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WHO Expert Committee on Leprosy

Sixth Report

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Geneva, 17–24 November 1987

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WHO EXPERT COMMITTEE ON LEPROSY

Sixth Report

The WHO Expert Committee on Leprosy met in Geneva from 17 to 24 November 1987. The meeting was opened on behalf of the Director-General by Dr R.H. Henderson, Director, Expanded Programme on Immunization.

In welcoming the participants, Dr Henderson referred to the need for the widest possible coverage for leprosy control and to the concern regarding how best to achieve leprosy control within primary health care. He also referred to the need for greater emphasis on prevention of disabilities in leprosy. He recalled the important progress being made in leprosy research in such areas as immunology and chemotherapy, particularly through the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

INTRODUCTION

In May 1987, the Fortieth World Health Assembly adopted a resolution on leprosy (WHA40.35), urging Member States to allocate adequate priority to the disease and to strengthen various aspects of its control. It requested the Director-General to support Member States in their multidrug therapy programmes, and to mobilize additional resources to support control and research. It also requested that the partnerships between nongovernmental organizations (NGOs), Member States and WHO be promoted in order to achieve leprosy control.

The purpose of this meeting of the Expert Committee on Leprosy was firstly to review current knowledge of leprosy, particularly in relation to disease control and research in the light of progress made since the last meeting of the Expert Committee in 1976 (*1*); secondly, to evaluate the various components of the current methods of and approaches to leprosy control; and thirdly, to make appropriate recommendations for the future on various aspects of leprosy control and research.

The last decade has seen important changes both in the leprosy situation and in the technology available for control of the disease. In many of the developing countries, numbers of cases have remained more or less unchanged, but the prevalence of severe disease appears to have declined. The most important development of this period, however, has been the alarming increase in the occurrence of resistance of *Mycobacterium leprae* to dapsone, the most commonly used drug in leprosy. Widespread primary and secondary dapsone resistance has threatened to nullify even the limited gains that were made in the control of the disease during the previous 20 years. Fortunately, the availability of more potent antileprosy drugs in recent years and the possibility of combating resistance through combinations of drugs have made it possible to apply new approaches to chemotherapy of leprosy. In 1981, WHO constituted a Study Group on Chemotherapy of Leprosy for Control Programmes; the Group's recommendations on multidrug therapy are recognized today as representing a major improvement in leprosy control (*2*).

Another major development of the last decade has been the vigorous search for new tools in the prevention of leprosy. The Scientific Working Group on Immunology of Leprosy (IMMLEP), a component of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), has made substantial progress towards developing an antileprosy vaccine.

Many countries are now giving a higher priority to leprosy control, particularly in view of the better opportunities available today through multidrug therapy. A number of NGOs and other contributing agencies have also recognized the disease as an important priority and available resources are now much greater than they were a few years ago. These developments suggest that control of leprosy is achievable in many countries in the foreseeable future.

After reviewing major developments the Committee concentrated on the priorities resulting from the introduction of multidrug therapy in leprosy control. The present report should be read in the light of the previous Expert Committee report (*1*) and the Study Group reports (*2, 3*), as many of the basic principles expressed therein remain valid.

1. GLOBAL LEPROSY SITUATION

1.1 Estimated cases

It is difficult to estimate accurately the number of cases of leprosy in the world. Diagnostic criteria and definitions are not always clear or consistent, and the enumeration of cases in many parts of the world is incomplete. Nevertheless, estimates are extrapolated from available data from time to time: the WHO estimates of prevalence for 1966 and 1976 were 10.8 and 10.6 million cases respectively, and prevalence is currently estimated at 10–12 million cases.

So far, the only reliable method for estimating the total number of leprosy cases in a particular country or area has been one based on random sample surveys. This is an expensive, time-consuming method, requiring special statistical support. Moreover, sample surveys often reveal a much higher prevalence of leprosy than expected because intensive investigation of the population results in the detection of many cases at a very early stage. There is thus a need to develop simple, standard methods for making rough estimates of the number of cases in a country, which would be adequate for planning and operational purposes.

1.2 Registered cases

Over the past twenty years, there has been a steady increase in the number of registered cases reported: about 2 850 000 in 1966, 3 600 000 in 1976 and 5 400 000 in 1985. This last figure represents an increase of 90% over that for 1966. The total number of registered cases in 1987 was about 5 100 000; geographic distribution is shown in Fig. 1.

Information on leprosy cases registered for treatment is more reliable than that on estimated cases. In general, the increase in registered cases over the past two decades suggests continuing progress in control activities in many countries. However, in some countries, a proportion of inactive cases who would normally be eligible for discharge are retained in the registers for various reasons, thus inflating the figures. Preliminary returns over the past two years suggest the beginning of a decline in the number of registered cases, associated with the institution of multidrug therapy.

