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LEPROSY REVIEW

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Leprosy Review

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

LEPRA

Editorial Board

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

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

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Editor's Choice

This issue of *Leprosy Review* is particularly exciting because we have a group of articles focusing on the topical questions of how many leprosy patients are there in the world and what effect has WHO–MDT had on the global numbers of leprosy patients? These are highly topical questions, asked at every leprosy meeting. In the News and Notes section we have reprinted two articles from the WHO *Weekly Epidemiological Record*, 'Progress towards leprosy elimination' and 'Global Cases Trends in Leprosy'. These articles are written from a WHO perspective and emphasize the success of MDT and look for evidence of a decline in numbers of leprosy patients. Accompanying these two articles are two editorials. Cairns Smith emphasizes the importance of measuring the incidence of leprosy on a country by country basis if we are to have a proper understanding of the impact of WHO–MDT and other antileprosy activities on the transmission of disease. Paul Fine also argues for looking carefully at the incidence trends and guides readers through the two reports. He highlights many important issues and I hope that these pieces will be stimulating and generate discussion and correspondence.

The efficacy of MDT was assessed histologically by Ebenezer *et al*. (p. 218) who showed that in a group of 24 clinically and histologically confirmed BT patients 33% had histopathological activity after completion of 6 months WHO PB–MDT. No acid-fast bacilli were seen and this emphasizes the immunological nature of paucibacillary disease.

There are several chemotherapy related items. A mild dapsone-induced haemolytic anaemia is common and Quieroz *et al*. (p. 212) show that slow acetylators are not at greater risk of developing haematological side-effects with dapsone. Many readers will appreciate Dr Michael Waters' informal report on the WHO meeting on chemotherapy research in leprosy in Chennai earlier this year. Notwithstanding the success of WHO–MDT it is important that new drugs should be tested and shorter regimes developed. Waters outlines the current WHO sponsored trials and gives a preliminary analysis of the trial of single dose rifampicin/ofloxacin and minocycline for single lesion paucibacillary patients. The data reported so far are encouraging and we shall be covering this topic in the next issue of *Leprosy Review* when we hope to be reprinting the full trial analysis from 'Leprosy in India.'

Nerve damage and how it is measured is a continuing theme in *Leprosy Review*. A useful letter from Ethiopia (p. 252) reports on a small group of patients who had loss of sensation to 10-g but not 1-g monofilament testing and were not treated with steroids. Of the patients who were followed up only one patient had further loss of sensation. As monofilament testing is being taken up widely it is important that studies should be done evaluating the risks of treating large numbers of patients with steroids against the neurological benefits gained from steroid therapy.

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Women with leprosy suffer a double jeopardy. Already often disadvantaged by their gender leprosy will then compromise their position even further. Amanda Le Grand has written a stimulating review looking at the many ways in which being a woman affects the risks and outcome of having leprosy. I hope this will encourage more research and action in this area.

DIANA N. J. LOCKWOOD

Poster Notice and Questionnaire

The last four issues of *Leprosy Review* have included a series of posters covering important areas of management and research in leprosy. These have been distributed free to subscribers and additional copies have been made available from LEPRA. The current issue contains one entitled 'Taking slit-skin smears', and the following issue will have 'Staining slit-skin smears'.

A further series is planned on topics such as 'Care of microscopes' and 'Ocular problems in Leprosy'. In order to ensure that these new posters are both well received *and* utilized, we would like to evaluate the first series of posters. We are therefore enclosing in this issue a very brief questionnaire which will help us to measure the success of the posters. Please take a few minutes to complete and return this to the Editor, *Leprosy Review*. In addition we would also welcome suggestions for future poster topics. Your comments will be most valuable when we are producing/planning further posters.

We would be happy for you to include the questionnaire with the subscription renewal form, and return them to the address given on the subscription form.

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Editorial

WE NEED TO KNOW WHAT IS HAPPENING TO THE INCIDENCE OF LEPROSY

Why we need to know

The current global strategy for leprosy is based on reducing the prevalence of the disease using short course multidrug therapy (MDT). The case for using prevalence as an indicator for the programme has been well argued in that it is easy to measure, responsive to change, and appropriate for a disease of long duration. However the argument may inadvertently imply that incidence is therefore not important, or certainly much less important. The prevalence of leprosy has dramatically fallen over the past 10 years (Figure 1) as a result of the global implementation of MDT although this now appears to be levelling off.[1] Prevalence is now no longer such a useful indicator, we need to know what is happening to the incidence of leprosy.

Incidence rates give us vital information on the transmission of disease. We need to know the underlying incidence of leprosy to know whether any impact is being made on transmission. It seems likely that transmission is decreasing in many countries and has been for many decades, indeed long term trends are more convincing.[2] At present the intense anti-leprosy activities in the major endemic countries make it difficult to assess the underlying trends in incidence in the countries where it matters the most. Knowledge of the trends in incidence would help in understanding which factors might have the greatest impact, chemotherapy, BCG or socio-economic changes. Information on the trends in incidence of leprosy is needed to plan for future anti-leprosy activities.

Registered prevalence and true prevalence of leprosy

Prevalence is the number of people with a disease at one point in time (point prevalence) or over a given period of time (period prevalence). The leprosy data usually presented is point prevalence, commonly at the end of the calendar year, but some programmes do use period prevalence. Actually, what is used is the number of patients registered for treatment which includes people who have been mis-diagnosed as leprosy, cured patients, and even patients who have died if the registers are not kept up to date. The registered prevalence excludes those who have leprosy but who have not been registered for treatment. The WHO global

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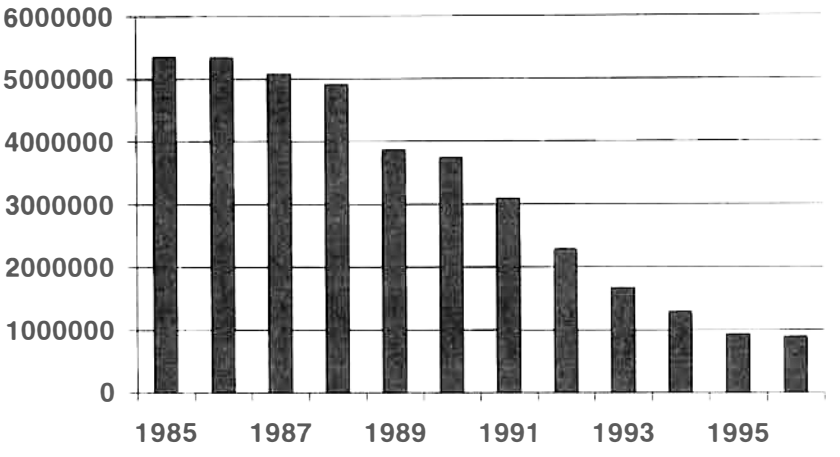

Figure 1. Global trend in registered cases, 1985–1996.

programme is well aware of this limitation and encourages national programme managers to estimate the true prevalence of leprosy each year based on guidelines[3] for such estimations, these estimates are also regularly published.[1] Over the past 10 years the gap between the estimated or true prevalence and the registered prevalence has narrowed and in 1997 it is estimated as around 260 000 or about quarter of the true prevalence. Vigorous efforts are underway to register and treat these patients through Special Action Projects and the Leprosy Elimination Campaigns. It is therefore important to recognised that the registered prevalence of leprosy is not the same as the true prevalence.

New case detection and the incidence of leprosy

The incidence of a disease is the number of new cases which occur over a given period of time, usually per year. New case detection is considered as a measure which may reflect the incidence of leprosy however cases detected over the past year include patients who developed the disease many years previously. New cases may be registered in different centres at the same time duplicating the numbers of new cases reported or patients defaulting from treat may be re-registered as new cases (so called re-cycling of patients) artificially inflating the figures. Case detection figures are readily influenced by operational factors such as the intensity of cases detection methods, their frequency as well as by diagnostic changes. In contrast to the trends in leprosy prevalence which have fallen dramatically over the past 10 years,[4] new case detection has remained remarkably unchanged over the same period (Figure 2). This global figure hides a range of different trends in case detection within individual countries (Figure 3). It is considered that these figures do not represent changes in the true incidence in these countries but reflect operational factors such as the expansion of geographical coverage by programmes, and intensification of case detection activities. It is therefore clear that not only are case detection figures a poor reflection of the true incidence of leprosy but also they are misleading. The constancy of the case detection figures over the past

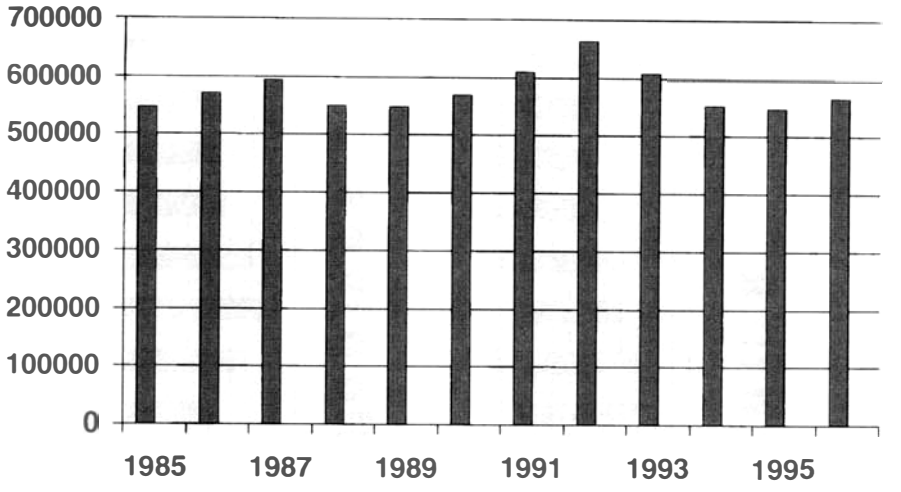

Figure 2. Global trend in new case detection, 1985–1996.

10 years at around 500–600 000 each year does not indicate a failure of the current elimination strategy but rather indicates its success in detecting and treating large numbers of previously undetected and untreated patients, the so called backlog cases. Similarly, any dramatic decline in new case detection in the next few years does not mean a sudden fall in disease incidence. It has been considered that the true incidence may be no more that a third of the annual case detection rate, this is a very rough estimate and is likely to vary greatly between individual countries. The current case detection figures do not tell us very much about the incidence of the disease.

Incidence of disability and impairment could be more relevant

It is often said that it is the disabilities which result from leprosy which set it apart from other diseases, both in terms of the primary impairments and the impairments secondary to nerve function loss. Disabilities or impairments could therefore be viewed as a relevant measure of the effect of anti-leprosy activities[5] although communities attitudes can handicap individuals who have no nerve function impairments. A single skin lesion may be of little or no consequence and the detection of increased numbers of such cases can greatly inflate case detection figures while making the percentage with disability at detection appear artificially low. It can be argued that the incidence of disability or impairment is a more relevant measure, counting the absolute numbers of patients with WHO grade 2 disability at detection and any who develop new, irreversible nerve impairments during or immediately after MDT. The global number of new cases with such disability at detection is shown in Figure 4, however the pattern varies between countries. A global target of aiming at zero disability incidence could be developed, it would be a target relevant to patients as well as easily measured. A fall in new case detection with an increase in disability would not be a real benefit to patients, their families nor their communities.

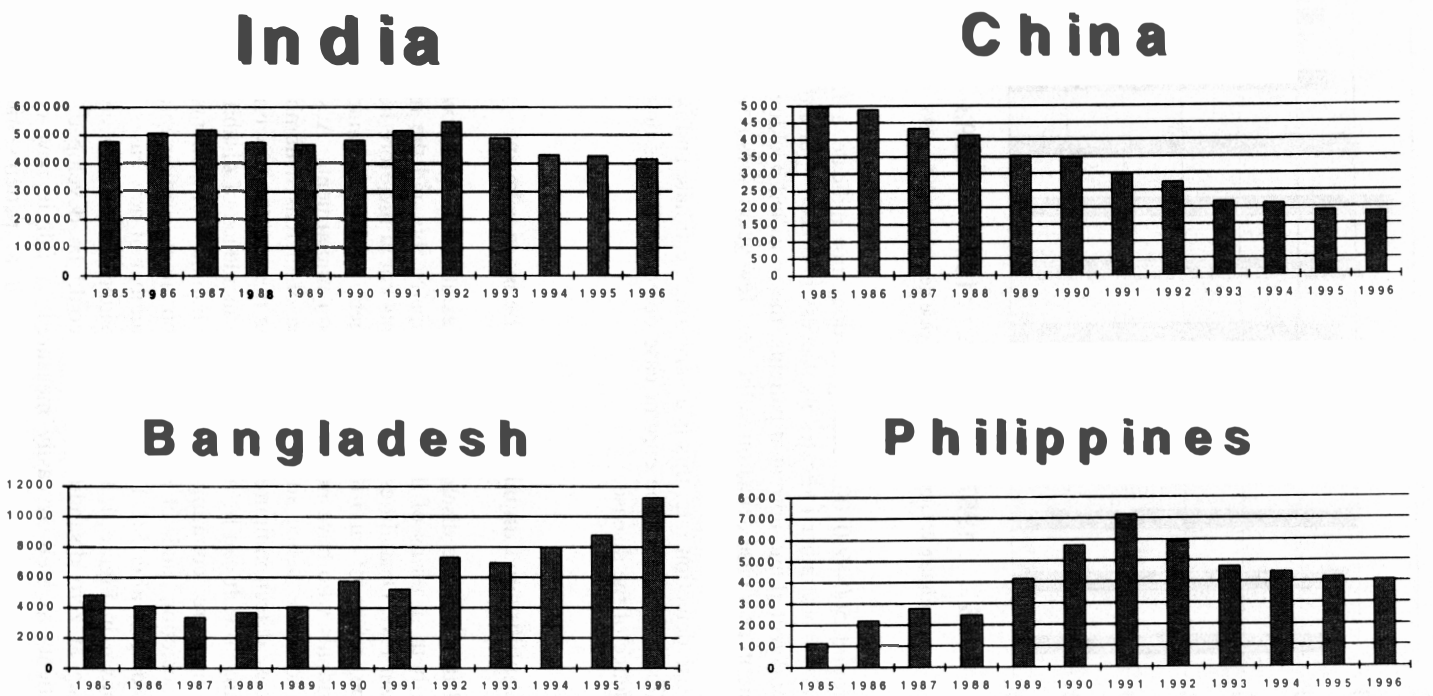

Figure 3. Global trends in cases detected in four endemic countries, 1985–1996.

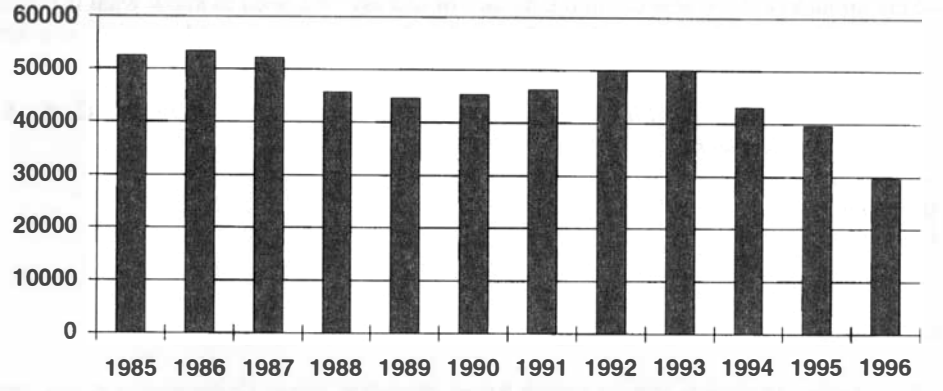

Figure 4. Global trend in new cases with disabilities, 1985–1996.

How can we find out what is happening to the incidence of leprosy

The collection of routine data on leprosy which is currently being undertaken, while necessary to monitor the elimination programme, does not tell us much about the incidence of leprosy in the main endemic countries. Special monitoring studies are needed to assess the incidence of leprosy as well as the application of new technologies and the use of simulation models to facilitate better understanding of what is going on.

Special studies are needed in population based programmes within the major endemic countries to monitor new case detection based on standardized case detection methods and consistent diagnostic criteria over many years. Collaborative studies which standardise methods and co-ordinate data collection in a number of populations in the endemic countries would begin to provide the data which are urgently required. These could start with retrospective analyses followed by the setting up of prospective monitoring. This is technically feasible as similar approaches have had to be developed for new case monitoring in the vaccine trials.

The development of the polymerase chain reaction (PCR) technology which has now been successfully applied in leprosy[6] has potential for tracking transmission and incidence of infection as well as disease. Studies are being set up, funded by the European Commission (MILEP2), to evaluate this approach in Africa and Asia. More work is needed in this field. The development of simulation models such as SIMLEP and their application using different data sets can be used to study the relative importance of different modes of transmission and other transmission parameters, and analyse the potential impact of different intervention strategies working towards leprosy eradication as opposed to elimination.

The priority for action

It is perhaps surprising how little we know about the transmission and incidence of leprosy. We do not even know what the current incidence of leprosy is, or its trend in the major endemic countries. The prevalence of leprosy has dramatically fallen following the widespread implementation of MDT. The target prevalence rate of 1 in 10 000 is approaching and

we are about to enter a new era in the history of leprosy. We need to know what is happening to the incidence of leprosy to be able to plan for the next era and to work towards the eradication of leprosy.

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Editorial

LEPROSY BY THE YEAR 2000—WHAT IS BEING ELIMINATED?

Several important statements on the current state of leprosy in the world have recently appeared. The article by Cairns Smith in this issue of *Leprosy Review* accompanies (see p. 195) position papers in WHO's *Weekly Epidemiological Record (WER)*. No fewer than four issues of *WER* were devoted to the subject within two months, timed to coincide with the meeting of WHO's Seventh Expert Committee on Leprosy.

In simplest terms, the world's leprosy situation is as follows: the WHO has declared 'Elimination of leprosy as a public health problem by the year 2000' as one of its goals, defining elimination in terms of a prevalence target. Prevalence has indeed declined rapidly, but this is largely the result of cleaning of registers and shortening the recommended duration of drug therapy. Though this is no doubt an achievement; the emphasis upon prevalence has obfuscated the issue of incidence trends.

The situation is disturbing, on two counts. First, although incidence appears to have declined in some countries, there is no convincing evidence that it has done so on a global scale. Second, the way that the elimination issue is being addressed is inadequate.

The *WER* report on 'Global case detection trend in leprosy' (13 June 1997) is not a simple document. We encourage all with interests in leprosy to study it. It begins by underlining the important question of whether declining prevalence impacts on 'transmission of the disease' (it would be better to speak of transmission of infection and subsequent appearance of disease). It is noted that 'globally, and at national level in many countries, detection has been increasing significantly over the past 10 years'. Indeed, when India is excluded, annual cases have almost doubled. In order to explain this observation, we are given an hypothesis: 'Assuming that introduction of MDT was successful in 'clearing' the accumulated backlog of prevalence, i.e. curing most of the already known cases, a new situation has now arisen. For the first time in the history of leprosy control, detection and prevalence are converging, and it is becoming increasingly obvious that detection to a large extent really reflects a hidden prevalence which was not very well perceived before' (the conclusion may not be obvious to all readers). The report then refers to 'indirect indicators, such as detection of children below 15 years, detection of multibacillary (MB) cases and proportion of disabled patients among newly-detected cases' and finds that 'the situation seems to be even more interesting'—with increases in child detection rates and proportions of multibacillary cases since 1985, and inconsistent trends in proportions of newly-detected cases with disabilities (declines in India, increases elsewhere). The implications of such figures, which are complicated by changing ascertainment criteria, are far from obvious. The report admits that 'At first glance one might think that [the] incidence of leprosy is remaining the same, or is even increasing in some parts of the world...', and follows by reference to 'some

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special studies' (which are not identified) that would suggest that the incidence is decreasing by about 10% per year. We then read, 'In one way, increasing detection trends provide reassurance, since they clearly demonstrate the effectiveness of the global elimination strategy in identifying the backlog cases for treatment with MDT'. We find the demonstration far from clear, and almost circular. The report then reviews the several WHO regions of the world, in none of which is there a consistent or convincing decline in leprosy in all member states, but ends on an optimistic note: 'The fact that the trend in the global leprosy detection (*sic*) has not changed over the last 12 years should not be interpreted as a weakness of the global elimination strategy.... While information is lacking on how to estimate the current annual incidence of the disease from case detection figures, it can reasonably be assumed that incidence represents no more than one-third of the annual detection. If this assumption is true, ... then one could expect a rapid and considerable decrease in global detection rates in the next 2–3 years.' Once again an assumption, out of nowhere and unsupported, this time followed by an inference which 'could' be true (readers of the WER report may wish to count the number of times this word is used). This is not the language of rigorous epidemiology.

Beyond the complexities of such logic, there is another disturbing element to leprosy figures today. The diminishing leprosy 'problem' recorded in some countries is likely to be at least partly attributable to amalgamation of leprosy control programmes into general health services. The increase in disability in new cases in endemic countries excluding India, as discussed by Cairns Smith, is to be expected when leprosy diagnoses are left to general health staff who increasingly recognize leprosy only when the patient presents with a classic disability. In such a situation, many early (and self-healing?) cases will be missed. As anyone knows, an efficient way to make a disease disappear is to stop looking for it....

The extent to which the year 2000 represents a watershed for leprosy is not widely appreciated. The considerable funds extended generously to leprosy control by the Sasakawa Foundation (10 million US $ per year for the last five years of this century) are not likely to be extended. The WHO's leprosy unit will almost certainly be reduced in size, and may cease to exist altogether. No doubt enthusiastic press reports will emanate from Geneva, declaring the elimination of leprosy as a public health problem to have been one of the successes of the twentieth century. These announcements will have an effect on leprosy charities, which will face further difficulties in raising funds, although these will be all the more needed with the discontinuation of alternative support—for no-one believes that leprosy will disappear by the year 2000, let alone its disabilities.

Given the importance and implications of the leprosy elimination target, we require harder logic and clearer vision than is evident today. Though the epidemiology of leprosy poses formidable difficulties, much could still be done to improve the quality of leprosy data, by insisting upon—and funding—external reviews which frankly document ascertainment methods and diagnostic criteria. And these data must be subject to critical and transparent analyses if they are to be convincing. Unsupported assumptions, and predictions of what 'could' happen are not enough. What if it only appears to be: or if it doesn't?

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REVIEW ARTICLE

Women and leprosy: a review

Summary Gender inequalities in health have a significant impact on women's health. In leprosy gender inequalities could be even more serious, as it is a highly stigmatized disease. A review has been made of the most recent literature dealing with gender and leprosy. First some data are presented on gender inequalities in rates of case detection, deformities and reversal reactions among leprosy patients. Then the major factors contributing to those differences are discussed. The paper ends with some recommendations for further research on gender and leprosy.

Introduction

Women's issues in health have, until recently, received little attention from health managers, policy makers and researchers.[1] There are, however, many gender inequalities in health which require due attention in health planning and management. Gender refers not only to sex, but also to the wide variety of social, cultural and economical variables attributed by social structures to men and women.[2] Men and women experience differential health risks stemming from their social roles and expectations. Women may have a different exposure to disease and infection, and diseases may have a different impact on women, not only in a medical sense, but also in sociocultural and economical ways. Some diseases affect women particularly or exclusively, such as reproductive health problems, and cervical and breast cancer. Other diseases affect both men and women, but have a different impact on wome such as nutritional morbidity, sexually transmitted diseases (STDs) and pelvic infections, and some tropical diseases such as malaria, schistosomiasis and tuberculosis.[3] Information on how women are affected differently is, however, still limited. Women may have less access to health services than men, they maybe treated differently to men, and diseases may manifest themselves differently in women, requiring a different treatment approach.

Gender and leprosy

In some tropical diseases, such as filariasis, and leprosy, gender inequalities may play an even larger role, because of their effect on physical appearance and the social stigma associated with them.[1] Although worldwide the number of registered leprosy cases has been reduced enormously in the past ten years, leprosy is still endemic in many countries in the world. The global registered prevalence was 1·7 per 10·000 in 1996.[4] There is probably a wide difference between the registered and the actual number of leprosy cases. Also treatment defaulting is still a problem; On average 5–20% of the patients do not complete their treatment and may thus remain a potential source of infection. Leprosy is therefore expected to remain a public

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health problem for at least the next decade. What is more, considerable differences exist in the registered incidence (case detection) rates of leprosy between the two sexes. Sex differences are also observed in the prevalence rates of deformities and reversal reactions due to leprosy.

GENDER DIFFERENCE IN CASE-DETECTION RATES

Worldwide, case-detection rates of leprosy vary considerably for men and women. In most areas of the world case detection rates are higher among men than women, at least in its clinical forms, at a ratio of 2 : 1. Already 50 years ago, studies in the Philippines, South India and Norway found that leprosy case-detection rates in males exceeded that in females, at least among adults.[5] More recent studies in Asia still find a similar difference in case detection rates between men and women: e.g. in rural Nepal sex ratios of 3 : 1 and 1·66 : 1 were found in 1982 and 1994 respectively,[6,7] and in Bhutan, these figures varied between 1·4 : 1 and 3·8 : 1. Also in several African countries (Senegal, Morocco and Tunisia), the male/female rtio varies between 1·5 : 1 and 2 : 1.[9,10]

There is however an important exception to the above noted sex ratios. In some African countries the case detection rates are similar for men and women, or even higher for women. In Kenya, for example, the male : female rates are similar (1 : 1),[11] while in Burkina Faso the male : female ratio is 1 : 1·5.[12] Also Uganda and Malawi have a higher prevalence of leprosy among women.[13,14]

GENDER DIFFERENCE IN DEFORMITY RATES

The epidemiology of deformities in leprosy has received little attention, but some data demonstrate significant differences in the frequency and types of deformities among each sex.[15] A study in India revealed that the incidence of deformities in males was more than twice as much as in females for grade I as well as grade II deformities ($n = 2285$).[16,17] Studies in Burkina Faso, Venezuela, Nigeria, Malawi and China reported similar findings.[12,15,18,19,20]

GENDER DIFFERENCE IN REVERSAL REACTIONS

Another finding is that, despite a predominance of men among leprosy patients, reversal reactions are more common among women: In Thailand, for example, reversal reactions occurred with significant greater frequency in women (47% against 26%) and did not appear to be influenced by age of onset of leprosy (cohort study, $n = 176$).[21]

The above data on sex differences in case-detection rates, deformity rates and reversal reactions suggest that men and women run indeed differential risk for leprosy and/or possibly do not have equal access to leprosy health services. In the sections below, some of the major factors which could influence gender differences are examined for different aspects of leprosy and leprosy health services: exposure to disease, utilization of health services, case-detection methods, treatment compliance, and outcome of the disease. The focus will be on the most commonly observed gender difference in leprosy, i.e. that leprosy case-detection rates are higher for men than for women in most countries.

1 Exposure to disease

Gender differences in exposure to disease could have a biological as well as a sociocultural

background. A biological factor which may influence gender differences in the incidence of leprosy is immunological. The main social factors influencing differences in exposure to leprosy are occupation and socioeconomic status.

IMMUNOLOGICAL REACTIONS

Women appear to develop stronger and possibly more effective immune reactions against infection with *Mycobacterium leprae* in a subclinical setting than men.[16] This immunological response is not limited to *M. leprae*, but is also presents for diseases, such as tuberculosis.

In pregnancy, the immunological response is suppressed. The effects of pregnancy and lactation have been studied in detail in Ethiopia, where a diminished and unstable immune response was found among 114 pregnant leprosy patients.[22] Pregnant women also had a higher risk of development of neuritis,[23] and relapse, although relapse rates are usually higher among men.[24] Another study found that adolescent girls have an increased risk of relapse of leprosy, compared to men of the same age.[25]

OCCUPATION

In many countries much of women's work is within the household. This might reduce their risk of infection. In Brazil, case detection of leprosy among women has been increasing since women started working outside the home and is now 1 : 1 for men and women.[26] On the other hand, if women stay indoors most of the time, their health problems may remain longer undetected. In general, it is assumed that risk and prevalence of infection among women is underestimated.[2]

SOCIOECONOMIC STATUS

Socioeconomic status is also recognized as a major determinant of exposure to disease risks. A leprosy study in Venezuela found a six times higher prevalence in areas of low economic development compared with areas of highest level (1·91 versus 0·3 per 1000), and an almost double incidence (3·39 versus 1·97 per 100·000).[27] About 75% of cases of leprosy among 8608 women were associated with low standards of living with regard to economic status, cultural level, nutrition, hygiene, and living quarters. A study in India found that the proportion of illiterate and unemployed female leprosy patients is considerably higher (74% versus 44% and 51% versus 25% respectively).[28] Few analytical and sociological studies have assessed these factors in detail.

