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Leprosy Review

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

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

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Editorial

MOLECULAR BIOLOGY OF THE MYCOBACTERIA

The molecular biology of the mycobacteria is poised at the threshold of making major contributions to the understanding of the biochemistry and pathogenic mechanisms involved in mycobacterial infections. The application of molecular biology to the study of mycobacteria has recently begun, with preliminary studies on the nucleic acids of mycobacteria, cloning and expression of a number of mycobacterial genes and the development of mycobacteria themselves as gene cloning systems. In this review, we will discuss the progress that has been made so far and the likely direction of future work.

The nucleic acids of mycobacteria

Both DNA and RNA have been isolated from mycobacteria, including armadillo-grown *Mycobacterium leprae*. They belong to the high guanine plus cytosine (G+C) Gram-positive group of bacteria; the cultivable mycobacteria have G+C in the range 60–67%, while *M. leprae's* G+C content is somewhat lower, at 56%.[1] The genome size for *M. tuberculosis* is similar to that for *Escherichia coli* ($2{\cdot}5 \times 10^9$ M_r), while that for *M. leprae* is smaller ($1{\cdot}3$–$2{\cdot}2 \times 10^9$ M_r).[2]

Plasmids and phages have been isolated from cultivable mycobacteria, but not, probably for technical reasons, from *M. leprae*. There is a sugestion that plasmids isolated from members of the *M. avium, M. intracellulare* and *M. scrofulaceum* (MAIS) complex may be associated with antibiotic resistance[3] and virulence.[4] A plasmid carrying a gene associated with mercury resistance has been reported.[5] One plasmid (pAL5000) from *M. fortuitum* has been sequenced and is being developed as a vector for cloning DNA into mycobacteria (see below). Both lytic and temperate bacteriophages have been isolated from mycobacteria[6] and these are also being developed as cloning vectors.

In growing cells, more than 90% of extractable RNA is ribosomal RNA (rRNA) which is present in many thousands of copies.[7] The genes coding for rRNA are present in several copies in most eubacteria; thus *E. coli* has seven rRNA genes,[8] *Bacillus subtilis* has 10^9 and *Streptomyces lividans* has 6.[10] By contrast, slow-growing mycobacteria (*M. tuberculosis* and *M. lepraemurium*) have one such rRNA gene while rapid growers (*M. smegmatis* and *M. phlei*) have two.[11,12] Bacteria contain 3 species of ribosomal RNA (5S, 16S, and 23S). Sequence analysis of the 16S molecule has allowed preliminary taxonomic analysis which shows that *M. leprae* is clearly a mycobacterium and that mycobacteria conform to the Gram-positive pattern.[13,14]

Cloning of mycobacterial genes and expression of the gene products

One of the most powerful tools available to molecular biologists is the ability to take DNA from one type of cell and transfer it to another cell in which it can be replicated in limitless amounts, as part of

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the host cell's own replication machinery. This construction of DNA 'libraries' is particularly important with difficult-to-grow organisms such as mycobacteria. Libraries of mycobacterial DNA have now been constructed in *E. coli* by a number of groups.[1,15–18] Ideally, libraries will be constructed such that the host cells, e.g. *E. coli*, contain segments of mycobacterial DNA, and that the entire mycobacterial genome is represented. Single *E. coli* cells which contain a particular mycobacterial gene of interest can then be grown up ('cloned') in large amounts, and the nucleic acid of that gene studied in detail or the corresponding gene product expressed.

Preliminary experiments indicated that mycobacterial promoters (sequences of DNA which are responsible for controlling the expression of genes) do not function very efficiently in *E. coli*.[1,19,20] Thus while the genes can be cloned they are not expressed (they do not produce the corresponding protein product). One way of overcoming this problem is to place the mycobacterial gene under the control of a foreign promoter which is known to work efficiently in *E. coli*. Such an approach has been successfully used to express the *M. leprae* gene which codes for citrate synthetase;[21] here the mycobacterial gene is expressed in *E. coli* under the control of a streptococcal promoter!

In what now has become a classic experiment, Young *et al.*[17] used a somewhat different approach. They took small fragments of mycobacterial DNA (*M. leprae* and *M. tuberculosis*) and inserted them into the middle of an *E. coli* gene (that encoding for the enzyme β-galactosidase). When this *E. coli* gene is switched on a hybrid (or fusion) protein is formed, consisting partly of a mycobacterial protein and partly of the *E. coli* protein. The 'vector' which is used to transfer the DNA into *E. coli* is a bacteriophage called λgt11. The λgt11 expression system does not usually allow for the high level production of the foreign protein, but once the gene has been identified and cloned in this way, other techniques can then be used to engineer *E. coli* (or other organisms) to produce large amounts of mycobacterial protein.

Expression of recombinant mycobacterial antigens and 'the heat-shock protein story'

Studies with monoclonal antibodies which are specific for mycobacterial proteins had identified a limited number of proteins (five in *M. leprae*) which were apparently 'immunodominant'. With the construction of libraries of mycobacterial DNA it then became possible to use these monoclonal antibodies to try to detect expression of the corresponding proteins in *E. coli*. Using the λgt11 approach described above, Young *et al*[17] were able to detect expression of the five *M. leprae* proteins which had been identified using monoclonal antibodies (in most, but not all cases, the *M. leprae* proteins were expressed, as fusions with β-galactosidase). To our knowledge the genes encoding three of these proteins, those with molecular weights of 65kDa,[22] 18kDa[23] and 28kDa[24] have been sequenced and the corresponding amino acid sequences of the proteins deduced. Recombinant mycobacterial proteins are becoming available in relatively large quantities,[25,26] and their immunological characteristics studied in detail. It now seems likely that the small number of proteins which have been concentrated upon does not adequately represent the immunogenicity of *M. leprae*; all of the original monoclonal antibodies were produced by immunizing one particular inbred strain of mouse. From work with *M. tuberculosis*[27] it appears that different mouse strains 'see' proteins other than the five originally described. For this reason a number of groups are attempting to identify important antigens using T cells rather than antibodies.[28,29]

One interesting aspect of the work in which immunodominant antigens have been studied using a molecular approach is that several of the mycobacterial antigens appear to be related to 'heat-shock' proteins found in other cells.[30] Heat-shock proteins are proteins whose production is increased when the cells are subjected to a sudden increase in temperature (or other forms of stress). It is thought that this response is a means by which cells protect themselves against stressful changes in environment. It has also become clear that stress proteins have been identified as being important in the immune response to other infectious agents,[31,32] and this has led to the suggestion that the process of infection stresses the infectious agents and leads to the overproduction of these proteins; hence their immunodominance.

One important outcome of the heat-shock protein story is that antibodies and T cells which recognize mycobacterial antigens (particularly the 65kDa protein, which is a major heat-shock protein) have been found in patients with apparently autoimmune phenomena. For example, T cells reactive to mycobacterial 65kDa protein are present in the synovial fluid of patients with active rheumatoid arthritis,[33,34] and antibodies to this protein are readily detected in such patients. One possible explanation for this is that there is a high degree of sequence conservation between stress proteins from different species, i.e. humans possess, for example, a protein equivalent to the mycobacterial 65kDa protein and which is very similar in terms of its amino acid sequence. Thus, if immune responses are directed towards parts of the protein which are similar in man and bacteria it could lead to an autoimmune response.

Molecular genetics of mycobacteria

Although the most obvious application of molecular biology is the production of recombinant proteins, perhaps the most exciting future applications will lie in the ability to manipulate genes in the mycobacteria themselves. Being able to delete, transfer or add genes to mycobacteria will enable a whole new approach to studies of virulence, pathogenicity, protective immunity and chemotherapy to be developed.

In order for such studies to become feasible it will be necessary to develop efficient methods for getting DNA into mycobacteria and for introducing genes into the mycobacterial chromosome. Jacobs *et al*[35] developed a vector for introducing DNA into mycobacteria by constructing a hybrid of an *E. coli* plasmid and a mycobacterial phage; this 'phasmid' was capable of growing as a phage in mycobacteria and as a plasmid in *E. coli*. The problem with this approach was that the phage lysed its mycobacterial host, whereas ideally one would wish to have the introduced DNA expressed in growing bacteria. This is being overcome by the use of lysogenic mycobacteriophages (phages which do not normally lyse their host, but whose DNA becomes stably integrated into the host chromosome).[36] An alternative approach has been to construct a hybrid plasmid from an *E. coli* plasmid and pAL 5000;[36] this hybrid can be introduced into mycobacteria by electroporation, and is reproduced. It is likely that other methods for stably introducing genes into mycobacteria, and for deleting specific genes will be developed in the near future.

Future applications of molecular biology in the study of the mycobacteria

The analysis of mycobacterial antigens at the molecular level has begun, but there is still much to be done. In addition, only two of the *M. leprae* recombinant proteins have been produced in sufficient quantities to carry out detailed studies on their immunogenicity. As more of these materials become available it will become possible to study their role in protective immunity. In addition, synthetic peptides based on known protein sequences could be developed as immunodiagnostic or immunoepidemiological tools. Enzymes which are potential targets for drugs could be produced by cloning and expressing the corresponding genes, thus enabling *in vitro* screens to be developed. The ability to transfer such genes to other mycobacteria will enable the effect of the permeability barrier posed by the mycobacterial cell wall to be investigated.

New methods for detecting small sequences of nucleic acids might enable us to detect the presence of *M. leprae* in tissue with a much greater degree of sensitivity than is currently possible. For example, a technique called the 'polymerase chain reaction' (PCR) involves the amplification of a single stretch of nucleic acid sequence to several thousand copies, which can then be readily detected; thus, in theory, it should be possible to detect the presence of a single bacillus. Information about nucleic acid sequences will enable much more rapid methods for species identification; for example the identification of species specific rRNA sequences has been used to rapidly differentiate

between *M. tuberculosis* and *M. avium intracellulare*.[37] Perhaps by using the PCR technique to amplify *M. leprae* specific rRNA sequences, it might be possible to detect strain differences between different isolates of *M. leprae*.

The use of molecular genetic techniques has been of great importance in understanding the basic mechanisms of pathogenicity with a number of bacterial pathogens. For example, the mechanisms of entry of *Yersinia pestis* into host cells has been defined at the protein level,[38] and genes which are responsible for virulence in a number of bacteria have been found to be closely associated. The ability to transfer genes between mycobacteria and to add or delete specific mycobacterial genes is likely to be of great importance in understanding the basic mechanisms by which mycobacteria invade and survive within their host cells.

Acknowledgment

We acknowledge the contribution of many of our colleagues, particularly the members of the Molecular Biology Subcommittee of IMMLEP and THELEP, who have discussed these issues with us on many occasions.

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Testicular dysfunction in leprosy: relationships of FSH, LH and testosterone to disease classification, activity and duration

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Summary Luteinizing hormone (LH), follicle-stimulating hormone (FSH) and testosterone levels were determined by radioimmunoassay (RIA) in leprosy patients and analysed for effect of disease classification, disease activity and duration of disease. LH and FSH levels were found to be significantly elevated in lepromatous patients compared to borderline–lepromatous, midborderline and borderline–tuberculoid patients. A positive correlation was seen between LH and FSH and a negative correlation was seen between testosterone and both LH and FSH. No correlation was seen between hormone levels and measures of disease activity: bacillary index and IgM to phenolic glycolipid I, a *Mycobacterium leprae* antigen. A significant correlation was seen between duration of disease and FSH when age was taken into account, indicating that testicular dysfunction is probably cumulative and irreversible. It is recommended that LL patients be routinely screened for hypogonadism using FSH, LH and testosterone levels.

Introduction

The testes are known to be a favoured site for focal damage in patients with leprosy. This is probably because bacillary growth is favoured at the lower temperature in the scrotum since *Mycobacterium leprae* grow optimally at about 30°C.[1] In spite of this, there are few studies of testicular disease in men with proven leprosy. We, therefore, thought it pertinent to examine men for evidence of testicular failure who are under treatment for leprosy. In the current study, 93 men classified according to the Ridley–Jopling system[2] were evaluated for FSH, LH, and testosterone levels, and the findings were correlated with bacillary index (BI) and IgM antibody to the phenolic glycolipid I (PGL-I), an *M. leprae* specific antigen. The results, indicating that hypogonadism is a primary manifestation of lepromatous leprosy are the subject of this report.

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Materials and methods

PATIENTS

Ninety-three male leprosy patients receiving treatment at the New York City Regional Hansen's Disease Program were clinically and histologically classified by the Ridley–Jopling scale[2] as follows: LL, lepromatous leprosy ($n=55$); BL, borderline lepromatous ($n=9$); BB, midborderline ($n=7$); BT borderline–tuberculoid leprosy ($n=22$). The BI, an estimation of the total bacillary load in leprosy patients, was measured on a semiquantitative scale (0 to 6+)[3] approximating that of Ridley.[4] Histology and BI were determined from skin punch biopsies at the Gillis W Long Hansen's Disease Center, Carville, LA. Serum samples were collected from leprosy patients and stored in aliquots at −70°C for antibody testing.

ELISA FOR SERUM ANTIBODIES TO PGL-1

IgM antibodies to the phenolic glycolipid I (PGL-I) antigen of *M. leprae* were detected by enzyme-linked immunosorbent assay as previously described.[5,6] PGL-I was incorporated into liposomes with sphingomyelin, cholesterol, and dicetyl phosphate. Control liposomes were made without PGL-I.

RADIOIMMUNOASSAY (RIA) FOR SERUM HORMONE LEVELS

Determination of serum LH and FSH level was done by RIA with commercially available kits (Corning Medical; Medfield, MA). The RIA for LH had a detection limit of 0·9 mIU/ml. The RIA for FSH had a detection limit of 1 mIU/ml. RIA for testosterone was performed with a kit from Diagnostic Products Corp., Los Angeles, Ca. RIA for testosterone had a detection limit of 0·11 ng/dl. Cross-reactivity of testosterone assay was less than 10% with dihydrotestosterone and much less with other androgens.

STATISTICAL ANALYSES

Statistical analyses were performed using the BMDP package. Analysis of variance was performed with patients divided into Ridley–Jopling classes and levels of significance calculated by the Bonferonni test to determine the effect of disease classification on BI, antiPGL-I IgM and hormone levels. Correlation coefficients were calculated to examine relationships between BI, antiPGL-I IGM and hormone levels. To examine the effect of duration of disease on hormone levels a subgroup of 16 recently diagnosed patients (<2 years) was analysed separately. In addition partial correlation analysis was performed on hormone levels, duration of disease, and age to determine if duration of disease had any effect on hormone levels, independent of age.

Results

TESTOSTERONE AND GONADOTROPIN LEVELS IN PATIENTS WITH LEPROSY

Nineteen of the patients examined had testosterone levels below the lower limit of normal for men (less than 300 ng/dl). In 4 out of 19, these low levels occurred without an elevation in LH or FSH. All 4 of these low testosterone normal FSH-LH patients were non-LL (2BT, 1BB, 1BL), while the remaining 15 low testosterone patients with elevated FSH and/or LH were all LL. The 4 non-LL low testosterone patients had testosterone levels that were significantly higher than the 15 LL low testosterone patients (mean testosterone ± SD: 284 ± 14 *vs* 143 ± 73, $p<0{\cdot}005$). In addition, LH and FSH levels were elevated in 31 and 32 of the total patient population, respectively. Thus, approximately one-third of the men with the diagnosis of leprosy had evidence of hypogonadism when only a single blood sample was used for hormone measurements.

Since testosterone regulates the secretion of LH, there is a clear causative relationship between a decrease in testosterone and a rise in LH. We, therefore, examined the relationship between testosterone and LH in patients with leprosy (Figure 1(a). There was a significant negative correlation between testosterone and LH ($r=0{\cdot}41$, $p<0{\cdot}001$). It was of interest to note, however,

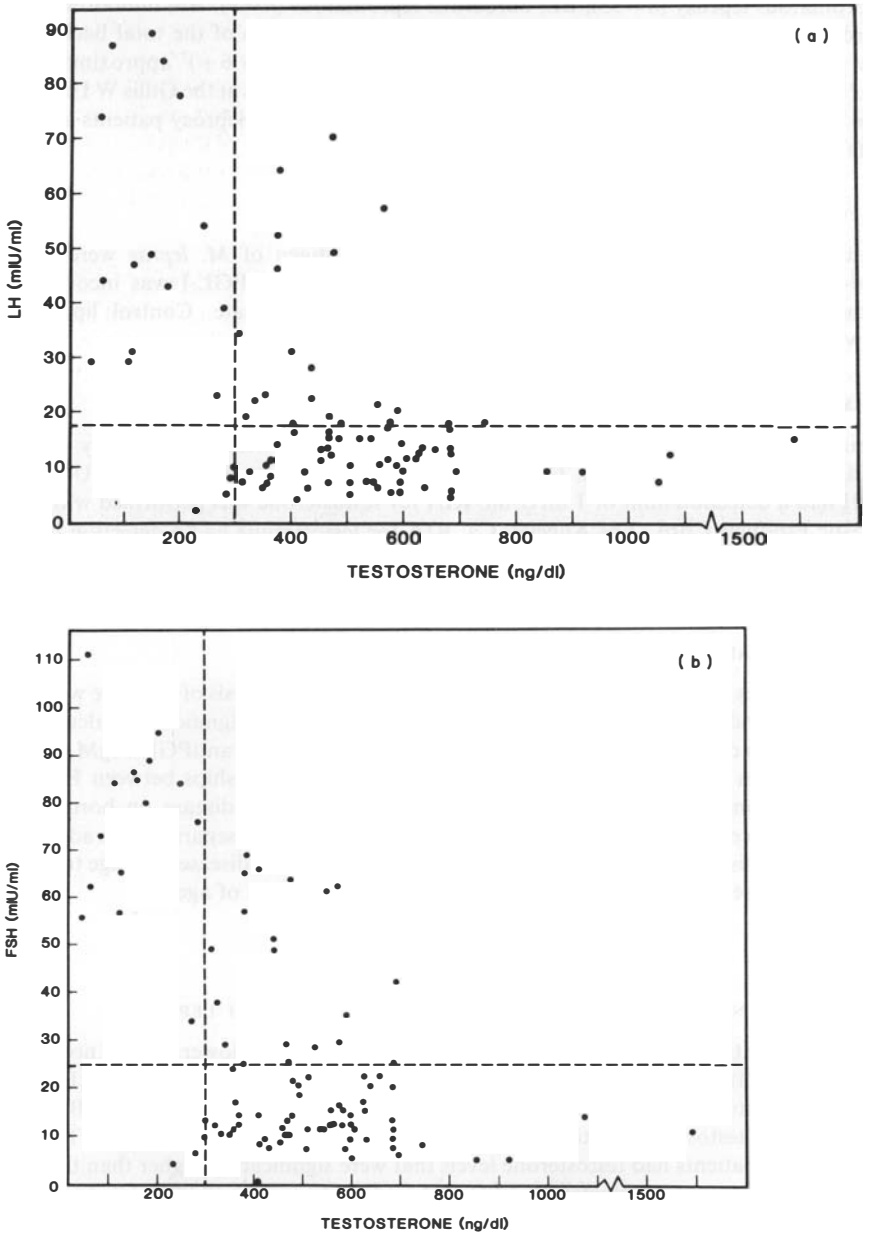

Figure 1(a). Testosterone *vs* luteinizing hormone (LH) for all leprosy patients ($r=-0{\cdot}41$, $p<0{\cdot}001$). (b) Testosterone *vs* follicle-stimulating hormone (FSH) for all leprosy patients ($r=0{\cdot}48$, $p<0{\cdot}001$).

that in 16 out of 31 individuals the elevation of LH occurred in association with a normal testosterone level suggesting that in spite of the altered Leydig cell function, testosterone secretion could still be increased in response to an elevation of LH such that testosterone secretion was maintained in a compensated state. By contrast, in 15 out of 31 individuals testosterone secretion could not be compensated by an elevated LH level.

Even though testosterone does not reciprocally regulate FSH secretion, there was also a negative correlation between this hormone and testosterone ($r = -0{\cdot}48$, $p < 0{\cdot}001$). This relationship is shown in Figure 1b. Since FSH increases as the seminiferous tubules are damaged, FSH should correlate inversely with testosterone only if damage to Leydig cells occurs concomitantly with that to tubules. As a rise in LH is the best index of abnormal Leydig cell function, the levels of this hormone were compared with those for FSH. The LH and FSH levels for the entire study population were significantly correlated ($r = 0{\cdot}82$, $p < 0{\cdot}001$) (Figure 2) and were even more strongly correlated for the newly diagnosed individuals ($r = 0{\cdot}95$, $p < 0{\cdot}001$, data not shown).

THE RELATIONSHIP BETWEEN HYPOGONADISM AND THE DISEASE STATE

LH levels are shown as a function of disease classification in Figure 3. LH and FSH levels were elevated in one-half of patients with LL (27 out of 55 for LH (Figure 3); 29 out of 55 for FSH, data not shown) and in only 10% of patients with BT, BB, and BL combined. Thus, patients with LL had significantly more hypogonadism as evidenced by elevated LH and FSH ($p < 0{\cdot}001$). Mean testosterone levels were not different between any of the four groups although there were more low values in patients with LL.

In the entire study population, both BI and anti-PGL-I IgM increased from the tuberculoid to the lepromatous pole of the disease spectrum. Patients with LL had significantly higher BI than those with BT ($p < 0{\cdot}01$) and significantly higher anti-PGL-I IgM than patients with BB and BT

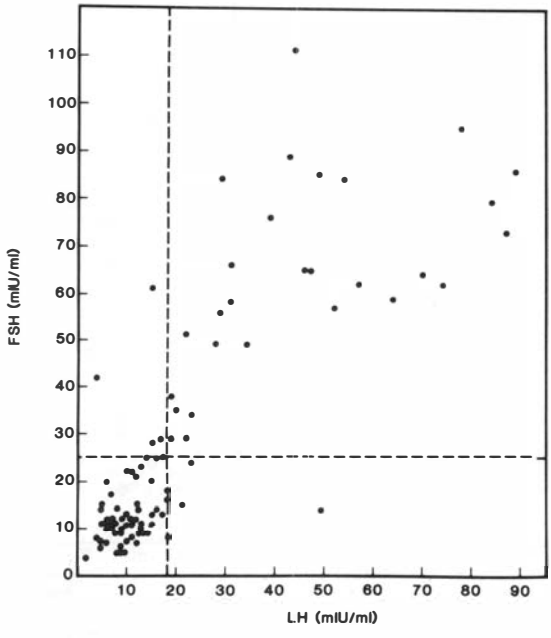

Figure 2. Luteinizing hormone (LH) *vs* follicle-stimulating hormone (FSH) for all leprosy patients ($r = 0{\cdot}82$ $p < 0{\cdot}001$).

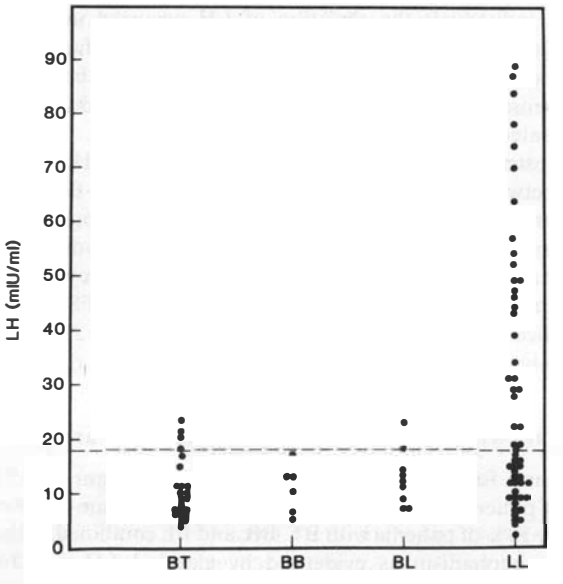

Figure 3. Luteinizing hormone (LH) by Ridley–Jopling disease classification. LL significantly higher than BL, BB, BT ($p < 0{\cdot}001$) by Bonferroni test. Dotted line is cut-off for normal range of LH (18 mIU/ml).