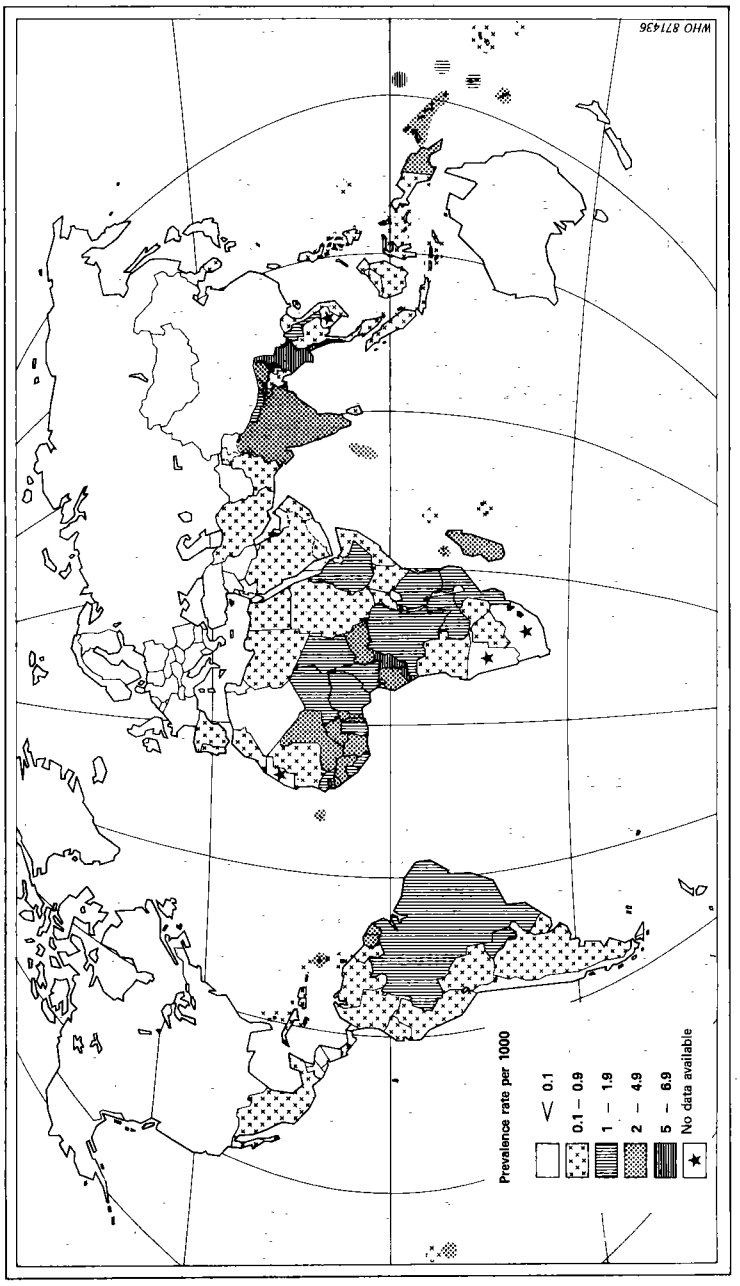

Fig. 1. Prevalence of registered leprosy cases in the world, 1987

1.3 Leprosy as a public health problem

More than 1.6 billion people live in countries where the estimated prevalence of leprosy is greater than one case per 1000 population, and it is generally assumed that all are at equal risk. However, in view of the irregular distribution of the disease within a country, it is possible that the risk of acquiring the disease varies among the population.

It should be emphasized that the problem of leprosy extends beyond that of simply the number of cases, since it involves disabilities, economic loss, psychological trauma and social ostracism.

Greater attention should be paid to analysing and defining those factors that make leprosy an important social problem. In the coming years, with the increasing use of multidrug therapy, it can be expected that the number of persons needing care because of disabilities will gradually outnumber those receiving antimicrobial treatment.

2. EPIDEMIOLOGY

2.1 Transmission

The portal of entry of the leprosy bacillus remains uncertain although it is increasingly accepted that, in most instances, it probably enters the body by the respiratory tract.

It is also widely accepted that the nose is a major portal of exit for the bacilli. Multibacillary patients can shed several millions of bacilli per day in their nasal secretions. However, the nasal discharge is rapidly rendered bacteriologically negative by chemotherapy, and this observation has great bearing on control. Broken skin may also serve as a portal of exit for the bacilli.

The role of environmental factors is not clear. A decline in leprosy has been documented in some countries at a time of improvement in living conditions but before the advent of modern control measures (although the role of segregation cannot be excluded). No specific environmental factors, however, have been identified as contributing to the decline. Mitigation of overcrowding and poverty, and improvements in hygiene have been given as reasons, but these are general concepts and not easy to quantify.

Longitudinal studies have repeatedly confirmed that multibacillary patients constitute the major source of infection. The possible role of paucibacillary patients needs to be better documented, especially in view of the large proportion of such patients in a number of highly endemic areas.

2.2 Reservoirs of infection

While the human being is considered the major host and reservoir of the leprosy bacillus, armadillos have also been found to be naturally infected with mycobacteria that are indistinguishable from *M. leprae*. Limited observations suggest that transmission of *M. leprae* infection from these animals to people exposed to them is possible. Natural infections in primates (chimpanzees and mangabey monkeys) have also been reported in recent years, but the significance of such observations is not known.

2.3 Subclinical infection

Until recently, the end-point for epidemiological studies of leprosy was the clinical disease since no reliable tool was available for recognition of subclinical infection. The lepromin test, developed more than 50 years ago, can disclose only the cell-mediated immunity status of a leprosy patient or the prior exposure of an individual to *M. leprae* (or related sensitizing mycobacteria). Over the past 15 years, several immunological tests have suggested that infection with *M. leprae* is far more common than is evidenced by cases of overt disease and that it can take place within a short time of initial exposure to the bacillus. If such tests could be made more sensitive, the study of the epidemiology of leprosy infection, as opposed to the disease itself, could be envisaged.

Cross-sectional and longitudinal studies with tests of the required sensitivity and specificity should throw light on a number of cardinal issues, such as the influence of age and sex on infection, the relative risks associated with exposure to multibacillary and paucibacillary cases, the effects of specific environmental factors, the influence of type and duration of exposure, the possible role of genetic determinants (HLA) in the development of the infection, and the distribution of the latent period from infection to overt disease.

Discrimination between infected and non-infected individuals will also be essential for distinguishing between the immunoprophylactic

and "immunotherapeutic" effects of the vaccines currently being developed and for screening the populations to be vaccinated.

2.4 Transition from infection to disease

Factors that influence the occurrence of disease among individuals infected with *M. leprae* may differ from those that influence the occurrence of infection itself. More specific and sensitive immunological tools for studying infection would permit more reliable assessment of the risk factors.

2.5 Time trends

A progressive decline in the incidence of leprosy was observed in a number of countries even before the advent of modern chemotherapy. Careful analysis of the time trends in some of these countries revealed a gradual increase over the years in the mean age of the patient at onset of the disease, and a gradual increase in the proportion of lepromatous forms among new cases, associated with decreasing incidence (*4*).

