Lepr Rev (1993) **64,** 368–408

XIVth INTERNATIONAL LEPROSY CONGRESS

Workshops

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0305-7518/93/064368+41 $01·00

Workshop 1 Microbiology

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The progress made on various aspects was reviewed as follows:

Purification of *Mycobacterium leprae*

Armadillo-derived *M. leprae* continue to be used for various biochemical, structural and antigenic studies. A modified hybrid protocol (containing alkaline treatment and 30% Percoll density gradient—1/79 and 1/77) particularly aiming to remove pigmented host material and useful for the purification of *M. leprae* armadillo liver has been developed. In addition, an assay based on the estimation of arabinose content to check the purity (mycobacterial content) of bacilli after purification has been described. However, it was felt that the effect of gamma irradiation on various viability markers/tests and integrity of DNA (which may influence the PCR signals) is not fully understood. Also, there are no objective techniques to monitor the contamination of purified *M. leprae* with soluble host material and other mycobacteria.

Cultivation

Attempts to grow *M. leprae* in modified conventional/earlier described media (7H9, Dubos and DH) as well as unconventional (simple media for chemoautotrophs) have been described. Chemoautrophic nocardioform (CAN) organisms from *M. leprae*-infected tissues have been repeatedly isolated, subcultured and shown to resemble *M. leprae* by enzymatic, chemical (mycolates and PGL), antigenic (lepromin), 36 kD PCR and pathogenic (mouse mutation) criteria. Further, coccoid, mycelial, cystic and spore-like forms (nocardioform arthrospores and blastospores) in the growth cycle of leprosy bacillus have been postulated in the recent reports. These investigations need to be further pursued and isolates taxonomically fully characterized. There were presentations which demonstrate that PCR could be a taxonomic tool. However, keeping in mind the danger of 'carry over', the need to try other genomic markers such as DNA/DNA, DNA/RNA hybridization (overall and using specific probes) as well as RFLP analysis was suggested, and the necessity of having confirmed 'pure' and 'viable' organisms in the cultivation attempts was emphasized.

Physiology/Biochemistry

Studies to investigate the physiology of *M. leprae* by biochemical and molecular approaches were reported. Enochelins and ferritins have been identified in *M. leprae*. Further studies have shown that while purine biosynthesis is undetectable in *M. leprae*, this organism is capable of pyrimidine biosynthesis and scavenging. *M. leprae* has been shown to have the capacity to utilize/hydrolyse several host lipids. Acetate has not been found to be incorporated in *M. leprae*, possibly because of the absence of phosphotransacylase: fatty acid syntheses have been detected, though at low activity. In contrast, fatty acid elongases were readily detectable in *M. leprae*. Phospholipids have been observed to be hydrolysed by *M. leprae* but this does not obviously damage the host membranes. The organisms have been reported to be capable of utilizing acylglycerols (using a model but not so far using any natural subtrates). It is not yet known if *M. leprae* can use sphingolipids, which are the major neural lipids. It has been suggested that the possibility of drugs that combat PGL and LAM biosynthesis, and an immunotherapy to block the entry and prevent persistence in Schwann cells and macrophages should be investigated.

Further proteins of *M. leprae* have been identified and, for many, their functions deduced. Their genes have been cloned and sequenced to varying extents. The important ones are: 10 kD (gro ES); LSR; 28 kD (SOD); 28 kD (IRG); major cell wall proteins (histone derived from host tissue); a major membrane protein (homology with bacterioferritin) and 6 'less abundant' proteins (2 possibly virulence factors—showing homology with alkyl hydroperoxide reductase and a thiosulphate sulphurtransferase, a 3rd with LT/LIC ribosomal protein homologue). Some of these proteins may have a role in the response of organisms to oxidative/other stresses and also in possible virulence.

Several recent studies have focused on the physiochemical factors important in the growth of *M. leprae*. Using bioluminescence, ^{3}H thymidine uptake and other parameters, several physiochemical factors like nutrients—gelatin, pyruvate, malate, silicone, fossil-fuel derivatives, purines, urea, glycerol, asparagine, etc., and physical conditions such as lower pH 6–6·5, temperatures of 3–30°C, and lower oxygen levels have been identified as possibly relevant for the *in vitro* growth of *M. leprae*. These factors and appropriate procedures like the processing of specimens, the addition of large quantities of lipids as cyclodertrin complex (sphingolipids, palmitic acid), etc., were suggested as methods to improve the ATP synthesis/possible growth in any future studies. The need to analyse experiences about other difficult-to-grow mycobacteria to identify critical factors that are possibly important for *M. leprae* was emphasized.

Sequencing of genes of *M. leprae*

Information detailing several gene sequences of *M. leprae* has become available, and on the basis of published data about ribosomal RNA genes, the leprosy bacillus has been shown to belong to the slow-growing mycobacterial cluster. In addition, the genome sequencing project on *M. leprae* has been progressing and about 15% genome has already been sequenced. This information has been reported to be complementary to data that is emerging about several genes coding for structural proteins of *M. leprae*. If the present funding levels are maintained, the entire genome of *M. leprae* could be sequenced in about 3 years.

Gene probes/amplification methods

Several gene probes and gene amplification techniques to detect *M. leprae* gene sequences have been developed and there are some others still under development. Among the important gene amplification techniques are those targeting 18 kD, 36 kD, 65 kD, ribosomal RNA and repetitive DNA sequences. Rapid genetic techniques are also being developed to detect mutations conferring resistance to rifampicin in *M. leprae*. Data about the application of different PCR assays in the clinical specimens as well as standard specimens (including IMMLEP trials) shows that the techniques are practicable. These assays appear to be generally sensitive for MB cases whereas sensitivity is about 50% for smear negative PB cases. The optimum methodology for specimen collection, storage, extraction and criteria of positivity (whether by EB/autoradiography) need to be further refined in greater detail to establish their applicability in clinical diagnosis and epidemiology.

***In vitro* estimation of viability**

In the absence of acceptable definition of 'cultivable unit' of *M. leprae*, all other criteria continue to be indirect. Data discussed showed that *in vitro* methods are proving to be useful for screening agents without encountering the problems of pharmacokinetics of mice. In addition to earlier discussed methods like MI, electronmicroscopy, FDA-EB staining, metabolite/substrate uptake assays, various macrophage assays, newer or modified techniques based on biochemical, bioluminescent and molecular approaches have been described as alternatives to mouse footpads. Data on the application of FDA-EB staining, bacillary ATP measurement, Na+/K+ ratio measurement by LAMMA, radiorespirometry (BACTEC/Buddemeyer systems) and gene probe/amplification (limited dilution PCR, different quantitative PCRs, ribosomal RNA based systems) show that several approaches can be useful for monitoring the responses to chemotherapy, drug screening and *in vitro* measurements of metabolic status of *M. leprae*. Since these methods assess different aspects of viability, even more than one method may be useful/necessary for a particular purpose. Using radiorespirometry, newer compounds active against *M. leprae* have been reported which have been shown to be promising in clinical trials later. Also, LAMMA, other uptake assays, and ATP decay assays have been shown to be useful for drug screening. Follow-up studies are required to adapt and assess these methods for their ultimate clinical or laboratory application.

Possible environmental sources of *M. leprae*

There appear to be relationships between the distribution of fossil fuels and endemicity of leprosy which should be epidemiologically investigated. New techniques will provide the necessary tools to further investigate the possibility of an environmental reservoir for *M. leprae*.

Areas of future research

(a) When considering the experience with tuberculosis, where, in addition to cultivation, rapid and alternative methods of research are also required, it is felt that parallel

efforts on cultivation, as well as on the development and application of some alternate methods for viability, detection and identification of the characteristics of *M. leprae* in patients should be researched, and therefore environmental and laboratory studies should be continued.

(b) Molecular approaches to fill the criteria gaps in the physiology/biochemistry, structural aspects, drug resistance and virulence factors should be investigated in future studies.

(c) Studies on the development and application of gene probes/gene amplification methods to diagnose and investigate the epidemiology of disease should be given special attention.

(d) In addition to already known taxonomic characteristics, newer molecular tools should be used to establish the identity of any 'cultivable' form of *M. leprae.*

(e) The need for bacillus and its component parts for various purposes remains high and it is still important to find answers to several questions (for example, even when the genome sequencing project is complete, it will still be necessary to know which genes are expressed). To meet these research demands, 'pure' *M. leprae* should be provided in the future and the supplies from armadillos/nude mice should continue to be a priority.

Workshop 2 Immunology

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Towards The Year 2000

Throughout history no infectious disease has been eradicated solely by chemotherapy, and it is unlikely that leprosy will be the first. Perhaps the greatest contribution research on immunology of leprosy has made has been its role at the cutting edge of basic immunology. Understanding protective immunity and immunopathology in leprosy has ramifications that stretch in the future, far beyond leprosy itself. It is essential to maintain current research momentum to understand the host–pathogen interactions in leprosy in order to develop the diagnostic tools and new immune-based therapies that are still needed in the treatment of disease. By the year 2000, many people will still be infected with *M. leprae* and the clinical disease will continue to emerge far beyond the turn of the century.

Immunology of the Disease Process

The aim of the workshop was to discuss current research on the immunology of leprosy and prepare a summary of research progress in the past 5 years and indicate areas that will continue to dominate future research directions.

Tuberculoid leprosy patients show a strong T cell-mediated immunity to *M. leprae* which is also seen in healthy contacts. Lepromatous leprosy patients have extremely high bacillary loads and widely disseminated lesions, with a striking absence of specific T cell-mediated immunity to *M. leprae*. While T cell-mediated immunity limits multiplication and dissemination of bacilli in tuberculoid leprosy, it does not provide protective immunity in patients and often leads to severe tissue damage. Immunology research seeks to understand the basis of protective immunity and those immune responses involved in tissue pathology such as that seen in nerve damage.

Infection and Disease

To establish infection in the host, *M. leprae* must be taken up by host macrophages, survive and multiply. The development of this relationship between the macrophage and the leprosy bacillus leads ultimately to the clinical spectrum of disease.

In the past 5 years, it has become clear that the successful intracellular multiplication of *M. leprae* leads to a loss of normal macrophage function, impairing the process of antigen-presentation and the subsequent activation of T cells. Within the last 2 years, methods have been developed to identify mycobacterial genes whose expression is induced in the microenvironment of the macrophage. Such gene products may be important in modulating macrophage function, such as intracellular pathways that are designed to inhibit bacterial multiplication. These studies should be extended to determine the genes of *M. leprae* that are induced in Schwann cells, as these may differ from those expressed in macrophages.

