerve damage and a gradual deterioration in the patient's condition. Reactions have previously been reported up to 5 or 6 years after diagnosis.[10,14] A reaction in the first year after diagnosis gave an increased risk of a later reaction and being HIV positive, while not associated with an increased risk of reversal reaction as such, was associated with recurrent episodes in those who had reversal reactions, the result just reaching significance at the 5% level. In an analysis of all the HIV-tested patients in the AMFES cohort, including those in the group who were relapses after dapsone monotherapy, a similar result was found, although that result just failed to reach significance.[16]

In conclusion, borderline leprosy is the major risk factor for developing a reversal reaction, while the major period of risk is the 12 months after the start of treatment for paucibacillary patients. In multibacillary patients the period of risk for first and repeat episodes lasts about 4 years from the start of treatment. Later episodes occur in only very few patients. HIV infection increases the risk of recurrent reactions. Pregnancy and lactation are shown to be risk factors at the time of diagnosis, but being female also seems to be of some importance as a risk factor, being associated with late first reactions in this study.

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We thank the staff of the ALERT Leprosy/TB Control Division for their dedication and perseverance in managing the patients and collecting data over so many years. The financial support of ILEP, through Netherlands Leprosy Relief (NLR), has been constant throughout the 12 years of the study and is gratefully acknowledged. We also thank ALERT as a whole for institutional and administrative support.

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ENL reactions in the multibacillary cases of the AMFES cohort in central Ethiopia: incidence and risk factors

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Summary Erythema nodosum leprosum (ENL), or type 2 leprosy reactions are an important complication of multibacillary leprosy. The AMFES cohort includes 300 new multibacillary cases that have been followed for up to 10 years from the start of treatment, in central Ethiopia. Sixteen (5.3%) patients had ENL reactions. The incidence of ENL was maximal in the second and third years after the start of treatment, reaching 6.9 episodes per 100 person years at risk. Factors associated with being lepromatous [LL classification and a high bacillary index (BI)] gave an increased risk of developing ENL; in the univariate analysis, LL classification gave a relative risk of 3.6 (95% CI 1.3–10) and a BI of 6 gave a relative risk of 8.6 (95% CI 2.3–32) for the development of ENL. HIV co-infection was found to be a risk factor in this cohort, but as the numbers involved are small (only two HIV positive patients had ENL), this finding must be confirmed in larger studies. Ten of the 16 cases had recurrent episodes and five had at least five episodes occurring over a period of more than 2 years. The management and prognosis of ENL reactions are discussed.

Introduction

While erythema nodosum leprosum (ENL) reactions, sometimes known as type 2 reactions, are the most serious immunological complications affecting patients with multibacillary (MB) leprosy, very little has been published on the epidemiology of the condition.[1] This may be partly because ENL reactions tend to occur some years after the start of multi-drug therapy (MDT) and few studies have involved a long enough follow-up period. Many studies are hospital based and may be expected to find higher rates of reaction than programme-based studies. There is evidence, however, of a wide variation in the frequency of ENL in different parts of the world, with 31% of MB cases affected in Brazil,[2] 19% in Nepal,[3] 12% in

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Thailand[4] and 5% in a previous report from Ethiopia.[5] The most important risk factor seems to be a high bacillary load,[3] with LL cases having a higher incidence than BL cases; the condition does not occur in paucibacillary, lepromin positive or smear negative leprosy.

ENL reactions were not reported in HIV-positive individuals until recently and it had been suggested that HIV infection may decrease the risk of this complication.[6] Case reports of ENL in HIV-positive patients have, however, started to appear.[7,8]

The pathological basis of ENL is considered to be related to circulating immune complexes and the clinical and histological features resemble serum sickness.[9] In addition to the typical skin lesions, which may rarely ulcerate, a variety of systemic complications have been described, such as orchitis, iridocyclitis, arthritis and nephritis.[10] Nerve damage may also occur.[11]

Materials and methods

In all, 660 patients were enrolled in the ALERT MDT Field Evaluation Study (AMFES) between March 1988 and March 1993. Ten patients were excluded, either because the diagnosis was changed or the enrolment procedures were incorrectly followed. A further 56 patients, who were relapses after dapsone monotherapy, are not included in this review. Of 594 new cases 300 were MB cases and form the current study population.

Cases were classified as MB if they were classified clinically as BB, BL or LL in the Ridley–Jopling classification. In addition, BT patients were classified as MB if they had a positive skin smear at any site, although three BT patients with a bacillary index (BI) of 1 were treated as paucibacillary cases in the first year of the study, under earlier guidelines. BT patients with many skin lesions were not classified as MB if their smears were negative. Skin smears were reported for all cases except one MB and 13 PB patients.

Patients were reviewed regularly by field supervisors and the diagnosis of ENL was made on clinical grounds only. Patients were seen on a monthly basis during MDT, and then every 6 months after completion of treatment. Those who did not attend for examination were actively sought, by a home visit if necessary. The diagnosis depended on finding multiple, tender, subcutaneous nodules, usually on the limbs, that were not related to existing leprosy patches. Systemic symptoms could include fever, oedema and other organ involvement. A detailed clinical examination for other organ involvement, including eye complications, was not possible in the peripheral clinics and would only take place for those patients admitted to the ALERT Hospital. If ENL was accompanied by nerve function impairment, steroids were given; otherwise symptomatic treatment with aspirin was given. Prolonged or complicated episodes of ENL were referred to ALERT, where steroids, additional clofazimine and/or thalidomide could be prescribed. The standardized course of steroids for adult MB patients used in peripheral clinics started at a dose of 40 mg prednisolone for 1 month, the dose being reduced gradually in monthly steps to finish after 24 weeks. Courses lasting longer than this or involving higher doses of steroids could only be prescribed by physicians to patients attending the ALERT Hospital and these courses varied according to the clinical response, often lasting for more than 12 months.

During the final 2 years of the study all patients with any visual problems who could be traced, were reviewed in the ophthalmology department at ALERT, to document eye pathology, whether leprosy related or not.

Results

PREVALENCE AT DIAGNOSIS

There were no cases with ENL at diagnosis.

TIMING OF THE FIRST EPISODE OF ENL

Sixteen (5.3%) of 300 MB cases developed ENL at one time or another. Figure 1 shows the timing of the first episode of ENL. Only two of the 16 cases (13%) presented before the currently advised end of MDT at 1 year. The majority of cases (11 of 16; 69%) first presented in years 2 and 3. There were no new cases of ENL in this cohort more than 6 years after diagnosis.

RISK FACTORS FOR THE DEVELOPMENT OF ENL

Factors linked to being lepromatous are important risk factors for ENL, as shown in Table 1. Sex, pregnancy, nerve function impairment at diagnosis, contact status and delay in presentation were not significant factors. As 25 patients (8.3%) did not have an HIV test result available, the multivariate analysis of risk factors was done twice, with and without HIV as a factor. Having a high BI and being HIV positive were important risk factors for ENL in this cohort. HIV status was not associated with BI in either the whole cohort or within the MB group alone.

Because the absolute number of cases with ENL is low and the number of cases in certain sub-groups (for example, HIV positive cases with ENL) is extremely low, Table 1 must be treated with caution. The confidence intervals are wide, reflecting this lack of precision. In this small group, HIV status made no noticeable difference to the clinical features of ENL.

INCIDENCE OF ENL REACTIONS BY YEAR

Figure 2 shows the incidence of ENL reactions by year after the start of treatment. As the disease tends to run a chronic course, it is possibly unhelpful to speak of discrete episodes and therefore of an incidence of reactional episodes. On the other hand, many patients experience remissions and relapses in the course of ENL and two episodes may be separated by a considerable gap. An episode of ENL was taken as a separate event if more than 3 months had

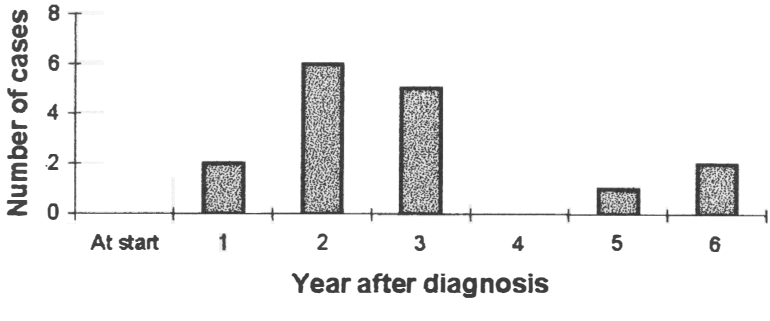

Figure 1. Year of first episode of ENL ($n = 16$).

Table 1. Risk factors for the development of ENL reactions. NB: one case out of 300 had no BI, while 25 cases had no HIV test done. Two multiple regression models were examined, one including and one excluding HIV as a factor

Factor	Value	Univariate analysis: Number of cases with ENL	Multivariate analysis relative risk and (95% CI)	Multivariate analysis (no HIV): relative risk and (95% CI)	(with HIV): relative risk and (95% CI)
Class	BT/BL	7/216	1·0		
	LL	9/84	3·6 (1·3–10)	1·4 (0·40–5·0)	2·0 (0·47–8·3)
Age	<20	3/76	1·0		
	20+	13/224	1·5 (0·42–5·4)	1·8 (0·49–6·9)	1·4 (0·35–5·3)
Sex	Male	10/205	1·0		
	Female	6/95	1·3 (0·46–3·7)	1·8 (0·60–5·5)	1·6 (0·50–5·3)
BI	≤ 4	4/181	1·0		
	5	6/81	3·5 (0·97–13)	3·3 (0·77–14)	2·8 (0·55–14)
	6	6/37	8·6 (2·3–32)	8·0 (1·6–42)	5·1 (0·87–31)
HIV	Neg	12/265	1·0	–	
	Pos	2/10	5·3 (1·0–2·8)	–	7·8 (1·2–52)

elapsed since the last episode. The figures indicate that episodes of ENL may occur up to 7 years after starting treatment.

CHRONIC AND RECURRENT ENL REACTIONS

Ten of the 16 cases (63%) reviewed here had more than one episode of ENL, which confirms the chronic nature of the condition. The mean and the median number of episodes was three (range 1–8). Amongst these 10 cases, the time between the first and last episodes was on average 22 months (range 4–64 months). Eight of these 10 cases were admitted to hospital at one time or another and another two cases with a single episode were admitted.

Five patients (1.7% of all MB patients, or 31% of all ENL cases) had frequent attacks of ENL reaction, with five or more episodes over a period of more than 2 years, but no specific risk factors can be identified, except age, in that all were between 20 and 45 years old. One patient was HIV positive, two were male and none of the females had a pregnancy during the period of observation. The initial BI was 4 in three cases and 5 in two cases. The ages at the start of ENL were 20, 22, 23, 42 and 44 years.

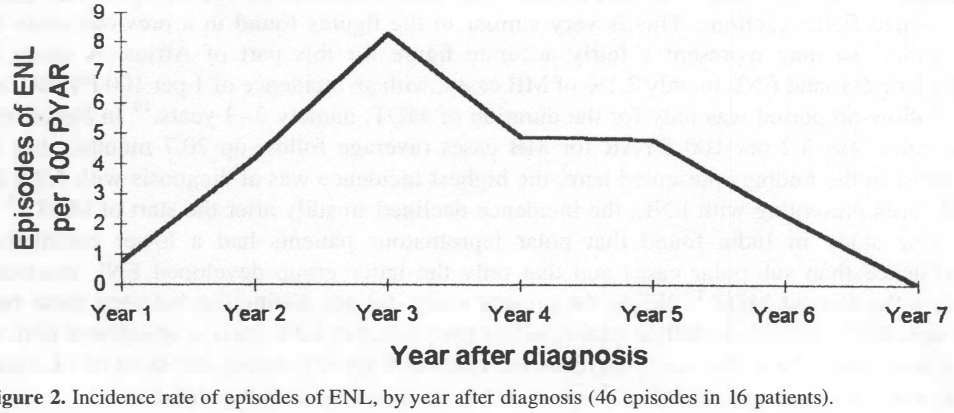

Figure 2. Incidence rate of episodes of ENL, by year after diagnosis (46 episodes in 16 patients).

MANAGEMENT AND OUTCOME OF CHRONIC ENL REACTIONS

The five cases of chronic ENL were managed with long courses of prednisolone and additional clofazimine, for periods of up to 5 years. The dose of prednisolone was titrated against the clinical features and symptoms of the disease, but a typical maintenance dose was 20 mg daily. Prolonged courses of prednisolone were usually required for symptomatic relief of rheumatic pain and general malaise, rather than for new nerve impairment.

Thalidomide was given to three of these five patients: one female patient (aged 45 at that time) was given it for 3 months as an in-patient when her ENL was at its worst; the short-term results were good in that steroids could be stopped, but there were subsequent episodes of ENL requiring further courses of steroids at varying doses over a period of 64 months in total. Two male patients were each given a short course of thalidomide, early on in the course of the illness. One other patient, without chronic ENL, also had a short course of thalidomide. No patients were treated with thalidomide alone, but received prednisolone as the mainstay of their treatment. Nerve function impairment was always treated with prednisolone, but thalidomide played a useful steroid-sparing role when rheumatic pain and general malaise were the main symptoms.

There was very little deterioration in impairment or disability status over the course of the disease in four patients; the fifth developed sepsis in both feet (at different times) while on steroids, which required debridement, but the eventual outcome has been good. One male patient now requires cataract surgery at the age of 46 years, which may be a complication of steroid treatment.

No systemic involvement was recorded in any of the patients with ENL and no ulceration of nodules occurred. Two patients had conjunctivitis while at ALERT as in-patients, but at the recent ophthalmological review, none of the ENL patients had residual eye pathology, except the cataracts noted above.

Discussion

ENL reactions have been said to occur in more than 50% of LL cases and in about 25% of BL cases, but these figures come from well before the MDT era.[12] They are known to be frequently prolonged or recurrent, and they are also said to occur more commonly during pregnancy and lactation.[13] In this cohort only 12% of LL cases and 3.6% of BL cases developed ENL reactions. This is very similar to the figures found in a previous study in Ethiopia,[5] so may represent a fairly accurate figure for this part of Africa. A study in Bangladesh found ENL in only 2.1% of MB cases, with an incidence of 1 per 100 PYAR, but the follow-up period was only for the duration of MDT, namely 2–3 years.[14] In Nepal, the incidence was 3.2 per 100 PYAR for MB cases (average follow-up 20.7 months), but in contrast to the findings presented here, the highest incidence was at diagnosis with 5.7% of MB cases presenting with ENL; the incidence declined steadily after the start of MDT.[11]

One study in India found that polar lepromatous patients had a lower cumulative prevalence than sub-polar cases and that only the latter group developed ENL reactions before the start of MDT.[15] While the present study did not distinguish between these two groups, this is unlikely to fully explain the low prevalence of ENL and the absence of ENL at diagnosis found here; this study includes BL cases and approximately one-third of LL cases that were biopsied had some histological features suggestive of sub-polar disease.

The incidence of ENL appears to have fallen with the introduction of MDT, possible explanations being the more rapid bactericidal effect of rifampicin and the specific effect of clofazimine in suppressing ENL.[1,16] It is clear that as the duration of MDT gets shorter, more ENL reactions will first occur after release from treatment. Patients must therefore be warned of the possibility, so that they may return for further management. While ENL symptoms are severe enough to force the patient to seek treatment, the condition may not be recognized by physicians as it becomes more and more rare. Patients may not volunteer a history of leprosy, so the diagnosis and appropriate treatment may be delayed.

A number of risk factors have been examined, but the low numbers of cases involved make these rather tentative findings. No link with pregnancy or lactation could be confirmed. There is a suggestion that HIV positive cases were more likely to develop ENL reactions. Age under 40 years was a significant risk factor in Nepal[3] but in this study age was not a risk factor, although the most chronic cases were all in the age range 20–45 years.

The majority of ENL reactions started in the 2nd or 3rd year after the start of MDT, and most cases had intermittent attacks over a period of about 2 years. Chronic cases were managed with steroids, sometimes over quite long periods, and had a generally good prognosis in terms of nerve damage and disability. Thalidomide use was generally controversial at ALERT Hospital, because of its teratogenic potential, with much discussion before it was prescribed. The drug was not always available, but it was used in 25% of our cases in short courses. Thalidomide was not given to outpatients in Ethiopia, because of the possibility that it would be shared with others, but it was generally possible to manage chronic ENL with moderate doses of steroids on an outpatient basis, with occasional admissions when necessary.

As approximately one-third of patients with ENL reactions go on to have chronic disease lasting more than 2 years, which requires experience to manage optimally, it is appropriate for most cases to be referred to a physician with such experience, if at all possible. A feasible approach would be to allow one course of treatment in a peripheral clinic (with aspirin or steroids, as indicated), but to advise referral for any subsequent episode of ENL.

Acknowledgements

We thank the staff of the ALERT Leprosy/TB Control Division for their dedication and perseverance in managing the patients and collecting data over so many years. The financial support of ILEP, through Netherlands Leprosy Relief (NLR), has been constant throughout the 12 years of the study and is gratefully acknowledged. We also thank ALERT as a whole for institutional and administrative support.

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Relapses after fixed duration multiple drug therapy: the AMFES cohort

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Summary Relapse rates after multiple-drug therapy (MDT) have been low, although there remains a concern about the possibility of late relapse in those with an initially high bacterial load. In all, 502 patients in the AMFES cohort completed fixed-duration MDT and are included in this report. There have been no confirmed relapses in the AMFES cohort, in a follow-up period of up to 8 years after completion of treatment, even in the 57 cases with an initial average bacillary index of ≥4.0, 20 of whom have been followed for more than 5 years after ceasing MDT. Methods of diagnosing a relapse are discussed.

Introduction

Relapse rates after multiple-drug therapy (MDT) for leprosy are widely reported to be low,[1] to the extent that the recommended duration of treatment for multibacillary (MB) cases has been reduced to 12 months.[2]

Making the diagnosis of relapse is not necessarily straightforward, and there is a possibility of overdiagnosis. For paucibacillary (PB) cases reversal reactions can be confused with relapse and there is no gold standard for comparison, as the organism cannot be isolated in these cases. In a review of over 40,000 PB cases released from treatment in India, 0.29% relapsed according to clinical criteria, but it was noted that it was likely that most of these cases recorded as relapses were late reversal reactions.[3] This is confirmed in a study from Ethiopia, where less than half of the 1.1% of PB cases who were recorded as having relapsed were thought to be true relapses on review.[4] Histological examination is often unable to distinguish between a reaction and a PB relapse.[4,5] A therapeutic trial with steroids is advocated as a means of making a clear diagnosis.[6]

Amongst MB patients reversal reactions may also be confused with relapse, but the

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possibility of confirming a relapse bacteriologically is available, either by skin smears to show a rise in bacillary index (BI) and/or a positive morphological index (MI), histology (using a stain for acid-fast bacilli) or by mouse-foot-pad inoculation. In the study in Ethiopia quoted above, 1.0% of MB cases were recorded as having relapsed, but none of these was confirmed on closer scrutiny: a common problem was to diagnose a relapse when only one skin smear result showed a rise in BI. Guidelines for the programme required a second smear to confirm the rise in BI, or an MI of 2% or more.[4]

Relapses are usually reported within 2–3 years after release from treatment (RFT), when reversal reactions are also more likely to occur. This is partly for logistic reasons with few studies being able to follow patients for long periods. In one long-term study of rifampicin-containing but non-standard multidrug regimens, relapses occurred in two groups: the majority had early relapses, before 3.5 years after release from treatment (median 22 months), while the remainder had late relapses more than 3.5 years after release from treatment (median 5 years).[7] It was suggested that the early relapses were likely to be due to insufficient treatment and the late relapses to persisting organisms.

A more recent long-term study showed a surprisingly high rate of relapse in those with an initial average BI of ≥ 4, using fixed-duration WHO-MDT; late relapses occurred in seven (20%) of these patients at 5 years (± 2 years) after release from treatment.[8] The relapses had an increased BI and new skin lesions, and were confirmed in four cases by growth in the mouse-foot-pad and in six cases by a positive MI.

Materials and methods

The ALERT MDT Field Evaluation Study (AMFES) recruited 660 patients between 1988 and 1993. There were 10 exclusions due to incorrect diagnosis or incorrect enrolment procedures. Of the 650 patients included, 56 were relapse cases after dapsone monotherapy and 594 were new cases. All were treated with fixed-duration MDT. A total of 502 (77%) of the 650 patients completed treatment and are included in the relapse study. Patients were reviewed every 6 months after release from treatment, although there was quite a large dropout immediately after stopping MDT. Random samples of urine were tested for dapsone during both treatment and surveillance.

Patients attending a 6-monthly review were examined clinically for signs of new or enlarging skin lesions and for signs of nerve function impairment (NFI). In MB cases a skin smear was routinely done each year, at four standard sites and from any suspect skin lesion. A relapse could be suspected because of findings in the skin, or in the skin smear results. The late appearance of reactions or nerve function impairment was also considered as a sign of possible relapse. For the purposes of this paper, all patients who were given steroids (indicating a severe reaction or NFI) more than 3 years after the diagnosis of leprosy had been made were defined as possible relapses.

Skin smears were all read at the ALERT Hospital laboratory, where smears were kept for review purposes for 1 year only. Smears were fixed and stained by the Ziehl–Neelsen method and examined using a binocular light microscope with an oil immersion lens at $\times 100$ magnification. The BI was reported for all four sites, so that although the BI was normally taken to be the highest reading, an average can be calculated for each test. The MI was taken as the percentage of solid staining bacilli in 100 examined.

The AMFES protocol clearly defined the management of suspected relapses. In summary,

an MB relapse would be indicated by a skin smear after release from treatment with an MI of at least 2%, or two skin smears in which the highest BI is 2 units above a previously recorded level. A PB relapse would be confirmed by the appearance of new lesions or the extension of existing lesions, after a course of steroids. If the diagnosis of a relapse is uncertain, as is commonly the case, patients should be treated with steroids (without anti-leprosy treatment) and reviewed within a period of 6 months for PB cases and 12 months for MB cases. If the changes in the skin resolve during this observation period, the likelihood of a relapse is reduced, while if the lesions remain or increase, a relapse is confirmed. Histological examinations should be carried out for all suspected relapses, but the results were not to be taken into account in reaching a clinical conclusion: these results would be used later to assess the correlation between histology and the clinical findings. The mouse footpad assay should be used for suspected MB relapses and would allow subsequent investigation for possible drug resistance.

Patients who were prescribed steroids for reactions and nerve function impairment after they had completed MDT were not given additional anti-leprosy drugs.

Results

Table 1 shows the length of follow-up of AMFES patients, including those with an initially high BI who may be considered at greatest risk of relapse. In all, 12/677 (1.8%) random urine specimens tested positive for dapsone during the surveillance period.

There have been no confirmed relapses in the AMFES cohort, although one patient was re-treated by another doctor on the basis of clinical suspicion alone. Relapse was suspected at some time in 40 (6%) patients and Table 2 shows the composition of this group.

New lesions in PB cases were usually noticed by the patient and presented to the health worker. In all four cases, these new lesions were thought by health staff to be on the same sites as previous lesions, but patients were unhappy not to be re-treated. One patient was thought by one doctor to have relapsed and by another to have had a reversal reaction and unfortunately this patient was re-treated without going through the correct AMFES procedures (namely, treatment with steroids alone in the first instance and re-assessment). The others were treated with steroids (two) or observed (one), with good results. One patient has had four biopsies over a 5-year period, all indicating varying degrees of delayed type hypersensitivity (DTH) in tuberculoid leprosy without any AFB; steroids have been helpful

Table 1. Follow-up after the end of MDT of AMFES patients who completed treatment

	PB patients (n = 246)	MB patients (n = 256)	Patients with BI ≥4 at start (n = 57)
Total follow-up	1009 person-years	1091 person-years	231 person-years
Mean follow-up per case	4.1 years	4.3 years	4.0 years
Range	0–8.8 years	0–8.6 years	0–8.1 years
Number (%) followed for 5 years or more	96 cases (39%)	97 cases (38%)	20 cases (35%)

Table 2. Reasons for suspecting a relapse in 40 patients

Reason for suspecting a relapse	Number of cases	Timing of suspicious events
Possible new lesions	6 (2MB, 4PB)	2–5 years after RFT
Bacteriological results	7 (6MB, 1PB)	Median 4 years
Late reactions/neuritis	27 (19MB, 8PB)	Variable
Total	40 (27MB, 13PB)	

on several occasions in this case, although the patient has continued to complain of the skin lesions, often insisting that they were new.

One of the MB cases with new lesions had a BI of 0 and was treated as a case of reversal reaction with good results. The other MB case had persisting fleshy nodules on the ear lobes with a slowly declining BI; the BI gradually settled to zero and a mouse foot-pad test (3 years after release from treatment) showed no growth.

The bacteriological suspects included one PB patient who had a nerve biopsy 10 months after release from treatment to define the nature of a reaction; one AFB was seen in the biopsy slide, but this was taken to be acceptable and the patient was not re-treated. Of the MB cases with suspicious bacteriological results, two were thought to be administrative errors as the BI rose from 0/1 to 4 and then returned to zero a few months later, remaining negative ever since; one of these had a mouse footpad assay done, which was negative. Three cases showed a slight rise in BI 4 years after release from treatment that was reversed in subsequent smears. One case remained with a persistently high BI (a reading at one site of at least 4) for 5 years and had recurrent neuritis and ENL; a mouse footpad assay was negative and smears became negative at 8 years, with no nerve function impairment at that time. The MI was never positive in any patient after release from treatment.

The 27 cases with late or prolonged leprosy reactions/neuritis were treated for their reactions and observed for any other signs of relapse; regular smears were done. No further signs of relapse were noted in any of them.

Discussion

The rate of confirmed relapses in the AMFES cohort is zero. While the number of patients lost to follow-up is significant (only 38% have completed 5 years surveillance), it is likely that any relapses in this group would have come to the attention of the staff involved in AMFES. Patients who move away from home often come to Addis Ababa and are likely to come to ALERT if they develop lesions suggesting a relapse. One patient was treated as a relapse at ALERT, contrary to the correct protocol, illustrating the fact that most such cases will attend ALERT eventually, occasionally denying their previous treatment. The very low turnover of staff involved in AMFES, makes it likely that patients will be recognized if they attend for re-treatment. However, it remains the cases that some relapses could have been missed by this study.

The appearance of new lesions in PB patients occurred most frequently 2 years after release from treatment and can be regarded as a manifestation of a reversal reaction. Most of the suspected MB relapses occurred at 4–5 years after release from treatment and were either reversal reactions (the appearance of new lesions) or unsubstantiated skin smear results.

PB relapses after MB leprosy have been reported,[9,10] but were not suspected in this cohort. MB relapses after PB leprosy are generally thought to be due to inadequate treatment because of misclassification at diagnosis;[4] although the definition of PB leprosy in this cohort is wide, classification was done with great care, so that all except three patients with positive smears got the MB regimen and there have been no suspected relapses in this category.

The major current concern is the possibility of relapse after 5 years in the group of patients with an initially high BI.[11–14] Many previous reports of low relapse rates in MB patients after MDT may be unreliable, as they included patients who had had many years of dapsone monotherapy and therefore had a low bacterial load at the start of MDT, or had MDT for more than 2 years, until smear negativity.[11]

In the AMFES study, 57 patients had an average BI of ≥4 at the start of MDT (four were true relapses after dapsone monotherapy) and were given fixed-duration treatment for 2 years. It has been suggested that in most programmes this will be a small group as compared with the overall leprosy burden,[2] but in this cohort it is 9% of the total case load, which is not insignificant. However, 20 patients in this group have been followed for more than 5 years, without a confirmed relapse, suggesting that the high relapse rates some years after fixed-duration MDT found in Mali[8] and elsewhere[12] may not be typical.

Reversal reactions and neuritis can occur at any time during the 5 years after release from treatment in PB patients, although they certainly become less common over that period, as shown in accompanying papers from AMFES. In such cases, management with steroids, especially if nerve function impairment is present is most important. The diagnosis of relapse is not urgent and can be made after a trial of steroids. Skin smears or a biopsy stained for AFB will indicate a multibacillary relapse.