2.6 The changing profile of leprosy

The clinical profile of leprosy has changed considerably over the past 20 years or so. Ulcerating nodular lesions and the leonine facies of lepromatous leprosy are now rarely seen. Likewise, the distressing complications of advanced laryngeal leprosy and perforation of the hard palate are rarely encountered. These changes are evident in areas where efficient leprosy control programmes have been in operation for some time.

Progressive ulcerating erythema nodosum leprosum (ENL) reactions resulting in amyloidosis, nephrotic syndrome and death have also been less frequently observed during the past decade. This may be attributable to more efficient treatment of ENL reactions.

3. CLINICAL ASPECTS OF LEPROSY RELATED TO CONTROL

3.1 Definition of a case of leprosy

At present, leprosy patients needing or undergoing treatment, those who have completed multidrug therapy and require or are

under surveillance, as well as those with deformities and disabilities resulting from leprosy in the past and needing care, are grouped together as "cases of leprosy". Lack of distinction between these categories continues to be a source of error in computing and comparing prevalence and other statistics necessary for planning and organizing leprosy control programmes.

A "case of leprosy" is a person showing clinical signs of leprosy, with or without bacteriological confirmation of the diagnosis, and requiring chemotherapy. It is recommended that this definition be adopted by all countries so that information on prevalence can be meaningfully interpreted. It is also recommended that separate lists of the other two categories (patients who have completed their treatment but require, or are under, surveillance, and those who have deformities and disabilities due to past leprosy) be maintained.

For operational purposes, those who have or have had leprosy will therefore fall into one of the following three categories:

(1) those requiring or receiving chemotherapy;
(2) those who have completed chemotherapy and require, or are under, surveillance; and
(3) those released from surveillance but in need of care or assistance because of disabilities.

A fourth category of individuals, who need not be maintained in any register or list, are those released from surveillance and not in need of further attention.

Prevalence of leprosy should be computed on the basis of the first category of patients.

3.2 Classification for control programmes

The new approach to leprosy control involving the use of multidrug therapy has resulted in some changes in terminology in the classification of patients. It must be stressed, however, that these changes were not an attempt to formulate another system of classification but only a method of grouping patients together for the purposes of multidrug therapy.

In this context, the WHO Study Group on Chemotherapy of Leprosy for Control Programmes (*2*) classified patients as having multibacillary (MB) or paucibacillary (PB) leprosy. This is essentially an operational categorization for purposes of multidrug therapy. The Expert Committee endorsed the principles upon which

this classification is based, but concluded that there are clinical and operational reasons for including all smear-positive cases in the multibacillary group. Consequently the following modifications to the Study Group classification are recommended:

(1) Paucibacillary leprosy will include only smear-negative indeterminate (I), polar tuberculoid (TT) and borderline tuberculoid (BT) cases in the Ridley-Jopling classification or indeterminate (I) and tuberculoid (T) cases in the Madrid classification. Any case belonging to these types but showing smear positivity will be classified as multibacillary for purposes of multidrug therapy programmes.

(2) Multibacillary leprosy will include all mid-borderline (BB), borderline lepromatous (BL) and polar lepromatous (LL) cases in the Ridley-Jopling classification or borderline (B) and lepromatous (L) in the Madrid classification, as well as any other smear-positive types.

For purposes of multidrug therapy, patients who have already been treated should be classified as follows:

(1) Those who would have been in the multibacillary group at the time of diagnosis of their disease should be classified as such, irrespective of their current bacterial index.

(2) Patients who would initially have been in the paucibacillary group should be classified according to their current clinical and bacteriological status.

3.3 Certain special issues in classification

The following special points are worth noting in connection with some types of leprosy.

3.3.1 *Indeterminate leprosy*

The indeterminate type of leprosy is recognized as a definite clinical entity, but there is no unanimity of opinion regarding its frequency, significance and prognosis. It presents as a single macule or as a few asymmetrical macules with alterations in colour but with no change in the surface, consistency or texture of the skin. The peripheral nerves are usually normal and slit-skin smears are usually negative for acid-fast bacilli. To confirm a diagnosis of indeterminate leprosy, there must be impairment of sensibility.

Impairment in thermal sensibility may occur earlier than loss or impairment of tactile sensibility.

3.3.2 *Primary neuritic leprosy*

Primary neuritic leprosy is increasingly being recognized as a clinical form of presentation of leprosy. While the majority of these cases will be of the paucibacillary type, correct classification by clinical examination alone is difficult and further investigations will be required. A lepromin test, the number of nerves affected, and nerve biopsy may give some indication, but further research is needed to provide reliable indicators for correct classification of primary neuritic leprosy patients within the Ridley-Jopling system.

3.3.3 *Borderline tuberculoid leprosy with multiple macular lesions*

Borderline tuberculoid patients with multiple macular lesions are often difficult to classify as paucibacillary or multibacillary for purposes of multidrug therapy. The prevalence of such cases varies widely in different parts of the world.

In this variety of BT leprosy, the multiple macular lesions are disseminated and bilaterally or symmetrically distributed; satellite lesions are often present. Frequently, there is clinical involvement of peripheral nerves. The larger lesions have a dry surface with loss of all or some modalities of sensation. The disease may become progressive. Classification of these patients should therefore be undertaken only after careful consideration of all clinical features.

Since these patients appear to be a high-risk group for the occurrence of reversal reactions and/or relapse, they must be carefully followed up during the surveillance period.

3.4 Bacteriological examination

Bacteriological examination is very important and highly relevant to leprosy control. Nevertheless, the quality of smears and of microscopy is probably the weakest link in most leprosy control programmes. It is therefore essential to train control programme personnel in taking smears of good quality and to organize an efficient service for collecting and processing skin smears. Attention is drawn to the guidelines for prevention of transmission of AIDS infection during the process of taking skin smears (*5*). Such

precautions will also help to prevent transmission of viral hepatitis B infection.