2 Utilization of health services

The observed gender differences in case-detection rates could be due to women having less access to and making less use of health services. Several studies on gender differences in utilisation of health services, show that women have less access to health services than men.[29] Women's access to health services is influenced by many factors, including availability of services, costs, quality of care, social structure, and women's decision making power.

Availability of services: India study found that detection rates were similar for both sexes in urban areas (1 : 0·9), but differed widely in rural (1 : 0·7) and tribal areas (1 : 0·6). These differences were probably related to lower coverage in those areas.[41]

Awareness/literacy: The same study, and other studies noted that women were generally less aware than men of the symptoms of leprosy and the availability of leprosy services.[30,31,41] In Nigeria, the spouse is the most important source of information for women about leprosy (30%). Only 22% of women get information from health workers, compared with 43% of the men.[32]

Decision making power: In many countries women;'s access to health care is determined by their status within the family. In India, the decision to call a doctor is generally taken by men or the mother-in-law. A married women often delays seeking treatment because of the husband's apathy or because of jealousy of the mother-in-law.[33] Similar lack of decision-making power for women is found in many other countries in Asia, Africa and Latin America.[3]

Mobility of women: Women's mobility is not only limited by lack of decision making power, but also by lack of time and money, their unwillingness to disrupt household duties or their inability to find other caretakers for their children. Women tend to be the main health provider for their families, and as such suffer greatest impact of diseases. They often have to carry the additional burden of caring for other members when ill.[34] The family has a considerable role in determining when women seek health. In India, the gap between noticing a symptom and suspecting it to be leprosy, as well as the gap between the suspicion and seeking medical confirmation was considerable longer for women than men (16 versus 11 months and 15 vs 10 months).[35] Similar findings were noted in another study in India (31 months delay in detection *vs* 17 months delay for men).[28]

While these factors are not specific for utilization of leprosy services, it affects leprosy patients more seriously due to the long duration of the treatment involved.

Quality of services: Women's access to and utilization of health services will also depend on the perceived quality of these services. It has been widely recognised that women are hesitant to seek treatment because they feel treated in an inferior way by health services.[1] In many countries, particularly Islamic countries, women are not allowed to be examined physically by men, although male staff predominate. In India, most leprosy clinics have only male staff.

Stigma: Finally, stigma attached to a disease may also be a serious barrier to seek medical care. Women might delay seeking medical care when they suspect having leprosy, since being diagnosed with leprosy might severely reduce their chances of marriage or may affect their position and role in the household when married. In Nepal, fear of stigmatization was found to be an important reason for some ethnic groups patients to visit treatment centres far from home.[42] The percentage of leprosy patients hiding their symptoms is smaller than previously, but still considerable. A study in India found that 18% of women were hiding their symptoms,[37] and another Indian study found that that women tend to hide more than men (26 versus 21%).[28]

Studies in Thailand and the Philippines on the stigma of leprosy showed that stigma is still an important barrier to the seeking of timely treatment.[38,39]

3 Case detection methods

Even if women have the same risk as men for infection with leprosy, and have equal access to and make equal use of health services as men, still a difference in case detection may occur due to gender insensitivity of the methods used for case detection.

In India, lower detection among females than males was observed in various modes of

detection: more women were detected in general surveys and contact surveys, while fewer women were detected by referral, voluntary reporting and school surveys.[40] The same study also noted that the proportion of voluntarily reporting among women is less than among men.

Passive case detection rates could also result in significant differences in rates per age group: A study in India found that the percentage of passively detected girls in the puberty age group (11–17 years) is almost half of that of boys of the same age (13% *vs* 24%), while in the age group 18–35, female case detection rates are higher than men of the same age group (32% *vs* 25%).[40] The association of low case detection with a specific age group could be related to religious and cultural taboos, i.e. girls and women who are not yet married are not allowed to show their body to male health staff and hence are not visiting health services and/or are not properly examined and diagnosed.

Treatment compliance

Gender differences may also exist in treatment compliance. Studies in Pakistan and India found that women are generally more compliant than men (95% *vs* 83% in India).[40,41] This was attributed to women being more socialized to conform to prescribed behaviour. Compliance can however be influenced by socialcultural perceptions and beliefs. Some traditional medical practices attribute the cause of illness to behavioural lapses by women, preventing them from obtaining prompt treatment and continuing adequate treatment.[3] Leprosy is believed to be the wrath of God, resulting in women delaying taking treatment until measures such as fasting and offerings had been made (18% of women compared to 6% of men did so).[35] In India, many women, after being diagnosed with leprosy, and despite MDT, continued to rely on religious and traditional sources. In leprosy colonies 10% of women did not take any treatment despite their awareness of the disease.[35]

Women could also be hesitant to take leprosy medication for different reasons, such as the perceived effects of the drugs: Rifampicin, one of the MDT drugs for leprosy, turns the urine dark. Many women were concerned about this side effect of the drug, as the change of colour is associated with jaundice, which is considered one of the deadliest diseases. Some women consulted a 'jaundice expert' and stopped taking treatment on his advice. This study from Pakistan, included only women, and did not report whether the same fear was present in men.[41] This study found that the dark skin coloration associated with Clofazimine, is a big problem for many women as a dark skin is often associated with lower social status.[41]

Furthermore, the Dapsone, causes problems as it looks similar to a popular brand of contraceptive pill (Mala D.) When provided in blister packs it resembles ''the pill'' even more. Health workers frequently face a mother-in-law who forbade her daughter-in-law to take MDT for this reason.

In Nepal, treatment compliance was also found to be related to the quality of the services.[42]

It is not known to what extent these examples of poor compliance have a negative impact on the outcome of leprosy treatment.

5 Outcome of disease

Outcome of disease can be measured both in medical and sociocultural terms: the consequences of leprosy could be different grades of deformities and disabilities, but also

social isolation or expulsion of the women from the family. Significant differences exist in disease outcome, deformities being more common among men than women. A biological explanation for this difference could be the fact that multibacillary (MB) leprosy, which involves an increased risk of deformities, is more common among men: in Venezuela and Ethiopia, a predominance of MB leprosy was found among men compared to women (2·5 : 1 in both countries).[15,43] The incidence of disabilities and deformities are found to be associated not only with sex and the type of disease (MB or PB), but also with nerve trunk involvement and the duration of the disease.[44,45]

A sociocultural explanation for the observed gender difference could be different occupations between men and women: Two studies attributed the gender difference in incidence of deformities to men working outdoors involving both hand and feet.[16,17] In India, men were found to be more affected by their feet, while women suffered more leprosy associated injuries on their hands. Feet are more vulnerable in agricultural and other outdoor occupations while hands are more exposed in indoor occupations. In many cultures, however, women also do much of the outdoor work, fetching fire wood and water, working on the fields, and are on their feet all day.

Considering sociocultural outcome of disease, several studies indicate that women are more affected by leprosy. They suffer more isolation, rejection from spouses, children and relatives, loss of freedom to touch and have more restrictions than men in India.[40] Women with leprosy are less likely to have the opportunity to marry.[46] In Brazil, women tend to remain single, separated or widowed, live with relatives or with their children without their spouse, and indicate leprosy as a reason for family separation.[26]

Discussion

The review of studies shows that there are many gender differences, biological as well as sociocultural, which are related to leprosy. Data are, however, not uniform. Case-detection ratios of leprosy vary considerably, not only for the two sexes, but also per country, per socio-economic group, per age group, and over different time periods. An important obstacle in analysing gender differences in case detection ratios is that routine data collected on case detection are not desegregated for sex. The available data on sex differences in case detection are too scanty and too diverse in geography to compare. A complicating factor is that case detection rates can vary considerably over time, even within a country, depending on the methods of case detection that have been used. Active case finding in India, involving among others house-to-house surveys carried out by scouts or school girls resulted in a large increase in case-detection rates over the past few years.[47]

It will therefore be hard to explain why sex differences in case detection exist within a country, or between countries in the same continent, let alone that any explanation can be given for the reverse situation which is found in some African countries. There is, however, a strong indication that sex differences in case detection are significant, and further research is needed to quantify and to explain these differences, and to know whether they are mainly sex or gender related or whether a combination of both groups of factors plays a role. In order to compare data on case detection from different countries, multicentre studies are required, using a standard research methodology, and using the same methods for case detection.

Even more important than knowing whether gender differences in case detection ratios are significant is to understand the factors contributing to the observed differences. The wide

variety of potential variables, biological as well as sociocultural, with sometimes contrasting data makes it difficult to establish the major contributing factors to observed differences. Existing data are too scanty to draw any conclusions.

The review of the available literature on gender issues related to leprosy reveals that many biological as well as sociocultural factors play a role in the lower case detection rate among women. More research is needed to determine the relative importance of the different groups of factors: biological, health services or community related. Within each group, again more insight is needed on the major factors contributing to gender inequalities in order to address these problems. How can health services be improved to increase their utilization by women? How can health education messages be improved to reach the high risk groups among women? Qualitative, comparative research will be needed to address these questions.

It should be noted that most studies on leprosy included in this review are from Asia and Latin America, while few studies were found from Africa. If the gender differences as observed in most countries are indeed significant, it would be interesting to know why some African countries show a different picture. Again, qualitative, comparative studies will be needed to explain these differences.

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Influence of acetylator phenotype on the haematological and biochemical effects associated with dapsone in leprosy patients

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Summary Methaemoglobinaemia and haemolytic anaemia were the principal side-effects observed in 30 leprosy patients undergoing long-term treatment with dapsone as a single drug or as part of multidrug therapy. Hepatic, pancreatic and renal evaluations showed no relevant clinical changes. Since N-acetylation is a major metabolic pathway for dapsone, slow acetylation phenotype may be a risk factor for the development of these reactions. To confirm this hypothesis we correlated acetylator phenotype and the haematological and biochemical effects induced by dapsone.

No excess proportion of slow acetylators was found. We conclude that slow acetylators are not at greater risk of developing haematological side-effects of dapsone than fast acetylators.

Introduction

N-acetyltransferases play an important role in the biotransformation of a number of clinically useful drugs such as isoniazid, procainamide, hydralazine, dapsone, sulphamethazine as well as some carcinogenic arylamines[1]. In some cases, acetylation capacity has been shown to be related to variation in drug response, susceptibility to adverse reactions and increased incidence of certain spontaneous disorders including cancer.[2-6]

Dapsone is a widely used drug, extensively employed in the treatment of leprosy [7] and the prophylaxis of malaria,[8] and more recently in the treatment of Pneumocystis carinii pneumonia in AIDS patients.[9] A number of side-effects are associated with dapsone therapy, including methaemoglobinaemia and oxidative haemolysis, haematological effects that frequently limit its clinical use.[10,11]

Zuidema *et al.* [12] reported no difference in serum or plasma concentration or in any pharmacokinetic parameters of dapsone or monoacetyldapsone between slow and fast acetylators. Also, the therapeutic response was the same for both acetylator phenotypes.

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It has been speculated that slow acetylators may have relatively more of the parent drug available for oxidative metabolism by cytochrome P-450 and thus may be at an increased risk to develop haematological side-effects in response to dapsone.[13] Although there is preliminary evidence that patients with the slow acetylator phenotype may be disproportionately represented among patients with haematological side effects, no conlusive data are available in the literature about the possible side effects of long-term treatment.

To confirm this preliminary finding, we investigated the influence of acetylation phenotype on the haematological and biochemical effects of a group of leprosy patients who were submitted to long-term treatment with dapsone as a single drug or as part of multidrug therapy (MDT), i.e., dapsone plus clofazimine plus rifampicin.

Methods

LEPROSY PATIENTS

Thirty white Brazilian leprosy patients (14 females and 16 males) on dapsone treatment for at least 6 months as a single drug or as part of multidrug therapy, seen at the Regional Sanitary Dermatology Outpatient Clinic of Ribeirão Preto (ARE-DSRP) participated in this study. No patient had a history of sulphonamide allergy or glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. Social alcohol intake was permitted, but chronic heavy alcohol users were excluded from the study. Elderly patients (older than 65 years), patients with acquired immunodeficiency and pregnant women were also excluded. The patients were divided into three groups according to therapeutic schedule: Control Group—15 patients of both sexes who had been on MDT for at least six months previously but who had been off all medication for a period of 6 months or more at the time of the study, with clinically and bacilloscopically inactive disease. The controls did not receive any medication during the study. DDS Group—15 patients of both sexes treated with 100 mg/day dapsone. Group MDT—15 patients of both sexes given dapsone 100 mg/day dapsone plus 100 mg/day clofazimine on alternate days, and a 300 mg dose given once a month under supervision, plus rifampicin, 600 mg once a month under supervision.

ACETYLATION PHENOTYPING

A single 2·5 ml heparinized blood sample was obtained 12 hr after administration of the daily dose of dapsone (CEME, Brasília, Brazil). Plasma was separated by centrifugation and stored at -20C pending analysis. The phenotype criterion of Reidenberg *et al.*,[14] i.e., a plasma (MADDS/DDS) ratio of less than 0·30, indicated slow acetylators.

ANALYSIS

Plasma dapsone and monoacetyldapsone concentrations were measured by the HPLC method of Queiroz *et al.* (in press), as follows.

A 1-ml aliquot of plasma supplemented with the internal standard (50 μl of the phenacetin solution) was alkalinized with 200 μl of a 1·5 N sodium hydroxide solution and extracted with 7 ml ethyl ether for 30 min in a mechanical shaker after the addition of 200 mg sodium chloride. The samples were centrifuged at 3000 rpm for 10 min and the

organic phases transferred to conic tubes to which 50 μl 1 N HCl in methanol were added. After extract evaporation under an air flow at room temperature the residues were reconstituted with 50 μl of the mobile phase and 50 μl of n-hexane. After shaking in a mixer for 1 min and centrifugation, 20 μl of the mobile phase were injected into the liquid chromatography apparatus.

Chromatography was performed using a Varian liquid chromatography apparatus model 5000 equipped with a Rheodyne injector model 7125 with a 20 μl sampler and a Varian ultraviolet absorbance detector model UV-100 operating at 286 nm. The chromatograms were obtained with a Varian integrator model 4290. Analysis was carried out on a reverse phase C_8 LiChrocart ® 100 column (4 × 125 mm, Merck) with 5 μm particles. The mobile phase used was a water:methanol mixture (70:30 v/v) with a flow of 1 ml min^{-1}.

BIOCHEMICAL AND HAEMATOLOGIC PARAMETERS

Three blood samples were collected from each patient at weekly intervals for a more judicious evaluation of haematological and biochemical data. The results obtained (means ± SD) were compared with those obtained for the controls. The samples were obtained in the morning from fasted patients after a protocol had been filled out with patient name, age, sex, weight, scheduled medication, collection time and associated medications. The study of the adverse effects of dapsone was carried out haematologically level (blood count, reticulocytes, osmotic fragility, detection of Heinz bodies and methaemoglobinaemia) and biochemically (transaminases, bilirubins, alkaline phosphatase, gamma-glutamyltransferase, amylase, urea, creatinine, and potassium).

GLUCOSE-6-PHOSPHATE DEHYDROGENASE

Glucose-6-phosphate dehydrogenase levels were measured by the spectrophotometric method of Lohr & Waller [15] using Sigma Diagnostics® (St Louis, MO, USA) reagents which are for quantitative, ultraviolet, kinetic determination in blood at 340 nm.

STATISTICAL METHODS

Data were analysed statistically by ANOVA and by the multiple comparisons post test (Tukey-Kramer) using the GraphPad Instant® and Statgraphics® software, with the level of significance set at $p < 0{\cdot}05$.

Results

None of the 30 leprosy patients were found to have G-6-PD deficiency. The acetylation phenotype was determined on the basis of the ratio of plasma MADDS and DDS concentration. The mean values (± SD) for slow (13) and fast acetylators (17) were $0{\cdot}28 \pm 0{\cdot}05$ and $0{\cdot}57 \pm 0{\cdot}01$, respectively. The percentages of slow and fast acetylators among the leprosy patients in the two groups studied were 43·3 and 56·7, respectively.

The haematologic and biochemical abnormalities observed in slow and fast acetylators are shown in Table 1 and are reported as means ± SD of the data for the slow and fast acetylator groups compared with control. Haemolytic anaemia in addition to

Table 1 Tukey-Kramer multiple comparison test of haematology and biochemical data

Parameter	Control ($n = 15$) Mean ± SD	Acetylators: Slow ($n = 13$) mean ± SD (95% CI)	Acetylators: Fast ($n = 17$) mean ± SD (95% CI)	Slow *vs* Fast *P* value
Red cell count (million/mm^3)	5·19 ± 0·28	3·95 ± 0·46† (3·67 - 4·22)	4·25 ± 0·39† (4·05 - 4·46)	NS
Packed cell volume (PCV) (%)	45·80 ± 2·70	34·54 ± 4·05† (32·08 - 36·98)	36·94 ± 3·68† (35·04 - 38·83)	NS
Haemoglobin (g/dl)	14·78 ± 0·83	10·39 ± 1·62† (9·41 - 11·37)	11·17 ± 1·34† (10·48 - 11·86)	NS
Mean cell haemoglobin (MCH) (pg)	28·46 ± 0·88	26·17 ± 1·64† (26·18 - 27·17)	26·20 ± 1·16† (25·60 - 26·80)	NS
Mean cell haemoglobin concentration (g/dl)	32·32 ± 1·00	29·97 ± 1·80† (28·88 - 31·06)	29·76 ± 1·66† (28·90 - 30·62)	NS
Reticulocyte count (%)	0·90 ± 0·08	2·16 ± 0·89† (1·41 - 2·91)	2·55 ± 1·36† (1·28 - 3·81)	NS
Methaemoglobin (%)	0·99 ± 0·34	6·92 ± 1·36† (6·10 - 7·74)	5·97 ± 1·56† (5·16 - 6·78)	NS
Eosinophilis (mm^3)	246·93 ± 180·01	787·86 ± 482·43† (520·7 - 1,055·1)	775·6 ± 617·1† (433·83 - 1,117·4)	NS
Lymphocytes (mm^3)	2,285·20 ± 661·28	1,595·12 ± 470·94* (1,201·4 - 1,988·9)	1,834·28 ± 319·07* (1,539·2 - 2,129·4)	NS
Total billirubin (mg/dl)	0·74 ± 0·12	0·83 ± 0·13* (0·75 - 0·91)	0·92 ± 0·22* (0·79 - 1·04)	NS
Creatinine (mg/dl)	0·94 ± 0·08	1·19 ± 0·12* (1·04 - 1·19)	1·24 ± 0·15* (1·16 - 1·32)	NS
Potassium (mEq/L)	3·94 ± 0·33	4·09 ± 0·23* (3·95 - 4·23)	4·22 ± 0·33* (4·05 - 4·40)	NS

* Analysis of variance - $P < 0·05$.
† Analysis of variance - $P < 0·01$.
NS - not significant ($P > 0·05$).

methaemoglobinaemia was also detected in fast and slow acetylators. Thirteen patients (6 slow and 7 fast acetylators) had anaemia with haemoglobin levels of 7·2–10·9 g/dL and packed cell volumes of 28%–37%. Reduction in total red cell number, macrocytosis, poikilocytosis and hypochromia were detected in most patients. Eleven males (5 slow and 6 fast acetylators) had normocytic, normochromic anaemia (haemoglobin levels of 10·9–12·3 g/dL and packed cell volumes of 33%–37%). The other patients had anisocytosis or poikilocytosis. Reticulocyte counts were elevated (> 1·8%) in 80% of the patients. The haemolytic action of dapsone was also evaluated by the osmotic fragility test, and a reduction in cell resistance was detected in 100% of the patients compared to controls regardless of acetylator phenotype. Heinz bodies were only detected in slow acetylators (6%).

Differential white cell counts showed significant eosinophilia for both slow (46·6%) and fast (53·3%) acetylators. Since no clinical symptoms or parasite infection that might cause the eosinophilia were detected, we postulated this as a possible allergic reaction to the medication.

Hepatic, pancreatic and renal evaluation by biochemical parameters showed occasional changes of no apparent clinical significance, although creatinine, potassium and

bilirubin values showed statistically significantly differences compared to the control when the data were submitted to analysis of variance (ANOVA), Table I.

The influence of acetylator phenotype on the haematologic and biochemical effects associated with long-term dapsone treatment was evaluated by the Tukey-Kramer multiple comparison post test (Table I). Comparison of the haematological and biochemical parameters of the patients classified as slow and fast acetylators did not reveal statistically significant differences between the two groups.

Discussion

This study did not reveal a statiscally significant excess of haematological side effects in slow acetylators among leprosy patients on long-term treatment with dapsone.

As also reported by Kelly & Griffiths,[16] we failed to observe any association between acetylator status and severity of haemolysis or methaemoglobinaemia, side-effects, which are thought to be mediated by the hydroxylamine metabolites.[17]

Dapsone hydroxylamine reacts with oxyhaemoglobin (Fe^{2+}) to form methaemoglobin (Fe^{3+}) and the nitrosoarene, which is in turn reduced to the hydroxylamine by either NADPH methaemoglobin reductases or glutathione. Each hydroxylamine molecule is capable of oxidizing up to five oxyhaemoglobin molecules, and the cycle only ceases when the erythrocyte is almost totally depleted of glutathione. As methaemoglobin cannot carry oxygen, it may cause, in proportion to blood levels, lethargy, headache, cyanosis, dyspnoea, tachycardia, nausea and, in extreme cases, death. Methaemoglobin levels of under 20% are not usually associated with symptoms, although in our study four females, with 8·1–9·8% methaemoglobinaemia reported symptoms of lethargy, headache and nausea. This is consistent with literature showing that some patients cannot tolerate even low levels of methaemoglobinaemia.[10,11]

Dapsone therapy also reduces erythrocyte survival time. Recent studies on rats have suggested that the hydroxylamine promotes the formation of disulphide-linked adducts between haemoglobin and red cell skeletal proteins. Dapsone hydroxylamine also interferes with potassium and chloride cotransport within rat red cells, and causes them to shrink and become less deformable. Overall, after exposure to dapsone hydroxylamine, erythrocytes are recognized as aged and prematurely removed from the circulation by the spleen. The presence of Heinz bodies has also been associated with reactive biotransformation products resulting from the oxidative denaturation of haemoglobin.[10,11]

Studies reporting the occurence of haemolysis and anaemia induced by dapsone have suggested that these clinical symptoms occur mainly in the presence of high doses (>100 mg/day) of the medication or in G-6-PD deficient patients.[17] However, in our study we showed that in patients with normal G-6-PD levels on therapeutic doses of 100 mg/day dapsone, some of them developed anaemia (44%) (Table I). And as also reported by Byrd & Gelber,[18] we observed that chronic dapsone treatment results in not only haemolysis but a significant decrease in haemoglobin concentration.

Attempts have been made to counteract the haemotoxic effects of the metabolite by the use of antioxidants such as vitamins E and C.[10] Recently, the coadministration of a metabolic inhibitor such as cimetidine has been shown to reduce significantly dapsone-dependent methaemoglobinaemia, without any change in drug efficacy . Such a therapeutic

strategy may be appropriate for patients who require high-dose dapsone and for those who are particularly susceptible to dapsone-induced haemotoxicity.[19]

This study, therefore, while supporting the view that a long-term treatment of dapsone (100 mg/day) may cause significant methaemoglobinaemia and haemolysis, also reveals that patients who are slow acetylators are not at greater risk of developing haematological side-effects of dapsone than fast acetylators.

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Lepr Rev (1997) **68,** 218–224

Clinical and histopathological activity in paucibacillary leprosy patients after fixed-duration multidrug therapy

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Summary In 37 clinically-diagnosed borderline–tuberculoid (BT) leprosy patients skin biopsies were done prior to starting multidrug therapy (MDT) and at the end of 6 months therapy. Clinical and histopathological activity, graded as active, resolving and inactive, were studied at the end of 6 months of MDT.

Of the 37 clinically-diagnosed BT patients 24 could be confirmed by histopathology as having BT leprosy, while the other 13 biopsies showed features of indeterminate (I) leprosy. After 6 months of MDT, out of the 24 histopathologically-confirmed BT patients, 4 (17%) showed clinical activity and 8 (33%) showed histopathological activity. Of the 13 histopathologically-diagnosed indeterminate cases all were clinically inactive but histological activity persisted in 3 cases (23%). Out of the 37 clinically-diagnosed BT patients 3 showed both clinical and histopathological activity at the end of MDT.

This study emphasizes the importance of performing histopathological examinations on leprosy patients undergoing research studies for the confirmation of diagnosis and for proper classification of the disease. The histopathological activity that outlasts the MDT may be due to the bacillary fragments that persist but clinical activity coupled with histopathological activity seen in 3 patients at the end of 6 months may foreshadow a relapse and these patients and others like them need to be followed up for longer durations.

Introduction

The World Health Organization (WHO) study group on chemotherapy of leprosy for control programmes had classified leprosy patients into multibacillary (MB) and paucibacillary (PB) groups. In 1982, the PB group included all polar tuberculoid (TT), borderline tuberculoid (BT) and indeterminate (I) cases diagnosed clinically or histopathologically with a BI of 2 or less than 2 on the Ridley scale.[1] The MB group consists of polar lepromatous (LL), borderline lepromatous (BL) and mid-borderline (BB) patients. In 1988 this was modified again and all smear positive patients were included in the MB group for treatment with multidrug therapy (MDT).[2] The paucibacillary type of leprosy constitute 70% of the total number of leprosy

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patients in India.[3] It has been observed that a significant number of patients present with a single lesion. These lesions may heal or progress towards the multibacillary part of the spectrum. WHO has recommended a fixed duration of MDT for PB patients, i.e. dapsone 100 mg daily and rifampicin 600 mg once a month for 6 months. The short duration of treatment and relapses in PB cases raises a few basic issues regarding the clinical activity and the histopathological changes which occur in patients on PB–MDT. This study has been carried out to elucidate such changes.

Materials and methods

This is a study of 37 leprosy patients who had been clinically diagnosed and classified according to the Ridley–Jopling classification[4] as BT patients, attending the Outpatient Department at the Schieffelin Leprosy Research and Training centre, Karigiri, S. India. Each patient had a complete clinical examination done, recording the morphology and the site of lesions. Skin-smear examination for acid-fast bacilli was done from routine and selective sites and were negative in all 37 patients. The characteristic clinical features of skin lesions of patients being categorized as belonging to the BT group included single or multiple, dry, hypopigmented, flat or raised patches of any size with ill-defined or well-defined margins. Modalities of sensation were lost to varying degrees in these patches. None of the patients had nerve trunk lesions.

A biopsy of skin lesion was taken before starting MDT. An elliptical piece of skin was biopsied from an active patch under local anaesthesia by the standard Khanolkar technique.[5] The skin biopsies were fixed in formol zenker. Serial sections of 5 μ thickness were stained with haematoxylin and eosin for routine study and a modified Fite-Faraco stain for acid-fast bacilli.[6] Patients were diagnosed and classified histopathologically according to the classification given by Ridley & Jopling.[4] Histologically, the lesions were classified as indeterminate leprosy when there was mild lymphocytic infiltration around skin adnexa and selective peri and intraneural infiltration with lymphocytes of dermal nerves.[17] All patients were reassessed clinically and histologically at the end of 6 months of MDT. Skin bopsies were taken from the same skin lesion but at a different edge. Clinical assessment was recorded as follows: 'active' when erythema or infiltration persisted, a new lesion appeared, anaesthetic areas increased and or any nerve trunks became tender; 'resolving' when there was a decrease in infiltration, anaesthesia and size of the patch; 'inactive' when the patches were without infiltration and erythema.