In MB patients, reversal reactions and neuritis may also occur at any time in the 5 years after release from treatment. Suspected relapses require at least two skin smears to show a rise in BI of more than 1 log unit, or to show an MI of at least 2%. In many programmes, the number of skin smears being done is greatly reduced, either to zero or to one at diagnosis, for technical and logistic reasons. In such situations a smear taken some years after release from treatment will be difficult to interpret, as rates of decline in BI vary quite widely. Some indication of the viability of the organisms found on the smear would be valuable.

The MI has been used as a method of assessing the efficacy of treatment regimens in leprosy. There are other methods of assessing the viability of mycobacteria in the tissues that are more sensitive, but they are much less applicable in leprosy endemic areas.[15] In one study the MI was positive in 59/68 specimens with viable bacilli, giving a sensitivity of 87%, and was 100% specific, in that an MI of 1% or more always indicated viable organisms, although testing did not include the mouse footpad assay.[16] Previous studies have shown, however, that the measurement of the MI is difficult to standardize and unreliable under field conditions.[17,18] The MI could become a useful indicator of MB relapse in future, but a well-functioning reference laboratory would be the only appropriate place for this to be done. It is suggested that positive skin smears from suspected relapses should be sent to a reference laboratory for estimation of the MI.

If skin smears cannot be taken and read at all, the diagnosis of relapse will depend on the clinical findings alone. The clinical experience required to suspect and diagnose a relapse is, however, also disappearing. In testing a number of different regimens, the Marchoux Chemotherapy Study Group have seen many multibacillary relapses in which the new lesions are mainly nodules and lepromas.[19] In view of the high acceptability of MDT, it may be

appropriate to advocate a low threshold for the diagnosis of relapse, based on the definite appearance of new lesions, in particular those that are nodular in form.

Steroids have been widely used in this study after completion of MDT without relapse, indicating that cover with anti-leprosy drugs is not required in this situation.

In summary, while relapse must always be considered, the reappearance of skin lesions in leprosy patients in the 5 years after release from treatment is likely to be due to a reversal reaction and should be treated as such, especially if there is accompanying nerve involvement. Definitely new lesions, especially if nodular in form, are more likely to be due to a relapse.

Skin smears should be done if possible, and if positive, further steps should be taken to identify true multibacillary relapses:

1. Review any previous smear results.
2. Refer the smear for measurement of the MI, if possible.
3. Biopsy an active lesion, one section being stained for acid-fast bacilli.

After collecting this evidence and reviewing the results of anti-reaction treatment, an informed decision can be made as to the need for a further course of MDT.

While no definitive conclusion can be made about the sub-group of patients with a high initial BI, the AMFES results suggest that 2 years of WHO-MDT is a satisfactory treatment regimen. It is proposed to follow this sub-group for a further 5 years.

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The pattern of decline in bacillary index after 2 years of WHO recommended multiple drug therapy: the AMFES cohort

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Summary With effective antibiotic treatment, the bacillary index (BI) in multibacillary leprosy patients declines over a number of years. This can be quantified as a rate of decline in log-units per year or as the time until smear negativity is reached. In the AMFES cohort 220 cases had data on the changes in their BI over time, while 170 cases are documented until smear negativity. The average BI at the start was 3·3 (SD 1·5; range 0·3–5·5) and the mean rate of decline was 0·85 units per year (median 0·7 units per year); in the first 2 years after diagnosis, the mean rate of decline was 1·15 units per year. The rate of decline was not related to any clinical features of the disease except delay in diagnosis: patients presenting for treatment early had a significantly faster rate of clearing the bacilli (adjusted relative risk 2·3; 95% CI 1·0–5·1). Fifty-eight percent of cases took longer than 3 years to reach smear negativity, but this time interval is largely determined by the initial BI and classification, making it a less useful indicator of bacterial clearance. More severe impairment at the start of treatment was associated with a faster return to smear negativity, for which no obvious explanation can be given. Reversal reactions, which occurred in 25% of the cases reviewed, are not associated with a more rapid clearance of bacilli.

Introduction

Multiple drug therapy (MDT) has been a very successful development in the treatment of leprosy, with rapid killing of the bacilli. After 2 years of treatment with the multibacillary regimen, relapses are as low as 0·77%.[1] This has given WHO the grounds to reduce the recommended length of treatment from 24 to 12 months,[2] although the wisdom of this change is questioned by some.[3–5]

One component of the evaluation of treatment regimens for leprosy is the examination of

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serial slit skin smears and the recording of changes in the bacillary index (BI), commonly reported as the average rate of decline in log-units per year,[6,7] or as the number of years taken to reach smear negativity.[8,9]

Reported average rates of decrease in BI range from 0·57 to 1·01 log-units/year,[6,7] but factors associated with different rates of decline have not been elucidated. One study in Paris used the time to smear negativity to examine possible risk factors affecting the removal of bacilli. The study was largely concerned with treatment results and the information regarding decline in BI is not given in detail. Forty-four MB cases (26 BB/BL and 18 LL cases) were followed, of whom 19 (43%) had reversal reactions and 18 (41%) had ENL reactions. The time to smear negativity was not significantly different for relapse cases (12) and previously untreated cases (32). The time to negativity was, however, said to be significantly shorter in those with a lower BI at the start ($P < 001$) and in those who had reversal reactions ($P < 0·001$). It was longer in those who had ENL reactions ($P < 0·01$). No multivariate analysis was done.[9]

The AMFES cohort is a large group of Ethiopian patients followed prospectively for up to 10 years, which has allowed the pattern of decline in BI to be closely examined and possible risk factors to be searched for. Such risk factors include the clinical features of the disease at diagnosis, factors that may modify the body's response to the disease and the variations in the clinical course of the disease after diagnosis.

Classification is associated with many of the initial clinical features of the disease, including the BI and number of skin lesions. Reversal reactions may occur before or after diagnosis and may be associated with nerve damage; they are caused by an upgrading of the cell-mediated immune response to leprosy bacilli in the tissues and could therefore be associated with an increased rate of clearance of bacilli. Impairment is assumed to be the result of excessive immunological activity focused on bacilli in and around the nerves, so may be expected to be associated with increased clearance of bacilli. A delay between the onset of symptoms and diagnosis is known to be associated with greater impairment at diagnosis[10] and could therefore be associated with increased clearance of bacteria. On the other hand, the down-grading of the immune response that occurs in the absence of treatment could lead to slower clearance of bacilli in those with a greater delay in starting treatment.

Materials and methods

In all, 660 patients were enrolled in the ALERT MDT Field Evaluation Study (AMFES) between March 1988 and March 1993. Ten patients were excluded, either because the diagnosis was changed or the enrolment procedures were incorrectly followed. A further 56 patients who had relapsed after dapsone monotherapy are not included in this review. Of 594 new cases, 300 were multibacillary cases and 220 of these cases, who have a series of at least three smears, are reviewed. The pattern of decline in BI is related to the clinical features and progress of each case. As only three BT cases are included in the study, they are grouped with the BL cases for analysis.

During and after MDT treatment, skin smears were taken every 6 months. Smears were taken from four sites—the two ear lobes, an elbow and a knee or from an active lesion, according to the protocol then in operation at ALERT. Smears were collected and transported for reading at the ALERT hospital by experienced laboratory technicians. The laboratory has a regular quality control service both for the technicians and the field

workers. In addition to basic patient characteristics (age, sex), the progress of their disease was characterized (Ridley–Jopling class, eye-hand-foot (EHF) impairment scores at different stages, delay on initial diagnosis, reactions and steroid therapy). Reversal reactions were defined as the occurrence of signs of inflammation in known leprosy skin lesions, while ENL reactions were defined as the presence of typical ENL skin lesions, away from the known leprosy skin lesions.

In addition, HIV testing was carried out on all but 14 of the 220 patients. HIV testing used a combination of two different ELISA systems and a rapid assay. Samples were first tested using Vironistika ELISA kit (Organon Teknika, Boxtel, Holland) and reactive samples were re-tested by Wellcozyme ELISA kit (Murex Diagnostics, Dartford, UK). A third, rapid test (HIV-SPOT, Genelabs Diagnostics, Singapore) was used for those sera which gave discrepant results in the first two ELISAs. All tests are sensitive for HIV-1 and HIV-2.

Data were managed using dBase and Epi-Info, whilst Egret was used for multivariate regression analysis.

Results

A total of 220 cases with an initial positive skin smear and more than one follow-up smear were included, and the rates of decline of the BI in units per year were calculated. The average BI at the start was 3·3 (SD 1·5; range 0·3–5·5). The mean rate of decline was 0·85 units per year, with a median of 0·7 units per year. In the first 2 years after diagnosis, looked at separately, the mean rate of decline was 1·15 units per year.

The patients were divided into two groups, those whose BI declined quickly at over 1 unit per year ($n = 62$) and those whose BI declined slowly at less than 1 unit per year ($n = 158$). Table 1 shows the factors associated with a slow decline in BI. Delayed diagnosis and a higher impairment score at the end of treatment were significantly associated with a slow decline in BI on a univariate basis, with only the former emerging as a significant factor on a multivariate basis. Since it could be argued that this might simply reflect a fast pre-diagnostic decline, the multivariate regression was repeated without this factor; this did not significantly change the other factors. The use of steroids is employed here as a marker for new episodes of neuritis, which together with reversal reactions and ENL reactions, may reflect increased immunological activity, but there is no evidence here to suggest that this promotes the clearance of bacilli from the body.

An alternative way to look at the decline in BI is to examine the time until the smears became negative. A total of 172 cases have smear results until negativity. Of these, 100 took longer than 3 years and 72 took less than 3 years to become negative. Table 2 examines the factors associated with a slow return to negativity. Three factors emerge as significant both in univariate and multivariate analyses: LL patients, a high initial BI and less impairment at diagnosis.

Discussion

The rate of decline of the BI in multibacillary leprosy patients treated with MDT is similar in most reported series and the rate found in this cohort is in the centre of the reported range of 0·57–1·01 log-units per year.

Table 1. Univariate and multiple logistic regression analysis of risk factors associated with a slow decline in BI in 220 Ethiopian leprosy patients

Risk factor	Category	Number of cases	Univariate relative risk	95% CI	Adjusted relative risk	95% CI
Age group	<20	58	1·0	–	1·0	–
	20–49	128	1·4	0·71–2·8	1·3	0·61–2·8
	50+	34	1·2	0·47–2·9	1·4	0·44–4·1
Sex	Male	148	1·0	–	1·0	–
	Female	72	1·6	0·82–3·0	1·6	0·76–3·2
RJ class	BL	151	1·0	–	1·0	–
	LL	69	0·85	0·46–1·6	0·90	0·39–2·1
Initial BI	<4	63	1·0	–	1·0	–
	4, 5 or 6	157	0·61	0·34–1·1	0·80	0·36–1·8
Delay before diagnosis	up to 2 years	144	1·0	–	1·0	–
	3 or more years	76	2·5**	1·3–5·0	2·3**	1·0–5·1
EHF at diagnosis	<3	160	1·0	–	1·0	–
	3 or more	60	1·6	0·8–3·2	0·71	0·26–1·9
EHF at RFT	<3	175	1·0	–	1·0	–
	3 or more	45	2·5**	1·0-5·9	2·0	0·65–6·3
HIV*	−ve	198	1·0	–	1·0	–
	+ve	8	0·63	0·14–2·7	0·57	0·12–2·8
Steroids ever used	No	123	1·0	–	1·0	–
	Yes	97	1·2	0·68–2·2	1·4	0·56–3·3
Reversal reaction(s)	No	164	1·0	–	1·0	–
	Yes	56	1·4	0·70–2·9	1·1	0·37–3·0
ENL reaction(s)	No	204	1·0	–	1·0	–
	Yes	16	0·36	0·13–1·0	0·39	0·11–1·4

*14/220 patients not tested.
**Significantly different at $P < 0·05$ level.

Our results show that the rate of decline in BI is independent of most observable clinical features. The rate of decline in log-units per year is not influenced by the initial BI. Early presentation and start of treatment (a delay of less than 3 years) were associated with a faster rate of decline in BI. The rate of decline in the first 2 years after diagnosis is higher than the overall rate, suggesting that the decline follows an exponential curve. It is therefore possible that some patients who present at a late stage in their disease have already passed through a period of rapid decline in BI and that the observed slower rate after diagnosis reflects their position on the flatter part of the curve. A possibly increased rate of clearance in those with less disability, especially at RFT (an EHF score of less than 3), is not confirmed by the multivariate analysis.

If the decline in BI is characterized as the time to smear negativity, Table 2 shows that the classification and the initial BI are very important confounding factors. These two factors themselves are of course closely related to each other. It is clear that for the same rate of clearance in terms of log-units per year, patients with a higher initial BI will take longer to reach negativity. This is the likely explanation for the previously quoted findings that BL

Table 2. Univariate and multiple logistic regression analysis of risk factors associated with a slow return to smear negativity in 170 Ethiopian leprosy patients

Risk factor	Category	Number of cases	Univariate relative risk	95% CI	Adjusted relative risk	95% CI
Age group	<20	49	1·0	–	1·0	–
	20-49	99	1·2	0·62–2·5	2·7	0·94–7·6
	50+	22	0·52	0·19–1·4	0·88	0·18–4·3
Sex	Male	112	1·0	–	1·0	–
	Female	58	0·68	0·36–1·3	0·78	0·32–1·9
RJ class	BL	130	1·0	–	1·0	–
	LL	40	22**	5·1–94	5·9**	1·0–33
Initial BI	<4	68	1·0	–	1·0	–
	4, 5 or 6	102	17**	6·1–44	9·3**	2·7–32
Delay before diagnosis	Up to 2 years	115	1·0	-	1·0	–
	3 or more years	55	1·0	0·53–1·9	2·4	0·81–7·1
EHF at diagnosis	<3	120	1·0	–	1·0	–
	3 or more	50	0·29**	0·15–0·58	0·14**	0·03–0·64
EHF at RFT	<3	127	1·0	–	1·0	–
	3 or more	42	0·50	0·25–1·0	2·3	0·52–9·7
HIV*	−ve	155	1·0	–	1·0	–
	+ve	5	0·16	0·01–1·5	0·11	0·07–1·5
Steroids ever used	No	86	1·0	–	1·0	–
	Yes	84	0·63	0·34–1·2	0·56	0·17–1·8
Reversal reaction(s)	No	117	1·0	–	1·0	–
	Yes	53	0·53	0·27–1·0	0·84	0·24–3·0
ENL reaction(s)	No	159	1·0	–	1·0	–
	Yes	11	8·0	1·0–64	5·3	0·38–75

*11/170 patients not tested.
**Significantly different at $P < 0·05$ level.

patients and those with reversal reactions reach smear negativity more quickly, while LL patients and those with ENL reactions do so more slowly. In the univariate analysis, the effect of reversal reactions in speeding clearance, and the effect of ENL in retarding clearance, just reach statistical significance, but these findings do not persist in the multivariate analysis, suggesting that they may be largely explained by the classification and initial BI. More severe impairment at the start of treatment was significantly related to a faster return to negativity and the multivariate analysis shows that this cannot be fully explained by the classification and initial BI.

In conclusion, it is suggested that the rate of decline in BI in log-units per year is a more appropriate method of assessing the removal of bacilli than the time to smear negativity, which is largely a reflection of the classification and initial BI. Our results show that a delay of less than 3 years between initial symptoms of leprosy and the start of treatment leads to significantly faster clearance of bacilli from the body. The relationship between impairment and the clearance of bacilli is obscure, although there is clearly no association between the occurrence of reversal reactions and the decline in BI.

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Lepr Rev (2000) **71,** 338–343

The effect of HIV status on the clinical picture of leprosy: a prospective study in Ethiopia

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Summary No major interaction between HIV infection and leprosy has been documented. The ALERT MDT Field Evaluation Study (AMFES) has allowed the examination of possible interactions in a prospective manner, although the total number of HIV-positive individuals was not high at 22 (3·8%) of 581 patients tested. There was an excess number of deaths in the HIV-positive group: 27% compared with 5·7% in the HIV-negative group, although the causes of death were not recorded (relative risk 4·8; 95% CI 2·2–10·2). HIV-positive individuals had a higher risk of ENL reactions (relative risk 5·2; 95% CI 1·7–15·9). Reversal reactions and neuritis (both acute and chronic) were not significantly influenced by HIV status, although there was a possible increase in recurrent reversal reactions in HIV-positive cases (relative risk 2·2; 95% CI 0·98–4·7). There was no evidence to suggest an increased risk of developing leprosy or of developing multibacillary rather than paucibacillary disease. There was no association between HIV positivity and the development of impairment.

Introduction

Infection with the human immunodeficiency virus (HIV) has had a major effect on many infectious diseases, notably tuberculosis (TB) and other mycobacterial diseases. Because of this, epidemiologists and clinicians have been expecting to see changes in the presentation and clinical course of leprosy. In general, no major interaction has been documented.[1–3]

Because the cellular immune response of a patient determines the type of leprosy that will develop, it was also expected that the lepromatous form of the disease may predominate in

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HIV-positive individuals.[4] Some reports from East Africa suggest a weak association between HIV positivity and multibacillary (MB) leprosy,[5,6] while another, from Tanzania, suggests an association between HIV positivity and leprosy (odds ratio 2·5; 95% CI 2·0–3·2), but no association with classification.[7] Studies in Malawi,[8] South India[9] and Brazil[10] found no association between HIV infection and leprosy, although the overall prevalence of HIV infection was very low in the Indian study.

Various authors have examined HIV positivity as a risk factor for the complications of leprosy. A study in Uganda found that type 1 reactions with neuritis were more common in MB patients who were HIV positive, although the study only included 12 HIV-positive and 40 HIV-negative MB cases.[11] Generally the response to both anti-leprosy and anti-reaction treatment has been found to be satisfactory,[11,12] although a study in Zambia of eight HIV-positive and 34 HIV-negative patients with leprosy found that neuritis was equally common in both groups, but that the outcome of treatment with steroids was poorer in the HIV-positive group.[13]

Erythema nodosum leprosum (ENL) reactions were not reported in HIV-positive individuals until recently and it has been suggested that HIV infection may decrease the risk of this complication.[14] Case reports of ENL in HIV-positive patients have, however, started to appear.[15,16]

Not surprisingly, HIV infection is associated with an increased death rate amongst leprosy patients.[17]

A long-term prospective study of leprosy in Ethiopia, designed to look at relapses and leprosy reactions, has given an opportunity to study possible interactions with HIV infection.

Materials and methods

The ALERT MDT Field Evaluation Study (AMFES) recruited 660 patients between 1988 and 1993. There were 10 exclusions due to incorrect diagnosis or incorrect enrolment procedures. Of the 650 patients included, 56 were relapse cases after dapsone monotherapy and 594 were new cases. All were treated with fixed-duration multiple drug therapy (MDT), as recommended by WHO. The research protocol involved taking a serum sample from each patient every year, although for logistic reasons fewer samples were in fact taken. Patients who died were not seen by the leprosy control staff at the time of death and as no procedure for registering deaths exists in the area where the study was carried out, the causes of death are not known.

In all, 581 (89%) patients had their HIV status determined. HIV testing was performed according to a previously evaluated and recommended testing algorithm, [18,19] which is based on the use of a combination of two different ELISA systems and a rapid assay. Samples were first tested using the Vironistika ELISA kit (Organon Teknika, Boxtel, Holland) and reactive samples were re-tested by Wellcozyme ELISA kit (Murex Diagnostics, Dartford, UK). A third assay which is a rapid test (HIV-SPOT, Genelabs Diagnostics, Singapore) was used for those sera which gave discrepant results in the first two ELISAs. All tests are sensitive for HIV-1 and HIV-2. The testing was done in early 1996, using the most recent serum sample from each patient. Two hundred and thirty-nine (41%) of the samples dated from 1988–1991, while 342 (59%) dated from 1992–1995. For those patients found to be positive, an attempt was made to test previous samples, to indicate, if possible, when they became HIV-positive.

Patients were reviewed regularly during MDT and 6-monthly thereafter. The skin lesions were examined for signs of reactions and nerve function was tested according to a routine protocol, using voluntary muscle testing (VMT) and sensory testing (ST) with a 10 g nylon monofilament, at 10 points on each hand and foot. The results were recorded and the WHO Impairment Grade (range 0–2) was noted for each eye, hand and foot. The EHF score (or Eye-Hand-Foot score), which is a summation of the six WHO Impairment Grades (and therefore has a range of 0–12),[20] can be calculated from the record of any review. Reversal reactions were defined as the occurrence of signs of inflammation in known leprosy skin lesions, while ENL reactions were defined as the presence of typical ENL skin lesions, away from the known leprosy skin lesions.

Neuritis was defined as the presence of new loss of function in a particular nerve, detected by VMT and ST examinations, or the presence of pain or tenderness in the nerve. The recent loss of one point on a three-point VMT scale or more than one point of sensory loss was taken as indicating active neuritis. Neuritis was said to be chronic if it recurred within 3 months of stopping steroids, or if the standard course of steroids had to be prolonged because of continuing signs and symptoms. Neuritis recurring after a gap of at least 3 months, during which the patient had no symptoms of neuritis and was not being treated with any anti-reaction medication, was termed recurrent neuritis.

Data analysis was carried out using EpiInfo v6.

Results

Twenty-two (3·8%) of the 581 patients were HIV positive, including nine (3·6%) of 253 paucibacillary (PB) cases and 13 (4·0%) of 328 MB cases. Six (27%) are known to have died, compared with 32 (5·7%) HIV negative patients: relative risk = 4·8 (95% CI 2·2–10·2). Female patients were more likely to be HIV positive than males: relative risk = 1·9 (95% CI 1·3–2·6). Although there are no matched control data, the Ministry of Health estimated the prevalence of HIV infection in Ethiopian adults to have been 3·2% in 1993.[21]

Ten of the 22 HIV-positive cases had previous samples that were tested. In two, the previous samples were also positive, but in eight cases the previous samples were negative, indicating seroconversion after diagnosis, during the period 1989–1994.

Table 1 shows the effect of HIV infection as a risk factor for various complications of leprosy. HIV infection was not associated with the development of reversal reactions as such, either for all patients or for MB and PB patients separately. There was, however, a possible association between being HIV positive and having more than one episode of reversal reaction (relative risk: 2·2; 95% CI: 0·98–4·7). Four of the five HIV-positive patients who had RR, including all three with recurrent reactions, subsequently died, suggesting that they may have been in an immunocompromised state during this period.

The 277 patients with one or more episodes of active neuritis can also be divided into those with only one episode (144 cases) and those with recurrent or chronic neuritis (133 cases). HIV status was not a significant risk factor for either of these patterns of neuritis.

Being HIV positive was significantly associated with the development ENL reactions, despite the small numbers involved (relative risk: 5·2; 95% CI: 1·7–15·9). All three HIV-positive patients with ENL had minimal neuritis, with most recent EHF scores of 0.

There was no association between HIV positivity and impairment at any stage of the disease: relative risk for an EHF score of more than 2 at diagnosis is 0·6 (95% CI: 0·2–1·7), at

Table 1. Characteristics of HIV-positive and HIV-negative individuals ($n = 581$)

Characteristic	Result Yes	HIV-positive cases	HIV-negative cases	Relative risk (95% CI)
RJ classification	TT	0	6	Relative risk for
	BT	11	248	being lepromatous:
	BL	7	216	
	LL	3	87	0·84
	NL	1	2	(0·5–1·3)
WHO classification	MB	13	315	1·05 (0·7–1·5)
	PB	9	244	–
Lepromin test ($n = 223$)	Neg	6	130	0·9 (0·5–1·5)
	Pos	5	82	–
Reversal reaction (RR)	Yes	5	93	1·4 (0·6–3·0)
	No	17	466	–
Recurrent reversal reaction	Yes	3	26	2·2 (0·98–4·7)
amongst 98 cases of RR	No	2	67	–
ENL reaction (MB cases only)	Yes	3	14	5·2 (1·7–15·9)
	No	10	301	–
Neuritis – all types	Yes	11	266	1·1 (0·7–1·6)
	No	11	293	–
Chronic or recurrent neuritis	Yes	5	128	0·9 (0·28–2·9)
amongst 277 neuritis cases	No	6	138	–

release from treatment (RFT), 1·1 (95% CI: 0·4–3·2) and at 5 years after RFT, 1·4 (95% CI: 0·3–5·8).

Discussion

This study was not designed to investigate risk factors for the development of leprosy, so does not contribute greatly to the debate as to whether HIV-positive individuals are at greater risk of developing the disease. The prevalence of HIV infection in Ethiopia is much greater in urban areas than in rural areas, so any prevalence figures are very dependent on the mix of the sample population. The AMFES cohort includes patients from both urban and rural areas, but with urban dwellers over-represented as compared with the total population of the country. The fact that eight of the 22 HIV-positive individuals became positive after leprosy was diagnosed, adds to the conclusion that there is very little evidence from this study to suggest that HIV-positive individuals are more likely than others to be diagnosed as having leprosy.

The results suggest that HIV positivity is associated with ENL reactions, and possibly recurrent reversal reactions. Only one of the four patients with chronic ENL lasting more than 2 years was HIV positive, however, so HIV status is not a sensitive predictor of who will develop this complication. Neuritis does not seem to be more severe, or different in character, in HIV-positive cases and there is no association between HIV positivity and increased impairment at the start of treatment, at RFT or at 5 years after RFT.

Most episodes of neuritis are thought to be, like reversal reactions, the result of cell-mediated, delayed type hypersensitivity, so may be expected to be reduced in HIV-positive individuals. However, it is known that the local cellular accumulation and differentiation in HIV-1-infected BT patients in response to infection with *M. leprae* are not impaired, as

compared with HIV-negative individuals.[4] ENL reactions, on the other hand, are thought to be due to circulating immune complexes and why these should be more prevalent in HIV-positive cases remains unclear. It is interesting to note that the dramatic increase in cutaneous disease and adverse drug reactions reported in HIV-positive individuals, for example, in patients with tuberculosis who react to the drug thiacetazone, is similarly unexplained, but presumed to be immunologically mediated.[22,23] These complications also show a worsening as immune function deteriorates.[24] It is known that, while CD4 lymphocytes are depleted as HIV disease progresses, cytotoxic CD8 cells are significantly increased in number,[25] including various specific subgroups currently being investigated.[26,27] Findings such as these may eventually help to explain some of this paradoxical over-expression of some types of immunological activity.

The findings suggest that HIV positivity is not a useful predictor of who will develop leprosy complications, but the increasing prevalence of HIV infection means that more people affected by leprosy may develop these late complications, which require time and skill to manage effectively. This is a further indication of the need to maintain expertise in the management of leprosy and its complications where it continues to exist, even if the prevalence is low. This study suggests that the response to treatment of leprosy and its complications is not impaired by HIV infection.

In summary, this study supports the conclusion that there is no major interaction between HIV infection and leprosy, although some of the known, immunologically mediated complications of leprosy may be more evident in HIV-positive individuals.

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Lepr Rev (2000) **71,** 344–354

The hand–foot impairment score as a tool for evaluating prevention of disability activities in leprosy: an exploration in patients treated with corticosteroids

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Summary The hand–foot (HF) impairment score in leprosy patients is the sum of the WHO disability grades for hands and feet. This retrospective study explored the possibility of using the HF score for evaluation of the effectiveness of corticosteroid treatment programmes for nerve function impairment (NFI). Changes in the score were compared with changes in sensory testing (ST) and voluntary muscle testing (VMT) for 42 leprosy patients who received corticosteroid treatment. The WHO grade did not change in 30/60 (50%) of extremities gaining, and in 4/10 (40%) extremities losing sensation and/or muscle strength. However, 18/24 (75%) patients with a definite gain in function improved in HF score, while the HF score remained unchanged in 10/11 (91%) patients with no change in nerve function. Five patients with impairment in multiple extremities showed both gain and loss of sensation and/or muscle strength in the same or different extremities. Overall, improvement, deterioration and absence of change in NFI, as indicated by changes in ST and VMT were reflected correctly by the HF score in 28 (76%) of the remaining 37 patients. It was also shown that the HF score does not give appropriate information on the extent of the effect of corticosteroid treatment. This study illustrates that the HF score can not be used to support management of corticosteroid treatment of individual patients, but indicates this score to be a promising device for the evaluation of the effectiveness of corticosteroid treatment programmes. This study used the HF score because information on (changes in) eye impairment was not considered reliable. However, in principle, we consider the EHF score, which is the sum of the WHO disability grades for hands, feet and eyes, preferable for evaluation purposes. We strongly recommend further validation of the EHF score as a tool for evaluation of corticosteroid treatment programmes for patient groups with different distributions of NFI through prospective studies.