Skin smears should be taken from a minimum of three sites, including one ear lobe and two representative active skin lesions. In paucibacillary patients, if there is only a single skin lesion, the two smears may be taken from its active edge at sites diametrically opposite to each other. Slides should be used once only.

Detection of acid-fast bacilli and assessment of their numbers require, besides properly collected skin smears, good quality stains, correct acid-fast staining technique and trained use of a microscope. The logarithmic scale proposed by Ridley for reading the bacterial index has gained wide acceptance over the last decade; it is recommended that it be uniformly adopted in all countries to facilitate comparison of results.

Quality control and continuous supervision and monitoring are necessary to ensure that high standards are maintained. Observer errors and reader variation can be avoided by standardized training and adequate supervision of laboratory technicians, and by a system of cross-checking.

3.4.1 *Bacterial index*

There is a widespread impression that multidrug therapy will hasten the attainment of smear negativity, but this is not substantiated by the available evidence. The rate of clearance of bacilli under multidrug therapy is approximately 0.6 to 1 log per year (*6*). It must be appreciated that the bacterial index is a late marker for the antibacterial action of drugs in leprosy, even though it is of prime importance for the diagnosis of relapsed cases. Clinical improvement is accelerated by multidrug therapy and precedes the fall in the bacterial index.

3.4.2 *Morphological index*

The morphological index gives an indication of the proportion of viable bacilli in the patient. However, there are problems with standardization and reproducibility, as well as operational difficulties in using this parameter under field conditions, and it is therefore not recommended for use in routine control programme activities.

3.5 Lepromin test

The Mitsuda lepromin reaction is an indicator of the ability of the host to mount a cell-mediated immune response to *M. leprae*. It may therefore be useful in classifying a patient after the diagnosis of leprosy has been made. However, the operational problems involved in obtaining lepromin, administering it and reading the results limit its usefulness in the field.

3.6 Reactions and their management

Immunologically mediated episodes of acute or subacute inflammation, known as "reactions", may occur in any type of leprosy except the indeterminate and, unless promptly and adequately treated, can result in deformity and disability. Referral facilities, including dermatological services, should be available for dealing with the more severe and problematic cases. Most reactions belong to one of two main types, namely erythema nodosum leprosum (type II, Jopling) and reversal reaction (type I, Jopling). The former occurs in lepromatous (LL) and occasionally in borderline lepromatous (BL) cases; the latter occurs throughout the borderline spectrum (BL, BB and BT).

3.6.1 *Erythema nodosum leprosum (ENL; type II, Jopling)*

This type of reaction, which is quite common during dapsone monotherapy, appears to be less of a problem in multidrug therapy programmes. The treatment of choice for ENL is thalidomide and the importance of making this drug available cannot be overstressed. It must be pointed out, however, that because of its well known embryopathic effects, it should be given only to men and postmenopausal women. Women of child-bearing age should never be given thalidomide; instead clofazimine (300 mg daily for not more than three months), supplemented with corticosteroids, may be used for controlling severe ENL reactions and complications of ENL, such as persistent neuritis and iritis.

3.6.2 *Reversal reaction (type I, Jopling)*

Reversal reactions have become relatively more prominent in leprosy control programmes since the introduction of multidrug therapy, possibly because of better monitoring of patients.

When they occur, reversal reactions usually do so during multidrug therapy, although BT cases treated for six months may present with reversal reactions some time after the completion of therapy. Increase in the size of the lesion is more often a sign of relapse than of reaction. Slit-skin smear examination should be done in suspected cases of reversal reaction, to exclude bacterial relapse, and biopsies should also be done, where possible, to confirm the diagnosis.

The crucial elements in the proper management of reversal reactions are early recognition and prompt treatment. Education of the patient to recognize the condition and to report promptly for treatment is essential.

The severity of clinical signs and symptoms in reversal reactions may be such as to warrant treatment with corticosteroid; neuritis associated with the reaction is an indication for starting corticosteroid therapy without delay. The dosage of corticosteroid will depend on the severity of the reaction and on the patient's body weight and response to treatment; it should be sufficient to relieve both nerve pain and tenderness. Administration of corticosteroid should be continued for several months, the actual duration of therapy depending on individual circumstances. Corticosteroids may also be used under field conditions for controlling reversal reactions, provided that they are administered by appropriately trained staff.

The issue of extending or reintroducing chemotherapy in such cases will be decided on the merits of the individual case.

Early diagnosis of the neuritis which so frequently accompanies reaction, as well as of quiet nerve paralysis, is made much easier if careful records of cutaneous sensibility (sensory maps) of palms and soles and of strength of hand and foot muscles are made in all cases at the time of diagnosis, at regular intervals thereafter and at the time of completion of multidrug therapy. It follows that medical and paramedical staff should become familiar with these techniques of examination.

3.7 Quiet nerve paralysis

Clinically evident acute or subacute truncal neuritis is a sign of impending paralysis. However, thickened nerve trunks quite frequently become paralysed "quietly", without manifest neuritis. The condition is usually missed in the early stages when recovery is

possible and is recognized only after serious and irreversible damage has occurred. The onset of nerve damage is insidious. The patient may have difficulty in describing the subjective sensory disturbances and the motor weakness is apt to be missed unless specifically looked for. This subject has not received sufficient attention from clinical and research workers and so there is no information regarding its frequency and little published guidance on its management or prevention. The use of corticosteroids, in substantial doses over a period of 3–6 months, is reported to prevent the establishment of nerve trunk paralysis in a high proportion of cases when the condition is identified and treated before the nerve is completely paralysed (*7*).

More information needs to be gleaned about this condition. In the meantime the following approaches are recommended:

(1) In patients with enlarged nerve trunks, routine clinical examinations should include history of subjective sensory disturbances (paraesthesiae) in the area of distribution of the nerve, sensory mapping of the palms and soles, and tests for muscle weakness.

(2) When sensory or motor deficit attributable to involvement of a nerve trunk is suspected, detailed examination should be carried out; if the onset of quiet nerve paralysis is confirmed, corticosteroid therapy should be instituted without delay.