The skin bopsies were assessed for the type of granuloma, granuloma fraction, nerve inflammation and for the presence of acid-fast bacilli (AFB). The histological findings were graded as 'active' when there was dermal infiltration by epithelioid granuloma and the granuloma fraction was more than 10% in the dermal tissue and nerve inflammation. It was graded as 'resolving' when the granuloma fraction was less than 10% and 'inactive' when epithelioid cell granuloma was absent and/or the lymphocytic infiltrate was less than 5%.

Results

Of the 37 clinically-diagnosed BT patients, 27 were males and 10 were females. The age of the patients ranged from 7 to 50 years with a mean of 15·5 years. Out of the 37 cases, 24

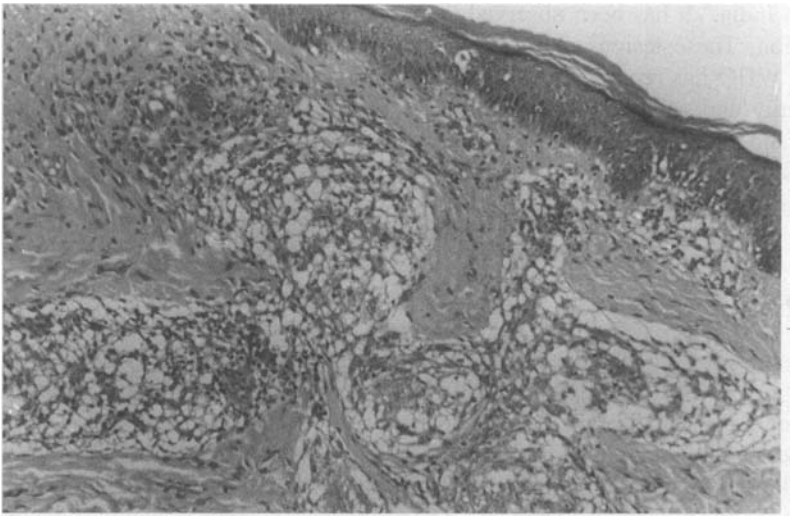

Figure 1. Photomicrograph to show tuberculoid granuloma composed of epithelioid cells, Langhan giant cells and lymphocytes infiltrating and replacing extensive areas of the dermis (active). H&E × 100.

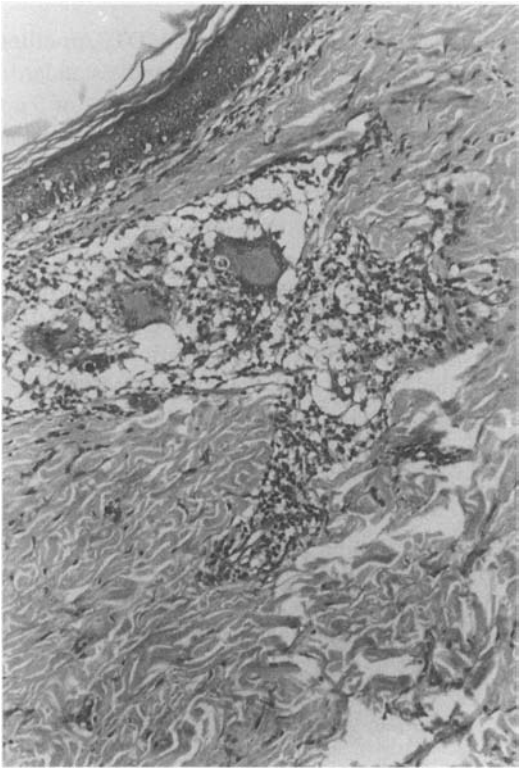

Figure 2. Resolving granuloma composed of a few Langhan giant cells in the small collection of epithelioid cells and lymphocytes (resolving). H&E × 100.

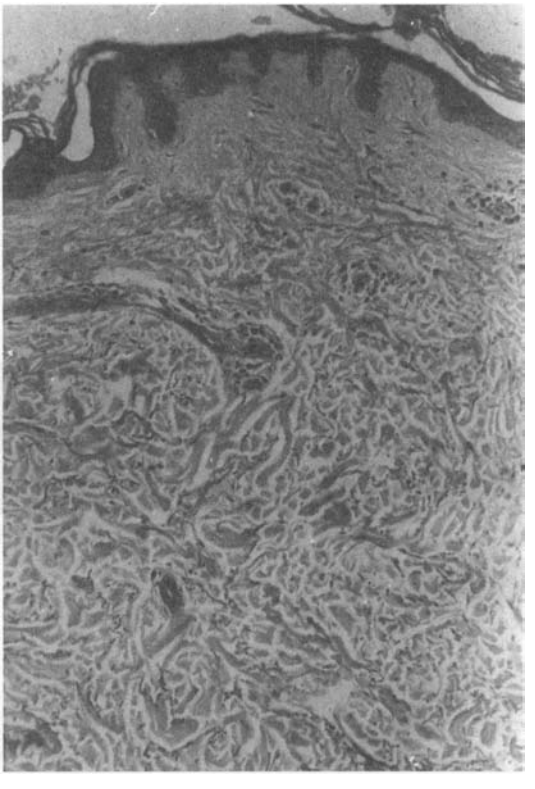

Figure 3. Photomicrograph to show a few scattered lymphocytes around blood vessels. Epithelioid granulomas are not seen (inactive). H&E × 100.

patients presented with single lesion and 13 of them had multiple patches but less than 5 in number. In 28 cases the lesions presented only in the upper and lower limbs and in 9 patients the patches were generalized. Histopathological examination of these 37 clinically-diagnosed BT patients showed that 24 of them had a histology that correspondedwith the BT type of the disease and 3 of these showed bacilli in the dermal nerves. The other 13 cases showed histological features that fitted in with the indeterminate type of leprosy. None of them had AFB.

The second examination was conducted after 6 months of MDT therapy. Of the 24 patients clinically and histopathologically diagnosed as BT, 4 were clinically active and 8 showed histologically-active persistent epithelioid granulomas (Figure 1). Of the 13 histologically-confirmed indeterminate cases none showed active signs of the clinical disease but histologically the lesions were active in 3 cases. Histological features of resolving granulomas (Figure 2) were seen in 5 BT cases and in 1 indeterminate case. Eleven BT and 9 indeterminate cases were found to be inactive, with either absence of epithelioid granulomas and/or the lymphocytic infiltrate was less than 5% (Figure 3). The granuloma fractions of BT leprosy patients before and after MDT is contrasted in Figure 4 and of indeterminate patients in Figure 5. None of the patients showed evidence of neuritis and none of the biopsies showed evidence of reversal reaction (RR) or acid-fast bacilli.

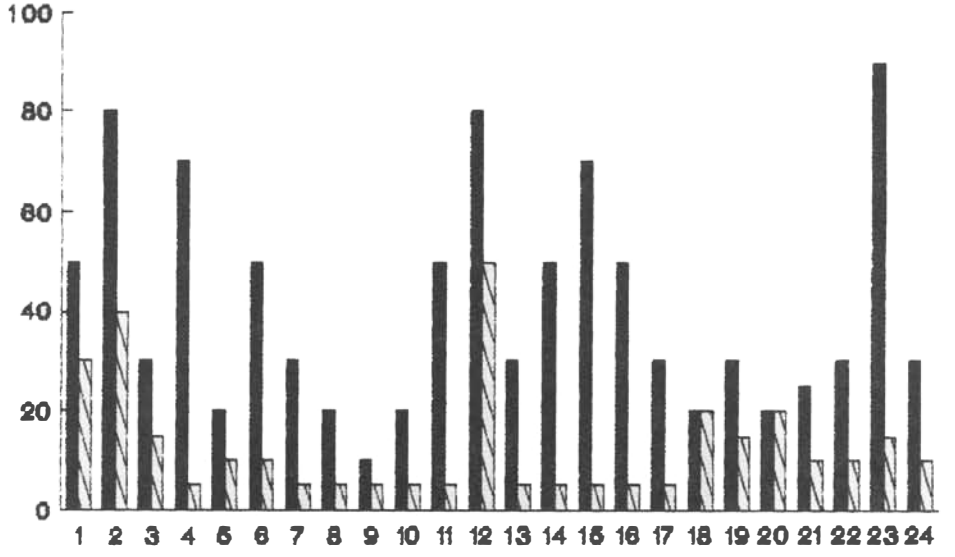

Figure 4. Granuloma fraction in BT leprosy.

Discussion

In this study, 37 patients were clinically diagnosed as BT following a precise categorization but on histopathological examination only 24 of them could be confirmed as having a BT histology while the other 13 showed features that were consistent with the indeterminate group of leprosy. Discrepancies have been reported by several authors between histopathological and clinical diagnosis of leprosy,[7–9] and our finding again emphasizes the importance

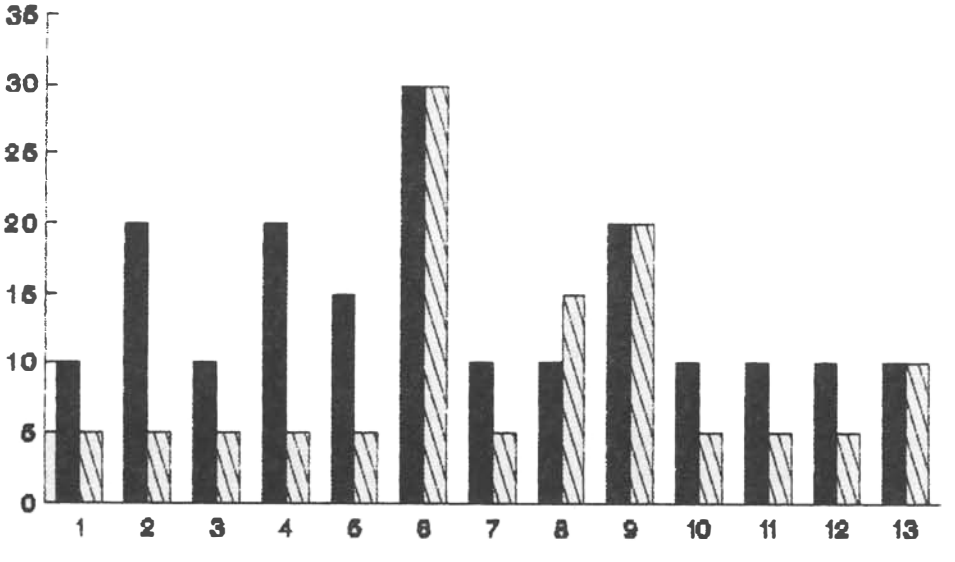

Figure 5. Granuloma fraction in indeterminate leprosy.

of performing histopathological examinations on leprosy patients undergoing research studies for the confirmation of diagnosis and for proper classification of the disease.

MDT is prescribed for PB leprosy patients with an aim to reduce the duration of treatment and to deal with possible drug resistance to dapsone and to increase cost-effectiveness by releasing the patients from continuing the treatment at the point of inactivity.[1] However persistence of disease activity has been observed in the skin lesions of the patients after 6 months of treatment.[10–13] The reported percentage of PB patients who showed persistent activity at the end of 6 months of PB regimen ranges from 4·3% to 67%.[14] The wide variations in the reported clinical response may be due to different concepts of classification and disease activity.

In our series of 24 BT patients 4 (17%) showed clinical activity and 8 (33%) showed histopathological activity after completion of therapy. In 13 indeterminate cases all were clinically inactive but histologically the activity persisted in 3 cases (23%) after 6 months of MDT therapy. The persistent activity in these patients may be the result of the continued presence of the antigens of the lepra bacilli.[15,16] Evidence of resolution of the inflammatory lesion (5 in BT and 1 in indeterminate) would suggest that in due course, even the active inflammation would clear up as has been stated and that adequate immune response present in PB patient would be expected to remove these antigenic fragments.

However among the 11 histologically-active cases, 3 cases showed features of clinical activity too. Of the 11 histopathologically-active patients it is reasonable to expect a small percentage of these patients to continue to be active with a likelihood of a relapse occurring in due course. The relapse rate among PB patients has been reported to be as high as 12·9%[18] and 12%[19] and as low as 0·34%[20] and 0·5%.[21] However WHO analysis of a large series of PB cases treated with MDT revealed the risk of relapse to be only 1·07%.[22] Therefore a careful follow-up of the patients under report for a longer period is imperative. Sequential biopsies every year on a much larger number of PB patients, who had persistent active lesions at the end of 6 months of MDT, and a careful follow-up of these patients for at least 5 years would be useful.

Acknowledgments

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Study on the detection of leprosy reactions and the effect of prednisone on various nerves, Indonesia

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Summary This paper presents a retrospective study on the detection of the treatment of leprosy reactions in a field situation, and the effect of prednisone on the various affected nerves.

Two patient cohorts were analysed.

The leprosy control programme in the testing area is not backed up by a specialized referral leprosy hospital, but patients are treated on an ambulatory basis at peripheral health centres by trained multipurpose health workers supervised by the health centre doctors. For operational purposes the guidelines and procedures for reaction management in the field were adjusted and partially simplified.

In both studies it appeared that the time of the occurrence of severe reactions was the same: 80% or more of the severe reactions occurred in the first year of treatment, the majority in the first few months after the start of the multidrug (MDT) treatment.

One third of all reaction patients suffered from a silent neuritis.

Well-instructed fieldworkers proved to be competent in detecting and treating leprosy reactions.

Treatment of severe reactions with prednisone in the field situation can preserve or considerably improve the functions of the affected nerves.

It is interesting that often the motor function of a nerve was found to be impaired without any loss in sensibility, which was tested using the ballpoint pen method.

Introduction

Central Sulawesi is one of the four provinces of Sulawesi Island in Indonesia. In 1985 treatment with MDT was gradually introduced and by 1992 all registered patients were on MDT.

In Indonesia the National Leprosy Control Programme is integrated with the general health services, provided at the health centres at subdistrict level. The health centre is the most peripheral health unit, serving a population of around 10,000–20,000 and is staffed by a doctor and 10–20 paramedical staff.

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Since 1991 increasing attention has been given to patient care at the health centre level, and a range of activities were introduced, aiming at the prevention of permanent nerve impairment and disabilities:[5–7,9,14,19] wound-care, patient education on self-care, early detection and treatment of complications like leprosy reactions and nerve function disorders, all these activities became a routine activity in the field; first as a pilot project, which was expanded step-by-step to the whole province. Fieldworkers received an intensive training course of 3 days on the aspects of prevention of disabilities (POD) after which they were allowed to treat reactions with prednisone under close supervision of the health centre doctors and supervisors.

This paper discussed two cohorts: the first contains 69 patients with severe reactions (125 nerves were affected), evaluated between March 1992 and March 1993. In this patient group the routine examination of the posterior tibial nerve was not included. The second cohort consisted of 85 patients with severe reactions (180 nerves were involved) and were assessed between March 1993 and March 1994. Fifty-one of the 85 patients had multiple nerve involvement.

Three people (2 district supervisors and 1 physiotherapist) were involved in doing the assessments.

Both groups of patients were treated with a similar minimum standard course of 10 weeks of prednisone.

For operational purposes leprosy reactions are only differentiated in mild and severe reactions: severe reactions include severe acute reversal reaction (RR) and/or a recent silent neuritis and/or a severe erythema nodosum leprosum (ENL).

The criteria for a severe reaction were:

a recent (less than 6 months) nerve function disorder (loss of sensation or muscle strength) in eyes, hands and/or feet;
nerve trunk tenderness;
ulceration of skin lesions; and
high fever and oedema of hands and feet.

All other reactions without nerve involvement were classified as mild reactions.

STUDY QUESTIONS

When is the majority of severe reactions detected?
Which nerves/nerve functions are affected most and what is the proportion of silent neuritis?
What is the effect of a standard prednisone course (see Patients and methods) given under field conditions, on the various nerves, as regards nerve tenderness, muscle strength and sensibility or a combination of these?[10,17]
Is a leprosy fieldworker capable of detecting severe reactions in time and of treating these reactions adequately?

The following definitions were applied

Nerve tenderness: of the ulnar, peroneal and tibial nerve. Tenderness was scored as 'present' or 'not present'.

Improvement was defined as going from 'present' to 'not present'.

The median and radial cutaneous nerves are not examined by fieldworkers (difficult to assess/less frequently affected).

Muscle strength of the ulnar, median, peroneal nerve. Three gradings were used: a strong; weak; and paralysed. Strong was defined as 5 on the VMT score (0–5; 0 = paralysed, 5 = normal strength); weak was defined as 3; paralysed was defined as 0. Improvement was defined as an upgrading of the score.

Muscle strength[3,11,12] of the facial nerve was assessed by the degree of lagophthalmos, but not measured, in millimetres. Lagophthalmos was scored as 'present' or 'not present'.

Sensibility of the ulnar, median and tibial nerves. Sensibility was tested by a light touch of the tip of a ballpoint pen. On the hands 10 points were examined: 5 for the ulnar part and 5 for the median part. On the feet: 11 points were tested. A difference of at least 2 points (within one nerve area) was considered to be a change in sensibility.

Silent neuritis was defined as recent sensory or motor nerve function impairment (i.e. developed within the last 6 months) without skin manifestation of RR, ENL or nerve tenderness.

Patients with nerve tenderness and/or nerve function loss of more than 6 months duration were excluded from being given prednisone, so they were not included in this study.

Patients and methods

Leprosy fieldworkers examined the nerve function of leprosy patients by using voluntary muscle testing (VMT), sensory testing (ST), and assessment of the disability/impairment status every 3 months. Quality control of the assessment was performed quarterly by supervisors. The status before and after prednisone treatment was compared in both studies by direct patient examination or data collection from individual patient records (disability/nerve function assessment form).

The standard prednisone treatment started with a dose of 30 mg for 2 weeks and tapered down with a minimum duration of 10 weeks. Every 2 weeks the patient was reassessed by the fieldworker and a decision was made on tapering down or extending the course or increasing the dose of prednisone. There was no maximum duration; the duration was fully determined by the condition of the individual patient and not by the type of leprosy or the type of reaction.[13,15,16,18,20,21]

FIRST COHORT

Out of 856 (130 PB, 726 MB) leprosy patients on the register 69 patients (8 PB, 61 MB) with severe reactions were observed, with 125 nerves involved.

Six patients suffered from an ENL reaction, 33 patients from an acute RR reaction, 3 patients from a combined RR and ENL reaction, and 27 from a recent silent neuritis. Thirty-seven out of 69 patients had a multiple nerve involvement.

Differentiation on the degree of tenderness, strength, sensibility or a combination of these after the treatment with prednisone was not recorded as such.

SECOND COHORT

Out of 751 (165 PB, 586 MB) leprosy patients on the register 85 patients (3 PB, 82 MB) with a severe reaction were observed, with 180 nerves involved.

Eleven patients were suffering from an ENL reaction, 2 patients from a combined RR/ENL

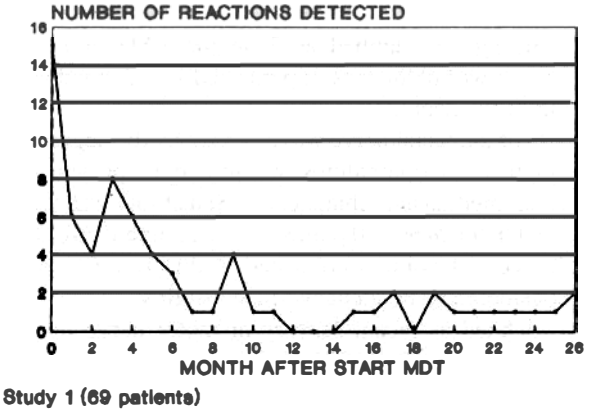

Figure 1

reaction, 44 from an acute RR, 28 from a silent neuritis. Fifty-one out of the 85 patients had multiple nerve involvement.

Nerve tenderness of the posterior tibial nerve was only routinely examined in the 2nd study.

In both studies there was no control group, as we regarded it as unethical to exclude patients from prednisone treatment.

Results

THE TIME OF DETECTION OF SEVERE REACTIONS

The first cohort (see Figure 1) showed that 80% of the reactions (55 out of 69 patients) were discovered within the first 12 months of MDT treatment. Fifteen out of 69 patients (21·7%) were detected with a severe reaction at the start of the MDT treatment.

Study of the second cohort (see Figure 2) revealed that 82·5% of the reactions (70 out of

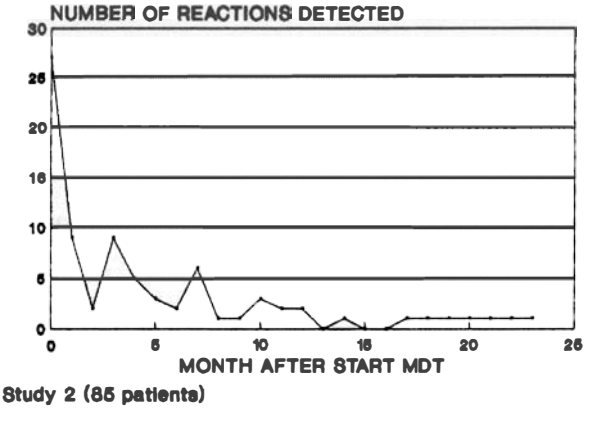

Figure 2

Table 1. Nerve involvement

	Cohort 1		Cohort 2	
		%		%
Facial	3	(2.5)	9	(5)
Median	3	(2.5)	9	(5)
Common peroneal	30	(24)	43	(24)
Tibial posterior	29	(23)	55	(30·5)
Ulnar	60	(48)	64	(35·5)
	125	(100%)	180	(100%)

Cohort 1 included 69 patients (8 PB, 61 MB).
Cohort 2 included 85 patients (3 PB, 82 MB).

85 patients) were discovered within the first 12 months of the treatment; 32% (27 out of 85) had a severe reaction at the start of treatment.

NERVE INVOLVEMENT

Table 1 shows the nerve involvement of the patients, included in both cohorts. The ulnar nerve is affected most frequently, the facial and median nerve the least.

In cohort 1 tenderness of the posterior tibial nerve was not included, which explains the lower incidence of tibial involvement in this study.

EFFECT OF PREDNISONE

In Table 2 the effect of prednisone on the affected nerves is given. Most nerves (75%–80%) improve either partially or totally.

Table 2. The effect of prednisone on the affected nerves

	Improvement	Same	Worse
Cohort 1:			
Facial	2	0	1
Median	3	0	0
C. peroneal	20	6	4
Tibial post.	19	7	3
Ulnar	50	7	3
	94 (75%)	20 (16%)	11 (9%)
Cohort 2:			
Facial	6	3	0
Median	7	2	0
C. peroneal	36·5*	6·5*	0
Tibial post.	41	10	4
Ulnar	54	10	0
	144·5 (80%)	31·5 (17·5%)	4 (2%)

* 0·5, partial improvement to one affected nerve.

Table 3. Nerve function involvement in the second cohort, before and after treatment with prednisone

Pattern of nerve involvement 'before'/'after' prednisone	Tender	Tender + weak	Tender + anaesthetic	Tender + weak + anaesthetic	Weak	Anaesthetic	Weak + anaesthetic
'change'	I/S/W	I/S/W	I/S/W	I/S/W	I/S/W	I/S/W	I/S/W
Facial					6/3/0		
Median					4/1/0	2/1/0	1/0/0
Peroneal	27/0/0	4,5/2,5/0			5/4/0		
Tibial P	13/1/0		3/3/0			25/6/4	
Ulnar	28/2/0	7/2/0	5/0/0	3/2/0	4/2/0	1/1/0	6/1/0
	68/3/0	11,5/4,5/0	8/3/0	3/2/0	19/10/0	28/8/4	7/1/0

'Weak' should be read as 'weak/paralysed'.

I, improved; S, same; W, worse.

The pattern of nerve disorder before treatment with prednisone is compared with the nerve disorder after treatment with prednisone.

In a few nerves we have found an improvement in tenderness while the degree of weakness/paralysis remained the same. This was recorded as '0·5'.

Several patients showed a partial improvement against a partial nonimprovement within one affected nerve (see also Table 3). Tenderness was often improved, while the weakness and/or sensibility loss remained the same.

Only 15 patients received a prednisone course with a duration longer than 10 weeks, which led to a total nerve improvement in only 8 cases. However, we cannot draw any conclusions on the standard minimal duration of the prednisone treatment because this study does not compare various regimens.

Table 3 explains the pattern of nerve function involvement in the second cohort, before and after treatment with prednisone.

Table 4 shows the percentage of silent neuritis (on the total of affected nerves) in the second cohort.

Table 4. Percentage of silent neuritis—second cohort

Nerves	Total number of affected nerves	Silent neuritis
Facial	9	9 (100%)
Median	9	9 (100%)
C. peroneal	43	9 (21%)
Tibial P.	55	35 (64%)
Ulnar	64	15 (23·5%)
Total	180	77 (42%)

Twenty-eight patients (out of 85, (33%)) were suffering from silent neuritis (2 PB, 26 MB patients).

All these patients had recent sensory or motor nerve function impairment without any other sign of reaction.

In this study the total number of patients with a silent neuritis was 28 (2 PB, 26 MB); this is 33% of all patients, involving 42% of all nerves.

Discussion/conclusion

Of all diagnosed severe reactions 81·25% were discovered within the first 12 months of MDT treatment. This is in line with other studies. Van Brakel[1,8] found an occurrence of 95% (however he included also mild reactions in this study), Becx-Bleumink[2] found an occurrence of 71%.

Moreover, 27% of all patients appeared to suffer from a severe reaction at the time of the first patient contact. This number varies among the abovementioned authors between 59% (Van Brakel) and 7·9% (Becx-Bleumink).

Further data from both our studies show that most of the nerves (75–80%) improved partially or completely with a standard prednisone course of 10 weeks minimum. The other authors used standard prednisone regimens of a much longer duration (12–20 weeks) with a higher starting dose of 40 mg. We should, however, note that most of the patients were examined not long after the full course of prednisone. There is still a possibility of recovery of the function of the nerve with time (like the tibial nerve which is known for its 'late' recovery) or the possibility of gradual deterioration of the nerve function, or the chance that a new reaction might occur.

Other studies are needed to define the optimal minimal duration of treatment and regimen of prednisone.

It is interesting that, contrary to the statement of Brandsma[4] that 'changes in sensation are often an earlier sign of nerve involvement than changes in muscle strength', in our study of the affected ulnar and median nerves often (for median nerve: 55·5%; ulnar nerve: 9·4%) the motor function was found impaired without any loss in sensibility (see the second cohort). One of the reasons could be that the sensibility test using the ballpoint pen is less sensitive than other methods. Still it occurs that a patient has had a clear weakness of his/her hand for sometime, while there is no deterioration of the sensibility of the hand.

The relatively high percentage of 'silent neuritis' (33%) proves that follow-up of the leprosy patient without a regular and proper VMT/ST examination will undoubtedly lead to impairments and disabilities in many patients.

This study also indicated that well-instructed leprosy fieldworkers are capable of detecting severe reactions in good time and are competent to treat these complications adequately in the field.[22]

Further studies wil be done with the same group of patients to detect 'late' recovery or deterioration of nerves, and with a new group of patients to verify the occurrence of a solitary muscle weakness of ulnar and median nerves, without sensory loss.

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Does clofazimine have a prophylactic role against neuritis?

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Summary A study was undertaken with the aim of testing the usefulness of clofazimine as a prophylactic agent against neuritis and nerve damage. A modified regimen, using initial high doses of clofazimine followed by regular multibacillary multidrug therapy (MB-MDT) WHO regimen, was given to a series of consecutive cases of high risk borderline leprosy patients, fulfilling defined selection criteria ($n = 65$). These patients were studied for the incidence of neuritis/Type I reaction, over a period of 2 years. Results were compared with a matched series of consecutive cases treated only with regular MB-MDT WHO regimen ($n1 = 57$).

The difference in incidence rates of neuritis between the two groups was significant ($p < 0{\cdot}01$), suggesting that clofazimine may have a useful prophylactic role against neuritis/Type I reaction and nerve damage.