Lipoarabinomannans (LAM) purified from *M. leprae* (Lep-LAM) are potent macrophage regulatory factors. Characterization of LAM from other mycobacteria have revealed unique chemical modifications in mannose capping that appear to correlate with function. For example, Ara-LAM from *M. tuberculosis* H37Ra, which is a rapid growing avirulent strain, lacks mannose capping and leads to the induction of levels of the cytokine tumour necrosis factor (TNF) which are 100–1000 fold greater than that induced by Man-LAM from virulent *M. tuberculosis* H37Rv. As the induction of TNF may be central in resistance, Man-LAM may be a tuberculosis virulent factor, and may be important also as a leprosy virulence factor. All LAM species inhibit the production of interferon-gamma (IFN-gamma). In murine macrophages, IFN-gamma induces the intracellular synthesis of nitric oxides which directly inhibit mycobacterial multiplication. Human macrophages are more difficult to understand. The pathway leading to the arginine-dependent induction of nitric oxides has not been identified in human macrophages; however, treatment of lesions in lepromatous leprosy patients with IFN-gamma appears to lead to the elimination of bacilli. The mechanism underlying this response is unknown.

A clear priority is to determine how human macrophages respond to infection with

M. leprae. It is also becoming important to identify differences in tissue-specific populations of macrophages, as well as the kinetics of macrophage turnover.

Protein Antigens of *M. leprae*

In the last 5 years the focus of work has been the definition of the immune repertoire of the host, and the identification of specific antigens of *M. leprae*. Between 15 and 16 different protein antigens have now been identified by antibody reactivity. T cell responses have been characterized to less than half of these proteins and there are few studies reporting direct comparisons, making direct evaluations difficult. In general, individual patients are capable of responding to a broad range of these antigens. There is extensive cross-reactivity of T cell responses to individual proteins between different species of mycobacteria. No single *M. leprae*-specific protein antigen has been defined, although a small number of species-specific T cell epitopes have been recognized. As yet, few proteins have been capable of stimulating protective immunity against *M. leprae* infection in mice. Although certain cell wall fractions, and the 35 kD and 10 kD proteins, may be capable of eliciting partial protection, other events induced at the time of exposure to these antigens may be more important in developing protective immunity.

There are now new methods which can be used to identify protein antigens expressed specifically within macrophages and secreted by mycobacteria. As the *M. leprae* genome will now be completely sequenced, novel techniques are required to make use of the new genetic information that will become available. These may include the definition of T and B cell determinants based on sequence motifs. Once isolated, new proteins must be rigorously purified to avoid contaminants which may confound immunological studies.

As yet, no immune responses to defined antigens of *M. leprae* have been associated with different patterns of immunopathology seen in clinical disease. This may indicate that quantitative rather than qualitative differences in immune responses are important.

Regulation of Immunity

In the past 5 years, emphasis has moved from the concept that there may be specific immunodominant proteins of *M. leprae* that are central to protective immunity, to the realization that the type of response of effector T cells to immunization or infection is likely to be more important for protection. The concept of suppression has become more firmly established but the mechanisms involved and the relationship to lepromatous leprosy remains to be determined. The complexity of the cell types that respond to infection or immunization has increased. These now include NK cells, T cells that express alpha/beta and gamma/delta T cell receptors, and cytotoxic cells in both CD4+ and CD8+ subpopulations. Nonetheless, their role in protection and immunopathology is still unclear. The concept of T_H1- and T_H2-like cells in both CD4+ and CD8+ T cell subpopulations in humans is widely accepted.

Current work is aimed at defining how different types of effector T cells are regulated and determining which cytokines are the primary mediators of immune responses. There is a need to understand the complexity of the cytokine network and how it dictates the outcome of an immune response. The mouse is now used extensively as a model for the genetic deletion of pathways involved in specific immune reactions and these studies are

providing new insight into the regulation of the immune system. Much can now be learned from studying the immunology of tuberculosis and other mycobacterial infections in parallel with leprosy.

Diagnostic Assays

Serodiagnostic assays using *M. leprae*-specific molecules like PGL (NT-P/ND-O-BSA), the 35 kD and the 36 kD proteins, and LAM have been carried out in the past to search for antibodies against these molecules. These studies clearly reveal that not all established cases of leprosy are detectable using these assays. FLA-ABS tests detect a proportion of subjects with subclinical stages of disease. Recent findings using recombinant proteins have detected far less leprosy cases compared to the natural proteins. The finding of antibodies against the cross-reactive 29 kD/33 kD antigens in leprosy sera shows promise; however, their utility in the detection of early cases of leprosy requires further evaluation. Assays for detecting *M. leprae* antigens in leprosy sera have proved to be far less satisfactory compared to the antibody-based assays. It has been pointed out that it would be worthwhile to develop antibody-based assays from slit-skin smears of early lesions of leprosy as a means of increasing the sensitivity of assays.

In reactions, a transient T-cell boost has been observed. Circulating immune complexes (CICs) and antigens like PGL, and 65 kD antigen in the CICs have been demonstrated in a certain number of reactional cases. There has been no association of HLA-DR antigens with any of the types of these reactions. Antibody to LSR2 peptides as well as TNF levels have been suggested as new predictors of ENL and require evaluation.

MLSA (Rees Ag/Convit Ag) and lepromin remain as DTH evoking antigens. The search for new low molecular weight proteins like the 12 kD and 10 kD antigens for use as DTH inducing antigens should be continued and their further evaluation is necessary to prove that these are better evaluators of *M. leprae*-DTH than the existing antigens.

Combinations of *M. leprae* and BCG, and other mycobacterial species-like ICRC, *Mycobacterium w*, have been used as immunotherapeutic agents and have been taken to vaccine trials. The first survey using combinations of *M. leprae* and BCG in protection showed marginal benefits. *M. habana* has been taken as another agent for future vaccine trials.

Research Priorities

These build upon the considerable research achievements of the past 5 years and are divided into basic and applied categories:

BASIC IMMUNOLOGY

(1) Determining how human macrophages respond to infection by *M. leprae*;
(2) defining the cells and mediators that regulate the induction and suppression of effector T cells and antibody responses in immune responses;
(3) continuing the search for new antigens of *M. leprae* and co-ordinating the comparative immunological analyses of standardized recombinant antigen preparations;
(4) using gene knockout technology to investigate cellular, intracellular and cytokine

pathways that combine to provide protective immunity to mycobacterial infections in experimental models;
(5) initiating approaches to the investigation of the immunological basis of nerve damage.

APPLICATION OF BASIC RESEARCH

(1) Develop a superior DTH-evoking antigen which specifically detects *M. leprae* sensitization, and design *in vitro* correlates;
(2) continue to search for the various immunological tests that detect preclinical leprosy, diagnose early leprosy, monitor therapy and detect relapse cases;
(3) emphasize the need for immunological markers for prediction of nerve damage, and for Type I and Type II reactions;
(4) work with microbiologists to find ways of determining the infectivity of *M. leprae* in the population.

Concluding Comments

As an infectious disease, leprosy has plagued mankind for centuries. The co-ordinated efforts of many dedicated individuals from all walks of life have had a dramatic effect upon reducing the prevalence and incidence of disease in the world. The difficulties that result from the length of time it takes to develop the clinical disease following infection and the lack of any sensitive tests that detect preclinical and early stages of the disease impose severe constraints on the efforts to eradicate the disease. The slogan 'eradication of leprosy by 2000 AD' is now beginning to place undue pressure on health and research workers alike. While health workers may begin to place less emphasis on diagnosing early signs of leprosy, to reduce patient lists, research workers are beginning to see the reluctance of funding bodies to continue supporting their activities as leprosy research is no longer a priority. At a time when diseases such as malaria, tuberculosis and AIDS are spreading, the dictum should revert to 'control of leprosy by 2000 AD' rather than eradication. Immunology remains a very real force in the improvement of health for all, and its contribution to leprosy will be substantial.

Workshop 3 Chemotherapy

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The Workshop reviewed the progress of multidrug therapy (MDT) in the context of reported side effects and relapse rates. The application of MDT has been accepted world wide over the past decade. More than 3 million leprosy patients have already received WHO and similar MDT and many have been released from control. However, about 50% of the currently-registered patients are not receiving MDT. Therefore, the greatest immediate need is to implement MDT to all registered cases.

In spite of the general acceptance of clofazimine, a drug which has the additional value of reducing the incidence of erythema nodosum leprosum (type II) reactions, its effect of increasing skin pigmentation may result in poor compliance in certain patients and ethnic groups. The alternative, prothionamide, has some gastric intestinal side effects and a dose-related hepatotoxic effect. Other problems encountered include those of geography (so that monthly supervised drug distribution may be difficult because of the terrain), intercurrent disease, inadequate infrastructure and in paucibacillary leprosy (PBL) the difficulty of distinguishing late reversal reaction from bacteriological relapse due to treatment failure. Fortunately, rifampicin resistance remains very rare although its prevention depends upon careful and correct implementation of MDT.

Relapses

It is now over 20 years since the start of the Malta trial and more than 10 years since the introduction of WHO-MDT. Some information on relapse rates in multibacillary leprosy (MBL) is now available, although this is largely based on the original groups of patients, many of whom had received prior, long duration dapsone monotherapy, so that their bacterial loads were often low. In Malta and Paraguay (using rifampicin and isoprodian) and in South India (using WHO-MDT and the similar THELEP regimen), rates have been extraordinarily low and very acceptable. The few relapses detected have occurred 5 or more years after stopping therapy. However, very recently reported studies in Africa, in which varieties of short course regimens were given to previously untreated MBL patients, have resulted in significant relapse rates, some of which are unacceptably high. Moreover, relapse rates were significantly higher in patients with a high BI (5·0 or more) compared with those with a BI of 4·0 or less. Latest results suggest that the rate is probably

unacceptable in a group which received the WHO MBL regimen for a fixed duration of 2 years. Therefore, the Workshop suggested that the fixed-duration regimen may prove to be inadequate in previously-untreated LL patients with a high bacterial load, and counselled caution in the widespread adoption of 2-year fixed duration treatment of WHO MDT until further data are available. It also noted that many relapses are occurring late and, therefore, 5 years' post-treatment follow-up appears to be very inadequate, 8–10 years being the minimum required. In view of a claim that a period of daily rifampicin has some advantages in terms of relapse rates over totally intermittent rifampicin, ongoing analysis of data from long-term follow-up of such regimens is needed.

PBL relapse rates have been acceptably low worldwide. There is a great need for the further development of tests for distinguishing reversal reactions from bacteriological relapses.

The Workshop emphasized the need for the careful investigation of all post-MDT relapse cases, according to standard protocols.