4. *MYCOBACTERIUM LEPRAE*

4.1 Cultivation and animal models

Investigations of the basic biology of *M. leprae*, including its metabolism and chemical structure, have been hampered by the fact that it has not yet been possible to culture the bacillus *in vitro*. Moreover, *M. leprae* has been demonstrated to multiply and produce disease in only a very limited number of animal species, most notably the armadillo.

4.1.1 *Cultivation in vitro*

Success in cultivating *M. leprae in vitro* would have a great impact on the development of new or improved chemotherapeutic, diagnostic and prophylactic measures for the control of leprosy.

However, there has been no significant progress in this area since the last Expert Committee meeting (*1*) and no confirmed methods for the cultivation of *M. leprae in vitro* are available to date. The application of genetic manipulation techniques may provide a solution to this problem.

4.1.2 *Growth of M. leprae in animals*

Armadillo

The nine-banded armadillo is currently the only source of the large amounts of *M. leprae* needed for research purposes and for vaccine production. As far as experimentation is concerned, a few other animal models are available or being developed.

Rodents

(1) Inoculation of the footpads of normal (immunologically intact) mice remains the basic tool for assessing the activity of drugs against *M. leprae* and for the study of drug resistance of *M. leprae*. It is also an important tool for evaluating the protective effect of candidate vaccines.

(2) Use of immunodeficient animals, i.e., thymectomized, irradiated, bone-marrow reconstituted (TR) mice, nude mice and neonatally thymectomized rats (NTR), is currently the most sensitive method available for monitoring the presence of viable *M. leprae* in patients receiving chemotherapy.

Primates

During the last decade, experimental transmission of leprosy to three species of monkey has been reported (*8*). Several mangabey monkeys were shown to develop lepromatous leprosy. Of three African green monkeys that developed skin lesions resembling human BL leprosy, all had active *M. leprae* infection in peripheral nerves. Lastly, a limited number of rhesus monkeys were reported to develop BL–LL leprosy after inoculation with 10^9 *M. leprae* bacilli.

4.2 Biology of *M. leprae*

A better understanding of the biology of *M. leprae* may provide clues for the development of new drugs, allow for the development of rapid methods of assessing drug activity, and perhaps help in the eventual *in vitro* cultivation of *M. leprae*.

4.2.1 *Cell wall*

Cell walls of all mycobacteria, both pathogenic and saprophytic, exhibit a similar complex structure. However, *M. leprae* appears to differ from other mycobacteria in the composition of the peptide units and in the multiplicity of peptidoglycan layers which constitute the complete cell wall structure. A detailed knowledge of the *M. leprae* cell wall structure will lead to a better understanding of drug susceptibility and metabolism of the organism and may also permit the identification of specific targets for new drugs. Successful work in this area could lead to the development of effective vaccine preparations and of sensitive methods for monitoring the viability of *M. leprae*.

4.2.2 *Metabolic pathways*

Studies of the metabolism of *M. leprae* continue to be hampered by inability to cultivate the organism *in vitro*. However, some progress has been made and many enzyme systems have been identified, including those controlling glucose metabolism. It has also been shown that *M. leprae* synthesizes adenosine triphosphate.

5. IMMUNOLOGY OF LEPROSY

A better understanding of the immunology of leprosy is essential to the elucidation of the disease process and its complications (including reactions and nerve damage), to the identification of persons at high risk of contracting the disease, and to the prevention of leprosy. During the past decade there have been many advances in this field.

5.1 Recent advances

By 1980, activities promoted by the Scientific Working Group on the Immunology of Leprosy (IMMLEP) had established:

—a bank of *M. leprae*-infected tissues from armadillos;
—a method of purifying *M. leprae* from armadillo tissues;
—evidence that cell-mediated immunity (CMI) could be induced in mice and guinea pigs by killed *M. leprae*, without the use of adjuvants;

—evidence that killed *M. leprae* could protect animals against subsequent infection.

The essential developments in recent years can be summarized as follows:

(1) Protocols for the purification of vaccine material have been developed and human vaccine trials have been initiated.

(2) The advent of monoclonal antibody techniques and T-cell cloning methods has permitted the identification of a number of epitopes (as opposed to entire protein molecules) unique to *M. leprae*.

(3) The entire genome of *M. leprae* has been cloned and expressed in *Escherichia coli* (*9*), an advance that opens new prospects for future research and allows the production of *M. leprae*-specific proteins and peptides despite the absence of *in vitro* culture methods for the growth of *M. leprae*.

5.2 Monitoring the immune response to *M. leprae*

In recent years, several tests have been developed to measure *M. leprae*-specific antibodies and antigens. These tests lack the sensitivity required for the detection of leprosy infection, however, and no reliable immunological tests are yet available for this purpose.

An indirect fluorescent antibody test has been developed for detecting subclinical infection, but it is not suitable for large-scale use in the field. Several tests based on *M. leprae*-specific antigens or epitopes are under development, including those defined by the recently produced *M. leprae* monoclonal antibodies and synthetic peptides derived from DNA sequences of the corresponding genes. Such tests may be useful for epidemiological studies of subclinical infection, for early clinical diagnosis, for early diagnosis of relapse, and for the assessment of response to vaccination, provided that the required criteria for sensitivity, specificity and applicability in endemic regions are met.

5.2.1 *Specific antigen and antibody assays*

Phenolic glycolipid-1 (PGL-1) was the first antigen specific to *M. leprae* to be identified and to have its antigenic moiety chemically synthesized (*10*). Antibodies to PGL-1 have been detected in the sera

of most multibacillary leprosy patients, in titres proportional to the bacillary load. In limited studies, high antibody titres have also been reported in some household contacts of multibacillary patients as well as in other inhabitants of endemic areas (*11*), confirming that infection is more frequent than overt disease. The predictive value of PGL-1 antibody tests for the detection of individuals at high risk of developing the disease is not yet known but epidemiological studies now in progress, including vaccine trials, should provide an answer.