Introduction

Leprosy produces disability and deformity through nerve damage. Type I reactions (reversal reactions) are generally known to be a major cause of nerve damage in borderline leprosy (BL) patients.[1] Prevention of deformity and disability is an integral part of leprosy control programmes, and they endeavour to achieve this through early detection and appropriate treatment of Type I reaction/neuritis.[2]

Reports of incidence rates of acute neuritis with or without associated inflammatory changes in the skin vary.[2–4] However, it seems that the incidence of neuritis and Type I reaction is more among the multibacillary (MB) cases of the borderline spectrum,[2,3] i.e. those cases of borderline-tuberculoid (BT), who are closer to the centre of the spectrum, midborderline leprosy (BB) and borderline lepromatous leprosy (BL). It is also known that the incidence of Type I reaction is more in the months immediately after the initiation of therapy—first 6 months for paucibacillary (PB) cases and first 12 months for MB cases.[3,5] This seems especially so when the regimen includes rifampicin.[3] Therefore, if an anti-inflammatory drug with prophylactic activity against Type I reaction, can be used to cover those vulnerable first few months of MDT,[6] especially in those who are at a higher risk for

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Type I reactions, perhaps the incidence rate of neuritis and consequent disability can be reduced.

Clofazimine is an effective antileprosy drug and its use in the treatment of Type II (ENL) reactions is well established.[7] It is also known to have a prophylactic effect against episodes of Type II (ENL) reactions, once significantly high tissue levels are achieved.[8,9] Though there were early reports of its use in Type I reactions,[10] later reports found it to be of limited use, as it took 3–4 months to act and by then irretrievable nerve damage had occurred.[11,12] There were also reports of clofazimine's probable modulating influence on Type I reaction when used along with steroids.[13] However, no studies investigating the possible prophylactic action of clofazimine against Type I reaction have been reported.

The aim of this study is to explore the potential of clofazimine in a prophylactic role against Type I reaction/neuritis, in a selected group of high risk borderline leprosy patients.

Patients and Methods

All Borderline leprosy (BT, BT–BB, BL), ie.e excluding indeterminate, tuberculoid and lepromatous leprosy, patients attending the outpatient clinic at the Schieffelin Leprosy Research and Training Centre, Karigiri during the year 1988 and 1989 were considered for the study.

Patients were initially assessed clinically, their lesions charted, involved nerves identified, any functional defects recorded and skin smears taken. Patients were classified clinically using the Ridley & Jopling classification and all except three (none of whom developed neuritis) had skin and nerve biopsies taken. Patients then underwent screening for tuberculosis and diabetes mellitus. Routine laboratory investigations including liver function tests and renal function tests were performed.

Type I reaction/neuritis was defined as an episode of acute inflammation in the nerves always accompanied by tenderness and often with pain in the affected nerves. Acute inflammatory changes in the skin lesions may also be present. From the population described above, patients who were estimated to be at a higher risk of Type I reaction/neuritis were termed as the high risk group.

The high risk group patients were selected as follows:

1 All cases of borderline lepromatous leprosy (BL). These patients had positive skin smears at routine sites. (The routine sites for Karigiri are right earlobe, left forehead, right chin, left buttock for male and left thigh for female and nasal scrapings from the mucosa over the anterior end of inferior turbinate.)
2 All cases grouped as BT–BB:[14,15] These were borderline patients who were smear negative at routine sites, fulfilling the following criteria:
3 or more skin lesions;
3 or more nerves involved as evidenced by thickening and/or functional defect. (Lesions on the skin and the involved nerves must be well distributed.); and
'glove and stocking type of peripheral sensory impairment.
Two out of the above three criteria must be present for inclusion in this group (BT–BB).

BT–BB was a composite group consisting of cases who present clinically and on smear examinations as Paucibacillary leprosy. Most of these cases showed a picture of borderline lepromatous leprosy in the nerves and a picture of BT/Indeterminate histology in the skin biopsy.

Patients falling into the above two groups (BL and BT–BB) constituted the high risk group.

Prophylactic potential of clofazimine was tested on these patients, subject to the following inclusion and exclusion criteria.

Inclusion criteria

All patients selected as the high risk group, as described above, formed the 'test group'.

All cases had received only dapsone monotherapy for less than 1–24 months prior to inclusion (Table 1).

Exclusion Criteria

Type I reaction/neuritis at the time of presentation.

Patients below the age of 16 years and above the age of 60 years.

Patients who had tuberculosis either diagnosed at the initial assessment or subsequently.

Patients who developed Type II (ENL) reaction, requiring increased dosages of clofazimine or steroids during therapy.

Hypersensitivity to any of the drugs used.

Female patients who were pregnant at the time of initial assessment.

The test group, thus selected was given the following initial regimen for 12 weeks: Cap. clofazimine 100 mg tid; and Tab. dapsone 100 mg od. The loading clofazimine dosage was 100 mg tid in all cases except in those with a bodyweight of less than 40 kg, for whom 100 mg bid was given for the same duration. After completion of 12 weeks, patients were put on the standard MB-MDT WHO regimen.[6]

CONTROLS

Controls were chosen retrospectively for this clinical trial from the case registers of 1986 and 1987. All borderline cases were considered and the same inclusion and exclusion criteria were applied. All patients in this group were either newly diagnosed or had received dapsone monotherapy for less than 1–19 months (Table 1). All controls were directly put on standard MB-MDT WHO regimen.

All the patients were seen once monthly, when they were given the supervised doses, and

Table 1. Duration of dapsone monotherapy

Duration of DDS (month)	Study Group	Control Group
<1	6	12
2–5	29	19
6–10	12	7
11–24	6	5
No DDS	–	3
Total	53	46

Table 2. Characteristics of the test group

Total no. of patients	65
Females	21
Males	44
Age	18–56 years
BT–BB	38 (58·5%)
BL	27 (41·5%)
Drop outs	12 (18·5%)
BT–BB	6
BL	6
Total no. of patients who completed the study	53 (81·5%)

examined carefully for the occurrence of Type I reaction/neuritis. Patients were also tested for any evidence of silent deterioration of nerve function by doing routine sensory and motor assessment. The maximum default period was 28 days, except for 4 patients among the test group and 6 patients among the control group, who had defaulted for periods ranging from 1 to 4 months during the course of their therapy. None of these patients give a history suggestive of Type I reaction/neuritis and their nerve status did not differ from previous records. All patients were followed up for a minimum period of 2 years.

Results

TEST GROUP

There was a total of 65 patients in the test group (Table 2), of whom 53 completed 24 pulses of MB–MDT after the initial 3 months of high dose clofazimine. These patients completed their therapy over a period ranging from 2 years and 4 months to 3 years and 1 month.

Drop outs were 12. Two patients dropped out between the 6th and 12th months of MB–MDT therapy, 7 patients between the 12th and 18th, and 3 patients between the 18th and 24th months. None of these patients had recorded an episode of neuritis during the period they remained on treatment.

Incidence of neuritis/Type I reaction, during this period is shown in Table 3. Two patients developed Type I reaction with neural involvement as defined. One other patient developed

Table 3. Incidence of Type I reaction/neuritis in the test group

No. of patients who completed the study		53
Type I reaction/neuritis		2
Silent nerve paralysis		1
Total no. of patients with nerve damage		3 (5·66%)
Incidence according to classification -	BL	2
	BT–BB	1

Table 4. Characteristics of the control group

Total no. of patients	57
Females	10
Males	47
Age	18–60 years
BT–BB	39 (68·4%)
BL	18 (31·6%)
Drop outs	11 (18·5%)
BT–BB	8
BL	3
Total no. of patients who completed the study	46 (81·5%)

silent nerve paralysis, detected after the 20th pulse of MB–MDT. Thus a total of 3 patients (5·66%) suffered nerve damage and were treated with steroids. Three others developed mild inflammation of the skin lesions without any neural involvement. They were treated with chloroquine and were not counted as neuritis/Type I reaction.

CONTROLS

There were a total of 57 patients in the control group (Table 4). Of these 46 completed 24 pulses of MB–MDT, over a period ranging from 2 years and 2 months to 2 years and 9 months. There were 11 drop outs. Seven patients dropped out before the completion of the first 6 months, 2 between the 6th and the 12th month, one between the 12th and the 18th month and one between the 18th and 24th month. One patient was diagnosed as having severe Type I reaction, with bilateral ulnar neuritis, just prior to dropping out. This case was included in the incidence rate for neuritis/Type I reaction.

The incidence rate of neuritis/Type I reaction in the control group is shown in Table 5. Twelve patients developed neuritis/Type I reaction as defined. One of them had a second episode after steroids were stopped. As this occurred within a month of stopping steroids, it was not clear whether it was a different episode or a continuation of the first. Therefore it was counted as one. One other patient developed inflammation of the skin lesions without neural involvement. He was treated with chloroquine and was not included in the incidence rate.

Table 5. Incidence of Type I reaction/neuritis in the control group

No. of patients who completed the study	46
Type I reaction/neuritis	12 (26·1%)
Silent nerve paralysis	Nil
Total no. of patients with nerve damage	12 (26·1%)
Incidence according to classification - BL	7
BT–BB	5

Table 6. Comparison of incidence rates; test *vs* controls

	Type I Reaction/Neuritis		
	Yes	No	Total
Test Group	3	50	53
Control	12	34	46
Total	15	84	99

χ^2 (Corrected)* = 7·74, df = 1, $p < 0{\cdot}01$
* Yates correction

The difference in incidence rates (Table 6) between the two groups was statistically significant ($P < 0{\cdot}01 \cdot \chi^2$ test).*

Discussion

Clofazimine was chosen for this study after considering a number of factors. It has known anti-inflammatory[16–19] and immuno-modulatory properties.[20,22] It has dose dependent increase in absorption[23] and cumulative retentive properties.[24,25] It was reported that clofazimine was still detectable in the skin and the macrophages, two years after stopping therapy.[26] Thus substantial tissue concentrations can be achieved and retained for a long

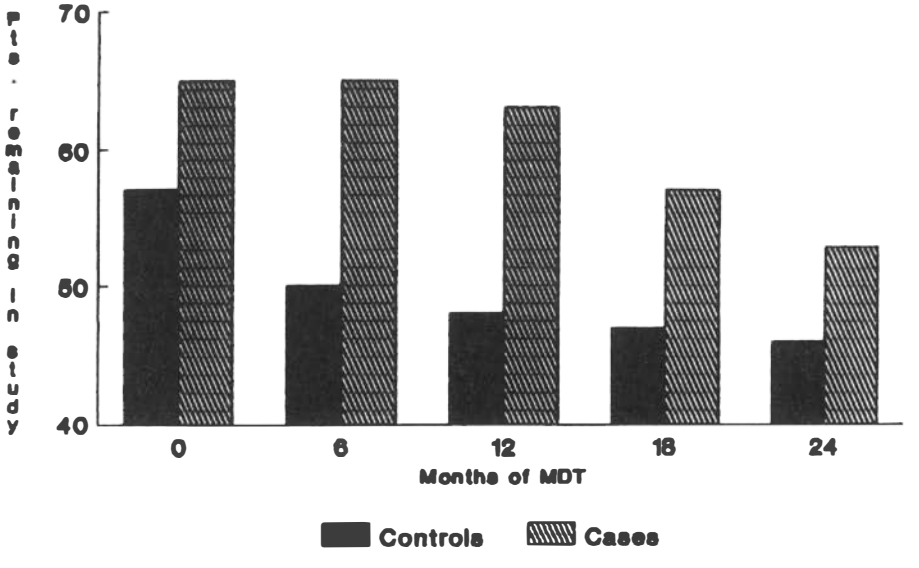

Figure 1. Pattern of drop outs. Comparison between the test group and the control group.

* None of the patients in the test group showed any significant side-effects to clofazimine, except discoloration.

period, by an initial intensive therapy as was done in this study. From our personal experience and the reports of the others it appeared that clofazimine would help to halt the progress of neural involvement and at the same time avoid the hazards of prolonged steroid therapy. Thus it was thought worthwhile to seek a treatment regimen which would most effectively halt and positively reverse neural involvement in leprosy.[10] Therapeutic prevention of the permanent neural sequel is usually not attained with conventional MDT. In many instances nerve involvement can be rapidly irreversible and can also be aggravated by conventional therapy.

Hence in this clinical study the trial regimen was designed in such a way as to achieve high tissue concentrations before the introduction of rifampicin as part of the standard MB–MDT WHO regimen. Low doses of clofazimine administered as part of the standard

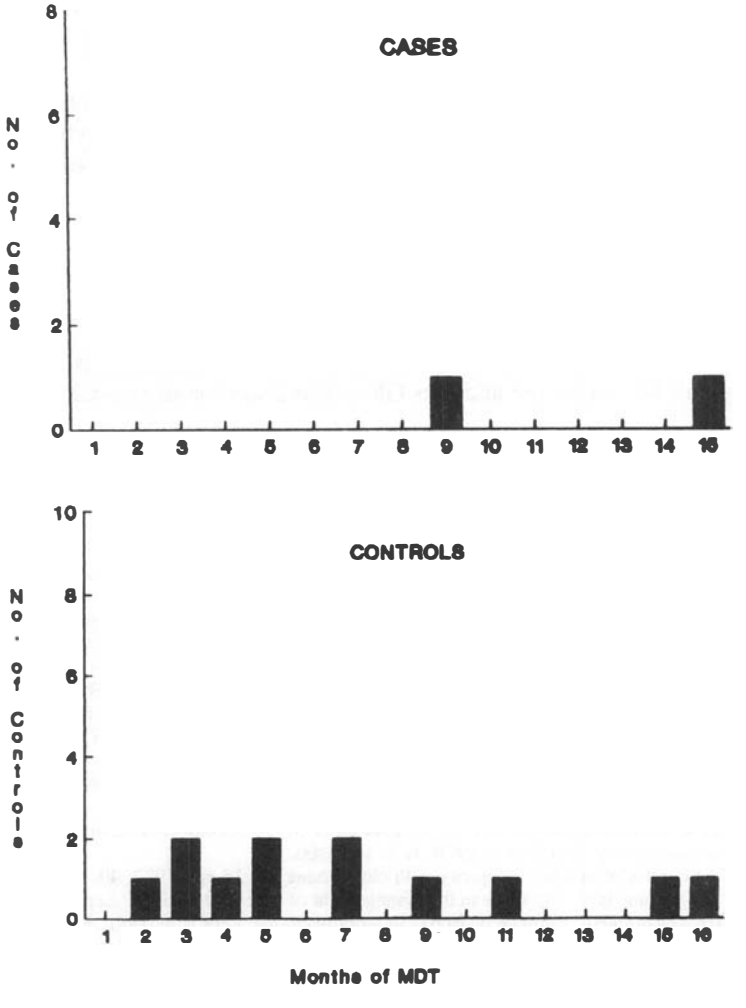

Figure 2. Time of occurrence of Type I reaction/neuritis in the test group and the control group. Note: only reactions involving nerves are shown.

MB–MDT regimen may have helped in maintaining high tissue levels through the risk periods of therapy.

Earlier investigations did not find clofazimine to be useful in Type I reaction. This was probably because it was used as a therapeutic agent rather than prophylactic, and hence could not have achieved high tissue levels fast enough to prevent irretrievable nerve damage.

The percentage of Type I reaction/neuritis which occurred in our test group seem significantly less even when compared with rates published from other centres. The drop outs in our study were a confounding factor and it is difficult to estimate their significance. One interesting finding was the difference in this pattern of drop outs between the test group and the control group (Figure 1). Drop outs were more in the second year for the test group while the reverse was true for the control group. The time of occurrence of reactions were also different (Figure 2). It appears that majority of the reactive episodes took place within the first 6 months for the control group while the two episodes in the test group occurred after 8 months after 14 months. If occurrence of reaction is an important reason for dropout, then it would be tempting to suggest that clofazimine given as it was in this study merely postpones reactive episodes, thus explaining the later drop outs in the group.

However, there seems to be enough evidence to warrant a carefully controlled prospective field-based clinical trial to confirm the trends seen in this study. The search for a prophylactic agent is becoming more important as investigations to delineate high risk groups, using clinical and laboratory findings are advancing.[27]

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Excretion of clofazimine in human milk in leprosy patients

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Summary Clofazimine is an important and effective constituent of multi drug therapy for leprosy. A study has been conducted to determine the distribution of clofazimine in maternal milk so that the safety of breast-feeding during maternal ingestion of the drug can be ascertained. Eight female leprosy patients (LL/BL) on clofazimine, 50 mg daily or 100 mg on alternate days for 1–18 months, (mean 5·0 ± 1·81 months; median 3·25 months) and in the early lactating phase were studied. Blood samples and milk specimens were collected 4–6 hr after the last daily dose. Clofazimine was assayed in the milk and plasma samples by HPTLC. Mean plasma and milk clofazimine levels were 0·9 ± 0·03 μg/ml and 1·33 ± 0·09 μg/ml respectively. The ratio of milk to plasma drug concentration ranged from 1·0 to 1·7 with a mean of 1·48 ± 0·08. The amount of drug ingested by the infants was 0·199 ± 0·013 mg/kg/day which represented 22·1 ± 1·9% of the maternal dose.

Introduction

Clofazimine, 3-(p-chloroanilino)-10-(p-chlorophenyl)-2, 10-dihydro-2-(isopropylimino) phenazine, is an effective antileprosy drug. It is a part of the multi drug therapy (MDT) for leprosy and is given at a dose of 50 mg daily or 100 mg on every other day.[1] It is also useful in the management of erythema nodosum leprosum at higher doses, usually 200–300 mg daily.[2] Slow absorption, relatively much slower distribution and longer retention in selective tissues are peculiar features of clofazimine metabolism.[3] The plasma concentration of the drug is dose related, although there does not appear to be a linear relationship between doses and plasma concentrations. A steady state is expected to be attained with oral administration of clofazimine 50 mg daily for more than 30 days.[4]

There are isolated reports on pigmentation of the infants born to leprosy patients on clofazimine therapy[5,6] and the mammary excretion of the drug in experimental animals.[7] Recently there has been a report on excretion of significant amounts of clofazimine in the breast milk of a woman in Nepal.[8] Since the safety of drug ingestion via maternal milk by suckling infants is of considerable importance, the present study was carried out to quantitate the mammary excretion of clofazimine in patients and determine milk to plasma concentration ratio as well as the approximate levels of the drug ingested by suckling infants.

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Materials and methods

Eight female leprosy patients (LL/BL) who were in the early lactation period of upto 4 months formed the subjects of the study. They were aged 19–35 years with the mean age of 28 ± 2·17 (SE) years. As a part of MDT (comprising of rifampicin 600 mg once a month, dapsone 100 mg daily and clofazimine 50 mg daily or 100 mg on alternate days) all patients had taken clofazimine for 1–18 months with a mean of 5·0 ± 1·81 months. One patient had received the drug 100 mg daily while 2 patients received 100 mg on alternate days and remaining patients were on 50 mg daily. Milk specimens and blood samples were collected 4–6 hr after administering the day's dose with breakfast.

Plasma was separated and both milk and plasma samples were either processed for clofazimine assay immediately or stored at −20°C till assay. Clofazimine was assayed by the method of Lanyi & Dubois[9] based on high performance thin layer chromatography (HPTLC) coupled with densitometric scanning. Briefly 1–3 ml of plasma/milk were acidified with 2 ml of acetate buffer (1M, pH 5·0) and extracted with 6 ml of toluene for 15 min. After brief centrifugation, the organic layer was removed and evaporated to dryness under a stream of nitrogen at 40°C. The residue was redissolved in 100 μl of methanol and applied on to HPTLC silica gel 60 Plate (Merck) predeveloped with chloroform : methanol (1 : 1 v/v) prior to use. The plates spotted with clofazimine extracts and standards were developed in toluene–acetic acid–water (50 : 50 : 4 v/v). *In situ* quantitation of the TLC spots were performed with a Shimadzu (Japan) TLC Scaner at 550 nm. Two samples containing aliquot of clofazimine extracts were also run on high performance liquid chromatography (HPLC) Shim pack C8 column using a mobile phase of 0·0425 M Phosphoric acid in 81% methanol (pH 2·4) at a flow rate of 1·5 ml/mt and quantitated at 285 nm.[10]

The ratio of milk to plasma clofazimine concentrations was calculated and the approximate amount of the drug ingestion by suckling infants was calculated assuming that an infant aged 2–3 months and weighing 2·5 kg would consume breast milk at a rate of 150 ml/kg bodyweight/day on average.[11] The percentage of last maternal dose, in mg/kg, ingested by the infants was also determined.

Results

The plasma clofazimine levels ranged between 0·8 and 1·0 μg/ml with mean value of 0·9 ± 0·03 μg/ml while the milk drug levels ranged from 0·8 to 1·7 μg/ml (1·33 ± 0·09). The ratio of milk drug concentration to plasma drug concentration (M/P) ranged from 1·0 to 1·7, (mean 1·48 ± 0·08) 4–6 hr after the last daily dose. The quantities of clofazimine ingested daily by suckling infants ranged from 0·120 mg/kg/day to 0·255 mg/kg/day (0·199 ± 0·013) which, when expressed as a percentage of the last maternal dose in mg/kg, represented 13·5 to 30% (22·11 ± 1·90) (Table 1).

Discussion

Clofazimine is a highly lipophilic drug. The mechanisms of its absorption, distribution and retention are far from clear. Leprosy patients receiving the drug at 100 mg thrice weekly or 100 mg daily for varying periods have shown plasma drug levels of 0·5 or 0·7 μg/ml

respectively.[12] A single oral dose of 200 mg results in a mean plasma level of 0·4 μg/g.[4] An average plasma concentration of 1·15 μg/ml has been reported in leprosy patients receiving a daily dose of 300 mg.[13] The patients included in the present study were on clofazimine 50 mg daily or 100 mg alternate days for 1–18 months. Since a daily continuous daily administration of 50 mg of the drug for 30 days is likely to result in a 'steady-state level',[4] plasma drug concentrations of 0·8–1·0 μg/ml presented by the patients in the present study might represent the steady-state levels and at this stage one could look for an equilibrium between plasma and milk compartments.

The distribution of clofazimine is relatively slower than its absorption. Clofazimine and related phenazines have been reported to show very selective tissue distribution. A significant proportion of the drug is found in adipose tissues and in cells of the reticuloendothelial system, where they can be seen concentrated in phagosome type inclusions and ultimately as crystals of pure drug.[14] Presumably clofazimine after absorption circulates bound to plasma proteins and is engulfed in this form by the cells of the reticuloendothelial system, where it remains after digestion of the proteins.[7] Clofazimine and its metabolites are excreted in urine in very small amounts constituting 1·6% of the daily dose (assuming 70% drug absorption).[15,16] The low excretion rate is probably due to retention of the drug in the body for a long time. Based on an observation that infants born to mothers who had received the drug during pregnancy were deeply pigmented at birth, it has been reported that clofazimine crosses the placenta.[5] However, no teratogenic effect has been reported with clofazimine.[6]

Decisions about the safety of breast-feeding during maternal ingestion of the drug require knowledge of the amount of the drug which might be present in the milk. There are only scanty reports on the excretion of dapsone, rifampicin and clofazimine in breast milk. Lactating mothers on 100–150 mg dapsone daily were found to have serum levels of 1·62 μl/ml with milk levels of 1·09 μg/ml resulting in milk : plasma (M/P) ratio of 0·7. The breast-fed infants had serum dapsone levels of 0·493 μg/ml.[17] Experimental studies in female mice, rats, guinea-pigs and rabbits have shown transmission of significant amounts of clofazimine to the offspring via mother's milk. In a TLC–NMR Spectroscopic analysis of milk from a Nepali woman, a considerable amount of clofazimine was found to be released from the body with the mother's milk.[8] Our study has included a larger number of lactating patients on varying lengths of chemotherapy and clofazimine has been quantitated in both plasma and single milk sample from all 8 patients.

Since the total quantity of milk during a period of 24 hr or part of it could not be collected the studies had to be limited to single samples. The drug ingestion by the suckling infants was calculated assuming that the volume of milk consumed by the infant aged 2–3 months is about 150 ml/kg/day.[11] The values for the suckling infants of 8 patients ranged from 0·120 mg/kg/day to 0·255 mg/kg/day with a mean of 0·199 ± 0·013 mg/kg/day. The highest level of drug ingestion by the infant of subject No. 1 would then represent 30% of last daily dose (mg/kg) by the subject who had taken 26·6 g of the drug cumulatively.

The accumulated total dose of clofazimine does not seem to proportionately influence the excretion of the drug in milk as shown by the figures of subject No. 5 versus subject No. 1 (Table 1). Even when the total intake by subject No. 5 was only 1·5 g, the amount of the drug excreted into milk was almost the same as in the case of subject No. 1 who had taken about 20 times more of the drug cumulatively. This indicates that the clofazimine mobilized from the fixed dose within the cells of the tissues into extra vascular space and subsequently into milk, may not be important in view of slow elimination phase for the drug. The extent of drug ingestion has, therefore, been expressed as a percentage of the last maternal daily dose in

Table 1. Milk and plasma levels of clofazimine in lactating female leprosy patients on administration of the drug orally for 1–18 months

Subject	Length of treatment (months)	Total intake (g)	Clofazimine levels 4–6 hr after last oral dose		M/P ratio	Drug ingested by infants (mg/kg/day)	% maternal doses‡
			Plasma (μg/ml)	Milk (μg/ml)			
1	18	26·6	1·0	1·7	1·7	0·255	30·0
2	6	17·6	0·9	1·5	1·7	0·225	13·5
3	4	6·5	0·8	1·3	1·6	0·195	23·4
4	4	6·0	1·0	1·4	1·4	0·210	25·2
5	1	1·5	0·8	0·8	1·0	0·120	14·4
6†	2	3·0	1·0	1·4	1·4	0·210	25·2
7	2	2·7	0·8	1·1	1·4	0·165	20·0
8†	3	4·3	0·9	1·4	1·6	0·210	25·2
Mean ± SE 5·0 ± 1·81 Median 3·25		8·53 ± 2·93	0·9 ± 0·03	1·33 ± 0·09	1·48 ± 0·08	0·199 ± 0·013	22·11 ± 1·90

* On clofazimine 100 mg daily.
† On clofazimine 100 mg on alternate days.
‡ Maternal doses as mg/kg.

mg/kg. The experimental data in animals have shown that the rate of drug passage between the mammary gland and plasma is more rapid for drugs that are highly lipid soluble and unionized.[18] The high lipid solubility and moderately low molecular weight of clofazimine might favour rapid passage between mammary gland and plasma of lactating mothers.

It may be concluded that in spite of clofazimine in breast milk in significant quantities and the infant ingestion of about 0·225 mg/kg/day discontinuation of clofazimine use need not be recommended to lactating mothers till further studies with toxicity data are available.

Acknowledgment

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CASE REPORT

Atypical post-kala-azar dermal leishmaniasis resembling histoid leprosy

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Summary An adult male with atypical lesions of post-kala-azar dermal leishmaniasis (PKDL) is described. He had extensive ulcerated noduloplaque lesions on his hands, feet and genitalia. He had been diagnosed and treated for leprosy in the past. He came from an area endemic for kala-azar and leprosy and had a previous history of kala-azar. There was an abundance of Leishman Donovan bodies in slit-skin smears and in histopathology sections. There was a good therapeutic response to sodium stibogluconate. An ulcerative variant of PKDL has been described but is extremely rare. Extensive lesions with ulceration have not been described before to the best of our knowledge. The epidemiological significance of the case is discussed.

Introduction

Post-kala-azar dermal leishmaniasis (PKDL) is a complication of visceral leishmaniasis occurring 1–5 years after recovery from the original infection.[1] The usual clinical presentation of hypopigmented macules and nodules are often a source of confusion with leprosy especially in areas where both the diseases are prevalent. Many people migrate to far-off places in pursuit of work, and one can be caught unawares, especially in areas where the disease is seen less often. This is particularly true if the presentation is atypical. Although a number of clinical variants of PKDL, including the ulcerative variety has been described, extensive ulceration has not yet been reported in literature. A case with extensive ulcerated noduloplaque lesions is presented here and the factors leading to initial misdiagnosis discussed.