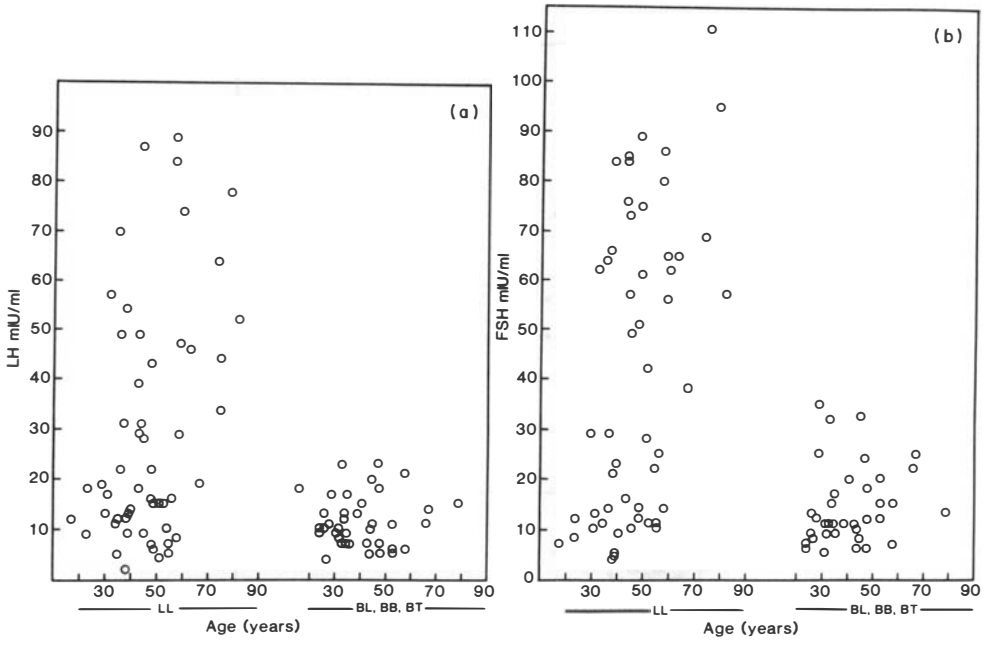

Figure 4(a). Luteinizing hormone (LH) *vs* age for LL patients and BL, BB, BT combined (for LL $r = 0{\cdot}37$, $p < 0{\cdot}01$; for BL, BB, BT $r = 0{\cdot}07$, $p > 0{\cdot}05$). (b) Follicle-stimulating hormone (FSH) *vs* age for LL patients and BL, BB, BT combined (for LL $r = 0{\cdot}46$, $p < 0{\cdot}001$; for BL, BB, BT $r = 0{\cdot}19$, $p > 0{\cdot}05$).

($p < 0{\cdot}01$ for LL *vs* BB; $p < 0{\cdot}001$ for LL BT, data not shown). As observed in previous studies,[5,6] anti-PGL-I IgM correlated with BI significantly for the entire study population ($r = 0{\cdot}50$, $p < 0{\cdot}001$) and more strongly in the case of the recently diagnosed individuals ($r = 0{\cdot}986$, $p < 0{\cdot}001$).

There was no statistically significant relationship between BI and FSH, LH, or testosterone, or between antiPGL-I IgM and any of these hormones regardless of whether all patients were analysed or just the recently diagnosed individuals.

A significant correlation was seen between age and levels of LH and FSH in LL patients but not in BL, BB and BT combined (Figure 4(a) and (b)). A statistically significant correlation was seen between duration of disease and both FSH (Figure 5) and LH ($r = 0{\cdot}30$, $p < {\cdot}05$ data not shown). However, when age was taken into account by partial correlation analysis only FSH was significantly correlated with duration of disease.

Discussion

A random survey of adult males in the New York Regional Hansen's Disease programme indicates that primary hypogonadism and testicular failure is a consequence of leprosy in a significant number of lepromatous patients. Roughly half of the lepromatous patients surveyed were affected as evidenced by elevated LH and FSH serum levels (> 18 and 25 mIU respectively) as well as reduced testosterone levels (< 300 ng/dl) in one quarter of LL patients. This is in agreement with previous studies that have shown changes in LH, FSH and/or testosterone in lepromatous males.[8–11] Half of the individuals with elevated LH had normal testosterone levels, indicating that damage to Leydig cells was not so extensive as to prevent compensation by elevated LH levels. These results

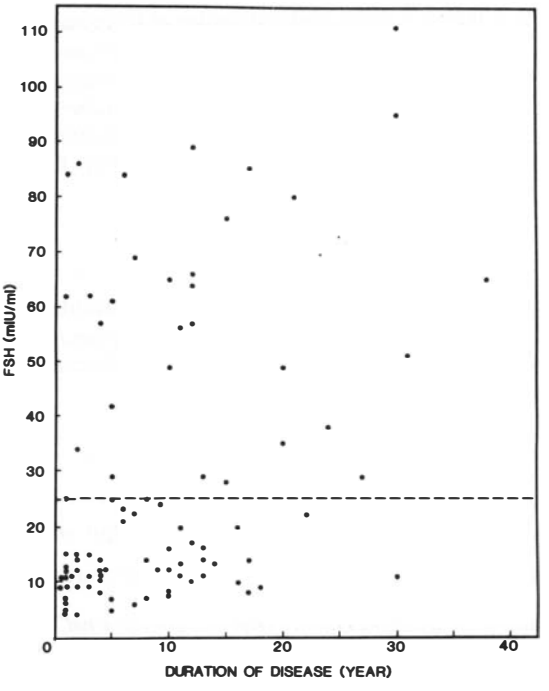

Figure 5. Follicle-stimulating hormone (FSH) *vs* duration of disease. Correlation between FSH and duration of disease; $r = 0{\cdot}37$, $p < 0{\cdot}02$, when age is taken into account by partial correlation analysis.

indicate that LL patients should be routinely screened for hypogonadism. Elevated FSH and/or LH detected hypogonadism in about half of the patients screened, while decreased testosterone was evident in only a quarter of the patients. Therefore, it is recommended that all three hormone levels be determined. Routine screening of BL and paucibacillary patients may not be cost-effective. However, should they be symptomatic, i.e. complain of impotence, they should be tested for hypogonadism. Toward this end, questions on sexual function and impotence should be a routine part of the examination.

Hypogonadal patients complaining of impotence were offered testosterone replacement therapy with 200 mg testosterone enanthate (delatestryl, Squibb, Princeton, NJ) twice monthly. Most of these patients expressed satisfaction with the replacement therapy. Further urologic and/or psychiatric evaluation was indicated in a minority of cases. Future studies on the frequency and quality of intercourse in those patients will aid in evaluating the success of replacement therapy.

The strong correlation seen between LH and FSH ($r=0{\cdot}82$, $p<0{\cdot}001$ for the entire study population; $r=0{\cdot}95$, $p<0{\cdot}001$ for the newly diagnosed group) was somewhat unexpected. Elevations in LH may be underdiagnosed to a greater extent than elevations in FSH when single samples are used as a result of the pulsatile secretion of LH.[12]

A study of disease activity parameters showed that the BI obtained in skin biopsy correlated well with the level of antiPGL-I IgM, in keeping with previous studies.[5,6] However, neither the BI nor antiPGL-I IgM showed any statistically significant relationship to FSH, LH nor testosterone in either the entire patient study group or the recently diagnosed group.

In males without leprosy FSH and LH have been reported to increase with ageing,[13] however, the correlation between duration of disease and FSH herein reported was independent of age. This is in apparent agreement with the findings of Ree *et al.*[10] and would indicate that infertility may precede hypogonadism. Many factors may contribute to testicular dysfunction, including the degree of testicular involvement and frequency and intensity of orchitis resulting from erythema nodosum leprosum (ENL), the immune-complex disorder of lepromatous leprosy. Other immune mechanisms could also play a role in both the hypogonadism and infertility of lepromatous orchopathy. Wall *et al.*[14] found increased cell-mediated immune response to testis extract in 9 of 13 LL males with evidence of testicular dysfunction compared to tuberculoid and normal subjects. This study suggests that testicular damage as a result of lepromatous leprosy is irreversible. However, longitudinal studies will be required to corroborate these findings and interpretations.

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Ocular changes in reactions in leprosy

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Summary A study of ocular changes in reactions in leprosy was undertaken to assign these changes, their proper place in the wide spectrum of ocular morbidity in leprosy. 76·1% of eyes of Type I reaction and 89·7% of eyes with Type II reaction showed some ocular involvement. Corneal hypoaesthesia, superficial punctate keratitis, a decrease of corneal film break up time (BUT), prominent corneal nerves, pigment on the endothelium of the cornea and a pigmented trabecular meshwork were the common ocular findings. The incidence of iridocyclitis in Type II reactions was low (8·1%). The significance of the ocular involvement in reactions in leprosy and the pathogenesis of iridocyclitis in Type II reactions is discussed.

Introduction

Ocular leprosy presents a formidable challenge to the leprologist as it is still responsible for some of the most distressing aspects of the disease. Around one million people of the world's leprosy population are blind.[1]

The potentially sight-threatening lesions of leprosy are iridocyclitis and its sequelae; corneal anaesthesia, exposure keratitis due to lagophthalmos, leprous keratitis, scleritis and secondary glaucoma.[2,3]

Leprosy patients may suffer from a variety of reactions, the most common being the reversal reaction (Type I) and the erythema nodosum leprosum (Type II). Reversal reactions are episodes of increased inflammatory activity in the skin lesions, peripheral nerves or both. Type II reactions are generated against intravascular and extravascular immune complexes and are characterized by acute inflammations in any organ or tissue where the *Mycobacterium leprae* are found.

Though textbooks on leprosy cover the ocular changes in reactions in leprosy,[1,4] as yet, there has been no systematic study of these changes. Some reports are anecdotal,[5,6] while others are by nonophthalmologists where the assessment of the eye may not have been adequate.[7,8]

We undertook a study of the incidence of the ocular changes in reactions in leprosy so that these changes could be assigned their proper place in the wide spectrum of ocular morbidity in leprosy.

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The study was initiated in 1986 by examining 32 consecutive leprosy patients in reaction, who had reported to the hospital for the first time and had not undergone any prior treatment for reactions.

Patients and methods

The patients in this study come from Pondicherry and its adjoining areas where the prevalence rate of leprosy is 10 or more per 1000.[9] The study was conducted by the Departments of Ophthalmology and Dermatology at JIPMER, Pondicherry, India. Thirty-two patients of leprosy in reaction were included in this study. The classification of leprosy by Ridley and Jopling was followed. Only those patients were taken up in this study, who were not on any treatment for the reactions at the time of the first examinations. The patients were evaluated by the dermatologist for the type of leprosy, its duration, the treatment taken; the type of reaction, the number and duration of reaction.

The eyes of these patients were examined in the following order: 1, ocular history; 2, visual acuity; 3, external examination of the anterior segment of the eye; 4, corneal sensations; 5, slit lamp examination; 6, corneal film break up time (BUT); 7, applanation tension; 8, gonioscopy; 9, near point of accommodation by RAF rule; 10, study of pupils; 11, fundus examination.

The methodology of Cochet and Bonnet was followed in the measurement of corneal sensations by Cochet–Bonnet Aesthesiometer.[10] Goldmann applanation tonometer and Goldmann 3 mirror lens were used for applanation tonometry and gonioscopy respectively.

The test for BUT was done on the slit lamp. The tear film was stained by fluorescein 2% and the time taken for the first dry spot to appear on the cornea after the last blink was noted.

The near point of accommodation was studied by the RAF rule, an instrument used to determine the power and near point of accommodation.

The method of Swift & Bauschard[11] was followed to study the pupillary reactions to adrenaline. The initial size of the pupil was noted by Cogan's pupillometery.[12] Two drops of 1% adrenaline were instilled in the conjunctival sac of both eyes and the pupil size was noted after 30 m. A response was considered positive if the pupil dilated by 0·3 mm or more over control values.

The control group comprised of 30 normal eyes of 15 patients of comparable age and sex, attending the outpatient Ophthalmic Department.

Results

There were 26 males and 6 females. The age variation was from 13 to 57 years (mean age 29·4 years). The duration of leprosy varied from 1 month to 6 years (mean duration 2·5 years). There were 25 patients of lepromatous leprosy and 7 patients of borderline–tuberculoid leprosy. There were 7 patients with Type I reaction and 25 patients with Type II reaction.

Sixty-two eyes of 32 patients were examined. Two eyes were excluded from the study as one had an adherent leucoma and the other had gone into pthisis due to trauma. Thirteen eyes (20·9%) were seen in patients having Type I reaction and 49 eyes (79·1%) were examined in patients of Type II reactions. Ocular involvement was seen in 10 eyes (76·9%) of Type I reaction and 44 eyes (89·7%) of Type II reaction (Table 1).

Visual acuity was decreased in only one eye with Type II reaction due to acute iridocyclitis. Erythematous plaques on the upper or lower lids were seen in 4 eyes (30·7%) of Type I reaction and in only 2 eyes (4·1%) of Type II reaction. Mild lagophthalmos was seen in 2 eyes with Type II reaction.

The cornea showed prominent corneal nerves and pigment on the corneal endothelium in both types of reaction. A peculiar pigment migration on the lower half of the corneal epithelium was seen in 6 eyes (12·2%) of Type II reaction. Superficial punctate keratitis was seen in 67·3% of eyes in Type II reaction. The corneal sensations as measured by Cochet–Bonnet aesthesiometer revealed a slight

Table 1. Summary of ocular changes

Ocular findings	No. of eyes (%) Type I	Type II
Ocular involvement	10 (76·9)	44 (89·7)
Decrease of visual acuity	—	1 (2·1)
Lids:		
Madrosis	—	16 (32·6)
Raised erythematous patch	4 (30·7)	2 (4·1)
Lagophthalmos	—	2 (4·1)
Cornea:		
Hypoaesthesia	5 (38·4)	34 (69·4)
Prominent corneal nerves	8 (61·5)	14 (28·5)
Superficial punctate keratitis	5 (38·4)	33 (67·3)
Keratic precipitates (KPS)	—	4 (8·1)
Pigmented on endothelium	4 (30·7)	26 (53·1)
Pigmented on epithelium	—	6 (12·2)
Anterior chamber		
Flare	—	3 (6·1)
Cells	—	10 (20·4)
Iris		
Acute iridocyclitis	—	1 (2·0)
Subacute iridocyclitis	—	3 (6·1)
Chronic iridocyclitis	—	1 (2·0)
Iris pearl	—	1 (2·0)
Gonioscopy		
Open angle	13 (100)	47 (96)
Narrow angle	—	2 (4·1)
Pigmented trabecular meshwork	8 (61·5)	32 (65·3)
Applanation tension		
Less than 12 mm	9 (69·3)	39 (79·5)
Pupillary reaction 1% adrenalin (+ve)	4 (30·7)	16 (32·6)

to marked decrease in 34 eyes (69·8%) of Type II reactions (Table 2). An abnormal BUT was seen in all eyes with 34 eyes (69·8%) of Type II reaction showing a BUT of 0–5 s (Table 3).

Acute iridocylitis was seen in only one eye (2%). Three eyes (6·1%) showed a subacute iridocyclitis while one eye showed evidence of old healed iridocyclitis. This was seen in Type II reactions only.

An applanation tension of less than 12 mm of mercury was exhibited in 79·5% of eyes of Type II reaction and 69·3% of eyes with Type I reaction.

Gonioscopy revealed a pigmented trabecular meshwork in 32 eyes (65·3%) of Type II reaction and 8 eyes (61·5%) of Type I reaction. The age matched control group of 30 eyes revealed a pigmented trabecular meshwork in 20% of the eyes.

There was no significant difference in the near point of accommodation of 26 patients below the age of 40 years with the aged-matched control group of 15 patients.

The pupillary reaction to 1% adrenaline was found to be positive in 4 eyes (30·7%) with Type I reaction and 16 eyes (32·6%) with Type II reaction. In the control group a positive pupil reaction to 1% adrenaline was seen in 2 eyes (6·6%). The fundus examination was normal in all the eyes.

Table 2. Corneal sensations as measured by Cochet–Bonnet aesthesiometer

Corneal sensation* measurement	No. of eyes (%)	
	Type I	Type II
Normal (No unit decrease)	7 (71·6)	15 (30·6)
Slightly low (One unit decrease)	6 (28·4)	10 (20·4)
Moderately low (2 unit decrease)	—	7 (14·2)
Markedly low (More than 2 unit decrease)	—	17 (34·6)
Total	13 (100)	49 (100)

* Refer to table given with the aesthesiometer.

Table 3. Tear film break up time (BUT)

BUT (s)	No. of eyes (%)	
	Type I	Type II
0–5	6 (46·2)	34 (69·4)
6–10	5 (38·4)	13 (26·5)
11–15	2 (15·3)	2 (4·1)
16	—	—
Total	13 (100)	49 (100)

Discussion

Most of the deformities of leprosy result from a fairly acute inflammatory reaction. More than half the number of leprosy patients exhibit this reaction at some time during the course of this disease.[13]

In our study there was no statistically significant correlation between the number and duration of attacks of reaction with any of the ocular complications. Ocular involvement was common in both types of reaction (76·9% in Type I and 89·7% in Type II). But considering the mean duration of leprosy (2·5 years) in our study, the ocular involvement was fairly high. Reactions in leprosy may accelerate the onset of ocular complications because the incidence of ocular involvement in leprosy is usually proportional to the known duration of leprosy and is infrequent during the first few years of the disease.[2]

Though the sample of eyes studied in Type I reaction was small, it revealed that the increased inflammatory activity also affected the ocular structures. The common ocular changes found were raised erythematous plaques on lids, corneal hypoaesthesia, superficial punctate keratitis, prominent corneal nerves, pigment on the endothelium of cornea and pigmented trabecular meshwork.

Madrosis, corneal hypoaesthesia, superficial punctate keratitis, a decrease in BUT, prominent corneal nerves, pigment on endothelium of cornea and pigmented trabecular meshwork were seen in Type II reactions.

Decrease of corneal sensations was more common in Type II reactions (67·3%) as compared to Type I reaction (38·4%). Superficial punctate keratitis paralleled the decrease of corneal sensations. BUT was found to be markedly decreased in Type II reaction (69·4%). Lamba *et al.*[14] found an abnormal BUT in 47·2% of patients with leprosy and attributed it to sympathetic denervation which produced an abnormal mucin layer of the tear film. Regression analysis of our results revealed a statistically significant correlation between decrease of corneal sensations and a decrease of corneal BUT (Figure 1). When the corneal sensations are normal, the tear film drying stimulates blinking and renewal of tear film, but when the corneal sensations get reduced blinking is delayed, hence the corneal BUT is decreased.[15] Further evaluation is required to establish the relationship of corneal hypoaesthesia in reactions to subsequent corneal changes in leprosy patients.

Denervation hypersensitivity of the pupil to 1% adrenaline was revealed in 30·7% of eyes in Type I reaction and 32·6% of eyes with Type II reaction. Swift & Bauschard[11] showed a 64·2% incidence of hypersensitivity of the pupil to 1% adrenaline in patients with Type II reaction. Postganglionic sympathetic nerve dysfunction of the iris has been suggested as the possible cause of this phenomenon.[11]

The significance of pigment on the corneal endothelium and pigmented trabecular meshwork is difficult to assess. There is scant literature on gonioscopic findings in leprosy patients hence further studies are required to find out, if a difference exists in the gonioscopic findings between patients who are in reaction and the general leprosy patients. Increased pigmentation may be a sign of silent iritis representing a slow breakdown of the iris muscle following autonomic denervation.[16]

The incidence of iridocyclitis in ENL (Type II) reactions in our study was low (8·1%). Previous reports also reveal a low incidence despite the fact that no slit lamp examination was done in these cases. Rea *et al*[17] found no eye signs in 32 patients in ENL reaction. Two studies[7,8] found a 12% and 3% incidence of iridocyclitis respectively. Swift & Bauschard[11] who studied 13 patients of ENL found iritis in only 2 patients (15·4%). The general belief that the ENL reactions are usually associated with iridocyclitis is refuted by our findings.

The pathogenesis of iridocyclitis in ENL reactions is still obscure. ENL reactions are associated with immune complexes of which the *M. leprae* antigen is a component. The antigen–antibody ratio

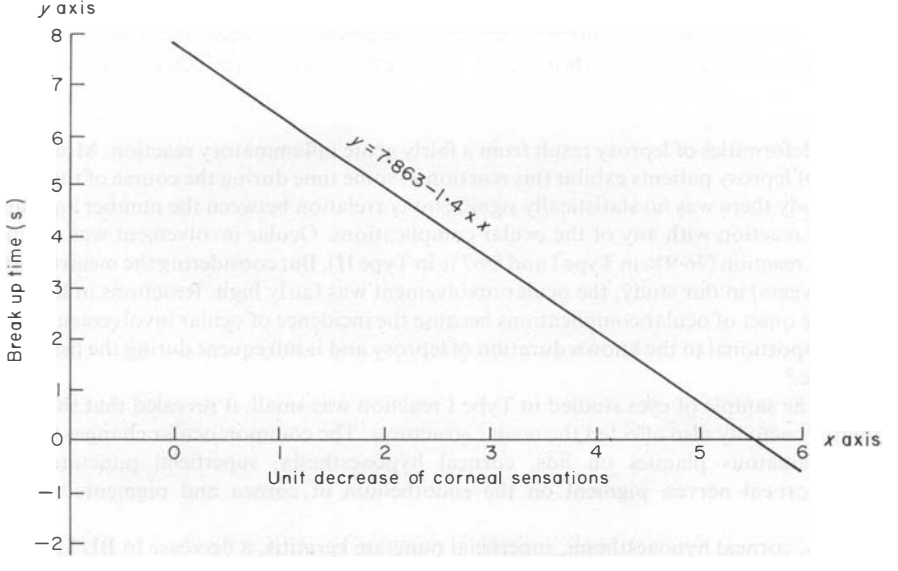

Figure 1. The unit decrease in corneal sensations shows significant correlation to decrease in corneal BUT. $y = 7{\cdot}863 - 1{\cdot}4x$.

is one of the many factors that determine the localization and deposition of the immune complexes. ENL may be precipitated if the antigen–antibody ratio is balanced or if there is a slight antigen excess. Thus, the lesions whether in the skin or other tissues that go into reaction are presumably those in which the amount of free antigen is appropriate to the antibody level at the site.[18]

In experimental models of lens induced uveitis, pathological changes consistent with immune complex formation have been described.[19] Increased vascular permeability, an essential feature of experimental uveitis, can be produced experimentally by intravenous injection of immune complexes.[20]

In lepromatous patients, large amounts of mycobacterial antigen are present within the macrophages for a long period of time being effectively separated from the precipitating antibodies occurring at the same time in the blood and interstitial fluid.[21] Hashizuma *et al*[22] in electron microscopic studies have demonstrated *M. leprae* laden macrophages in iris stroma, smooth muscle of iris and pigment epithelium. Thus, acute iridocyclitis in ENL reactions may be precipitated when an equilibrium is reached of the antigen–antibody ratio mediated by a disintegration of macrophages, resulting in deposition of immune complexes in the uveal tissue.

There is much individual variation in the onset of ENL from person to person and from one lesion to the other.[18] The same corollary can be extended in explaining the low incidence of iridocyclitis in our study. It is not possible to say why most of the eyes of patients with ENL reactions do not react but a host of factors like blood flow, vascular permeability, antigen affinity for the uveal tissue, decrease of T suppressor cell population may orchestrate a uveal reaction individually or in unison.[1,5,13,18]

Since more than 50% of patients with leprosy go into reaction during the course of their infection, it seems probable that reactions sensitize the uveal tissue and lay the foundation for the future edifice of uveitis, the cause par excellence of blindness in leprosy.[23]

Ocular complications in reactions in leprosy may vary in severity in different parts of the world, being more severe in colder climates.[1] As the mean duration of leprosy in our study was 2·5 years and the patients come from a tropical country, the ocular complications in a majority of cases did not cause any sight-threatening lesions. But sight-threatening ocular complications should be expected in patients in reaction who have a duration of leprosy of 10 years or more.