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Introduction

In view of the forecast elimination of leprosy as a public health problem, changes in leprosy control programmes are inevitable. The diminishing number of patients on multidrug treatment (MDT) in particular leads to more emphasis on the prevention of impairments and disabilities (POID). POID projects have now been implemented in many leprosy control programmes.

One important activity to prevent development of disabilities is to treat patients who suffer from recent nerve function impairment (NFI) with corticosteroids. Registration of nerve function assessments is required in individual patients treated this way. Ideally, POID programmes provide patient cards which include information on these assessments. The interpretation of subsequent assessments is often complicated because several nerves and many testing sites are involved. Adequate methods for interpreting nerve function assessments could lead to better management of individual patients treated with corticosteroids.

In addition, there is a need to evaluate the effectiveness of POID activities, such as treatment with corticosteroids, at programme level. This calls for methods of scoring impairment and disability that are sufficiently accurate to determine the relevant changes induced by POID activities for the related groups of patients. A further requirement is that it should be feasible to collect and process the field data from which the scores are to be derived. Evaluation at programme level poses less strict demands on the sensitivity of scoring methods than are required for individual patient management.

In the field, the standard method of detecting recent NFI is to carry out sensory testing (ST) and voluntary muscle testing (VMT) on a regular basis. The decision of the health worker to treat the patient with corticosteroids is based on the patient's history as determined at intake, and on initial ST and VMT results and subsequent changes. One method used to track changes in sensation and muscle strength between start and end of multidrug treatment for groups of patients is to combine point-wise data on ST and VMT results for individual nerves.[1,2] However, it is not considered feasible to computerize data on ST and VMT for all points and nerves tested on a routine basis in a field programme.

At present, the main indicator used to assess impairments and disabilities is the WHO disability grading system. This score has three possible outcomes (0, 1 and 2) that are determined by different types of information: sensory testing results and the presence of visible deformity or damage. Eyes, hands and feet of the patient are given a score, and the part of the body with most damage determines the overall score of the patient.[3] This 'maximum WHO disability grade' is at present primarily used for statistical purposes to compare the impairment and disability status of newly detected patients across countries.[4] It is, however, questionable whether the crude WHO disability grading system is an appropriate tool to evaluate the effectiveness of POID activities.

In 1994, de Rijk *et al.*[5] introduced two scores which are related to the WHO disability grading system: the hand–foot score (HF) score and the eye–hand–foot (EHF) score. These scores describe the severity of the patient's disability in more detail, because they are the summation of the WHO disability grades for the extremities (HF score: maximum value 8) and for the extremities and eyes (EHF score: maximum value 12). The HF score can be used instead of the EHF score when the reliability of data on eye impairment is limited.

Validation of impairment and disability scoring methods is necessary for sensible application in leprosy control. This paper explores the validity of the WHO disability grading system and the HF score in the context of one specific POID activity: corticosteroid

Table 1. WHO disability grades for hands and feet as defined in 1988 by the WHO Expert Committee on Leprosy

Grade	Condition of the hand or foot
0	No anaesthesia, no visible deformity or damage due to leprosy
1	Anaesthesia present, no visible deformity or damage due to leprosy
2	Visible deformity or damage present due to leprosy

treatment. Two issues are addressed, namely their potential (1) to assess impairment changes relevant to the individual patient in order to support patient management, and (2) to serve as tools for evaluation of the effectiveness of treatment with corticosteroids as a programme activity. This is done by investigating how well changes in the WHO disability grades for extremities, the maximum WHO disability grade and the HF score relate to changes in ST and VMT results in extremities and patients before and after corticosteroid treatment.

Materials and methods

This study was conducted at the All African Leprosy, Tuberculosis and Rehabilitation Training Centre (ALERT) in Addis Ababa, Ethiopia. Included in this study are a selection of patients who were treated with corticosteroids in the past 8 years because of recent or threatening NFI. The study reports retrospectively on the findings of nerve function assessments in these patients as performed in ALERT's field programme. This group of patients was not part of the ALERT MDT Field Evaluation Study (AMFES), although they were managed in the same programme and according to the same guidelines as patients in that study. These patients were selected on the basis of having had a course of steroids in the previous three years and their prior history of nerve damage was variable.

ALERT field workers carry out ST and VMT on a regular basis for each patient in order to detect NFI. Sensory testing is conducted by applying a 10 g filament to 10 points on the palm and fingers of the hand, and to 10 points on the sole and toes of the foot. Points for which the 10 g filament is not felt are marked on the patient card. For this study, the possible ST outcomes 'felt' and 'not felt' were assigned 0 and 1 point, respectively. Voluntary muscle testing is done for eight nerves: left and right facial nerves, left and right ulnar nerves, left and right median nerves and left and right peroneal nerves. The results of these tests are documented as 'strong', 'weak' or 'paralysed' on the ALERT field programme patient card.

ST and VMT are also conducted at the start and end of treatment with corticosteroids. On both occasions, the patients' ST results (40 points) and VMT results (eight nerves) are recorded on the ALERT prednisolone treatment and release form. WHO disability grades for the extremities and eyes at the start and end of treatment are also specified on this form. At the time of this study, the 1988 WHO disability grading system was used (see Table 1). This paper analyses to what extent changes in ST and VMT results are reflected in changes in WHO disability grades for individual extremities (extremity level), and to what extent overall changes in ST and VMT results for patients are reflected in changes in the maximum WHO disability grade and HF score (patient level). Reporting on impairment changes of eyes was not considered reliable enough for this study. Eye impairments are therefore excluded from

the present analysis and disability grades for the eyes were not considered in the calculation of the maximum WHO disability grades. Similarly, the HF score was used instead of the EHF score.

In order to investigate to what extent changes in ST and VMT results are reflected in changes in WHO disability grades at extremity level, changes in ST and VMT of the extremities were categorized as follows:

- 'Full recovery': an improvement in ST of 2 points or more and/or an improvement in VMT, with complete absence of NFI at the end of treatment.
- 'Recovery': an improvement in ST of 2 points or more, without sensory loss at the end of treatment, but with some remaining loss of muscle strength, or *vice versa* (an improvement in VMT with normal muscle strength at the end of treatment, but with some remaining sensory loss).
- 'Improvement': an improvement in ST of 2 points or more and/or an improvement in VMT, in hands, for either the ulnar or median nerve or both, with some NFI remaining at the end of treatment.
- 'No change': no change in ST and VMT, or an improvement or deterioration in ST of 1 point and no change in VMT.
- 'Deterioration': deterioration in ST of 2 points or more and/or deterioration in VMT.
- 'Both': improvement in ST of 2 points or more and deterioration in VMT, or *vice versa.*

In this definition, 'recovery' in a hand through regained motor function implies that the VMT result is 'strong' for both the median and the ulnar nerve. Improvement (and the converse, deterioration) in ST by 2 points or more is defined so as not to occur together with deterioration (and the converse, improvement) in the categories 'full recovery', 'recovery', 'improvement' and 'deterioration'.

In order to investigate to what extent overall ST and VMT changes in patients are reflected in changes in the maximum WHO disability grades and HF scores, changes in ST and VMT have also been categorized at patient level. This was, on the basis of the categorization for extremities, done as follows:

- 'Full recovery': full recovery of both sensation and muscle strength in at least one extremity, without 'deterioration' in other extremities.
- 'Recovery': full recovery of sensation or full recovery of muscle strength in at least one extremity, without 'deterioration' in that and other extremities, but with (some) remaining NFI in that extremity at the end of treatment.
- 'Improvement': improvement in sensation and/or muscle strength in at least one extremity, without 'deterioration' in that and other extremities, also with (some) NFI remaining in that extremity at the end of treatment.
- 'No change': no change in any extremity.
- 'Deterioration': deterioration in sensation and/or muscle strength in at least one extremity, without improvement in that and other extremities.
- 'Both': improvement or full recovery in at least one extremity and deterioration in the same or another extremity.

For example, a patient with an improvement in sensation in the right hand and a recovery of muscle strength, with no change in the left hand, and with improvements in sensation of the feet is recorded as a 'recovery'.

Table 2. Distribution of the maximum WHO disability grade and HF score among the 42 study patients at the start of treatment with corticosteroids

Maximum WHO grade	Number	Percentage
0	4	10%
2	14	33%
Total	42	100%

HF score	Number	Percentage
0	4	10%
1	2	5%
2	11	26%
3	7	17%
4	13	31%
5	1	2%
6	3	7%
7	0	0%
8	1	2%
Total	42	100%

Results

A total of 42 patients were included in this analysis. Thirty-three (78·6%) of the patients were classified as multibacillary (MB) and nine (21·4%) as paucibacillary (PB). The mean age was 33·4 years (range 16–56). The patients suffered from different types of reactions requiring different steroid regimes. The time between the assessment at the start of the treatment and the assessment at the time that it was decided to stop treatment varied considerably: from less than 3 months (four patients) to more than 1 year (again four patients). At the start of the corticosteroid treatment, three out of the 42 (7%) study patients had no extremity affected with NFI as diagnosed through ST and VMT. Again 3/42 (7%) had one extremity affected, 11/42 (26%) had two, 11/42 (26%) had three and 14/42 (33%) had four. NFI was present in 114 out of the 168 (4×42, 68%) involved. The distributions of the maximum WHO disability grade and the HF score of the patients at the start of treatment are shown in Table 2.

CHANGES IN EXTREMITIES

Table 3 shows the changes in ST and VMT in the 168 extremities of the 42 patients, and the relation between those changes. Out of the 114 extremities with NFI at the start of corticosteroid treatment, 60 ($53 + 7 = 60$, 53%, see Table 3) had partial or complete return of nerve function. Improvement of sensation only, was observed in 36 (60%) of these 60 extremities. This figure is 7/60 (12%) for partial or complete return of motor function only. One extremity lost sensation and gained motor function.

Table 4 compares the changes in ST and VMT with the changes in the WHO grade for the individual extremities. 21/23 improvements in extremities are not rewarded with a change in WHO disability grades. Also, 7/12 extremities with a recovery, and 2/25 extremities with a

Table 3. Changes in ST and VMT between start and end of corticosteroid treatment in individual extremities*

Change in VMT	Change in ST Improvement or recovery	No change	Deterioration	Total
Improvement or recovery	17	7	0	24
No change	36	98	10	144
Deterioration	0	0	0	0
Total	53	105	10	168

* At the start of corticosteroid treatment, 59/105 extremities with no change in ST had full sensation, 123/144 extremities with no change in VMT had normal muscle strength, and 48/98 extremities with neither a change in ST nor in VMT had both full sensation and normal muscle strength.

full recovery do not improve in WHO grade. This implies that 50% (30/60) of the improvements, recoveries and full recoveries in extremities are not reflected in an improvement in the WHO grading system. Out of these 30 extremities, 27 were not free from sensory loss at the end of corticosteroid treatment. Sensation returned in 3·4 points on average (range: 1 point deterioration to 7 points improvement) with 24 extremities at least showing improvement. On further analysis of these 30 extremities, recovery in motor function was seen in eight of the 17 extremities with initial loss of motor function. The WHO grading system also did not pick up 4/10 (40%) deteriorating extremities. In all, 90/98 (92%) of the extremities with no relevant change (1 point ST or less and no change in VMT) in nerve function showed no change in WHO grade.

The WHO grade improved in 30/60 (50%) of the extremities with some gain in nerve function. This was seen in 2/23 (9%) extremities with improvement, 5/12 (42%) extremities with a recovery, and in 23/25 (92%) extremities with a full recovery. Twenty-eight of these 30 extremities recovered from sensory loss, one remained with sensory loss (the WHO grade changed from 2 to 1), and the average number of points gaining back sensation was 5·5 points (range of improvement: 0–10 points). The motor function recovered in six out of the 11 extremities with initial loss of motor function amongst these 30. In only two of these 30 extremities did the WHO grade improve from 2 to 0. The WHO grade deteriorated by 1 point in 6/10 (60%) extremities that deteriorated.

Table 4. Comparison of changes in ST and VMT and changes in WHO disability grades between start and end of corticosteroid treatment for the individual extremities*

Change in WHO grade	Full recovery	Recovery	Change in nerve functioning Improvement	No change	Deterioration	Total
−1	0	0	0	3	6	9
0	2	7	21	90	4	124
1	23	4	1	4	0	32
2	0	1	1	1	0	3
Total*	25	12	23	98	10	168

* No extremities showed improvement in ST and deterioration in VMT or *vice versa* (category 'Both') . At the start of corticosteroid treatment, 48/98 extremities with neither a change in ST nor in VMT had both full sensation and normal muscle strength, and 55/124 extremities with no change in WHO grade had grade 0.

Table 5. Comparison of overall changes in nerve functioning and changes in maximum WHO disability grade between start and end of corticosteroid treatment for the study patients.

Change in maximum WHO grade	Overall change in nerve functioning						
	Full recovery	Recovery	Improvement	No change	Deterioration	Both	Total
−1	1	0	0	1	0	0	2
0	11	4	3	10	2	5	35
1	5	0	0	0	0	0	5
Total*	17	4	3	11	2	5	42

* Changes in maximum WHO grade equal to −2 or +2 did not occur.

CHANGES IN PATIENTS

Changes in nerve function of patients are compared with the change in the maximum WHO disability grade in Table 5. It is seen that gain in nerve function is missed by the maximum WHO grade in 19/24 (79%) patients, including 12/17 (71%) patients with a full recovery in at least one extremity.

The results of the comparison between changes in nerve function and changes in the HF score are shown in Table 6. In the 42 study patients, changes in the HF score were as follows: improvement 19/42 (45%), no change 19/42 (45%) and deterioration 4/42 (10%). Overall changes in nerve function were as follows: any gain 24/42 (57%), no change 11/42 (26%), deterioration 2/42 (5%), and both improvement and deterioration in ST and/or VMT in the extremities of the same patient 5/42 (12%). The last group of patients (both improvement and deterioration in the same patient) is excluded from the discussion of Table 6, below.

In 6/24 (25%) patients with a gain in nerve function (i.e. improvement, recovery or full recovery), the HF score did not change. Out of these six, three patients had a ST improvement with some remaining loss of sensation in one extremity without other changes in sensation. This was accompanied by an improvement or recovery in motor function in the same extremity in two of them. In the third patient, motor function was always normal. The fourth patient had a total recovery in motor function in three extremities without changes in sensation. In the fifth patient sensation improved, but loss of sensation remained in two

Table 6. Comparison of overall changes in nerve functioning and changes in the HF score between start and end of corticosteroid treatment for the study patients

Change in HF score	Overall change in nerve functioning						
	Full recovery	Recovery	Improvement	No change	Deterioration	Both	Total
−2	0	0	0	0	0	2	2
−1	0	0	0	1	0	1	2
0	2	2	2	10	2	1	19
1	10	0	1	0	0	0	11
2	2	0	0	0	0	1	3
3	1	1	0	0	0	0	2
4	2	1	0	0	0	0	3
Total	17	4	3	11	2	5	42

extremities. In a third extremity, motor function improved but did not recover while all loss of sensation disappeared. The sixth patient recovered from loss of sensation in two extremities with recovery of motor function in one of them, but kept sensory loss and developed a visible deformity in the other two extremities.

The HF score did not register change in two patients with a deteriorating nerve function in at least one extremity. The HF score also remained the same in 10/11 (91%) patients without changes in nerve function.

In 1/3 patients with improvement and in 2/4 patients with a recovery of either sensation or motor function in at least one extremity, the HF score improved. This is also seen in 15/17 (88%) patients with full recovery of both sensation and motor function in at least one extremity. The improvement in HF score ranged from 1 to 4 points in the 18 ($1 + 2 + 15 = 18$) patients gaining both in nerve function and in HF score.

Overall, gain, deterioration and absence of change in nerve function impairment (NFI) as indicated by changes in ST and VMT were reflected correctly by the HF score in 28 ($10 + 18 = 28$, 76%) of the 37 patients who did not show both improvement and deterioration in ST and/or VMT in the same or different extremities.

Discussion

Leprosy is a serious disease because of the impairments and disabilities that it may cause. Measurement of impairment and disability is therefore of vital importance for leprosy control. Two major purposes for measuring can be distinguished: (1) support of individual patient management, and (2) evaluation of leprosy control activities. To meet the first purpose, measurement tools are required that detect new NFI, and changes in existing impairment and disability, early enough to enable appropriate decision making on POID activities for individual patients. The second purpose involves issues such as comparison of impairment and disability in new patients between areas or countries and over time, comparison of impairment and disability at detection, at release from MDT and during post-treatment surveillance, and evaluation of the effectiveness of POID programmes.

Several scoring systems have been introduced in the past.[2,3,5–15]. Undoubtedly, the most frequently used scoring system is the WHO disability grading system with the grades 0, 1 and 2.[3,14] In its latest update in 1998, the grades for the eyes were re-defined.[14] Some of these systems, including the WHO grading system, have been used to determine changes in impairment and disability between start of MDT, release from treatment (RFT) and (sometimes) post-treatment surveillance.[1,2,5,13] The EHF score was shown to be more sensitive in detecting change in impairment and disability than the maximum WHO disability grade.[16] The same was shown for a newer scoring system, that specifies proportions of patients who worsen in ST, VMT, wound count or bone loss.[2]

Nevertheless, it still remains attractive to use the simple WHO grading system and the directly associated HF or EHF score for assessment of changes in order to support patient management and to evaluate POID activities. In this study, ST and VMT results (which can be regarded as the 'gold standard' for measuring NFI) were used to explore the validity of the WHO grading system and the HF score to assess changes in patients that are relevant for patient management, and at aggregated level in order to evaluate POID programmes, in particular corticosteroid treatment.

Firstly, changes in nerve function in individual extremities were compared with changes in WHO disability grade. Half of the extremities with gain in nerve function and 40% of the extremities that deteriorated were not detected by the WHO grading system. Most extremities with a gain in nerve function that were not recognized by the WHO grading system had improvement in sensation without recovery. Recovery in motor function was also missed frequently by the WHO grading system. Changes in ST and VMT in individual extremities are thus very poorly described by the WHO disability grading system. This is not surprising considering the definition of the WHO disability grading system, which ignores differences in the extent of loss of sensation and only accounts for loss of motor function that is accompanied by visible deformity (e.g. clawing, drop foot).

Secondly, changes in overall nerve functioning were compared with changes in the maximum WHO grade and HF score. The maximum WHO grade did not improve in 19/24 (79%) patients with an improvement, a recovery or a full recovery in overall nerve function (Table 5). This is also not surprising because the maximum WHO grade only improves when all initially impaired extremities (eyes were not considered in this study) improve in WHO grade. All 19 patients with gain in nerve function but not in WHO grade had some remaining loss of sensation in one or more extremities (data not shown in tables).

The HF score, which is the sum of the WHO grades of the individual extremities, is more sensitive to change. The proportion of patients for whom an improvement, a recovery or a full recovery in nerve function was rewarded with improvement in HF score was18/24 (75%). In addition, gain, deterioration and absence of change in nerve function was reflected correctly by the HF score in 28 (76%) of the 37 patients who did not show both improvements and deteriorations in ST and/or VMT. These proportions are low from the perspective of individual patients, but the HF score does indicate change in overall nerve function in a definite majority of patients in the study group. Further analysis revealed that the HF score does not provide appropriate information about the degree of nerve function change: 7/11 patients with a change of 1 point in the HF score gained in nerve function in at least two extremities.

Because their sensitivity in recognizing ST and VMT changes in the individual patient is clearly insufficient, the individual WHO disability grades, the maximum WHO disability grade and the HF score are not at all suitable for supporting the management of NFI in individual patients. The WHO disability grading system and (E)HF score were definitely not developed for this purpose. The findings were expected but quantitative evidence was lacking so far. Alternative methods to support patient management have been described elsewhere.[15,16]

The HF score appeared adequate for the study group as a whole. The small group size and retrospective nature are clear limitations of our explorative study. The study group is a random mix of cases that received treatment with corticosteroids, reflecting field programme conditions. Our results suggest that the HF score has the potential to give an overall picture of the effectiveness of corticosteroid treatment under such conditions. Our study group was affected considerably by NFI; at the start of corticosteroid treatment, 60% of patients had three or four extremities affected. One might expect that in a different case mix with a lower level of NFI, more patients would fully recover from nerve function loss when given corticosteroids. In such situations, the HF score may give an even better reflection of the success of treatment with corticosteroids. This assumption needs further substantiation.

In this study, we used the HF score because information on (changes in) eye impairment was not considered reliable. Compared with other scoring systems, the HF and EHF score

have the advantage of being very simple and reproducible; they are based on information that is already routinely collected in many programmes (the WHO grades for extremities and eyes). For possible future evaluation, we advocate use of the EHF score instead of the HF score because eye impairment is very important, its prevalence varies greatly in different patient populations, and score results should be comparable between different projects and centres.[16]

The limitations of our study necessitate further validation studies involving larger patient groups before the EHF score can be used effectively for evaluation of POID programmes. The extent to which changes in nerve function in patient groups with different mixtures of complications leading to NFI are reflected in changes in the EHF score should be investigated in prospective studies. When further validated in this way, the EHF score will be useful for evaluating the effectiveness of different corticosteroid treatment programmes. Another issue that needs clarification through such studies relates to the significance of what is, and what is not detected by the EHF score. To be an effective tool in programme management, the EHF score must be sensitive enough to detect those levels of change in nerve function that lead to lasting disabilities and handicap.

Other POID activities such as health education, provision of footwear and reconstructive surgery also call for evaluation. It is appreciated that different POID activities have different outcomes in terms of health, physical ability, and social functioning and acceptability. Different POID activities may thus require scoring methods other than the EHF score for effective evaluation.

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High dose prednisolone treatment of leprosy patients undergoing reactions is associated with a rapid decrease in urinary nitric oxide metabolites and clinical improvement

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Summary Evidence is accumulating that nitric oxide (NO) produced by macrophages has a role in the pathogenesis of reactions in leprosy. We followed the urinary levels of the metabolites of NO [nitrite (NO_2^-) and nitrate (NO_3^-)] and the clinical response to prednisolone treatment in leprosy patients ($n = 9$) admitted to ALERT leprosy hospital Addis Ababa, Ethiopia, because of reversal reaction (RR) or erythema nodosum leprosum (ENL). In untreated reactional leprosy patients, the levels of urinary NO metabolites (1645 ± 454 μM, $n = 9$, ENL = 4, RR = 5) decreased significantly 2 weeks after high dose prednisolone treatment (1075 ± 414 μM, $P < 0.05$), and remained stable 4 (895 ± 385 μM, $P < 0.02$) and 6 weeks following treatment initiation (1048 ± 452 μM, $P < 0.02$). This decrease was also present when the reactional patients were subdivided according to the type of reaction (ENL, RR) and coincided with a clinical improvement. In patients showing a poor clinical response to steroids, no or minor effects on the urinary NO metabolite levels were observed. We conclude that there is a correlation between the decrease in urinary NO metabolites and a favourable clinical response after high dose prednisolone treatment of reactional leprosy patients.

Introduction

Leprosy caused by *Mycobacterium leprae* is a polar disease with a spectrum ranging from lepromatous leprosy (LL) with a marked Th2 type response and large numbers of bacilli, to the tuberculoid type (TT) showing a Th1 response with small numbers of bacilli.[1,2] It is a

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chronic inflammatory disease primarily affecting the skin and peripheral nerves and the clinical manifestations depend on the host immune response. Reversal reactions (RR) that occur in the unstable borderline cases [borderline lepromatous (BL) and borderline tuberculoid (BT)], are associated with acute inflammation in skin lesions and an increase in cell-mediated immunity, where nerve damage from acute neuritis may be rapid and severe.[3,4] Erythema nodosum leprosum (ENL) occurs in LL and BL cases and is thought to be a immune complex mediated reaction,[5] but cell mediated immunity has also been implicated in this type of reaction.[6] Both ENL and RR patients are treated with high dose corticosteroids to prevent irreversible nerve damage and subsequent loss of function.[7]

In response to Th1 cytokines, high levels of nitric oxide (NO) are produced from L-arginine by activated inflammatory cells such as macrophages expressing the inducible nitric oxide synthase (iNOS).[8–10] NO is highly unstable and decays to its stable end products nitrate and nitrite, which are eliminated in the urine.[8] We have previously shown increased urinary levels of the NO metabolites NO_2^-/NO_3^- in leprosy patients in RR.[11] A recent report has described the presence of iNOS in tissue macrophages from patients undergoing reversal reaction.[12] Thus, NO seems to play a role in the pathogenesis of reactional leprosy. The aim of this study was to investigate the effects of prednisolone treatment on the urinary levels of NO metabolites in correlation to the clinical response in patients suffering from the two different types of reactions in leprosy.

Materials and methods

PATIENTS

Patients included in the study were subjects admitted to the wards of ALERT hospital, Addis Ababa, Ethiopia in August to October 1998 who had a typical clinical picture of ENL or RR and did not show signs of co-existing diseases ($n = 9$, Table 1). One patient was excluded because of displacement of the treatment record. The reactional patients were diagnosed and classified as described by Jopling and Ridley[1,3] by experienced leprosy physicians. The clinical criteria used for the definition of the reactions were: *RR*, erythematous swelling of the existing leprosy lesions, appearance of new lesions that were not relapsing leprosy or ENL and onset or worsening of neuritis (new sensory or motor symptoms, peripheral nerve tenderness); *ENL*, painful and/or tender erythematous subcutaneous nodules in the skin not related to former leprosy lesion, fever and malaise and any of the following symptoms: tender peripheral nerves (neuritis), painful testicular swelling (orchitis), joint pain (arthritis), or painful swollen fingers (dactylitis). The clinical diagnosis were confirmed through histopathological diagnosis according to the classification by Jopling.[1]

The patients were initially treated orally with 40–60 mg prednisolone per day for 2 weeks and the dose was reduced by 5–10 mg every second week according to the clinical response. Multidrug therapy (MDT) was continued in previously treated patients and initiated in previously untreated patients. Peripheral nerve function were assessed during prednisolone treatment by voluntary muscle testing (VMT) and sensation testing (ST) of the hands and feet of the patients.

The clinical response to prednisolone treatment during the study period was evaluated by the leprosy physician and classified as follows: *poor response*, no improvement of erythematous skin lesions (such as diminishing erythema, nodules), persisting pain or tenderness of skin lesions and/or peripheral nerves and loss of peripheral nerve function assessed by VMT/

Table 1. Reactional leprosy patients included in the study. BL = borderline lepromatous, BT = borderline lepromatous, LL = lepromatoid lepromatous, RR = reversal reaction, ENL = erythema nodosum leprosum, SR = sedimentation rate, BI = bacillary index, MDT = multidrug treatment, ND = no data

Patient	Diagnosis	Sex/Age	SR	BI	Previous treatment	Initial treatment	Clinical response	Initial nitrite + nitrate level
1	BL/RR	M/44	60	3	Untreated	Pred 40	Good	1658
2	BT/RR	M/30	10	0	Untreated	Pred 60	Good	2467
3	BT/RR	M/57	28	ND	Untreated	Pred 40	Good	1956
4	BT/RR	F/13	10	0	MDT-MB	Pred 40	Poor	1615
5	BL/RR	M/44	ND	0	Untreated	Pred 40-60	Poor	1114
6	BL/ENL	F/16	76	5	Untreated	Pred 30	Good	2055
7	BL/ENL	M/14	ND	3	Untreated	Pred 30	Good	1313
8	LL/ENL	F/43	84	ND	MDT-MB	Pred 40	Good	1529
9	BL/ENL	F/15	8	2	MDT-MB	Pred 40	Good	1098

ST; *good response*, improvement of erythematous skin lesions, no pain or tenderness of skin lesions or peripheral nerves and no or minor loss of peripheral nerve function assessed by VMT/ST compared to the VMT/ST on admission.