New Drugs

The Workshop welcomed the discovery and development over the last 5 years of the new anti-leprosy drugs. These include certain of the 4-fluoroquinolones, minocycline and clarithromycin. Studies on mice have shown these drugs to be both bactericidal and second only to rifampicin in their rates of killing *M. leprae*. Pilot clinical trials in lepromatous leprosy have been completed, and have confirmed that these new drugs are highly effective both clinically and microbiologically. The Workshop also noted the current work on other drugs, such as fusidic acid and the combination of brodimoprin plus dapsone.

There is now a need for the setting up of long-term clinical trials (in addition to the current ofloxacin trial) of a number of carefully selected regimens, noting both efficacy (judged chiefly by long-term relapse rates) and also drug interactions, toxicity, acceptability and effect (if any) on reactions.

These new drugs (ofloxacin, pefloxacin, sparfloxacin, minocycline and clarithromycin) should be used with care and caution, and not be given as monotherapy. In the short-term, they may prove important in the treatment of patients who are intolerant to 1 or more of the standard drugs, or who suffer from proven drug resistances (especially to rifampicin) or from intercurrent disease precluding the use of a standard drug.

The Workshop considered the possible value of chemoprophylaxis and immunoprophylaxis in areas of low and falling endemicity, but there were insufficient data on which to base recommendations.

Although the outlook for leprosy is now very hopeful because of the widespread application of MDT and the potential application of the new drugs, there is still a great need for continued long-term and careful chemotherapy work, both in leprosy control programmes and in the various integrated programmes.

Workshop 4 Reaction and Nerve Damage

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Progress in the Past 5 Years

CLINICAL

The use of graded, nylon monofilaments (Weinstein) has been accepted as the best way to monitor nerve function in an accurate and highly reproducible way under field conditions. With serial testing 'silent neuropathy' can be identified objectively and treatment instituted promptly. Serial testing can also identify therapeutic responses in silent neuropathy or overt neuritis.

Although much nerve injury occurs as overt neuritis during reactions, silent (asymptomatic) neuropathy is common and may occur either during a reaction or in the absence of any reaction.

In the treatment of reversal reactions, aggressive use of corticosteroid therapy has been found to be reasonably safe under field conditions, and need not be restricted to hospitalized patients. In erythema nodosum leprosum, if thalidomide is not available, corticosteroid treatment with clofazimine as adjunctive therapy is valuable. In either reaction for refractory patients the use of cyclosporin A or immunosuppressive antimetabolites has been shown to be effective.

With the use of operating microscopes, surgical decompression procedures are now associated with better results and reduced morbidity, and these operations should be reintroduced as a part of the established management of leprosy.

INVESTIGATIVE

Recent studies reaffirm the central role of delayed-type hypersensitivity to antigens of *M. leprae* in the immunopathogenesis of reversal reactions. Studies of T cell infiltrates in nerves and of the cytokines produced (in particular tumour necrosis factor alpha and IL-1 beta), are elucidating the mechanisms of nerve injury in reversal reactions.

M. leprae may also injure nerves by interference with Schwann cell metabolism, by eliciting antibodies, by stimulating autoantibodies, or by antigenic mimicry, via either antibody or T cell pathways.

Recommendations

DEFINITIONS AND TERMINOLOGY

For clarity and comparability a definition of 'silent neuropathy' is needed. A single standard name for reversal reactions would make this important problem accessible in Medline and other computer databases. A uniformly used terminology for disability, functional impairment, or nerve impairment is needed to establish comparability of clinical and investigative studies.

CLINICAL

For the early identification and prompt treatment of potentially reversible silent neuropathy or neuritis, standardization of nerve functional assessment and scoring is needed in the parameters of tests used, frequency of use and conditions of use. Once identified, recent onset neuritis or neuropathy should be promptly treated with an aggressive use of corticosteroids at an initial dose of 40–60 mg of prednisone or prednisolone daily with a slow taper after 4 weeks with monitoring of function (reduction of daily dose by 5 mg at 2-week intervals) until the level necessary to suppress the reaction is achieved. Treatment for 3–6 months or longer is needed. Caution should be exercised in patients with hepatitis B, strongyloides or tuberculosis. For instance, resting the limb is essential, with the elbow at not less than 110 degrees of extension.

If painful neuritis does not promptly respond to vigorous oral corticosteroid therapy or to parenteral dexamethasone administration, then surgical consultation regarding decompression should be sought before the injury is irreversible (ideally within 2–3 weeks of onset), but a favourable response to surgery may still occur after prolonged delay.

Following surgery or medical intervention, monitoring of nerve function should be carried out as long as the patient can be followed up.

FURTHER STUDIES

The identification of risk factors for neuritis would help its early identification and prompt treatment.

Because of its ability to inhibit tumour necrosis factor alpha, a known neurotoxin, a trial of thalidomide in non-ENL neuritis may be warranted.

Where possible, other methods of nerve assessment should be studied, such as laser-Doppler blood flow, electroneuromyography, or electronic vibrometry.

The use of corticosteroids in selected field areas should be monitored so that refined, better recommendations can be made for field use. Studies of other agents is encouraged.

Criteria or tests for the accurate differentiation between relapse and reactions (reversal or ENL) are needed for the increasing number of patients receiving short-term multidrug therapy (MDT).

Continued exploration of the mechanisms of reaction and nerve injury is needed. The devastating type II reactions in Latin America are a particularly vexing problem needing further study. Also, immunomodulating agents, such as drugs, mycobacterial components, cytokines or vaccines, should be developed for the treatment and prevention of nerve damage.

Since nerve injury or neuropathy may occur after completion of MDT, 3-month monitoring is necessary in paucibacillary patients for at least 2 years, and in multibacillary cases for at least 5 years.

Workshop 5 Experimental

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Progress in the last 5 years

NUDE MICE

These athymic animals were first reported in leprosy studies in 1976 by Drs Kohsaka, Colston and colleagues. This model continues to be used in the evaluation of drug regimens for the treatment of leprosy because they can support the growth of large inocula to levels of 10^{10} per footpad. Dr McDermott-Lancaster (London) described how rifampin-resistant mutants selected in nude mice with a frequency of 1 to 8×10^7 viable organisms grow better in nude than in normal immunologically intact mice. Studies of anti-leprosy drugs combined with interferon-γ demonstrated a lack of synergy in reducing *M. leprae* growth except in combination with a therapeutic dose of rifampin but not with subtherapeutic doses or with DDS. A new anti-leprosy agent, ofloxacin, was found to be more effective when administered with daily dapsone than with monthly rifampin. It was found that *M. leprae* exposed to rifampin for 6 hours *in vitro* did not grow in nude mice whereas minimal killing by ofloxacin could only be detected after 96 hours exposure. As few as 10^1 to 10^2 organisms inoculated into nude mice, but not normal mice, showed growth over a 12-month period, demonstrating the value of nude mice in *M. leprae* viability studies. Professor Ito (Bangkok) reported that human-derived *M. leprae* multiplied as readily in nude as in normal mice. However, a strain of *M. leprae* (Thai-53) that had been passaged for many years in nude mice multiplied more readily in nude than in normal mice. Dr Hastings (Carville, LA) reported on a number of current uses for nude mouse-derived bacilli. As many as 10^9 *M. leprae* could be harvested weekly from nude mouse footpads for experimental use in metabolic studies, drug screening using radiometric methods, in culture with rodent Schwannoma cell lines, and in macrophage culture studies. Adoptive transfer studies using cells from Balb/c-nude heterozygotes immunized with a combination of *M. leprae* plus BCG resulted in the development of reversal reactions. In addition, transmission studies found that *M. leprae* applied and abraded (e.g., with thorns) onto cool but not warm skin resulted in growth of the organisms. This finding corresponds with observations made on armadillos caught in the wild that also showed evidence of *M. leprae* infection via contaminated thorns. The nasal mucosa appeared to be the primary site of infection in experimental transmission studies in nude mice. In chemotherapy studies, monthly rifampin by gavage was found to be less effective than daily rifampin in mouse food. Future studies in nude mice will evaluate new drug regimens for efficacy against persisting *M. leprae*.

BEIGE MICE

These immunologically-deficient (lack of NK cells, defective granulocyte chemotaxis, increased susceptibility to opportunistic infections) mice have been used for a number of years in biomedical research but are new in studies of leprosy. Dr Dhople (Melbourne, FL) reported that *M. leprae* multiplication in spleen and liver could be detected at least as early as 4 months in mice inoculated i.p. or i.v. Statistically significant enhancement of growth of *M. leprae* in footpads of beige compared to normal Balb/c mice was also observed. Dr Dhople also found the model to be suitable for chemotherapy studies.

SCID (SEVERE COMBINED IMMUNODEFICIENT) MICE

These mice have an enzymatic defect that results in a lack of functional T and B lymphocytes. They have attracted attention in recent years in infectious disease research due to their tolerance of functional xenogeneic mononuclear cells transplanted into the mice. Dr Converse (Baltimore, MD) summarized studies by investigators in Addis Ababa and Tokyo as well as his own that have shown that these mice are indeed susceptible to *M. leprae* infection when 5×10^3 to 10^7 bacilli are injected in the footpad. Dr Converse found that spread beyond the footpad to the popliteal lymph node and spleen could occur. In 1 mouse massive numbers of organisms were found in the nasal turbinates. Growth in SCID mice could not be enhanced by administration of a single dose of transforming growth factor b to abrogate NK cell function. Co-inoculation of *M. leprae* with cell-wall activated mononuclear cells from an *M. leprae* immune human donor but not a non-immune donor resulted in a reduction of organisms in footpad homogenates 3 months after infection. Dr Yogi (Tokyo) has observed dissemination of *M. leprae* after infection in the footpad. Dr Yogi reported that *M. leprae* inoculated i.v. resulted in significantly greater dissemination to footpads, bone marrow, liver, lips and ears of SCID mice than nude mice 14 months after infection. In addition, it was found by reverse transcriptase/polymerase chain reaction techniques that mRNA of cytokines that influence macrophage function was more detectable in 14-month infected SCID than nude hind feet whereas splenocyte cytokine mRNA was more readily detected in nude mice. In the experience of Dr Ishaque (Montreal) initial results also indicated greater susceptibility of SCID mice to *M. leprae* infection in terms of footpad swelling. However, subsequent experiments enumerating organisms found equivalent growth at 9 months and higher growth in the nude mice at 10 months after infection. Dr Ishaque was not able to detect bacilli in spleens or livers in SCID mice at this time. Dr Gelber (San Francisco, CA) reported that SCID mice reconstituted with immune T cells from Balb/c mice homed to the spleen, maintained long-term immune function, and limited multiplication of *M. leprae*.

NEONATALLY THYMECTOMIZED LEWIS RATS (NTLR)

Dr Gelber described earlier studies in which NTLR were proved to be a highly sensitive rodent model for detecting persisting *M. leprae* in patients undergoing initial chemotherapy. More recent studies using NTLR treated with various regimens involving newer anti-leprosy drugs demonstrated the value of this model in evaluating anti-persister drug regimens.