In conclusion, reactional states of leprosy may hasten the onset of ocular complications. These complications may be the precursors to sight-threatening lesions like keratitis and uveitis and may push the unfortunate leprosy patients in reaction to an earlier ocular morbidity than is normally the case.

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Combined regimens of one year duration in the treatment of multibacillary leprosy—I. Combined regimens with rifampicin administered during one year

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Summary In 1981, 1982 and 1983, 216 multibacillary patients in Anjouan (Comores) and Burundi were treated for 8 weeks with daily rifampicin (600 mg) ethionamide (500 mg) and dapsone (100 mg) or clofazimine (100 mg) followed for 44 weeks by once weekly rifampicin (600 mg) and daily ethionamide (500 mg) and dapsone (100 mg) or clofazimine (100 mg). There were 109 previously untreated patients and 107 patients who had had dapsone monotherapy, 16 of whom were infected with proven dapsone resistant *Mycobacterium leprae*. Clinical and bacteriological results were excellent but hepatotoxicity of this regimen remains a problem.

No relapses were observed during a 2 to 6 years (mean: 4·29 years) follow-up period after the end of treatment (upper 95% confidence limit of 0·40 per 100 persons years). It is concluded that multibacillary leprosy can be successfully treated with a regimen of one year duration, but less toxic regimens, more easily applicable in the field, are necessary.

Introduction

At present, 4 drugs are known to be active against *Mycobacterium leprae*. Their characteristics have been thoroughly studied in experimental infections in mice[1–9] and in man.[10–12] Two of them, rifampicin (RMP) and the thioamides ethionamide (ETH) or prothionamide (PRO), are bactericidal, the two others, dapsone (DDS) and clofazimine (CLO), are primarily bacteriostatic and slowly bactericidal.

The optimal use of these drugs for the treatment of leprosy, particularly of multibacillary (MB) leprosy, is still unknown. The combined therapy regimen advocated by the WHO,[13] based on the most recent knowledge regarding bacteriology of *M. leprae*, immunology of the patient, and epidemiology of the disease, is one of many possibilities. In order to establish the ideal combination

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of drugs, with a minimal duration of treatment, and minimal side-effects, the organization of prospective therapeutic trials is needed.[14,15]

The results of two combined regimens of one year duration, with a follow-up period of 4 and 5 years, have been published.[16] The shortcomings of these regimens, one using 2 drugs and the other 3 drugs, were discussed. The two-drug regimen, consisting of RMP and DDS, is unacceptable in the light of the high and increasing prevalence of DDS resistance (DDS-R), which was unknown at the moment the trial was initiated.[17] In fact, a substantial number of patients, harbouring DDS-R organisms, would receive RMP in monotherapy, implying the risk of selection of RMP-R mutants of *M. leprae*, which would lead to relapses not responding to RMP.

A prospective therapeutic trial in MB leprosy patients, using a triple drug regimen of 1 year duration, was conducted in Burundi (BUR) and on the island of Anjouan (ANJ), part of the République Fédérale Islamique des Comores, from 1981 to 1984. The results of the patient cohorts of 1981, 1982 and 1983 who have been followed up for 5 to 7 years after the start of treatment are presented in this analysis.

Patients and methods

Patients were diagnosed either after self-reporting to the leprosy service, or through referral or examination of contacts. All patients were examined clinically and neurologically by experienced paramedical workers. Disabilities were noted using the WHO scale.[18,19] Twelve (6 right and 6 left) peripheral nerves (*n. retroauricularis, n. ulnaris, n. medianus, n. radialis* (*ramus cutaneus*), *n. peroneus communis* and *n. tibialis posterior*) were routinely examined for hypertrophy, tenderness at palpation, and spontaneous tenderness. A skin smear was taken at 3 sites (one earlobe and two skin lesions), and examined locally. Only the number of bacilli was taken into consideration. The quality of the locally performed bacteriological examination was checked by regularly sending skin smear slides to Antwerp for verification. All results were recorded on specially designed files, a copy of which was sent to Antwerp.

In Burundi most patients were biopsied routinely from the start, in Anjouan after the trial had been going on for about 6 months. They were fixed in 10% formalin and sent to Antwerp. Sections were stained by the Trichrome Fite-Farracco technique.

Multibacillary (MB) leprosy was diagnosed when the bacteriological index (BI) was 2 or more (Ridley scale)[20] at any of the 3 sites examined. Patients were taken into the trial if they agreed to stay in or near the treatment centre for 12 months, or if they were capable of coming to the treatment centre daily. Thus all treatments were supervised.

Follow-up examinations are performed yearly, and are identical to those at intake. Most patients were biopsied 2 years after the end of treatment. Follow-up biopsies are taken annually till histopathological cure is established. Criteria for evaluation of the therapy are: absence of active clinical lesions, decrease of the BI in skin smears and biopsies, absence of solidly staining bacilli in the biopsies, decrease or even disappearance of histopathological lesions, and absence of side-effects. Evaluation of neurological complications was done in two ways. The disability score at the last folow-up examination was compared to the score at intake, and each change was noted. Likewise, the number of hypertrophied nerves at the last follow-up examination was compared to the number at intake, and each change was noted.

The drug regimen used (8-44 RED) was: RMP 600 mg, ETH 500 mg and DDS 100 mg daily (except on Sundays) for 8 weeks, followed by RMP 600 mg once a week, with ETH 500 mg and DDS 100 mg daily for 44 weeks. This regimen was given to all previously untreated patients, to Anjouan patients previously treated with DDS or DDS–CLO for less than 5 years, and to previously treated Burundi patients shown, during a previous DDS-R survey,[21] to harbour DDS-sensitive *M. leprae*. An identical regimen, but with CLO replacing DDS (regimen 8-44 REC), was given to previously treated Burundi patients shown to harbour DDS-R organisms.[21] In Anjouan, none of the patients

had a history of more than 5 years of previous treatment. Therefore no DDS resistance was suspected in those patients. Four of the 16 proven DDS-R cases, as well as 2 of the 8 previously treated DDS-sensitive Burundi patients, had received one dose of 1500 mg RMP 12 to 24 months prior to inclusion in the present study.

Every drug administration, as well as the occurrence of complications (mainly reactions and hepatitis) and their treatment, was noted on a treatment file. Upgrading reactions were treated with acetyl-salicylic acid, antiphlogistics and corticosteroids. ENL was treated with the same drugs, with the addition of thalidomide in males, and in females of unfertile age. SGOT, SGPT and serum bilirubin were determined monthly on Anjouan. Since 1982 in Burundi, serum tests were performed when hepatitis was clinically suspected.

If a patient showed an increase in liver enzymes, RMP and ETH administration was stopped till serum levels returned to normal.

Statistical analysis was done by the Student t-test, the χ^2 test with Yates' continuity correction for 2×2 tables, and the Mantel–Haenszel χ^2 test for comparing rates. Confidence limits, assuming a binomial distribution, were taken from *Tabulae Scientificae*.[22]

Results

Five groups of patients are considered: BUR patients, previously untreated, receiving 8-44 RED, ANJ patients, previously untreated, receiving 8-44 RED, BUR patients, previously treated, receiving 8-44 RED, ANJ patients, previously treated, receiving 8-44 RED, BUR patients, previously treated, receiving 8-44 REC. One BUR patient, previously untreated, was erroneously given 8-44 REC.

Two hundred and thirty-one patients were started on the trial regimen in 1981, 1982 and 1983. Before the first year of follow-up, 2 patients died of liver complications, 6 died of unrelated causes, and 7 (3·0%) were lost to follow-up. Two patients found to have taken leprostatic drugs after the end of the study regimen were also eliminated from the analysis, which totals 214 patients: 3 were followed for 1 year, 14 for 2 years, 24 for 3 years, 81 for 4 years, 60 for 5 years and 32 for 6 years after the end of treatment (Table 1). This gives a total of 919 person years of follow-up with a mean of 4·24 years.

The bacteriological characteristics of the patients at the moment of intake are summarized in Table 2. The mean BI at intake of previously treated patients: 2·80 is significantly lower than that of previously untreated patients: 3·43 ($0{\cdot}001 < p < 0{\cdot}01$).

Once treatment was started, clinical improvement in all patients was rapid. The BI's were by no means negative at the end of treatment, but they continued to decrease steadily afterwards, although the decrease differed considerably from patient to patient. Of the 212 patients followed-up

Table 1. Follow-up of the multibacillary patients taken into the study in Birundi and Anjouan in 1981, 1982, 1983

	1981	1982	1983	1984	1985	1986	1987	1988
Patients taken in	52	96	66	—	—	—	—	—
Patients								
died	—	—	—	—	4	1	1	—
lost	—	—	—	—	—	7	22	—
Patients seen	—	—	52	148	210	202	179	128
Patients not yet seen								51

Table 2. Bacteriological characteristics of patients at intake

Regimen	8-44 RED (BUR + ANJ)		8-44 REC (BUR)	
Treatment history	Untreated	Treated	Treated*	Total
n of patients	106	91	17	214
BI at intake†				
Mean	3·43	2·74	3·18	3·13
SD	1·06	1·19	1·24	1·18
Median	3·5	2·5	3·5	3·5
Range	1–6	0·5–5	0·5–5	0·5–6

8-44 RED/8-44 REC, see Patients and methods.

BUR, Burundi; ANJ, Anjouan; *n*, number; SD, standard deviation.

*1 previously untreated patient, who erroneously received this regimen, had a BI at intake of 3·5.

† Calculations are based on mean BI per patient rounded to the nearest 0·5. Thus a skin smear result of 4-2-2 becomes 2·5, while a result of 2-0-0 becomes 0·5.

until recently, 186 (87·7%) have a negative BI (Table 3). All 26 patients with a positive BI at the last follow-up examination show a satisfactory clinical and bacteriological evolution, except for one patient, whose initial BI was 4 and still is 3·5 at 5 years. However all bacilli are granular and the skin lesions have all but disappeared.

During follow-up none of the patients showed any sign of relapse as defined clinically by the appearance of new lesions or aggravation of existing lesions, and bacteriologically by a BI becoming positive again after negativation or increasing with at least 2 units at any site. The 95% confidence intervals for 0 relapses according to the person years per year of follow-up, are given in Table 4.

There were 12 cases of hepatitis (5·1%) 2 of whom died. No differences between any of the groups could be demonstrated. Upgrading reactions were observed in 16·1% of the patients. They occurred more frequently in previously untreated (21·7%) than in previously treated (9·1%) patients, but the difference is not significant ($0{\cdot}1 < p < 0{\cdot}05$). Five of the upgrading reactions (= 20·8%) started after stopping treatment, at 4, 8, 20, 25 and 28 months after the end of therapy. These are late reversal reactions, with a mean incubation time of 17 months, and a median of 20

Table 3. Evolution of the bacterial index after stopping treatment

Number of patients		214
Annual decrease of BI in units	*n*	%
0		0
0·01–0·49	11	5·1
0·50–0·99	86	40·2
1·00–1·49	66	30·8
1·50+	51	23·8
Negative at moment of analysis	186	86·9
Mean annual decrease		1·12

Table 4. Ninety-five per cent confidence intervals for 0 relapses, according to the person years of follow-up, and assuming a binomial distribution of the occurrence of relapses

Years of follow-up	Number of patients seen	Person years of follow-up (cumulative)	Confidence interval for 0 relapses per 100 person years
1	214	214	0–1·73
2	211	425	0–0·87
3	197	622	0–0·59
4	173	795	0–0·46
5	92	877	0–0·42
6	32	919	0–0·40

months. ENL reactions occurred in 16·8% of the patients. They were more frequent in Anjouan (20·8%) than in Burundi (7·0%), but the difference is not significant ($0{\cdot}1 < p < 0{\cdot}05$). Although only 1 upgrading reaction and no ENL were observed in the 17 patients receiving 8-44 REC, this was not significantly different from the observations in the 8-44 RED patients ($0{\cdot}8 < p < 0{\cdot}7$ for upgrading reaction; $0{\cdot}2 < p < 0{\cdot}1$ for ENL).

Table 5 shows the changes in neurological observations. The number of hypertrophied nerves at intake is compared to the number hypertrophied at the last follow-up examination. Table 5 gives the number of patients in whom the number of hypertrophied nerves remained unchanged, increased (by 1 to 4 nerves), and decreased (by 1 to 10 nerves). Overall, 8·9% of the patients show an increase

Table 5. Neurological evolution of the patients: change between last follow-up examination and examination at intake

	8-44 RED				8-44 REC	
Regimen	Untreated		Treated		Treated	Total
Treatment history						
Country (*n*)	BUR (19)	ANJ (87)	BUR (8)	ANJ (83)	BUR (17)	(214)
Nerve hypertrophy						
Unchanged: *n* (%}	2(10)	21(24·1)	2(25)	26(31·3)	4(23·5)	55(25·7)
Increased: *n* (%)						
By 1 to 2 nerves	1(5·2)	5(5·7)	3(37·5)	5(6)	2(11·7)	16(7·5)
By 3 to 4 nerves	1(5·2)	1(1·1)	1(12·5)	—	0	3(1·4)
Decreased: *n* (%)						
By 1 to 3 nerves	9	38	1	37	3	88
By 4 to 6 nerves	4	19	—	13	8	44
By 7 to 10 nerves	2	3	1	2	—	8
Total	15(80)	60(69)	3(37·5)	52(62·7)	11(64·7)	140(65·4)
Disability scores						
Unchanged	81(71)	482(92·3)	41(85)	421(84·5)	66(65)	1091(85)
Worsened 1–2 units	30(26·3)	36(6·9)	3(6·2)	58(11·6)	25(24·5)	152(12)
Worsened 3 units					3(2·9)	3(·2)
Improved 1–2 units	3(2·6)	4(·7)	2(4·2)	19(3·8)	8(7·8)	36(2·8)
Improved 3 units			2(4·2)			2(·1)

8-44 RED/8-44 REC *see* Patients and Methods.
BUR, Burundi; ANJ, Anjouan; *n* number.

in hypertrophied nerves: 84% of these have 1 or 2 additional hypertrophied nerves, and 16% have 3 or 4. There is no significant difference between previously treated and previously untreated patients nor between REC and RED groups nor between Anjouan and Burundi patients. An often dramatic decrease in hypertrophied nerves was seen in 65·4% of patients. No differences are manifest between Anjouan and Burundi patients, nor between previously treated and untreated patients, nor between REC and RED patients.

Table 5 also shows the changes in disability scores (WHO scoring system, 6 scores per patient) between the examination at intake and the last follow-up examination. At the last follow-up 2·9% of all scores were improved, while 12·2% of the scores were worse. Increase in disability score was significantly worse in REC (35·3%) than in RED (7·0%) patients ($0{\cdot}001 < p < 0{\cdot}005$). It was also significantly worse in Burundi (28·3%) than in Anjouan (4·1%) patients ($p < 0{\cdot}001$). It should be noted that all REC patients are Burundi patients.

Discussion

The necessity for combined chemotherapy in MB leprosy has been recognized for about 15 years,[19] but how to apply such a combined therapy was entirely unknown, particularly with respect to the drugs to be given, the frequency of their administration and the duration of therapy.

The regimen investigated was conceived in 1980 well before the regimen for chemotherapy of leprosy for control programmes by the World Health Organization was conceived and published. By analogy with what is known about the therapy of tuberculosis we suggested that in leprosy an association of two, preferably three bactericidal drugs (but only 2, RMP and ETH, are available in leprosy) have to be given with the addition of one bacteriostatic drug.[15]

In this interpretation the use of a second bacteriostatic drug would be unnecessary. Therefore we used DDS in new patients never treated before and replaced it by CLO in patients with proven DDS-R leprosy and in those treated for 5 years or more with DDS monotherapy, because these patients are at risk of harbouring DDS-R *M. leprae*. Since that time it has been made clear[23] that the multibacillary patient harbours three populations of leprosy bacilli: 1, an overwhelming number of drug sensitive organisms; 2, several small populations of naturally occurring mutants resistant to individual drugs; and 3, a small population of drug sensitive nonmultiplying bacilli known as persisters, which by definition, are untouched by any drug or drug combination. The great majority of the population, being RMP-S is killed by RMP, while the RMP-R fraction has to be eliminated by the other drugs administered, in this case either ETH and DDS or ETH and CLO.

It was also thought that treatment could consist of two phases: an intensive introductory phase of 2 months during which RMP is given daily, followed by a second less intensive phase during which RMP is given only once a week. From experiments in mice and studies in man it is known that RMP in contrast to ETH is still active against *M. leprae* when administered only once a week.[1,3,4,11] This would allow RMP to be administered under supervision in field conditions once a week during the second phase of treatment.

The opinion prevails that MB leprosy has to be treated until bacteria are completely cleared from the skin, and even longer. This was probably true as long as only monotherapy with the mainly bacteriostatic drug dapsone was available. However this opinion has to be revised when powerful bactericidal drugs are administered, leading to a dissociation between rapid bacterial killing and slow elimination of the dead bacilli from the skin. The more so since Shepard[24] showed that in mice, drug combinations, particularly ETH–DDS and ETH–CLO with or without RMP are additive in bacterial killing. It may therefore be justified in these circumstances to stop antibacterial treatment in MB leprosy before bacterial negativity in the skin is reached. On a purely empirical basis it was hoped that the different actively metabolizing subpopulations of *M. leprae* would be killed by the three drugs within one year and therefore this duration of treatment was chosen. The judgement of the efficacy of treatment regimens in MB leprosy has to be based on clinical, bacteriological, and

histopathological evaluation of the disease process and above all on the absence of relapse. Relapse is defined clinically as appearance of new lesions or aggravation of existing ones, and bacteriologically (BI increasing by at least 2 units at any site examined, compared with a previous examination) confirmed by histopathology (increase of the BI by at least 2 units and increase of the morphological index as well).

In the present study, no relapses were observed after a mean follow-up period of 4·29 years after the end of treatment and a total of 919 person years of follow-up. It is expected that for 95% of the time, the regimen under study will give rise to less than 0·40 early relapses per 100 person-years of follow-up. This absence of relapses should be compared to the relapse rate after DDS monotherapy. The literature was searched for studies looking at clearly defined MB patients whose treatment was stopped and mentioning the person-years of follow-up. Three studies mention relapses after stopping short-course (mean: 3·5 years) DDS monotherapy: Erickson[25] observed 5 relapses in 11 patients, with a total of 22 person-years of follow-up; Price[26] found 6 relapses among 24 patients with a total of 20·2 person-years of follow-up; Lowe[27] found 15 relapses among 139 patients with a total of 255 person years of follow-up. The comparison of each of these relapse rates with the O relapse rate found in the present study, gives highly significant results ($p < 0{\cdot}0005$).

One study[28] covered relapses after prolonged (19–22 years) DDS monotherapy. The patients were followed up to 8 and 9 years. During the first 4 years of follow-up, 11 relapses were observed for a total of 1297 person years of follow-up. Compared with the present study in which treatment was stopped after 12 months, regardless of the BI at that moment, this difference is highly significant ($p = 0{\cdot}007$). The regimen studied did not only kill the RMP sensitive *M. leprae* population, but the daily ETH–DDS combination for one year also eliminated the RMP resistant mutants. The BI continues to decrease after therapy is stopped, illustrating once more that it is not necessary to continue treatment until the BI is negative. The mean annual decrease (1·12) is near the theoretically expected decrease of 1·00. However, 65·5% of the patients are slow decreasers ($< 0{\cdot}5$ units per year), while 23·8% are rapid decreasers ($> 1{\cdot}5$ units per year). It is possible that these rapid decreasers were originally BT patients who downgraded to BL or LLs but who, aided by the therapy, return towards the tuberculoid pole of the spectrum. The slow decreasers could be originally lepromatous patients who remain at the lepromatous end of the spectrum throughout their evolution. The data assembled in the present study do not permit us to check this assumption. A considerable number of patients (87%) have become bacteriologically negative at the moment of the present analysis. In view of the continuing decrease in BI, it is expected that all those patients will eventually become negative.

Hepatotoxicity is the most serious complication.[29] There were 11 cases of icterus, incidence 4–7%, two patients died (one in Burundi and one in Anjouan). The incubation time for the appearance of hepatitis varied between 25 and 364 days, with a mean of 104 days and a median of 150 days. In three sera from Burundi obtained during the acute phase of the disease, hepatitis B, anti-HBs and anti-HBc antibodies were present, indicating an infection with hepatitis B virus in the past. Hepatitis, in the absence of therapy is sometimes seen in leprosy patients, but its incidence in Central Africa can be estimated at about 1%. Although RMP and the tioamides are hepatotoxic to a certain degree, their association however is more so.[29,30] Fear of possible greater nerve damage due to the use of rapidly bactericidal drugs was not confirmed. Upgrading reactions occurred in 16·1% of the patients. This is comparable to the 17% observed after WHO therapy,[31] but less than the 50·2% observed after a regimen consisting of 182 administrations of RMP.[30] The regimen under study consists of 92 RMP administrations. The higher frequency in previously untreated patients is in agreement with observations made in other areas.[30] The overall ENL frequency of 16·8% is also comparable to the 13·2% observed previously.[31]

The reactions did not lead to increased nerve deterioration. In fact, many more patients showed neurological improvement than aggravation. The Burundi patients performed worse than the Anjouan patients in terms of neurological complications. This is probably due to the small surface of Anjouan, which makes the well-staffed leprosy service easily and immediately accessible at the onset of neurological complications.

The observations in this study do not make any assumptions about the protective action of CLO against upgrading reactions,[31] although they point in this direction.

The present study shows that MB leprosy can be successfully treated with a regimen of 1 year duration, in terms of clinical improvement, bacteriological decrease and absence of relapses. However, the hepatotoxicity of the combination RMP–ETH constitutes a serious drawback to its generalized use in the field, where close monitoring of the hepatic function is difficult. Moreover the amount of RMP used, as well as the necessity for close supervision of the patient often necessitating hospitalization, may prove to be too much of a financial and logistic burden for many leprosy control programmes. After this study was initiated, it has been shown that no difference in the killing effect against *M. leprae* can be demonstrated between daily and monthly RMP treatment.[32] The search for alternative regimens, less toxic, and more easily applicable in difficult field situations, needs to be continued.

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Combined regimens of one year duration in the treatment of multibacillary leprosy—II. Combined regimens with rifampicin administered during 6 months

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Summary From 1981 to 1983 all multibacillary patients presenting at the collaborating centres in Zaire and Rwanda were treated with one of the following regimens: 6 months supervised daily RMP 600 mg, ETH 500 mg and DDS 100 mg or CLO 100 mg followed by 6 months unsupervised daily DDS 100 mg or CLO 100 mg with ETH 500 mg added or not. These regimens gave rise to hepatotoxicity, reversal and erythema nodosum leprosum reactions as described previously.

Bactericidal activity was excellent. Among the 289 patients in the trial, with a mean follow-up period of 3·88 years, no relapses were observed, with an upper 95% confidence limit of 0·35 per 100 person years.

Because of the hepatotoxicity, alternative short-course therapies need to be tested.

Introduction

In the accompanying paper[1] it is shown that multibacillary (MB) leprosy patients can be successfully treated with a combined regimen of one year duration with rifampicin (RMP) administered during one year. One of the drawbacks of this regimen is the logistic problem created by the need to keep to patients under close supervision for 12 months, often necessitating hospitalization. The application in the field of combined regimens could be considerably simplified if the supervised phase could be shortened to 6 months. Therefore a prospective therapeutic trial was organized in Zaire and Rwanda, studying regimens of one year duration but in which RMP was administered during the first 6 months only. The results of the patient cohorts taken into the trial in 1980, 1981, 1982 and 1983 who have been followed up to 5 years after the end of treatment are presented in this analysis.