ANALYSIS OF NITRITE AND NITRATE

All urine samples were morning urine samples and were stored at −20°C until analysed. The sum of the nitrate (NO_3^-) and nitrite (NO_2^-) concentration in urine was determined as described previously.[11] Urine was diluted in PBS. Nitrate in the samples was reduced to nitrite by incubating the sample with 10 μl nitrate reductase from *Aspergillus* (10 IU/ml) (Boehringer Mannheim, Freiburg, Germany) and 10 μl nicotinamide adenine dinucleotide phosphate (reduced NADPH (Boehringer Mannheim); 1 mM) for 2 h at 37°C. The nitrite level was then determined by Griess reaction. The final reaction volume of 300 μl contained 218 μl HCl (0.45 M), 26 μl sulphanilic acid (2 mg/ml) (Merck, Darmstadt, Germany), 26 μl N-(1-naphthyl) ethylenediamine (1 mg/ml) (Sigma Chemical Co., St Louis, MO, USA) and 30 μl of the diluted urine sample. The urine samples were then analysed on an ELISA multiwell reader (Titertec Multiscan Plus) at 542 nm.

STATISTICAL ANALYSIS

Statistical evaluation was done with the Wilcoxon signed rank test for evaluation on the effect of treatment on the patients. Data are presented as mean ± SD.

Results

URINARY LEVELS OF NO METABOLITES IN REACTIONAL LEPROSY PATIENTS

The urinary levels of NO metabolites and the clinical response to prednisolone treatment in leprosy patients admitted because of RR or ENL ($n = 9$) was studied during 6 weeks (Table 1).

The levels of urinary NO metabolites in reactional leprosy patients before high dose

prednisolone treatment (1645 ± 454 μM, $n = 9$, ENL = 4, RR = 5) were decreased 2 weeks after treatment (1075 ± 414 μM, $P < 0.05$) and remained stable 4 (895 ± 385 μM, $p < 0.02$) and 6 weeks (1048 ± 452 μM, $P < 0.02$) following treatment initiation (Figures 1, 2 and 3). No difference in the levels of NO metabolites in RR (1762 ± 497 μM, $n = 5$) or ENL (1499 ± 410 μM, $n = 4$) patients was observed. When the three patients (nos 5, 7 and 9) who did not have increased levels of NO metabolites (defined as less than 1500 μM) initially were excluded, the decrease was even more pronounced with initial levels for untreated reactional patients of 1880 ± 353 μM ($n = 6$, ENL = 2, RR = 4); there was a significant reduction 2 weeks after treatment (1061 ± 510 μM, $P < 0.05$) which was also stable 4 weeks following treatment initiation (893 ± 493 μM, $P < 0.05$).

KINETICS OF URINARY NO METABOLITES AND THE CLINICAL RESPONSE IN RR PATIENTS

RR patients had initial urinary NO metabolite levels of 1762 ± 497 μM ($n = 5$), with a reduction 2 weeks after start of prednisolone treatment (1018 ± 546 μM) which remained on similar levels 4 weeks after treatment (843 ± 494 μM) (Figure 2). One patient (no. 5) had an initial low level of urinary nitrite and nitrate (1114 μM) despite being clinically in reversal reaction (Figure 2). This patient showed a poor clinical response to steroid treatment and only a slight decrease in NO metabolite levels was observed (Figure 2 and Table 1). One patient (no. 4) showed a poor clinical response to high dose prednisolone treatment and also maintained relatively high levels of NO metabolites, in contrast to the other patients where a marked decrease in urinary NO metabolites coincided with a favourable clinical response (nos 1, 2 and 3) (Figure 2 and Table 1). Patient 3 experienced increasing pain and tenderness in the peripheral nerves (neuritis) between the samples taken at weeks 2 and 3 after treatment initiation which subsided after week 4. In association with this clinical relapse a peak of NO metabolites was observed 3 weeks after treatment initiation in this patient (Figure 2).

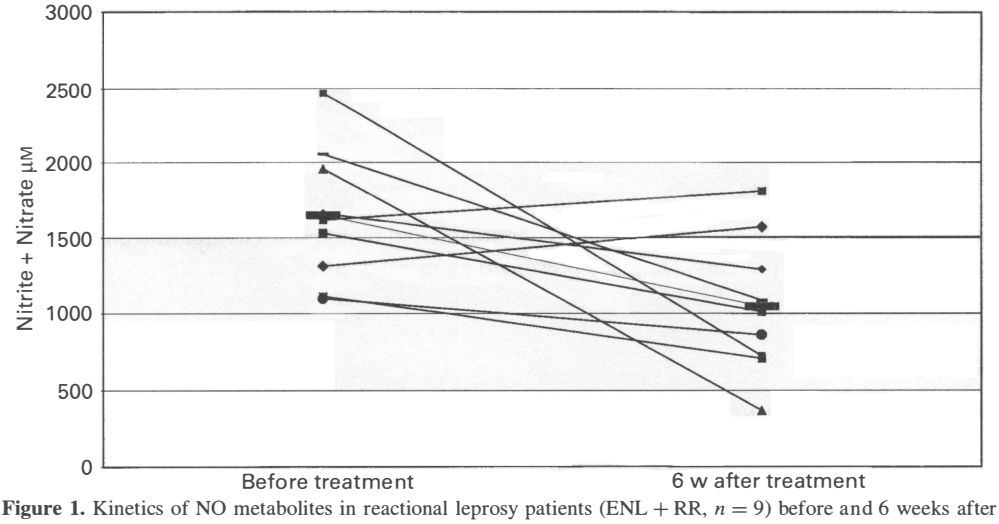

Figure 1. Kinetics of NO metabolites in reactional leprosy patients (ENL + RR, $n = 9$) before and 6 weeks after initiation of prednisolone treatment. The bold lines indicate the mean levels of nitrite and nitrate before and after treatment.

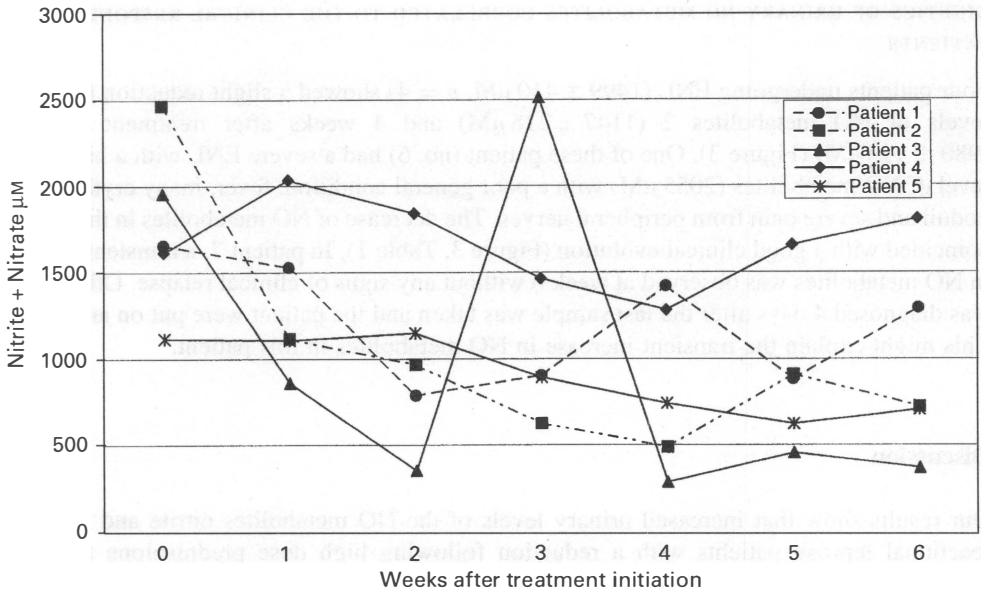

Figure 2. Kinetics of NO metabolites in leprosy patients in reversal reaction (RR, $n = 5$) before (week 0) and up to 6 weeks after initiation of prednisolone treatment. The weekly urinary level of nitrite and nitrate of each patient is indicated.

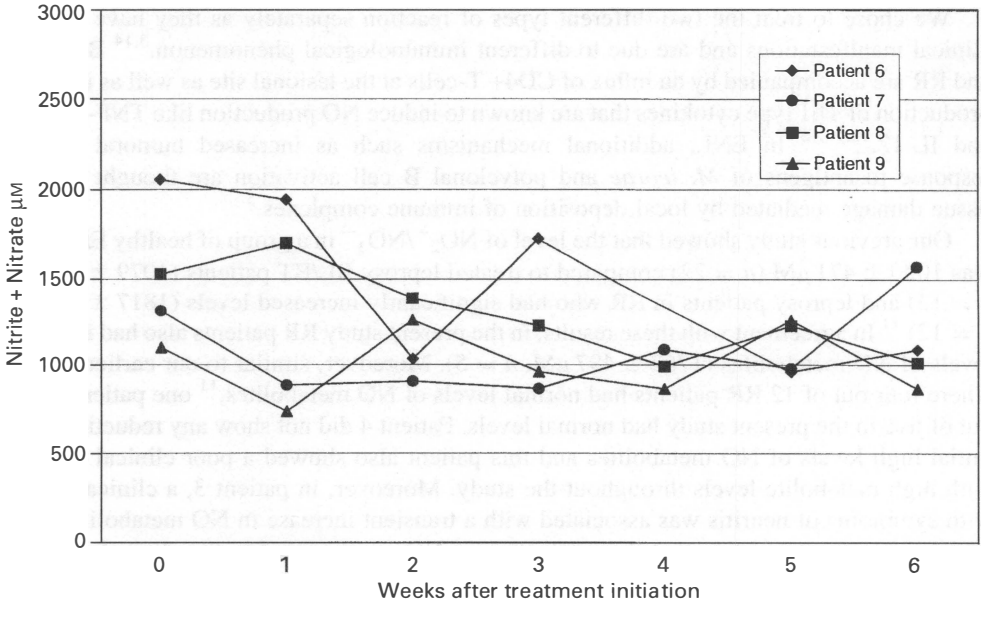

Figure 3. Kinetics of NO metabolites in leprosy patients in erythema nodosum leprosum (ENL, $n = 4$) before (week 0) and up to 6 weeks after initiation of prednisolone treatment. The weekly urinary level of nitrite and nitrate of each patient is indicated.

KINETICS OF URINARY NO METABOLITES CORRELATED TO THE CLINICAL RESPONSE IN ENL PATIENTS

Four patients undergoing ENL (1499 ± 410 μM, $n = 4$) showed a slight reduction in urinary levels of NO metabolites 2 (1147 ± 218 μM) and 4 weeks after treatment initiation (980 ± 113 μM) (Figure 3). One of these patient (no. 6) had a severe ENL with a high initial level of NO metabolites (2055 μM) with a poor general condition, fever, many erythematous noduli and severe pain from peripheral nerves. The decrease of NO metabolites in this patient coincided with a good clinical evolution (Figure 3, Table 1). In patient 7, a transient increase in NO metabolites was observed at week 6 without any signs of clinical relapse. Otitis media was diagnosed 4 days after the last sample was taken and the patient were put on antibiotics. This might explain the transient increase in NO metabolites in this patient.

Discussion

Our results show that increased urinary levels of the NO metabolites nitrite and nitrate in reactional leprosy patients with a reduction following high dose prednisolone treatment coincides with a favourable clinical response.

It has been shown previously that our method, using an early morning urine sample after an overnight fast, will limit the dietary contribution of nitrite and nitrate and can be used when comparing groups.[13] Moreover, it is unlikely that dietary factors could explain our results, since the level of urinary NO metabolites in reactional leprosy patients diminished after initiation of prednisolone treatment and remained stable on the same levels as we have shown previously in healthy Ethiopian individuals.[11]

We chose to treat the two different types of reaction separately as they have different clinical manifestations and are due to different immunological phenomenon.[3,14] Both ENL and RR are accompanied by an influx of CD4+ T-cells at the lesional site as well as increased production of Th1 type cytokines that are known to induce NO production like TNF-α, IFN-γ and IL-12.[10,15,16] In ENL, additional mechanisms such as increased humoral immune response to antigens of *M. leprae* and polyclonal B cell activation are thought to cause tissue damage mediated by local deposition of immune complexes.[5]

Our previous study showed that the level of NO_2^-/NO_3^- in a group of healthy Ethiopians was 1020 ± 471 μM ($n = 22$) compared to treated leprosy BL/BT patients (1079 ± 446 μM, $n = 12$) and leprosy patients in RR who had significantly increased levels (1817 ± 492 μM, $n = 12$).[11] In agreement with these results, in the present study RR patients also had increased levels of NO metabolites (1762 ± 497 μM, $n = 5$). Moreover, similar to our earlier findings where four out of 12 RR patients had normal levels of NO metabolites,[11] one patient (no. 5) out of five in the present study had normal levels. Patient 4 did not show any reduction of the initial high levels of NO metabolites and this patient also showed a poor clinical response with high metabolite levels throughout the study. Moreover, in patient 3, a clinical relapse with symptoms of neuritis was associated with a transient increase in NO metabolite levels, supporting our observation that the production of NO is associated to the clinical response. One possible explanation for our results might be that prednisolone treatment prevents NO mediated tissue damage, as RR cases left untreated are often severely disabled because of nerve damage. However, other NO independent pathways of tissue damage also seems to be present as in some patients suffering from RR, no increase in urinary NO metabolite levels is

observed. Other explanations could be that there is a small local production of NO in the skin which can not be detected by urinary NO metabolites or lack of the substrate for NO production, L-arginine, because of malnutrition.

In this study, we also describe a role for NO in ENL patients as these patients had increased levels of NO metabolites that were reduced after prednisolone treatment accompanied by a favourable clinical response. Further studies with higher numbers of patients are necessary to confirm the role for NO in ENL, but it has been shown that tissue injury resulting from deposition of immune complexes is L-arginine dependent,[17] indicating that NO might be an important mediator in immune complex mediated diseases such as ENL.

It has been shown that glucocorticoids inhibit iNOS and NO production directly through inhibition of the translocation of nuclear factor kappa beta as well as indirectly by suppressing the production of cytokines such as TNF-α.[18] The main mechanism by which prednisolone exerts its effects in reactional leprosy patients remains to be established as the drug affects many inflammatory mechanisms such as inhibition of the cyclo-oxygenase.[19]

This study indicates that an iNOS inhibitor drug might be of benefit for the treatment of reactions in leprosy and that the relatively fast and cheap method of determining the NO metabolites nitrite and nitrate in morning urine samples might be useful in monitoring the response to treatment in leprosy reactions. Specific iNOS inhibitors with fewer side effects than high dose steroids need to be searched for in the treatment of reactions in leprosy patients.

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Predisposing factors for recurrent skin ulcers in leprosy

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Summary This study was designed to determine the factors associated with recurrence of leprosy ulcers. Between April and August 1992, 55 consecutive leprosy patients admitted with skin ulcers were studied. Factors predisposing to recurrence, e.g. patient's age, disease duration, ulcer site, ulcer depth and physical deformity (taking into account neuromuscular and skeletal damage) were evaluated. Ulcer recurrence occurred in 40/55 (75%) patients. Recurrent ulceration was associated with location in the lower extremity ($P = 0{\cdot}02$), where recurrences were more common in the midfoot and heel ($P = 0{\cdot}01$). Recurrence was also associated with severity of physical deformity ($P = 0{\cdot}01$), which increased the odds of recurrent ulceration by 4·2 times (95% confidence interval, 1·01–18·3). The severity of physical deformity itself was associated with the age of the patient ($P = 0{\cdot}04$) and the disease duration ($P = 0{\cdot}02$). In conclusion, there is a need to focus on identification of risk factors for recurrent leprosy ulceration. Targeted prevention strategies would be required if morbidity associated with recurrent skin ulceration is to be avoided.

Introduction

With the introduction of new therapeutic regimens, leprosy can now be cured. However, complications of the disease such as sensory loss, muscle palsy, absorption of extremities and recurrent ulcers still lead to substantial morbidity.[1] Of the 10–12 million leprosy patients in the world, it is estimated that 1.8 million suffer from skin ulcers,[2] and ulcers remain the most common reason for hospitalization in these patients.[3] Recurrent ulceration, in particular, also carries a risk of development of squamous cell carcinoma.[4] Factors predisposing to recurrence, therefore, need to be elucidated with view to prevention. Literature on predisposing factors for ulceration in leprosy is limited.[5,6] In particular, little attention has been given to deformities and their effect on recurrence of ulceration. The objective of this paper was to study the predisposing factors associated with recurrence of leprosy ulcers and to determine the effect of site and severity of physical deformity on ulceration.

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Materials and methods

During the period April to August 1992, 55 consecutive leprosy patients with skin ulcers requiring hospitalization were evaluated at the Marie Adelaide Leprosy Centre, Karachi, Pakistan. During the course of their illness, all patients had received regular health education by trained teachers and each patient had been given advice about adequate footwear and had been offered special orthopaedic shoes. The suggested methods of prevention included daily inspection of anaesthetic hands and feet for skin injuries, regular baths and care with Vaseline afterwards to restore loss of seborrhoeic function.

On recruitment in this study, a detailed history including disease activity and duration; ulcer localization and recurrence; and previous treatments and complications were noted for each patient. Information on the aetiology of the ulcers was generally not available due to the long time lag between ulceration and hospitalization. Examination was conducted to assess the neurological system, musculoskeletal system and the form and depth of each ulcer. Loss of pain sensation was examined by using a sterile pin. Patients were asked to close their eyes and their response to sharp stimuli was noted. Touch and light pressure sensation were also examined by using a wisp of cotton wool. The motor system was examined for musculoskeletal function and deformity. Muscular functions were assessed including tone, power and reflexes. Severity of physical deformity was graded according to a uniform classification,[7] taking into account neuromuscular and skeletal damage as shown in Table 1.

The factors associated with recurrence of ulceration were elucidated using patient as the unit of analysis. This formed the basis for testing our primary research hypothesis regarding the effect of physical deformity on recurrence of ulceration. Secondary analyses were conducted using ulcer as the unit of analysis. Continuous variables were assessed for differences with Student's *t*-test for two groups and analysis of variance was used for multiple comparisons. Proportions were assessed for differences using the Chi-square test (with Yates' correction when expected cell value was <5) and their trends were analysed with Chi-square for trend. In addition, the association of deformity with site of ulceration was explored in detail for ulcers on the planter aspect of the foot. A two-tail *P*-value of <0·05 was regarded as significant. Epi-info Software[8] was used for statistical analysis.

Table 1. Classification of physical deformity in leprosy

Grade*	Hand deformity	Foot of deformity
Grade 1	Loss of sensitivity	Loss of sensitivity
Grade 2	Ulcers and wounds	Ulcers and wounds
Grade 3	Mobile minimal clawhand, slight bone absorption	Hyperextension of first toe, mobile claw toes, slight bone absorption
Grade 4	Mobile complete clawhand, moderate bone absorption	Fixed claw toes, flat foot, moderate bone absorption
Grade 5	Fixed complete clawhand, wrist drop, severe bone absorption	Contracture of ankle joint, foot drop, severe bone absorption

* Based on Kunst (1993).

Results

Out of a total of 55 leprosy patients with skin ulcers, there were 40 male and 15 female patients. Their mean age was 49 years (SD 17·4) and the mean duration of disease was 14 years (SD 10; range 1–35). Recurrent ulcers occurred in 40/55 (73%) patients. Mean time to recurrence was 7 years (SD 5·8; range 1–24). As shown in Table 2, patients with recurrences were older (mean age 50·2 years versus 45·0 years) and had longer duration of illness compared to those without recurrence (16·1 years versus 10·9 years); these differences were not statistically significant. However, there was a significant trend towards higher odds of recurrence with worsening grade of physical deformity ($P = 0{\cdot}01$). Severity of deformity increased with age ($P = 0{\cdot}04$) and disease duration ($P = 0{\cdot}02$). Compared to patients with deformity grade 1–2, those with grade 3–5 had higher odds of having recurrent ulcers (odds ratio 4·2, 95% confidence interval 1·01–18·3, $P = 0{\cdot}02$).

The total number of ulcers was 82, nine (11%) in upper extremities and 73 (89%) in lower extremities. Of the 82 ulcers, 54 (66%) were recurrent. As shown in Table 3, recurrences were more common in the lower extremity compared to upper extremity (51/73 versus 3/9, $P = 0.02$). In the upper extremity 6/9 (67%) ulcers occurred on the hand. In the lower extremity 57/73 (78%) were localized to the plantar aspect of the foot. Of these, 40/57 (70%) occurred on the forefoot, 7/57 (12%) on the midfoot, and 10/57 (17%) on the heel. In the foot, recurrence was more often in the midfoot and heel compared to forefoot (16/17 versus 23/40, $P = 0{\cdot}01$). The ulcers were superficial in 51/82 (62%), deep in 22/82 (27%) and had sinus formation in 9/82 (11%) cases. In the lower extremity, deep ulcers accounted for 7/40 (17%) forefoot ulcers, 5/7 (70%) midfoot ulcers and 8/10 (80%) heel ulcers. Sinus formation occurred in 6/40 (16%) forefoot ulcers and 3/6 (50%) hand ulcers. Depth of ulceration was not associated with recurrence ($P = 0{\cdot}25$). The relation of grade of physical deformity with recurrence of ulceration, using ulcer as the unit of analysis, showed a statistically non-significant trend toward recurrence ($P = 0{\cdot}1$). Compared to ulcers associated with deformity grade 1–2, those with grade 3–5 had higher odds of having recurrent ulcers (odds ratio 2·2, 95% confidence interval 0·8–6·2, $P = 0{\cdot}1$).

Table 2. Characteristics of leprosy patients with skin ulcers according to recurrence

Characteristics	Recurrent ulcer ($n = 40$)	Non-recurrent ulcers ($n = 15$)	*P*-value
Patient's age (years)	50·2 (SD 17·5)	45·0 (SD 18·5)	NS
Duration of illness (years)	16·1 (SD 10·4)	10·9 (SD 9·7)	0·09
Patient's sex			
Male	30	10	
Female	10	5	NS
Distribution of patients according to grade of physical deformity*			
Grade 1–2	7	7	
Grade 3	4	3	0·01
Grade 4	7	2	
Grade 5	22	3	

* See Table 1 for detailed description for physical deformity grading.
NS = not significant.

Table 3. Site and physical deformity associated with leprosy ulcers according to recurrence

Characteristics	Recurrent ulcer ($n = 54$)	Non-recurrent ulcers ($n = 28$)	*P*-value
Site of recurrence			
Upper extremity	3	6	
Lower extremity	51	22	0·02
Localization of 57 ulcers in planter aspect of lower extremity			
Forefoot	23	17	0·01
Heel and midfoot	16	1	
Distribution of ulcers according to grade of physical deformity*			
Grade 1	12	7	
Grade 2	5	7	
Grade 3	7	3	0·10
Grade 4	22	5	
Grade 5	8	6	

* See Table 1 for detailed description for physical deformity grading.

The relation of specific deformities to site of ulceration was explored. In the plantar aspect of the lower extremity, this analysis revealed that flat foot was more often associated with midfoot and heel ulceration than with metatarsal head ulcers ($P < 0·0001$), whereas claw foot, foot drop and absorption were not associated with the site of ulcer ($P < 0·05$) (Table 4).

Discussion

In this study, ulcer recurrence was found to be associated with location in the lower extremity, where recurrences were more common in the midfoot and heel; and with severity of physical deformity, which substantially increased the odds of recurrent ulceration in patients with

Table 4. Relation between physical deformity of the lower extremity and foot ulcers location on the planter aspect ($n = 57$)

	Associated deformity (*n*)			
Site of ulcer	Bone absorption[1]	Claw foot[1]	Flat foot[2]	Foot drop
Metatarsal heads* ($n = 25$)	13	14	6	–
Toes ($n = 15$)	1	7	–	1
Heel ($n = 10$)	4	5	5	–
Mid-foot ($n = 7$)	6	5	6	–

Data presented as number of ulcers; sum of column data exceeds totals because more than one deformity was associated with several ulcers.

* At first metatarsal head there was hyperextension of first toe in 9/16 (56·3%) ulcers.

[1] Claw foot and absorption not associated with site of ulceration ($P < 0·05$).

[2] Flat foot associated more frequently with midfoot or heel ulcers than with metatarsal head ulcers (11/17 versus 6/25, $P = 0·009$).

more severe grade of deformity. The severity of physical deformity was associated with the patient's age and disease duration.

In determining the conformity of the general findings of this study with other reported literature, we found consistency with regard to the observation of male predominance[9] and advanced patient age.[10] Moreover, the distribution of ulcers in the plantar aspect of the foot in this study is concordant with findings of other series.[11] We also found an association between midfoot ulcers and a loss of foot arch, which has been described as a predisposition.[11] However, the lack of an association between site of ulcer and claw foot, foot drop and absorption is perhaps due to type II statistical error (inability to find an association when one actually exists) related with the small sample size of our study. The relation of age with severity of physical deformity found in our study was also consistent with prevailing evidence.[10]

The main finding of our study was the relation of physical deformity with recurrence of ulceration. In studying this association, we could also have used the WHO classification, which is an indicator for an overview of the frequency of deformities in a leprosy programme. However, the WHO classification is not considered to be a good indicator for the assessment of individual patients.[12] Therefore, we used a modified classification.[7] This revealed a strong association with recurrent ulceration using patient as the unit of analysis (odds ratio for recurrence in relation to severity of deformity 4·2, 95% confidence interval 1·01–18·3, $P = 0{\cdot}02$). This association was strengthened by the strong trend in the secondary analysis using ulcer as the unit of analysis (odds ratio for recurrence in relation to severity of deformity 2·2, 95% confidence interval 0·8–6·2, $P = 0{\cdot}1$). As our primary hypothesis was based on patient as the analysis unit, we are confident that our results are not spurious.

The relationship of occupation and health education with leprosy ulcers has been analysed in a separate study.[13] This analysis has shown that high grade physical deformity was associated with unemployment and there was a trend of higher unemployment among those with recurrent ulcers. With regard to health promotion, there was poor compliance with advice about protective footwear and care of insensitive extremities. Level of knowledge about the leprosy ulcers and use of prevention strategies was also inadequate despite health promotion. For example, with regard to use of footwear, it was evident that patients only realized the necessity of protective shoes after a deformity had developed.

It has been shown that surgical treatment of deformities can contribute to elimination of predisposing factors for recurrent ulceration.[4] This is of importance, in particular, because duration of recurrent ulceration has a significant influence on malignant degeneration as epidemiological studies have shown that up to 2% of patients with a mean ulceration time of 12 years develop squamous cell carcinoma.[14] Since many patients with chronic ulceration are not supervised regularly, malignant change can be easily overseen.[15] There are limited resources to allow full development of people affected with leprosy,[16] so if morbidity associated with recurrent skin ulceration is to be avoided, then targeted prevention strategies would be required. Our study indicates that there is a need to focus on identification and correction of physical deformities that predispose to recurrent ulceration.

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Lepr Rev (2000) **71,** 369–376

Towards an understanding of non-compliance. An assessment of risk factors for defaulting from leprosy treatment

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Summary Within the Eastern Leprosy Control Project of Nepal, a retrospective case control study looked for simple factors that might be used operationally to predict non-compliant behaviour in patients. Patients with these factors would then become the targets of measures such as intensified health education messages and home visits in order to reduce the risk of defaulting. A study of 1442 patient cards (half defaulters, half treatment completed) revealed occasional small but significant demographic and clinical differences, but none was of a sufficient magnitude to be operationally useful. Review of the attendance of patients in the first few months of treatment suggested that eventual defaulting was strongly associated with irregularity from the commencement of treatment. It is possible that an early indicator based on attendance over the first months can be used to target patients who are in danger of non-completion of treatment.