NORMAL MICE

Dr McDermott-Lancaster reported that sparfloxacin was superior to ofloxacin in infected mice at doses of 25 and 50 mg/kg by daily gavage for 60 days as determined by the proportional bactericidal test.

ARMADILLOS

This model was first described by Dr E. Storrs and Dr W. Kirchheimer in 1971. Dr Dhople discussed the history of the Florida armadillo colony, which has had contracts to supply infected tissues. More than 2300 armadillos have been inoculated for these projects. Until 1988 no problems with cultivable mycobacteria were encountered. Since then cultivable organisms have been found in approximately 30% of animals with disseminated leprosy. There has also been a decrease in the yields of *M. leprae*. The workshop participants discussed possible causes of and remedies for these problems in addition to the intensive efforts already undertaken by Dr Dhople and colleagues. Dr Dhople also confirmed previous observations of Dr J. Convit that Venezuelan 9-banded armadillos are not as susceptible to *M. leprae* infection as armadillos from the USA. None of 25 Venezuelan armadillos developed disease while 70% of USA armadillos inoculated with the same suspension developed leprosy. Dr Dhople found that armadillos metabolize dapsone in a manner very similar to humans. Biopsies of cutaneous samples obtained from infected armadillos receiving DDS revealed decreasing ATP levels during the course of treatment.

Dr Truman (Carville, LA) presented a comprehensive report on the history, distribution, migration, physiology and husbandry of armadillos. The epidemiology of sylvatic leprosy in armadillos in the USA appears to follow a corridor along the southern Mississippi River valley and then along the Gulf coast to the Mexican border. The prevalence of infection in adult armadillos is estimated to be 30% in this corridor. This pattern correlates with the distribution of indigenous human leprosy in the USA. He also reviewed the pathogenesis of *M. leprae* infection in experimentally-infected armadillos. As few as 10^3 organisms can result in a successful infection but typically 10^8 are inoculated i.v. in order to shorten the incubation period to an average of 14 months. Early indications of 'takes' are a nodule at the injection site, IgM antibodies to PGL-1, and detection of *M. leprae* specific DNA in PCR. Usually there are few clinical signs of infection. If cutaneous lesions develop and ulcerate, they represent a source of organisms in the environment. Dr Job (formerly Carville, LA) reported that armadillos whose reactions to lepromin had a histological resemblance to tuberculoid leprosy were usually resistant to subsequent infection whereas those with a lepromatous type response were the most susceptible and 6 weeks after immunization with either 10^7 BCG or 10^7 BCG plus $1{\cdot}6 \times 10^7$ heat-killed *M. leprae*, lepromin conversions were observed in 20% of armadillos. Only 3% of control armadillos converted. Dr Job also found that footpad infections were more successful with larger inocula and that infections proceeded from footpad granulomas and then to regional lymph nodes, the spleen and finally other organs. Dr Job pointed out that at a pre-clinical stage *M. leprae* is found in the reticuloendothelial system before invading the nerves. Finally, 2% of 'road-kill' armadillos were found to have disseminated disease, suggesting the potential for trillions of organisms to be discharged into the environment allowing spread to other hosts by means of skin abrasions.

CYNOMOLGUS MONKEYS

Dr dela Cruz (Cebu, the Philippines) described experimental studies in Philippine cynomolgus monkeys. Thus far, 4/22 animals have developed AFB positive nasal smears after inoculation with *M. leprae* and the positivity of the nasal mucosa correlates well with PGL-1 antibody levels in these animals. PCR examinations of nasal smears were positive in the 3 animals with available specimens as well as in 2 additional inoculated animals that were AFB negative by conventional methods. Sooty mangabey monkey isolates containing Simian Immunodeficiency Virus (SIV) were used to infect several groups of cynomolgus and the presence of SIV appears to enhance susceptibility of this species to leprosy. Surveys of ferral cynomolgus monkeys revealed serological evidence of natural leprosy in 3/596 monkeys. Additional studies of these 3 animals as well as more ferral monkeys are in progress.

CHIMPANZEES

Dr Gormus (Covington, LA) reviewed naturally acquired leprosy in 3 chimpanzees. The first chimpanzee with leprosy was from Sierra Leone and had been in the USA only a short time before diagnosis. The remaining 2 chimpanzees had been in the USA for more than 10 years before diagnosis and retrospective serological studies revealed that the disease was probably incubating in these animals when they were imported from Africa. Current efforts involve serological testing of chimpanzees maintained in various colonies for other biomedical investigations.

OTHER OLD WORLD MONKEYS

Naturally-acquired leprosy was described in 2 sooty mangabey monkeys (SMM). It is likely the first mangabey acquired the disease in Africa and was the source of infection for the second animal with whom it was caged for a number of months. This appears to be the first case of monkey to monkey transmission. Experimental leprosy studies in SMM revealed that this species was very susceptible to leprosy. Although dose–response studies demonstrated a variety of individual responses in terms of time and extent of disease, the SMM is undoubtedly the most susceptible non-human primate species studied to date. Variations in the course of leprosy in inoculated animals may be reflected in the cyclic variations in lymphocyte responses to mitogens observed in normal and *M. leprae* infected SMM. Experimental studies also demonstrated that rhesus monkeys were susceptible and developed BB to LL leprosy after infection with *M. leprae*. Captive SMMs are asymptomatic carriers of SIV but rhesus monkeys inoculated with SMM isolates develop simian AIDS together with leprosy. Many succumb to SAIDS-related opportunistic infections. SIV appears to enhance susceptibility of rhesus monkeys to leprosy. Experimental studies in African green monkeys demonstrate that they will develop a BB/BL form of leprosy involving primarily nerves.

Future Directions

Recognizing the contribution of animal models and their continuing role in providing information on the epidemiologic, chemotherapeutic, immunologic, microbiologic, and pathogenic aspects of leprosy, the following aims for future work are recommended.

1 Additional studies in SCID mice should be carried out to resolve questions concerning *M. leprae* dissemination, reproducibility, and the overall utility of the model including vaccine and cell transfer experiments.
2 Nude mice continue to have value (a) as a source of viable *M. leprae* for *in vitro* and other experimental studies (e.g., transmission and animal inoculations), (b) as a relatively inexpensive model for chemotherapy studies, and (c) as a means of detecting small numbers of viable bacilli.
3 Future studies in beige mice will involve histopathology and additional experiments on the pathogenesis of leprosy infection.
4 The normal mouse footpad assay remains the most readily available model for viability, drug screening, and drug sensitivity testing.
5 The NTLR will continue to be used in *M. leprae* persister studies.
6 The armadillo has as yet untapped potential in studies of the transmission, epidemiology, chemotherapy, and immunology of leprosy. Investigations of these various aspects of leprosy in wild-caught animals should be continued. This model's potential for assessing candidate vaccines and new drugs may be particularly worthwhile areas to investigate. New techniques in assisted reproduction may overcome the present barriers to breeding in captivity. Understanding the differences in susceptibility of Venezuelan and North American 9-banded armadillos may be a rewarding avenue of investigation.
7 In non-human primates, studies should: (a) ascertain natural infection in ferral and captive primates and investigate the contribution of retroviruses to the development of leprosy in these species; (b) continue studies evaluating the susceptibility of cynomolgus monkeys to experimental infection with *M. leprae*; (c) continue to evaluate the relevance of the SSM vaccine model; (d) continue to study the African green monkey as a model for neuritic leprosy; (e) investigate *M. leprae* strain differences in the pathogenicity of infection in rhesus monkeys as a model to determine if strain differences play a role in the spectrum of human leprosy.

Workshop 6 Pathology

Chair: Ashok Mukherjee
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Summary and recommendations

Pathology continues to make an important contribution to the study and control of leprosy. Although the histopathology of leprosy is well known, there are a number of

areas in which recent advances have been made and some in which the pathologist should respond to advances in other disciplines. In leprosy pathology, as in many other fields of leprosy research, there is a need to distinguish cause from consequence. The workshop makes the following recommendations:

We recommend the application of standard diagnostic criteria for early leprosy.
2 Planning and implementation of all new trials of treatment should include a pathologist.
3 For the distinction between relapse and reaction, demonstration of solid-staining AFB appears to be the most reliable histological criterion.
4 There is an urgent need for detailed pathogenetic studies of the Lucio phenomenon.
5 In view of the global pandemic of HIV infection, the relationship between AIDS and leprosy requires careful clinico-pathological study.

Early leprosy

The diagnosis of early leprosy is often uncertain clinically and histologically. However, there are many patients in which histology either confirms the suspicion of leprosy or provides an alternative diagnosis. Histological examination of clinically indeterminate lesions and lesions suspected of leprosy is an important diagnostic tool. However, individual pathologists differ widely in the certainty with which they diagnose leprosy and there is clearly a need for the standardization of diagnostic criteria. The following criteria should be applied for the diagnosis of biopsies from clinically suspicious lesions of leprosy:

(a) A diagnosis of early leprosy can be given if one or both of the following criteria are satisfied.
(i) The presence of convincing acid-fast bacilli (AFB): the participants agreed that a minimum of 6 serial sections of every biopsy should be stained by an appropriate modified Ziehl–Neelsen method such as the Wade–Fite or Fite–Faraco for AFB. Certain sites are more likely to harbour AFB and should be searched in the following order: nerve-bundles, sub-epidermal zone, arrector pili muscle, and areas of inflammation.
(ii) The presence of endoneurial inflammatory cells (lymphocytes and macrophages usually predominant), preferably with disruption of neural architecture.
(b) A report of findings compatible with leprosy should be given if the following suggestive features are present.
(i) A chronic mononuclear cell inflammatory infiltrate with a superficial and deep dermal pattern surrounding nerves, vessels and adnexae, without neural disruption or AFB. In such cases, re-examination for AFB and possibly further biopsy is indicated.

Procedures which may be of help include the use of sections cut at deeper levels to determine the relationship of inflammatory foci to nerve. Special staining procedures (e.g. S100 and Neuron-specific enolase for nerves) and the demonstration of mycobacterial antigens may be helpful with appropriate controls, but require further evaluation.

Biopsies should generally be taken from the edge of the lesion, but in lesions less than 1·5 cm diameter, a central biopsy is more likely to be diagnostic. The diagnosis and classification of established leprosy is not usually problematic. In evaluating the

differential diagnosis of granulomatous dermatitis the above principles apply. Clinical consultation is an important part of the diagnostic process.