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Patients and methods

Diagnostic procedures and criteria for evaluation are identical to the 12 month RMP trial, and are detailed in the accompanying paper.[1] However, in Zaire and Rwanda biopsies were taken routinely. Thus all patients were thoroughly evaluated clinically, neurologically, bacteriologically, as well as histopathologically, at the moment of intake and at each annual follow-up examination. All results were entered on specially designed files, a copy of which was sent to Antwerp.

Multibacillary (MB) leprosy was diagnosed when the bacteriological index (BI) was 2 or more (Ridley Scale[2]) at any of the 3 sites examined (1 earlobe, 2 skin lesions), or in the skin biopsy. Patients were taken into the trial if they agreed to stay in or near the treatment centre for 6 months, or if they were capable of coming to the treatment centre daily. Thus the RMP phase of the therapy was fully supervised. The second phase of the therapy, 6 months without RMP, was unsupervised. Every month the patient came to the treatment centre to collect his monthly provision of ethionamide (ETH) and dapsone (DDS) or clofazimine (CLO). Patients were thus seen daily during the first 6 months of therapy, at least once a month during the next 6 months of therapy, and after stopping treatment at least once a year for the annual follow-up examination. Male patients never treated before or treated previously for less than 5 years with DDS were randomly allocated to one of the following two regimens:

RED/D: daily (except Sundays) supervised RMP 600 mg ETH 500 mg DDS 100 mg during 6 months, followed for 6 months by daily, unsupervised DDS 100 mg.

RED/ED: identical with RED/D during the first 6 months, but followed for 6 months by daily, unsupervised ETH 500 mg and DDS 100 mg.

All female patients, and male patients treated previously during 5 years or more with DDS were randomly allocated to one of the following regimens:

REC/C: identical with RED/D but DDS replaced by CLO 100 mg.

REC/EC: identical with RED/ED but DDS replaced by CLO 100 mg.

No other antileprosy drug than DDS had been available previously in these regions.

DDS was replaced by CLO in females because of the supposed protective action of CLO against ENL reactions that cannot be treated with thalidomide in women of child-bearing age, and in patients treated previously for 5 years or more because resistance to DDS could be suspected in those patients. Every drug administration or delivery, as well as the occurrence of complications (mainly reactions and hepatitis) and their treatment, was noted on a treatment file. Reactions were treated,[3] but without using CLO, to avoid interference with the trial results by the leprostatic action of CLO. Hepatitis was diagnosed mainly on clinical grounds, since most centres participating in the trial did not have facilities to determine SGOT, SGPT and serum bilirubin. If a diagnosis of hepatitis was made, RMP and ETH were stopped and the patient was continued on DDS or CLO.

Statistical analysis was done by the Student *t*-test, the χ^2 test with Yates' continuity correction for 2×2 tables, and the Mantel–Haenszel χ^2 test for comparing rates. Confidence limits, assuming a binomial distribution, were taken from *Tabulae Scientificae*.[4]

Results

Three hundred and fifty-six patients were started on one of the trial regimens in 1980, 1981, 1982 and 1983. Before the first year of follow-up, 4 died of liver complications, 17 died of unrelated causes, and 43 (12·1%) were lost to follow-up. Three patients who took leprostatic drugs after the end of the study regimen were eliminated from the study, leaving 289 patients for analysis. As shown

Table 1. Annual intake and follow-up of patients

	1981	1982	1983	1984	1985	1986	1987	1988
Intake	71	98	120					
Died	—	—	—	1	3	5	4	1
Lost	—	—	—	1	2	15	29	—
Patients seen	—	—	71	167	282	262	229	110
Patients not yet seen								118

Table 2. Annual decrease of the bacteriological index after stopping treatment

Number of Patients		289
Annual decrease of BI in units	*n**	%
0	3	1
0·01–0·49	23	8
0·50–0·99	125	43·7
1·00–1·49	86	30·1
1·50 and more	49	17·1
Mean		1·01
Negative at moment of analysis	205	(71·7%)

* Data for 3 patients incomplete.

in Table 1, 13 patients were followed for 1 year, after the end of treatment, 24 for 2 years, 64 for 3 years, 100 for 4 years, 60 for 5 years and 28 for 6 years, or a total of 1121 person years of follow-up. The mean duration of follow-up was 3·88 years. Previously treated patients were followed for a longer period than previously untreated (4·03 *vs* 3·64 years), and patients receiving CLO were followed for a longer period than patients receiving DDS (4·04 *vs* 3·55 years). These differences are statistically significant ($p < 0{\cdot}0025$).

The bacteriological characteristics of the patients at the moment of intake were comparable in all groups. The BI at intake* ranged from 0·5 to 6, with a mean of 3·54 (standard deviation 1·14) and a median of 3·5.

Clinically all patients improved rapidly, and continued to do so after the end of therapy. The BI continued to decrease after the end of treatment in almost all patients. The annual decrease for 286 patients (3 files were incomplete) is summarized in Table 2. the mean annual decrease in all patients was 1·01 units/year. There were no differences between mean decreases in each group that were significant at the 5% level. In 3 patients the BI did not decrease, but they could be followed for only a relatively short time: 1 patient was lost after 1 year, two others died after 1 and 2 years respectively. In 4 patients the BI did not decrease as expected. In patient A from 5 to 3·5 in 5 years, in patient B from 3 to 2·5 in 4 years, in patient C from 5·5 to 4·5 in 5 years, in patient D from 5 to 4·5 in 5 years. These 4 patients show a satisfactory clinical and histopathological evolution (all bacilli are extremely granular). In the biopsies the macrophage granulomas in most cases persisted, they contained very granular bacilli and finally became empty.

*Calculations are based on mean BI per patient, rounded to the nearest −·5. Thus a skin smear result of 4-2-2 becomes 2·5, while a result of 2-0-0 becomes 0·5.

In total, 9 patients died while still bacteriologically positive. Of the remaining 277, 205 (74%) have become bacteriologically negative at the moment of the present analysis. No differences between any of the groups are manifest.

No relapses were seen in any of the patients (a relapse is defined clinically by new lesions or aggravation of existing lesions, and bacteriologically by a BI becoming positive again after negative, or increasing by at least 2 units at any site). The 95% confidence intervals for 0 relapses according to the person years per year of follow-up are given in Table 3, and reaches at present between 0 and 0·35 per 100 person years.

Eleven patients presented a reactivation of existing lesions after the end of treatment. This reactivation was not accompanied by an increase in BI and responded well to anti-inflammatory treatment. Four of the reactivations were biopsied: 3 showed a BT image, and one showed an aspecific perivascular cellular infiltrate. These reactivations are late reversal reactions. Their incubation time reaches from 2 to 50 months after the end of treatment, with a mean of 22·5 months and a median of 24 months.

As described earlier,[5] hepatotoxicity occurred in 5% of patients receiving the regimens under study. No differences between any of the regimens were manifest. Upgrading and ENL reactions, as well as the neurological evolution, were described in detail for two of the centres participating in the trial.[3] The situation is comparable in the other participating centres.

Compared with the situation at the start, 15·1% of the patients at the last follow-up examination showed an increase and 54·5% a decrease in the number of hypertrophied nerves.

Previously untreated patients showed a significantly higher increase in the number of hypertrophied nerves (23·1%) than previously treated patients (9·7%) ($0{\cdot}005 < p > 0{\cdot}001$). Previously treated patients receiving DDS also showed a significantly higher increase of nerve hypertrophy than previously treated patients receiving CLO (26·3% *vs* 7·7%, $0{\cdot}05 < p > 0{\cdot}025$). However, patients receiving DDS had by definition less than 5 years of previous treatment, whereas patients receiving CLO had by definition more than 5 years previous treatment. Whether CLO in itself protects the nerves cannot be concluded from this study.

Mutilations, coded by the WHO disability score[6,7] deteriorated in 80 (27·4%) patients and improved in 96 (32·9%). No difference in deterioration is manifest between patients receiving DDS or CLO, nor between previously treated and previously untreated patients.

Discussion

Antibacterial regimens in MB leprosy should be evaluated on clinical and bacteriological grounds, and on the incidence of relapses after treatment. The results presented here show that MB leprosy can be successfully treated with regimens of 1 year duration, and that RMP administration can be

Table 3. Ninety five per cent confidence intervals for 0 relapses, according to the person years of follow-up, and assuming a binomedial distribution of the occurrence of relapses

Years of follow-up	Number of patients seen	Person years of follow-up (cumulative)	Confidence interval for 0 relapses per 100 person years
1	289	289	0–1·27
2	276	565	0–0·66
3	252	817	0–0·45
4	188	1005	0–0·37
5	88	1093	0–0·35
6	28	1121	0–0·35

limited to the first 6 months, which confirms the observations made in a smaller previous study.[8] All patients improved clinically, and the BI continued to decrease after therapy ended in 98·9% of the patients. The mean annual decrease of the BI (1·01) is comparable to the decrease observed after the 8-44 RED(C) regimen discussed in the accompanying paper.[1] As was the case there, slow (0·01–0·49 units per year) and rapid (more than 1·50 units per year) decreasers are observed unrelated to the BI at intake.

The mean follow-up period for the 8-44 RED(C) study[1] is longer than for the present study: 4·29 *vs* 3·88 years. There are more patients negative at the moment of analysis after 8-44 RED(C) than after the present regimens (87·7% *vs* 74%). However, this may be due to the higher BI at intake in the present study (3·54 *vs* 3·13) and the shorter period of follow-up. The reasons previously treated patients attended follow-up examinations more regularly and for longer than previously untreated ones may be the result of a long-standing habit.

No relapses were observed in any of the patients. Since they were followed for a total of 1121 person years, with a mean follow-up of 3·88 years, we may state that the regimens in the present study are expected to give rise to less than 0·35 early relapses per 100 person years, 95% of the time.

The present results are comparable to the 0 relapses observed after 8-44 RED(C) in the accompanying paper.[1] They are significantly better than the results obtained after short-course DDS monotherapy: 5 relapses for 22 person years of follow-up;[10] 6 relapses for 20·2 person years of follow-up;[11] and 15 relapses for 255 person years of follow-up[12] (all: $p < 0{\cdot}0005$). Compared with the relapses observed after prolonged DDS monotherapy[13] (11 relapses for 1297 person years of follow-up) the present regimens are also significantly better ($p < 0{\cdot}001$).

The increase in nerve hypertrophy, as well as the deterioration of the mutilations in the present study (results not shown) are comparable to the results found in the accompanying paper[1] after 8-44 RED(C) in Burundi patients.

The present study suggests that it is possible to treat MB leprosy successfully with a 1 year combined regimen with RMP administered during the first 6 months. The 4 regimens under study are comparable in terms of clinical improvement, mean bacteriological decrease and absence of relapses. The addition of ETH during the second 6 months of therapy does not improve any of the results.

The hepatotoxicity of the regimens under study is unacceptable, the more so, since it was only detected on clinical ground. These regimens were therefore abandoned in February 1984. The search for equally successful, but less toxic regimens, easily applicable in difficult field situations, needs to be continued.

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Improved staining of leprosy bacilli in tissues

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Summary A technique which reliably demonstrates *Mycobacterium leprae, M. tuberculosis* and fungi in tissues is described. It is based on the oxidation of cell wall lipid substances by chromic or periodic acid, and the subsequent release of aldehydes which are then capable of reducing ammoniacal silver salt solutions to metallic silver. The organisms so demonstrated appear uniformly solid. The sensitivity of the method and the ease of examination and recognition of bacilli and their products are recommendations for the use of the method in diagnosis and research, disregarding morphological appearances.

Introduction

For unknown reasons it is often difficult to demonstrate *Mycobacterium leprae* in tissues. This is especially so with material which has been fixed for long periods in formalin, or when organisms are in an advanced state of decay, or if they are not acid-fast by the conventional Ziehl–Neelsen staining method. Greater sensitivity of staining can be achieved using prior oxidation with periodic acid and subsequent staining in carbolfuchsin,[1,2] or carbol-pararosanilin.[3,4] Silver impregnation, originally used to demonstrate fungi in tissues[5] is another reliable means of staining mycobacteria.[6–8] Harada[9,10] made use of prior oxidation followed by silver impregnation to enhance the demonstration of mycobacteria in tissues.

The method described below is based on the same principle. Leprosy bacilli, tubercle bacilli, other mycobacteria and certain fungi can be clearly visualized by this technique.

Materials and methods

TISSUES

Human skin lesions of various forms of leprosy, pulmonary lesions of tuberculosis and fungal lesions were examined. Tissues were fixed in 10% neutral buffered formalin for 24–48 h, dehydrated, blocked in paraffin wax and sectioned at 5 μm. Egg albumin–glycerin adhesive was used to attach the sections on to clean glass slides.

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METHOD

The chromic acid or periodic acid-ammoniacal silver reaction to demonstrate mycobacteria and fungi in tissues is carried out as follows.

1 Deparaffinize sections in xylene and hydrate through graded alcohols to water.
2 (a) Oxidize in 5% chromic acid for 1 h followed by 2% sodium bisulphite briefly, or (b) oxidize in 1% periodic acid overnight.
3 Wash in running tap water, and rinse in 3 changes of distilled water.
4 Place sections in a Coplin jar containing freshly prepared ammoniacal silver solution, and place the jar in an oven at 60°C for about 1–2$\frac{1}{2}$ h, until the sections turn brown to black (see below).
5 Rinse in 2 or 3 changes of distilled water at 60°C, and then in several changes of distilled water at room temperature.
6 Tone in 0·1% gold chloride for 5 min.
7 Rinse in distilled water.
8 Fix in 2% sodium thiosulphite for 2 min.
9 Wash in tap water.
10 Stain nuclei with nuclear-fast red solution for 15 min.
11 Rinse in tap water.
12 Counterstain with 0·01% methyl blue (Merck, art. 16316), or with 0·03% methyl blue (Merck, art. 16315) in saturated aqueous picric acid solution for 5 min.
13 Dehydrate directly in absolute alcohol.
14 Clear in terpineol-xylene (1 : 1), followed by xylene. Mount.

AMMONIACAL SILVER SOLUTIONS

Solutions are prepared in one of three ways.

1 Ammoniacal silver nitrate: to 25 ml of 10% aqueous silver nitrate solution add 28% ammonia water until a clear solution is formed. Then add 10% silver nitrate drop by drop till a faint cloudiness appears. Add 25 ml distilled water.

2 Ammoniacal silver carbonate: to 10 ml of 10% aquaeous silver nitrate add 40 ml of 5% anhydrous silver carbonate. When the precipitate has settled, remove the supernatant and wash the deposit several times with distilled water. Decant. Add 28% ammonia water drop by drop till the precipitate is dissolved. Add 10% aquaeous silver nitrate drop by drop till the solution becomes cloudy. Make up to 100 ml with distilled water.

3 Ammoniacal silver hydroxide solution: to 10 ml of 10% silver nitrate solution add 5 ml of 4% NaOH till a black precipitate is formed. Add 28% ammonia drop by drop till the solution is cloudy. Make up to 100 ml with distilled water.

STAINING TIMES	After chromic acid oxidation	After periodic acid oxidation
1 Ammoniacal silver nitrate:	2 h	2h
2 Ammoniacal silver carbonate:	1 hr 40 min	2 h 45 min
3 Ammoniacal silver hydroxide:	50 min	1 h 10 min

NUCLEAR STAIN 1 g nuclear-fast red (CI 60760)
5 g aluminium sulphate
100 ml distilled water.

Results

Mycobacteria and fungi stain black, mucin brown-black, melanin grey, nuclei pink-red, and connective tissue green-grey-black. In pulmonary lesions carbon remains black (see Figures 1, 2 and 3).

Discussion

The method described for mycobacteria, including *M. leprae* and *M. tuberculosis*, and fungi in tissues is based on a chemical reaction which is both sensitive and reliable. The mechanism of the reaction depends on the oxidation of lipid hydroxy-amino groups in the mycobacterial cell wall and the release of free aldehydes. These aldehydes can be revealed either by a modified Schiff procedure using carbol-pararosanilin,[3,4] or by treatment with silver salt solutions which are reduced to metallic silver. The present method utilizes ammoniacal silver salts rather than the methanamine used previously.[9,10] Ammoniacal silver is used to demonstrate melanin. After oxidation melanin is only poorly recognizable but other substances like argentaffin, ascorbic acid, uric acid and polyphenols react with argyrophilic stains in a manner similar to aldehydes, and silver is deposited at the site of interaction. This in no way hinders the recognition of the mycobacteria or fungi, though carbon particles in the lung can sometimes mask bacilli in that tissue.

Chromic acid has the same oxidizing potential as periodic acid, but strict control of the oxidation time is necessary. Prolonged oxidation in chromic acid carries the risk of losing the aldehydes released, upon which the subsequent binding by carbol-pararosanilin,[3,4] or impregnation

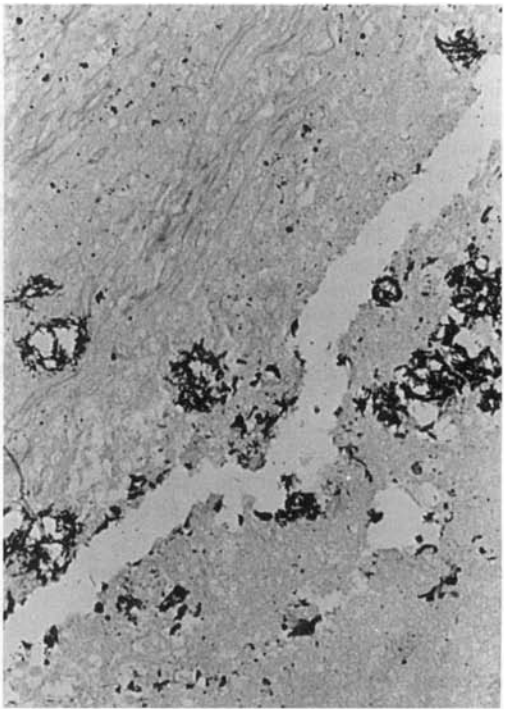

Figure 1. Tubercle bacilli in pulmonary tuberculosis. Periodic acid-ammoniacal silver hydroxide stain.

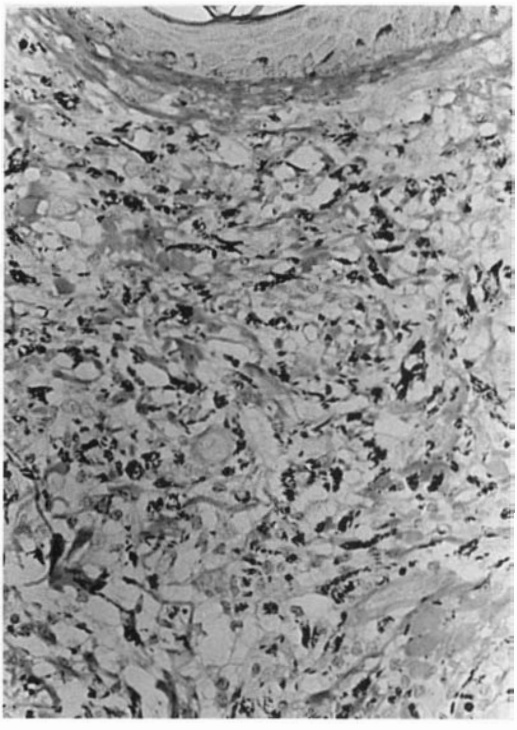

Figure 2. Leprosy bacilli in lepromatous lesion of skin. Periodic acid-ammoniacal silver hydroxide stain.

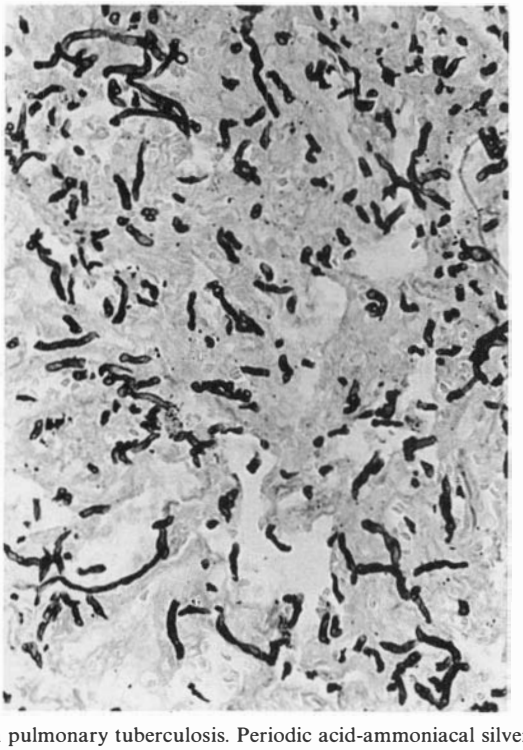

Figure 3. Fungi in pulmonary tuberculosis. Periodic acid-ammoniacal silver hydroxide stain.

with silver depends. For this reason periodic acid is to be preferred in spite of the longer time required for the oxidation.

The majority of the *M. leprae* stained by the chromic or periodic acid-ammoniacal silver technique, stain with a uniform solid appearance. Even nonsolid bacilli appear rod-shaped. Thus the usefulness of the method does not extend to studies on viability or assessment of the bacteriological state of the patient. Nevertheless, its application in diagnosis and research cannot be emphasized too strongly. In research the ease of identifying organisms and degradation products, which are often difficult to detect by acid-fast staining, is comparable in many ways to the sensitivity of immunocytochemical methods using antiBCG antibody. Material stained by the two methods in parallel correlated very well (M J Ridley, personal communication 1988). The fact that granular and degraded bacilli stain with a solid appearance is understandable considering that it is the lipid moiety in the bacterial cell wall itself that is the key substance on which the reaction is effected. The disintegration of cell walls is achieved with difficulty in the case of *M. leprae*, especially so in lepromatous infections in which clearance of bacilli presents further problems.

Acknowledgments

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Management information system for leprosy eradication programme—an alternative information system*

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Summary For efficient monitoring of multidrug therapy programmes for leprosy both at microlevel (individual patient monitoring) as well as macrolevel (programme monitoring), DANIDA decided to develop an alternative, simple and quick information system using a computer. A patient data base system was designed using dBase III Plus package. The field workers of the National Leprosy Eradication Programme were trained in transcribing data on to coded data sheets. The data of 1750 patients of six leprosy control units from the 4 MDT districts were processed and feedback reports were sent to paramedical workers and programme managers. The initial experience in the field over the past year has shown that a computerized management information system is feasible and well accepted by the field staff for the purpose of improving monitoring.

Introduction

A population-based multidrug therapy programme for leprosy, the new technology available for containing the disease, needs to be closely monitored and assessed both operationally and epidemiologically if the programme is to be successful. Realizing this need, the National Leprosy Eradication Programme (NLEP) in India has recommended a highly sensitive monitoring system to ensure smooth and coordinated progress of planned MDT activities.[1] If a monitoring system is to be functionally effective, the data flow must be timely and relevant to each action level of the programme. In the MDT programme, a quick performance analysis of key activity areas is important, especially as a feedback to field workers (paramedical workers).

The current monitoring, through voluminous manually compiled data that pass upwards from the peripheral field workers through several levels of the NLEP hierarchy in the form of monthly progress reports (MPR) has definite limitations especially for individual patient monitoring. Recognizing this, the Independent Evaluation Committee of NLEP, Governing of India, 1987 recommended that the tendency to compile data only for onward transmission should be discouraged and assessment should be backed-up by complete and relevant feedback.[2]

The usefullness of computers at the field level in a limited way and in other health programmes has been reported.[3,4] However the application of this technology has not yet been tried in a routine leprosy programme though some experience has been reported from Malawi.[5] The OMSLEP group has designed a simple recording and reporting system for routine leprosy programmes which can be

* Based on the paper presented at the Indian Association of Leprologists workshop on 'Monitoring and evaluation of leprosy programmes' in Bombay, 4–5 June 1988.

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adapted to computerization.[6] However, reports of its effectiveness both at microlevel (individual patient monitoring) and at macrolevel (programme monitoring) are awaited. Hence, DANIDA (Danish International Development Agency) in its assistance to the NLEP–MDT Programme in India decided to develop a simple Computerized Management Information System (COMIS) and evaluate its potential in improving the efficiency of the MDT programme especially at field level. A pilot study was designed to examine: (a) the possibility of developing a field-based model for microlevel as well as macrolevel monitoring; (b) the feasibility of using a computerized system by field staff; and (c) the usefulness of a bottom-up monitoring system at peripheral level.