Introduction

In the Eastern Leprosy Control Project of Nepal, the defaulter rate is high. Based on the 1996/1997 cohort of newly registered patients, 42% of PB and 48% of MB patients failed to complete treatment within the time limits set by WHO (9 months for PB, 36 months for MB at that time). A programme was in place to try to reduce the defaulter rate, and increase the treatment completion rate to the national target of 85% set by His Majesty's Government of Nepal. The programme included identification of patients who were late for appointments followed by sending of reminder letters, and eventually a home visit. There was no apparent improvement resulting from this programme.

This retrospective study was undertaken to try to identify any commonality in patients who eventually default, based on the information readily available on the patient registration/treatment card. Such commonality, if found, would be of value to target resources such as health education and counselling to prevent defaulting.

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The study had two main objectives: (i) to examine potential risk factors for non-compliance so that patients at risk of becoming a defaulter can be identified at registration; and (ii) using the clinic attendance pattern, to try to find an early indicator that will identify patients who will become defaulters, whilst they are still in contact with the clinic.

Materials and methods

SELECTION OF VARIABLES

A literature review suggested that defaulting, irregularity and non-compliance have been attributed to a variety of causes. Since this study was to be retrospective, the variables available for study were limited to those recorded on the patient treatment card. Only those variables recorded on the Nepal patient treatment card, and previously shown to be significant by another author, were used as the basis for this study.[1,4,5,6,8–12]

The possible variables were reviewed and placed into five groups:

1. Simple demographic variables: age, gender, distance of home from treatment centre and leprosy in the family.
2. Seasonal variables: month of registration.
3. Variables relating to clinical condition at registration, presence of a visible patch on the face and presence of visible impairment (as measured by WHO disability grade).
4. Variables related to treatment history: previous treatment with dapsone monotherapy.
5. Variables related to pattern of attendance after registration: total number of visits made, number of visits in first 2 months, number of visits in first 3 months, number of visits in first 4 months and number of visits in first 6 months.

DEFINITIONS

PB/MB

In Nepal, patients are classified PB if only one body area is affected with skin patches or enlarged nerves. MB patients have two or more affected body areas.[2,3]

MDT

Multi-drug therapy (MDT) is according to the WHO regimen. PB patients received six doses. MB patients received 24 doses at the time of the cohort under study (WHO MDT regimen 1982–1998). A patient is released from treatment (RFT) if they completed six doses in 9 months (PB) or 24 doses in 36 months (MB).

Defaulter

A defaulter is a patient who can no longer complete the MDT regimen, regardless of whether s/he is still coming to the treatment centre. An MB patient becomes a defaulter as soon as they have missed 13 months of treatment. A PB patient is a defaulter when they have missed 4 months of treatment.[2]

Dapsone monotherapy

Some patients in the study received dapsone only, prior to the start of MDT. It was a policy to give a newly registered patient dapsone for 2–3 months to see if they would take treatment regularly, and only if regular on dapsone would they be transferred to MDT. This policy no longer applies in Nepal, but affects some of the patients in the cohort under study.

CHOICE OF COHORT

At the time of the study, PB patients registering in the Nepali year equivalent to 1994/1995, were at least 9 months after registration. MB patients registering in 1992/1993 were 36 months after registration. These cohorts were the most recent groups of patients who could have completed treatment, and were chosen for the study. Cases (defaulters) were those who had failed to complete the WHO regimen of MDT. Controls (RFT) were patients who had completed the WHO regimen within the time limit. The study was restricted to patients registering for the first time at Biratnagar sub-regional referral centre. Patients who transferred into the treatment centre after starting treatment elsewhere, and patients who transferred out to complete treatment at another centre, were excluded from the study.

SAMPLING

The size of the study was restricted by the number of patient treatment cards available. Since the study area is on the border with India, both Nepali and Indian patients are registered for treatment. The defaulting rate is different for the two groups of patients and the study was to be stratified for stated country of domicile. For Nepali patients all available cards for the defined cohort were used. For Indian patients a simple random sample was drawn (250 each defaulters/RFT).

DATA COLLECTION

All the required data were tabulated directly from the patient cards. Distance from the treatment centre was measured using a score for each possible village, combining distance, availability of public transport and cost. Visits to the treatment centre were defined as any visit by the patient, either to collect MDT of for any other follow-up. Visits made on behalf of the patient (proxy visits) of by health workers to the patient's home, were excluded.

DATA ANALYSIS

Data were processed using EPI INFO (6.04). The data were stratified for type of leprosy (MB/PB) and country of domicile (Nepal/India). For binary variables, odds ratios (and their 95% confidence intervals) were calculated. For multilevel variables, a χ^2 test for trend was used. For assessment of the visiting pattern, the number of patients NOT meeting the set criteria (e.g. two out of the first two visits) was taken as presence of the attribute; the number meeting the criteria was absence. Sensitivity, specificity, positive and negative predictive values were calculated as if the indicator was being used to judge the benefit of intervention.

Results

Table 1 gives the data for the variables available at registration. Table 2 shows the results for variables calculated from the pattern of attendance in the first few months of treatment.

DEMOGRAPHIC VARIABLES

In only one case (gender in Indian MB patients) was there any evidence of a difference between patients who became RFT and those who defaulted. There is some evidence (OR = 0.58, 95% CI = 0.38–0.98) that Indian MB patients who are male default less than females.

SEASONAL VARIABLES

There is no evidence, in any of the subgroups, that the time of year of registration affects compliance.

CLINICAL CONDITION

For neither variable (facial patch, visible impairment) was there consistent evidence of an

Table 1. Data for the variables available at registration

		PB Nepali	MB Indian	Nepali	Indian
Demographic					
Age	Odds,	1·21	1·14	1·16	1·19
<15 years	ratio	0·59–2·47	0·66–1·98	0·41–3·31	0·61–2·33
≥15 years	95% CI				
Gender	Odds,	1·12	0·81	1·59	0·58
Male	ratio	0·67–1·89	0·56–1·18	0·81–3·14	0·38–0·98
Female	95% CI				
Distance (4 levels)	χ^2 test, *P*	0·98	0·29	0·15	0·002
Leprosy in family	Odds,	0·52	0·89	1·57	1·09
Yes	ratio	0·22–1·23	0·50–1·56	0·58–4·28	0·67–1·78
No	95% CI				
Seasonal					
Month of registration (12 levels)	χ^2 test, *P*	0·40	0·28	0·86	0·31
Clinical					
Facial patch	Odds,	1·09	1·48	0·56	0·87
Yes	ratio	0·59–2·02	0·90–2·44	0·30–1·05	0·60–1·26
No	95%				
WHO disability grade 3 levels	χ^2 test, *P*	0·14	0·43	0·05	0·44
History					
Prior dapsone	Odds,			0·46	0·68
Yes	ratio	N/A	N/A	0·25–0·87	0·46–1·02
No	95% CI				

Table 2. Results for variables calculated from the pattern of attendance in the first few months of treatment

Visiting pattern		PB	MB	ALL
2 out of first 2	Sensitivity	45%	30%	38%
	Positive predictive value	86%	76%	82%
3 out of first 3	Sensitivity	68%	48%	58%
	Positive predictive value	82%	71%	78%
4 out of first 4	Sensitivity	84%	59%	72%
	Positive predictive value	78%	69%	74%
6 out of first 6	Sensitivity		79%	
	Positive predictive value		65%	
2 out of first 3	Sensitivity	39%	16%	28%
	Positive predictive value	98%	92%	96%
3 out of first 4	Sensitivity	63%	32%	49%
	Positive predictive value	96%	89%	94%

effect on compliance. For both variables one of the four subgroups shows a significant or borderline significant effect, but there is no consistent pattern.

TREATMENT HISTORY

Previous treatment with dapsone monotherapy results in significantly fewer defaulters in the Nepali group, and is borderline significant in the Indian group.

PATTERN OF ATTENDANCE

For PB patients, the median number of visits made by defaulters was two ($25^{th}/75^{th}$ centile 1–3). For MB patients, this figure rose to seven (4–13). There were no significant differences between Nepalis and Indians.

As would be expected, the later in the treatment regimen that the pattern of attendance is calculated, the better the predictive nature. However, all of the patterns selected for study were associated with significant risk of becoming a defaulter.

Discussion

A previously reported study[8] found that women tend to be less compliant than men. This was found in only one group of our study (Indian MB patients), and may result from the reduced freedom to move outside the house unescorted. The Purdah system is observed more in the Indian states bordering Nepal than in Nepal itself. The greater number of visits required for

MB treatment, and the minimal symptoms associated with PB type disease, may be reasons why this effect is noted only in MB patients. In terms of accessibility, this study suggests that Indian men are more compliant when they come a greater distance to the treatment centre. This is in direct contrast to other studies[7,10] where good accessibility was positively related to compliance. There is a difference between the requirement to travel a great distance because treatment is not locally available, and the choice to travel either for improved facilities, or because of the fear of being recognized in one's own community. If the patients in this study are travelling out of choice, then this could be expected to be reflected in good motivation, and therefore explain these findings.

In general, however, despite being selected as potential indicators on the basis of prior published research, none of the demographic, seasonal or clinical indicators show a consistent or large enough effect to be suitable indicators to enable targeting of messages or activities aimed at enhancing compliance.

Prior dapsone therapy appears to be associated with reduced defaulting dapsone was given for 2 or 3 months, and only those patients compliant on dapsone therapy were registered for MDT. The underlying reasoning was that MDR would be reduced. Since the median number of visits for PB defaulters is just two, the pretreatment had the effect of ensuring that many non-compliant patients defaulted before MDT started. The observed effect of prior dapsone therapy is therefore likely to be due to the fact that it was given for two or three visits before MDT registration and not a reflection of the drug treatment, or any reduced compliance with MDT.

It is clear that none of the variables recorded at registration are operationally useful in predicting patients who are at risk of defaulting. Based on the information about visits to the clinic, the time available to give any message targeted at reducing defaulting is very short, including time left for Health Education. Only 50% of PB patients who default make two visits to the clinic, whilst 50% of MB defaulters make at least seven visits. These findings suggest that prospective, qualitative studies about the patient's first visit to the treatment centre and their experience with treatment, may be of value in understanding non-compliance. Review of the potential early indicators based on attendance patterns reinforces the issue of the few visits that defaulters seem to make. Maybe the length of the treatment, the need to work, particularly, in rural communities, at certain times of the year, or the increased risk of exposure in the community with multiple visits, are the source of non-compliant behaviour.

In this study, patients who did not take at least two out of the first three MDT doses on time, would have been a reasonable sub group to target to try to prevent defaulting, either at their next visit, or by home visit/letter. The positive predictive value overall is 96%. In this study, there were 211 patients who would have been flagged by such a warning, of which less than 4% (8), went on to complete treatment.

In centres where the number of defaulters, and therefore the workload in tracing and trying to prevent defaulting would be less, a more sensitive indicator such as 'not taking four out of the first four doses' would be appropriate.

In conclusion, we found no factors recorded at registration which would help identify patients who would go on to become defaulters. Other studies have suggested associations between the factors chosen for study and non-compliant behaviour. This inconsistency only serves to highlight the complexity of the issue of non-compliance and the necessity for further qualitative research.

The study highlighted the very short time available to the health worker to present a

message that might prevent defaulting, and the speed with which the treatment centre needs to react to a pattern of attendance which is predictive of defaulting. If a health education message in the clinic setting is chosen as the primary method of ensuring compliance, the message needs to be given and understood at the first or second clinic visit. For most patients, there will be other information that needs to be given at the same time. If patient compliance is seen as an important factor, then some traditional messages may need to be delayed to prevent overloading the patient at the first visit. All Health Education messages necessary must be given in this short time, this to enable the patient to understand his/her disease, its treatment and treatment procedure. The findings suggest the need to develop a patient education list, which structures which messages to give at which visit.

If a treatment centre is to introduce an early indicator of non-compliance, in order to highlight patients who need follow up outside of the clinic, then there is a balance between speed of getting the warning, sensitivity to maximize the number of defaulters targeted, positive predictive value to ensure that patients targeted or visited are really likely to become defaulters and the overall number of patients highlighted by the indicator.

The correct balance is different in each centre. Where the defaulting rate is very high, and the overall number of patients is high, then significant improvements might be achieved by targeting patients who fail to take at least two of the first three doses on time. In centres where the problem is less acute, a more sensitive indicator, such as failing to take all of the first four doses on time, may yield better results.

The issue of non-compliant behaviour is complex. The objectives of this study were simply to try to find indicators that would be operationally useful to highlight patients who might become defaulters, before they have lost all contact with the treatment centre. In this way, it is hoped that defaulting might be prevented, rather than waiting until defaulting has occurred, at which point finding the patient and motivating them to take treatment regularly would be more difficult. Only an indicator based on actual behaviour in the first few months showed any predictive capability in this study.

Suggestions for further research

This study shows how complex the concept of non-compliance is. To really understand non-compliance, a fuller understanding must be sought of all factors involved. A patient's willingness to comply depends also on his/her ability to comply! Because decisions to discontinue treatment are taken in the course of everyday life, qualitative research into what non-compliance means to the patients themselves is suggested; the patients' understanding of their experience with their disease and its treatment, as well as the divers situations in which they have them.

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Lepr Rev (2000) **71,** 377–381

Modified leprosy elimination campaign (MLEC) for case detection in a remote tribal area in the State of Orissa, India

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Summary A leprosy project was established in a difficult to reach area under guidelines of Government of India. The leprosy services were provided by Koraput Leprosy Eradication Project (KORALEP) and general health services by Primary Health Care (PHC). Leprosy elimination campaigns (LECs) were suggested by WHO to detect more cases in the community. A modified leprosy elimination campaign (MLEC), carried out utilizing the services of primary health care workers is discussed in this paper. Apart from the trained health workers, Anganwadi workers along with some literate people from the district were also included in the search teams. In all, 1543 cases were shortlisted from the suspects identified and on re-examination 576 cases were confirmed as active cases. Sixty percent of the cases detected were very early cases with two to three skin lesions. This could be achieved with a very brief training of health workers and involving village voluntary workers. MLEC was found to be a useful tool for case finding in such areas.

Introduction

A leprosy project was established in 1992 in a hilly tribal area of Orissa State in India. The tribal people live on forest produce and their main occupation is agriculture. They move into deep forests or to areas where agriculture is possible in the forest and mountains. The terrain is hilly and criss-crossed by rivers and rivulets. Half of the villages are approachable only by foot.

The leprosy project was planned with the components of survey, education and treatment (SET) according to guidelines framed by the Government of India.[1] In a situation where the prevalence rates are high and population coverage is poor, WHO suggested Leprosy Elimination Campaigns (LECs). These were planned for rapid case finding and improving the level of awareness among people. The LECs are slightly modified in India depending on various local factors and conditions and the availability of trained personnel and required

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Table 1. Details of the area and personnel involved

1	Project	KORALEP
2	Area	14494 km^2
3	Population	1.47 million
4	No. villages and hamlets	6545
5	Average population of hamlets	150 (15–1500)
6	No. of PHCs	88
7	No. of MPHWs	676
8	No. of Anganwadi workers	1869
9	No. of voluntary workers	2925

infrastructure. Modified LECs (MLEC) were planned to involve staff from the general health care system. The experience with MLEC in a predominantly tribal area of Orissa, India geographically inaccessible and culturally different is described in this paper.

AREA OF OPERATION AND PERSONNEL INVOLVED

The project area covers nearly 1.5 million populations in Koraput and Malkangiri districts in the western part of Orissa, where 75% of the people are tribal. The villages are associated with small hamlets, which are scattered on the hilltops and valleys. The average population of a village is 1500 and that of a hamlet 150. There are 16 different tribes living in many of the 1940 villages, using 12 different dialects, which are very difficult for the health staff to understand. There are three main rivers and many tributaries crossing the district, which flood during monsoon months and disrupt road communications in the district.

Leprosy services in the district are provided by Koraput Leprosy Eradication Project (KORALEP) of Lepra India, with two medical officers and 30 paramedical workers (PMWs), each covering a population of 50,000.

General health care is provided by the state Government in 88 primary health care centers (PHC). Each centre has a medical officer and 1–20 multi-purpose health workers (MPHW) depending on the population covered by the centre. The state Government has employed female grass-root level workers under an Integrated Child Development Scheme (ICDS), each worker covering 500–1000 population. The workers are called *Anganwadi* workers. For the MLEC, in addition to health care workers, voluntary workers such as students, youth club members and some literate persons of the village were also involved. Details of the area and personnel involved employed for the MLEC programme are given in Table 1.

Materials and methods

The MLEC was planned to cover all the villages and hamlets in the district. The method of execution of the programme was to screen the entire population, identify persons with suspected signs of leprosy, have the suspected cases diagnosed by the confirmation team and register the confirmed cases for treatment.

The MPHWs were given 3 days training to enable them to suspect leprosy. Anganwadi workers and other voluntary workers were given 1 day's training to support MPHWs. Each MPHW had to visit 8–10 villages/hamlets. In each village a search team was formed with a

Table 2. Findings on previous surveys

Examination status in previous surveys	MB	PB	Total
Not examined	84 (48%)	173 (43%)	257 (45%)
Examined but free of leprosy	90 (52%)	229	319 (55%)
Total	174	402	576

local Anganwadi worker and one or more village voluntary workers. The team had to complete the search operation with in 6 days. On the first day, the locally formed team met with the important persons in the village, seeking their cooperation. The team visited every house in all villages and hamlets. Every household contacted by the members of the team was given a visit card *(chirkut),* which was later collected by the members of the confirmation team on their follow-up visit to keep account of household visits. The confirmation team consisted of KORALEP staff and medical officer of PHCs. They received a list of suspects from the search teams and examined each suspect to confirm or rule out leprosy.

Results

The search team visited all the houses allotted in the villages and hamlets and identified 13,907 suspects. These persons were subjected to preliminary examination by 70 teams comprising of PHC medical officers and MPHWs. Of these suspected persons, 1543 were short-listed. These short-listed suspects were re-examined by the confirmation team and 576 persons were found to have leprosy. The survey registers were checked to find out whether any of these 576 patients were examined during previous surveys. Table 2 gives details.

It can be seen that 257 (45%) of the patients diagnosed in the MLEC were not examined in previous surveys. The survey registers showed that they had migrated to the villages/hamlets after the last survey completed 2 years earlier. 319 patients were examined earlier and diagnosis was missed. The details of these 319 patients are presented in Table 3. Further analysis of these 319 patients showed that 73% had obviously been missed since the previous survey. The remaining 85 (27%) developed the disease subsequent to that survey.

The clinical details of 576 patients detected by the MLEC programme are analysed and presented in Table 4. Sixty percent of the cases were very early, with one to three lesions. There were only 62 cases with obvious deformity. It is interesting that the workers were able to identify cases with diffuse skin infiltration. There were as many as 32 (5.5%) bacteriologically positive cases.

Table 3. Duration of disease in missed patients

Duration in years	MB	PB	Total
>2 years	68 (76%)	166 (72%)	234 (73%)
<2 years	22 (24%)	63 (28%)	85 (27%)
	90	229	319

Table 4. Clinical details of patients detected in MLEC

	Number of patches				Other features	Deformity			Stain smears	
	1	2–3	4–5	>5	Infiltration	G0	GI	GII	Positive	Negative
MB	–	–	35	124	15	60	56	58	32	142
PB	38	347	17	–	–	394	4	4	–	402
Total	38	347	52	124	15	454	60	62	32	544

While analysing the patient cards, it was found that 29 patients had at least one of the family members as patients who could possibly have been a source of infection.

Discussion

The study shows that MLEC is an effective method of detecting cases in 'difficult-to reach' populations as it is in the plains and other parts of India. The MLEC has made the general public sensitive to the problem of leprosy. The approach involving the MPHWs and Anganwadi workers initially with an awareness generation programme, followed by visits to the village in groups, has sensitized the people. The response of the community was very helpful in conducting the programme successfully.

By the quick methods of search adopted, the search teams were able to visit a large majority of houses and conduct an enquiry survey of about 70% of the population. The 576 patients detected gave a new case detection rate (NCDR) of 3·9/10,000, compared with NCDR of 8·6/10,000 in the project adopting different detailed methods of case detection over a period of 150 working days. Nearly half of the case detection was achieved by adopting MLEC in a short span of 6 days.

Thirty-eight single lesion cases and 347 cases of two or three lesions were detected by MLEC. Obvious leprosy cases with visible deformity were only 62. It is significant to note that even briefly trained Anganwadi workers and village voluntary workers could detect very early cases. A further 15 patients with only oily and shiny skin were also identified during the campaign. A total of 32 out of 576 patients were bacteriologically positive, indicating that by adapting special campaigns, skin smear positive cases can also be detected.

MLEC has incidentally helped in exposing the MPHWs and other health care staff to leprosy services. This could have a great impact in future integration of leprosy work into general health care services.

The success of this MLEC programme could be attributed to the very intensive short time frame, which created interest in the community and health workers. Further, having worked with tribal people for a number of years, it has been our experience that the tribal people would at first distrust outsiders, since they are very shy and elusive. However, after getting to know us, they overcome their apprehension and become extremely cooperative, showing implicit faith in the services rendered.

MLEC could thus be an effective tool in such tribal areas, where difficult geographical factors, migration, cultural and poor health-seeking behaviour hinder the routine health programmes. Therefore, MLEC could be a suitable supplement not only to routine case

finding in the vertical leprosy programme at present, but also in an integrated approach with general health services in future.

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Lepr Rev (2000) **71,** 382–387

CASE REPORT

Acro-osteolysis prior to diagnosis of leprosy

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Summary Acro-osteolysis (bone resorption) has been observed in a heterogeneous group of congenital and acquired bone disorders. Leprosy is the main cause of peripheral neuropathy leading to acro-osteolysis in endemic countries. Pure neuritic leprosy, a less common form of the disease, is difficult to diagnose. Two unrelated leprosy patients with acropathy whose disease began as pure neuritic are discussed.

Introduction

Acro-osteolysis is part of a heterogeneous group of disorders in which progressive skeletal rarefaction leads to disappearance of one or more bone segments of the distal part of the extremities, i.e. the phalanges, or the tarsocarpal bones.[1,2] Spontaneous progressive idiopathic bone resorption has been described with minimal soft tissue loss and may be associated with additional systemic manifestations.[1] Acquired or secondary acro-osteolysis may be due to metabolic disease, peripheral neuropathy, exposure to chemicals, or may result from inflammatory and vascular processes.[1,3] Leprosy is an important cause of acral bone resorption.

Impairment more frequently occurs towards the lepromatous end of the spectrum of leprosy[4] and may occur at any stage of the disease. Mutilation, defined as the partial or total loss of a segment,[5] represents the last stage of deformity; it disables the individual for simple activities and increases the stigma carried by the disease even more. Mutilations are not as common today due to rigorous implementation of control programmes, leading to case finding and better management of the disease. Early detection of nerve damage is essential for the prevention of disability in leprosy.[6] Pure neuritic leprosy is more difficult to diagnose due to the absence of skin lesions as well as acid-fast bacilli (AFB) in slit-skin smear. Hence, for many patients with pure neuritic disease the disease progressed without treatment.

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Case reports

CASE 1

A.C.F. was a male, 39 years of age, Caucasian, native from Rio de Janeiro, illiterate and supported by welfare benefits. He was apparently healthy until November 1982, when he developed a post-traumatic vesicular lesion on the second left toe that became ulcerated and would not heal. During ambulatory follow-up, Raynaud's phenomenon, 'mal perforant du pied', painless oedema of ipsilateral great toe, alteration of sensation on extremities, plantar and elbow hyperkeratosis and multiple scars on the extremities were observed. No leprosy skin lesions were found. Neurological evaluation revealed loss of pain and temperature sensation with preservation of light touch in glove and stocking distribution, together with thickening of several nerves. Biopsies of normal skin and sural nerve showed non-specific inflammation and chronic neuritis, respectively (see Figure 1). Biopsy of bone was compatible with neurotrophic arthropathy. In later evaluations, thinning of both fifth fingers and mild shortening of the second right finger, of fourth right toe, and of both great toes was observed. Due to persistence of signs and the development of hepato-splenomegaly he was hospitalized on three occasions (1983, 1984, 1985). Over the next 5 years, he was followed without having a definitive diagnosis. Various aetiologies were considered, such as primary amyloidosis, bone tumour, leprosy and hereditary sensory and autonomic neuropathies, the latter considered to be the most likely diagnosis.

Five years later, a hypochromic hypoaesthetic macula was observed on the patient's back. The skin smear was negative but a skin lesion biopsy revealed AFB; leprosy was therefore the final diagnosis. By that time, severe deformities had developed in the form of bilateral clawing, moderate shortening of fingers and toes and chronic plantar ulcers. Treatment with MDT according to World Health Organization standards (MDT/WHO) was started on December of 1987.

In 1990 he was released from MDT/WHO with disability grade 2, but was kept under surveillance by physiotherapy and dermatology. No reactive states were diagnosed during treatment or at follow-up. Alteration of sensation persisted. He suffered from chronic plantar

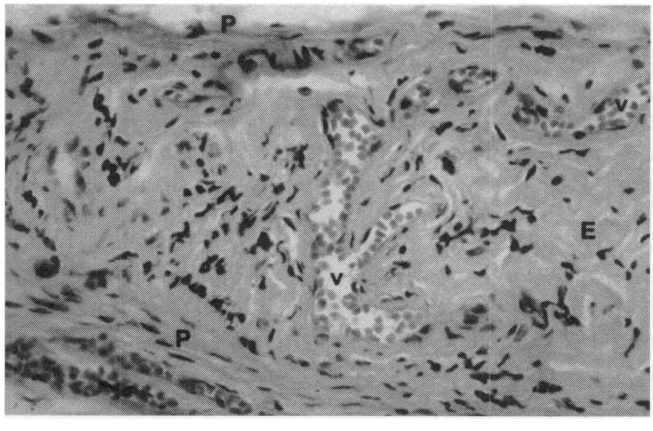

Figure 1. Case 1. Nerve histology (sural nerve, haematoxylin eosin, ×400) showing inflammatory cells and neovascularization (v) within the endoneurium (E). Fibrotic tissue is observed in substitution of nerve fibres both in the (E) and the perineurium (P).

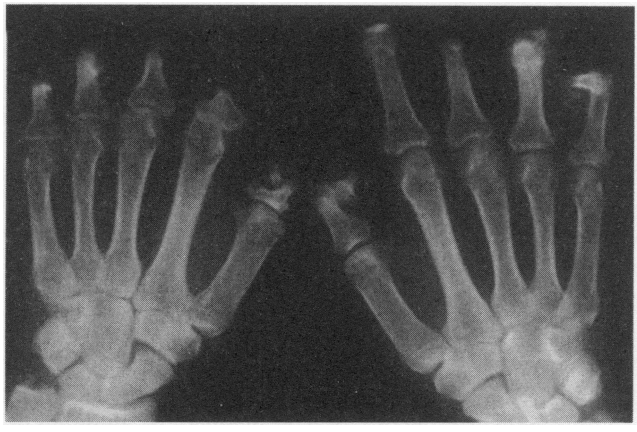

Figure 2. Case 1. Anteroposterior X-ray of hands showing various patterns of bone resorption: lateral, frontal and distal osteolysis with fragmentation. Also subluxation of 1st, 4th and 5th distal interphalangeal articulations.

ulcers and successive episodes of osteomyelitis, which led to amputation of two fingers and continuous extrusion of sequestra. Chronic Achilles tendonitis and severe acral deformities developed (see Figure 2).

CASE 2

M.F.S.B. was a female, 57 years of age, widow, seamstress and native of the State of Paraiba. She was referred to our outpatient clinic after local anaesthesia was observed following an extensive burn on the left forearm. She reported developing illness 10 years earlier with right foot anaesthesia. She sought medical assistance because of right foot drop and development of an ulcer on the fourth right toe. At that time, no investigations were done. She observed progressive shortening of the 4th right toe and development of a chronic plantar ulcer under the 4th and 5th metatarsals. The patient reported no family history of similar disease or alcohol habit.