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Case report

A 35-yr-old man from Bihar (an endemic area for kala-azar and leprosy) working as a mason in Chandigarh (a city in the north-western part of India in which kala-azar is nonendemic) had had ulcerated plaque lesions over his hands and feet for 3 years. The lesions started over the dorsa of feet as asymptomatic papules which slowly increased in size and ulcerated in the centre. Over a period of 3 years similar ulcerated plaques appeared over the dorsa of the hands, scrotum and penis. He gave a history of hypoaesthesia over the extremities. He had consulted numerous doctors and had been consistently diagnosed as a case of leprosy and took treatment irregularly. He was subsequently referred to us for management.

On examination he was well built, nonicteric with no pallor. There was no significant lymphadenopathy except for 2–3 firm, discrete mobile nodes in the axilla about 1 cm in diameter. There was no hepatosplenomegaly.

There were firm, nontender skin-coloured plaques of varying sizes over the interphalangeal joints of the fingers, toes, feet (Figure 1) scrotum and glans penis (Figure 2). Most of the plaques were ulcerated and had some crusting. Scarring was evident in some plaques. A hypopigmented patch about 6×8 cm in size was noted on the left shoulder. Its margins were irregular but well defined. On testing for sensation, an inconsistent response was noted as regards the degree and extent of loss over both the patch and the extremities. There was an interobserver variation as far as the peripheral nerves were concerned with some insisting that there was nerve thickening on the right side. All mucosae other than the glans were free of lesions.

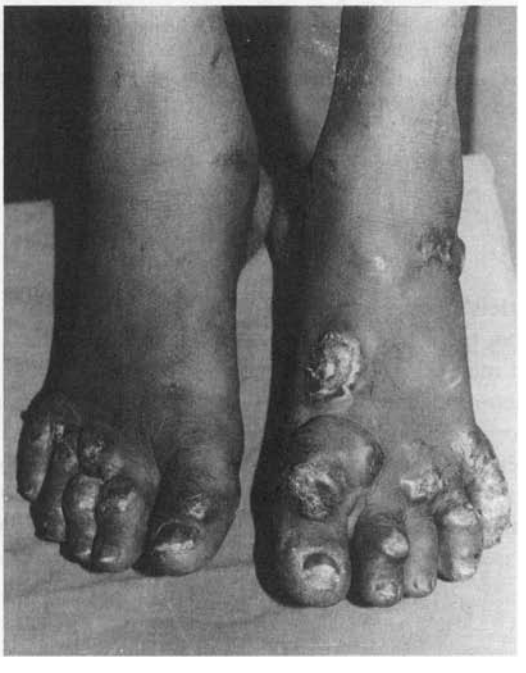

Figure 1. Ulcerated nodulo-plaque lesions on feet.

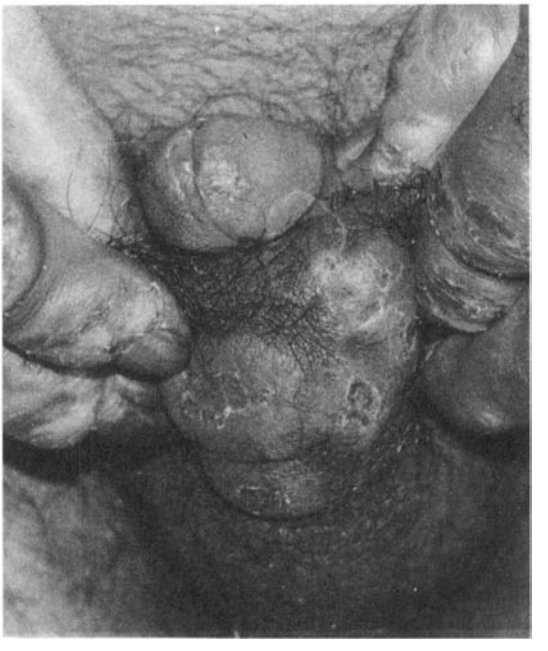

Figure 2. Ulcerated nodulo-plaque lesions on hands, scrotum and glans penis.

A provisional diagnosis of subpolar lepromatous leprosy with either lepromas or histoid lesions was made and the patient was further investigated.

Routine examination of blood and urine including haemogram, liver and renal function tests were normal except for minimal hypergammaglobulinaemia on electrophoresis. The chest X-Ray and ECG were also normal. Repeated slit-skin smear examination from routine and lesional sites were negative for acid-fast bacilli. On staining with Giemsa an abundance of Leishman Donovan (LD) bodies was seen in smears from the plaques. LD bodies though scanty were also noted in the smears from the hypopigmented patch. On histopathology, dense dermal infiltrate of plasma cells, lymphocytes and few neutrophils with a clear Grenz zone and numerous LD bodies were seen (Figure 3). The hypopigmented patch showed epitheloid granulomas in the dermis alongwith LD bodies. A biopsy from the right radial cutaneous nerve was of normal morphology and no organisms were seen even with special stains. Fine needle aspiration of the lymphnodes showed reactive lymphoid tissue and no organisms. Bone marrow trephine aspirate showed normocellular marrow with adequate representation of all cell lines. No LD bodies were seen.

Culture in NNN medium was positive from the plaques and hypopigmented patch. Neither the bone marrow aspirate nor the nerve specimen grew leishmania on culture. When questioned the patient admitted to having kala-azar about 10 years ago when he was probably treated with sodium stibogluconate for 18 days.

With a diagnosis of PKDL the patient was started on sodium stibogluconate injected 20 mg/kg/day with a remarkable improvement. At the end of 2 months of therapy the plaques had flattened considerably and all the ulcers had healed. He received stibogluconate for another 2 months at a dose of 750 mg every alternate day as he was unable to tolerate the pain

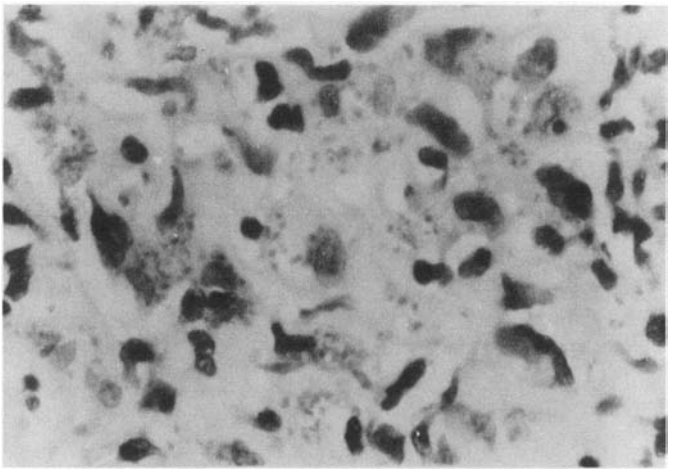

Figure 3. Numerous LD bodies in dermal infiltrate from nodule. (H&E, ×240).

and discomfort at the injection site. After 4 months of therapy all plaques had flattened and the treatment was stopped. He is regularly followed up.

Discussion

PKDL can have varied manifestations, the commoner presentations being the hypopigmented lesions, erythema or butterfly rashes and nodules.[1] The other less common variants are the verrucous, papillomatous, hypertrophic and xanthomatous lesions. Periungual induration, extensive erythema and fibroid types have also been described.[2]

Ever since the first description by Brahmachari in 1922,[3] PKDL has been frequently misdiagnosed as leprosy. The findings of a large hypopigmented patch and bilateral symmetrical ulcerated nodulo plaques over the hands, feet, scrotum and penis coupled with the history, albeit vague of hypoaesthesia over the lesions as well as in a glove and stocking distribution misled us. The hypopigmented lesions in PKDL generally do not attain a size larger than 1 cm but larger lesions, even occupying an entire limb, are well described.[1] Ulceration in lesions of PKDL is extremely rare. It has been described after treatment with potassium iodide, trauma[4] and mucosal stretching with granuloma.[6] Though trauma can partly explain ulceration over the hands and feet related to his job, it cannot explain ulceration over the scrotum and glans. An ulcerative variant of the nodular type has been described by Smith & Halder[2] but in all the three cases described by them the ulcerated nodules were limited in distribution. However, the extensive ulceration seen in our patient, to the best of our knowledge, has not been described before.

Neuritis has been described in cutaneous lesions of PKDL[7] but peripheral neuritis is not known. In our opinion repeated questioning about lesional and peripheral sensory loss resulted in autosuggestion.

Refractoriness of PKDL to therapy and the fact that parasitic load may determine the response to therapy is well known.[8] Though to date the response in the patient has been

excellent, it remains to be seen how the disease behaves on follow up. The response to therapy of this variant and the long-term prognosis is not known due to paucity of such cases.

This report exemplifies the pitfalls of diagnosis made only on basis of history and clinical examination. PKDL should always be considered in differential diagnosis of any patient from an endemic area for kala-azar, however atypical the lesions might be.

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Letters to the Editor

SENSORY TESTING OF THE HANDS IN LEPROSY

Editor,

In a recent paper Kets *et al*. examined methods for testing sensation in the hands (and feet) of healthy Nepalese volunteers.[1] They conclude that the use of a 200-mg monofilament is a sensitive and specific test for loss of sensation (LOS) in the hand, and therefore a reliable basis on which to diagnose and treat median and/or ulnar neuritis in leprosy patients. We would like to put forward an alternative view on the best way to test sensation in the hand in a routine control programme.

A previous study at the All Africa Leprosy and Rehabilitation Training Centre (ALERT), in Addis Ababa, compared 1-g and 10-g filaments for testing sensation in the hands, in both leprosy patients and healthy controls.[2] It was concluded that the 1-g filament might 'detect insidiously developing neuritis earlier than by using a ball-point pen or a 10-g filament.' In that study, 15 out of 47 patients (31·9%) would have been treated for neuritis if the 1-g filament had been used as the criterion for treatment; they were not treated, however, as they did not meet the criterion then, and still, in force in the ALERT programme, namely insensitivity to the 10-g filament. The authors noted that interobserver variation was present with both filaments but, not surprisingly, was greater with the 1-g filament. It is interesting that, at least until very recently, the team in Nepal already quoted has also used the 10-g filament as the criterion for diagnosing neuritis in the hand in their routine programme.[3,4]

Because a prospective trial of treatment based on two or more different criteria would be a major undertaking, we decided to review the 15 patients mentioned above to see if they had 'insidiously developing neuritis' or a mild and perhaps insignificant neuritis, not leading to loss of protective sensation. The first assessment of patients in the original study was done in 1990, with follow-up examinations later in 1990, in 1991 and a few in 1992.

Method

All 15 patients were looked for through a variety of tracing methods. Ten (67%) were found and examined in 1996 by the leprosy control supervisor for the area. The hands were tested at 10 points (4 in the ulnar area and 6 in the median area) using a range of monofilaments (50 mg, 200 mg, 1 g, 50 g and 300 g); it was noted whether the hands were dry or sweaty and whether there were wounds, cracks or bone loss; any treatment with steroids after the first study period, was noted.

In addition, the clinic cards of the other 5 patients were reviewed and the most recent findings noted. Two of these had been seen recently, but three were lost at the end of the previous study in 1991–2 and are therefore not included in the analysis. The three excluded patients all had normal sensation to 10 g when they were last seen.

Results

Eleven of the 12 cases under review completed multidrug therapy (MDT) and have not been treated with

steroids for neuritis affecting the hands since the first study took place (one patient had steroids in 1994 for LOS in the feet). All of them had had additional LOS in the hands as detected by the 1-g filament during the first study, but no additional LOS to 10 g.

All these hands are now in good condition. Six of the 12 patients have slight damage which was present before the start of treatment and before the previous study was carried out; they have no additional damage. Two of the 12 patients have slightly improved sensation compared with their status at diagnosis. Three patients were normal at the start and remain so now—in these cases 'normal' means sensitive to 10 g at all 10 points and no wounds, cracks or absorption. The twelfth case is described in more detail:

Case report: C.H. is a female patient with multibacillary leprosy, who was born in 1940. She started treatment in 1988. She had normal sensation in the hands at the start of treatment, but already had significant LOS in both feet. When she was enrolled in the filament study in April 1990, she had normal sensation to 10 g, but 1 point of LOS was noted to 1 g in the left ulnar area. When seen a month later, she still had normal sensation to 10 g, but marked LOS to 1 g in both the ulnar and median areas of the left hand (of two observers, one found LOS at 5 points and the other at all 10 points).

In that study, steriod treatment was only given if there was more than one additional point of LOS to the 10-g filament, so the patient did not receive steroids at this point. In December 1990, 7 months after LOS was noted with the 1-g filament, she was started on steroids for further LOS noted with the 10-g filament. In October 1991, she had a further course of steroids. In 1996, she had lost the tip of the left little finger and her hands are dry; there were no wounds or cracks; she could not feel the 1-g filament anywhere on either hand, but felt the 300-g filament everywhere; with both the 10-g and 50-g filaments she can feel at 4 points in the right median area only.

Discussion

Nylon monofilaments are among the most reliable and easily applied tests of sensation available for a field programme.[5,6] However, the best method of utilizing them in a routine situation remains under debate. The use of several different monofilaments to determine a threshold of sensitivity, as proposed and evaluated by van Brakel,[6] seems overly complex for routine use in a field programme.

This review has shown that 11 out of 12 patients (92%) have had a good long-term result, even though their suspected early neuritis, as detected by a 1-g filament, was not treated with steroids. One patient has not done well in terms of preserving sensation, although her hands have been well looked after, so that she has minimal disability. It is, of course, unknown how she might have responded to steroids started 7 months earlier.

It seems likely that, in view of the increased interobserver variation with the more sensitive 1-g filament, there is a significant loss of specificity with this test and that the one patient with subsequent damage may have been the only one with a significant early neuritis. In other words, false predictions of clinical neuritis with the 1-g filament may be very common.

In a field programme where much of the work of disability prevention is carried out by busy junior staff, in difficult surroundings, a simple and reliable test for neuritis is required. Because the steroid regimen is complex and not without side-effects, a test with a high degree of specificity is required.

Our conclusion from this simple review is that the attempt to detect and treat very early or mild neuritis, whilst reasonable in an ideal world, may be an unnecessary and counter-productive burden in leprosy control programmes, which are beginning to integrate with the general health services. In such programmes a 'basic minimum' of activities for general staff has still to be worked out.

We would suggest that the use of a filament near the sensory threshold for normal subjects, as suggested by Kets *et al.*,[1] will lead to a large number of patients (at least double the present load) being treated for neuritis, many of whom may not really need it. A less sensitive but highly specific test, using the 10-g filament, clearly indicates significant neuritis that requires aggressive treatment.

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UNRECOGNIZED OCULAR MORBIDITY IN LEPROSY

Editor,

Ocular complications in leprosy patients are well known. It is also equally well known that most of these are preventable. Furthermore they have the same risk of becoming blind due to nonleprosy associated factors as any other person. To be effective in reducing blindness and ocular morbidity in leprosy patients, preventive measures are necessary. In order to organize such preventive programmes it is essential to determine the degree to which patients are aware that their eyes can be affected in leprosy and whether they take steps to have their eyes examined. An ideal way to get this information is through a population-based longitudinal study of patients within a defined control area programme. There are several constraints in doing this which led us to study the eye complications encountered in patients who had not presented themselves for an ocular examination at an eye clinic, but who attended the outpatient clinics of a tertiary leprosy hospital.

Patients and methods

All consecutive leprosy patients who presented at the supervised multidrug therapy (MDT) clinics in the hospital in the months of July and August, 1995 but who had no intention of attending the eye clinic of the same facility, the Schieffelin Leprosy Research and Training Centre, Karigiri, a tertiary leprosy hospital situated in South India, were included in the study.

After patients were seen in the MDT clinics where there are no eye-care activities they were specifically asked a set of questions from a pre-formed questionnaire. The questionnaire included questions about the last visit to the hospital and to the eye department, their knowledge about eyes in leprosy, the intention of visiting the eye clinic and their present eye problems.

The general demographic characteristics of these patients and their leprosy data were collected from their records. Visual acuity was tested with the Snellens E-chart and if necessary with finger counting. Both eyes of all the patients were examined by direct oblique illumination and by slit lamp biomicroscopy.

Table 1. Demographic information of the study group

Age (years)	Never attended				Attended			
	M	F	Total	%	M	F	Total	%
>20	6	5	11	(21·1)	14	5	19	(10·1)
20–29	12	3	15	(28·9)	27	12	39	(20·6)
30–39	8	5	13	(25·0)	30	12	42	(22·2)
>40	7	6	13	(25·0)	57	32	89	(47·1)
Total	33	19	52		128	61	189	
	63·5	36·5	100·0		67·7	32·3	100·0	

The lids, eyebrows, conjunctiva, sclera and the lacrimal system were examined carefully with focal illumination. The cornea was checked for opacities and pannus, and the iris for signs of iridocyclitis. Pupil size, shape and reaction to light were noted. The corneal sensitivity was tested with a cotton wisp. All the findings in both eyes were recorded on a preformed-format.

Results

Of the 241 patients who attended the MDT clinic during the study period and were screened for ophthalmic complications, 52 (21·6%) had never visited the eye department formed the study group. The age and sex distribution of this group together with the rest of the patients who were seen earlier in the eye clinic are given in Table 1.

Among the leprosy patients who had never attended the eye clinic, 1 was of the indeterminate (IND) type, 1 a polar tuberculoid (TT) patient, 27 were borderline tuberculoid (BT), 2 were borderline borderline (BB), 18 were borderline lepromatous (BL) and 3 were polar lepromatous (LL). Out of the 52 patients 23 (44%) belonged to the multibacillary (MB) group of patients.

Only 4 (7·7%) patients knew about ocular leprosy; 3 knew that leprosy can cause blindness. Among patients ($n = 189$) whose eyes had been examined previously, 63 (33%) had some knowledge of ocular leprosy. Six patients from the study group had eye complications such as burning sensation, watering, pain and defective vision. The visual acuity of patients who had never been to the eye clinic and those who had been is given in Table 2. Eight patients (15·4%) had a vision of less than 6/18 in one or more eyes, 1 patient had a blind eye (less than 3/60) and an eye with poor vision (6/60). The eye complications present in the patients who had never visited an eye clinic is given in Table 3. Six (11·5%) of the 52 patients had at least one eye complication.

Table 2. Visual acuities of the study patients

Visual acuity	Never visited the eye clinic		Had visited the eye clinic	
	Unilateral	Bilateral	Unilateral	Bilateral
<3/60	1	0	8	2
3/60–5/60	0	0	6	2
6/60–6/18	2	5	14	30

Table 3. Description of patients with eye complications

Patient No.	Age	Sex	Type	Duration of MDT (months)	Eye complications
1	35	F	BT	11	Lagophthalmos (LE), Corneal opacity (LE) Pterygium (BE), Trichiasis (BE)
2	32	M	BL	12	Pterygium (LE)
3	62	F	BL	19	Cataract (secondary) (BE)
4	64	M	LL	18	Cataract (BE)
5	69	M	BL	15	Iridocyclitis (RE) Aphakia (BE)
6	36	M	BT	11	Pterygium (LE)
7	35	F	BL	8	Iridocyclitis (LE)
8	18	F	BT	5	Bitot spots (BE)
9	25	M	BL	7	Bitot spots (BE)

Among the patients who had attended the eye clinic (out of a total of 378 eyes) 12 eyes had a visual acuity of less than 3/60, 10 had visual acuity between 3/60 and 5/60, 74 had a visual acuity of more than 5/60 but less than 6/9 and the remaining 282 eyes had a visual acuity of better than 6/18. Lagophthalmos was present in 22 eyes, trichiasis in one eye, ectropion in one eye, pterygium in 26 eyes, corneal opacities in 24 eyes, chronic iridocyclitis in 10 eyes, complicated cataract in 4 eyes, age-related cataract in 48 eyes and aphakia in 5 eyes.

Discussion

Deformities and disabilities of hands and feet have always been accorded a place of high prominence in disability prevention programmes while ocular disabilities have not received similar attention.

Our finding that 21·6% of patients who attended the MDT review clinics during the time of the study have not had their eyes checked at any time is revealing. It highlights the need for patients to recognize the importance of eye care and gives priority to inculcating these patients with the knowledge required for it.

Six out of the 52 patients (11·5%), in spite of having eye problems, did not feel the need to attend the eye clinic. Furthermore, our finding that a relatively high proportion of patients (15%) had reduced vision (less than 6/18) emphasizes the need for patients to be aware of the need for seeking professional help immediately. Two of these patients had bilateral cataracts and although these may not need immediate attention they do contribute to preventable ocular morbidity among leprosy patients.

Lagophthalmos, which has been categorized as a potentially sight-threatening lesion, was present in 2 patients. Previous literature show the advantage of early recognition of lagophthalmos and its treatment compared to the less effective treatment available for advanced cases.[1] It is also well recognized that exposure problems are common and can occur at any time in lagophthalmos patients. It is imperative that such patients have adequate knowledge to seek help early. Iridocyclitis, which constitutes one of the pathways to blindness in leprosy was found in one eye of a patient.

Pterygium is very common in tropical countries like India. In our study 3 patients had pterygium. Pterygium which moves into the pupillary are will also contribute to the ocular morbidity even if surgical treatments is provided. Thus, it should be recognized earlier before it causes visual disability in spite of treatment.

We advocate that all medical and surgical departments of large leprosy centres should arrange for routine eye check-ups, especially if specialized eye departments and facilities are available. All leprosy personnel, in particular medical staff, must be trained to recognize eye complications and to educate leprosy patients on potential eye complications, their prevention and early identification.

Acknowledgements

We thank Ms Padma for the secretarial help and Mr P. Yowan and Mr Demitrius Charles for their help in the study.

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Teaching Materials and Services

Meeting the information needs of health workers in developing countries: INASP-Health, UK

Dr Neil Pakenham-Walsh, Programme Manager, INASP-Health, International Network for the Availability of Scientific Publications, PO Box 2564, London W5 1ZD, contributed the following to the *British Medical Journal*, **314**, 90:

Health workers in the developing world are starved of the information that is the lifeblood of effective health care.[1,2] As a direct result, their patients suffer and die. In the words of the late James Grant, former executive director of Unicef, 'The most urgent task before us is to get medical and health knowledge to those most in need of that knowledge. Of the approximately 50 million people who were dying each year in the late 1980s, fully two thirds could have been saved through the application of that knowledge.'[2]

Providing access to reliable health information for health workers in developing countries is potentially the single most cost effective and achievable strategy for sustainable improvement in health care. Cost effective because the amounts of money required are negligible compared with those invested in health services. Achievable because providers of health information have the will and commitment to make it happen, and because information technology presents exciting new opportunities to complement conventional methods of dissemination. And sustainable because information access is the sine qua non of the professional development of all health workers—the most vital asset of any healthcare system.

In 1994 and 1995 the *BMJ* hosted international meetings to look for ways to improve the dissemination of health information to, from, and within the developing world.[1] The meetings showed that the overall impact of providing health information would be greatly enhanced by increased coordination, analysis, and funding. A new programme was needed to serve as a point of reference for those who supply and receive information, to build a global picture of their activities and needs, and to argue their case with others. This programme is now being introduced within an existing non-profit organization, the International Network for the Availability of Scientific Publications (INASP). Founded in 1991 by the International Council of Scientific Unions, INASP is a cooperative network of providers and recipients of science information, promoting the exchange of quality information (both printed and electronic) between and within the developed and developing world.

The new programme, INASP-Health, serves three main functions. Firstly, it provides a referral and advisory service for information providers and potential recipients. For example, institutions seeking health information can approach INASP directly and be put in touch with the organizations most likely to help. INASP-Health acts as a catalyst for new collaborations and initiatives and will soon be launching a dedicated email discussion list to facilitate cooperation and debate.

Secondly, INASP-Health aims to build a global picture of health information priorities in the developing world and the most appropriate ways of addressing them. It is developing a specialized database of needs assessments, evaluations of cost effectiveness, and other material related to the provision of health information. These data will be made freely available to help with the planning and setting up of new programmes, to provide support for funding applications, and to help develop future strategies.

The third function of INASP-Health is advocacy, both at a specific and a general level. For example, it works with organizations such as the Association for Health Information and Libraries in Africa (AHILA) to promote their needs to a wider audience, negotiating with publishers and others on their behalf. On a wider scale, INASP-Health will work increasingly with international organizations like the World Health Organization and World Medical Association and with governments and funding agencies to promote the development of cost effective strategies and to strengthen political and financial commitment.

INASP-Health aims to ensure that the developing world does not get left behind by the information revolution. Rather, it wants to harness the enormous potential to provide the developing world with the information that for too long it has lacked.

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WHO. Treatment of Tuberculosis: Guidelines for National Programmes, Second Edition 1997

This first revision has been prepared by WHO to give practical guidance to national TB programmes in the effective management of TB control. The Preface emphasizes that the basic principles of TB control, as set out in the first edition in 1993, remain the same. The revision updates the guidelines in the light of experience gained during the past 4 years and is intended for use in any country where there are high TB incidence populations. The main objectives are listed as follows: 1, to describe briefly the global TB burden and the framework for effective TB control; 2, to describe standardized treatment regimens according to TB case definitions and categories; 3, to describe the monitoring of individual patients and how to ensure their adherence to treatment; 4, to describe the special considerations in treating HIV-infected TB patients; and 5, to provide information on anti-TB drug supply in the context of national pharmaceutical policies and essential drug programmes. The guidelines are primarily for TB programme managers, policy makers in Ministries of Health, non-government organizations and donor agencies, but health workers and teachers and students in medical schools and nursing schools will also find them helpful. The main chapter headings are: Introduction, Strategy and framework for effective TB control, Case definitions, Standardized treatment regimens, Monitoring the patient, Adherence to treatment, HIV infection and TB, and Antituberculosis drug supply and use. Five annexes cover: Standardized management plan for TB patients, Essential anti-TB drugs, Fixed-dose combinations of antiTB drugs, Price list of essential antiTB drugs, and Cost of recommended treatment regimens.

Both the amount of detailed information and the importance of this publication from WHO defy brief analysis or description and it should be studied in the original by those engaged in the formidable task of tuberculosis control, notably in developing countries. This document, together with that on the management of drug-resistant TB (reviewed below) will leave few readers in doubt about the complexity of controlling TB worldwide, with the drugs and other resources currently available. Many of those working in leprosy, with its relatively clear-cut regimens of drugs, low toxicity and the absence (as yet) of an epidemiological association between leprosy and HIV/AIDS, will be struck by the comparison between the approach to the two diseases. Whilst an action programme for the elimination of leprosy is already under way, it would appear that TB faces a worsening situation, complicated not only by the effect of HIV/AIDS but also by increasing levels of drug resistance.

Further information: Global Tuberculosis Programme, WHO, 1211 Geneva 27, Switzerland. WHO/TB/97.220

WHO. Guidelines on the management of drug-resistant tuberculosis.

This outstandingly important document from the *Global Tuberculosis Programme* of WHO has been written by Sir John Crofton, Professor Emeritus of Respiratory Diseases and Tuberculosis, University of Edinburgh, Scotland, Pierre Chaulet and Dermot Maher, Global Tuberculosis Programme, Geneva, with contributions from Jacques Grosset, William Harris, Norman Horne, Michael Iseman and Bryan Watt. The Foreword reads as follows:

1. About one third of the world's population is infected by *Mycobacterium tuberculosis*. Worldwide in 1995 there were estimated about nine million new cases of tuberculosis with three million deaths. *M. Tuberculosis* kills more people than any other single infectious agent. Deaths from TB comprise 25% of all avoidable deaths in developing countries. 95% of TB cases and 98% of TB deaths are in developing countries, 75% of these cases are in the economically productive age group (15–50).
2. As a consequence, the world is facing a much more serious situation in the twenty-first century than that of the mid-1950s. Due to demographic factors, socio-economic trends, neglected TB control in many countries, and in addition, the HIV epidemic, there are many more smear positive pulmonary TB cases, often undiagnosed and/or untreated. When TB cases are treated, poor drug prescription and poor case management are creating more TB patients excreting resistant tubercle bacilli.
3. In 1991, the World Health Assembly adopted Resolution WHO 44.8, recognizing '*effective case management as the central intervention for tuberculosis control*', and recommending the strengthening of national tuberculosis programmes by introducing short course chemotherapy and improving the treatment management system. Since 1992, the WHO Global Tuberculosis Programme has developed a new strategy, to meet the needs of global tuberculosis control.