Methodology

The following steps were taken while designing this computerized information system as an action research programme using field staff of the leprosy programme:

Problem Oriented Medical Record System (POMRS): A basic file (patient card) as described by Lloyd was designed to obtain all the relevant information about the individual patient.[7] These cards were introduced in all the 4 MDT districts assisted by DANIDA.

2 Patient identification number (Figure 1). A patient is identified by a 14-digit identification number consisting of a 6-digit Indian Postal Pin Code (Leprosy Control Unit code), a 2-digit paramedical worker code, a 3-digit village code and a 3-digit patient code.

3 Coded data sheets I (basic information) and II (clinical information) were designed for transcribing patient data into numerical language for feeding into the computer. A coding structure was designed to assist field workers in filling up data sheet.

4 A DCM-Tandy 3000 PC/AT was installed at the Delhi office and dBase III Plus software was used to design a patient database system. A patient file structure was designed to enter all the basic and clinical data. Another file structure was designed to enter the code of the state, the district and the leprosy control unit, in order to generate computerized reports at different levels. A foxbase compiler was used to improve the efficiency of the programme.

5 Computerized reports. Six different kinds of computerized reports were designed for use as monthly progress reports to monitor achievements in relation to specific objectives of the MDT programme:

Report I (Figure 2) and Report II (Figure 3) were designed for subcentre paramedical worker (PMW) to monitor individual patients from a specific subcentre registered for MDT in each village. Report I gives details of all the patients registered during the month. Report II gives details of previously registered as well as newly registered patients during the month including their treatment status and compliance.

Report III (Figure 4) provides village with aggregated data from a subcentre indicating total size of problems like needs for footwear and surgical correction and reasons for treatment discontinuity.

Reports IV/V/VI (Figure 5) provides aggregated data at control unit level for a medical officer, at district level for a district leprosy officer and a state level for a state leprosy officer, respectively for programme monitoring.

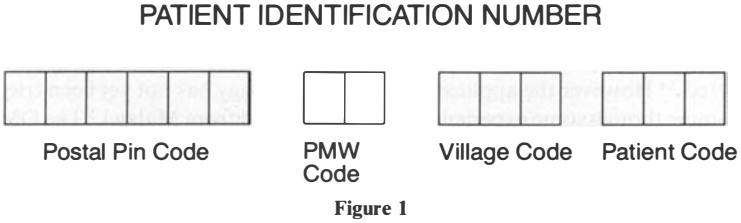

Figure 1

REPORT 1
MONTHLY PROGRESS REPORT FOR SUBSCENTRE PARAMEDICAL WORKER
(Leprosy Patients Registered during the month)

LCU NO:
PMW NO: MONTH: YEAR:

VILLAGE NAME	PATIENT NAME	M F	MB +ve -ve	PB	AGE >14 <14	DISABILITY I II III NO
Total						

Figure 2

REPORT II
MONTHLY PROGRESS REPORT FOR SUBCENTRE PARAMEDICAL WORKER
(Patients Registered Upto End of Reporting Month Since Beginning)

LCU NO:
PMW NO: MONTH: YEAR:

VILLAGE	PATIENT	M F	MB +ve -ve	PB	AGE >14 <14	URINE CHECK +ve -ve	TABLET COUNT C W	PULSE DATE	NO. OF DOSES COMPLE-TED
TOTAL									

Figure 3

REPORT III
MONTHLY PROGRESS REPORT FOR SUBCENTRE PARAMEDICAL WORKER

LCU NO.
PMW NO. UPTO:

VILLAGE NAME	MODE OF DETECTION* 0 1 2 3 4 5 6 7 8 9	FOOTWEAR NEED NOT KNOWN YES NO	SURGICAL NEED NOT KNOWN YES NO	ULCER NOT KNOWN YES NO	REHAB. NEED NOT KNOWN YES NO.	REASON FOR** DISCONTINUITY 0 1 2 3 4 9
Total						

* *00-Not known: 01-General Survey; 02-Contact Survey; 03-Target Survey; 04-Rapid Survey; 05-Voluntary Reporting; 06-Referal by PHC; 07-Referal by GP; 08-Referal by Target people; 09-Others.*

** *0-Not known; 2-Left Control area; 3-Died; 4-Complications due to therapy; 9-Others.*

Figure 4

*REPORT IV/V/VI
MONTHLY PROGRESS REPORT FOR
Medical Officer/District Leprosy Officer/State Leprosy Officer

LCU No./District No./State No.
PMW No: UPTO MONTH: YEAR:

Total No. of Patients (Old + New) MB: PB: Total:
Total No. Released from Treatment (RFT) MB: PB: Total:
Reasons for Discontinuity:
Unknown: By Default: Left Area: Died: Complications due to Therapy: Others
Total No. Completed Surveillance:
Physiotherapy Treatment Given: Yes: No: Not Available:
Footwear Needed: Yes: No: Not Available:
Footwear Provided: Yes: No: Not Available:
New Cases since Start of MDT till today
MB (Positive): MB (Negative): PB:
Age: >14: <14 Sex: Male: Female:
Disability: Grade I Grade II Grade III No Disability
No. of MB patients whose BI not given
No. of patients whose disability status not given:
Total No. of Disabled Cases (Old + New): No disability: Grade I: Grade II: Grade III Not available:
Mode of Detection:
General Survey: Contact Survey: Target Survey: Rapid Survey:
Voluntary Reporting:
Referral by PHC: Referral by General Practitioners: Referral by Target People:
Not Known: Others:

**IV-Medical Officer, V-District Leprosy Officer, VI-State Leprosy Officer*

Figure 5

IMPLEMENTATION IN THE FIELD

To test the feasibility and utility of this computerized system, 6 leprosy control units out of 31 from these 4 MDT districts were chosen and a selected number of staff were given training in the field for 3 days. The contents of the training were: transcribing data from patient cards on to data sheets, internal consistency checking, computer demonstration and use of computer reports for monitoring their work Table 1.

Observations and discussions

With this training, 20 paramedical workers transcribed the data of 1750 patients on to data sheets; the data were processed at Delhi and reports were sent back to the field workers as well as to the programme managers. Review meetings were held to determine the effectiveness of these computerized reports in identifying field problems, improving standards of patient care, generating reliable statistics and producing better programme monitoring at both unit and district level.

Table 1. Staff trained in the computerized monitoring system

District	Leprosy control unit	Paramedical worker	Nonmedical supervisor	Medical officer
Cuttack	Athagarh	6	4	1
Durg	Bhilai	6	2	1
	Durg	3	1	1
	Bemetara	2	1	—
Rajnandgaon	Rajnandgaon	1	1	1
Salem	Tiruchengode	2	2	1
	Total	20	11	5

Over the past year it was observed that: (1) a basic training of three days was sufficient for transcribing data with negligible errors; (2) a maximum of 5 minutes per patient was required to fill in data sheets I and II for the first time after the registration for treatment and subsequently a maximum of half a minute per patient was required to fill in data sheet II with monthly information such as attendance for pulse dose, reactions and complications if any; (3) computerized reports were found to be more useful for monitoring both at microlevel as well as macrolevel; (4) the field workers realized the need for reliable data collection; (5) the staff found that they saved the time previously spent preparing monthly progress reports manually; (6) Reports I, II and III could be used as registers, eg. known case register, treatment register and disability register; (7) the staff were more enthusiastic to adopt this alternative system as they were learning a new technology.

WORKLOAD ON PARAMEDICAL WORKERS (PMWS)

While implementing this system, it was considered as an additional workload on the field staff. Hence the estimated time required for one paramedical worker for his population of 20,000 with an estimated prevalence rate (P R) 10/1000 and incidence rate (I R) 1/1000 was worked out (Table 2). It was presumed that all the 200 patients were brought under MDT at one time. A worker will have to spend a maximum of 16 hours (3 working days) for the first time. Subsequently for both old and new patients, a maximum of 2 hours per month will be spent. With this, all the six reports are generated. No additional time is required to generate Reports IV, V and VI. The field workers and the programme managers at different levels will receive their respective monthly reports directly, quickly and with accurate, reliable and meaningful statistics. On the other hand, in the existing monitoring system, a full day is spent by a field worker preparing an MPR for his subcentre and 2 days are spent at control unit and district level preparing MPRs for a medical officer and a district leprosy officer respectively. In this system delays and inaccuracies are inevitable. These aggregated reports are not useful for individual patient monitoring.

Table 2. Workload on a Paramedical Worker

Transcribing data for the first time for 200 patients put on MDT (5 minutes/patient both Data sheets I and II)	16 hours — 3 working days
Updating 200 patient files (data sheet II) every month (1/2 minute/patient)	1·6 hours/month
New cases every month approximately 2 (Data Sheets I and II)	10 minutes/month

Table 3. Cost of district computerized monitoring system

Hardware/Software	Approximate expenditure (US$)
1 Computer (PC-XT), accessories and floppy discs	6296·0
2 Data sheets and stationaries etc. (5 years)	29700·0
3 Programme package	833·0
Total	36829·0

Thus our initial experience shows that a computerized monitoring system is feasible in a routine leprosy control programme and the field staff can use it for the purpose of improving monitoring. The system can, also, be used for developing a bottom-up monitoring system.

DISTRICT LEVEL COMPUTERIZATION

On a pilot basis, district data were processed at the DANIDA Office in Delhi. Approximately one week was required to receive the data by post and an equal time was required for the staff to receive the computerized reports. To overcome this time lag for despatching and possible loss of records or reports, it was decided to process data at the district level. Hence an approximate expenditure for establishing a district computerized monitoring system was worked out (Table 3).

The cost is worked out for a district with a population of 2 million and an estimated PR 10/1000 assuming that all 20,000 (MB 4000 and PB 16,000) patients are brought under MDT. The initial cost of establishing a computerized monitoring system is high but this expense is offset by the many advantages resulting from the installation of such a system.

Acknowledgments

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Thanks are also due to Mr S Sriram and Mr Ravi Kumar for their active secretarial assistance.

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Delivery of MDT through blister calendar packs in leprosy eradication programmes—a multicentre field study (Phase I)

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Summary To overcome operational problems and improve patient compliance in leprosy programmes, DANIDA introduced blister calendar packs (BCP) to deliver MDT in four districts in India. A questionnaire study of 1470 patients from these districts showed that more than 90% accepted BCP and found them to be very convenient for domiciliary treatment. A similar study of 127 treatment providers indicated that delivery of MDT through BCP was found convenient to overcome logistic problems.

Introduction

One of the important factors for the success of the MDT programme is to obtain maximum compliance for pulse doses as well as for self-administered doses. Compliance is influenced by many factors. Of relevance here are a continuous and regular supply of all the three drugs and simple methods of preserving these drugs at the patients' houses without damage or loss. As the disease is still associated with social stigma, making drug delivery in a socially acceptable attractive form is an additional factor which influences patients' compliance. Other operational factors like easy storage, easy transportation without any loss or damage, easy accounting and preparation for clinics at control unit level could also affect the efficiency of the MDT programme in general.

To overcome operational problems in the field, delivery of antileprosy drugs through BCP similar to oral contraceptives was conceptualized as early as 1983.[1] Ciba-Geigy Basle (1986) designed and manufactured BCP following a WHO recommendation on MDT for multi- and paucibacillary forms of leprosy.[2]

DANIDA is assisting the National Leprosy Eradication Programme (NLEP) in India in four districts (Cuttack in Orissa, Salem in Tamil Nadu, Durg & Rajnandgaon in Madhya Pradesh). As an alternative strategy of drug delivery, it was decided to use BCP for an estimated 160,000 patients (MB 40,000 and PB 120,000) with the following objectives:

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Improved drug supply:
Safe—no pilfering, no spoilage.
Effective—right drug regimen is given.
Efficient—easy drug delivery.

Improved patient compliance:
Safe—self-protected, easy storage at patient's house.
Regular—self-monitoring possible.

Increased cost-effectiveness:

Pharmanova, Copenhagen designed and manufactured these packets for MB-adults (red colour), PB-adults (green colour) and PB-children 6–14 years (blue colour) suitable for the Indian MDT programme.[3] As no published reports are yet available on evaluation of this alternative approach in improving operational efficiency of the programme, DANIDA decided to undertake a multicentre field study to find out: (a) feasibility of using BCP in the vertical leprosy programme; (b) influence of these packed drugs on patients and field staff; and (c) cost-effectiveness of using blister packs.

In this paper results of Phase I of the study are reported.

Material and methods

This multicentre study was designed in two phases:

Phase I. A structured questionnaire study was designed to obtain subjective impressions of patients and staff regarding the acceptance and use of BCP in a routine MDT programme.
Phase II. A study of patient compliance comparing patients receiving blister packs with patients in the same district receiving bulk drugs.

METHODOLOGY FOR PHASE I STUDY

1 Under NLEP-India, MDT is being delivered through a circuit plan (a circuit consists of 2 subcentres of 2 paramedical workers with approximately 40,000 population).[4]
2 Subcentres which had completed a minimum of 6 months' treatment with BCP were selected randomly.
3 At the time of this study a total of 48,000 patients were given BCP in all the four districts. A total of 10,000 patients had completed 6 months of MDT in 105 subcentres. Out of these, 57 subcentres were selected randomly and 1470 (14%) adult patients were interviewed.
4 To overcome any bias, the interviews were conducted by volunteers not connected with the programme.
5 From the same subcentres 127 control unit staff were randomly selected for interview.

Table 1. Number of leprosy patients interviewed

	Type		Sex	
No. of patients interviewed	MB	PB	M	F
1470	615	855	947	523
%	42	58	64	36

Table 2. Impressions of patients on blister calendar packs (BCP)

Questions		No. of patients with positive answers	%
1	BCP are attractive	1433	97
2	Preservation and handling are easy	1449	99
3	Tablets could be taken out easily from BCP	1446	98
4	Drugs are not spoiled	1395	95
5	BCP helps patients to take drugs regularly	1357	92
6	Drugs are taken regularly	1362	93
7	Drugs are very effective	1351	92
8	Printed numbers on BCP are not understood	802	55
9	Instructions for preservation are not understood	996	68
10	Last tablet reminds the patient of clinic day	772	49

Table 3. Impressions of staff on blister calendar packs (BCP)

Questions		No. of staff with positive answers	%
1	BCP attractive	126	99
2	Easy to handle, transport and preserve	124	98
3	Attendance rate for pulse clinic increased	113	89
4	Regularity for self-administered doses increased	120	94
5	Tablet count shows correct self-administered dose	108	85
6	Clofazimine capsules stick inside the pack	74	58
7	Blister packs are not lost by the patients	109	86
8	BCP suits the circuit plan and pulse clinic	105	83
9	Drug accounting, dispensing and instructing patients easy with BCP	101	79
10	Time required for counting BCP for a clinic:		
	(a) less than 1 hour	111	87
	(b) 1–3 hours	16	13
11	Time required for counting and packing loose drugs for a clinic:		
	(a) 3–5 hours	84	66
	(b) more than 5 hours	43	34

Results and discussion

A total of 1470 were interviewed, 1213 (83%) had treatment for 6–12 months and 257 (17%) had more than 12 months treatment with blister calendar packs (Table 1).

1 These answers (Table 2) indicate that blister calendar packs were well accepted by the patients. They were attractive, could be preserved easily at home and drugs were not spoiled. Only 5% of patients reported that clofazimine capsules were sticking to the PVC and broke when removed.

2 More than 92% of the patients said that they were taking drugs regularly. More than 50% of the patients were not able to read the numbers and instructions written on the BCP. This indicates that there is further scope for improving the design of BCP. Perhaps their sequence could be given in pictorial form, i.e. showing arrow marks for directions, symbolic presentations for days, etc. Only 392 (27%) said that they could understand instructions written in English.

3 Of the patients 92% said that these drugs were very effective. This impression could be due to the attractive exterior of BCP.

The answers (Table 3) indicate that the staff of leprosy control units from all these four districts found that the BCP were attractive, easy to deliver and that less time was used in preparing for

clinics compared with using bulk drugs. This was based on their experience during the first 14 days of intensive therapy where all the drugs were delivered loose. The subjective impression of the staff on the increase in regularity is to be confirmed by an objective study which is in progress.

This preliminary study has shown that BCP were accepted both by the leprosy patients and the staff. The BCP design was suitable for the MDT programme and facilitated delivery of the right drugs by the colour of the packs. Drug accounting, storage and transportation was also found to be easier. These findings support our initial observations reported earlier.[5]

One reservation about the use of BCP on a mass scale would be the additional cost over bulk drugs. However, once economies of scale are achieved in the production of BCP, it is believed that the price differential will probably be no more than 15%.

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Will the leprosy endemic in Rwanda soon be under control?

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Introduction

It appears that leprosy in Rwanda is becoming a rather rare disease. By the end of 1987, 1142 cases were still under treatment, a prevalence rate of 0·17 per thousand. Prevalence rates declined from 0·26 per thousand in 1982, by an average of 0·018 per thousand a year. However, it is necessary to know whether the number of known patients reflects reality, and if case finding has been adequate. In other words: has the detection rate been a reliable indication of the incidence rate? This paper studies the problem, and tries to see if any conclusions can be made about the transmission of leprosy in the Rwandan population.

In the past, it has been suggested that a prevalence survey would be the most accurate way to evaluate leprosy prevalence. A preliminary study of the project however showed that, if we wanted to obtain acceptable margins of error, the sample to examine would be of about 225,000 persons.[1] A survey of such size would be costly in time, money and personnel. Unfortunately, these disadvantages would outweigh any advantages to be gained from this procedure. So, we had to look for other methods to evaluate the importance of the leprosy problem in Rwanda, and particularly evaluate some epidemiological indices relating to the incidence rate.

Materials and methods

From 1964 to 1984, leprosy control in Rwanda was essentially organized by the Damien Foundation Belgium (DFB), in cooperation with the Rwandan Authorities. Detection and treatment of ambulatory patients was done by mobile units covering most of the country. In 1984, the Ministry of Health created a National Service for Leprosy Control (Service National de Lutte Contre la Lèpre, SNLCL). The SNLCL, sustained by the Damien Foundation Belgium, continued working with mobile units, insisting particularly on the integration of leprosy control with primary health care. Over 200 health centres out of 260 existing in Rwanda are visited at least 4 times a year.

Detection of new cases is done in a semipassive way—patients presenting themselves at the dispensaries or health centres visited by the mobile units. Leprosy cases are identified by the dispensary nurse, or by the person in charge of the mobile unit, during dermatology consultations. Information campaigns are being organized to inform people about the early signs of leprosy so as to motivate them to present themselves at the dermatology consultations. New patients are invited to bring along their children and household contacts for examination.

From 1977 to 1987, 564 new cases of leprosy were diagnosed and registered in Rwanda. At the

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end of each year, a statistical form was made up by the representative of the Damien Foundation Belgium, from the patients' individual forms. The data of these statistical forms are used in this paper.

From 1982 multidrug therapy (MDT) was introduced for all newly detected cases. An individual form was completed at the moment of detection for all new patients, including clinical examination in detail, skin smear results and histopathology, using the protocols elaborated by Professor Pattyn of the Antwerp Institute for Tropical Medicine. The individual forms for new cases 1982–7 have been reviewed, excluding those who died or disappeared; 233 forms out of 257 were studied and the following data were extracted:

age at detection (from identity cards);
index cases (did the patient know any leprosy patients personally?). Those with first degree family ties and husbands and wives were considered as household contacts. Most of the index cases who were household contacts and some of the other index cases were known leprosy patients under treatment;
disability grade on presentation, using the previous 0–3 grades WHO code for hands, feet and eyes.[2] A patient was considered as disabled if he had at least one member or one eye disabled at grade 2;
leprosy classification, based on clinical examination, skin smears (examined by the Service National de Lutte Contre la Lèpre) and histopathology (Professor Pattyn). A bacteriological index (BI) of 0 and 1 was classified as paucibacillary (PB), a BI of 2 or more as multibacillary (MB);
sex;
number of skin lesions for PB patients. (We separated those presenting 3 skin lesions or less, and those presenting more than 3 skin lesions.)

Population figures are based on those of the 1978 census, the 1983 'Enquête National sur la Fécondité' (National Investigation on Fertility) and the estimated annual growth rate. All these figures were presented by the National Office for Population (ONAPO).[3] The average number of household contacts, people living in the same house as the leprosy patients, was estimated according to a sample taken at random from 200 of the questionnaires of all known leprosy patients, established by the social workers of the Service National de Lutte Contre la Lèpre. Operational indices after detection will not be discussed in this paper.

Statistics

The differences between groups of patients were analysed using the χ^2 test, or the χ^2 test including Yates' correction if the number of patients was too small. Results were accepted as statistically significant if $p \leqslant 0{\cdot}05$. Graphical tendencies were evaluated by means of Spearmans' correlation coefficient of order.

Results

1 Table 1 shows the annual number of newly detected cases (NC), the number of cases under 15 years of age, the number of multibacillary cases (MB), the number of patients disabled at detection, the population covered and the detection rate (DR) per 100,000. The percentages are given in brackets for the different data.

2 The distribution by age and by year of detection of new patients 1982–87 is shown in Table 2. The distribution by age and sex of new cases 1982–7 is represented in Table 3 together with the number of multibacillary cases (MB), the number of patients disabled at detection, the number of patients with an index case and the number of patients whose index case was a household contact. The data of Tables 2 and 3 were collected from 233 individual forms.

Table 1. New cases registered and detection rate in Rwanda 1977–87

Year	NC	Age	0–14 (%)	MB	(%)	Disabled (%)	Population	DR per 100,000
1977	56	4	(7·2)	28	(50·0)		4,645,822	1·2
1978	81	10	(12·3)	40	(49·4)		4,819,317	1·7
1979	49	4	(8·2)	21	(42·8)		4,992,812	1·0
1980	57	2	(3·5)	33	(57·8)		5,172,554	1·1
1981	64	4	(6·3)	24	(37·5)		5,358,766	1·2
1982	52	4	(7·6)	13	(25·0)	16 (30·7)	5,542,042	0·9
1983	55	2	(3·6)	15	(27·3)	11 (20·0)	5,739,061	1·0
1984	56	1	(2·0)	16	(28·5)	17 (30·3)	5,943,085	0·9
1985	25	5	(20·0)	7	(28·0)	8 (32·0)	6,154,362	0·4
1986	25	3	(12·0)	7	(28·0)	4 (16·0)	6,373,591	0·4
1987	44	4	(9·1)	14	(31·8)	9 (20·5)	6,603,040	0·7
Total:	564	43	(7·6)	218	(38·7)	65 (25·3)		

Table 2. Distribution by age and by year of detection of new patients in Rwanda 1982–7

Age	0–14	15–29	30–44	45–59	60+	?
1982	4	11	14	12	6	
1983	2	10	17	14	5	1
1984	1	13	17	14	6	
1985	3	5	8	6	2	
1986	4	3	7	5	4	
1987	3	8	10	9	7	2
Total	17	50	73	60	30	3

Table 3. Distribution by age and sex of new patients in Rwanda 1982–7

Age	0–14	15–29	30–44	45–59	60+	?	Total
New patients 1982–7	17	50	73	60	30	3	233
Males	11	26	36	27	16	2	118
Females	6	24	43	28	14	1	115
MB	5	24	22	12	5	1	69
Disabled at detection	1	10	22	17	13	2	65
Patients with index cases	17	18	30	22	6	—	93
Household contact index cases	15	12	13	6	3	—	49

In 3 cases (adults), age was not marked on the patients' individual form. Out of the male patients, 39 were MB, and 31 were disabled at detection. Out of the female patients, 30 were MB and 34 disabled. Eight out of 49 patients with household contact index cases were disabled at detection.
3 The number of paucibacillary (PB) cases showing 3 skin lesions or less at detection was 26 out of 164 PB cases. Out of 26, 2 were disabled, 14 were male and 12 female. The distribution according to age groups is shown in Table 4.