With the advent of *M. leprae*-specific monoclonal antibodies and improved T-cell cloning techniques, the mapping of protein epitopes of cloned *M. leprae* gene products has generated a battery of tests based on chemically defined antigens. Further definition of the sensitivity and specificity of these tests is required.

Levels of PGL-1 and other *M. leprae* antigens are presumably correlated more closely with current infection than are antibody levels. It has been reported that levels of the PGL-1 antigen in serum and body fluids fall rapidly during the initial months after institution of chemotherapy.

5.2.2 *Skin tests*

Two new antigen preparations, both soluble extracts of *M. leprae*, have been employed for assessing vaccination-induced conversion from immune nonresponsiveness to responsiveness (*12*). However, it should be pointed out that the relationship between skin test conversion and protection against disease is not fully understood.

5.2.3 *In vitro tests for cellular immunity*

Direct methods of assessing specific cell-mediated immunity, such as lymphocyte transformation and lymphokine production tests, are laboratory procedures that cannot as yet be applied in the field.

In summary, it can be stated that there are clearly identified needs in the area of immunodiagnosis for leprosy control as well as research, and that the progress made in the development of immunodiagnostic tools is highly promising. The routine use of these tools, however, will depend upon the establishment of their validity and on their applicability to the actual requirements of leprosy control programmes.

5.3 Immunoprophylaxis

The value of any antileprosy vaccine in reducing the incidence of the disease will depend very much upon its effectiveness in preventing infection, and thus the disease, in uninfected individuals (immunoprophylactic effect), and in preventing disease in infected individuals ("immunotherapeutic" effect), as well as upon the proportion of these two populations in any community. Highly endemic areas are likely to benefit much more from "immunotherapeutic" vaccines since the proportion of infected individuals is likely to be quite high in these situations. These assumptions are corroborated by epidemiological models.

5.3.1 *BCG vaccination*

More recent information on the value of BCG vaccination against leprosy is now available, based on the results of five large field studies conducted in Burma, India, Malawi, Papua New Guinea and Uganda. The protective effect of BCG was generally high (80%) in Uganda, moderate (45–55%) in Malawi and Papua New Guinea and low (20–30%) in Burma and India. In all these studies the observed protective effect of BCG was primarily against paucibacillary leprosy.

5.3.2 *M. leprae-based vaccine*

Attempts to develop a vaccine against leprosy are based on the assumption that induction of a cell-mediated immune (CMI) response to *M. leprae* will lead to protection against the bacillus. This assumption is supported by the correlation between levels of cell-mediated immunity and the ability to restrict the growth of *M. leprae*, both in man and in animals.

Studies have established that the killed *M. leprae* preparation, even in the absence of adjuvants, is capable of producing strong delayed-type hypersensitivity reactions in mice (*13, 14*) and guinea pigs (*15*). The same preparation has also been shown to limit the multiplication of *M. leprae* in the mouse footpad model (*16*).

In Venezuela it was demonstrated that a vaccine consisting of a mixture of killed *M. leprae* plus BCG was capable of upgrading the immune status of some CMI-deficient lepromatous and borderline patients (*17*). This suggested that such a vaccine should be capable of doing the same in susceptible healthy individuals, and thus

prevent the occurrence of manifest disease. It was also demonstrated that killed *M. leprae* plus BCG was capable of inducing high levels of sensitization among contacts. A double-blind trial on the protective effect of *M. leprae* plus BCG, compared with BCG alone, was initiated in 1984 in Venezuela, in a high-risk population comprising about 30 000 contacts (household and nonhousehold). No serious side-effects attributable to the vaccine have been reported and participant intake into the trial is now complete. It will be another 5–10 years before the results are known, because of the low incidence of leprosy in the area and the long incubation period of the disease.

The *M. leprae*-based vaccine preparation produced by IMMLEP was first tested in a nonendemic country in 1983. In 31 Norwegian volunteers (who had previously been vaccinated with BCG), the killed *M. leprae* vaccine was shown to be well tolerated and immunogenic (*18*).

The encouraging results of the Norway trial prompted a sensitization study in an endemic population in Malawi. Comparison of the effects of killed *M. leprae* alone, BCG alone, and a mixture of both has shown that the mixed preparation induced sensitization more frequently than either BCG or killed *M. leprae* alone (*19*). Only minor side-effects were noted with all three preparations. A large-scale, long-term immunoprophylactic trial has since been initiated in Malawi to compare the protective effects of a vaccine containing killed *M. leprae* plus BCG with that of BCG alone. The intake of the 120 000 trial participants is expected to be completed in 1989, and results of the trial will be determined by surveys of the total population conducted at 4-year intervals.

5.3.3 *Vaccines based on cultivable mycobacteria*

In India, two studies have shown that killed vaccine preparations based on cultivable mycobacteria belonging to the *M. avium* complex (the "ICRC" bacillus and mycobacterium "W") are capable of producing skin-test conversion responses to lepromin in human subjects (*20, 21*). However, these preparations have not been shown to protect against *M. leprae* infection in the mouse footpad model (*22, 23*).

5.3.4 *Second-generation vaccines*

In the next 5–10 years, vaccine trials will indicate whether or not an *M. leprae*-based vaccine has a significant protective effect. The recent advances in the cloning and expression of *M. leprae* genes in *Escherichia coli* open the way for the production of defined peptide and/or protein antigens. Methods for determining the reactivity of human T-cell clones to individual *M. leprae* antigens have been developed, and it should be feasible to identify protective antigens (epitopes) that could then be produced by recombinant DNA techniques or by chemical synthesis.

5.4 Immunotherapy

The purpose of immunotherapy in leprosy is to try to correct the antigen-specific immunodeficiency in lepromatous leprosy patients, through immunological intervention, in order to accelerate the clearance of dead organisms as well as the elimination of persisting *M. leprae*. This in turn may be expected to minimize the frequency and severity of leprosy reactions and nerve damage and also reduce the risk of relapses.