TB control requires effective, inexpensive, simple and largely standardized technology, and the managerial skills to implement them as a large scale intervention in each country.

4. The success of the WHO case management intervention or 'DOT,S strategy' depends on the implementation of a policy package with 5 components:

- government commitment;
- case detection by microscopy through predominantly passive case finding in existing primary health care (PHC) services;
- **D**irectly **O**bserved **T**reatment, **S**hort course chemotherapy: standardize short course chemotherapy regimens administered under close control, given free of charge, for new and retreatment cases smear positive;
- regular drug supply of all essential anti-tuberculosis drugs;
- establishment and maintenance of monitoring mechanisms of case detection and treatment outcomes, based on recording individual patient information in district registers and a system of quarterly reporting.

5. In all countries that have adopted the 'DOTS strategy', under programme conditions the cure rates (and the success rates) of TB smear positive cases are already over 80%. When this strategy is implemented over a long period for the standardized treatment of TB smear positive cases, there will be a huge reduction in sources of infection and in transmission.

For the future, the top priority remains to administer standardized short course chemotherapy regimens to all smear positive cases (new and retreatment cases). This priority requires the maximum of effort, time, drugs and money in a national tuberculosis programme, without diverting funds and resources to smear negative and/or chronic cases.

6. The issue of the treatment of those pulmonary TB patients who remain sputum smear positive following fully supervised WHO retreatment regimen should be considered. Although these cases represent a small minority of TB patients, they constitute a permanent problem for programme managers.

Due to the lack of financial resources and/or information on the second line drugs, many countries cannot afford to provide the range of these expensive drugs which might give some hope of cure to patients. However, more economically prosperous countries might wish to do so, especially if they have inherited a significant number of patients with multi drug resistant (MDR) TB from a period when treatment was unorganized and chaotic.

The WHO Tuberculosis Control Workshop held in Geneva, October 1995, discussed this issue and made the following recommendations:

a. a country prepared to go to this expense should only provide these drugs for a **specialized unit** (or units in large countries), in close connection with a **laboratory** able to carry out cultures and reliable susceptibility tests of *M. tuberculosis* to the drugs.
b. **Guidelines prepared by WHO** for treating such patients should only be made available on request to properly established units.

The '*Guidelines for the management of drug resistant tuberculosis*' is prepared to meet this request/need.

The main sections are entitled—Introduction, Basic principles for management of multi-drug resistant (MDR) tuberculosis, Assessing the individual case of apparent MDR tuberculosis, Available drugs for MDR tuberculosis, Choosing a chemotherapy regimen for a patient with apparent MDR tuberculosis and Place of surgery. An Annex (page 31) gives detailed information on second-line anti-tubercolisis drugs (aminoglycosides, thioamides, fluroquinolones, cycloserine (and terizidone) and para-aminosalicylic acid (PAS). Under 'Magnitude of the problem', section 1.3.2 on page 7 reads:

> During the early stages of implementation of a national tuberculosis control programme, *old cases* (previously treated by usually inappropriate and non-standardized chemotherapy regimens) may represent up to half of notified cases. In this situation, acquired resistance emerges as a priority problem, as the rate of acquired resistance is 50% to 80% in previously treated cases. The priority solution is to standardize at country level and to adopt the WHO recommended standard regimens of chemotherapy for new cases and for retreatment cases, in order to stop the creation of more cases with bacterial resistance. Even if the proportion of MDR tuberculosis among drug resistant tuberculosis is high, **the top priority is not the management, but the prevention, of MDR tuberculosis**.

Under section 1.3.4 on page 8, attention is drawn to the lower rates of primary resistance in new patients, usually 5% or less in good national programmes, and 15% or more in new programmes implemented after a period of unorganized and chaotic chemotherapy.

Table 3 (page 23) lists no fewer than 15 drugs (including PAS, now hardly ever used for the treatment of drug-*sensitive* cases), available for the treatment of MDR tuberculosis and Table 4 summarises the costs of defined daily doses (DDD) for one month, in US dollars. Pages 37–40 carry 42 references covering all aspects of this vitally important (and disconcerting) subject. It bears repetation that these Guidelines have been prepared by WHO to meet the requests/needs of *properly established* (specialized) units in close connection with a laboratory able to carry out cultures and reliable susceptibility tests of *M. tuberculosis* to the drugs. Its essential messages, however, deserve wide distribution and serious consideration, for it is increasingly clear that failure to address this problem without delay may jeopardize the entire future of chemotherapy for tuberculosis.

Further information: Global Tuberculosis Programme, WHO, 1211 Geneva 27, Switzerland WHO/TB/96.210.

Leprosy: basic information and management

Leprosy: basic information and management was first published in 1987 with support from the *Ciba-Geigy Leprosy Fund* (title now changed to the above), a fourth edition has now been produced and is

available free of charge from Novartis Foundation for Sustainable Development, PO Box K-1313.4.40, CH-4002, Basel, Switzerland. The 40-page booklet has been up-dated and revised to include information on the progress which has been made in recent years towards the WHO goal of elimination of leprosy as a public health problem by the year 2000.

Managing drug supply

Improved policy decisions and management of essential drugs can make a positive impact of the health of a nation. *Managing Drug Supply* provides health planners and managers with the insights and tools to manage their pharmaceutical expenditures more rationally. Since the first edition was published in 1981, this 600-page handbook has been translated into French and Spanish, and has become a standard in the field of essential drugs management in developing countries. The first edition has been used by organizations such as UNICEF; as a reference manual by ministries of health, nongovernmental organizations and private consultants; and in training programmes in the USA, Europe and developing countries.

The new edition has been extensively revised and expanded in collaboration with the Action Programme on Essential Drugs (and other WHO programmes). It provides up-to-date descriptions of the process of drug selection, procurement, distribution and use. Policy and the economic environment in which pharmaceuticals are used are also critically examined using current management experience and procedures from around the world.

Illustrated with over 300 figures, tables, 'how-to' boxes and sample forms, *Managing Drug Supply* can be used by pharmacists and other health professionals, policy makers and trainers. Glossaries, address lists, lists of further reading and references, and a comprehensive index offer the reader tools for research and follow-up.

Managing Drug Supply. The Selection, Procurement, Distribution, and Use of Pharmaceuticals, (2nd ed.), J. D. Quick, J. R. Rankin, R. O. Laing, R. W. O'Connor, H. V. Hogerzeil, M. N. G. Dukes, A. Garnett (eds.), 1996, 832 pp.

Available from: Kumarian Press Inc., 14 Oakwood Avenue, West Hartford, CT 06119-2127, USA. Price: US$84·95 (developed countries) and US$22·95 (developing countries).

Tuberculosis and HIV, a clinical manual by A. D. Harries and D. Mahar

This manual provides a pocket-sized guide to the clinical management of tuberculosis, particularly in patients suffering from HIV co-infection. It promotes the best possible diagnosis and treatment in low-income countries where prevalence is high, case loads are heavy and laboratory support may be limited. With these needs in mind, the manual combines the latest scientific knowledge with authoritative advice based on extensive field experience in several of the hardest hit countries.

Though primarily addressed to clinicians working at district hospitals in sub-Saharan Africa, the publication is also suitable for use in areas of Asia and South America where the problem of tuberculosis and HIV co-infection presents a growing clinical challenge.

Available in English, (French and Portuguese in preparation), from: World Health Organization, Distribution and Sales, 1211 Geneva 27, Switzerland. Price: Sw.fr.12/US$10·80, and in developing countries Sw.fr.8·40.

WHO/TB/96.200.

Tuberculosis and Children, AHRTAG, 1996

The Appropriate Health Resources and Technology Action Group (AHRTAG) has published a special supplement to its quarterly newsletter, *Child Health Dialogue*, entitled *Tuberculosis and Children.* It

provides health workers in developing countries with practicals up-to-date information on how to tackle this preventable disease. The supplement outlines the principles: of TB control and provides clear guidelines on the detection, diagnosis, treatment and prevention of TB. *Tuberculosis and Children* complements another AHRTAG publication on tackling TB and HIV—*Aids Action* No. 31.

Available from: AHRTAG, 29–35 Farringdon Road, London EC1M 3JB, UK. Price: For individuals. in Europe, North America, Australasia and Japan £2·50 each for £4·50 for both publications. Available free of charge to readers in developing countries.

Molecular immunology of infectious diseases, 8-week course, autumn 1997, London, UK

This 8-week course on 'Principles and practice of molecular immunology of infectious diseases' has a free-standing syllabus of lectures, tutorials and laboratory sessions designed to illustrate current concepts and methodologies in the immunology of infectious diseases.

Participants

Scientific research workers at all levels including technicians and Principal Investigators, PhD students and clinicians from within the United Kingdom and overseas who wish to obtain a concise and clearer understanding of the basic principles and practical techniques in host resistance against infection.

Course aims

To provide a thorough grounding in the mammalian immune system and its response to infection of the host. This will be achieved by a combination of lectures, tutorials, practical classes and free study periods involving members of staff at the School actively involved in research in these fields plus selected experts from other institutions. The course will cover aspects of innate versus acquired resistance, current concepts in leucocyte activation and function in response to microbial stimuli, as well as immune-mediated pathology and new advances in vaccination. General lectures presented in weeks 1–4 will use examples of clinically important pathogens to illustrate key concepts in leucocyte biology, while week 5 will provide an additional focus on the specific immune responses relevant to particular microbial groups including viruses, bacteria, parasites and fungi. Students are encouraged to attend the British Society of Immunology Annual Congress in week 7. Students will also have some opportunity to attend ongoing research seminars presented within the School as part of our existing research programmes on tropical medicine and infectious disease immunology.

Speakers
London School of Hygiene and Tropical Medicine:

FACULTY

LSHTM:
Dr G. J. Bancroft, Dr H. M. Dockrell, Dr P. Fine, Dr P. M. Kaye, Dr J. Raynes, Prof M. W. Steward, Dr A. Thomas.

INVITED SPEAKERS:
Dr A. Akbar, Dr D. Lowrie, Dr P. Life, Dr D. Male, Prof T. McDonald, Dr H. Stauss and Prof M. Turner

COURSE TIMETABLE

FOUNDATION:

22 October Welcome and Orientation

0930 Welcome and Introduction to the Department
1000 Round table introduction to the course
1100 Safety orientation
1400 Library tour

23 October Foundation I:

0930–1030 Innate resistance to infection
1100–1200 Antibodies and resistance

24 October Foundation II:

0930–1030 T cell and cytokine responses to microorganisms
1100–1200 Evasion of immune responses by pathogens

CORE IMMUNOLOGY COURSE:

LECTURE/TUTORIAL TOPICS	**LABORATORY TOPICS**
WEEK 1:	
Innate versus adaptive immune responses	Antibody purification and function
Microbial immunogens and antigens	
Antibody structure and function	
Generation of diversity	
Phagocytes	
WEEK 2:	
Complement	Phagocyte isolation and function
Lymphoid systems	Lymphoid cell separation
MHC genes and function	Flow cytometry
Antigen processing & presentation	
T cell receptor structure and function	
WEEK 3:	
T cell activation/costimulation	Lymphocyte proliferation
T cell derived cytokines	Cytokine protein assays (ELISA)
Phagocyte derived cytokines	
Cytokine receptors/inhibitors	
Regulation of immunity	
Adhesion molecules in infection	
WEEK 4:	
Inflammation	Immuno-assays
Hypersensitivity	
Allergic responses	
Apoptosis in the immune system	
Tolerance/autoimmunity	
Cell mediated cytotoxicity	

WEEK 5:

Immunity to viruses	ELISA based methods
Immunity to bacteria	Parasite detection methods
Immunity to parasites	
Immunity to fungi	

WEEK 6:

Vaccines	Cytokine mRNA assays (PCR)
Mucosal immunity	
Genetics of resistance to infection	
Novel vaccination strategies against infection	
T cell/antibody epitope mapping	
Anti-disease vaccination	
Recombinant DNA vaccines	

WEEK 7:

Attend British Society of Immunology Annual Meeting	Immunocytochemistry
Tumour immunology	
Neuroimmunology	

WEEK 8:
Revision tutorial sessions
Student presentations
Course test.

FEES

The fee for the course is £3,100. Fees are for tuition only. In addition participants will need funds for travel, accommodation and meals in London and for optional attendance at BSI conference.

A certificate of attendance will be provided following completion of the course.

APPLICATIONS

Applicants should complete an application form and return it as soon as possible to the Registry at the address below:

Registry
London School of Hygiene & Tropical Medicine
Keppel Street
London
WC1E 7HT

Telephone: **+44(0) 171 927 2409**
Fax: **+44 (0) 171 323 0638**
E-mail: **registry@lshtm.ac.uk**

ALERT Training Calendar 1998

January 12–February 20
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).

March 9–March 20
Introduction to leprosy for physicians
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 by physicians responsible for diagnosis, treatment and care of leprosy patients in either a hospital or a control programme setting.

March 23–April 24
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 resources, training, health promotion and POD. A brief review of the essentials of TB is included, but leprosy expertise is a prerequisite. Participants lacking the latter should also take the preceding 'Introduction to Leprosy' course.

May 11–May 27
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.

September 21–October 30
Essentials of leprosy and tuberculosis for physicians
Target group: physicians with limited experience in either leprosy or TB. Emphasis on clinical aspects of leprosy and TB, individual patient care and its application in the context of a combined programme, with an introduction to health promotion and managerial issues, paying special attention to POD and supervision.

November 2–November 13
Introduction to 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 16–December 11
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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. A brief review of the essentials of TB is included, but leprosy expertise is a prerequisite. Participants lacking the latter should also take the preceding 'Introduction to Leprosy' course.

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News and Notes

Progress towards leprosy elimination

The following is extracted from *Weekly Epidemiological Record*, 1997, **72**, 165–172:

Following the implementation of the global plan of action for eliminating leprosy as a public health problem, as elaborated in 1992, there is continuing evidence from endemic countries that multidrug therapy (MDT) is highly effective in curing patients and reducing disease prevalence. The process of implementing MDT has by itself contributed to a better understanding of the disease and its distribution. The fact that by 1996 almost all known patients were being treated with MDT is a tremendous achievement. The challenge now is to bring this effective technology to cases who have little or no access to MDT, and to implement it even where health facilities are minimal.

Information for monitoring the elimination of leprosy in endemic countries is now well standardized and is generated by national information systems. However, a major difficulty, particularly in the context of elimination, is to assess the proportion of the population covered by the programme. WHO, in collaboration with national programmes of the top endemic countries, is promoting new initiatives such as Leprosy Elimination Monitoring (LEM) and the use of the Geographical Information System with the objective of identifying difficult operational and/or epidemiological situations calling for special intensified efforts.

Although the performance of national elimination programmes is assessed by reductions in prevalence, MDT coverage and number of patients cured, increasing attention is now being given to the geographical coverage and quality of MDT services, timely detection of cases, and prevention of impairments or disabilities attributable to leprosy and its complications.

The prevalence of leprosy in the world continued to show a declining trend in 1997, and most of the countries endemic for leprosy have reported considerable progress against the disease. The number of countries showing prevalence rates above 1 per 10 000 population has been reduced from 122 in 1985 to 55 at the beginning of 1997. However, in some of the major endemic countries, epidemiological trends over the past few years indicate a slowing down of further reduction in prevalence. The present report records the progress that has been made towards the goal of elimination of leprosy as a public health problem, and updates figures published in June 1996.

Global and regional leprosy situation

COUNTRIES ENDEMIC FOR LEPROSY

In 1985, before large-scale implementation of MDT, 122 countries were showing prevalence rates above 1 case per 10 000 population. After more than 10 years of intensive activities, most of these countries have reviewed their leprosy registers and have treated patients in need of it with MDT. As a result, 67 countries have reduced the leprosy prevalence to below 1 per 10 000 population. Although it is too early to judge whether or not this situation is sustainable, one can be reasonably confident that leprosy as a public health problem has been eliminated in most of these countries. In some others, further investigation might be needed to make sure that remaining pockets of leprosy have not been missed and that detection rates continue to decline.

PREVALENCE

At the beginning of 1997, it is estimated that there are about 1 150 000 leprosy cases in the world, out of whom 888 340 are registered for treatment.

Distribution of estimated and registered prevalence by WHO Region is shown in Table 1. Only a modest reduction in the number of registered cases has been noted between 1996 and 1997. The global prevalence rate of registered cases, which was constantly decreasing over the last 10 years, is still about 1·6 per 10 000 population. More importantly, in the 16 major endemic countries which represent 91% of the global leprosy problem, the prevalence rate is still 4·3 per 10 000, indicating that additional efforts will be required to achieve elimination of leprosy as a public health problem. It is possible that some of these countries might need to continue and intensify activities beyond the year 2000 to reach their leprosy elimination targets.

Detection of leprosy cases

The number of cases detected in 1996, by WHO Region, is shown in Table 2. About 555 000 cases were detected during 1996 as notified by 79 countries. Some endemic countries (Cameroon, Papua New Guinea, Paraguay and Zaire) were not able to send information at the time of the preparation of this report. Assuming that these countries would have detected the same number of patients during 1996 as during 1995, the global detection can be estimated to be as high as 566 000 (9·8 per 100 00 population). About 535 000 cases (95%) were detected in the 16 major endemic countries, and 73% of the newly detected cases are living in India alone. Among newly detected cases more than 85 000 (16%) are children, about 170 000 (31%) are multibacillary (MB) cases and about 30 000 (5·5%) were showing severe disabilities at the time of diagnosis.

The increase in detection that is observed in many endemic countries reflects an increase in case-finding activities and geographical coverage of leprosy elimination programmes rather than changes in the incidence of the disease. Although the situation varies from one WHO Region to the other, and from one country to another within the same Region, the global detection trend remained stable over the last 12 years. However, analysis of disaggregate information is needed for a better understanding of the impact of the elimination strategy. The geographical distribution of leprosy as well as its clinical profile have changed dramatically, and the disease is now shrinking to a limited number of countries, or of districts within countries. Furthermore, it should be recognized that there is no direct relationship between detection trends and intensity of transmission of the disease, and therefore detection trends should be interpreted with great caution. This complex matter will be discussed in detail in the next issue of the *Weekly Epidemiological Record.*

Progress with MDT coverage

Almost all leprosy patients registered for treatment are now treated with MDT, even in countries facing difficult practical problems. During 1996, about 1·4 million patients were treated with MDT and more than 550 000 were cured. Table 3 gives details on notified and estimated MDT coverage for registered patients and the cumulative number of persons cured with this treatment, by WHO Region. This impressive progress made in MDT coverage is the direct result of the efficacy of MDT and of efforts made by governments, WHO, nongovernmental organizations and other agencies to ensure the free supply of drugs to all patients in need. During the last 2 years, WHO, through a contribution from the Nippon Foundation, has supplied MDT for more than 1·7 million patients living in 35 endemic countries.

While treating all registered patients with MDT is a considerable achievement in the fight against leprosy, it should be recognized that the geographical coverage of health facilities able to provide MDT services is far from satisfactory. This is mainly because leprosy has always been considered as a special

Table 1. Number of estimated and registered cases of leprosy, by WHO Region, and percentage change between 1996 and 1997

Tableau 1. Nombre estimé et enregistré de cas de lèpre, par Région OMS, et variation en pourcentage entre 1996 et 1997

WHO Region—Région OMS	Estimated number of cases (rate per 10 000) Nombre estimé de cas (taux pour 10 000)	Number of registered cases (rate per 10 000) Nombre de cas enregistrés (taux pour 10 000)		Percentage change Variation en pourcentage
	1997	1996	1997	
Africa—Afrique	140 000 (2·4)	95 901 (1·77)	82 758 (1·39)	(–) 14
Americas—Amériques	140 000 (1·7)	123 537 (1·64)	127 866 (1·63)	(+) 4
South-East Asia—Asie du Sud-Est	800 000 (5·7)	651 562 (4·72)	637 413 (4·50)	(–) 2
Eastern Mediterranean—Méditerranée orientale	30 000 (0·6)	23 005 (0·54)	13 038 (0·28)	(–) 43
Western Pacific—Pacifique accidental	40 000 (0·2)	32 254 (0·20)	26 533 (0·16)	(–) 18
Europe	Less than – Moins de 1 000	–	732 (0·01)	–
Total	1 150 000 (2)	926 259 (1·67)	888 340 (1·54)	(–) 4

Table 2. Detection of leprosy, by WHO Region, 1996[a]

Tableau 2. Détection de la lèpre, par Région OMS, 1996[a]

WHO Region—Région OMS	Number of new cases notified Nombre de nouveaux cas notifiés	Detection rate per 100 000 Taux de détection pour 100 000 habitants
Africa—Afrique	46 489	7·80
Americas—Amériques	43 783	5·59
South-East Asia—Asie du Sud-Est	457 921	32·36
Eastern Mediterranean—Méditerranée orientale	5 761	1·25
Western Pacific—Pacifique occidental	12 613	0·77
Europe	37	–
Total	566 604	9·84

[a] Or latest available information. – Ou dernières donnés disponibles.

disease requiring special systems for dealing with it. As a result, the procedures and norms for diagnosing and treating the disease were seen as beyond the capabilities of the majority of general health services.

With the large experience gained in using MDT, even under difficult conditions, WHO is now promoting simplified procedures aimed at making access to MDT easy for all patients. In so doing, it is estimated that programmes in endemic countries should detect and treat about 2 million cases over the next 4 years.

Most of the leprosy elimination programmes are now using cohort reporting systems to assess cure rates with MDT. Since 1996, independent monitors are collecting detailed information from some of the major endemic countries in order to validate the cure rates, and to analyse the quality of and coverage with MDT services. In general, compliance with MDT is high and cure rates are ranging from 75% to 95%. Flexibility in delivering MDT to patients and the use of blister calendar packs have helped to improve cure rates, especially for patients living in difficult-to-access areas. However, in some countries, cure rates are relatively low, notably for MB patients. This is observed either in programmes not following fixed-duration MDT and therefore keeping patients for too long in treatment registers, or among patients defaulting from treatment for various reasons. However, defaulting rates are relatively low in leprosy, ranging from 1% to 25% according to countries, with a global average of 11%.

Detailed situation in the top 16 endemic countries

Leprosy remains a public health problem in 55 countries or areas, but 16 countries account for 91% of the leprosy problem in the world. Table 4 shows the number of registered cases, the number of cases detected in 1996, and the achievements with MDT in the top 16 endemic countries.

Conclusion

Most of the purely technical problems hindering the process of eliminating leprosy as a public health problem have been solved over the past 15 years, but many operational issues are still to be overcome in order to reach remaining patients and to accelerate the progress. The main challenges for national programmes are (i) to reach geographical areas and populations which have not yet benefited from MDT services, (ii) to reduce the delay in detecting and diagnosing the disease, and (iii) to continue to provide patients with good quality services, including the supply of drugs free of cost. This can only be achieved

Table 3. Registered cases of leprosy and coverage with multidrug therapy (MDT), by WHO Region, 1997

Tableau 3. Cas de lèpre enregistrés et couverture par la polychimiothérapie (PCT), par Région OMS, 1997

WHO Region—Régions OMS	Registered cases Cas enregistrés	Cases on MDT Cas sous PCT	Reported MDT coverage (%) Couverture par la PCT Signalée (%)	Estimated[a] MDT coverage (%) Couverture par la PCT estimée[a] (%)	Cured with MDT (cumulative total) Guérisons par la PCT (total cumulé)
Africa—Afrique	82 758	81 764	98·8	58	507 123
Americas—Amérique	127 866	121 144	94·7	75	235 116
South-East Asia—Asie du Sud-Est	637 413	620 798	97·4	77	7 377 199
Eastern Mediterranean—Méditerranée orientale	13 038	12 166	93·3	45	58 455
Western Pacific—Pacifique occidental	26 533	26 400	99·5	71	236 483
Europe	732	726	99·2	–	1 945
Total	888 340	862 998	97·1	76	8 416 321

[a] Calculated according to the number of estimated cases requiring treatment.—Calculée selon le nombre estimé de cas nécessitant un traitement.

Table 4. Registered prevalence of leprosy, coverage with multidrug therapy (MDT) and detection rate in the top 16 endemic countries[a]

Tableau 4. Prévalence enregistrée de la lèpre, couverture par la polychimiothérapie (PCT) et taux de détection dans les 16 principaux pays d'endémie[a]

Country—Pays	Registered cases beginning of 1997 Cas enregistrés début 1997	Prevalence per 10 000 Prévalence pour 10 000 habitants	Cases on MDT Cas sous PCT	MDT coverage (%) Couverture par la PCT (%)	Cured with MDT (cumulative total) Guérisons par la PCT (total cumulé)	Cases detected in 1996 Cas détectés en 1996	Detection rate per 100 00 Taux de détection pour 100 000 habitants
India—Inde	553 793	5·9	537 180	97·0	6 862 000	415 302	44·0
Brazil—Brésil	105 744	6·6	101 000	95·5	181 763	39 792	24·7
Indonesia—Indonésie	33 739	1·7	33 739	100·0	175 104	15 071	7·5
Bangladesh	13 385	1·1	13 385	100·0	70 063	11 225	9·4
Myanmar	18 758	4·1	18 758	100·0	148 982	6 935	15·1
Nigeria—Nigéria	14 309	1·2	14 309	100·0	45 720	6 871	6·0
Nepal—Népal	12 828	5·8	12 828	100·0	42 362	6 602	30·0
Zaire[b]—Zaïre[b]	6 082	1·3	6 069	99·8	49 422	5 526	11·8
Mozambique	10 905	6·1	10 091	92·5	7 414	4 225	23·7
Ethiopia—Ethiopie	8 272	1·4	8 272	100·0	71 291	4 747	8·2
Madagascar	6 656	4·3	6 656	100·0	23 112	3 921	25·5
Sudan—Soudan	3 471	1·3	3 471	100·0	8 566	2 126	7·8
Philippines	8 663	1·3	8 663	100·0	70 967	4 051	5·9
Cambodia—Cambodge	2 960	2·9	2 960	100·0	7 792	2 404	23·4
United Republic of Tanzania—République-Unie de Tanzanie	3 077	1·0	3 077	100·0	47 192	2 747	8·9
Guinea—Guinée	3 732	5·0	3 732	100·0	28 127	3 326	44·2
Total	806 374	4·3	784 190	97·2	7 839 877	534 871	28·3

[a] The top 16 endemic countries included in the above table have the following characteristics: (i) they have a prevalence of more than 1 in 10 000 population, and (ii) the number of prevalent leprosy cases is more than 5 000, or the number of newly detected cases is more than 2 000. Ranking of countries is based on the number of estimated cases.—Les 16 principaux pays d'endémie figurant dans le tableau ci-dessus présentent les caractéristiques suivantes: i) la prévalence y dépasse 1 pour 10 000 habitants et ii) le nombre total de cas de lèpre est supérieur à 5 000 ou le nombre de cas de lèpre nouvellement détectés dépasse 2 000. Les pays sont classés d'après le nombre de cas estimés.

[b] 1995 data.—Données de 1995.

through increased community involvement, sustained political will and continuous support from the international community. The findings that MDT coverage is now reaching the highest possible level and that case detection continues to improve indicate that elimination of the disease is well under way. However, reaching patients in remote areas and hidden cases will continue to be a major challenge as these problems are interlinked with overall problems of poverty and underdevelopment. While the progress made so far in eliminating leprosy is very impressive, these remaining problems call for further intensification of efforts using focused yet flexible approaches.

Global case detection trend in leprosy

The following is extracted from *Weekly Epidemiological Record*, 1997, **72**, 173–180:

Background

Since the advent of chemotherapeutic drugs against *Mycobacterium leprae*, control of leprosy has been based on case-detection and treatment of patients, with the aim of reducing the infection pool and thereby the transmission of the disease. This strategy, based on detection and mass treatment with dapsone monotherapy, was reasonably effective for many years but failed subsequently with the emergence of resistance of *M. leprae* to dapsone. After the introduction of multidrug therapy (MDT) in the 1980s, achievements during the first 5 to 6 years of implementation were so impressive that the possibility of eliminating leprosy as a public health problem was envisaged. The level of prevalence to be reached was set at 1 case per 10 000 population, and it was decided to evaluate the success of the strategy by monitoring mainly the prevalence of the disease.