Evolution of Disease

Several presentations addressed the issue of disease progression in skin, nose and nerve. There is scope for further research in this area and for sequential biopsy studies. Bacilliferous lesions may be present in the nasal mucosa and nerve prior to the development of skin lesions. It is possible that early nerve damage occurs in the absence of bacilli, but further work on the pathogenesis of nerve destruction before, during and after treatment is required, ethical considerations permitting. In particular, the pathogenesis of progressive neural deficit and fibrosis following cessation of therapy requires elucidation. The interaction between *M. leprae* and endothelial cells may be an important determinant of localization and lesion development. Further work is also required in this area.

Reactions

The basic criterion for diagnosis of erythema nodosum leprosum (ENL)—infiltration by neutrophils—is well known, but in a proportion of cases with clinical evidence of ENL, no neutrophils are present. Participants felt that this discordance might be due to timing of the biopsy and the importance of changes in vascular dynamics which are not seen by the pathologist. ENL has an appreciable mortality rate and in these severe cases, ENL lesions are often found in internal organs at necropsy. The pathogenesis of ENL requires clarification in relation to neuritis, glomerulonephritis, iridocyclitis, arthritis, testicular involvement, amyloidosis, immune complexes and reversal reaction.

The clinical and histological features of the Lucio phenomenon have been fully described, but the pathogenesis of this reactional state remains obscure. Clearly, vascular bacillation and associated thrombotic phenomena are important. However, the genetic and immunological factors involved need substantial research investment.

The histological diagnosis of reversal reaction is often difficult and does not appear to correlate well with clinical signs. This may reflect the lack of histological features associated with erythema and induration. However, immunological changes such as increased IL2R or HLA-DR expression and CD4+ lymphocyte infiltration can be seen and quantified in histological sections. Reversal reaction may represent qualitative or quantitative immunological differences among patients. An effort should be made to distinguish between both possibilities. The relative importance of other factors such as disease load, treatment, timing of biopsy, sex and age has yet to be determined.

The participants were unanimous in their opinion that relapse could only be reliably distinguished from reversal reaction following MDT when solid-staining AFB are demonstrated. The most difficult biopsies are those in which there are no bacilli and the appearances are of tuberculoid type.

Monitoring treatment

In clinical trials, the response to therapy should be monitored by histological as well as clinical, bacteriological, and immunological means. There was concern at the lack of

histological evaluation in several current chemotherapeutic trials. The inclusion of a pathologist at the planning stage of these trials is a necessity.

Recent studies have demonstrated the utility of sequential biopsies to measure many parameters, including granuloma fraction, bacterial index, antigen load, and cell surface antigen expression. These can be used as surrogate markers of response to chemotherapeutic and immunochemotherapeutic regimens.

After completion of MDT, there is often persistence of foam cells without solid bacilli (MBL) or epithelioid granulomas (PBL) in the absence of clinical activity. The significance of these changes is not understood, and there is no consensus as to whether histological normality should be a condition for release of patients from treatment.

Systemic involvement

Systemic involvement in leprosy is common, particularly in lepromatous patients. Regression in the skin may occur during treatment without complete clearance of visceral, ocular and neural bacilli, leading to later relapse. Involvement of the larynx and testis are of particular importance. Secondary amyloidosis occurs which can best be diagnosed by the biopsy of minor salivary glands, and may regress following treatment.

Eye involvement is common, but usually seen by the pathologist at a late stage in its development. There is a need to follow ocular changes by regular examination during treatment and to obtain material for pathology where possible.

The pandemic of HIV infection and AIDS involves many leprosy endemic areas. The effects of HIV on leprosy are not yet clear and require further clinico-pathological study.

There is need for all tissue removed from leprosy patients to be sent for pathological examination and for further necropsy studies to be performed.

Training, quality assurance and audit

The workshop identified a lack of trained leprosy pathologists, particularly in endemic countries. There is an urgent need to educate practising and trainee pathologists in the diagnosis and classification of leprosy. One method is the organization of regular training workshops. In many countries technical standards of skin section preparation require improvement. This could best be achieved by visiting senior technical staff from existing laboratories. Achievement of these aims could be assisted by the development of quality assurance and audit schemes for histopathology laboratories.

Workshop 7 Training of Professionals

Chair: Djohan Kurnia
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Introduction

The Workshop on Training (as well as on other topics in leprosy control) has been a standard feature at the International Leprosy Congress for many years.

The Workshop on Training of Professionals in Leprosy before the IVth ILA Congress was attended by trainers from all parts of the world and 20 papers were presented.

With reference to the global MDT situations, the workshop reviewed the current status of training in various areas and made some recommendations to ensure that training activities were more effective and efficient in assisting the leprosy control programmes toward the goal of eliminating leprosy by the year 2000.

OBJECTIVES

The objectives of the workshop were:

(1) to review the present status of the training activities for the professionals in leprosy in the world;
(2) to identify important unresolved issues in the training of professionals in leprosy;
(3) to recommend guidelines for approaches to resolve these issues.

REVIEW OF THE PROGRESS

During the last 5 years, progress has been made in the field of training in the following areas:

1 *Approach in learning and evaluation methods*
Learning in leprosy is moving mainly from subject to task orientation using problem-based, student-centred methods.

2 *Emphasis on curricula priorities*
In addition to the basics of clinical leprosy and control many training programmes are

realizing the need to include better management training, more emphasis on communication skills, training in prevention of disabilities and health system research.

3 *Training of trainers*
In recognition of the need to upgrade the education skills of trainers, some workshops were organized at national and international levels.

4 *Production of materials*
The use of modular training material has increased. Local production and adaptation has been encouraged. In some countries, materials have been produced for undergraduate healthcare workers.

Recommendations

Although progress has been made in the areas mentioned above, the participants feel it is essential to continue to strengthen and consolidate what has already been achieved.

The following recommendations are made for the future of the training of professionals in leprosy:

Approach in learning and evaluation methods

1.1 Strengthening of the problem-based, task-oriented approach to learning needs to be continued. Education should be continuous. Learning can continue in the field using self-learning materials, distance learning, training follow-up and feedback.

1.2 There should be a multidisciplinary team approach to training.

2 *Emphasis on curricular priorities*

2.1 Training needs to be tailored to programme needs, e.g., in areas where MDT coverage is low, emphasis could be placed on the implementation of MDT, early detection and complete treatment. In some areas, courses held in special training centres can be shortened. In areas of high MDT coverage, training could concentrate on prevention of disabilities, vocational training and all aspects of rehabilitation. The hidden programme needs, which are often neglected, should be emphasized, such as patient education, communication skills, management and psycho-social aspects. As we move toward the elimination of leprosy, it will be necessary to develop appropriate training strategies to cope with integration, e.g., training primary healthcare workers, medical students, combined TB-leprosy courses and community-based rehabilitation. This will involve the production of materials and training modules for undergraduates in medical fields.

3 *Training of trainers*

3.1 Training capacity can be multiplied through training of trainers. Specialized centres should equip regional training teams to pass on their knowledge and skills.

3.2 Training centres should be linked so that there is a networking of expertise and

sharing of developments and ideas. This may entail the identification of global co-ordinating centres.

4 *Production of materials*

4.1 Appropriate training materials need to be produced. The distribution of these materials needs to be rationalized.

5 *Selection of students*

5.1 This is an area that needs to be looked into. We would recommend that criteria for selection be drawn-up by centres. Selection of trainees should be based on local needs.

All these recommendations depend on an increase in resources, which will necessitate a channelling of funds into training and material production.

Workshop 8 Approaches to Epidemiology, Prevention and Control

Chair: Kumar Jesudasan
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P. W. Samdup
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Vijayakumaran
H. Wiher

There has been a significant fall in the prevalence of leprosy in all parts of the world where MDT has been implemented. There has been a decrease of nearly 60% in registered cases between 1985 and 1993. The estimated number of cases has also fallen from 11 million in 1985 to 3·1 million in 1993. The statistics for 1993 on registered cases indicate that 80% of the registered cases of leprosy come from India, Brazil, Nigeria, China and the Sudan. In 1991, the World Health Assembly adopted a resolution on the elimination of leprosy as a public health problem. Elimination was defined as a prevalence of less that 1 per 10,000.

Our current understanding of the epidemiology of leprosy has not changed significantly since the last congress. No new light has been shed on factors relating to the transmission, evolution or any other factors relating to the epidemiology of the disease.

There is a need to have simplified indicators relevant to leprosy control and which are based on minimum and essential data. Measurements of trends of leprosy should ideally be done using incidence rates. The true incidence and prevalence of leprosy are difficult to

measure and case detection rates and prevalence rates should be used for following trends in leprosy, taking care to use correction factors by adopting the appropriate adjustments.

Findings from Venezuela on the immunoprophylactics with BCG and killed *M. leprae* (armadillo derived) combination have been inconclusive. Results from other vaccine trials using BCG and killed *M. leprae* and other combinations such as ICRC, *Mycobacterium w*, are expected to be available after 1995. As of now no second generation vaccines against leprosy are available. The present priority for immunoprophylaxis should be to complete the current vaccine trials and to assess their outcome before considering new trials.

While chemoprophylaxis may have a limited role in individuals, it is not a tool that can be recommended for the prevention of leprosy at the community level, therefore the mainstay for leprosy control is chemotherapy. Thus the priority for leprosy control is to increase MDT coverage in all parts of the world and ensure a high case detection level.

While looking into the effect of MDT on the trends of leprosy, it can be seen that in many areas the case detection rates (proxy for incidence rates) have stabilized and are not showing signs of decline, even after the implementation of MDT for between 8 and 10 years. For instance, in some hyperendemic areas in India the stabilization has been in the region of 1 per 1000. There is a need for a health systems approach to investigate this phenomenon in the light of the proposed target of the elimination of leprosy by the year 2000.

Better strategies for leprosy control can be discovered by improving our knowledge of the epidemiology of the disease. A test to identify *M. leprae* infection is expected to help in achieving this goal and should be given high priority in research. The tools based on molecular biology and immunology, as well as newer tools, should be investigated further in this respect. Epidemiological studies need to be taken up to establish the magnitude and dynamics of infection. A holistic approach to understand the micro-epidemiology of leprosy is needed and such work can be done in sentinel centres with appropriate samples of population. The interruption of leprosy transmission in the community will depend on the identification of all leprosy cases and their effective treatment. The proportion of leprosy cases remaining undetected (unknown patient load) would contribute to continued transmission. It is also necessary to look into the possibilities of non-human reservoirs for *M. leprae* in this connection. This would involve the collection of epidemiological, immunological, bacteriological, environmental, socio-economic and behavioural data from selected areas of high and low endemicity from different parts of the world. Establishment of these sentinel centres are of paramount importance.

There is a need to develop appropriate epidemiological indicators to study leprosy epidemiology after the level of elimination is reached.