Palmar and plantar erythema and cyanosis, right fibular nerve thickening, ipsilateral foot drop, and severe shortening of 4th and 5th right toes were observed upon admission. No leprous skin lesions were observed. Examination of sensation revealed tactile, thermal and pain anaesthesia on the topography of medial and lateral cutaneous nerves of left forearm, together with sural, fibular, saphenous, calcaneous and lateral and medial right plantar nerves. There was tactile hypoaesthesia in the distal region of the left lower extremity. Reduction in muscular force of the distal right lower extremity and of intrinsic left hand muscles was also observed. Slit-skin smears were negative for AFB. Electromyography was performed and showed lack of response of right sural and fibular nerves, with axon damage in the median, ulnar and left fibular nerves, compatible with mononeuropathy multiplex (see Figure 3). A biopsy of the right sural nerve demonstrated total fibrosis without signs of inflammatory infiltrate. Treatment for pure neuritic leprosy with multidrug therapy for paucibacillary patients (600 mg of monthly supervised rifampicin and 100 mg of daily dapsone) was initiated. She developed a plantar ulcer on the right foot, which healed after physiotherapy and care.

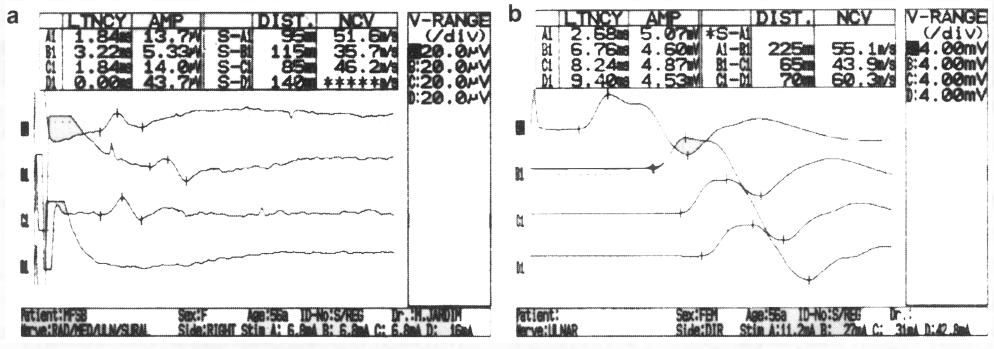

Figure 3. Case 2. Nerve conduction study compatible with mononeuropathy multiplex. (a) Sensory conduction of ulnar, radial and sural nerves shows lack of response of right sural nerve with axon damage in the median, ulnar, and left fibular nerves. (b) Motor conduction of right ulnar nerve. There is a reduction in conduction velocity and axonal damage of the nerve below the elbow.

Discussion

Neuropathy in the absence of skin lesions, known as 'pure neuritic' or 'primary neural' leprosy, is considered rare. Kundu *et al.*[7] reported a frequency of 34 in 11,000 cases of leprosy in Calcutta, while other authors report a global prevalence of 45–5%.[8,9] However, with electrophysiological evaluation and nerve biopsies, a higher prevalence is reported nowadays. In our Brazilian practice during the last 5 years, we have seen 34 cases of pure neuritic leprosy among a total of 635 patients. We have observed an increase in the detection of leprosy cases that are pure neuritic, from 192% in 1994 to 1053% during 1999.

Any neurological disease that results in loss of pain sensation in extremities without paralysis of the affected segment may result in bone resorption. Pandya[10] described the acrodystrophic neuropathies as a heterogeneous group of acquired and hereditary diseases of sensitive fibres in which ulceration of palms and soles were a prominent sign. In addition to neuropathic acro-osteolysis, primary and other acquired causes have been described[1–3] and must be considered in the differential diagnosis.

Hereditary sensory and autonomic neuropathy type I is a dominantly inherited ulcerative-mutilating acropathy with insidious onset of symptoms in the second or later decades of life.[11,12] There is progressive sensory and autonomic loss over feet and distal aspects of legs with no or slight involvement of acral parts of upper limbs. Although case 1 reported no family history of similar illness, it remained as the diagnosis of his disease due to the similarity in progression[13] until the bacillus was found. This uncommon neuropathy is to be considered as a diagnosis of exclusion. Instead, leprosy should be the most probable diagnosis in an endemic region, in the knowledge that slit-skin smear is negative for AFB in all patients with neuritic leprosy and that nerve histology can be inconclusive.[14,15] The characteristic features of electromyography in leprosy may facilitate the diagnosis; however, in many areas in endemic countries performing this study may not be possible.

In the two cases presented here, the difficulties encountered in diagnosing pure neuritic leprosy at an early stage permitted the disease to develop unchecked for several years, without receiving specific treatment. Even in endemic areas in which the clinical

features of thickened nerves accompanied by nerve deficit are known to reflect neuritic leprosy, accurate diagnosis remains hard to come by and it is often delayed if diagnosed at all. As a result, there are greater opportunities for these patients to develop deformities and mutilations especially if we take into consideration that both clinical and electrophysiological abnormalities positively correlate to the duration of symptoms of leprosy.[6]

Various epidemiological factors such as age, occupation, gender and form of leprosy have been reported to contribute to the development of disabilities and deformities.[16] Pure neuritic leprosy, either due to the difficulty in diagnosis or to the delay of patient's perception of loss of sensation, especially among illiterate individuals, allows the insidious evolution of the disease to occur unchecked. Pure neural leprosy undoubtedly adds to the prevalence of deformities in Hansen's disease. However, whatever the cause of the peripheral nerve damage, appropriate teaching about self-care of anaesthetic areas can prevent much of the secondary deformity.

As stated above, deformities and mutilations have been observed in all forms of leprosy, even in the absence of clinical signs of infection or ulcers. It is our intention to draw special attention to the not-so-uncommon pure neuritic form of leprosy that is little diagnosed. For this reason, it is imperative that neurologists keep this cause of sensory neuropathy in mind and that leprosy clinics ensure that an experienced neurologist is readily available for consultation.

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Lepr Rev (2000) **71,** 388–391

Letters to the Editor

'WALL JOURNAL' ON LEPROSY – A NOVEL METHOD TO EDUCATE MEDICAL STUDENTS

Editor,

The concept of leprosy management as a whole has changed in recent times in tune with the various operational and basic studies that are being conducted all over the world. Advances in the fields of chemotherapy, microbiology, operational aspects and rehabilitation have taken place rapidly during the past few years. We believe that the teaching medical colleges play an important role in building the health capacities needed for achieving the Alma Ata declaration of 'Health for All' by 2000 AD. Since the concepts and strategies of managing leprosy are changing so fast, the pace of keeping abreast the knowledge of medical students on many aspects is slow even today. Current knowledge regarding leprosy management has still not been adopted into the curriculum of the teaching medical colleges.

In order to provide updated information on leprosy, Bombay Leprosy Project (BLP) started the new concept of the 'Wall Journal', (WJ), which has been displayed in four medical colleges in Bombay every month since July 1991. Issues include research articles, case reports of academic interest, summary of papers presented in national and international conferences and recent publications on leprosy, besides articles on general health including TB and AIDS. The staff of the project selected the material from the literature as well as BLP's own contributions. Computers, photocopier and color photographs were freely used to make the displays attractive and arresting (Table 1).

The primary objective of this academic activity ranges from kindling an interest for leprosy in the minds of clinical undergraduate novices to honing and upgrading the knowledge of post-graduates and faculty members directly responsible for patient care as well as teaching. In order to assess its impact whether the WJ has fulfilled its objectives or otherwise, a questionnaire study was conducted.

Material and methods

For the questionnaire study, two groups of respondents were selected:

A. UNDERGRADUATE MEDICAL STUDENTS

Undergraduate medical students who had completed either a Skin & VD term or at least medicine and surgery term so as to be exposed to the clinical aspects of leprosy. The respective medical college enrollment register was consulted and the students who had completed one term of the second year were assigned numbers. The list of students was sorted out by name in an alphabetical order. All students from this sorted list were selected for the study. They were personally approached and requested to fill in the questionnaire. No questionnaires were sent by post or e-mail and the questionnaires were collected on the same day.

Table 1. Location of Wall Journal in medical colleges

Site no.	Name of medical college	Location	Started since
1	Lokmaniya Tilak Memorial Medical College, Bombay	PSM Dept	July 1991
2	Grant Medical College, Bombay	Skin & VD Dept	October 1993
3	Topiwala National Medical College, Bombay	PSM Dept	October 1993
4	Seth G.S. Medical College, Bombay	Library	May 1994

B. POSTGRADUATE AND FACULTY

Postgraduates and faculty who were directly involved in patient care were interviewed. A list of postgraduate students and the faculty members from the respective departments was obtained and the names sorted according to alphabetical order. Every fifth person was selected for the study. The procedure followed was same as for the undergraduates.

The questions ranged from preliminary information regarding how useful the information was, to the location of the WJ. Out of 80 individuals (50 undergraduates and 30 postgraduates) who were asked to fill the questionnaire, 10 declined to respond, giving a response rate of 87·5%. The questionnaire comprised eight open-ended questions. The responses were analysed. All the respondents were aware of the WJ before filling the questionnaire and the responses were graded as 1) useful, 2) satisfactory and 3) not helpful.

Results

1. Eighty to 90% of the respondents found that the WJ was useful in their academic research work and also to prepare for the leprosy competitive examination. However 60–70% felt the need for more pictures and clinically oriented material. Twenty percent thought that the contents of WJ should be comprehensive enough to enable them to read the material displayed in the shortest possible time.
2. Ninety percent of the respondents observed that the WJ should be located at a central and most frequented place such as the library and corridor of the seminar or conference halls. While 90% of the respondents thought that the ideal location for display of WJ was near the library, 80% suggested that it could also be displayed near the General Medical and Surgical Outpatient Departments. Only 2% thought that the WJ should be displayed in their own department.
3. Ten percent of the respondents thought that the quality of the WJ content should be upgraded so as to make it more attractive.
4. All the respondents strongly emphasized the need to continue the WJ, which has become one of the important sources of information about leprosy.

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WHO LEPROSY ELIMINATION CAMPAIGN — BEYOND 2005

Editor,

In this letter I should like to discuss some aspects of the WHO campaign to eliminate leprosy. Furthermore I shall advocate the prevention of nerve damage as an alternative objective for the fight against leprosy and lastly I have some remarks on leprosy control after 2005.

Elimination

WHO advocates the concept of elimination (as a public health problem), defined as being reached when the prevalence rate drops below 1/10,000. The campaign failed to reach 'elimination' in 2000. WHO has reset the target for the realization of its goal until the year 2005. The elimination would only take a 'Final Push'. To this end WHO has conceived the 'Global Alliance for the Elimination of Leprosy' (GAEL), which was joined by the Japanese Nippon Foundation (funding), Novartis (drugs) and governments of endemic countries. In addition, ILEP decided to take part in the 'Global Alliance', despite the many questions still to be answered. GAEL is an alliance of partners with often differing perspectives on elimination and it remains to be seen how well it will work.

Prevalence/incidence

I think the prevalence-related WHO target is hardly justifiable, which makes it difficult to be positive about the WHO campaign. In leprosy, many targets are more meaningful than the 1/10,000 prevalence rate.

Elimination of a communicable disease requires the reduction of transmission. WHO claims that the chain of transmission will be broken when the prevalence rate drops below the target rate, which would automatically phase out the disease. However, this crucial assumption is not supported by convincing evidence. To my mind it is highly speculative, if only because most infectious leprosy patients have already transferred the bacteria to the people around them before they are diagnosed and placed on MDT.

An effective vaccine would be helpful, but this is not available. BCG may reduce the incidence of leprosy, but most of that effect is already included in current statistics. Improvement of the socio-economic situation would also help, but this is a most unlikely scenario for most endemic regions. For operational purposes, therefore, I suggest to accept that transmission will not decrease in most endemic areas for many years to come, irrespective of the interventions now at our disposal. We should not be surprised if 6, 10, or even 30 years from now, the number of new cases will still be in the region of 500,000 per year world-wide. Leprosy is no disease for a 'final push'.

It is good to realize that prevalence has stabilized. Today it is the logical consequence of current case detection, while in the dapsone era the registers accumulated over the years. The 'dramatic' decrease in prevalence since the introduction of MDT resulted from the screening of the DDS treatment registers. Most probably, the majority of the millions patients who were 'cured' in the 1980s either never had leprosy, or no longer required any (further) treatment. Naturally the shortening of the duration of treatment also contributed to the decrease in prevalence.

Nerve damage

Leprosy is not just another communicable disease and a leprosy patient is not just someone in need of MDT. There is more to be done than merely destroying bacteria. The disabling consequences of the disease are the reason why it is a special case. Therefore, anti-leprosy programmes should be focused on the occurrence of nerve damage and disability.

An important 'hidden' problem in this field is the time lag between the appearance of leprosy in a patient and the start of MDT. This delay is a major cause of nerve damage and therefore a major leprosy control problem. Yet it is not reflected in official prevalence and case detection rates. Shortening the time lag is much more meaningful than increasing the case detection as such.

The other problem area is the occurrence of nerve damage during MDT. The patient may be found in time and put on MDT, but the programme staff fail to recognize neuritis and treat it. This is unacceptable, because once the nerves are impaired, the major battle is lost.

Alternative elimination goal

We may never rid the world of leprosy as a bacterial disease, but we do have the means to eliminate leprosy as a disabling disease. Prevention of nerve damage and disability in every patient should become the core of leprosy control. Thus, instead of focusing on a WHO defined prevalence rate, we should improve the quality of leprosy control programmes in terms of the prevention of nerve damage and disability. This implies that we should find ways of using the incidence of nerve damage as a performance indicator. I trust our public health experts will be able to translate this into meaningful targets such as earlier detection, improved monitoring of patients during MDT and training of health workers in nerve damage control.

We should also ask scientists to increase our understanding of the nerve damage process, in order to improve our ability to prevent nerve impairment during and after MDT.

Beyond 2005

What will happen after 2005? Even if the prevalence target is reached, the epidemiological situation will have scarcely changed. WHO and its sponsors may be looking for new challenges outside the leprosy field. National health authorities may follow WHO in declaring that leprosy has ceased to be a public health issue. Certainly, the disabled 'ex'-leprosy patients and the millions who will need MDT after 2005 will lose out.

In 2006 the contributions of leprosy NGOs such as those in ILEP (contributing some $60 million/year) will be needed even more urgently than today. Most of these NGOs are fund-raising organizations. Their hundreds of thousands of supporters, reading about the 'final push' and 'elimination', will be happy to conclude that other causes more urgently need their donations. The WHO campaign risks damaging the credibility of those raising funds for leprosy, if donors perceive their fundraising efforts as contrary to WHO publicity. Credibility is the Achilles' heel of the fund-raiser.

For the efforts of GAEL to be translated into long lasting and sustainable benefits to all people affected by leprosy now and in the future, such potential problems need to be addressed in a spirit of true partnership based on mutual respect.

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Teaching Materials and Services

ALERT Training Calendar 2001

January 24–February 28
Prevention and management of disabilities

Target group: physiotherapists, occupational therapists, podiatrists as well as experienced leprosy workers involved in POD. Emphasis on both patient care (early detection of nerve deterioration, health promotion, problem solving) and programme management (POD management, home based care and rehabilitation).

February 12–March 2
Clinical leprosy and tropical dermatology for physicians

Highly recommended for the participants in the following 'Management of Combined Programmes' course who need to refresh their knowledge of clinical leprosy and tropical dermatology. The course can also be taken on its own by physicians responsible for diagnosis, treatment and care of patients with leprosy in either a hospital or a control programme setting.

March 5–March 23
Management of combined leprosy and tuberculosis control programmes for physicians

Target group: experienced physicians responsible for managing a leprosy and TB control programme at the regional level or above. Emphasis on programme management: needs analysis, action plan, implementation of activities, supervision, evaluation, management of POD. Participants without leprosy experience should also take the preceding 'Clinical leprosy' course.

May 7–May 25
Essentials of leprosy and tuberculosis for administrative and programme support staff

Target group: administrative and managerial staff without a medical background, working in leprosy and TB programmes and donor agencies. Objectives: to gain a better understanding of the two diseases, to communicate more effectively with the medical staff, and to contribute more efficiently in decision making and priority setting.

October 1–October 12
Introduction to leprosy

Course specifically aimed at the participants in the following 'TB Programme Managers Course' who want to profit from their visit to ALERT to learn about leprosy. The course can also be taken on its own.

October 15–November 2
Tuberculosis Programme Managers Course

This course is organized jointly with the Nuffield Institute for Health, Leeds University, UK. Target audience: health managers responsible for TB control activities at the national or intermediate level. Course objective: to present the concepts on which TB control strategies are based and to identify key programme elements. The course modules are organised around the stages of the programme management cycle.

November 12–November 23
Clinical leprosy for senior field staff

Highly recommended for the participants in the following 'Management of Combined Programmes' course who need to refresh their knowledge of clinical leprosy. The course can also be taken on its own.

November 26–December 14
Management of combined leprosy and tuberculosis control programmes for senior field staff

Target group: experienced nurses, paramedical workers or supervisors responsible for leprosy and TB control at the district (or equivalent) level. Emphasis on planning, implementation, supervision and evaluation of control activities, with special attention for POD, health promotion and support functions. Participants without leprosy experience should also take the preceding 'Clinical leprosy' course.

In-Service Training

In-service training, tailor made to the individual trainee's needs and interest, can be arranged in surgery, physiotherapy, dermatology, ophthalmology, laboratory etc.

For further information, please contact: ALERT Training Division, PO Box 165, Addis Ababa, Ethiopia. Tel.: +251-1-711524 or +251-1-712792, Fax: +251-1-711199 or +251-1-711390, e-mail: Alert@telecom.net.et

International Course for leprology physicians

This course will be held from 24th to 28th October 2000, at the Generalidad Valenciana and General Hospital, Valencia, Spain. The course is aimed at residents in their 3rd year of specialization in dermatology and qualified physicians who are working in leprosy-endemic countries. For details and registration, please contact: Dr Jose Terencio de las Aguas. Tel: +34 966 42 5322, Fax: +34 966 42 3353, e-mail: drjoseterencio@hotmail.com.

Asian Leprosy Congress

The Asian Leprosy Congress will take place between 9th and 13th November 2000, in Agra, India. Delegates may register up to 10th October 2000. Contact details: Asian Leprosy Congress, c/o The Leprosy Mission India, CNI Bhawan, 16 Pandit Pant Marg, New Delhi 110 001, India. Tel: +91 11 6889492, 4675262, 3716920, Fax: +91 11 4678030, 3710803, e-mail: info@asianleprosy.com/ tlmindia@del2.vsnl.net.in. Online booking available through www.asianleprosy.com.

The Wellcome Trust, London: Training Fellowships and Awards

Training Fellowships for Research into Infectious Diseases for Scientists from Tropical and Developing Countries

The Trust recognizes the continuing threat of infectious diseases in tropical and developing countries and wishes to develop research expertise which is sustainable in these countries in order to address health problems arising from infectious diseases. The awards are intended to provide both training and research experience for applicants, who must be based in a developing or tropical country. The training will be obtained at international centres of excellence in either the UK, Republic of Ireland, or any country in the developing or restructuring world, and a substantial period of research will be undertaken in the applicant's home country. For instance, a 4 year award would normally include a minimum of 2 years' research in the home country over the period of the award AIDS/HIV related studies relevant to tropical regions are fully supportable.

ELIGIBILITY

Applications are invited from postdoctoral basic scientists or medical graduates of up to 6 years' research experience (postdoctoral) who are nationals of developing countries. Applications may be considered in exceptional circumstances from those who are educated to first degree or Master's level, who are able to demonstrate substantive potential for research and operational leadership and who have research experience equivalent to a PhD, as evidenced by their publication record. Applicants will wish to become independent research scientists through high quality research into infectious diseases of regional significance to their home country. The research proposal must include a clear argument outlining the relevance of the project to the home country. Applications will be assessed on the basis of the candidate's achievements in research, the scientific merit of the proposal and the appropriateness of the research for the proposed location. The nature of the training component and the training site chosen must be appropriate for the proposed research.

FUNDING

Awards will be for a maximum of four years, non-renewable. Fellowship support may include a salary/stipend appropriate to the countries in which the candidate will be studying/working, as well as project-dedicated and travel expenses. All expenses must be fully justified. Consideration may also be given to the expense of attending a course leading to a recognized qualification in a discipline relevant to the fellowship research programme.

APPLICATION PROCEDURE

The preliminary approach to the Trust should include an outline of the proposed research, an approximate budget and *curriculum vitae* of the applicant, together with a written guarantee of subsequent employment from the host institution in the applicant's home country and a letter of support from a suitable sponsor at the training institution. Applications will be considered throughout the year. Further information about the initiative can be obtained from:

The Grants Section (Tropical)
The Wellcome Trust
London NW1 2BE
Tel: +44 (0)207 611 8409
Fax: +44 (0)207 611 7288
Email: tropical@wellcome.ac.uk

Information is also available on the Web site **www.wellcome.ac.uk**

NB: *Applicants may not apply for more than one Trust fellowship scheme at any one time.*

Health Services Research Awards for Medicine in Developing Countries 2000

The Trust has a long-standing interest in tropical medicine research and awards are offered to encourage research into the effectiveness of health interventions in developing countries. Applicants for these awards may relate to any disease, infectious or non-infectious, that is of importance in tropical regions. Cancer research and HIV-related studies relevant to tropical regions are also acceptable.

Health Services Research is defined as the identification and quantification of health care needs, and the quantitative study of the provision and use of health services to meet them. Such research is usually multidisciplinary and should preferably involve formal links to ministries of health, or non-government organizations, and provide evidence that the research findings might be adopted in policy and practice.

PROJECT GRANTS IN TROPICAL HEALTH SERVICES RESEARCH

These awards will provide research costs for up to three years for studies that focus upon issues relating to the effectiveness of health services in tropical countries. Applicants for *project grants* must hold an established post in an eligible university or research institute in the UK or Republic of Ireland, or in a developing country.

Project grant proposals in Tropical Health Services Research will be considered three times a year and applications will be considered by the next available meeting of the advisory committee.

Enquiries should be directed to:

The Grants Section (Tropical)
The Wellcome Trust
183 Euston Road
London NW1 2BE
Tel: +44 (0)207 611 8641
Fax: +44 (0)207 611 7288
Email: tropical@wellcome.ac.uk

The Trust offers a range of awards for UK and overseas nationals who wish to undertake research in any branch of the natural or clinical sciences, which has a bearing upon human or animal health. Further schemes that may be relevant to individuals with an interest in tropical medicine are available. Details of all awards are available upon request from the Trust or can be viewed on **www.wellcome.ac.uk**

The Robert Cochrane Fund for Leprosy

We are indebted to Caryl Guest, Administrator, The Royal Society of Tropical Medicine and Hygiene, London, and Irene Allen, Editorial Assistant, LEPRA, Colchester, for the following information:

The Robert Cochrane Fund for Leprosy was created in February 1983, using funds left over following the closure of the Leprosy Study Centre (formerly the Leprosy Research Fund). It was established at the request of the Leprosy Study Group, which granted the Royal Society of Tropical Medicine and Hygiene the use of both the capital and the interest on the balance of their funds. The intention was that the Society should '... use the accruing interest and the capital of the Fund at its discretion in any ways that would encourage the study of leprosy.' (Minute 5.1 of 17 February, 1983). This was accepted with acclamation and the Fund has been administered by the Royal Society ever since.

Robert Cochrane died in August 1985, after a long and distinguished career in the field of leprosy. Obituaries published in *Leprosy Review* (1986), 57, 67–69 and in the *Times* newspaper of 6 August 1985 paid tribute to an outstandingly gifted, dedicated and energetic contributor to many aspects of leprosy. He graduated in medicine from Glasgow University in 1924 and in the same year sailed for India under the auspices of the Mission to Lepers (now The Leprosy Mission) and joined Dr Ernest Muir in Calcutta, before appointments in Purulia and Bankura in West Bengal. He began a long association with BELRA (now LEPRA) in 1929 and attended a meeting in Manila in 1931, leading to the formation of the *International Leprosy Association*, of which he was the first Secretary-Treasurer. Later he became Chief Medical Officer in Chingleput, South India and Director of the Leprosy Campaign in Madras State. In 1944 he was appointed Director of the Christian Medical College in Vellore. In 1948, with support from the Wellcome Medical Foundation, he founded the Leprosy Research Fund (later the Leprosy Study Centre) in Wimpole Street, London, for research and training. His influence during the ensuing years and the wide contacts he made with people working in many areas of research, clinical medicine and surgery was of crucial importance in helping to transform leprosy into a subject worthy of 'respectable' recognition.

The Fund in his name was intended to be used to finance up to three travel Fellowships per year, to a maximum of £1000 each. Support has been offered for 1) leprosy workers who need to obtain practical training in field work or in research and 2) experienced leprologists to provide practical training in a developing country. There is no restriction on the country of origin or destination, provided these requirements are fulfilled. All applicants must be sponsored by a suitable representative of the applicant's employer or study centre, and agreed to by the host organization.

Awards have been made every year since 1986 by applicants from diverse fields of leprosy, including surgery, rehabilitation, immunology, pathology, dermatology, ophthalmology, molecular medicine and social aspects. A review of the 44 applicants in the 14 years of the existence of the Fund reveals many exchanges between the United Kingdom and South-East Asia, together with others from workers in Nigeria, Zambia, Uganda, China, Malaysia, USA, Canada and Peru. All applicants are required to submit a brief report on return to their country of origin and these have invariably recorded appreciation and thanks for timely financial support which, in many cases, would have been difficult to obtain from other sources.

The Robert Cochrane Fund for Leprosy, created 17 years ago in the name of one of the UK's most distinguished leprologists, is still active, financially viable and interested to receive applications, based on the conditions given above, from leprosy workers or leprologists in any part of the world. Further information is obtainable from The Administrator, The Robert Cochrane Fund for Leprosy, The Royal Society of Medicine, Manson House, 26 Portland Place, London W1N 4EY, United Kingdom. Fax +44 (0)20 7436 1389. Tel +44 (0)20 7580 2127.

Access to reliable drug information in resource-poor countries

The following appeared in the latest issue of the Newsletter of INASP (International Network for the Availability of Scientific Publications), No 14, May 2000:

'A prerequisite for rational prescribing, dispensing and safe drug use'

By Neil Pakenham-Walsh (INASP-Health) and Philippa Saunders (Essential Drugs Project)

'The rational use of drugs demands that the appropriate drug is prescribed, that it is available at the right time at a price people can afford, that it is dispensed correctly, and that it is taken in the right dose at the right intervals and for the right length of time. In addition, the appropriate drug must be effective, and of acceptable quality and safety.' WHO 1987

Rational prescribing and use is a vital principle in all healthcare systems. In resource-poor countries—where health spending might be less than 10 dollars per person per year—cost-effective

use of drugs is important not just for the individual patient but for the viability of the health system as a whole.

However, protagonists of rational prescribing in developing countries are struggling to make themselves heard, and the rational use of drugs is neglected in schools of medicine, nursing and even pharmacy. In many countries, the sociocultural, professional and regulatory environment works against the safe and prudent use of medicines. For example:

—there may simply be no relevant, up-to-date, comparative information available, or, if there is, such information may be unaffordable, or it may not be used
—there may be no national drugs policy supported by legislation and a functioning regulatory authority—an essential drugs list, up-to-date national formulary, and therapeutic guidelines may not exist
—rational use of drugs may be excluded from the pre-service training curriculum and continuing medical education of doctors and other prescribers—drugs are commonly prescribed by nursing staff in many health services; their education, too, requires that there is access to appropriate information and training
—prescribers may be reliant on, or have become used to, free information provided by individual pharmaceutical companies—as one colleague has put it: 'Drug companies offer inducements to prescribe their products to doctors virtually as soon as they enter medical school, a practice that continues throughout their professional careers.'

It is tempting to point a finger at the pharmaceutical industry, whose promotional practices can encourage the over-use of drugs, as well as sales of drugs that are inappropriate and unnecessarily expensive. We should expect companies to provide consistently reliable information about their products. However, it is the responsibility of governments and health professionals to ensure that comparative information is produced and distributed, and to provide a context which supports the safe, effective and economical use of drugs. In countries where self-medication, even with prescription drugs, is a fact of life it is essential that information for consumers is usable (performance tested) and complete.