Although it was logical to consider monitoring of incidence as a more appropriate and theoretically more relevant measure for evaluating progress towards leprosy elimination, it was clear that this was not technically possible for reasons outlined below. The overall elimination strategy is based on (i) timely case-detection, (ii) cure of all diagnosed cases with fixed duration MDT, (iii) simplified case-management and (iv) monitoring progress through appropriate information systems. So far, this concept has proved to be valid and the prevalence pool has been reduced by more than 85% in a span of 15 years. The question that now arises is how to demonstrate whether or not this reduction in prevalence has had an impact on the transmission of the disease. Unfortunately, dependable tools for measuring infection and for monitoring incidence trends in leprosy are still not available. Assessing incidence requires special prospective studies which involve large amount of resources and would have to be repeated using consistent procedures over several years if trends are to be assessed.

The purpose of this report is to analyse trends in leprosy over the last 12 years in 28 endemic countries and to discuss the extent to which changes in the detection and in the profile of newly detected cases reflect changes in the transmission of the disease.

Intensification of leprosy control activities through expansion of MDT services to every available health facility in the country is an important step towards elimination. However, the availability of health services and their capacity to implement MDT services for leprosy vary widely in different countries. In theory, if all the cases were to be detected within the first year of onset of disease and treated with MDT, the impact on transmission should be visible within a few years. In practice, the detection of leprosy globally has remained unchanged over the last 10 years, in quantitative and to some extent even in qualitative terms. What is not clear is the extent to which these changes can be attributed to the level of transmission, improved case-finding, expansion of health services, changes in case definition, increased population at risk, or a combination of these factors.

During the early years after the introduction of MDT, the problem was mainly the burden of cumulative prevalence (10–12 million estimated cases and 5·4 million registered cases in 1985), and the main objective was to treat, and cure, the large number of already registered patients. At that time, it

could be estimated that the average duration of the disease (from diagnosis to cure) ranged between 15 and 20 years. The gap between registered and estimated cases was enormous and was most probably over-estimated. Before introduction of MDT, information on the number of new cases detected each year was rather scanty. Even so, one could estimate this figure to be between 250 000 and 300 000 globally at that time.

From 1985 to 1996, MDT was widely, but slowly, implemented to reach a coverage of 97% of all the registered cases, which is equal to about 75% of the estimated cases. As a result of this, the average duration of the disease (from diagnosis to cure) was reduced to between 2 and 4 years (taking into consideration defaulting and incomplete treatment), as shown by the annual prevalence reaching 1·4 million cases in 1996 (period prevalence including new case detection of 0·56 million cases during the same year).

Assuming that introduction of MDT was successful in ''clearing'' the accumulated backlog of prevalence, i.e. curing most of the already known cases, a new situation has now arisen. For the first time in the history of leprosy control, detection and prevalence are converging, and it is becoming increasingly obvious that detection to a large extent really reflects a hidden prevalence which was not very well perceived before. A large part of detection currently consists of cases accumulated over a period of time and therefore the situation should now be analysed from a different perspective. It is a fact that globally, and at national level in many countries, detection has been increasing significantly over the last 10 years to reach a plateau of about half a million new cases per year. How can this increase and its persistence be explained? Is the incidence of leprosy really increasing in many countries? Is it the result of the impact of the elimination strategy leading to stronger political commitment and improved coverage of health services? Is it just the effect of an improved information system, or changes in case-finding methods? Is it an after-effect of the ''cleaning of registers'' forcing some programmes to bring back some patients from the cleaned prevalence pool to the new detection pool? Was the leprosy problem so much underestimated that the backlog is much higher than expected? In all probability several of the factors mentioned above have contributed to the current situation. However, it is difficult to estimate the proportionate contribution attributable to any one of the above factors to the stagnation of case detection trends.

Available information on global leprosy trends, 1985–1996

Consistent information on leprosy covering a period of 12 years has been provided to WHO by the majority of national programmes. The top 28 countries have been included in this report and they represent 95% of the current leprosy burden in the world and 80% of the leprosy burden as it was in 1985. This information is presented in Table 1.

Between 1985 and 1996, while a steep reduction in prevalence can be observed (78%) in this group of top leprosy endemic countries, the trend in cases newly detected every year (absolute numbers and rates) is stable. Interpretation of this trend needs to take into consideration many factors, including the extent of the reliability and coverage of information systems. The weight of India in relation to global figures is so important that it could mask variations observed in other parts of the world. Table 2 shows leprosy trends in 27 endemic countries with the exception of India. The prevalence trend is steeply decreasing (70%), while the detection trend is significantly increasing, especially after 1991. When analysing indirect indicators such as detection of children below the age of 15 years, detection of multibacillary (MB) cases and proportion of disabled patients among newly detected cases, the situation seems to be even more interesting. While the child-specific detection rate per 100 000 population was 8·0 in 1985 and 8·9 in 1996 (1·1 and 2·3 excluding India), the peak of 15 per 100 000 was reached during 1991. The proportion of patients disabled at the time of diagnosis decreased from 9·7% to 5·4%, but excluding India, this proportion has increased from 6·8% to 10·3%. While the detection rate per 100 000 of MB leprosy was 5·9 in 1985 and 7·1 in 1996 (1·9 and 4·7 without India), the peak of 10·2 was reached in 1992. All these indirect indicators are traditionally used to interpret detection tends and assess the level of transmission of the disease.

Table 1. Leprosy trend in 28 endemic countries combined,[a] 1985–1996

Tableau 1. Tendances de la lèpre dans l'ensemble de 28 pays d'endémie,[a] 1985–1996

End of the year / Fin de l'année	Prevalence (rate per 10 000) / Prévalence (taux pour 10 000 habitants)	Detection (rate per 100 000) / Détection (taux pour 100 000 habitants)	New case-detection (rate per 100 000) / Détection de nouveaux cas (taux pour 100 000 habitants)					
			Children (below 15 years) / Enfants (moins de 15 ans)		Disabled (WHO Grade 2) / Incapacités (catégorie 2 OMS)		Multibacillary / Multibacillaire	
			Number / Nombre	%	Number / Nombre	%	Number / Nombre	%
1985	3 870 547 (20·2)	543 965 (28·4)	60 869 (8·0)	11·19	52 725 (2·8)	9·69	112 881 (5·9)	20·75
1986	3 940 462 (20·2)	568 583 (29·1)	67 597 (8·7)	11·89	53 876 (2·8)	9·48	117 922 (6·0)	20·74
1987	3 871 164 (19·4)	590 368 (29·6)	72 663 (9·1)	12·31	51 045 (2·6)	8·65	130 475 (6·6)	22·10
1988	3 643 687 (17·9)	548 642 (27·0)	71 432 (8·8)	13·02	44 881 (2·2)	8·18	118 377 (5·8)	21·58
1989	3 411 895 (16·5)	546 420 (26·4)	81 909 (9·9)	14·99	43 904 (2·1)	8·03	122 009 (5·9)	22·33
1990	2 882 077 (13·6)	567 411 (26·8)	83 220 (9·8)	14·67	45 118 (2·1)	7·95	150 629 (7·1)	26·55
1991	2 333 762 (10·8)	608 429 (28·2)	131 467 (15·2)	21·61	46 176 (2·1)	7·59	188 354 (8·7)	30·96
1992	1 806 352 (8·2)	661 549 (30·0)	110 041 (12·5)	16·63	49 875 (2·3)	7·54	223 849 (10·2)	33·84
1993	1 478 352 (6·6)	610 524 (27·2)	105 995 (11·8)	17·36	50 020 (2·2)	8·19	213 889 (9·5)	35·03
1994	1 162 333 (5·1)	549 100 (23·9)	94 989 (10·4)	17·30	43 043 (1·9)	7·84	191 329 (8·3)	34·84
1995	916 305 (3·9)	548 266 (23·4)	89 150 (9·5)	16·26	39 633 (1·7)	7·23	191 603 (8·2)	34·95
1996	837 571 (3·5)	544 639 (22·8)	85 002 (8·9)	15·61	29 488 (1·2)	5·41	168 406 (7·1)	30·92
Total		6 887 896	1 054 334	15·31	549 784	7·98	1 929 723	28·02

[a] Bangladesh, Brazil, Cambodia, Chad, Colombia, Congo, Egypt, Ethiopia, Guinea, India, Indonesia, Madagascar, Mali, Mexico, Mozambique, Myanmar, Nepal, Niger, Nigeria, Pakistan, Philippines, Sudan, Thailand, Venezuela, Viet Nam, Yemen, Zaire, Zambia.—Bangladesh, Brésil, Cambodge, Colombie, Congo, Egypte, Ethiopie, Guinée, Inde, Indonésie, Madagascar, Mali, Mexique, Mozambique, Myanmar, Népal, Niger, Nigéria, Pakistan, Philippines, Soudan, Tchad, Thailande, Venezuela, Viet Nam, Yémen, Zaïre, Zambie.

Table 2. Leprosy trend in 27 endemic countries combined,[a] India excluded, 1985–1996

Tableau 2. Tendances de la lèpre dans 27 pays d'endémie,[a] sans l'Inde, 1985–1996

End of the year Fin de l'année	Prevalence (rate per 10 000) Prévalence (taux pour 10 000 habitants)	Detection (rate per 100 000) Détection (taux pour 100 000 habitants)	New case-detection (rate per 100 000) Détection de nouveaux cas (taux pour 100 000 habitants) Children (below 15 years) Enfants (moins de 15 ans)		Disabled (WHO Grade 2) Incapacités (catégorie 2 OMS)		Multibacillary Multibacillaire	
			Number Nombre	%	Number Nombre	%	Number Nombre	%
1985	954 547 (8·3)	66 965 (5·8)	4 869 (1·1)	7·3	4 548 (0·4)	6·8	22 251 (1·9)	33·2
1986	923 462 (7·8)	61 583 (5·2)	4 597 (1·0)	7·5	4 697 (0·4)	7·6	21 592 (1·8)	35·1
1987	909 164 (7·6)	71 368 (5·9)	4 663 (1·0)	6·5	7 968 (0·7)	11·2	26 675 (2·2)	37·4
1988	808 687 (6·6)	74 642 (6·1)	5 432 (1·1)	7·3	6 961 (0·6)	9·3	28 317 (2·3)	37·9
1989	778 895 (6·2)	80 420 (6·4)	5 909 (1·2)	7·3	7 090 (0·6)	8·8	28 809 (2·3)	35·8
1990	752 077 (5·9)	86 411 (6·8)	7 220 (1·4)	8·4	9 043 (0·7)	10·5	35 189 (2·8)	40·7
1991	660 762 (5·1)	91 429 (7·0)	9 467 (1·8)	10·4	7 918 (0·6)	8·7	38 424 (2·9)	42·0
1992	639 352 (4·8)	114 549 (8·6)	10 041 (1·9)	8·8	11 038 (0·8)	9·6	54 279 (4·1)	47·4
1993	536 352 (3·9)	116 524 (8·6)	11 995 (2·2)	10·3	12 780 (0·9)	11·0	65 689 (4·8)	56·4
1994	422 333 (3·0)	122 100 (8·8)	12 989 (2·3)	10·6	13 013 (0·9)	10·7	63 229 (4·6)	51·8
1995	343 305 (2·4)	122 695 (8·7)	13 150 (2·3)	10·7	13 247 (0·9)	10·8	63 932 (4·5)	52·1
1996	283 778 (2·0)	129 337 (9·0)	13 359 (2·3)	10·3	13 381 (0·9)	10·3	68 203 (4·7)	52·7
Total		1 138 023	103 691	9·1	111 684	9·8	516 589	45·4

[a] Bangladesh, Brazil, Cambodia, Congo, Chad, Colombia, Egypt, Ethiopia, Guinea, Indonesia, Madagascar, Mali, Mexico, Mozambique, Myanmar, Nepal, Niger, Nigeria, Pakistan, Philippines, Sudan, Thailand, Venezuela, Viet Nam, Yemen, Zaire, Zambia.—Bangladesh, Brésil, Cambodge, Colombie, Congo, Egypte, Ethiopie, Guinée, Indonésie, Madagascar, Mali, Mexique, Mozambique, Myanmar, Népal, Niger, Nigéria, Pakistan, Philippines, Soudan, Tchad, Thailande, Venezuela, Viet Nam, Yémen, Zaïre, Zambie.

At first glance, one might think that incidence of leprosy is remaining the same, or is even increasing in some parts of the world, despite the considerable reduction in the size of the reservoir. This is in contradiction with information collected through some special studies which show that the incidence of leprosy is decreasing by about 10% a year. However, an increasing detection trend with a decreasing incidence trend is compatible when a significant number of backlog cases exist in the community. In one way, increasing detection trends provide reassurance, since they clearly demonstrate the effectiveness of the global elimination strategy in identifying the backlog cases for treatment with MDT. This is likely to be the scenario in countries which still have a high endemicity for leprosy and where the programmes are continually expanding their activities to previously uncovered areas, leading to improvement in their case-finding activities. However, considering that leprosy distribution is very uneven among countries and that different countries in the world started with different levels of prevalence and incidence, and considering the variations in the intensity of control operations among countries, it is useful to analyse the situation according to different country groupings and regions of the world.

AFRICA

Leprosy prevalence and detection have significantly decreased in some previously highly endemic countries such as Benin, Burkina Faso, Côte d'Ivoire, Kenya, Malawi, Togo and Uganda. In most of these countries, leprosy elimination was the result of large-scale implementation of MDT starting more than 10 years ago, increased coverage with BCG immunization and involvement of general health services in leprosy control activities.

On the other hand, countries presented in this study (Chad, Congo, Ethiopia, Guinea, Madagascar, Mali, Mozambique, Niger, Nigeria and Zaire) have not yet reached the elimination target. In most of these countries (Chad, Guinea, Madagascar, Mali, Mozambique and Nigeria) detection has considerably increased as a result of vigorous efforts to expand leprosy control activities and to implement MDT on a large scale during the 1990s. Preliminary information collected through special monitoring indicates that incidence of leprosy could still be very high in some districts of Guinea and Madagascar. In Ethiopia, where an excellent MDT programme had been implemented in the 1980s, it is not clear why the detection trend remains stagnant. It seems that, after the impressive results achieved with the MDT programme, lower priority was given to leprosy elimination activities. In Zaire, the detection trend is closely related to operational factors considering that less than 50% of the country is covered by leprosy control activities.

AMERICAS

While leprosy is declining in almost all countries of the Region, the weight of Brazil explains the increasing detection trend. The detection trend has been on the increase in Brazil since the beginning of the national programme. This has been analysed extensively, and the most likely explanation is that the increase is linked with the expansion of control activities and the number of health staff involved in the programme. Considering the geographical and demographic peculiarities of Brazil, one could expect that the detection will continue to increase over the next few years, along with implementation of the elimination programme in uncovered northern states.

SOUTH-EAST ASIA

With the exception of India, the leprosy trend in South-East Asia follows the same pattern as in Africa and Latin America. Declining detection trends were observed only in Maldives, Sri Lanka and Thailand. The detection trend is increasing in Bangladesh, Indonesia, Myanmar and Nepal. In Bangladesh, increased detection can be explained by the more recent and relatively late implementation of a national elimination programme. The Indonesian and Nepalese leprosy pattern could be explained by the slowly increasing geographical coverage. In Myanmar, the rapid expansion of leprosy elimination activities to

all townships started only in 1992, leading to an initial increase in detection followed by the current tendency to stabilize.

Levels of prevalence and detection in India are much higher than in any other country and thus are presented separately in Table 3.

Although the detection trend is declining in India, the current rate is still very high and the decline is not as fast as one could expect. This can be explained by the fact that over the last 40 years, efforts were mainly concentrated in the states which were originally considered as major endemic states. In these states (e.g. Andhra Pradesh, Maharashtra and Tamil Nadu), both prevalence and detection rates have significantly decreased. The profile of cases newly detected in these states (high proportion of single lesion leprosy, low incidence of MB, low disability rate) indicates that the disease is being diagnosed very early through a very active vertical programme involving thousands of workers. In this context, target setting for detection as well as low specificity of diagnosis could partly explain the slow decrease in trends. On the other hand, states which were originally not considered as highly endemic (e.g. Bihar, Madhya Pradesh and Uttar Pradesh) are now getting higher priority. In these states implementation or strengthening of leprosy elimination activities in recent years has led to an increasing detection rate, mainly of backing cases. The combination of these factors could explain the overall high rates and slow progress in India, which is a matter of concern. Considering that MDT on a wide scale has been implemented only recently in these states, and that the geographical coverage with MDT services is still low, it would be unrealistic to expect major changes in the epidemiological trend of the disease in the near future.

EASTERN MEDITERRANEAN

While leprosy is no longer a public health problem in most of the countries of this Region, it is felt that the disease has often been underreported. This renders trend analysis difficult. However, recent implementation of national elimination programmes in some countries, notably Sudan, explains why the detection trend is on the increase, though the levels of detection remain very low (around 2 per 100 000).

WESTERN PACIFIC

Remarkable results were registered in many countries of this Region, where leprosy was eliminated as a public health problem during the current decade. However, countries included in this analysis are reporting increasing detection trends. In Cambodia, this can be explained by the relatively more recent introduction of a national elimination programme. In the Philippines, despite the early implementation of MDT, the detection trend is increasing. This increase is linked with improved geographical coverage, implementation of community awareness campaigns and an improved information system.

Conclusions

Because data reproduced here cover several countries with large populations, it is very likely that changes in detection trends mainly reflect changes in the intensity of programme activities, rather than variations in the transmission of the disease. High and increasing detection rates are more often related to expanding geographical coverage of leprosy services. The main factor which contributes to increasing and then stabilizing global detection trends during the studied period is the expansion of geographical coverage with MDT services through dynamic national elimination programmes, the integration of leprosy activities within general health services and, more recently, introduction of elimination campaigns and special action projects with the specific aim of reaching uncovered areas and underserved populations. It can be estimated that before 1985, coverage with adequate MDT services was less than 20% which has steadily increased to reach around 75% in 1996.

The fact that the trend in the global leprosy detection has not changed over the last 12 years should

Table 3. Leprosy trend in India, 1985–1996

Tableau 3. Tendance de la lèpre en Inde, 1985–1996

End of the year Fin de l'année	Prevalence (rate per 10 000) Prévalence (taux pour 10 000 habitants)	Detection (rate per 100 000) Détection (taux pour 100 000 habitants)	New case-detection (rate per 100 000) Détection de nouveaux cas (taux pour 100 000 habitants) Children (below 15 years) Enfants (moins de 15 ans)		Disabled (WHO Grade 2) Incapacités (catégorie 2 OMS)		Multibacillary Multibacillaire	
			Number Nombre	%	Number Nombre	%	Number Nombre	%
1985	2 916 000 (38·6)	477 000 (63·1)	56 000 (18·5)	11·7	48 177 (6·4)	10·1	90 630 (12·0)	19·0
1986	3 017 000 (39·1)	507 000 (65·7)	63 000 (20·4)	12·4	49 171 (6·4)	9·7	96 330 (12·5)	19·0
1987	2 962 000 (37·6)	419 000 (65·9)	68 000 (21·6)	16·2	43 077 (5·5)	10·3	103 800 (13·2)	24·8
1988	2 835 000 (35·3)	474 000 (59·0)	66 000 (20·5)	13·9	37 920 (4·7)	8·0	90 060 (11·2)	19·0
1989	2 633 000 (32·1)	466 000 (56·8)	76 000 (23·2)	16·3	36 814 (4·5)	7·9	93 200 (11·4)	20·0
1990	2 130 000 (25·5)	481 000 (57·5)	76 000 (22·7)	15·8	36 075 (4·3)	7·5	115 440 (13·8)	24·0
1991	1 673 000 (19·6)	517 000 (60·6)	122 000 (35·7)	23·6	38 258 (4·5)	7·4	149 930 (17·6)	29·0
1992	1 167 000 (13·4)	547 000 (62·8)	100 000 (28·7)	18·3	38 837 (4·5)	7·1	169 570 (19·5)	31·0
1993	942 000 (10·6)	494 000 (55·6)	94 000 (26·4)	19·0	37 240 (4·2)	7·5	148 200 (16·7)	30·0
1994	740 000 (8·2)	427 000 (47·1)	82 000 (22·6)	19·2	30 030 (3·3)	7·0	128 100 (14·1)	30·0
1995	573 000 (6·2)	425 571 (46·0)	76 000 (20·5)	17·9	26 386 (2·9)	6·2	127 671 (13·8)	30·0
1996	553 793 (5·9)	415 302 (44·0)	71 643 (19·0)	17·3	16 107 (1·7)	3·9	100 203 (10·6)	24·1

not be interpreted as a weakness of the global elimination strategy. More detailed analysis shows that the detection trend is even on the increase in many of the endemic countries. With the exception of India, trends and patterns in newly detected cases are comparable in most countries. Africa, the Americas and South-East Asia show similar increasing trends and similar rates (detection rate around 10 per 100 000 population, child-specific detection rate of 2 per 100 000 population). The Eastern Mediterranean and the Western Pacific also show increasing trends but at a lower level. India alone, while showing a decreasing trend, presents a very high level of endemicity with a detection rate of around 45 per 100 000 population and a child-specific detection rate of around 20 per 100 000 population. The fact that in all the countries studied the specific detection of MB cases has increased should be interpreted with caution if we consider that the definition of MB cases has changed several times during the studied period. However, the number of skin-smear positive new cases has significantly decreased to reach an estimated number of about 70 000 in 1996. This indicates that important epidemiological and operational changes are occurring in the process of eliminating the disease.

While information is lacking on how to estimate the current annual incidence of the disease from case detection figures, it can reasonably be assumed that incidence represents no more than one-third of the annual detection. If this assumption is true, and if vigorous efforts such as leprosy elimination campaigns, including community awareness activities continue to be organized, then one could expect a rapid and considerable decrease in global detection rates in the next 2–3 years. However, it should be recognized that in a limited number of countries or areas where levels of endemicity are still very high, or where it will be operationally difficult to increase the geographical coverage, there are considerable challenges to achieving the elimination target on time.

Genetic traits in common diseases: is autoimmunity the price paid for eradicating infectious diseases?

The following, by A. G. Wilson and G. W. Duff of the Section of Molecular Medicine, Dept of Medicine & Pharmacology, University of Sheffield, Royal Hallamshire Hospital, Sheffield S10 2JF, is extracted from the *British Medical Journal*, **310,** 1482:

An important current topic of medical research is the localization of genes implicated in the susceptibility to common chronic diseases such as insulin dependent diabetes, rheumatoid arthritis, and multiple sclerosis. This has been greatly facilitated by the use of the polymerase chain reaction to characterise polymorphic microsatellite markers and the advent of automated technology and computer software to construct high resolution genetic maps covering the entire genome.

A recent example of the success of these methods occurred in the genome-wide search in families for genes conferring susceptibility to insulin dependent diabetes.[1] Population studies, based on epidemiological principles, test the association of disease with specific genetic markers, and recent advances have also been made with this approach.

Most of these common diseases are clearly polygenic, involving several loci, and many population association studies leave little doubt that an appreciable genetic component of immunopathology lies in the major histocompatibility complex. This is a four megabase stretch of DNA (about 0·1% of the human genome) located on the short arm of chromosome 6 and containing up to 200 genes, many of which are immunologically relevant. Within the major histocompatibility complex lies the gene for tumour necrosis factor α, a potent proinflammatory cytokine implicated in the pathogenesis and clinical manifestations of many inflammatory and infectious conditions.[2] In view of its chromosomal location and biological effects there has been speculation that polymorphism within the gene for tumour necrosis factor α may play a part in the genetic association of the major histocompatibility complex with at least some of these diseases.[3]

A biallelic polymorphism has been described in the gene for tumour necrosis factor α in a region that controls transcription.[4] The rarer allele, TNF2, is part of the HLA Al-B8-DR3-DQ2 haplotype,[5] which is associated with many autoimmune diseases.[6,7] A preliminary study in coeliac disease, which is

strongly associated with HLA-DQ2, found carriage of TNF2 in 96% of patients compared with 21% of controls, suggesting that a second susceptibility locus on this haplotype may lie close to, or within, the locus for tumour necrosis factor.[8]

In malaria high plasma concentrations of tumour necrosis factor α are associated with more severe disease, with the highest concentrations occurring in fatal cases of cerebral malaria.[9] A study of genotypes for tumour necrosis factor α in west African patients with malaria has shown that homozygosity for the TNF2 allele is associated with a sevenfold increased risk of death or severe neurological complications due to cerebral malaria.[10] Furthermore, the TNF2 allele in gene assays directs higher levels of transcription of the gene compared with the common allele, suggesting that this polymorphism directly affects production of tumour necrosis factor α.[11]

Malaria or systemic lupus erythematosus?

An interesting observation is the apparent protection from autoimmune diseases in areas of west Africa where malaria is endemic,[12] in contrast to the high incidence of systemic lupus erythematosus in Afro-American populations, who are mostly of west African descent.[13] This has led to speculation that high concentrations of tumour necrosis factor α induced by malaria in west Africa may protect against systemic lupus erythematosus. In support of this idea, protective effects of recombinant tumour necrosis factor α in the $(NZB \times NZW)_{F1}$ mouse model of lupus have been cited,[14] and infection of this strain with *Plasmodium berghei* prevents the development of the lupus-like disease.[15] The TNF2 allele may be responsible for the lower incidence of lupus in Africa, resulting from endemic malaria, while the absence of this stimulant of the production of tumour necrosis factor α allows for the increased incidence of this disease in Afro-Americans. If this is correct it would be a good example of the old clinical adage that "autoimmunity is the price paid for eradicating infectious diseases."

Despite the adverse effects of homozygosity in malaria, TNF2 is maintained at a similar frequency in west African and northern European populations, which suggests that compensatory pressures in Africa exist to maintain the allele. Perhaps it has beneficial effects in other important infectious diseases such as measles, meningococcal disease, leprosy, or tuberculosis. There may also be heterozygous advantages.

The efficacy of treatment with antibodies to tumour necrosis factor α is being investigated in several diseases and has been shown to be beneficial in rheumatoid arthritis.[16] Determining patients' genotype for tumour necrosis factor before starting treatment may permit the selection of patients who are genetically predisposed to produce high concentrations of this cytokine and who might therefore benefit most from this treatment. The prospect of targeting treatment at those predicted to gain most therapeutic benefit clearly has important clinical and economic consequences, particularly in diseases of high prevalence such as malaria. Clinical benefits may result from this research by the end of the decade.

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WHO Report of the Second Meeting of the Leprosy Elimination Advisory Group (LEAG), 14 October 1996, New Delhi, India

The participants were welcomed to the meeting by Professor M. F. Lechat (LEAG Chairman) and Dr S. K. Noordeen, Director of WHO's Action Programme for the Elimination of Leprosy (LEP). Dr Noordeen then reviewed the current world leprosy situation. The total numbers of estimated and registered cases in the world have continued to decline and currently stand at 1·3 million and 940 0000 compared with 10–12 million and 5·4 million respectively in 1985. Thus far 8 million cases have been cured by MDT, reducing the leprosy burden by 80–85%, but we will need to reduce it by 97% to reach the goal of 1/10 000 by the year 2000. An additional 2 million cases (1·5 million from South-East Asia) will be added to the total between now and the year 2000, with over 500 000 now being diagnosed annually. To achieve elimination, our efforts must be intensified and strategies utilized to reach every patient in every village; 60% to 65% could be reached by current control efforts, another 30% by LEC and 5–10% by SAPEL projects. There is excellent commitment to the goal, and at a separate meeting the 14 health ministers attending the Conference all agreed to fully cooperate in reaching it.