To date, only limited data are available on the value of immunotherapeutic agents such as transfer factor and locally administered gamma-interferon, although a combination of heat-killed *M. leprae* and viable BCG has been tested in a considerable number of multibacillary patients in Venezuela. The therapeutic value of these treatments needs to be studied further in controlled trials.

6. CHEMOTHERAPY OF LEPROSY

6.1 Drug resistance

6.1.1 *Dapsone resistance*

There is extensive evidence to show that the emergence of secondary resistance of *M. leprae* to dapsone is a worldwide phenomenon, occurring in as many as 40% of treated multibacillary patients in some areas. The majority of secondary resistant strains have been shown to be resistant to high or intermediate levels of dapsone.

Primary dapsone resistance has been found in up to 70% of newly detected, untreated multibacillary cases in the past decade, and may also occur in paucibacillary cases. The majority of primary resistant strains of *M. leprae* have been shown to be resistant to low or intermediate levels of dapsone.

6.1.2 *Rifampicin resistance*

From data collected over the past ten years it has become clear that secondary rifampicin resistance develops easily and rapidly in multibacillary leprosy patients when this drug is used alone. Until now, however, no primary rifampicin-resistant strain of *M. leprae* has been demonstrated.

6.1.3 *Clofazimine resistance*

Despite the fact that many patients have been treated with clofazimine monotherapy since 1962, there is no independently confirmed evidence for the existence of clofazimine-resistant strains of *M. leprae*.

6.1.4 *Resistance to thioamides*

Secondary resistance to ethionamide has been demonstrated in patients treated with ethionamide alone. Resistant strains of *M. leprae* have also shown cross-resistance to protionamide, thioacetazone and thiambutosine.

6.2 Microbial persistence

Viable, fully drug-susceptible *M. leprae* that are able to survive for many years in lepromatous patients, despite the presence of bactericidal concentrations of an antileprosy drug, are termed "persisters". In chemotherapy trials supported by THELEP (Scientific Working Group on Chemotherapy of Leprosy), persisters have been detected in about 10% of all biopsy specimens from lepromatous patients receiving drug regimens containing rifampicin, irrespective of the regimen or duration of treatment (*24*). It therefore seems likely that none of the existing drugs, used alone or in combination, greatly affects the occurrence of persisters.

No clear relationship has yet been established between the existence of persisting organisms and the occurence of relapses, and

accumulating evidence from the THELEP trials is beginning to suggest that persisters may not pose a serious threat of relapse in patients who complete multidrug therapy, at least as far as early relapses are concerned.

6.3 Available drugs

For multidrug regimens of limited duration, only four potent drugs (if ethionamide and protionamide are considered together) are available at present.

6.3.1 *Dapsone*

In a dosage of 100 mg daily, dapsone has been shown to be weakly bactericidal against *M. leprae*. The resulting peak serum levels exceed the minimum inhibitory concentration of dapsone against *M. leprae* by a factor of about 500. This is important since dapsone in the adult dosage of 100 mg daily should inhibit the multiplication of *M. leprae* strains with low or even moderate levels of dapsone resistance.

6.3.2 *Rifampicin*

Rifampicin kills *M. leprae* with exceptional speed: within a few days of a single dose of 600 mg or 1500 mg, 99% of *M. leprae* have been killed.

6.3.3 *Clofazimine*

Clofazimine is weakly bactericidal against *M. leprae*. It is most active when administered daily or three times a week.

6.3.4 *Thioamides (ethionamide and protionamide)*

The two drugs in this category are virtually interchangeable and are bactericidal against *M. leprae*, but their bactericidal activity is much slower than that of rifampicin. Thioamides must be used with care and under medical supervision as they can cause significant liver damage. Liver function tests must be done at the start of treatment and periodically thereafter.

6.4 New drugs

6.4.1 *Quinolones*

A variety of analogues of compounds active against *M. leprae* and other mycobacteria have been tested. The most promising of these seem to be the fluorinated quinolone derivatives, pefloxacine and ofloxacin (*25, 26*), and clinical trials of these drugs are under way.

6.4.2 *Ansamycins*

It appears that certain ansamycins (the rifamycin derivatives), with half-lives much longer that that of rifampicin, might also prove to be useful antileprosy drugs.

6.5 Multidrug therapy for leprosy control

6.5.1 *Results with multidrug therapy*

In 1981, having regard to the problem of drug resistance and the need to introduce more effective and practicable treatment regimens of finite duration for leprosy control, the WHO Study Group on Chemotherapy of Leprosy for Control Programmes recommended new standard regimens (*2*). These included rifampicin as one component and have been widely accepted as the minimum necessary treatment in leprosy control programmes.

Most endemic countries have accepted and introduced, or are in the process of introducing, these multidrug regimens and large numbers of patients are being treated, or have been treated, accordingly. In general, patients in all national programmes have shown satisfactory acceptance and tolerance of these standard regimens. Regularity of treatment has been excellent and side-effects, including skin coloration due to clofazimine, have not been a serious problem. Operationally, these regimens have proved to be feasible in a variety of countries and in different programmes. High motivation of patients as well as health workers has also been reported.

According to the data available to WHO at the time of the Expert Committee meeting, about 1.8 million leprosy cases in 65 countries/territories were undergoing or had completed multidrug treatment. However, since a number of countries had not provided information on leprosy cases receiving multidrug therapy, it is likely that the real number is higher.

6.5.2 *Experience with relapse after multidrug therapy*

Multidrug therapy has generally been monitored by periodic clinical and bacteriological assessments and by measurement of relapses after completion of treatment.

Relapses have been reported following multidrug therapy in paucibacillary cases but these, together with additional data from post-treatment surveillance of over 18 000 cases for periods of 12–37 months, show that the number of such relapses is extremely low (about 1 per 1000).