Prevention of disability starts with the control of leprosy. Nevertheless the occurrence of disability in patients on treatment and new disability after release from treatment is a cause for concern. The Sixth Expert Committee on Leprosy (WHO) has recommended that prevention and management of impairments and disabilities, which have long been recognized as essential components of leprosy control programmes, should be implemented effectively. Leprosy is a public health problem because of the deformities it causes and there is a need to give very high priority to disability prevention. The possible use of disability rate and occurrence of new disability during treatment and after cessation of chemotherapy should be considered for evaluating the quality of leprosy control.

The development of epidemiological models is important in order to predict and

simulate the trends of leprosy under various operational conditions. This exercise should be related closely to the actual implementation and monitoring of leprosy control activities.

There has not as yet been demonstrated any relationship between HIV infection and the risk of leprosy or susceptibility to any particular type of leprosy. The effect of HIV infection on relapses, reactions and neuritis needs to be studied.

The area of urban leprosy control needs to receive special emphasis in view of the rapid growth of cities and migrations from the countryside to urban slums. Efforts should be made to trace such migrant cases as soon as possible and treat them with effective MDT. Health systems research could contribute to our understanding of the dynamics of urban leprosy and thus facilitate the evolution of new strategies for urban leprosy control.

This workshop ended with the optimistic view that a concerted approach will help us to develop a better understanding of the disease, which in turn will help us formulate improved strategies for the elimination and eventual eradication of leprosy.

Workshop 9 Consumer and Community Participation in Care and Rehabilitation Programmes for Persons with Leprosy

Chair: Maria Leide W. de Oliveira (Brazil)
Co-Chair: Anwei Skinsnes Law (USA)
Rapporteur: Judith Justice (USA)

Participants:

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Heather Smith (Thailand)
Samuel Solomon (India)
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Introduction

The Workshop on 'Consumer and Community Participation in Care and Rehabilitation Programmes for Persons with Leprosy' combined 3 Workshop topics from the XIIIth International Leprosy Congress, including Social Aspects, Health Education and Rehabilitation.

The emphasis of the Workshop was on the individual who is suffering from the disease and the community as consumers and the Leprosy Control Programme as the production process which encompasses all aspects of care, extending beyond chemotherapy and the reduction of prevalence rates. The Workshop emphasized the social and economic aspects of leprosy without ignoring the bio-medical aspects. In keeping with this approach, Social Science Research needs to provide the appropriate theories and methodology for studying the Leprosy Control Programme with special efforts to include perceptions of individuals with the disease and the community.

The following invited formal presentations were made by Workshop participants:

'Status of Health Education in Leprosy Control' by Dr R. Mutatkar (India);
'Physical Rehabilitation and the Community' by Dr H. Srinivasan (India);
'Socio-Economic Rehabilitation' by Dr J. Lew (Korea) and Mr S. K. Jung (Korea);
'The Priorities of Social Science Research in Leprosy' by Dr Judith Justice (USA);
'Case Study of Economic Rehabilitation in India' by Dr Jal Mehta (India);
'Hawaiian Storytelling' by Makia Malo (USA).

Discussion

The Workshop participants were divided into 3 discussion groups: Health Education, Rehabilitation and Social Science Research.

The Health Education Group addressed the following questions.

How can leprosy treatment (in its present short-term form) be managed so that the individual's life, work and family relationships will not be interrupted? Has MDT really altered the social isolation felt by individuals suffering from leprosy? What can be done to lessen their social isolation?

How can individuals with leprosy be brought into the public health education process?

The Rehabilitation Group addressed the following questions:

Can Leprosy Rehabilitation Programmes be successfully integrated into the General Health Care System? If so, how would this be possible? Is this always desirable?

How can individuals who have suffered from leprosy, and have been living in colonies or other isolated situations, be empowered to participate in community activities? How can they be re-integrated into the community and what can be done for those for whom integration is not possible?

How can individuals with leprosy improve their socio-economic status in order to become fully accepted as productive members of the community?

How can fund-raisers be brought into the public education process?

The Social Science Research Group addressed the following questions:

What should be the priorities of social science research in leprosy?

How can the results of the projects in social science research be applied in order to improve the efficiency of leprosy control?

Recommendations

RECOMMENDATIONS FOR HEALTH EDUCATION

1 The management of leprosy treatment can be successful at the individual and family level without interrupting normal life, work and family relationships. To achieve this, drug delivery and other services should be combined with personal and family counselling and appropriate health education for the individual, his family and the community.

2 A combination of MDT and health education has reduced the social isolation felt by individuals with leprosy.

3 Health education efforts should be periodically evaluated and updated to include the latest scientific information.

4 As leprosy programmes are increasingly integrated into the general health care system, the number of leprosy workers and health educators is often reduced. Serious consideration should be given to training individuals suffering from leprosy to fill these positions so that health education efforts are not diminished.

5 Networks should be devised whereby information can be distributed to individuals with the disease.

6 It is recognized that each country has its preferred terminology for the disease. However, the use of derogatory terms such as 'leper' should *never* be used.

7 In integrated programmes, community participation becomes even more necessary. Organized community groups such as youth groups, women's groups and service organizations, should be utilized to help disseminate information on leprosy. Information provided should take into consideration socio-cultural factors of the people.

8 Religious leaders should also be encouraged to be health educators to educate the community about leprosy.

9 Every effort should be made to ensure that the mass media does not give incorrect information which perpetuates stigma and fear.

10 Ultimately, the responsibility for health education should be transferred from health providers to the community.

11 Health education will help to achieve the stated goal of the elimination of leprosy, but this must be continued even after leprosy is no longer considered 'a public health problem'.

Recommendations for Rehabilitation

Multi-Drug Therapy has brought great benefits to a large number of people and future development in chemotherapy promises simpler and shorter treatment. These changes suggest a possible shift in emphasis and increased allocation of human and financial resources to the physical and socio-economical rehabilitation of individuals who have leprosy-related handicaps. The participation of individuals with such handicaps in the delivery of rehabilitation services at all levels is seen not only as a response to their demands, but also as a beneficial contribution. In view of such future developments, the participants of the discussion group on Rehabilitation made the following recommendations:

Each country should develop a national policy suited to its requirement to deal with leprosy-related problems other than chemotherapy. Such a policy should make a political commitment to deal with the massive problems of physical and socio-economic rehabilitation, allocate necessary funds, generate the needed infrastructure and ensure the participation of people with leprosy-related handicaps in the efforts of governments and non-governmental organizations.

2 Action plans for physical, socio-economic and psychological rehabilitation of the individuals with leprosy-related handicaps need to be prepared and adequate budgetary allocation ensured.

3 It is strongly recommended that, wherever possible, physical rehabilitation and disability prevention programmes operate through the general health delivery services. With MDT, contact between providers and persons with the disease is reduced, increasing the risk of neglect of disability prevention. To achieve effective implementation of programmes, appropriate training should be given to all connected personnel.

4 It is recognized that leprosy and poverty are inter-related. Therefore, stigma associated with the disease can more easily be eliminated through improving the individual's economic status rather than through education of the community. Experiences in Korea and India confirm that large-scale initiation of programmes designed to improve the socio-economic status of individuals with leprosy-related handicaps can be very successful and are needed urgently in other areas.

5 In countries such as Japan and the USA where economic well-being is not as serious a problem as in developing countries, individuals with leprosy still encounter problems of self-respect related to society's attitudes. For example, Japanese laws require individuals with leprosy to inform officials every time they travel, even within the country. The Workshop therefore recommends that discriminatory laws such as in Japan and India be removed and individuals with leprosy-related handicaps be respected.

6 Socio-economic projects have a greater chance of success if they are planned and controlled by the beneficiaries. Modes of control, format and management may vary, e.g. handicraft subcontractors, agro-based groups, co-operatives, registered small-scale industry, etc., depending on the situation in each country, with the common factor being full participation of the beneficiaries in the decision-making process.

7 'Leprosy colonies' need not always be viewed as a negative development but one that fulfilled a need and therefore the situation must be utilized to the best advantage. An extreme example is Korea where the non-disabled moved into such villages because of their economic prosperity. Brazil provides another example where people in colonies are free to leave, and those who choose to remain must be allowed to live undisturbed. However, it must be strongly stated that *no new colonies or segregated hospitals or settlements* should be created.

8 In countries where special privileges are given to persons with hearing, visual and orthopaedic disabilities, similar privileges should not be denied to those with leprosy-related social disabilities.

9 The use of photographs and pictures depicting poverty, deformity and deprivation that shock people, promote pity and appeal to emotions should not be used in fund raising. The information provided today should depict reality and appeal to the intellect. In practical terms, earlier appeals were for grants for charitable purposes. Appeals should now be based on the need for investment in development and how this involvement would provide relief in the short-term and eliminate dependency in the long-term.

Recommendations for Social Science Research

Recommendations were made taking into account the individual, community, health services, technology, and social science theory and methodology.

1 The group endorses the definition of leprosy as given in the Sixth WHO Expert Committee Report on Leprosy. Social science research, therefore, should address all aspects of leprosy, including epidemiology, chemotherapy, deformity prevention and rehabilitation.

2 Social science research should document and evaluate the process of integrating leprosy control programmes into the general health services.

3 Social science research should address the concept of cure, including the perceptions of patients, community and health workers, particularly related to the implementation of MDT at the global level.

4 Social science research methodology workshops should be held for leprosy workers who are interested in social science inputs in leprosy control work.

5 Training materials should be developed for medical officers and other health workers to look at problems of individuals with the disease and of the community, which result from disability, ulcers, threat of social isolation and dehabilitation.

6 Social science research should be used to help individuals with leprosy.

7 A recording system for non-medical work needs to be developed, including qualitative and quantitative parameters.

8 Funding for social science research in leprosy needs to be generated from international and national agencies, including the international organizations such as WHO, UNICEF, ILA, ILEP, ALM, national and international NGOs, and national social and medical research councils.

9 Social science research should be used for research, documentation and evaluation of community participation programmes designed to share responsibilities of the health services in leprosy control.

10 Social scientists should study social, economic and political issues related to the decline of leprosy colonies.

11 Participatory research approaches involving individuals with leprosy, community and health workers should be encouraged.

12 Social scientists should give special attention to identifying research problems and implementation of studies in collaboration with individuals, the community and health care providers.

13 Research results should be disseminated in accessible forms, including publication in international and national scientific journals, particularly in countries where research is conducted, and made available to patients, communities and leprosy control programmes.

14 Because it is not possible for many social scientists to attend international meetings, national and international networks of social scientists should be formed to enhance the training of social scientists, to increase social science research, and to ensure the dissemination of research results. Social scientists should be recognized as one of the scientific groups of the International Leprosy Association with specialized meetings at the International Congress.