In the United Kingdom a variety of agencies operate international schemes with the aim of improving access to reliable drug information in developing countries. These include:

—The Pharmaceutical Press is currently developing a CD-ROM that gives step-by-step guidance on how to write a formulary.
—The International Society of Drug Bulletins (ISDB) supports independent drug bulletins worldwide.
—The Commonwealth Pharmaceutical Association and Book Aid International together distribute thousands of used and new copies of the British National Formulary and Martindales to developing countries through a scheme called Pharmaid.
—Teaching-Aids at Low Cost (TALC) includes the BNF in its catalogue at a special low price, with the agreement of the publishers—the Pharmaceutical Press and the BMJ Publishing Group.
—Practical Pharmacy, a training newsletter which addresses the needs of district and sub-district pharmacy staff and prescribers is sent free to several thousand recipient organizations. WHO'S Essential Drugs Monitor is also obtainable free.
—Specialized electronic discussion networks, notably E-Drug and INDICES, facilitate exchange of information, and are available to anyone with access to email.
—The World Health Organization's web site is a good source of pharmaceutical information and the WHO Model List of Essential Drugs can be found there. An online formulary will shortly be available.

WHAT NEXT?

Much is already being done by a range of organizations, but there is little evidence that international efforts are having the impact they should at a global or national level. The task ahead is formidable but achievable and will require concentrated effort, better cooperation, and also resources.

As access to electronic media improves, the potential for obtaining necessary drug information via CD-ROM, e-mail, and web-sites will increase. However, while information technology offers great opportunities, print media will for some time continue to be the only means of access for many end users.

All efforts to improve access to information must harmonize with national essential drugs policies, national formularies and therapeutic guidelines and improved education for consumers as well as prescribers. Drug information specialists in developing countries need access not only to information, but also to professional support, equipment, standards and guidelines, and training. Meanwhile, better indicators are needed to demonstrate the impact of irrational prescribing on the health and welfare of patients, and the financial burden on national healthcare systems.

In September 2000, the Health Information Forum will hold a special meeting at the British Medical Association, London, on 'Access to reliable drug information in resource-poor countries'. All with an interest are invited to attend or to contribute by email.

For further details, please contact Neil Pakenham-Walsh at: INASP Health@compuserve.com

Email addresses and Web sites in this article

Essential Drugs Project	edp@gn.apc.org
Practical Pharmacy	gstock1@compuserve.com
BMJ Publishing Group	www.bmjbooks.com
Book Aid International	www.bookaid.org
CPA	www.jr2.ox.ac.uk/Pharmacy/CPA/CPAhomepage.html
INASP	www.inasp.org.uk
ISDB	pm.usm.my/isdb
Pharmaceutical Press	www.pharmpress.com
TALC	www.talcuk.org
WHO	www.who.int

Public libraries in Africa. A Report and Annotated Bibliography

The following is taken from the latest issue of the Newsletter of INASP, PO Box 2564, London W5 1ZD:

Over the past 10 years much has been written in the professional press about the state of and role for public libraries in Africa. The overall impression has been one of declining budgets and failures in established public library services. In the midst of this overall trend, however, there have been some notable achievements in alternative and innovative approaches to the provision of a public library service in Africa.

Public Libraries in Africa: A Report and Annotated Bibliography provides an analysis of these trends, based on literature reviews of recent publications and reports from selected countries in Africa.

The study that resulted in the compilation of this book is a first step in a process being undertaken in order to initiate a programme to revitalise services to the public so that they can fulfil their role of providing relevant information to the majority of the population. Without access to this information, the people will not be empowered to participate in the development that is necessary for the improvement of their living standards.

The book comes with an extensive annotated bibliography and country reports. The information provided in these is drawn together into a short synthesis report which summarizes the overall position of public library services and proposes directions in which services to the public should be moving. A short additional literature review is also included.

The consensus of opinion arising from the study is that African librarians need to rethink what a

public library service is all about. Public libraries in Africa need to be more aggressive and introduce services that are attractive to their users. Librarians must get to know their potential users, and not automatically assume that they are simply students and school children who uses a library only for study purposes.

The introduction of alternative services, and a balance between the services offered to urban and rural populations, are areas requiring particular attention. The report suggests that long-term realistic strategic plans are required for public library development. Such plans should be prepared on a country basis and should be founded on professionally conducted user-needs and user-satisfaction surveys.

Issak, Aissa
Public Libraries in Africa: A Report and Annotated Bibliography.
Oxford: International Network for the Availability of Scientific Publications (INASP), 2000. 199p.
ISBN 1 902928 00 8
Price: £15.00 + p&p.

The publication can be ordered from INASP. A limited number of complimentary copies is available for libraries in Africa.

Videos on leprosy from WHO

The latest catalogue from WHO on videos for a) the general public, b) school children and c) the specialist training of health professionals, includes two on leprosy:

Dawn
1991, 20 minutes

Subject
Leprosy

Audience
Health workers, public health officials

This film describes the importance and effectiveness of multidrug therapy as a tool for the treatment and control of leprosy. As stories about individual cases show, the possibility of a cure gives leprosy patients a compelling reason to seek immediate treatment, rather than try to hide the disease.

The film also illustrates the role that family and community support play in making an effective treatment have the greatest impact. In a supportive environment, patients are far more likely to recognize early signs of the disease, seek prompt treatment, and take the medication exactly as instructed.

A Winnable War
1991, 25 minutes
Co-produced by WHO and Worldwide Television News (WIN)

Subject
Leprosy

Audience
General public, public health officials

Filmed in India and Zambia, this dynamic television reportage shows how the introduction of a modern treatment for leprosy may make this 'ancient scourge' a disease of the past. Multi-drug treatment, developed and promoted by WHO, is a powerful weapon in the battle to control and eventually eliminate leprosy. Moreover, with an effective treatment now available, sufferers of leprosy can take heart that their disease has a cure.

In scenes from India and Africa—two ancient strongholds of leprosy—we watch the dramatic success of multi-drug therapy, the striking cures it produces, and the hope it reawakens in individuals and communities. These scenes make it clear that, if resources are made available, the war against leprosy can be won.

Further enquiries Distribution + Sales, WHO, 1211 Geneva 27, Switzerland.

Lepr Rev (2000) **71,** 400–416

News and Notes

The genome mapping of the leprosy bacillus completed

The genome of the leprosy bacillus has been completely sequenced thanks to collaboration between Stewart Cole's team at the Institute Pasteur in Paris, and the Sanger Centre in the United Kingdom. The comparison with the genome of the tuberculosis bacillus (whose genome sequencing was published by the same teams in 1998) provides essential information on the two diseases, as Professor Stewart Cole will explain during the international seminar *Genomes 2000*, being held this week at the Pasteur Institute in Paris. Keep in mind that WHO estimates there are around 800,000 new cases of leprosy in the world each year, and that 2 million people suffer from severe disabilities as a consequence of this disease.

Comparative studies on comparing the TB and Leprosy Bacillus genomes have already begun. This could help to identify the growth factors absent in leprosy that would make its study easier, which would be useful in the eventual production of a vaccine.

Some genes present in the leprosy bacillus are not found in the TB bacillus. These genes could be used to provide diagnostic tools for skin tests to detect leprosy, and might also provide information on the nerve damaging characteristics of the bacillus.

The comparative approach being used might allow the identification of new therapeutic targets and could be useful in the rational creation of drugs for the treatment of leprosy.

Blocking natural killer cell activity

The latest issue of *Isis Innovation News*, University Offices, Wellington Square, Oxford OX1 2JD, United Kingdom, e-mail innovation@isis.ox.ac.uk; Web: http://www/isis-innovation.cm/ carries the following report from Professor Andrew McMichael's group in the *Institute of Molecular Medicine*, Oxford:

Recently acquired knowledge of the molecular interaction between HLA-E molecules and Natural Killer (NK) cells yields commercial opportunities for quantitating and manipulating these cells in vivo and ex vivo, screening for pharmacophores which block NK action, as well as to explore a genetic engineering approach for improving the 'take' of transplanted donor organs.

Background

Natural Killer cells, accounting for up to 15% of blood lymphocytes, are cytotoxic cells capable of mediating the immune response by recognizing and killing, for example virally-infected and tumour cells. Their ability to kill is generally considered to be inversely correlated with the expression of Class I major histocompatibility (MHC) molecules on the target cell surface. A subset of T Cells also expresses NK receptors.

The Oxford Invention

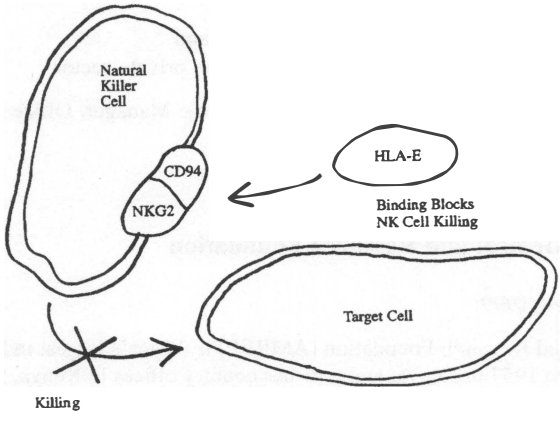
Professor Andrew McMichael and his team at the Institute of Molecular Medicine, Oxford have discovered that HLA-E, a non-classical MHC molecule, acts as a ligand for the CD94/NKG2 receptor

complex in the NK cell surface membrane. The interaction blocks NK cell killing, and hence may be exploited in order to modulate the immune response, for example to suppress or activate NK cell activity, or to identify and isolate NK cells, as set out below:

1. Diagnostic Reagent. HLA-E tetramers (biotinylated HLA-E molecules linked via streptavidin) provide a convenient NK-specific reagent, allowing NK cells to be separated by FACS analysis. This approach would enable monitoring for NK cell levels in, for example, patients with lymphoma, leukemia or other cancers, infectious diseases and transplantation, where NK cells may mediate graft-versus-host disease.
2. Depletion and Killing. HLA-E tetramers, coupled to toxins, can be used to deplete NK cells, for example, in bone marrow grafts prior to transplantation.
3. Isolation. Recovery of NK cells is feasible using the HLA-E/CD94/NKG2 interaction. This may be of value in patients with low NK cell levels, the isolated cells being expanded *ex vivo* and re-infused.
4. Screening. An *in vitro* cell assay system is available for screening combinatorial libraries of small molecules to identify pharmacophores capable of inhibiting NK cell activity.
5. Genetically-Engineered Resistance *In Vivo.* Immunotherapy for transplantation applications is envisaged whereby gene vectors encoding HLA-E sequences are integrated into target cells of donor organs in order to invoke NK cell 'resistance'.

Commercialization

Professor McMichael and his group welcome expressions of interest from manufacturing companies interested in co-developing products under the various applications of this invention.



Alliance For Health Policy and Systems Research

An information brochure from WHO carries the following introduction:

'The Alliance for Health Policy and Systems Research promotes the widest possible participation of institutions using and producing health policy and systems research to ensure a bottom-up source of direction and advice for its activities. The Alliance benefits from the support of a Board under the auspices of the Global Forum for Health Research.

WHO will implement this initiative through the Global Programme for Evidence on Health Policy.

This ensures the Alliance close collaboration and co-ordination with WHO activities for HPSR, and links WHO directly to a widespread collaborative network of institutions for the ground-up expression of demands and views related to HPSR.

The Alliance seeks the partnership of institutions in countries involved in the production or use of health policy and systems research, particularly when it relates to developing countries. Interested institutions can apply for partnership either by mailing the attached form, by mailing a separate letter of intent or by completing the Web site notice.

A contribution will be requested from partners, with an exemption for institutions in low-income countries. The contribution will be requested from institutions from the second year after joining the Alliance and its amount will be established in consultation with partners.'

The Priorities for HPSR are listed as follows:

The Alliance Board proposes the following general priorities, identified through consultations in 1998–99:

Health system functions of regulation, organisation, financing and delivery of services.
Social and economic policies with consequences for health care system development and reform.
Policy implementation in the context of global trends influencing policies, yet differing country health systems and needs.
Health system equity in financing, coverage, access, use and quality of care, conceived as risk factors for health.

These priorities are consonant with the work of WHO's cluster on Evidence and Information for Policy, particularly with the following tasks of the Global Programme on Evidence for Health Policy:

- measuring health system performance, especially responsiveness, fair financing and equity
- improving health system descriptions
- analysing health financing and organizational methods, and
- developing evidence to support public policy towards the private sector.

Further information: Miguel A. González-Block, Programme Manager, Office No. 3148, WHO, 1211 Geneva 27, Switzerland.

AMREF: African Medical and Research Foundation

From the *Annual Review* 1999:

The African Medical and Research Foundation (AMREF) is Africa's largest indigenous health charity. AMREF was founded in 1957 in Kenya, and now has country offices in Kenya, South Africa, Tanzania and Uganda. AMREF also has field offices in Ethiopia, Mozambique, Rwanda, Somalia and Sudan.

AMREF UK is one of 11 international offices in Europe and North America that raise funds to support the charity's work in Africa. AMREF has 500 staff representing 15 nationalities; 97% of them are Africans. Its annual total budget is over £10·5 million, to which AMREF UK contributes over £1 million.

AMREF is about innovation. It is about research, and it is about communities. But above all, AMREF is about health—good health.

AMREF works with East Africa's poorest and most vulnerable people. Our goal is for them to gain the knowledge, means and power to improve their own health.

For 42 years, AMREF has pioneered effective health care in East Africa. The innovation continues. This year we appointed a new Director General and a new professional, international Board. Working from our Nairobi headquarters, they will focus on increasing our impact all over Africa.

After successful work in South Africa, AMREF has also opened offices in Mozambique, Ethiopia

and Southern Sudan. There, we train district health teams to pass on affordable and appropriate schemes to local health workers and villagers.

This year too AMREF won the prestigious $1 million Conrad Hilton Prize, given for the first time to an African organisation. Smithkline Beecham and AMREF have also started work on a major $1 million project to teach basic hygiene and sanitation at primary schools throughout Kenya.

Intercapital, the UK's largest derivatives broker, supported AMREF with a share of the £1·3 million raised at their annual charity day. Chairman Michael Spencer summed up the reason why his company chose AMREF. 'It makes sense to enable local experts, in partnership with communities, to get on with what really works for them, rather than providing what we in Britain imagine they require.'

Further information:
AMREF
4 Grosvenor Place
London SW1X 7HJ
Telephone 0207 201 6070
Facsimile 0207 201 6170
E-mail amref.uk@amref.org
Website www.amref.org

'Molecular Pathology' edition of the *Journal of Clinical Pathology* (UK)

Molecular Pathology is a bimonthly edition of *Journal of Clinical Pathology*. It is a multi-disciplinary journal which draws together in one publication basic molecular research and new molecular techniques relevant to diagnostic pathologists and scientists.

The journal publishes original articles of molecular studies on human material relating to pathogenesis and disease processes, expert reviews, brief communications, a regular Demystified series and occasional focused issues such as the August 1999 issue on Cell Adhesion Molecules. Molecular Pathology is fully refereed.

Molecular Pathology is indexed in ISI Current Contents, Index Medicus, Excerpta Medica and is available through Ovid, BIDS/Ingenta, and OCLC.

Papers should be submitted to:
The Editors
Molecular Pathology
Department of Histopathology
Birmingham Heartlands Hospital
Bordesley Green East
Birmingham B9 5SS
Fax: 0121 773 1182
Email: molpath@bhamheartlands.freeserve.co.uk

WHO Liaison: newsletter of the WHO Library and Information Networks for Knowledge

Liaison is published three times a year in English, French and Russian by the World Health Organization, Library and Information Networks for Knowledge, 1211 Geneva 27, Switzerland.

Telephone: Int. code 41—(22) 791 20 68
Cables: UNISANTE GENEVA

Fax: Int. code 41—(22) 791 41 50
Telex: 415 416
E-Mail: LIBRARY@WHO.CH

Editors: Mrs I. E. Bertrand and Miss V. L. Paterson

The latest issue received carries articles on:

(1) lack of resources for research libraries in developing countries, (2) managing information in research institutions: the role of the library, (3) the state of the world's refugees, (4) new books and journals for the WHO 'Blue trunk libraries' and (5) Internet tips (subject catalogues, search engines and meta search engines).

TDR: *Special Initiatives to Support Academic Programme Development*

The February 2000, No. 61 issue of TDR News carries the following information:

TDR's Research Capability Strengthening programme supports the development of selected academic programmes in developing countries in line with TDR's policy of promoting training within a trainee's own country or region. Current initiatives include support to three MSc programmes in clinical epidemiology and biostatistics in Africa (National University of Benin, University of Witwatersrand—South Africa, Makerere University—Uganda). The University of Witwatersrand programme commenced in January 2000, with the other two programmes expected to enrol their first student by October 2000. Past initiatives have included two regional MSc programmes in health economics (University of Capetown—South Africa, Chulalongkorn University—Thailand).

Further enquiries: TDR News: UNDP/World Bank/WHO Special Programme for Research + Training in Tropical Diseases, WHO, 1211 Geneva 27, Switzerland.

The Heiser Program for Research in Leprosy and Tuberculosis

The current 2000 information brochure opens as follows:

Dr. Victor George Heiser devoted his life to the study and treatment of tropical diseases, leprosy in particular. An associate director of the international health division of the Rockefeller Foundation, he circled the earth 17 times on his medical missions, and recounted his experiences in a best-selling autobiography, *An American Doctor's Odyssey*, published in 1936.

In 1969, he recalled that 'sixty years ago it became my responsibility and duty to gather up 10,000 lepers in the Philippines and transport them to a leper colony. The hope then was that isolation could reduce the incidence of the disease and perhaps eventually wipe it out. It didn't work. Now we have a new system—the clinic system—and that, too, has had practically no effect whatever in statistically reducing the incidence of leprosy. Indeed, it is apparently increasing in many parts of the world. But we must not sit idly by while so many people suffer from this horrible disease.'

The current world leprosy situation has vastly improved since Dr. Heiser's time. The World Health Organization has estimated that the total number of estimated and registered cases now stands at 1·3 million and 940,000, compared to 10–12 million and 5·4 million respectively, in 1983, and the WHO has set a goal of reducing the leprosy burden to one patient per 10,000 population over the next few years.

The Heiser Program for Research in Leprosy and Tuberculosis has made a major commitment of funds for the completion of the ongoing project for determining the DNA sequence of the entire genome of *Mycobacterium leprae*.

The Program will now commit funds in the form of research grants to accelerate WHO efforts to eliminate leprosy as a public health problem throughout the world.

Research grants provide limited support to scientists to allow them to contribute to the global goal of leprosy elimination.

Postdoctoral research fellowships support young biomedical scientists in beginning postdoctoral training for research in leprosy and/or tuberculosis.

Address applications and inquiries to:
Barbara M. Hugonnet, Director
Heiser Program for Research in Leprosy and Tuberculosis
450 East 63rd Street
New York, New York 10021 USA

'Drug-resistant tuberculosis can be controlled' says WHO

From the *British Medical Journal*, volume **320**, 25 March 2000, www.bmj.com:

The World Health Organization (WHO) has for the first time assembled hard evidence that the emergence of drug resistant tuberculosis can be held back by properly controlled treatment programmes.

It warns, however, that the 'window of opportunity' to prevent the spread of drug resistant strains will be missed if urgent action is not taken to persuade more health authorities and doctors to use its recommended treatment strategy, which still reaches only 1 in 5 patients with tuberculosis worldwide.

The warning comes in a global report released this week on World Tuberculosis Day at a ministerial summit in Amsterdam. It shows a disturbingly high prevalence of drug resistant strains of *Mycobacterium tuberculosis* in parts of eastern Europe and Asia.

By contrast, countries that have used the recommended treatment strategy tend to have very low rates of resistance. 'We only see significant drug resistance in countries without good control programmes,' said Dr. Marcos Espinal, an epidemiologist and head of the report's team of authors.

The WHO has been arguing for directly observed treatment, short course ('DOTS') for years on the basis of small scale studies that show it helps to prevent the emergence of resistance.

But this report is the first that allows it to show a clear inverse relation between the numbers of patients receiving DOTS and the prevalence of resistant strains in a widespread sample of populations. 'This conclusion is a ''no brainer'' to those of us who have been involved in DOTS, but now we have the evidence,' said a WHO spokesman.

The report is only the second global survey of the prevalence of drug resistant strains of *M. tuberculosis*. The first, in 1997, was based on just 35 sample populations.

The new report has data from 58 countries and other settings (such as provinces of China) and enough data to detect trends in 28. Its authors warn, however, that the picture is still incomplete. The scale of drug resistance is not fully known in the five countries with the highest incidence of tuberculosis worldwide: India, China, Indonesia, Bangladesh, and Pakistan.

As before, a high rate of resistance to one or more drugs was found in new tuberculosis cases in Estonia, with 37% of all strains resistant to any drug and 14% multidrug resistant. The prevalence of resistance in Estonia had grown substantially since the last survey, both in new cases and previously treated cases.

Other countries and settings with worrying rates of drug resistance included Latvia; two Russian 'oblasts' (territories); Iran; the Henan and Zhejiang provinces of China; and Tamil Nadu state in India. Germany and Denmark have both seen increases in drug resistance, but the scale of the problem is small.

In the parts of eastern Europe where rates of resistance are high, a tradition of treating patients for lengthy periods in hospital has encouraged resistant strains to flourish.

Anti-tuberculosis Drug Resistance in the World is available from the Publications Department, World Health Organization, 1211 Geneva 27, Switzerland.

TB: a clinical manual for South East Asia

This is a spiral-bound booklet of 145 pages, published by the World Health Organization in 1997. It is in fact an adaptation of a previous publication '*TB/HIV: A Clinical Manual*' by Mukund Uplekar, previously of the Foundation for Research in Community Health, Bombay, India and now with the Stop TB Initiative, WHO, Geneva. The reference number is WHO/TB/96.200 (SEA). The other authors are Anthony Harries, University of Malawi and Dermot Maher, Global TB Programme, WHO.

The main chapter headings are: background information on tuberculosis; diagnosis of tuberculosis in adults; diagnosis of tuberculosis in children; standardized TB case definitions and treatment categories; treatment of TB patients; side-effects of anti-Tb drugs; framework for effective TB control; background information on HIV/AIDS; HIV-related TB; diagnosis of HIV infection in adults with TB; diagnosis of HIV infection in children with TB; management of other HIV-related diseases in TB/HIV patients; coordinated care in different settings; prevention of TB.

Further information: Office of Publications, WHO, 1211 Geneva 27, Switzerland.

Global Tuberculosis Control. WHO Report 1999

This is a 179-page Report, WHO/CDS/CPC/TB/99.259 which reviews the global situation in great detail. The key findings were as follows:

- By the end of 1997, 85% of all TB cases were living in 102 countries which had adopted the WHO DOTS strategy for control.
- The key to meeting WHO targets lies in expanding case detection in high-burden DOTS countries: in 1997, 83% (2·5 million) of all unnotified TB cases were living in countries which have already shown that they can achieve high treatment success rates by using DOTS.
- The greatest number of cases without access to good treatment is in Asia, especially Bangladesh, India, Indonesia, Pakistan and Philippines.
- Only in Africa were treatment success rates relatively low (average 58%), because many patients did not complete treatment, or the outcome of their treatment was not evaluated.
- The number of new smear-positive TB cases notified by DOTS programmes has increased by an average of 100,000/year since 1994, reaching 16% of cases in 1997. By adding 250 000 extra cases each year (10% of the unnotified cases living in DOTS countries), the global target of 70% case detection could be reached by 2005.
- DOTS can succeed in a variety of settings: among major endemic countries showing relatively high treatment success ($\geq$70%) and case detection rates ($\geq$50%) were representatives from Africa (Kenya, Tanzania), Asia (Cambodia, Viet Nam) and Latin America (Peru).
- Marked upward trends in case notification rates from 1980 to 1997 variously reflect failing TB control (Eastern Europe), the impact of HIV (sub-Saharan Africa), and better case finding (China); marked downward trends (Western Europe) represent the direct (chemotherapy against TB) and indirect (general improvements in health) impact of TB control.
- Standardized short course chemotherapy, promptly delivered, can have a major impact on tuberculosis morbidity and mortality, but this impact has not yet been adequately quantified.

The *Technical Summary* reads:

Background and aims

This is the third global report on TB control, based on case notifications and treatment outcome data supplied by national control programmes to WHO. Four consecutive years of data allow us to present the most thorough appraisal of worldwide progress in TB control to date, focusing on 22 countries that account for 80% of all new cases. The main aim is to assess progress towards meeting WHO targets

for case detection (70%) and treatment success (85%). We also consider the potential of these data to assess the impact of control on cases and deaths averted.

Methods

Standard data collection forms A and B were sent to 212 countries via WHO Regional Offices. Part A requested, from DOTS areas, the number of types of TB cases notified in 1997, and treatment results for smear-positive cases registered in 1996. Part B is for areas that have not implemented DOTS, and required fewer details of notified cases and treatment outcomes.

Results

173 countries reported to WHO. 102 of these had satisfied the technical criteria for DOTS implementation by the end of 1997, including all 22 of the highest-burden countries except Brazil and Zimbabwe. The number of new smear-positive TB cases notified (detected) by DOTS programmes was 547,432 in 1997, or 16% of estimated global incidence. This number has increased by 100,000/year on average since 1994, though recruitment was slower in 1997. Among the 84% of smear-positive cases that were not notified under DOTS in 1997, 18% were living outside DOTS countries, 60% were living in DOTS countries but outside DOTS areas, and 23% were living in areas said to be covered by DOTS. Therefore 83% (2·5 million) of all smear-positive TB cases not detected under DOTS were living in countries which had partially implemented the WHO control strategy.

Whilst DOTS programmes have been reporting more cases each year, the total number of notifications has changed little: 3,368,879 TB cases were reported from all control programmes in all countries in 1997, 436,000 fewer (12%) than in 1996, and about the same as in 1995. A total of 1,292,884 sputum smear-positive cases was reported in 1997, about the same as in the two previous years.

Although case finding has been expanding slowly, most DOTS programmes have demonstrated that they can achieve high treatment success rates. The average for the 1996 cohort was 82% in the 22 high-burden countries (3% less than the target) and 78% globally. Only in Africa were treatment success rates relatively low under DOTS (average 58%); the reason is that many patients did not complete treatment, or the outcome of treatment was not evaluated.

Among the best performing, high-burden countries (case detection rate under DOTS, DDR $\geq$50%, treatment success rate, TS $\geq$70%) were representatives from Africa (Kenya, Tanzania), Asia (Cambodia, Viet Nam) and Latin America (Peru). Bangladesh, China, Ethiopia and Myanmar maintained acceptably high treatment success rates ($\geq$70%) whilst steadily expanding coverage (DDR 10–49%). India, Indonesia, Philippines, South Africa and Thailand have shown that they can achieve acceptable treatment success rates under DOTS, but case detection rates remained low (DDR $<$ 10%). Treatment success was low ($<$ 70%) or in doubt in Nigeria, Uganda and Russia. No data, or incomplete data, were supplied by Afghanistan, Brazil, DR Congo, Pakistan and Zimbabwe.

There were marked trends in case notification rates from 1980 to 1997 that differ by country and region, falling in Western Europe and Latin America, and rising in Eastern Europe, sub-Saharan Africa and Asia. A detailed analysis of new and re-treatment cases reported in China indicates that countries using DOTS cut the case fatality rate from 37% in 1991 to 6% in 1997.

Conclusion

Although treatment success needs to be improved in some countries, especially in Africa, the key to meeting WHO targets lies in expanding coverage in high-burden countries that have already implemented DOTS. The greatest number of cases without access to good treatment is in Asia, especially Bangladesh, India, Indonesia, Pakistan and Philippines. By maintaining the current rate of DOTS expansion, the WHO global target for case detection would be reached in 2015; by finding an

extra 250,000 smear-positive cases annually (10% of undetected cases in DOTS countries), the target could be reached a decade earlier. Trends in notification and cure rates portray, more or less clearly, the failures or successes of TB control. New indicators and methods of analysis must be developed to quantify the full impact of control on TB transmission, incidence, prevalence, deaths, and on the prevention of drug resistance.