Table 4. Age distribution of new PB patients presenting 3 skin lesions or less at detection, Rwanda 1982–7

Age	0–14	15–29	30–44	45–59	60+	total
New PB patients 1982–87	12	26	51	48	25	164
Patients with 3 skin lesions or less	2	3	9	8	4	26

Discussion

1 If we want to study the incidence of leprosy in a given population, the first index to look at is the detection rate, which is represented in Table 1 and Figure 1. Since 1977, this rate shows a general decrease. This tendency was tested by means of Spearmans' correlation coefficient of order, which is $-0{\cdot}891$ ($dl=9$). The test gives a statistically significant result ($p \leqslant 0{\cdot}01$).

Some of the annual detection rate figures need further comment. The steep dip during 1985–6, the years of transition, may be due to diminished control activities while the Service National de Lutte Contre la Lèpre was being set up. The 1987 rise could then be seen as a 'catching-up' manoeuvre of previously undetected cases, and is probably a good sign.

How can we ascertain whether the detection rate is representative of the incidence rate? We used three indices for this:

1.1 The most reliable index to estimate the quality of detection is to follow the proportion of disabled patients among newly detected cases. Indeed, if patients are detected at an early stage of disease, they are not yet disabled. In the best projects for leprosy control, the proportion of disabled patients is about 5–8% of the new patients.[4] For projects having a higher proportion of disabled new cases, a gradual decrease of this percentage means that detection is improving.

For Rwanda, reliable figures can be found from 1982 onwards. (Table 1). In total, 65 of 257 new cases detected since 1982 were disabled, or 25·3%. This is a relatively high percentage, compared with other countries and services. The evolution of the proportion of disabled new cases is represented in Figure 2. There is no significant decrease of the proportion. (Spearmans' test $r'=0{\cdot}31$, $dl=4$, nonsignificant result.)

1.2 The second index we studied is the proportion of new PB patients showing 3 skin lesions or less at detection. Among these patients are those who presented themselves at the first sign of the

Figure 1. Evolution of detection rate per 100,000, Rwanda 1977–87.

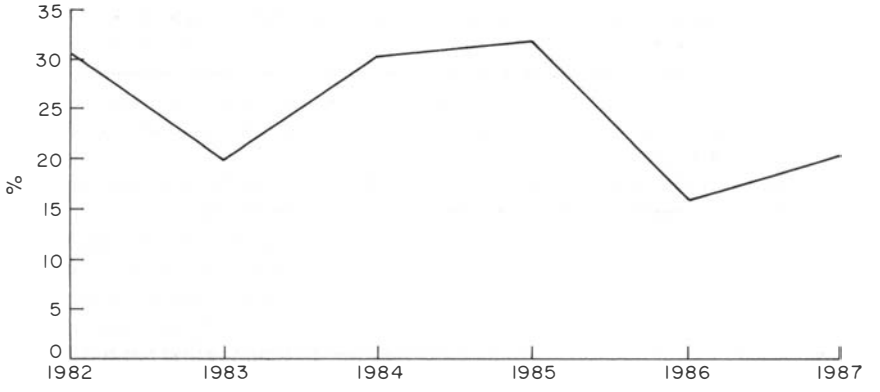

Figure 2. Evolution of the percentage of new cases disabled at detection, Rwanda 1982–7.

disease, and were also recognized at an early stage. We chose this index according to the study of new therapeutic schemes of Professor Pattyn of the Antwerp Institute for Tropical Medicine, in which we collaborated, that shows significantly better therapeutic results for patients showing 3 skin lesions or less.[5] If we study the new patients 1982–7, we find significantly less disabled patients among those presenting 3 skin lesions or less, than among the PB patients presenting more than 3 skin lesions (2 out of 26 *vs* 47 out of 138, χ^2 (Yates) = 6·055, $0{\cdot}02 > p > 0{\cdot}01$). These statistics confirm the assumption that detection is particularly early in the group of patients presenting 3 skin lesions or less. Out of 164 new PB cases 1982–7, 26 or 16% presented 3 skin lesions or less at detection. Even if it is difficult to compare these figures with other leprosy control centres or countries, it is obvious that this percentage is not high.

1.3 The third index is the evolution of the proportion of MB cases to the total of newly detected cases. At the start of a leprosy control programme, this proportion is elevated. When the programme is under way, the proportion gradually decreases, and stabilizes when the detection rate becomes close to the true incidence. If early detection is taking place, the proportion should be constant too.[6]

For Rwanda, the proportion of MB cases to the total of new cases is represented in Table 1 and Figure 3. This proportion shows an important decrease, coming from ± 50% before 1981 to 25% after 1982. During the period 1982–7, the proportion stabilizes between 25 and 31%. (Spearmans' test $r' = 0{\cdot}743$, $dl = 4$, not significant).

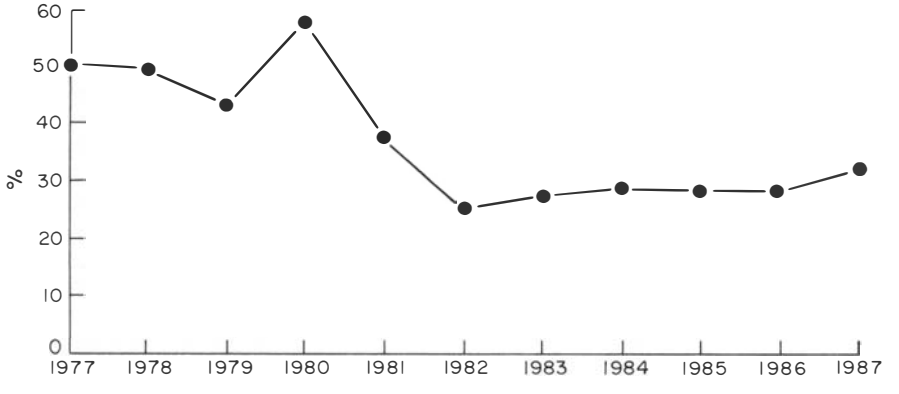

Figure 3. Evolution of the percentage of new MB cases among the total of new cases, Rwanda, 1977–87.

Here, it is important to watch more closely the diagnostic tools used during the 1977–81 period versus those used in 1982–7. Before 1981, diagnosis and classification of patients was essentially based on clinical aspects: skin smears and biopsies were not systematically performed. After 1982, every new patient had at least one skin smear and one skin biopsy taken. Obviously, diagnoses made from 1982 onwards were much more reliable, and it is possible that MB cases were overdiagnosed during the 1977–81 period.

The stabilization of the proportion of the new MB cases to the total of new cases after 1982 seems to indicate that detection rate approaches the true incidence rate.

When we look at the first two indices of quality of detection, we have to conclude that detection of cases in Rwanda is certainly not very early. This implies that probably a number of cases are not detected. However, it is impossible to determine more accurately the number of patients.

The evolution of the proportion of new MB cases to the total of new cases seems to be in contradiction with the first two indices, indicating that the detection rate is not too far away from the true incidence rate. It may be that, although patients are obviously not detected in the early stage, most are actually detected later on, the time lapse between the appearance of the first signs and detection being long but fairly constant. The evolution of the detection rate therefore is a correct indication of the evolution of the incidence rate, and the underestimation of the incidence rate is constant, not detecting the one-macule cases, as they often heal spontaneously.

The causes of overall late detection are complex and will not be discussed in detail here. We want to mention however three reasons, which we feel are important: as the disease is becoming rare, early signs are not easily recognized by the population or by medical workers; leprosy still carries an important social stigma; and in Rwanda, detection seems to be generally late for most diseases and leprosy is no exception.

2 After discussion of the detection rate, a second criterion studied is the distribution of the new cases by age and sex. This results in important information regarding endemicity of the disease and its transmission in a population.

2.1 The distribution of new cases according to age groups. This distribution is very similar in many high endemic areas, where there is a clear peak at ages 10–14 followed by a depression which in turn is followed by a rise and a plateau covering 30–60.[7] If there is a peak in the adult ages, and the detection rate is low or becomes minimal among children and young people, one can expect an extinction of the leprosy endemic.[8] Li *et al.* demonstrated a gradual shift towards older age groups in Shandong, China, over a 25-year period when incidence rates were declining.[9]

In Rwanda, the period of time for which we have reliable figures regarding age distribution and the numbers of patients are too limited to show any significant evolution during that period. Age distribution over the years 1982–7 show the same characteristics and therefore all new patients were seen as one single patient group.

Table 5 represents age distribution of the new cases 1982–7, as drawn from the individual patients' forms, including the relative percentage of each group in the total of new cases. The percentage of the total population belonging to each age group, the average number of people for the 1982–7 period in each age group and the average annual age-specific detection rate (1982–7) per 100,000 are shown.

The average annual age-specific detection rate (1982–7) is represented graphically in Figure 4. The relative risk for each age group and its confidence interval are represented in Table 6. The relative risk is the risk for any individual of a certain age group to be detected, in comparison with the other age groups.

Looking at these figures, however, we should ask ourselves whether they reflect reality: perhaps detection among children is of very poor quality? To answer this question, we wanted to compare the indices for quality of detection for the different age groups. But, as children are known to develop a generally benign form of leprosy leading to few disabilities,[10] the first index is of little value. Even if we find statistically less disabled patients among children (as is the case in Rwanda, $p \leqslant 0{\cdot}05$), this is exactly what we should expect to find, even if detection is not early at all. As for the

Table 5. Average annual age-specific detection rate per 100,000 Rwanda 1982–7

Age	0–14	15–29	30–44	45–60	60+
New patients	17	50	73	60	30
% of new patients	7·4	21·7	31·7	26·1	13·0
% of population	48·4	25·9	12·6	8·3	4·8
Average population	2,932,651	1,569,332	763,459	502,913	290,841
Average annual detection rate per 100,000	0·1	0·5	1·6	2·0	1·7

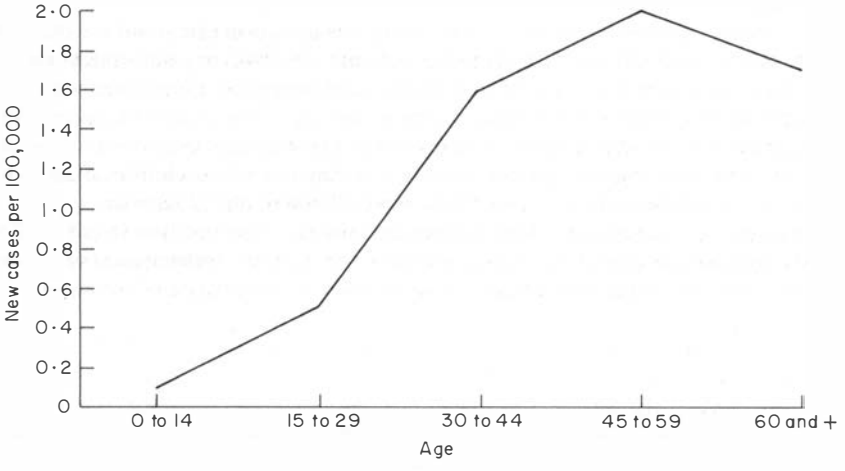

Figure 4. Average annual age-specific detection rate per 100,000, Rwanda 1982–87.

Table 6. Relative risk for different age groups, new cases in Rwanda 1982–7

Age	Relative risk	Confidence interval
0–14	0·09	(0·05–0·14)
15–29	0·80	(0·58–1·09)
30–44	3·23	(2·45–4·25)
45–59	3·90	(2·90–5·22)
60+	2·98	(2·03–4·35)

number of new cases presenting 3 skin lesions or less at the moment of detection, there was no significant difference between age groups. We can only conclude from this that we see no reason why detection should be particularly late among children.

As the overall detection rate among children and young adults is indeed very low, the age distribution of new cases in Rwanda shows the characteristics of a region where there is extinction of the leprosy endemic.

2.2 The sex distribution of new cases 1982–7 is represented in Table 3. Before 1982, no reliable figures are available. The 1982–7 figures do not show any statistically significant differences in

detection rates for male and female, in proportion of MB cases for male and female, or in the indices of quality of detection.

As sex distribution for leprosy seems to vary a lot world-wide, we prefer not to make conclusions regarding these findings.

3 Finally, it is interesting to study more closely the group of household contacts of the leprosy patients, as the occurrence of leprosy in family clusters has been particularly observed in low endemic areas.[1]

The Rwandan leprosy patient has an estimated average number of household contacts of 4·6. For 1984, the 1626 known patients under treatment or under observation had 7480 household contacts. Out of these, 49 were found to have developed leprosy over a period of 6 years. The relative risk of household contacts versus the total population minus the household contacts, is extremely high: 216·88 (158·31–296·31).

Detection of new cases among household contacts was not particularly early: 8 out of 49 were disabled at detection, versus 57 out of 208 patients without index cases or whose index case was not a household contact ($\chi^2 = 2{\cdot}58$ $p \leqslant 0{\cdot}20$, not significant). Eight out of 32 PB patients with household contact index cases had 3 skin lesions or less, versus 18 out of 132 other new PB patients ($\chi^2 = 2{\cdot}50$ $p \leqslant 0{\cdot}20$, not significant). The assumption that leprosy patients play an important role as detection agents, was not confirmed. Sex distribution among new cases with household contact index cases was the same as for the total of new cases. There were 27 males and 22 females.

The elevated relative risk of household contacts and the fact observed that 15 out of 17 infected children had index cases who were household contacts, indicate that transmission of the disease in recent years has been, to a high degree, limited to the household contacts of the leprosy patients.

Conclusion

The three criteria studied: the detection/incidence rate, the age and sex distribution of new cases and the new cases among household contacts of leprosy patients, suggest that leprosy transmission in Rwanda is low—certainly outside the family clusters—and still diminishing. Taking into account the decreasing prevalence rates, we believe that the leprosy endemic in Rwanda can be controlled within a limited period of time, certainly before the goal of the World Health Organisation for leprosy control worldwide by the year 2000.

As to our own strategy in the field, we conclude that there should be more emphasis on contact survey and on informing the public and the medical staff of the first signs of the disease so as to make early detection easier. In this way, we hope to prevent more patients from becoming disabled.

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DDS-induced photosensitivity with reference to six case reports

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Summary Photosensitivity as an adverse reaction to DDS was recognized in 6 patients of our hospital during the summer of 1988. The clinical manifestations and also the management of those patients are given in detail. All doctors and health workers involved with leprosy need to be aware of such a problem and to take correct decisions after weighing the risk of photosensitivity against the potential benefit of DDS.

Introduction

Among all the side-effects of dapsone, drug-induced photosensitivity is a relatively rare phenomenon. DDS, a substrate competitive inhibitor of *p*-aminobenzoic acid in the folate metabolism is similar to sulphonamides in not only the mechanism of action, but also in causing a variety of skin manifestations as side-effects like chemical photosensitivity. In tropical countries like India where the intensity of ultraviolet radiation due to sunlight is relatively high, DDS-induced photosensitivity is likely to be observed more frequently.

Case Report 1

This female patient, aged 19, commenced a WHO paucibacillary regimen (DDS and rifampicin) on 7 February 1987.

On March 25 the patient came to the hospital with itching, diffuse desquamation and swelling of the extremities of 2 weeks duration. Clinically the patient had oedema and desquamation only on exposed areas: face, neck, both forearms and dorsum of both feet.

She was hospitalized and managed with prednisolone for a short period after discontinuing DDS. The swelling and desquamation then subsided. On 4 April the patient was given DDS 100 mg and observed for any skin reaction. As it was thought initially the skin lesions were due to hypersensitivity phenomenon, the patient was kept indoors while being tested with DDS. Despite that, the patient developed itching and papules over the extremities after 1 h. So DDS had to be discontinued permanently.

The patient came again with the same skin manifestations and swelling of the extremities on 16 April. She was then managed with prednisolone for 2 weeks. The lesions subsided and she was discharged. Later on there was no recurrence and clofazimine was given instead of DDS.

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Case Report 2

This male patient, aged 49, started a WHO multibacillary regimen (DDS, clofazimine and rifampicin) on 28 December 1987.

On 9 February 1988 the patient came to the mobile clinic with desquamation, papules and hyperpigmentation over upper extremities and fissures over the lips. The lesions were confined only to exposed areas.

The patient was admitted after 2 days and treated with a short course of prednisolone after having withdrawn DDS from the regimen. The skin lesions had then subsided. On 25 February the patient was given DDS 100 mg and checked for any skin reaction. As in the first case the patient was kept indoors. The patient had no itching or skin lesion, hence DDS was continued.

After 1 week the patient came with recurrence of the same skin lesions and itching present over both the forearms, face and lips. DDS was stopped and the patient was managed with systemic antihistamines and topical zinc oxide ointment as a sunscreen. Later on DDS was discontinued permanently and he was given INH instead.

Case Report 3

This female patient, aged 35, started a WHO multibacillary regimen (DDS, clofazimine and rifampicin) on 30 December 1987.

On 18 March 1988 the patient came to the hospital with itching and skin lesions. On examination the patient was found to have skin coloured papules and plaques over the extensor aspect of both forearms and erythematous papules over the nape of the neck. The patient was treated as an out-patient. DDS was stopped and the skin lesions were treated with systemic prednisolone. During that period of 3 weeks, the patient was advised to stay indoors and to apply *p*-aminobenzoic acid ointment during the daytime. After the skin lesions had subsided, she was given DDS 100 mg and exposed to sunlight for 2 hours. As the patient had no itching or skin lesion, DDS was continued. Since then the patient has had no problems with DDS.

Case Report 4

This female patient, aged 38, commenced a WHO multibacillary regimen (DDS, clofazimine and rifampicin) on 21 September 1987.

On 2 May 1988 the patient came to the mobile clinic with itching, diffuse desquamation and hyperkeratosis of the forearms and dorsum of both hands. Clinically the lesions were found only over exposed areas. DDS was then stopped and the patient was managed with topical application of zinc oxide ointment, systemic antihistamines and advised to stay indoors during the daytime.

On 17 May the patient was hospitalized as there was no relief with the above management. She was then treated with oral prednisolone and topical zinc oxide ointment. The lesions subsided after 2 weeks. She was then given DDS 100 mg and kept outdoors to expose herself to sunlight. Since there was no itching or any skin lesion after 2 h of exposure, the patient was advised to continue DDS. After 2 months, she again came with hyperkeratosis of the exposed areas of the dorsum of both feet and desquamation of the dorsum of both hands. As the skin lesions were mild when compared to the first episode, DDS was continued while reducing exposure to sunlight using topical zinc oxide ointment as a sunscreen. When she came to the next clinic she still had mild desquamation of the hands which was not troublesome to her.

Case Report 5

This female patient, age unknown, commenced treatment of a WHO multibacillary regimen (DDS, clofazimine and rifampicin) on 19 August 1987.

On 11 May 1988 the patient presented herself with itching and erythematous papules over the exposed areas, i.e. extensor aspect of both forearms, face, dorsum of both feet and abdomen, of 2 week's duration.

She was managed as an outpatient with oral prednisolone in combination with *p*-aminobenzoic acid topically as a sunscreen during the daytime. The lesions disappeared. On 1 June 1988 the patient was given DDS 100 mg and observed for photosensitivity. The patient had no itching or skin lesions after an hour of exposure. DDS was then continued.

On 29 June the patient came again to the clinic with the recurrence of the same skin lesions over the extensor aspect of both forearms and face. DDS was again stopped and the skin lesions were treated with topical zinc oxide and systemic antihistamine. Afterwards, DDS was withdrawn from the regimen while clofazimine and rifampicin were continued.

Case Report 6

This female patient aged 37 commenced a WHO multibacillary regimen (DDS, clofazimine and rifampicin) on 11 May 1988.

On 8 July 1988 the patient presented herself with the complaints of papules of one week's duration on both forearms, neck, abdomen, face and both legs. On examination the papules were erythematous and seen only over the exposed areas extending slightly beneath the blouse.

DDS was stopped while clofazimine and rifampicin were continued. The patient was treated with antihistamines systemically and zinc oxide ointment topically with the advice to keep indoors. The skin lesions and itching had subsided after 1 week. She was then tested for photosensitivity with DDS 100 mg in combination with sunlight. As the patient developed no skin lesions after an hour of exposure, DDS was continued.

But the patient came again with the recurrence of the same skin lesions the very next week. Actually the lesions had started the same evening on the day of restarting DDS. DDS was then stopped permanently and the photosensitivity was managed with zinc oxide ointment as a sunscreen and systemic antihistamines. She had no problem when she came for the next clinic and ethionamide was given instead of DDS.

Discussion

Photosensitivity reactions can be broadly classified into phototoxic and photoallergic. The former depends upon the intensity of ultraviolet radiation and the concentration of the offending agent and is independent of the immune system. The latter involves the cell-mediated immune system and is independent of the intensity of ultraviolet radiation. Clinically the phototoxic reactions are the exaggeration of sunburn, i.e. erythema, swelling and even bullae. Hyperpigmentation and desquamation can also occur. Photoallergic reactions consist of erythematous eruptions, discrete papules and plaques.

In the first case report, though initially the patient had phototoxic reaction, later on when tested with DDS, she also developed photoallergic reaction, i.e. multiple papules. She also came with a recurrence of the same type of skin lesions after 10 days. Though the long half-life of the DDS due to enterohepatic circulation may account for this event even after stopping the drug, the concentration may not be adequate to induce 'phototoxic' photosensitivity.

The photosensitivity is mainly phototoxic in the second case report as hyperpigmentation and desquamation were the main manifestations. The presence of a few papules may also indicate the involvement of a photoallergic mechanism. Likewise case reports 3, 5 and 6 also had both phototoxic and photoallergic reactions. The fourth case report reveals the presence of a phototoxic reaction only.

It is obvious from the case reports that the photosensitivity occurred during the months of April, May and June which are supposed to be the hottest months in India, i.e. when the intensity of ultraviolet radiation is high. In all the case reports, the photosensitivity was recurrent and most of them needed systemic corticosteroid therapy.

Regarding the management aspects, mild photosensitivity may respond to the withdrawal of DDS, topical sunscreen and systemic antihistamines. Systemic corticosteroid is needed if the reaction is severe. In the first two case reports the patients were not kept outdoors as it was thought that all skin reactions were due to hypersensitivity. The question of continuation or withdrawal of DDS after one episode of photosensitivity is difficult to answer. As DDS is a potent antileprotic drug and the photosensitivity reactions are less harmful when compared to the other allergic skin manifestations of sulphones, DDS can be continued. If the patient develops severe skin reaction during testing with DDS, the same drug can be stopped temporarily with the intention of continuing after the summer period. In the case of a patient also developing recurrent severe skin reaction during the winter, DDS should be stopped permanently.

If the recurrent reactions are mild, DDS may be continued with the advice to keep indoors and/or use sunscreens topically during the daytime. Other physical measures such as wearing long-sleeved shirts or blouses and using an umbrella during the daytime to minimize exposure to sunlight can also be valuable adjuvants in the management of mild photosensitivity.

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SPECIAL ARTICLE

Changes in epidemiological indices following the introduction of WHO MDT into the Guyana leprosy control programme*

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Summary In December 1981 the multidrug regimen recommended by the WHO Study Group of October 1981, was introduced into the Guyana Hansen's Disease Programme. This paper examines the changes that occurred in epidemiological indices over the 6 years following the introduction of MDT and also evaluates changing work loads and staffing patterns.

Introduction

The present Guyana Leprosy Control Programme began in 1971, when dapsone monotherapy had been in use for nearly 20 years. Clofazimine and rifampicin gradually became available and by the late 1970s multibacillary patients were receiving all 3 drugs together; rifampicin for a course of 3 weeks at the beginning of treatment and repeated annually until smear-negativity. All drugs were self-administered. Paucibacillary patients were treated for 2–10 years after inactivity and multibacillary patients, while remaining indefinitely on maintenance dapsone, were kept on the active register for 5 years after inactivity. Since MDT all patients have been moved onto a surveillance register on completing treatment and only those patients receiving treatment have been included in statistical returns. This paper describes the changes that occurred in epidemiological indices when the supervised treatment regimen recommended by WHO was introduced into a programme in which multibacillary patients were already receiving multiple drugs but were not receiving supervised treatment.