Workshop 10 Management of Physical Disability

Chair: Frank Duerksen
Rapporteurs: Dinkar Palande
Roland Kazen

Participants:

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S. Partheebarajan
Silvano Renzo
Atul Shah
Trevor Smith
Germano Traple
Marcos Virmon
Jean Watson
Ruth Winslow

Although multidrug therapy (MDT) has changed the bacteriological aspect of leprosy, the position regarding deformity and disability remains the same. For a patient with a deformity and disability the cure consists of either its prevention or its correction.

In the last 5 years there has been an increasing recognition of the importance of including prevention of disability (POD) as an essential part of leprosy management.

Within all leprosy rehabilitation theories are world views which must be addressed within the social, cultural and psycho-social context.

The workshop considered the following issues:

(1) prevention of disability (POD);
(2) early detection of nerve damage;
(3) monitoring;
(4) training;
(5) care after cure.

1 Prevention of Disability

The prevalence of patients with impairment continues to rise over the years. The incidence of disability has only been slightly diminished, therefore the number of patients in need of disability control is still very high.

The most common use of the WHO disability grading is as a new case-finding indicator. If it is to be used to determine disability caseload, it is essential that discharged patients and grade 1 disabilities are included. WHO grading is neither intended nor appropriate for monitoring changes in levels of impairment. For this purpose more detailed measurable clinical information is needed.

Leprosy control programmes need to secure funding and ensure effective training of staff in the early identification and monitoring of impairment and prevention of further deterioration.

One of the tried methodologies is given in the ILEP publication 'Prevention of Disability, Guidelines for Leprosy Control Programmes' (March 1993).

It has to be recognized by all concerned that impairment of function can occur before, during and after chemotherapy.

Public awareness has an impact on early detection and consequently on prevention of

disability. Disability prevention and rehabilitation ensures the credibility of leprosy control programmes. The number of presentations under rehabilitation in this Congress attests to the increasing awareness of its importance.

2 Early detection of nerve damage

Early detection of nerve damage is the key to prevention of deformity and consequently of stigma in leprosy. Adequate training of the staff in the evaluation of clinical, sensory and motor aspects of nerve function is essential and feasibile.

Motor and sensory testing by quantitative methods is available and feasible under field conditions, and essential for proper monitoring of nerve damage. Tests should be performed at the time of diagnosis and periodically during and after treatment. We recommend the use of the well-documented and widely used standardized graded nylon monofilaments for sensory testing.

Methodology should be adapted to regional conditions, but it is essential that some type of periodic quantitative assessment is used.

A patient with any clearly defined loss of sensation in the eyes, feet and hands has to be regarded as being at high risk to suffer further deterioration and consequently will need careful monitoring.

The patient's awareness of the risk factors and self-examination is essential to ensure voluntary reporting.

3 Monitoring

It is time that the leprosy programme manager assumes responsibility for disability control during and after treatment. This includes monitoring of:

1 vision, wounds and cracks of any insensitive parts;
2 needs of footwear, its acceptability and distribution;
3 ongoing self-care programmes; and
4 the required protective and adaptive appliances.

4 Training

The need for training includes the patient, his family, the community and staff.

THE PATIENT

The patient should be trained to recognize symptoms and signs of early nerve involvement and the deterioration of any present condition, especially of his eyes, feet and hands. The patient also needs to be trained in self-care and in the use of protective measures. The training is not complete until the patient's compliance is observed.

THE COMMUNITY

The community needs to be made aware that persisting deformities in a cured patient do not indicate any threat to the public.

STAFF

Staff should be trained to recognize impairment, disability and handicap, respond to the patient's needs and work with his/her initiative to overcome them.

5 Care after cure

Irrespective of chemotherapy, patients will continue to develop impairments and are in need of care almost indefinitely. It is suggested that patients with risk of, or with any grade of disability, are entered into a separate register after release from treatment (RFT). This is to ensure that there is a mechanism in place for further follow up, if necessary. It will also ensure that the patients do not feel unwelcome when they report any complications that arise.

Rehabilitation services should progressively be integrated into general community services.

Leprosy rehabilitation personnel should strive towards 'reverse integration' and teach colleagues in general health services the basic techniques known to work in leprosy.

Workshop 11 Guidelines for Leprosy Control Managers

Chair: P. Feenstra
Rapporteur: R. de Soldenhoff

Participants:

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K. M. A. Gubara
L. Janssens
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Introduction

The current MDT regimens for MB and PB leprosy are appropriate for routine field conditions. Experience has shown that they are effective, safe and operationally feasible. They are acceptable to patients and field staff.

Regular and complete treatment with MDT of all known leprosy cases and early diagnosed new cases is the most cost-effective element of the strategy to achieve the leprosy control objectives. Therefore the establishment of early case finding and treatment with MDT remains the top priority for leprosy control programmes. The diagnosis can be made with simple techniques in the vast majority of cases and there are

only 2 groups within the classification, each with its own standardized treatment which can be safely applied under field conditions.

In April 1993 the total number of leprosy cases was estimated at 3·1 million in 90 endemic countries of whom 2·3 million were registered for chemotherapy. The MDT coverage varies widely between the leprosy endemic countries and within individual countries. The fall in MDT coverage from 55% in 1990 to 48% in 1993 indicates that it has become more difficult to reach the remaining patients. The reasons for this failure to consolidate MDT implementation are multiple and vary from country to country and also within individual countries. The major explanations are: lack of political commitment, competition with other health problems in the countries, weak management capacities and organizational problems of the health services, inadequate training in leprosy of general health staff, lack of resources, lack of an appropriate plan of action and/or an operational manual, poor referral facilities and the rigid and demanding requirements for the introduction of MDT which were identified in the early 1980s.

Far too many leprosy patients do not yet have access to the benefits of MDT. Successful introduction of MDT so far has been achieved mainly in those countries or areas where the conditions are relatively 'easy' for the implementation of MDT: countries or regions with a good infrastructure or with sufficient numbers of well-trained health workers, a good coverage with health services, or with a pre-existing, well-managed leprosy control programme based on dapsone monotherapy, adequate financial resources, etc.

A lot has to be done in order to achieve and to sustain full MDT coverage. Unless the obstacles are really insurmountable, such as war situations, all known cases must be submitted to MDT within the next 3 to 5 years. We have to rationalize the leprosy control strategy in order to achieve this goal and to maintain adequate and appropriate services. The MDT coverage of registered cases is often taken as the only measure for progress in MDT implementation. This is wrong. We must also look at the coverage of the real case load and the cure rate (MDT completion).

WHO and ILEP publications have called for increasing attention to the basic rather than the optimal requirements to enable programme managers to achieve full MDT coverage. Further progress has been made with the acceptance of the essential indicators which should reduce the data requirements, the recent publication and the distribution of the ILEP document on guidelines for programme managers for the prevention of disability and the introduction of the WHO modules on training of programme managers in leprosy control.

Even more simplification and flexibility will be required for universal MDT implementation and to sustain it under low endemic conditions. Creative local approaches, sometimes specific for individual patients, will have to be developed by local health staff.

Recommendations for further simplication of guidelines for programme managers

HEALTH EDUCATION, AWARENESS AND STIGMA

Managers should encourage the widespread use of the mass media for promoting early case presentation. Groups in the community, particularly patients and ex-patients, can be utilized to support leprosy control services, promote case-finding, case-holding and

prevention of disability. Despite this and the widespread use of MDT, stigma is still a major problem in many areas and is even a problem within the health and medical professions. Integration of the leprosy services, more effective health education to the population and improvement of the socioeconomic status of patients, particularly those with disability, will assist in diminishing stigma.

CASE-FINDING, DIAGNOSIS AND CLASSIFICATION

Passive case-finding is the mainstay of new patient detection. This voluntary reporting should be supported by health education and awareness programmes, especially using the mass media. Good quality services, presented in a user friendly manner, should promote early case detection. Furthermore, contact examination should be prompt and should be stimulated by the newly-diagnosed leprosy patient. It does not have to be done repeatedly.

Diagnosis should be made at the peripheral health unit and must result in the immediate start of MDT. Only the PB/MB classification should be used in the field. The hoped-for adoption of a single agreed drug regimen will enable classification in the field to be finally abandoned. The presence of slit-skin smear services are not a pre-requisite for the implementation of MDT and these services do not need to be developed at the peripheral level. While there is still a role for skin smear microscopy at the referral centre level, histopathology services and the lepromin test have no relevance in routine leprosy control.

CASE-HOLDING

Services to patients must be flexible and encourage regularity of attendance. The fixed drug treatment regimens of 6 and 24 months should be adopted forthwith. Supervised intake of the once monthly pulse is still advocated but this does not necessarily require fixed monthly clinic days. When necessary patients or their relatives can be given several months of MDT. The use of blister packs is indicated in these circumstances.

In view of the low relapse rates, no active post-cure surveillance is indicated. Following adequate health education, it is the responsibility of the patient to report promptly any adverse developments, including any nerve function loss.

REFERRAL SERVICES, PREVENTION OF DISABILITIES (POD) AND REHABILITATION

Effective POD is not only for the benefit of the patients concerned, but also for the credibility of the programme. Increased credibility results in earlier self-reporting of new cases and leads to better treatment compliance. As such, POD will contribute to the elimination of the disease. Secondary referral services must be available. POD activities should be an integral part of the job description of the primary worker at the peripheral health unit. The simplest possible, reliable, method to identify new nerve function loss should be used, including asking the patient; and a quick VMT/ST should be able to be performed by all health workers dealing with patients. The earliest interventions for POD (reactions and neuritis) are the priority but, where circumstances permit, rehabilitation services should be made available, preferably as a part of the national rehabilitation services for the disabled, from whatever cause.

INTEGRATION AND COMBINATION

Vertical programmes hold clinics only periodically (monthly) and are often associated with the stigma of leprosy. As such they hinder an optimal relationship between the leprosy services and the community. Poor accessibility and acceptability result in delayed case detection and reduced compliance with chemotherapy. It is obvious that the general health services, which usually are closer to the community, permanently accessible and more acceptable must be involved in the treatment and retrieval of patients. The peripheral general health services staff should be aware of, should feel responsible for and should be involved in the management of leprosy. Integration does not mean that specialized services disappear, but rather that they should be available at a higher level, possibly in conjunction with other referral services.

While the support of technical expertise at national, regional and district level is required, a large work force of peripherally based technical staff is not likely to be cost-effective, especially in low prevalence areas. Co-operation with other vertical programmes may, in these circumstances, be more cost-effective and the chosen combination (TB, TB and chest diseases, tropical dermatoses, prevention of blindness, etc.) will depend on the local situation.