What is DOTS? WHO 1999

This is the title of a 30-page publication, WHO/CDS/CPC/TB/99.270, sub-headed 'A guide to understanding the WHO-recommended TB Control Strategy Known as DOTS'. The Summary reads as follows:

DOTS (Directly Observed Treatment, Short-course) is the most effective strategy available for controlling the TB epidemic today. DOTS has five key components:

- Government commitment to sustained TB control activities.
- Case detection by sputum smear microscopy among symptomatic patients self-reporting to health services.
- Standardized treatment regimen of 6–8 months for at least all confirmed sputum smear positive cases, with directly observed treatment (DOT) for at least the initial 2 months.
- A regular, uninterrupted supply of all essential anti-TB drugs.
- A standardized recording and reporting system that allows assessment of treatment results for each patient and of the TB control programme overall.

This cost-effective strategy was developed from the collective best practices, clinical trials and programmatic operations of TB control over the past 2 decades.

Government commitment to sustained TB control is essential for the other four components to be implemented and sustained. This commitment must first translate into policy formulation, and then into the financial and human resources and administrative support necessary to ensure that TB control is an essential part of health services.

An important feature of DOTS is the basic management unit—usually covering a population of 100,000 to 150,000—that has the staff and resources to diagnose, initiate treatment, record and report patient treatment progress, and manage supplies. This basic management unit operates successfully within existing general health services, which is critical for the full integration and effectiveness of TB control services in the primary health care network, particularly during this era of health sector reform.

Another important feature is a recording and reporting system used by health care workers to systematically monitor patient progress and TB programme performance. This results-oriented system enables quality assurance of programme implementation and treatment and cure of TB patients. Data collected as part of TB management can be a useful indicator of access to and quality of the general health system.

Apply: Office of Publications, WHO, 1211 Geneva 27, Switzerland.

Guidelines for the control of tuberculosis in prisons

This is a publication of 83 pages, WHO/TB/98.250 produced by the World Health Organization and the International Committee of the Red Cross. The Preface reads as follows:

The World Health Organization (WHO) and the International Committee of the Red Cross (ICRC) have joined forces to produce these guidelines. The goal is to improve the control of tuberculosis in prisons and other institutions where people are incarcerated. The guidelines apply wherever people are in custody: prisons, police stations, remand centres, detention centres for asylum seekers, secure hospitals, penal colonies and prisoner of war camps.

Several international conventions (see Annex 1) guarantee the welfare of prisoners. Prisoners lose liberty but retain certain rights in prison. These include protection from harm and access to a standard of health care equivalent to that provided in the community. In practice, few prison authorities comply fully with these conventions. Low standards of general custodial care and of health care are common. Despite the often limited information available on the health of prisoners, there is increasing recognition of the health needs of prisoners, including the need to control tuberculosis. Contracting tuberculosis should not be part of a prisoner's sentence.

Tuberculosis is common in many prisons worldwide and treatment is often ill-informed and inadequate. Prisons form a reservoir of tuberculosis, including drug-resistant tuberculosis. Tuberculosis is a problem both inside prisons and outside in the wider community, since people enter, leave and re-enter prisons. There is therefore an urgent need to institute effective control of tuberculosis in prisons. Successful tuberculosis control in a country requires effective tuberculosis control in prisons. The WHO recommended strategy for tuberculosis control (known by the 'brand name' of DOTS) relies on the detection and cure of tuberculosis patients, with a priority for the infectious cases. The specific features of prisons and of prisoners necessitate specific approaches to implementation of the DOTS strategy. The prison health services must implement the DOTS strategy in close collaboration with national tuberculosis control programmes.

Practical guidelines are necessary for prison authorities to be able to implement the DOTS strategy. Policy-makers and decision-makers may be unaware of the extent of the problem of tuberculosis in prisons, the potential for spread to the wider community, and the emergence of drug-resistance. The guidelines therefore also highlight to policy-makers and decision-makers the need to control tuberculosis in prisons. Several countries, usually with low tuberculosis prevalence, have developed their own guidelines. However, there is a need for global guidelines for use in any country with high tuberculosis prevalence populations. WHO's Global Tuberculosis Programme (GTB) and ICRC contribute to these guidelines expertise in tuberculosis control and in the welfare of prisoners.

The objectives of the guidelines are the following: a) to describe briefly the burden of tuberculosis in prisons; b) to highlight the specific difficulties in implementing effective tuberculosis control in prisons; c) to outline the benefits of improved control of tuberculosis in prisons; d) to guide administrators in establishing and running tuberculosis control services in prisons; e) to guide prison health service staff in the detection and cure of prisoners with tuberculosis.

The guidelines are primarily for prison authorities (administration, health staff), policy-makers and decision-makers in relevant ministries (e.g. justice, interior, health), NGOs and donor agencies, and National Tuberculosis Programme (NTP) staff. Part I provides background information on tuberculosis and prisons, of particular relevance to prison authorities and decision-makers in relevant ministries. Part II provides guidelines for the control of tuberculosis in prisons, of particular relevance to prison health staff. Part III gives guidance to national prison authorities and NGOs on how to establish a prison tuberculosis control programme.

These guidelines require field testing in different situations. Comments on the guidelines are welcome and will help to improve future editions. Please send any comments to the WHO Global Tuberculosis Programme.

To order copies of these guidelines, please contact:

WHO Publications, Distribution and Sales, 1211 Geneva 27, Switzerland or ICRC Public Information Division, 1202 Geneva, Switzerland.

INASP-Health

INASP-Health is a co-operative network created by health information providers, for health information providers. Its goal is to facilitate co-operation across the health information community towards universal access to reliable information for healthcare workers in developing and transitional countries.

The network currently involves more than 600 participants. North and South, representing non-governmental organizations, international agencies, library services, publishers (print and electronic), and others. Visit our website at: www/inasp.org.uk for further information about our range of services and activities.

We welcome all those who are willing to share their experience and expertise with others to improve access to reliable information. Participation is free of charge and without obligation. Please write to:

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We are grateful to the following organisations for their support:

British Medical Association, Danida, Department for International Development (UK), CDSI (ICSU-Press), World Health Organization.

WHO: drugs used in HIV-related infections

Under the broader heading of *WHO Model Prescribing Information*, this valuable document of 58 pages (WHO/DMP/DS1/99.2) complements WHO's *Model List of Essential Drugs*. The *summary* on the back cover reads:

WHO Model Prescribing Information is being prepared to provide up-to-date and independent clinical information on essential drugs, including details of dosage, uses, contraindications and adverse effects. It is intended as source material for adaptation by national authorities, in particular in developing countries, that wish to produce drug formularies, data sheets and teaching materials.

This update of the volume on HIV-related illnesses covers drugs currently used for the prophylaxis, treatment and palliative care of patients with opportunistic infections and other illnesses related to HIV infection. For further information on the drugs used in the treatment of early HIV infection see The implications of antiretroviral treatments WHO/ASD 97.2 and Guidance Modules on Antiretroviral Treatments WHO/ASD 98.1 UNAIDS 98.7.

Opportunistic infections:

Infectious diseases constitute the immediate cause of death in up to 90% of patients with advanced HIV. Some are caused by common pathogens, but many are *opportunistic*, meaning that they are caused by microbes which usually do not cause disease in the immunocompetent host. Knowledge of these is incomplete and new forms of opportunistic infections attributed to previously unrecognized and uncharacterized microbes are still being discovered.

The incidence and spectrum of these infections differ in important respects from those associated with other immunosuppressive disorders. Whereas *all* immunocompromised patients are vulnerable to *Toxoplasma* encephalitis, oral candidiasis and pulmonary tuberculosis, many opportunistic diseases including *Pneumocystis carinii* pneumonia (PCP), and systemic infections due to *Cryptococcus*

neoformans, cytomegalovirus (CMV), the *Mycobacterium avium* complex and *Cryptosporidium* species have occurred more frequently in people infected with HIV.

The pattern of infection varies between different socio-ecological settings. In some African countries as many as 50% of patients with advanced HIV disease will develop tuberculosis. In contrast, *Pneumocystis carinii* pneumonia is less frequent in these countries. This may be because many patients die before their immune defences are severely attenuated or because of under-reporting. In the immunocompromised patient infections often present atypically; disseminated disease is common and two or more infections may occur concurrently. The systems commonly involved in manifestations of the opportunistic infections are given below.

Other infections such as those due to *M. tuberculosis*, *Shigella*, and *Salmonella* species occur in people with normal immunity and are not classified as 'opportunistic infections'. They are, however, included as they occur with increased frequency in people with HIV.

Pulmonary tuberculosis:

Tuberculosis is the commonest cause of death in people with HIV infection world-wide. There are indications of a resurgence of tuberculosis almost everywhere where HIV is prevalent. HIV infection increases a person's susceptibility to infection with *M. tuberculosis* and is the most potent factor known to increase the risk of progression from *M. tuberculosis* infection to disease. In an individual infected with HIV the presence of other infections including TB allows HIV to multiply more quickly. This may result in more rapid progression of HIV infection.

The initial signs of disease may become apparent at any time during the evolution of HIV infection. In HIV-infected patients TB may be pulmonary or extrapulmonary. Pulmonary TB is still the most common form of TB. The presentation depends on the degree of immunosuppression. In advanced HIV disease the immune system is less able to prevent the growth and local spread of *M. tuberculosis*; thus, disseminated and extrapulmonary disease is more common, and unilateral or bilateral infiltrates in the lower lobes are seen more often than upper lobe lesions and cavities. The commonest forms of extrapulmonary disease are lymphadenitis, pleural effusion, pericarditis, miliary disease and meningitis.

The essential elements of tuberculosis control are the same in populations where HIV is common and where it is rare. The objectives are to decrease morbidity, mortality and transmission of tuberculosis, while avoiding the emergence of drug resistance. One of the essential elements of the WHO strategy is to provide short course chemotherapy under direct observation to at least all identified smear positive cases. The central strategy recommended by WHO is one of the most cost-effective of all health interventions.

Treatment regimens have an initial (intensive) phase and a continuation phase. The initial phase lasts for 2 months and utilises three or four drugs. During this phase there is rapid killing of TB bacilli, infectious patients become non-infectious within about 2 weeks and symptoms improve. The vast majority of patients with smear-positive TB become sputum smear negative within 2 months. Directly observed therapy is recommended in the initial phase to ensure that the patient takes every single prescribed dose. This protects against the development of drug resistance. The risk of drug resistance is higher during the early stages of anti-TB drug treatment when the number of TB bacilli is very high.

The continuation phase lasts for 4–6 months depending on the combination of medications used. During this phase the drugs eliminate the remaining TB bacilli. Killing the persistent bacilli prevents relapse after completion of therapy.

There is little evidence, as yet, of atypical patterns of antibiotic resistance in *M. tuberculosis* isolates from patients with HIV. However, reports from the USA describe clusters in which isolates shared multi-drug resistance. This is the result of the spread of TB infection with rapid progression of disease in this population. The limited data on treatment failure in TB/HIV dually infected patients and relapse rates following antituberculosis therapy are comparable to those prevailing in the population at large.

Mortality is, however, considerably higher in HIV seropositive than HIV seronegative TB patients. Furthermore, the incidence of adverse reactions may be substantially higher in TB patients with HIV infection. In particular, thiacetazone is associated with a high risk of severe, and sometimes fatal, skin reactions in HIV-infected individuals.

TB preventive therapy

There is evidence showing the efficacy of TB preventive therapy among HIV-infected people. TB preventive therapy can be given to people with HIV who have been screened to exclude active TB and who are PPD positive. Isoniazid is the recommended drug. A dose of 5 mg/kg (maximum 300 mg) may be given daily as self administered therapy for 6 months.

For further information in the treatment of TB in patients with HIV infection see

(i) *TB/HIV. A clinical manual*. Geneva, World Health Organisation, 1996 (WHO/TB1996.2000).
(ii) *Treatment of Tuberculosis, Guidelines for National Programmes*. Geneva, World Health Organisation, 1997 (WHO/TB1997.220).

Further information: Office of Publications, WHO, 1211 Geneva 27, Switzerland.

AIDS cuts life-expectancy in sub-Saharan

From the *British Medical Journal*, volume 319 of September 1999:

The spread of HIV and AIDS in sub-Saharan Africa has far exceeded the worst projections, according to speakers at the 11th international conference on AIDS and sexually transmitted diseases in Africa. In 13 countries the prevalence of HIV infection is more than 10%, and in some it is as high as 30%. At the conference in Lusaka, Zambia, last week, the epidemic was described as an unprecedented threat to the region's economic development.

At the end of 1998, 22·5 million people out of the region's population of 600 million were living with HIV or AIDS; this number includes 1 million children. The epidemic in sub-Saharan Africa accounts for two thirds of the worldwide total of 34 million people with HIV/AIDS. About 7500 people are infected daily.

In only two countries, Uganda and Senegal, does the epidemic seem to be abating. Strong governmental leadership in these countries ensures that there is universal health education, that condoms are easily available, and that there is coordinated action from the government.

Life expectancy in the region has decreased from 64 to 47 years. Sixty five per cent of patients in medical wards in Zambia, and 75% in paediatric wards, are infected with HIV or have AIDS, and the underfunded health system is near to collapse. Even common drugs such as co-trimoxazole are scarce.

In Zambia, a 15 year old has a 60% chance of dying of AIDS. As the epidemic, which is driven largely by poverty, continues to grow, there is little sign of widespread change in sexual behaviour, especially among teenagers, one of the most vulnerable groups.

Tsepo Sitali, aged 8, described to the conference the anguish of her friend who will mark her eighth birthday without a mother or a father because both died from AIDS last year.

Tsepo's friend is not alone: the number of children orphaned by AIDS in Zambia is forecast to reach 500,000 by the year 2010. The epidemic affects children not only directly through infection being spread from mother to child but also through the deaths of their parents which results in their being forced into prostitution and other forms of exploitation.

Children, especially girls, are taken out of school to nurse sick relatives or because school fees are no longer affordable. Only an estimated 10% of the predicted illness and death has occurred: the full impact on people, communities, and economies is still to come.

St Joseph's Leprosy Hospital

The following history of St Joseph's Leprosy Hospital, Tamil Nadu, India, was supplied by the Superintendent.

St Joseph's Leprosy Hospital was started in 1949 by Mgr. Francis T. Roche, S. J. with the help of three sisters of the Institute of Franciscan Missionaries of Mary (F.M.M.). By the end of 1958 it had developed into a well-equipped hospital with 300 beds. The first Survey Education Treatment Unit was started with three roadside clinics in 1961 and the number of leprosy patients treated rose to 2245. In 1963 the entire administration was handed over to the F.M.M. Sisters, who now collaborate with the Government of India in its Leprosy Eradication Programme.

In 1972 the Leprosy Control Unit was extended, covering an area of 2160 sq. km. with 11 sub-centres and 28 roadside clinics, catering to a population of 2,20,000. In 1994 there were 13 main clinics with 54 roadside sub-clinics. From 1949 to 1998 a total number of 6950 leprosy patients were detected and treated by the Institution.

In 1998, we undertook Tuticorin Urban area which contains 2,04,000 population. This area is divided into 8 zones and one leprosy Inspector is posed in each zone.

Our service

The hospital provides in-patient care for the treatment of lepra reaction, stabilization on anti-leprosy drugs, treatment of trophic ulcer and other infections. Regular exercises are given to patients by the Physiotherapy Section to prevent deformities or to correct them. As a result of multi-drug therapy and ROM treatment patients are cured in a comparatively shorter period.

About half of the inmates of the Hospital are permanent residents, who are disabled and rejected by their families. A few of them are employed in gainful rehabilitation work like candle making, weaving, agricultural, poultry and dairy farming. We also have a shoe making unit where microcellular rubber foot wear are made to protect the anaesthetic feet of leprosy patients. In all our rehabilitation work we aim at allowing the patients to continue their work in their own environment.

All the patients in our hospital and clinics are treated free of charge, irrespective of caste, creed, community or social status. All in-patients are provided with food, clothing and shelter free of charge.

Owing to the successful implementation of the Leprosy Eradication Programme, the number of persons infected by leprosy in the area is now steadily decreasing. We have now launched into process of integrating a Tuberculosis Control Programme, Malaria, Aids along with the leprosy Eradication Programme. This will be a boon for Tuticorin, where a good number of people suffer from this disease.

Regional conferences of leprosy workers

The following is taken from the report of Mr Udary Thakar Secretary, Hind Kusht Nivaran Sangh, Maharashtra Branch, Mumbai.

Hind Kusht Nivaran Sangh, Maharashtra Branch has been organizing Regional Conferences of leprosy workers in Maharashtra for last several years. This has been with the primary objective of providing opportunities to grass root level workers to express their views and actual field experiences. This year, two regional conferences were organized, i.e. 1) Western Maharashtra region (Dist. Satara, Sangli, Kolhapur and Ratnagiri) at Richardson Leprosy Hospital, Miraj on 11th and 12th March 2000 and 2) Kokan region (Dist. Mumbai, Thane, Raigad and Sindudurg) at Kushtarog Nivaran Samiti, Cantina, Painful on 14th and 15th March 2000.

Both the conferences were dedicated to the memory of pioneering efforts of Late Shri S. S. Naik, the past secretary, Hind Kutht Nivaran Sangh, Maharashtra Branch in starting this event for leprosy workers.

Over 150 field workers from Government and NGOs participated in the Conferences and presented 58 papers (25 papers at Miraj and 33 at Cantina) on various aspects of leprosy, i.e. Epidemiology, clinical aspects, MLEC, Rehabilitation and Social aspects etc.

The Conferences at Miraj and at Cantina were inaugurated by Shri Patil, Mayor of Sangli and by Shri Chandrashekhar Dharmadhikari, Ex. Chief Justice, respectively.

The highlights of paper material, discussion and the suggestions in both the Conferences were as follows:

1) The papers based on case detection in special groups of population like fishermen, prisoners, tribal population, commercial sex workers etc. showed significant high N.C.D.R. Hence, it was suggested to include these groups in routine surveys.
2) The results of last three MLECs in Maharashtra showed decline in New Case Registration. However, the experience with VRCs, this was encouraging.
3) Since the routine surveys do not reveal smear +ve cases, it was suggested to make special efforts to get the hidden smear +ve cases.
4) In case of smear +ve cases, along with the household contacts, the contacts at the work place, travel and at social activities should also be examined.
5) If properly trained, it was expressed, that leprosy patients can also disseminate information on leprosy.
6) In the conference, information on various rehabilitation schemes for leprosy patients was made available to the field workers for future references.
7) To solve the problem of duplication of registration and to trace the drop out cases who leave the area, it was suggested to create a State level Central Registry of leprosy patients.
8) All the field workers expressed that the Integration of Leprosy Services into General Health Services should be made only after proper training and motivation of general health workers.

In both the conferences, field workers participated in the deliberations with keen interest and expressed their views and experiences freely.

Leprosy Focus Group for Podiatrists

Mission statement

The Leprosy Focus Group for Podiatrists and Other Healthcare Professionals will clarify and develop the role of podiatry within the field of leprosy.

Aims

To link up a multinational group of podiatrists and other healthcare workers with an interest or experience in the leprotic foot and to facilitate the development of podiatry within the leprosy framework.

To bring the specialized skills of podiatry into leprosy project work throughout the world.

Objectives

1. To clarify and promote the role of podiatry within the field of leprosy.
2. To develop a comprehensive information pool regarding prevention and treatment of foot pathologies in people with leprosy.
3. To provide links between appropriately skilled podiatrists and leprosy organizations.
4. To act as a support mechanism for podiatrists and other related healthcare professionals working in the field.

5. To inform and update relevant professional bodies about the group's activities, and to gain their help in disseminating information through professional journals.
6. To promote the inclusion of leprosy and the role of the podiatrist in the prevention of disability into the undergraduate and postgraduate curriculum.
7. To encourage podiatric postgraduate research into leprosy.

Philosophy

We believe that podiatrists have specialized skills that can be utilized to benefit people with leprosy in preventing and treating disability.

We believe that podiatrists are obliged to broaden these skills to encompass all aspects of prevention of disability in people with leprosy.

To date the podiatry profession has not been used effectively in leprosy care and this situation can now only change with a positive, and mutual, input from the podiatry profession and leprosy organizations.

We believe that these specialized skills can be transferred via education and practical training to local staff at all levels leading to sustainable development.

We are a secular organization that respects all faiths and cultures.

If you wish to become actively involved with this group, please send an E-mail to the following address podiatry@lepra.org.uk

Poster contest on leprosy (Hansen's disease)

Leprosy of yesterday was shrouded in mystery and fear, and patients were isolated far from the community. Today, it is society's responsibility to inculcate confidence in the patient. Leprosy can only be eradicated if society throws away its baseless prejudices, and if the community works together with the Health authorities.

The role of Health Education has already been emphasized. People have to be closely associated with Public Health Programmes, as the health measures are for their benefit and that of their families. Local communities should be made aware of the scientific facts of leprosy to encourage individuals with early signs of the disease to come forward for treatment. It should then be the community's task to motivate patients to take treatment regularly, to care for their hands and feet, to provide retraining with job opportunities and to integrate them back into society.

In observance of 'anti-leprosy day', SWAPLAP (Society for the Welfare and Awareness of the Poor and Leprosy affected people) and We Care Trust, in collaboration with Directorate of Health & Family Welfare Services and AMICI were jointly organized a State level poster contest on leprosy on 30th January 2000 for school and college students, to bring about an awareness among youth. This poster contest was conducted at Media Centre, 96, Lavelle Road, 3rd Cross, Bangalore-1.

Aims of the contest

- To discover the extent of students' knowledge about leprosy.
- To allow them for practice in communication skills.
- To understand and respond to their needs on leprosy.
- To develop positive attitudes in participating leprosy awareness programmes.
- To give an opportunity to children and young people, who have the talent of creativity.
- To develop proper education and communication skills among children and young people which can change attitudes towards people living with leprosy.

The contest was conducted for School and College students. The response was indeed very good. There were in total 50 participants from various schools and colleges.

Results and findings of this contest

- Teenagers and adolescents are interested to learn about leprosy.
- Young people have their own language and it is important to learn that language.
- The right information will enable students to act responsible.
- It is not difficult to develop a sustainable leprosy programme in schools/colleges.
- It is more important to keep reference materials on leprosy in schools/colleges.
- Awareness programmes among youth has its own impact and effectiveness.
- More number of such programmes will definitely increase the awareness among more teenagers and adolescents.

It was indeed a very successful programme, under the able guidance of Dr. Jangay (leprosy), H & FWS, Karnataka, and the financial support given by We Care Trust, St Anthony's Friary, 86, Hosur Road, Bangalore-95 and AMICI, 58, 4th Cross, Kaveri Layout, Thaverekere Main Road, Dharmaram College Post, Bangalore.

Instructions to Authors

Article submission. Articles submitted for publication in Leprosy Review should be sent to the Editor at the following address: Diana Lockwood, 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 indicated clearly below the title of the article. Degrees and diplomas are not to be included.

It is understood that the article is offered to Leprosy Review alone, that it will be subject to editorial revision, and that its copyright becomes the property of LEPRA.

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Electronic submission. Articles produced using a word-processor should also be supplied in electronic format (preferably Word or Wordperfect 5.1) if possible. Please submit a disk with the final revised version of the article. The electronic file should correspond exactly to the hard copy.

Illustrations and Tables. Contributors must send the original artwork and two copies on separate sheets. In addition electronic versions may be submitted in the form of compressed tiffs, eps, jpegs or bitmaps. The recommended resolution is 600 dpi or above.

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CONTENTS

246 **Editor's Choice**

Editorials

247 **Remaining challenges towards elimination of leprosy.** M. P. Neira and D. Daumerie

253 **The Global Alliance for the Elimination of Leprosy (GAEL).** T. Vasey

256 **Leprosy research in the new millennium in the Special Programme for Research and Training in Tropical Diseases (TDR).** P. Nunn

Review

258 **Monitoring motor nerve function in leprosy patients.** J. W. Brandsma

Science commentary

268 **Are cytokines our key to immunity against mycobacterial diseases?** R. Weir

Commentary

270 **A prospective cohort study comes of age.** R. P. Croft

Papers

273 **The ALERT MDT Field Evaluation Study (AMFES): a descriptive study of leprosy in Ethiopia. Patients, methods and baseline characteristics.** P. Saunderson, S. Gebre, K. Desta and P. Byass

285 **The pattern of leprosy-related neuropathy in the AMFES patients: definitions, incidence, risk factors and outcome.** P. Saunderson, S. Gebre, K. Desta, P. Byass and D. N. J. Lockwood

309 **Reversal reactions in the skin lesions of AMFES patients: incidence and risk factors.** P. Saunderson, S. Gebre and P. Byass

318 **ENL reactions in the multibacillary cases of the AMFES cohort in central Ethiopia: incidence and risk factors.** P. Saunderson, S. Gebre and P. Byass

325 **Relapses after fixed duration multiple drug therapy: the AMFES cohort.** S. Gebre, P. Saunderson and P. Byass

332 **The pattern of decline in bacillary index after 2 years of WHO recommended multiple drug therapy: the AMFES cohort.** A. Amenu, P. Saunderson, K. Desta and P. Byass

338 **The effect of HIV status on the clinical picture of leprosy: a prospective study in Ethiopia.** S. Gebre, P. Saunderson, T. Messele and P. Byass

344 **The hand-foot impairment score as tool for evaluating prevention of disability activities in leprosy: an exploration in patients treated with corticosteriods.** S. M. Broekhuis, A. Meima, L. F. Koelewijn, J. H. Richardus, C. Benbow and P. R. Saunderson

355 **High dose prednisolone treatment of leprosy patients undergoing reaction is associated with a rapid decrease in urinary nitric oxide metabolites and clinical improvement.** T. Schön, R. Leekassa, N. Gebre, T. Sundqvist, E. Bizuneh and S. Britton

363 **Predisposing factors for recurrent skin ulcers in leprosy.** H. Kunst

369 **Towards an understanding of non-compliance. An assessment of risk factors for defaulting from leprosy treatment.** M. L. Heynders, J. J. Meijs and A. M. Anderson

377 **Modified leprosy elimination campaign (MLEC) for case detection in a remote tribal area in the State of Orissa, India.** P. V. Ranganadha Rao, R. A. Bhuskade and K. V. Desikan

Case Report

382 **715: Acro-osteolysis prior to diagnosis of leprosy.** X. Illarramendi, M. R. Jardim, A. M. Sales, J. A. C. Nery and E. N. Sarno

Letters to the Editor

388 **'Wall Journal' on leprosy – a novel method to educate medical students.** G. Shah, V. V. Pai, C. R. Revankar and R. Ganapati

390 **WHO leprosy elimination campaign – beyond 2005.** K. L. Braber

392 **Teaching Materials**
Alert Training Calendar 2001 ● International Course for Leprology Physicans ● Asian Leprosy Congress ● The Welcome Trust, London: Training Fellowships and Awards ● The Robert Cochrane Fund for Leprosy ● Access to reliable drug information in resource-poor countries ● Public libraries in Africa. A report and annotated bibliography ● Videos on leprosy from WHO

400 **News and Notes**
The genome mapping of the leprosy bacillus completed ● Blocking natural killer cell activity ● Alliance for Health Policy and Systems Research ● AMREF: African Medical and Research Foundation ● 'Molecular Pathology' edition of *Journal of Clinical Pathology* (UK) ● *WHO Liaison:* newsletter of the WHO library and Information Networks for Knowledge ● TDR: special initiatives to support academic programme development ● The Heiser Program for Research in Leprosy and Tuberculosis ● 'Drug-resistant tuberculosis can be controlled' says WHO ● TB: a clinical manual for South East Asia ● Global Tuberculosis Control: WHO Report 1999 ● What is DOTS? ● Guidelines for the control of tuberculosis in prisons ● INASP-Health ● WHO: drugs used in HIV-related infections ● AIDS cuts life expectancy in sub-Saharan Africa ● St Joseph's Leprosy Hospital ● Regional conferences of leprosy workers ● Leprosy Focus Group for Podiatrists ● Poster contest on leprosy (Hansen's disease)