Prevalence rates

During the 6 years before MDT, 1975–81, the prevalence rate fell by steps from 0·9 to 0·6 per thousand—a fall of 33% or 5·5% a year—whereas over the 6 years following MDT the rate of fall doubled to 67% or an average annual rate of fall of approximately 11%. In the last 3 years, 1985–87, the prevalence rate has been stable at 0·2 per thousand. The stepwise fall in prevalence before MDT is clearly shown in Figure 1 (the rise in 1982 is an artefact due to the fact that following MDT all patients on treatment, regardless of activity, are included in prevalence calculations whereas before MDT only clinically active patients were so included). Over the 3 years before multiple drugs were used the prevalence rate fell by 0·1 per thousand, in the next 3 years—when both multiple drugs and

* The above paper was presented at the XIII ILA Congress in The Hague, September 1988.

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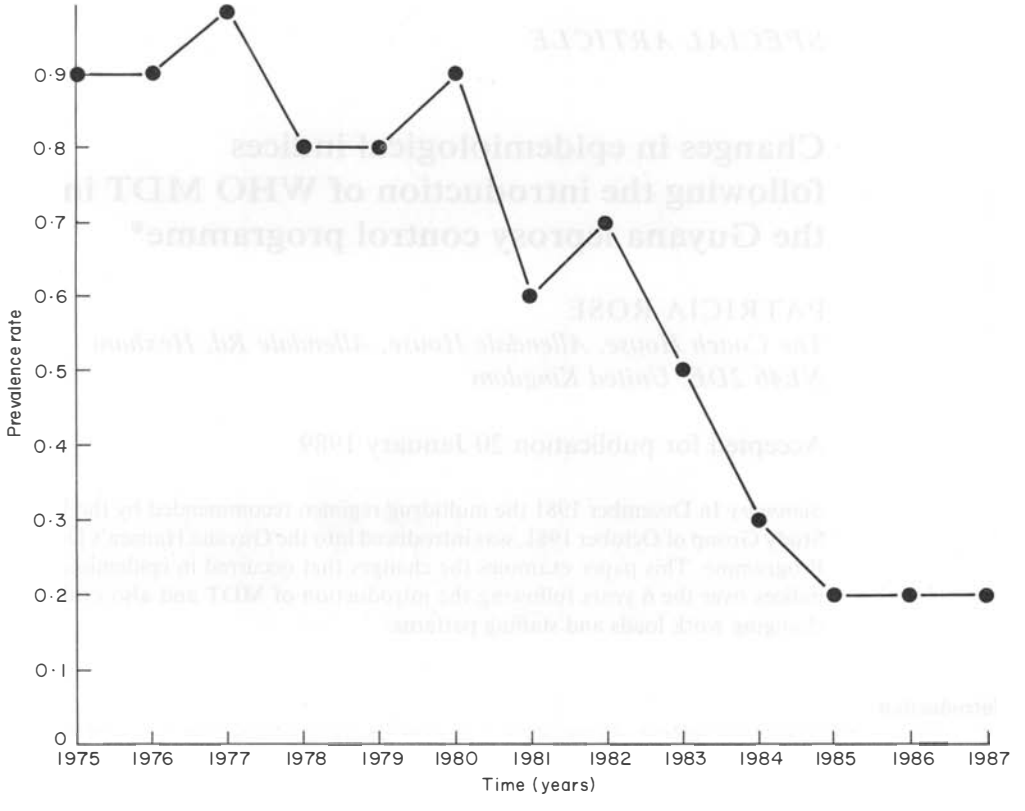

Figure 1. Prevalence rates per thousand population, 1975–87.

grant aid were available—prevalence fell by 0·2 per thousand and in the first 3 years of MDT the rate fell by 0·3 per thousand.

So, when introduced into a programme in which the prevalence rate was already falling, MDT produced an appreciable and sustained increase in the rate of decline of prevalence. Any further decline is likely to be slow as the use of MDT has altered the composition of the pool of patients on treatment from one almost equally divided between paucibacillary and multibacillary to one where about 70% of the patients at year-end are multibacillary.

Incidence rates

Incidence measures the number of new cases occurring in a defined population during a specific time, usually a year. This implies a state of perfection in which all new cases are identified as they occur but because this is difficult to achieve a case-detection rate may be calculated instead. Figure 2 gives the case-detection rates per 100,000 population for the period 1975–87. The rate increased in the late 1970s, following programme expansion on receipt of external budgetary support, peaked at 14/100,000 in 1982 and fell to a level of 7/100,000 in 1986 and 1987. However, before using these figures to judge the effect of MDT on incidence it is wise to ensure that the case-detection rate is

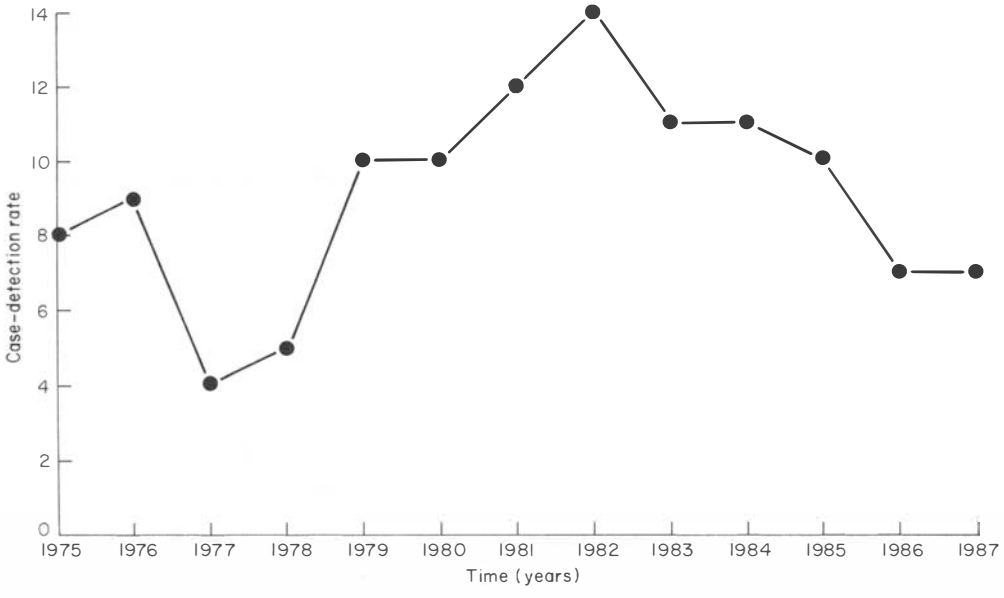

Figure 2. Case-detection rates per 100,000 population, 1975–87.

actually representative of incidence. There are three ways of gauging the validity of case-detection rates with regard to incidence.

ASSESSMENT OF THE PROPORTION OF DISABLED NEW PATIENTS

Firstly, the assessment of the proportion of disabled new patients is helpful. As deformities usually take a long time to develop patients should, ideally, be identified before they become disabled and a large number of disabled new patients indicates that many are suffering from long-standing disease. A study of the ages of new patients in Guyana between 1971 and 1986 has shown that disabled patients have been at least 8 years older, on diagnosis, than nondisabled patients and in 13 of the 16 years under review the age differential was at least 15 years. Ideally the proportion of disabled patients should tend towards zero as the case-detection rate approaches the incidence rate. Figure 3 shows that there was a gradual fall from a disability rate of just below 20% in 1975 to a rate of 1·3% in 1985. In 1986 and 1987 disability rates have been rather higher, at 11% and 9%, respectively—possibly resulting from a fall in the numbers of new patients and more aggressive case-finding.

PROPORTION OF MULTIBACILLARY PATIENTS AMONGS NEW PATIENTS

The second way of validating case-detection rates is to calculate the proportion of multibacillary patients amongst new patients. At the start of a programme this proportion will be high but should tend to fall to a baseline corresponding to the true proportion of new multibacillary patients. So, when this proportion stabilizes the detection rate can be assumed to be close to the incidence rate. In Guyana the proportion of multibacillary new patients fell from 36% in 1978 to 12% in 1983 and has since risen gradually to 22% in 1987.

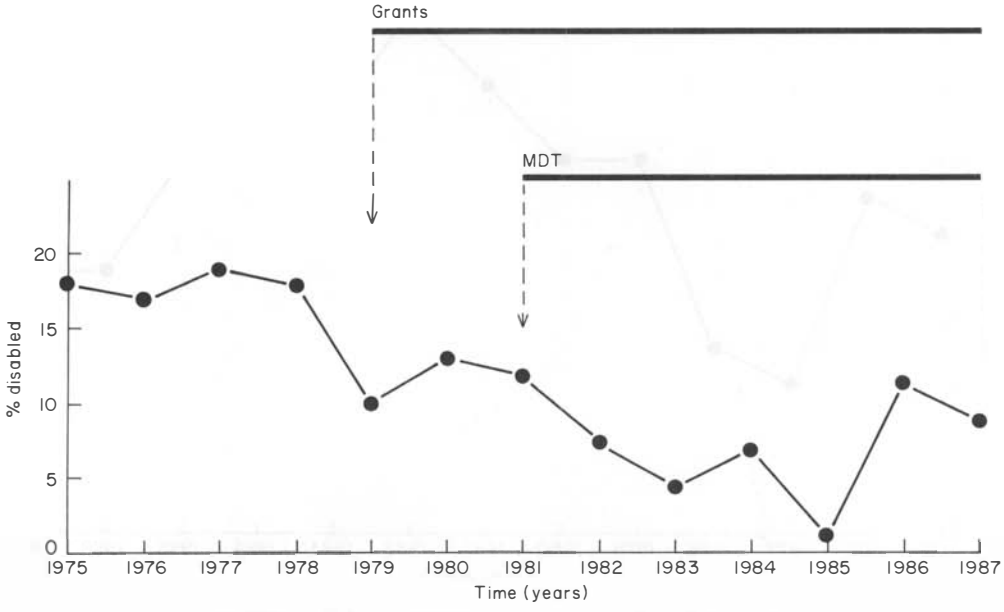

Figure 3. Percentage of new patients disabled (Grades I and II), 1975–87.

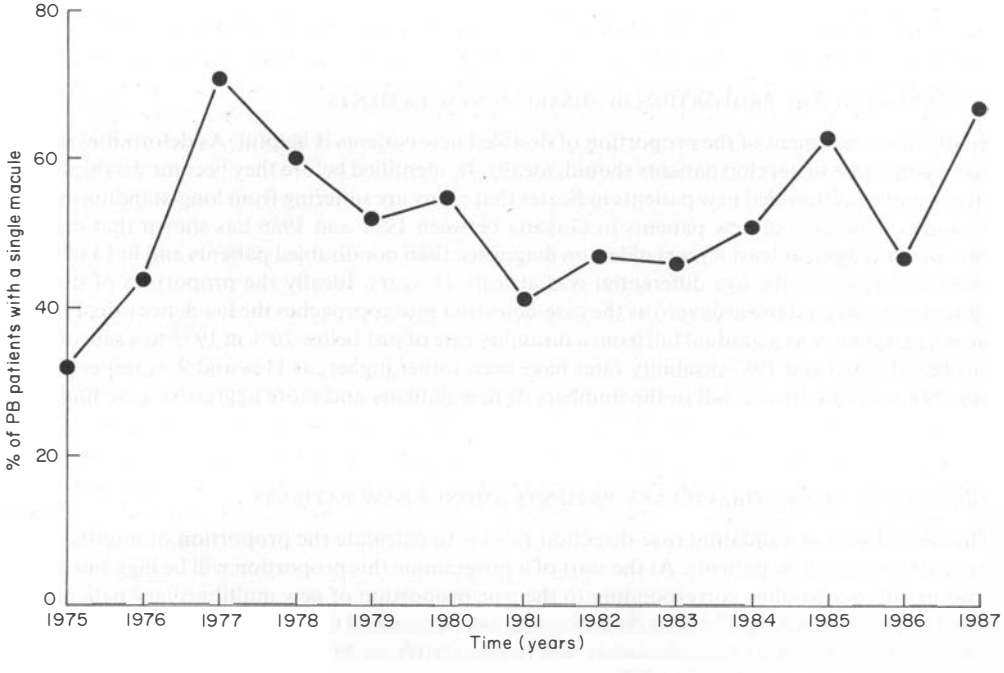

Figure 4. Percentage of paucibacillary patients with a single macule, 1975–87.

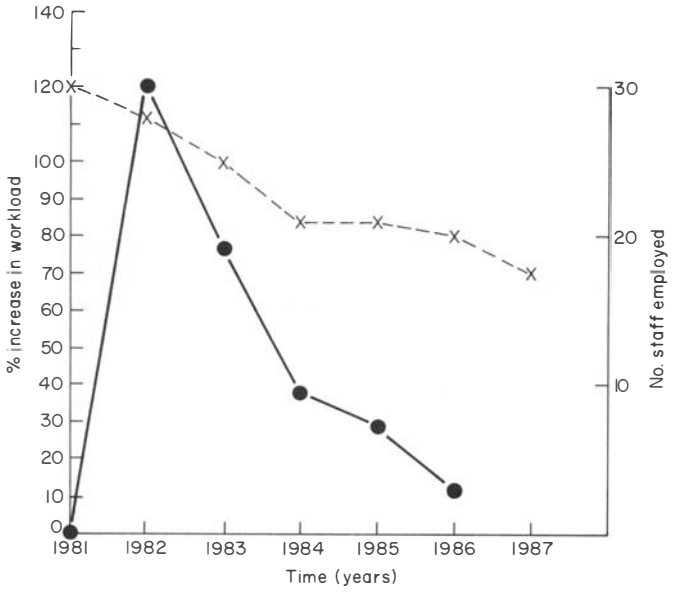

Figure 5. _____, increase in workload on the introduction of MDT; × -- × -- ×, staff numbers.

PROPORTION OF PAUCIBACILLARY PATIENTS PRESENTING WITH A SINGLE MACULE

Thirdly, the proportion of paucibacillary patients presenting with a single macule should increase as case-finding intensifies and Figure 4 shows that this proportion rose from 32% in 1975 to 72% in 1977 and then fluttered around the 50% level with peaks of 63% in 1985 and 67% in 1987.

So, there are reasonable grounds, from all three methods of assessing validity, to accept the case-detection rates of Figure 2 as an indication of incidence rates. The fall in incidence from 1982 is very striking and although undoubtedly other factors are involved, this definite and sustained fall can be attributed in large part to the introduction of MDT.

Increase in workload

Changing from a programme where all drugs are self-administered and in which most patients are seen quarterly to one in which patients attend monthly for supervised drugs has resulted in a considerable increase in workload. One way of monitoring this increase is to compare clinic attendance figures. Figure 5 shows that domiciliary clinic attendances rose by 120% in 1982, taking 1981 as a baseline. This tremendous increase had fallen to 12% by 1986. Where there is no possibility of obtaining additional staff members, constant improvement in working methods is needed to absorb this additional burden. Figure 5 also shows that there was a fall in the number of staff employed over this period, from 30 in 1982 to $17\frac{1}{2}$ in 1987—partly due to financial constraints and partly to improved working methods.

Conclusion

In conclusion there can be no doubt that the introduction of the WHO multiple drug regimen into

the Guyana programme in December 1981 has had an advantageous effect on both prevalence and incidence rates. The tremendous increase in workload that was at first experienced had almost returned to pre-MDT levels by the end of 1986 and as the workload declined it was possible to reduce staffing levels without adversely effecting the standard of care given to patients.

Acknowledgments

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Obituary

VILHELM MØLLER-CHRISTENSEN MD 1903–1988

Vilhelm Møller-Christensen died at the age of 85 in his home town of Roskilde, Denmark, on 15 November 1988. In 1941, as a general practitioner with a special interest in medical history and paleopathology, he began a series of excavations in the burial ground of a large medieval Augustinian Abbey in Aebelholt, North Sealand. Three years later he unearthed a skeleton with puzzling bone changes which he suspected might be due to leprosy, even though it was not customary in the Middle Ages to bury leprosy sufferers in monastic cemeteries. As these puzzling bone changes could not be explained by contemporary leprologists and paleopathologists, he decided to gain information by finding the graveyard of one of the 30 or more St Jørgen's (St George's) hospitals which were thought to have housed Danish leprosy sufferers in the Middle Ages. Hearing that human bones had been accidentally unearthed near Naestved, South Sealand, in the region where a St Jørgen's hospital had existed, he began a systematic search for the site. Travelling from farm to farm making inquiries, he reached a dairy farm where the owner admitted to having found human bones when digging a drain in the farmyard, so in 1948 he began exhumations at this site, aided by Naestved Museum and the National Museum of Copenhagen, and funded by the Carlsberg Foundation. Further work revealed that he had found a St Jørgen's hospital, which had existed between 1250 and 1550, thus establishing that leprosy was a health problem in north-west Europe in the Middle Ages. The last exhumations were carried out in the summer of 1968, enabling him to complete his meticulous studies of skeletal material from about 650 persons, bringing to light some previously unknown changes of leprosy, particularly those in the rhinomaxillary region of the skull which he named *facies leprosa*. He recorded his observations in a number of papers and books, the last being *Leprosy Changes of the Skull* (1978).

During these years he studied clinical leprosy in Malaya and Thailand, and visited leprologists and paleopathologists in various capitals of Europe, accompanied by his inseparable travelling companions in the form of a selection of bones and skulls from Naestved. When I spent a week with him in 1963, looking for signs of *facies leprosa* in the skulls of the Catacombs in Paris, I recall marvelling at the unconcerned way in which he walked through the streets carrying skulls in a string bag, oblivious of the sidelong glances of passers-by!

In 1964 Vilhelm Møller-Christensen was appointed Professor of Medical History at the University of Copenhagen, later becoming Professor Emeritus, and in the same year he was appointed Director of the University Medical History Institute and Museum. In the latter capacity he spent much time and care in establishing within the Museum a leprosy section containing the best osseous material from Naestved. He was President of the Danish Society of the History of Medicine from 1964 to 1974, and Director of the World Health Organization Institute for the History of Leprology in 1973. Honours conferred on him included that of Knight of the Order of Danneborg (1954), and Commander of the Papal Order of St Silvester (1973).

Vilhelm Møller-Christensen has won a well-deserved place in the annals of medical history, leprology, and paleopathology.

W H JOPLING

Lepr Rev (1989) **60,** 158–162

Letters to the Editor

REPLY: SLIT-SKIN SMEARS FROM THE FINGERS IN LEPROSY

Sir,

I must take issue with Dr Macrery when he states in his letter (*Lepr Rev* 1988; **59:** 360) that his experience with finger smears on multibacillary patients in Malaŵi is, 'clearly at variance with those already reported in the literature', for his report is on 'multibacillary patients on active antileprosy chemotherapy as well as any new ones who presented themselves'. The fact is that there have not been any previous reports on such patients, for these have been on new lepromatous patients,[1] on lepromatous patients long-treated with dapsone,[2-4] and on multibacillary patients on long-term follow-up after MDT.[5] Therefore his findings are not at variance with those of others. I suggest that the explanation lies in the fact that all published papers, with one exception, have been on lepromatous (not multibacillary) patients, the one exception being my paper from Malta which reported a long-term follow-up study.

Dr Macrery has performed a useful task in showing that in Malaŵi there is no point in including finger smears when assessing patients for MDT, and I do not doubt that the same will apply in other regions of the world. However, if he is interested in the possibility of finding solid-staining bacilli ('persisters') in the follow-up of his lepromatous patients, he will be well advised to include smears from fingers.

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REPLY: SLIT-SKIN SMEARS FROM THE FINGERS IN LEPROSY

Sir,

I read with interest the letter, by R T Macrery (*Lepr Rev* 1988; **59:** 360–1). Skin smears have always been a subject of interest for leprosy workers. However its practical implementation is not universally identical, hence different documentation on this subject is equally contradictory.[1,2] These differences can be attributed to the manual variations in performing the smear test. The role of geographical variance[3] is debatable yet could be a subject for further study.

It was difficult to understand in this letter the role of the finger smear, as the data presented are

not classified according to the type of leprosy, and a separate analysis of follow-up smears of patients under treatment is not available. In our opinion the role of finger smears in suspected new patients and in clinically doubtful cases is controversial. In contrast, finding the finger as a sole positive site in long-treated inactive/released multibacillary leprosy patients may be of much importance and is significant. This can be a warning indication of relapse.[1,4]

I take this opportunity to present our observations regarding finger smears. In 1982–3 we, in Alert, India (Association for Leprosy Education, Rehabilitation and Treatment, India, Bombay) used to take smears from the finger (right middle finger—middle phalange) as one of the four routine sites, right earlobe, left forehead and an active skin lesion being the other three. We took this chance to analyse the available data to observe the bacterial trend in fingers in comparison with earlobes, which are incidentally the universal routine site. Since this was the beginning of the project our analysis was restricted to a few patients. Nevertheless, the findings were not disappointing and the following are excerpts from them.[5]

We studied available data in three groups. The first being the group of 39 untreated lepromatous (L) and borderline (BL) leprosy patients. The second consisted of 22 L and BL cases treated for 5 years or more. Bacteriological follow-up of patients treated with multi drug therapy (MDT) having a minimum Bacteriological Index (BI) of 2, formed the third group. The interval between initial and follow-up smears was 12 months (± 2).

In the first group we observed that, in untreated L patients the mean BI of ears and fingers was 3·8 and 3·7, respectively. The BI of these sites was more than the average bacteriological index (ABI) in 47·4% and 52·6% of cases, respectively. Similarly an equal number of patients showed the highest BI among routine sites, i.e. 21%. Unlike L, untreated BL patients showed different trends in finger bacteriology. The mean BI being 2·8 and 2·3, while BI more than ABI was seen in 50% and 45% of cases in ears and fingers respectively. However only 5% showed a higher BI in fingers against 35% in ears. Interestingly, 71·4% patients showed a higher BI than ABI in forehead smears (second routine site). We attribute this difference to the fact that ears and faces are clinically more affected than fingers in BL, unlike L-type, where generalization of the disease is characteristic.

Similar phenomenon was seen in the group of patients treated for 5 years and above. Mean BI of ears and fingers was 2·8 and 2·5 in L, and 1·4 and 1·0 in BL. BI was noticeably higher than ABI in 46·6% and 40·0% in L and 71·4% and 28·6% in BL leprosy in ear and finger sites respectively. Once again in treated BL patients the highest number of cases (83·3%) showed a BI higher than ABI in forehead sites with the highest mean BI 1·6 in this group.

It was noticed that in group three, fingers were showing a bacterial swing more or less similar to that of ears. When compared with the fall in ABI, 14 and 15 of 26 patients showed decrease in BI in ear and finger smears, respectively, while 7 cases had static BI at both the sites. Similarly when the ABI was static in six of 26 cases, BI of ear and finger smears was also unchanged in two of them.

We feel our findings, though based on few patients, are not discouraging. Moreover, we could draw the conclusion that the finger is also as informative as the ear, which is the universally accepted routine site. Its role as the early site for bacterial relapse[1,3] probably contributes to this. However, we experienced some practical limitations while collecting smears from finger sites: it is not always possible to pinch enough to collect sufficient tissue pulp; bleeding is often excessive and difficult to control, hence blood-free smears are unusual; and the finger is a most painful site and therefore disliked by patients. Yet, we had results of finger smears similar to that of other routine sites. As its inclusion in the routine sites is somewhat impracticable, we strongly believe that it should be considered at the time of declaring patients inactive/cured. The additional knowledge about the bacterial status of the finger at this crucial time might prove valuable.

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A PRABHAVALKAR

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REPLY: SLIT-SKIN SMEARS FROM THE FINGERS IN LEPROSY

Sir,

When I read the initial report of the higher frequency of positivity and the higher Morphological Index (MI) of smears taken from fingers, I tried to confirm this in my programme in Northern Nigeria but could not. I found the most highly positive sites were invariably the ear and brow. It was true that most patients with a highly positive (5+ to 6+) smear were also positive from a finger, and that the MI tended to be higher from fingers than smears taken elsewhere.