TRAINING

Multipurpose health workers should receive training in leprosy in their basic training curriculum. In addition, those posted in the field should have adequate, appropriate training followed by post-training supervision, suitable for their job description. All training should conform to the nationally agreed curricula. Training, including training in management, implies that the trainees are appropriately posted and can carry out the duties expected of them. Training of district level managers should also include the provision of more patient oriented services and in dealing effectively with the media.

MOTIVATION OF STAFF

Maintenance of a high quality of work performance is often difficult in the field. Job satisfaction is provided by enabling staff to do the work they are trained for, by providing the necessary facilities and drugs and by having supportive, regular supervision. Feed-back to peripheral staff on their performance and the progress of the programme will promote the feeling of direct involvement. Financial security does not necessarily require special incentives but a realistic salary and allowances should be paid promptly. A career structure is a necessity.

MONITORING AND EVALUATION

Despite the general adoption of the 6 essential indicators of leprosy control, there should be no pre-requisite that all or any of these indicators are in place before the implementation of MDT. The most essential indicators which should be available are the number of patients newly diagnosed and the proportion of these patients cured.

Workshop 12 Elimination of Leprosy

Chair: S. K. Noordeen
Rapporteur: Robert R. Jacobson

Participants

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The success of the multidrug therapy (MDT) regimens for the treatment of leprosy developed by a WHO study group in 1981 prompted the World Health Assembly to pass a resolution in 1991 on the elimination of leprosy. Through this resolution the WHO declared its commitment to continue to promote the use of all control measures, including multidrug therapy, together with case-finding, in order to attain the global elimination of leprosy as a public health problem by the year 2000. Elimination is defined as the reduction of prevalence to a level below 1 case per 10,000 population. In 1990, the International Federation of Anti-Leprosy Associations (ILEP) had adopted the target of MDT for all by the year 2000.

Achieving this goal through improved control efforts and provision of MDT for all leprosy cases does not mean complete eradication of the disease. It must, however, be considered the first essential step toward eventual eradication. It will lead to a situation where the disease is no longer a public health problem, i.e., where transmission of infection is expected to be drastically reduced.

New cases will still occur, since the fall in incidence to be expected if transmission has been interrupted may lag many years behind the fall in prevalence, and this fall depends on the early introduction of MDT with sustained high coverage. This, consequently, will also lead to reduced occurrence of disabilities.

Since the elimination strategy was adopted, progress with the widespread implementation of MDT has continued. By mid-1993, over 4·1 million patients had been cured with relapse rates of less than 1% overall. Likewise, the global current and cumulative MDT coverage of registered patients has reached 48% and 82%, respectively, with the number of registered cases reduced from 5·4 million in 1985 to 2·3 million now. Thus, the goal is achievable and presents a unique opportunity in the history of this disease. Its achievement, however, will require a continued major effort on the part of the endemic countries, the WHO and non-governmental organizations (NGOs) in order to increase MDT coverage as rapidly as possible.

Strategy

The first priority must be to treat rapidly all registered cases with MDT and improve case-finding in terms of coverage and early detection. Strong political commitment and collaboration between national governments, WHO and national and international NGOs and other donor agencies requires further strengthening to ensure the availability

of the necessary resources. National plans of action are a must which will guide activities. Resources must be mobilized to assure, among other things, adequate long-term supplies of drugs and equipment. Appropriate organization of the existing leprosy services, whether vertical or integrated, and updating of existing information by clearing the registries to accurately identify the number of cases needing MDT will then allow proper implementation of the plan.

The elimination strategy aims to stratify the situation at different levels, identify priority areas for action, set intermediate targets and monitor them. Such an approach, however, should not neglect areas of low prevalence within countries or countries with a low prevalence. This requires review of the situation country by country and, within each country, area by area.

Improved case detection is important to the success of the programme. Self-reporting of suspect lesions is the most cost effective approach. Training of peripheral health services to recognize the disease is also vital. Self-reporting can be encouraged through the use of volunteers and community workers and through innovative use of the media to increase community awareness of the problem and reduce the stigma.

Regular monitoring and evaluation of the programme is essential to see that progress continues toward specific targets, and problems are identified early. Health systems research may be helpful to identify and solve problems early.

In spite of widespread implementation of MDT and its contribution to prevention of disabilities, there will remain a significant number of persons either with or at risk of disability who will require care and rehabilitation.

Constraints

Bringing MDT to the remaining patients still poses a considerable challenge. In existing programmes an effective infrastructure will need to be maintained, but seeing fewer patients. This would mean increasing cost per patient. Furthermore, many patients will be in areas that are operationally difficult due to geography, infrastructure or civil disturbance.

As prevalence decreases, increased efforts to maintain the political commitment for the programme will be necessary as the needs of leprosy control may be considered in relation to the needs of other health problems and health policy in general. Programme planning must now look beyond attainment of the elimination to the maintenance of the necessary skills to detect cases where the prevalence becomes very low. This may be accomplished by training personnel to suspect leprosy whenever appropriate and the maintenance of a core area of expertise to confirm the diagnosis of cases on referral and manage complicated cases. In this and in the urban control efforts, the private medical sector may play a significant role in certain countries provided they follow the national guidelines regarding classification and therapy.

Existing cases requiring MDT and cases expected to be detected between now and the year 2000 may total as many as 6 to 7 million patients. It is estimated that 400–500 million USA dollars will be required for this effort. Thus, the continued commitment of national governments, NGOs and the WHO until the year 2000 and beyond is vital if this effort is to succeed.

Research

Current research efforts may yield shorter-term therapy and/or fully supervisable therapy for those cases who require other than standard MDT. These would accelerate attainment of the elimination goal. Other areas of research should include improved anti-reaction therapy and prevention of nerve damage.

Conclusion

Intense efforts on the part of all involved are required to eliminate leprosy as a public health problem by the year 2000. The basic resources and technology exist. It would be inexcusable if the efforts are not made and this historical opportunity is missed.

Workshop 13 The Eye

Chair: Dr Felix Brandt
Rapporteur: Dr Timothy ffytche

Participants:

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G. Chandrasekhar
Ebenezer Daniel
Tafessawork Girma
Margaret Hogeweg
Mary Jacob
Murat Karacorlu
Wiebe Jan Lubbers
M. A. Rajan
Swapan K. Samanta
Alberte Schipper
Shi Zhenrong
William J. Woods
Zhou Huiming
Elsbeth Zyp-Klaver

The meeting was opened by Dr Margaret Brand who reviewed the current situation of ocular leprosy, highlighting some of the problems of the disease facing workers in the field.

Following this there were 6 sessions on wideranging topics which included the prevention, cure and care of blindness in leprosy, ocular pathology in the disease, ocular surgery and ocular complications seen at presentation, during and after chemotherapy.

The final session was devoted to a discussion of the setting up of various projects to be undertaken by members of the group in anticipation of the next meeting. Due to lack of time several important subjects could not be addressed, these included epidemiology and the training of medical staff.

Summary of the main points of discussion

OCULAR SURVEYS

It was generally agreed that the value of horizontal surveys was limited, although important in drawing attention to the current ocular problems in the areas surveyed. It

was recommended that longitudinal surveys should be encouraged with the standardization of data wherever possible. Too often there are differing definitions of such important measurements as blindness and visual impairment, and the evaluation of clinical entities such as lagophthalmos, diminished corneal sensation and iris atrophy needs to be standardized.

OCULAR PATHOLOGY

The group recognized that there is still a great lack of pathological studies on tissues of the eyes of leprosy patients in all stages of ocular involvement, even when there is little or no evidence of this. It was recommended that specimens should be retained for histological examination and sent to ocular pathologists identified by the group. It was emphasized that wherever possible specimens should be accompanied by clinical data on the patient, and that the specimens should be fixed in 10% formalin, or, in the case of small biopsy tissues, in 2·5% glutaraldehyde if available. At autopsy, eyes and skin specimens taken from sites known to be affected should also be sent. This aspect of research was regarded as a high priority.

Immunological studies on ocular tissue should also be encouraged where the appropriate facilities for examination exist.

CLINICAL EXAMINATION

The group recommended that registry cards used in any leprosy programme should include a section dealing with the eyes, and that training manuals for leprosy workers and eye workers should give more attention to eye care and the prevention of ocular complications.

On more specific points the group agreed on a definition of blindness to be used in future surveys: 'Blindness' was defined as corrected vision of less that 3/60 in the better eye. Vision less than 6/60 in the better eye was termed 'severe visual impairment'.

There was a long discussion on facial nerve involvement, including muscle weakness, lagophthalmos and exposure. It was admitted that the current classification of this condition was unsatisfactory and the group spent a great deal of time on grading the clinical examination of the condition. It was agreed that lagophthalmos should be graded as:

1 normal;
2 orbicularis muscle weakness;
3 lid gap with cornea cover in mild closure;
4 lid gap with cornea exposed in mild closure.

It was generally agreed that impairment of corneal sensation is one of the most important factors in the production of eye complications in leprosy. Quantitative measurements remain difficult and the traditional method of testing with a cotton wool wisp is probably the best—3 levels of sensation can be recorded in this way: normal, diminished and absent, although grading diminished sensation can be a problem. It is recommended that corneal sensation is tested by touching the centre of the cornea, and this should be carried out routinely by paramedical workers.

There were several presentations on iris atrophy and its early diagnosis. It was

suggested that measurement of the pupil/cycle time (PCT) would be an interesting clinical examination in early cases.

It was generally agreed that treatment carried out at the early stage of the disease reduces the incidence of ocular complications. But evidence was presented showing that problems can exist at the time of diagnosis and also arise during treatment. An important finding was that a significant proportion of patients released from treatment (RFT) had sight-threatening lesions requiring continued follow-up and management, and there is evidence that new ocular problems due to leprosy can occur in patients classified as 'cured'.

Although the results of intraocular surgery, particularly cataract removal, are not as bad as expected, there is room for improvement and the introduction of intraocular lenses will add a new dimension which will need to be carefully considered. This subject was discussed at length and recommendations were made for future comparative studies of different types of cataract surgery.

PROJECTS SET UP

It was agreed the following projects should be set up in advance of the next ILA meeting:

(a) pathology scheme. Supervisor—F. Brandt;
(b) cataract study. Supervisor—M. Rajan;
(c) IOL study. Supervisor—M. Karacorlu;
(d) chemotherapy. Supervisor—M. Rajan;
(e) pupil/cycle time. Supervisor—M. Karacorlu.

Final summary

The group expressed their gratitude to the ILA for making this workshop possible and drawing attention to the ocular complications of leprosy. It was noted that many participants who planned to attend were unable to because of financial restrictions and difficulties in obtaining visas. It is to be hoped that the ILA will be able to overcome these problems when the next workshop is organized.

The group congratulated Felix Brandt on his organization of an excellent meeting despite the difficult circumstances.