In discussion following Dr Noordeen's presentation three questions were raised. One concerned the accuracy of the prevalence and detection figures, but all agreed that the current approach to data collection by countries and through other documentary sources is the best we can do at this point. The second related to the extent of over-diagnosis of paucibacillary (PB) disease, and the third raised the issue of recycling patients, i.e., repeatedly re-treating cases who do not quite receive 6 doses of MDT within 9 months (PB) or 24 doses within 36 months (MB). As regards the second question, efforts to improve diagnosis and simplify treatment of single-lesion leprosy are underway, while the third question was dealt with in part by the Chemotherapy of Leprosy Study Group in 1993, i.e., evaluation of each case to determine if they need re-treatment. Nonetheless, the group felt that both issues should be addressed in the upcoming 7th Expert Committee Meeting.

The main headings of the report include—report of Special Action Projects (SAPEL), progress with Leprosy Elimination Campaigns (LEC), Task Force on Monitoring and Evaluation (MEE), Capacity Building and Health Systems Research (CBH), Drug Supply Management, Post-elimination issues and leprosy elimination in the WHO Regions. The section on drug supply management is of considerable practical importance and reads as follows –

An overview of this topic was given by Dr Daumerie. Careful management of the available drug

supply is vital if waste is to be avoided. In particular, countries are encouraged to utilize the oldest stocks of drugs first, before they expire. Reviewing 1996, it was noted that the number of requesting countries is increasing (40) and MDT coverage is over 90%, packaging of drugs has improved and the price has been reduced. MDT drugs are now shipped as perishable goods and more than 7.5 million blister packs were delivered in 1996, which provided treatment for about 920 000 patients. Distribution at the sub-national level is still not adequate, but slow progress is being made in making MDT available at all health centres. Various quality control steps are also in place, including batch testing, field testing of MDT from various manufacturers and package testing.

Monitoring of the drug supply is an important part of the distribution. Positive points insofar as monitoring is concerned are the improved quality of treatment and motivation of health workers. MDT blister packs are now available at the national level in all endemic countries, and distribution to patients is free. Furthermore, the reporting and monitoring systems have improved even in the difficult countries. The availability of buffer stocks in the various countries could help in decentralizing MDT treatment. Negative points in the monitoring system include difficulties in accurately estimating MDT needs and the large quantities of loose drugs (i.e., those not in blister packs) available in some areas, in particular among other programmes which use rifampicin, such as tuberculosis. There continues to be some lack of coordination with government and other agencies which provide MDT, and difficulties remain in updating information on the drug flows. Finally, there is often a lack of involvement of general health services.

Actions being taken to improve drug supply management include providing more information on availability of MDT, widely distributing guidelines, posters and a pocket guide, and implementing standardized procedures for assessing drug supply. MDT monitoring teams will be set up to review the situation at the country level, and the use of GIS will be promoted as will the use of MDT at the most peripheral levels.

Since 1995, about 1·5 millions patients are treated annually with MDT and about 700 000 patients are cured annually. Current global stocks of MDT are 13 million blister packs, or the equivalent of 1·5 million patient-years of treatment. The global buffer stock is sufficient and national managers can be confident that it is now possible to implement MDT in every health facility. Nonetheless, there is a need to maintain the highest possible coverage with MDT and to improve involvement of national managers in the drug supply. Simplification of the global information system on MDT management would help, as would improved and focused monitoring at the national level.

During the discussion that followed the presentation, it was noted that buffer stocks of drugs are vital because of occasional blocks in the government supply. It was also noted that storage is sometimes a problem, particularly at the peripheral level where proper storage may not be available. As a remedy for this, it was suggested that stocks be kept at a more central level, where proper facilities are available, and be sent out somewhat closer to the time they will actually be used.

Currently MB blister packs cost US$1·72 each, or about US$40·00 for 24 packs, while PB blister packs cost US$0·5 or US$3·0 for 6 packs. At the present time WHO is providing 100% of the drug needs in 22 of the 40 countries where the drugs are distributed.

Annex 1 (pages 10 + 11) of this Report gives the Recommendations of the *2nd International Conference on the Elimination of Leprosy*, 11–13 October 1996, New Delhi, India, which read as follows:

The Second International Conference on the Elimination of Leprosy, convened on the initiative of the World Health Organization in New Delhi, India, from 11 to 13 October 1996, mindful of the commitment of all Member States of WHO, under World Health Assembly Resolution WHA44.9, of 1991, ''to continue to promote the use of all control measures including Multidrug Therapy (MDT) together with case-finding in order to attain the global elimination of leprosy as a public health problem by the year 2000'', endorses the updated WHO global strategy and the intensified plan of action, and RECOMMENDS that:

- All parties concerned—national governments, non-governmental organizations and international agencies—should recognize the unprecedented opportunity available now to reach the goal of

eliminating leprosy as a public health problem, particularly in the light of the remarkable progress made so far, and that they intensify their political commitment and efforts to reach the remaining patients before the year 2000, bearing in mind that there is no room for complacency if the goal is to be attained.

- The remaining problem of leprosy treatment will be far more difficult as it includes hitherto neglected areas, population groups and communities. It is important that programme managers develop special intensive operations to reach them through such mechanisms as leprosy elimination campaigns (LEC) to detect hidden cases and special action projects (SAPEL) to reach difficult-to-access patients among under-served population groups such as nomads, refugees, migrants, etc.
- Ministries of Health in endemic countries should take immediate steps to further involve health personnel from the general health services in the treatment of leprosy patients, as well as in case-detection, so that these activities are adequately integrated into the general health services. Even as integration within the general health services is achieved, the quality of services provided to patients should be assured.
- As the technology employed to reach the leprosy elimination goal is essentially through the treatment of patients with multidrug therapy (MDT), it is extremely important that the free supply of WHO recommended MDT drugs in blister packs to patients be continued without interruption to ensure every patient has access to MDT.
- In order to ensure that all patients have access to MDT and that the progress being made towards leprosy elimination can be accurately assessed, the special initiative of leprosy monitoring (LEM) should be implemented as soon as possible.
- In view of the continued social problems faced by persons affected by leprosy, it is highly important to further intensify our efforts at creating community awareness of the disease and its curability, and to mobilize community action towards the elimination of leprosy. It is important that persons affected by leprosy be actively involved as partners in this process.
- Even as leprosy patients are being cured of the disease, many of them continue to face problems in rehabilitating and reintegrating themselves within their communities, and consequently every attempt should be made to bring persons disabled due to leprosy and their rehabilitation within the general ambit of all disabled in the community and within existing community-based rehabilitation programmes.
- At this critical stage in the progress being made towards reaching the target, there is an urgent need for all to step up the coordination and mobilization of the resources needed—finance, manpower and planning for the future. This is particularly important for all partners, including governments, international donors and nongovernmental organizations.
- It is important that research activities in leprosy be continued, especially with regard to the operational aspects, chemotherapy and treatment of complications of leprosy. The understanding of the basic biological mechanisms of this disease is important for developing potential tools that may lead to eventual eradication.
- Countries, as they reach the elimination goal at the national level, should focus their attention on the target of elimination at the sub-national levels, and sustain leprosy treatment and rehabilitation activities. It is important to ensure that services are capable of continuing to detect and treat new cases, and to respond to physical and social needs faced by individuals who have been affected by the disease. The efforts to ensure elimination as a public health problem will lay the foundation for our ultimate vision of the total eradication of leprosy in the future.

WHO Meeting on Chemotherapy Research in Leprosy, Madras, India, 6–7 January 1997

About 30 Principal Investigators Experts and WHO Leprosy Staff met for two days in the ICMR Tuberculosis Research Centre, Chennai (Madras) to assess the current status of WHO-organized drug trials in the chemotherapy of leprosy.

In his opening address, Dr S. K. Noordeen commented that, although the first generation of anti-leprosy chemotherapy regimens (WHO MDT) was giving good results, an interesting stage had been reached in the investigation of second generation regimens. However, although we now possessed 'more than enough' anti-leprosy bactericidal drugs, it was not possible to try out all possible combinations, to find which were the most effective and acceptable, because we were limited both by the shortage of suitable trial patients and by a shortage of animals and animal facilities. Therefore a careful assessment of current data was desirable.

Before reporting on experimental chemotherapy results, Dr Ji noted that the main problems with WHO MDT were to ensure that drugs were locally available for every patient, and that the full course of all the prescribed drugs was taken by each patient. In low prevalence areas, drug regimens should be designed for easy administration by non-specialists. He then listed six objectives for second generation MDT regimens, some general, some for specific chemotherapeutic or field situations. All new regimens should be as least as active as standard WHO MDT.

Since 1990, various regimens had been studied in nude mice, involving the standard drugs, rifampicin, clofazimene and dapsone and the 'new' drugs ofloxacin, minocycline and clarithromycin. Experimental chemotherapy had its own limitations, in that normal, immunocompetant mice could only be used to detect killing of viable *M. leprae* by 4 orders of magnitude (10^{-4}), and nude mice to detect killing of about 6 orders of magnitude (10^{-6}). Nevertheless, such studies confirmed that rifampicin was more bactericidal than the 'new' drugs, and it remained essential to prevent the development of rifampicin resistance. As a single combined dose of ofloxacillin and minocycline, with or without clarithromycin, did have some significant bactericidal activity, such combinations could be used to replace clofazamine when patients refused the latter drug because of its effect on skin colour, or rifampicin in those same cases of rifampicin resistance, allergy, or toxicity. Surprisingly, 12 weeks of daily dapsone and clofazamine given to lepromatous mice resulted in a kill of more than five orders of magnitude (10^{-5}), the number of viable leprosy bacilli falling to the limits of detectable levels. This result suggested that the duration of treatment with clofazemine and dapsone could be somewhat shorter than two years without risking the emergence of rifampicin resistance should relapse occur (although it gives no indication of the likely relapse rates obtained by shortening WHO MBL MDT—Reviewer's Comment).

The rest of the first day was spent on the controlled chemical trial in single lesion paucibacillary leprosy (smear–negative T7, B7 and Indeterminate) of a single combined dose of rifampicin 600 mg, ofloxacillin 400 mg and minocycline 100 mg (adult dosage) compared with standard WHO PBL MDT. The trial design was 'double-blend', with placebo tablets being given to the trial regimen group for six months, with a follow-up period of 1 year after completing treatment, individual patients being studied for a total of 18 months. Altogether 1,484 patients had been admitted to the trial in nine centres in India, and progress reports were submitted by the Principal Investigators.

Dr Pamikar presented an analysis of 1011 patients who had completed their 18 months in the trial, more than 500 on each regimen. A simple method of scoring five different measures of clinical improvement was presented, including how invisible the lesion was, its degree of infiltration and of hypopigmentation, its size and the depth of hypo- or anaesthesia remaining. Only 4 'ROM' and 5 WHO regimen patients showed no improvement. However, two parameters) and the total score (from adding together the scores of all five parameters/showed a mild but statistically significant greater improvement among the WHO MDT patients compared to the ROM patients; three parameters showed no significant difference between the two regimens. In total, 9 patients suffered from mild reversal reactions and 12 (9 WHO and 3 ROM) developed drug reactions. It was hoped that all 1,484 patients could be analysed in time for the 7th Expert Committee on Leprosy, meeting in Geneva at the very end of June.

If the full analysis confirms the preliminary findings, then a single day's treatment of triple drug therapy will have been shown to yield a good clinical response in single lesion paucibacillary leprosy, although slightly inferior to standard PBL MDT. (What the trial has not attempted, is to assess whether there is any significant difference in the long-term relapse rates between the two regimens; it is to be

hoped that some of the collaborating centres will continue such long-term follow-up of the trial patients, to obtain data on this most important parameter—Reviewer's Comment).

The second day was spent in reviewing two other WHO drug trials, and a study of MB patient defaulters.

The Ofloxacillin Trial protocol was written in 1988, and intake of patients commenced in 1992, with 15 centres collaborating from three continents.

In MB leprosy, untreated patients with a bacterial index of 2+ or greater were eligible for admission, by random distribution, to one of four regimens, either WHO MBL MDT for 2 years (the control regimen), WHO MBL MDT for 1 year, WHO MBL MDT for 1 year plus ofloxacillin 400 mg daily for the first 28 days, or rifampicin 600 mg plus ofloxacillin 400 mg both drugs daily for 28 days (the three trial regimens. Intake was completed (of 1651 MB patients) by June, 1994; therefore all trial patients have completed their course of chemotherapy, and are now under long-term follow-up to assess relapse rates between the four regimens.

In PBL, a total of 1815 patients had been admitted, allocated by random distribution to either WHO PBL MDT (the control regimen) or to a trial regimen of rifampicin 600 mg and ofloxacillin 400 mg daily for 28 days. Long-term follow-up to assess relapse rates is likewise underway.

In both the MBL and PPL trials, the regimens are also being assessed for incidence of drug toxicity and of reactions, and their general acceptability.

The more recent trial, a second ''ROM'' study, has commenced in three field programmes. The trial, which is uncontrolled, consists of monthly doses of rifampicin, ofloxacillin and minocycline. In MBL, half the intake will receive 24 doses, and half 12 doses. In PBL, half will receive six doses, and half three doses. Every drug administration will be supervised, with patient contact every 4 weeks or month. Long-team follow-up is planned. To date, the ROM regimen has been well accepted and is technologically very simple.

Finally, three studies were presented of the subsequent fate of patients who had absconded from WHO MBL MDT before completing 24 doses. Defaulters could be difficult to trace because of incorrect or wrong addresses. Most of those traced showed a continuing fall in their BIs, and many had become smear negative, confirming how 'robust' standard MBL MDT. It is, of course, possible is (as one presenter suggested), that patients who had run into trouble had already reported back, but the general impression was of continuing improvement. Further studies, especially long-term studies over 5–10 years would be of interest.

WHO should be thanked for organizing such a stimulating and informative meeting.

4th International Leprosy Meeting, Istanbul, Turkey held 28–30 April 1997

This international meeting was organized by Professor Türkan Saylan and colleagues from the Istanbul Leprosy Hospital and the Turkish Association for Leprosy Relief Work. Its main topic was ''Where are we in the struggle of leprosy while approaching to 2.000?'' Thus the purpose was to consider lessons learned from the past 20 years of leprosy work in Turkey and their implications for the years ahead.

Participants included leprosy experts from various parts of Turkey and colleagues from overseas, the chief of whom was Dr. S. K. Noordeen, Director of the W.H.O. Programme for the Elimination of leprosy. Other contributors came from Denmark, Ethiopia, India, the Netherlands, the United Kingdom and the United States of America. All had earlier been involved as facilitators in the Turkey programme. The meeting was formally opened by speeches from the Rectors of Istanbul's two main Universities followed by the reading in absentia of an address submitted by Dr. Paul W. Brand that emphasised the need to preserve with leprosy work until all problems were seen to have been resolved. Mrs. Rina Perolini–Bohner represented Emmaus Suisse and spoke of their support of the work in Turkey over many years.

In his first address to the meeting Dr. S. K. Noordeen described the benefits of setting the year 2,000

as a target for leprosy elimination as a public health problem, stressed the success of MDT in drastically reducing the disease endemicity and spoke of remaining challenges: those of reaching patients not yet having access to MDT and of improving rehabilitation of the disabled. He referred to the awakening of a scientific outlook towards medical aspects of leprosy over the past 150 years its emphasis being more towards studying the descriptive aspects of leprosy, including the various clinical manifestations, and less towards findings ways to effectively deal with the disease situation in the individual and the community.

Meeting sessions focused on the history and development of leprosy programmes in Turkey and elsewhere, on state of the art treatment of leprosy, on current drug trials, on action to counter eye and nerve impairment and on the contribution of reconstructive surgery. The final day was spent in a visit to the Istanbul Leprosy Hospital, with further presentations regarding leprosy work in Turkey and the training programme offered by ALERT, Ethiopia. At a closing forum, participants summarised their conclusions as follows:

1 It is clear that Turkey has made phenomenal progress in reducing leprosy dramatically during the past 10 to 15 years, both in regard to the incidence and prevalence burdens and in regard to new case occurrence. It is vital that the pressure to identify and treat the remaining cases is maintained. An objective is to identify and treat new cases before they develop nerve function impairment. Hence the importance of community understanding that cure is possible and recognition of the early signs of leprosy.
2 WHO-recommended MDT remains the centrepiece of leprosy chemotherapy. However there is considerable promise of improved drug regimens for the future involving newer drugs such as Ofloxacin, Minocycline and Clarithromycin.
3 It is important that persons affected by leprosy (PALs) and their family members have opportunity to learn how they can help themselves and one another and are encouraged in self-reliance where ever feasible. Initiatives of IDEA (International Association for Integration, Dignity and Economic Advancement) provide welcome examples of mutual support activities.
4 Staff activities both to prevent impairment and handicap, and to rehabilitate those already handicapped, involve teamwork so that social, psychological and functional problems are countered. Social help needs to be offered together with action to prevent disability. Turkey is to be congratulated on the effective teamwork that has already been established between social workers, psychologist, ophthalmologists, surgeons, physiotherapist, nurses, shoemakers and dentists. Many experts contribute their services on a voluntary basis.
5 The importance of eye care is emphasised. Ophthalmologists are few and where there is no nearby support to overcome developing eye problems, blindness may result. This is potentially catastrophic where accompanied by hand or foot sensory loss. Hence the urgent need for the training of general health workers in eye care. It is proposed that specialist eye care training be given to nurses so that they can become a local resource.
6 One aim of rehabilitation is that PALs become economically self-supporting. A further aim is that family members of disabled or elderly PALs can be helped to acquire a profession by which they will be able to give needed financial and social support to disabled or elderly PALs.
7 The tasks of elimination of leprosy and support for the leprosy-affected will not be complete until no new cases emerge and existing PALs receive needed support throughout their lifetime. These needs call for involvement of young people in the struggle and for support and treatment to be available in integrated settings. Each country where leprosy is endemic needs to set its own objectives and to tailor these to its own situation taking into account the local, social conditions and the levels of impairment of those affected.
8 It is at most importance for the leprosy workers and their programs to be supported by the donor NGO's specially ILEP group as the work of leprosy due to the PALs continuous.
9 In conclusion, Dr. Noordeen stated that the phenomenal progress made so far should not lead to any complacency as this is the time to redouble our efforts to reach the year 2000 target and further ensure that progress made is sustained beyond the year 2,000 so that we can look forward to a totally leprosy-free world some time during the early part of the next century. In congratulating Professor Saylan and

Turkish leprosy workers on their achievements he said. ''This is the kind of story that I want to see in every country''.

Source: Professor Turkan Saylan, Cüzzamla Savaş Derneği Istanbul Lepra Hastanesi, Bakirköy, 34747 Istanbul.

Turkey has a total of 2,953 registered of which 2,596 are under the care and supervision of the Instanbul Leprosy Centre. Only 81 patients remain on multiple drug therapy, 1,624 having already completed treatment. In 1996, only 20 new cases were registered for the whole country. It is considered that the leprosy endemic is declining to very low levels and the main problems which now call for attention centre on the large number of patients with grade 2 disability, many of whom are aged 65 or more. The programme is supported by Aide aux Lépreux Emmaüs-Suisse (ALES) and the Novartis Foundation for Sustainable Development (previously Ciba-Geigy Leprosy Fund). A. C. McDougall.

Compliance becomes concordance

The following is extracted from the *British Medical Journal*, **314,** 691:

At long last the ''compliance problem'' may be getting a new name and, with it, a new view of the patient's role in the doctor-patient relationship. A report published this week by the Royal Pharmaceutical Society of Great Britain's working party on medicine taking recommends that ''concordance'' should replace the term ''compliance.''[1] Although substitute terms have been suggested and used previously without much impact, this eloquent analysis of the importance of a new concept by a highly visible and distinguished panel may hold the promise of change. Moreover, the panel recommends a £1·8 m ($2·7 m) research budget to support analysis of the problem and training of health professionals.

Compliance has long been criticised as denoting obedience—''following doctors' orders.'' Although many researchers and practitioners have carefully avoided the term,[2] the common alternatives—''adherence'' or ''cooperation''—do not take the user very far from compliance. One member of the working party, David Sackett, in his 1976 landmark publication, *Compliance with Therapeutic Regimens*, had already anticipated the approach advocated by the Pharmaceutical Society's report.[3] Included in the book were sensible ideas such as the ''tailored consensual regimen,'' the need for a no fault approach to behaviour relating to following a regimen,[4] and consideration of the effect of frequency of administration, side effects, delivery system, and the like—all aspects of the medication that affect compliance.[5] A subsequent publication raised the idea of a clinically relevant definition of adherence, based on the properties of a particular drug and not solely on the doctor's instructions.[6] Thus if seven days are sufficient to achieve the therapeutic effect of a drug then patients who stop the medication after ''only'' seven, eight, or nine days should not be deemed to be non-compliant even if it was prescribed for 10 days.

Despite the predominance of the term compliance, interventions have not all been aimed at the patient. Manufacturers, for example, have responded with less complex delivery mechanisms such as patches, more convenient doses such as sustained release drugs, incentives for patients to fill their first prescription and to get refills, advertising to increase the perceived value of the drug, and direct patient education. In part these developments indicate that the manufacturers understand clearly the effects of non-compliance on drug sales. But they also suggest that clinicians value drugs with features that enhance compliance.

Changes in drug trials reflect recognition of the effect of compliance on statistical power and interpretation of results.[7,8] After initial resistance to including compliance experts, some investigators began to include them when planning the trial rather than attempting to fix problems later.[9] Another approach has been pre-randomisation screening of potential participants, usually with a placebo. This approach assumes that non-compliance is a general characteristic of the person: thus a pretrial test of drug taking can reveal non-compliers.

The change in terminology will have an impact only if the culture change that the working group is advocating succeeds and clinicians take a more egalitarian view "of the relationship between prescribing and medicine-taking, between patient and prescriber."[10] It is possible to envisage doctors and patients engaging in more productive discussion of medication regimens, but the barriers are substantial. A prescription is a traditional means of ending a consultation, after most of the time has been spent on diagnosis. Perfunctory questioning about the drug at the next visit may lead patients to assume that the doctor does not place high priority on drug taking. Clinicians may simply assume the patient's compliance and see any continuing symptoms as indicating the need for more or a different medication.

More time spent should be spent assessing not only the best medication for a particular condition but also the best for a particular individual with a certain lifestyle and preferences. The concept of concordance suggests frank exchange of information, negotiation, and a spirit of cooperation. Compared with the US, conditions in Britain favour this approach. Patients and practitioners are more likely to have known one another for longer, dispensing is less impersonal, and ancillary personnel are available for follow up.

Moreover, evidence of effectiveness is available from rigorous trials, and no single method of improving compliance appears to be inherently superior.[11] With coaching and a non-judgmental attitude from the prescriber, patients are more likely to describe drug taking truthfully. Patients can be informed about dosing options and asked what would work best for them. Initial prescriptions can be regarded as a trial, not only of the drug's effect but also of the feasibility of taking it. Treating the patient as a decision maker is a fundamental step away from the compliance model.

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'Basic' elimination of leprosy in China

A remarkable contribution by He Da-xun and Ye Gan-yun, respectively Vice-president and President of the China, Leprosy Association, in the latest edition of *Indian Journal of Leprosy*, Volume **68**(4),

Oct-Dec 1996, describes the intention of the Ministry of Public Health to achieve 'basic elimination of leprosy' by the year 2000, with a reduction of prevalence to, or below 0·01‰ (< 1 case per 100,000 of the population). This is of course a higher target than that of WHO for elimination at less than 1 case per 10,000 of the population. The authors outline the variable prevalence situation in different parts of China which indicate that ''... it would be more reliable to calculate and evaluate the criteria for basic elimination of leprosy on a county basis.'' Up to now, Shanghai and three provinces have been approved by the Ministry of Public Health as having already met the criteria for ''basic'' elimination. The article concludes with emphasis on the attention which is being given to improving the quality of MDT implementation, epidemiological surveillance, overcoming irrational fear and discrimination and actively extending the rehabilitation programme - ''... so as to strike a blow for eradication of the disease from China biologically, psychologically and socially.''

Further enquiries; Professor Ye Gan-yun, Chinese Academy of Medical Sciences and Peking Union Medical College, 12 Jiangwangmiao Road, Nanjin-210 042, People's Republic of China.

15th International Leprosy Congress, Beijing, China, 7–12 September 1998

MESSAGE FROM THE ILA PRESIDENT

The first International Leprosy Congress held in Berlin in 1897 opened in the era of modern leprosy control. The first century of that period is now closing, with gratifying reduction in the global leprosy burden. However, there is much more to be done. We must keep leprosy, as an infectious disease, firmly under control. More significantly, we must strengthen and improve measures to deal with leprosy as a disability producing disease. These are tasks we must still face in the second century of our modern fight against leprosy.

The 15th and ''Centennial'' Congress is being organized under the main theme of ''Working toward a World without Leprosy.'' The members of our association have been the main force behind the great achievements so far, and no doubt will remain so in the new century. The last few congresses have become much more than a meeting of our members, non-member participants outnumbering members two or even three to one. These are mostly field workers, both medical and nonmedical, of the leprosy-endemic countries. Their share of responsibilities are bound to increase. The 15th International Leprosy Congress intends to meet their interests and needs as much as those of our own members.

I extend my cordial invitation to all those interested and concerned in solving leprosy problems. Let us make the Beijing Congress an opportunity to renew our commitment to eradicate leprosy during the next century.

Yo Yuasa
President

CONGRESS ISSUES

Presentations and discussions at the Congress will be organized around three groups of issues related to the theme of the Congress ''Working toward a World without Leprosy.'' They are, the control of the disease, including the progress toward elimination of leprosy as a public health problem and sustainability of the control service after that, social aspects and rehabilitation, and causative organism and host response. Each group of issues will be dealt with by keynote addresses, panel discussions, workshops and consensus forming sessions, in addition to oral and poster presentations of individual papers in concurrent sessions. Maximum opportunities will be given to the Congress participants to interact at various plenary sessions.

[There will be no pre-Congress workshops.]

POSTER SESSIONS

Special attention will be given to poster presentations in order to maximize the personal discussions and explanations of participants' research and work. The Organizing Committee will provide a well-planned schedule of poster presentations during the Congress in connection with Congress themes.

TEACHING & TRAINING SESSIONS

Teaching sessions will be held on Tuesday, Wednesday and Thursday evenings at the Convention Center.

EXHIBITS

Exhibitions will be arranged for organizations or institutions wishing to display teaching and learning material, including books, video tapes and compact discs, footwear, medical supplies and equipment and other items of interest to participants. If you plan to exhibit please request information on the enclosed form.

Congress Organizing Committee:

Dr Yo Yuasa, Dr Pieter Feenstra, Dr W. Felton Ross, Dr Robert C Hastings, Dr Wayne Meyers, Dr Michel Lechat, Dr J.-P. Shenkelaars, and Dr S. K. Noordeen.

Chinese Organizing Committee:

Prof. Chen Min Zhang, Prof. Yin Da Kui, Prof. Dai Zhi Cheng, Prof. Li Shi Chuo, Prof. Zhao Tong Bin, Prof. Ye Gan Yun, Ms Sufet Ma Haide, and Ms Lu Man Hua

Dates: 7–12 September 1998

Location: Beijing International Convention Center and Beijing, People's Republic of China

Congress Language: English

Posters/Exhibition Space: Posters illustrating participants' work and research will be on exhibit throughout the Congress. In addition, paid exhibit space can be reserved for product or organization displays. For exhibit space costs and information, write separately to the Secretary for Administration

Free Communications:
A book of abstracts will be part of each registration packet

Social Events/Tours: A reception and dinner will be held for conference participants

Registration/Fees/Scientific Abstracts: in order to receive information regarding fees and registration, and for information about submitting abstracts write to: Secretariat; 15th International Leprosy Congress, c/o Sasakawa Memorial Health Foundation, 3-12-12 Mita, Minato-ku, Tokyo 108, JAPAN.

***Leprosy Review* poster: Taking slit-skin smears**
The poster included with this issue of the Journal is 'Taking slit-skin smears'. The next poster will be 'Staining slit-skin smears'. We hope that these two combined will help the quality of slit-skin smears taken.

Poster notice and questionnaire: See Editors Choice, p. 194

Instructions to Authors

Papers submitted for publication in *Leprosy Review* should be sent to the Editor, Dr 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 clearly indicated below the title of the paper. Degrees and diplomas are not to be included.

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

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

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