It would be interesting to determine what may be the reason for this difference, but apparently, according to this letter from Malaŵi, it is true for at least a wider geographic area of Africa. It would be worthwhile investigating this matter further. Is it a geographic, climatic, or racial difference? Or is there possibly some other factor producing this variance?

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REPLY: CARCINOMA IN PLANTAR ULCERS OF LEPROSY PATIENTS: A REPORT OF FOUR CASES FROM TURKEY

Sir,

The above letter (*Lepr Rev* 1988; **59:** 360–1) prompts me to write that it is necessary to recognize that the development of malignancy is a relatively common occurrence in neglected plantar ulcers. In a large majority of ulcers that have been present for more than 10 years, a malignant degeneration will take place, but it does occasionally occur much earlier. There is also a variation in the speed of progression of a malignancy, and of its potential for metastasis. Most are slow growing and do not metastasize readily. On the other hand, the opposite is occasionally true.

The ulcers with a low grade malignancy can sometimes be cured by local excision and skin grafting. By the time the majority of these present themselves they will require amputation. This of course is true when there is skeletal invasion.

As is true in all aspects of medical care, by far the most important aim is prevention. It is most obvious that malignant degeneration will never occur if ulcers are not allowed to persist. So, the vital thing is to see that all plantar ulcers are promptly healed, and necessary measures instituted to keep the skin intact and to prevent damage to all tissues.

This, of course, is more easily said than done; but to prevent malignant degeneration, it must be done. The essentials for prevention of tissue damage are well known and I need not make reference

to them. The important thing is that it is extremely difficult to convince patients of the necessity of instituting these preventive measures.

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Pfaltzgraff RE. Management of Ulceration in Anesthetic Extremities, *Lepr Rev*, 1984; **55:** 424–6.

DAPSONE AND ERYTHEMA NODOSUM LEPROSUM

Sir,

Dapsone has been widely used for various other dermatological conditions besides leprosy. These include dermatitis herpetiformis, subcorneal pustular dermatosis, pemphigus foliaceus, bullous pemphigoid, erythema elevatum diutinum, acropustulosis of infancy etc.[1] Most of these conditions are characterized by an inflammatory infiltrate predominantly consisting of polymorphonuclear leucocytes (PMNL). It has been shown that the drug primarily interferes with the myeloperoxidase—H_2O_2— halide mediated cytotoxic system in the PMNL *in vitro*.[2] Because this system fulfils the antimicrobial activity and is suggested to be a modulator of the inflammatory reaction as well, the action of dapsone in dermatitis herpetiformis may in part be explained by its effect on this system.[2]

The lesions of erythema nodosum leprosum (ENL) are characterized by an infiltrate of PMN leucocytes in regressing lepromatous granulomata.[3] However, dapsone has no role whatsoever in either prevention or treatment of ENL. Two possibilities exist: either the myeloperoxidase—H_2O_2—halide system of lepromatous patients is not susceptible to the action of dapsone or other lysosomal enzyme systems in the PMNL are responsible for the inflammatory response in the ENL. The second possibility seems more plausible because Type 2 reaction is characterized by constitutional symptoms while the dermatoses in which dapsone is useful are not. It will be interesting to identify the enzyme systems in the PMNL that are responsible for the inflammatory response in ENL in order to develop the drugs that would specifically act at this level rather than causing a profound immunosuppression like the systemic corticosteroids.

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ANXIETY-INDUCED ULNAR PARALYSIS—A CASE REPORT

Sir,

A young girl aged 16 years reported to one of our subclinic centres with a hypopigmented anaesthetic well-defined patch on the left thigh. She was put on paucibacillary multidrug therapy on 22 August 1987 (RMP and DDS). The drugs were given on 19 September 1987 and on 9 October 1987, she reported to the subcentre with flexion of left ring and little fingers.

On examination by a therapist, flexion of left ring and little fingers was confirmed and weakness of hypothenar muscles, interossei and lumbricals to ring and little fingers were also found. The left ulnar nerve was neither thickened nor tender. No other trunk or cutaneous nerves were thickened or tender. She had loss of sensation over the ulnar supply of the hand and also slight overlapping on the median and radial nerve supplied areas. The diagnosis of silent paralysis was made and she was put on anti-inflammatory treatment and physiotherapy treatment was started. On 17 October 1987 no flexion of fingers was seen, but lumbrical weakness was noted and on 26 October 1987 weakness of muscles was absent. On 20 November 1987 she was readmitted to hospital for recurrence of flexion of left ring and little fingers. On 25 November 1987 while trying to stretch the ring finger, the patient resisted. The therapist could not understand the unfamiliar stretch-resistant action of the patient as the flexion was of recent origin with no inflammatory change in the joints of the finger. The physiotherapist questioned the patient extensively the next day, as doubt had risen in his mind about the behaviour of the patient. On 26 November 1987 the patient revealed that during her mat-weaving training, she used to work with women leprosy patients who had clawing of the ring and little fingers. She believed that she too would have the same clawing fingers, since she had been diagnosed and was being treated for leprosy.

The nature of the disease was explained to the patient and also the fact that deformities are rare in leprosy. Since she was made to realize that her hand was normal, she has been able to fully stretch her hand-muscle and sensory status has been reassessed and found to be normal. She finished her MDT therapy and lives happily thereafter.

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Teaching Materials and Services

Skin Diseases; Program for Appropriate Technology in Health

PATH, 4 Nickerson Street, Seattle, WA 98109–1699, USA, publishes *Directions* three times a year, devoted to the development and application of appropriate health technologies for primary health care programmes in developing countries. The latest, Volume 8, Number 3, 1988, is entitled *Skin Diseases* and explores the technologies available under the headings of Diagnosis, Treatment and Prevention. The concluding paragraphs emphasize the importance of the treatment of skin diseases in developing countries in 1, reducing physical pain and discomfort at relatively low cost; and 2, enhancing the credibility and reputation of health workers in the eyes of the community members, thus paving the way for the acceptance of less tangible health services, such as immunization and family planning. Under 'Materials Available', this issue has details of four sources of further information on skin diseases:

1 Slide sets with English scripts for training doctors, nurses, and auxiliary health workers about skin diseases are available from TALC (Teaching Aids at Low Cost). *Common Skin Diseases of Children in the Tropics* is in self-mounting (£2.75) or mounted (£4.40) slide sets. For airmail, add 60 pence. Address: PO Box 49, St Albans, Hertfordshire AL1 4AX, UK.
2 *Primary Child Care* (Book 1) is an excellent resource with an entire chapter on diagnosing and treating skin diseases. It is available from TALC and costs £4.50.
3 *Where There is No Doctor* also contains a good section on skin diseases, including drawings and directions for making topical treatments locally. It is available in more than 18 languages. For ordering information, write to: Hesperian Foundation, PO Box 1692, Palo Alto, CA 94302, USA.
4 *Caring for Skin Infections and Sores* is a filmstrip on preventing and treating skin diseases with soap and water. It is available in English, Spanish and French for US $10 each, plus shipping. (Surface is US$1; air is US$2 for Latin America and US$3 elsewhere.) Order it from: World Neighbors, 5116 North Portland Avenue, Oklahoma City, OK 73112, USA.

A bibliography on skin diseases is available from PATH.

WHO Regional Training Centre for Health Development, Australia

The WHO Regional Teacher Training Centre in the Faculty of Medicine was established in 1973 by a tripartite agreement between the World Health Organization, the Australian Government, and the University of New South Wales. In March this year the Centre's name was changed to the **WHO Regional Training Centre for Health Development,** reflecting a broader involvement in education and training for health management and community development as well as training of the health professions.

The Centre collaborates with governments, international agencies, professional associations and educational institutions in: 1, identifying the training needs of health personnel and designing educational programmes directed to national health care priorities; 2, developing the abilities of teachers to plan, manage, and evaluate educational programmes; 3, cultivating leaders and strengthening management systems to promote health development; 4, conducting organizational development activities within teaching institutions, hospitals and health systems, aimed at supporting initiation and management of change; 5, developing in-service training and staff development capabilities and programmes; 6, designing and conducting evaluation of educational and health programmes; and 7, conducting health workforce research and planning.

Apply: School of Medical Education, University of New South Wales, PO Box 1, Kensington, NSW 2033, Australia.

New slide–text set on AISA; TALC, UK

Teaching Aids at Low Cost (TALC, PO Box 49, St Albans, Herts AL1 4AX, England) have now produced a colour transparency–text set on *HIV infection—virology and transmission.* In fact it also covers epidemiology and immunology. Prevention, precautions for health workers, counselling and clinical aspects will be dealt with in later sets. There are (as usual in TALC sets) 24 slides with detailed written explanations and questions, followed by three appendices (further information on HIV antibody tests, autotransfusion techniques and

further sources of information on AIDS). The code for ordering the set is HIVv. This is an invaluable item of teaching material on an outstandingly important—and fast-changing—subject; many of the concepts discussed are highly educational with regard to basic immunology and relevant to the study of defence mechanisms against mycobacteria.

Wellesley Bailey Scholarship

The Leprosy Mission (International) has funded a training and research scholarship named after the Mission's founder, Wellesley Bailey. The Scholarship(s) will be awarded annually up to a maximum value of £5000 to enable a leprosy worker to engage in an approved research project or in training in one of The Leprosy Mission's centres. Application forms and further details are available from the International Director, The Leprosy Mission (International), 80 Windmill Road, Brentford, Middlesex TW8 0QH, U.K. Applications may be submitted at any time and will be considered at the earliest possible meeting of the scholarship committee.

LEPRA Prize Essay Competition, 1989

Following the tradition of previous years (back to the early 1970s), LEPRA is offering prize money to a total of £500 (to be awarded at the sole discretion of appointed judges), for an essay on either 'Future requirements for the prevention, early diagnosis and treatment of leprosy neuritis under field conditions' or 'Association between rheumatoid arthritis and mycobacterial infection'. The competition is open to registered medical students in the United Kingdom only. Further details from LEPRA, Fairfax House, Causton Road, Colchester CO1 1PU, England. Closing date: 8th January 1990.

Ministerial Consultation on Medical School Education, Lagos, July 1989

From 5 to 7 July 1989 a Ministerial Consultation will be held in Lagos, Nigeria, between the Ministeries of Education and Health, to discuss radical changes in the content of the curriculum for medical students in Africa. The detailed agenda is not available at the time of writing, but the most important improvements to be considered include those in the *Edinburgh Declaration* of 12 August 1988:

1 Enlarge the range of settings in which educational programmes are conducted, to include all health resources of the community, not hospitals alone.
2 Ensure that curriculum content reflects national health priorities and the availability of affordable resources.
3 Ensure continuity of learning throughout life, shifting emphasis from the passive methods so widespread now to more active learning, including self-directed and independent study as well as tutorial methods.
4 Build both curriculum and examination systems to ensure the achievement of professional competence and social values, not merely the retention and recall of information.
5 Train teachers as educators, not solely experts in content, and reward educational excellence as fully as excellence in biomedical research or clinical practice.
6 Complement instruction about the management of patients with increased emphasis on promotion of health and prevention of disease.
7 Pursue integration of education in science and education in practice, also using problem solving in clinical and community settings as a base for learning.
8 Employ selection methods for medical students which go beyond intellectual ability and academic achievement, to include evaluation of personal qualities.

Other improvements require wider involvement in order to:

9 Encourage and facilitate co-operation between the Ministries of Health, Ministries of Education, community health services and other relevant bodies in joint policy development, programme planning, implementation and review.
10 Ensure admission policies that match the numbers of students trained with national needs for doctors.
11 Increase the opportunity for joint learning, research and service with other health and health related professions, as part of the training for team-work.
12 Clarify responsibility and allocate resources for continuing medical education.

Further information: Sir Henry Walton, International Medical Education, World Federation for Medical Education, The Medical School, University of Edinburgh, Teviot Place, Edinburgh EH8 9AG, United Kingdom.

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News and Notes

Essential Drugs Revolving Fund (FORMED)

In 1984 the provision of essential drugs was identified as one of seven priority areas under the Plan for Priority Health Needs in Central America and Panama. Since that time, the countries, with assistance from PAHO/WHO, have directed significant international financial and technical resources toward strengthening drug supply and quality control systems, promoting national production of drugs, supporting the formulation of national drug policies and their standardization throughout the subregion, and setting up a revolving fund for the joint purchase of essential drugs.

The availability and use of drugs in Central American countries is limited by numerous socioeconomic, technical, and administrative factors, as well as by the structure of the drug industry and the international and national pharmaceutical markets. An analysis done by PAHO of one of these factors, government procurement of drugs, confirmed that the prices paid by the governments not only varied greatly from country to country but also were considerably higher than prices obtained through PAHO or UNICEF.

In an effort to make the most efficient use of economic resources, particularly scarce foreign exchange, and faced with reduced purchasing power, in 1984 the ministries of health in the subregion proposed the establishment of a technical and financial mechanism to assist in the procurement of drugs at a substantial saving. A revolving fund was established in 1986. It was initiated with a donation of US$4,000,000 from the Government of the Netherlands to finance the joint purchase of a selected number of drugs, and a contribution of US$277,000 from the Government of Sweden to finance the technical cooperation necessary to implement the program. The Essential Drugs Revolving Fund (FORMED) permits prompt payment of supplies and allows the countries a grace period in which to reimburse the fund.

Some of the characteristics of FORMED that gave rise to the savings over the 1985 prices are (1) competitive international bidding, (2) prompt payment in dollars, (3) purchases packaged in economical units, (4) large volume of purchases, and (5) selection of the most economical method of transportation.

The first round of purchasing revealed a number of specific operational problems, such as unacceptable expiration dates, inadequate, external packaging, wrong language on the labels, delays in receiving analysis results from reference laboratories, and incorrect shipping documents. More important were the delays caused by long delivery times (which made programming difficult and necessitated emergency purchases) and by slow customs clearances. In addition, some countries had regulations limiting the procurement and importation of drugs through FORMED or hindering prompt reimbursement of the fund. However, because they are motivated to make the FORMED mechanism work, the countries have succeeded in overcoming most, if not all, of these obstacles. And PAHO, based on the experience of the first purchase, has adjusted its purchasing process, particularly the selection of suppliers, in order to ensure maximum compliance with the terms of the bidding process.

Sources: Pan American Health Organization; Technical Cooperation Among Countries (TCC) in Subregional Initiatives (SPP9/5), Annex II: Essential Drugs Revolving Fund for Central America and Panama (FORMED): Washington, D.C., 13 November 1987; *and* Pan American Health Organization; Priority Health Needs in Central America and Panama: Analysis of Priority Areas; Washington, D.C., December 1987.
(Extracted from *Bulletin of the PAHO*, **Volume 22,** No. 3, 1988)

A combined capsule of clofazimine and dapsone

In correspondence with Earnest Healthcare Ltd, Earnest Estate, Bombay Agra Road, Rajendra, Nagar, Indore 542 012, India, information has been received concerning the production of a capsule combining clofazimine 50 mg in an oil base with dapsone 100 mg in powder form (as a tablet). The technical director, Dr P K Powal, has indicated that this has been approved by the State Drug Authorities and that it will be marketed in a blister pack (from October 1988). These details are given here only be way of information and do not constitute recommendation for clinical use. Further details, including bio-availability studies and cost, etc, should be obtained from the drug company in India, address as above.

WHO Expert Committee on Leprosy: Sixth Report

The following is taken from the *WHO Technical Report Series*, No. 768, 1988. It has 51 pages and is available in English; French and Spanish in preparation: Reviews world-wide developments in leprosy research and control that have occurred over the past 10 years. Emphasis is placed on knowledge relevant to the success of control operations, particularly in view of the alarming increase of primary and secondary resistance to dapsone.

The report opens with a brief discussion of the global significance of leprosy as a public health problem, followed by a summary of epidemiological features important to control. Clinical issues are addressed in the third section, which proposes changes in case definitions and classifications necessitated by the use of multidrug therapy, discusses ways to improve the collection and processing of skin smears, and outlines protocols for the management of drug reactions. The neglected problem of quiet nerve paralysis is also considered. Other sections interpret the practical significance of advances in basic biology and immunology, high-lighting prospects for the development of an anti-leprosy vaccine. Of particular practical value is a state-of-the-art review of leprosy chemotherapy, incorporating what has been learned following the widespread introduction of standard regimens for multidrug therapy. Readers are given guidance on the problems of drug resistance and microbial persistence, the use of standard treatment regimens, and the recommended duration and frequency of post-treatment surveillance. In view of the prediction that the number of persons needing care because of disabilities will gradually outnumber those receiving antimicrobial treatment, the report also includes advice on the prevention and management of disabilities, the grading of disabilities to facilitate data collection, and strategies for patient rehabilitation. The concluding sections review the components of leprosy control in the light of current knowledge and identify priorities for further research in a number of different fields.

Apart from its value as a state-of-the-art report on the leprosy situation, the book also serves as a practical alert to a range of operational problems, whether concerning the collection and interpretation of data or the administration of new drugs, that can influence the success of leprosy control.

Main headings: global leprosy situation; epidemiology; clinical aspects of leprosy related to control; *Mycobacterium leprae*; immunology of leprosy; chemotherapy of leprosy; disabilities, rehabilitation and social problems in leprosy; leprosy control; research needs; and conclusions and recommendations.

Apply: Office of Publications, WHO, 1211 Geneva 27, Switzerland. Price Swiss Fr 8.

Implementing Multiple Drug Therapy; OXFAM's Practical Guide Number 3

The fourth, revised edition of this booklet, previously called *Questions and Answers on the Implementation of Multiple Drug Therapy (MDT) in Leprosy* is now available from OXFAM Publications, 274 Banbury Road, Oxford OX2 7DZ, England at £2.95 per copy, plus postage. Written in the form of extended answers to a series of questions, this booklet deals with many aspects of the care and management of patients treated with multiple drug therapy, as recommended by WHO in 1982. It is aimed essentially at those in senior positions concerned with teaching health workers, programme planning and implementation of leprosy control programmes. It is currently available in English only, but a translation into Spanish is in hand.

Centre for Tropical Disease Research, Acapulco, Mexico

Towards the end of 1988, Professor Roberto Estrada, Centre for Tropical Disease Research, Faculty of Medicine, Apartado 25A, Acapulco, Mexico, visited the UK to meet people working in medical research and to discuss the establishment of further links with his Centre in Mexico. It was inaugurated in March 1985 to develop postgraduate training and research on priority health problems in Guerrero, one of the poorest states in Mexico. Major research areas since then have included diarrhoeal diseases, acute respiratory tract infections, tuberculosis, dengue, malaria, Chaga's disease, leprosy and other skin diseases, scorpion stings and child labour in the tourist trade. Much of the Centre's manpower for field work is drawn from 1000 students in the Medical Faculty.

International Agency for the Prevention of Blindness

IAPB News is published twice yearly, has a press run of 6,000 and is mailed to 136 countries world-wide. Address: IAPB, c/o National Institute of Health, Building 31, Room 6A03, Bethesda, Maryland 20892, USA. The November 1988 issue includes items on: 1, the Zambia Flying Doctor Service, which during 1987 saw 2,144 patients with cataracts and operated upon 140 in the field, referring many others to central hospitals: and 2, a 'Primary Eye Care Pamphlet' published by Nepal's Lumbini Eye Care Project (Project Manager; Dr Chet Raj Pant), specifically for village eye care projects in Nepal, developed with local volunteers.

Précis de Leprologie; *Acta Leprologica*, 1988

We are grateful to the Comité Exécutif International de l'Ordre de Malte in Geneva for sending a copy of *Acta Leprologica* No. 109, April–December 1988, New Series Volume VI. This is a 387-page publication, with index, which is virtually a textbook of leprology, since it covers all major aspects of the disease in considerable detail. It has been produced by J Languillon with the cooperation of A Carayon. Address: Ordre de Malte, 3 Place Claparède, 1205 Geneva, Switzerland.

St Francis Leprosy Guild, London

The Guild collects donations to help missionaries and others in their work among victims of leprosy throughout the World. Address: 21 The Boltons, London SW10 9SU. Director: The Very Reverend Father Provincial, OFM. Medical Advisor: Dr Terence Ryan, Department of Dermatology, Oxford. In 1987 grants went to 109 leprosy-endemic countries and totalled £333,666.

Immunopathology Symposium, Amsterdam, September 1989

Immunodermatology Symposia were previously organized in Lyon, London and Milan. These meetings aim to attract immunologists interested in dermatology and dermatologists interested in immunology. The 4th Immunodermatology Symposium will be held in Amsterdam, September 21–23, 1989. An outstanding faculty of internationally renowned scientists will present guest lectures on the most important and recent developments in the field of immunodermatology. The programme will have a number of plenary sessions, in which a selection of free oral presentations will be scheduled. In addition, poster sessions will be organized. The programme will be completed by two social events and most of it will be held in the Sonesta Hotal in the heart of 17th-century Amsterdam.

Guest lectures are:

Human immunodeficiency viruses J C Gluckman, Paris. Regional immunology of the skin J W Streilein, Miami. Biological and dermatological significance of the HLA-system. R R P de Vries, Leiden. Leukocyte adhesion molecules T A Springer Boston. Ciclosporin in dermatology. J J Voorhees, Ann Arbor. Immunobiology of the skin; an upate G Stingl, Vienna.

Free communications in all areas of immunodermatology are welcome. Apply Dr J D Bos, Academisch Medisch Centrum, Meibergdreef 9, 1105 AZ, Amsterdam, Netherlands.

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Book Reviews

***Peripheral denervation of the hand. Volume 1* (188 pp) and *Peripheral denervation of the foot. Volume 2* (144 pp).**
C D Enna

The author has a vast experience in the management on sequelae of peripheral nerve damage of leprosy patients. Even though the author refers to other pathological conditions that may result in peripheral denervation of hands and feet, it is clear that most of the text and illustrations are based on the author's experience with leprosy patients. This also becomes evident when the author states that the volume on *Peripheral Denervation of the Foot* is a companion volume to *Peripheral Denervation of the Hand*.

Both volumes are well illustrated, though there is repetition of figures in both volumes. There are still typographical errors and many misspellings in the foreign language references. The author apologizes in the prefaces of both volumes that due to space limitations not all relevant literature could be quoted. . . . I consider one of the great weaknesses of both volumes is that the author has referred to very little relevant literature published in the last 10 years. As a consequence we do not have any updated material on the latest principles and treatment techniques with regard to the assessment and management of the denervated hand and foot.

Volume 1, Peripheral denervation of the hand, has the following chapters:

1, Functional anatomy of the hand; 2, Secondary deformities and the insensitive hand; 3, Deformities and peripheral nerve paralysis; 4, Rehabilitation; 5, The consequence of neuropathy.

I fail to understand why a chapter on secondary deformities should follow the chapter on functional anatomy. Should the primary results, e.g. loss of sensation and functional defects of motor loss not be discussed first? These are now discussed in Chapters 2, 3 and 5. There is also an overlap between Chapters 2 and 5 as the titles suggest.

Volume 2, Peripheral denervation of the foot, also has 5 chapters;

1, Anatomy and function; 2, Primary paralytic deformity; 3, The insensitive foot; 4, Complementary changes; 5, Consequences of the neuropathic foot.

I would recommend these books for surgeons, medical officers and therapists working with leprosy patients if the price is reasonable. Both volumes are too technical for other paramedical professionals working with leprosy patients. Medical officers and therapists working with diabetic patients could have some use of the volume on the foot, but they need to be aware that recent information regarding assessment and treatment is missing. Hand-surgeons and hand-therapists can do without the volume on the hand. Personally, I would like to have seen another edition of *Surgical Rehabilitation in Leprosy*, a book that was edited by the author and published in 1974, but has been out of print for many years.

Wim Brandsma

Published by Alan R Liss Inc., New York, 1988.

Instructions to Authors

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

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

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

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