Preliminary findings from THELEP trials, and data collected from field programmes reporting on post-treatment surveillance of over 9000 cases for periods of 12–40 months, indicate that relapses in multibacillary cases following the use of multidrug regimens have so far been extremely infrequent (about 0.2 per 1000).

6.5.3 *Recommended regimens*

In view of the very favourable results so far, the Committee strongly endorses the continued use of the standard regimens.

The recommended standard regimen for paucibacillary leprosy is as follows:

Rifampicin (600 mg for patients weighing over 35 kg and 450 mg for those weighing less) once a month for six months, plus dapsone 100 mg (1–2 mg/kg of body weight) daily for six months. The administration of rifampicin should invariably be fully supervised, but dapsone may be given unsupervised. The treatment should be completed within a period of nine months.

The recommended standard regimen for multibacillary leprosy is:

rifampicin:	600 mg once a month, supervised;
dapsone:	100 mg daily, self-administered;
clofazimine:	300 mg once a month, supervised, and
	50 mg daily, self-administered.

Treatment should be continued for at least two years and, wherever possible, up to smear negativity. In many programmes, dapsone-treated multibacillary patients continue to receive dapsone monotherapy indefinitely, often for life, even after becoming smear-negative. Where resources permit, it is recommended that such patients should be given multidrug therapy for two years and that chemotherapy should then be stopped.

In multibacillary leprosy, rifampicin should never be used alone, or in combination with dapsone without a third bactericidal drug, because of the high prevalence of dapsone resistance, primary or secondary, and the consequent high risk of the development of rifampicin resistance.

The Committee does not recommend the addition of monthly supervised doses of ethionamide/protionamide to this regimen since the triple-drug therapy is adequate in itself.

Substitution of ethionamide or protionamide for clofazimine is not recommended either, unless absolutely necessary, because it is now clear that clofazimine, at the recommended daily dose of 50 mg, is well accepted by patients in the field and has a marked influence on the frequency and severity of reactive phenomena. Moreover, ethionamide and protionamide can have serious toxic side-effects, particularly when administered with rifampicin. If, in exceptional situations, thioamides need to be administered, this should be done under medical supervision, with periodic checks for hepatotoxicity.

6.6 Post-treatment surveillance

The responsibility of the health system towards the patient does not cease with the completion of chemotherapy. Surveillance of leprosy cases following completion of chemotherapy has two main objectives: the detection of relapse and the recognition of reactive phenomena occurring after completion of multidrug therapy. Patients should continue to have access to facilities for the detection and treatment of relapse and for the detection and management of post-treatment reactive phenomena.

In order to ensure early diagnosis of reactive phenomena and relapse without need for frequent attendance by patients, steps must be taken to ensure that patients are aware of the possibilities of reactions and relapse for some time after completion of chemotherapy. They must also be able to recognize the early signs of these phenomena and clearly understand that they must report for immediate check-up should signs and symptoms of relapse or reaction occur.

6.6.1 *Recognition of relapse*

Relapse in multibacillary cases (including those erroneously classified as paucibacillary and treated for six months) is relatively

easy to recognize clinically; it should be confirmed bacteriologically by slit-skin smear examination. Where facilities are available, biopsy and mouse footpad inoculation may be done to confirm the diagnosis.

Relapse in paucibacillary cases may be difficult to distinguish clinically from reversal reaction occurring some time after therapy is completed. The diagnosis of relapse must be confirmed by slit-skin smear examination (and preferably by biopsy also). All cases of relapse in paucibacillary leprosy should be re-treated with the six-month multidrug regimen.

In order to obtain accurate information about the efficacy of treatment and to forestall loss of confidence in the regimens, the Committee recommends that every case in which relapse is suspected should be thoroughly investigated.

6.6.2 *Duration and frequency of surveillance*

It is recommended that paucibacillary cases be clinically examined once a year for a minimum of two years and that multibacillary cases be examined both clinically and bacteriologically once a year for a minimum of five years. Provision must also be made for the bacteriological examination of paucibacillary cases if suspicious lesions are found.

7. DISABILITIES, REHABILITATION AND SOCIAL PROBLEMS IN LEPROSY

The Committee endorses the statement made in the Fifth Report of the Expert Committee that "It cannot be stressed too strongly that deformity is not an inevitable or necessary part of leprosy... In a well conducted leprosy control programme, almost no leprosy patients on first diagnosis will be suffering from some deformity attributable to neglected disease" (*1*).

7.1 Strategies for prevention and management of disabilities

Diagnosis of the disease at an early enough stage, adequate treatment of cases, and effective detection and management of neuritis and reactive phenomena constitute the best strategy for primary prevention of impairment. Even in patients who present

with permanent sensory loss or other disabilities and in whom impairments and disabilities have occurred during treatment, further deterioration can and should be prevented by proper instruction regarding protection of insensitive extremities and by monitoring the patients. The necessary techniques exist but too few leprosy control programmes are structured to carry out the tasks that are involved in disability prevention. The Committee recommends that prevention and management of impairments and disabilities, which have long been recognized as essential components of leprosy control programmes, should be implemented effectively.

Six specific managerial steps are recommended for the practical implementation of disability prevention and management at the peripheral level.

(1) The team leader, normally a physician, accepts responsibility for prevention of primary and secondary impairments and disability as part of his or her responsibility for patient care.

(2) Specific, limited, measurable objectives are set for preventing and limiting disability, and activity plans based on these objectives are formulated.

(3) Impairment and disability records are included in the clinical recording system.

(4) Arrangements are made for the provision of protective footwear and other aids.

(5) Patients are instructed in self-care and in behaviour designed to prevent further disability.

(6) Staff are trained to implement the disability prevention programme, to teach patients self-care and to monitor and support the practice of self-care by patients.

7.2 Prevention of blindness

Blindness as a consequence of leprosy can be prevented by simple measures in the early stages of ocular involvement, and yet it remains a significant problem.

The same principles apply to the primary and secondary prevention of blindness as to the prevention of other disabilities, and properly trained basic health workers can play a key role in the detection and management of ocular problems. In addition, there is a particular need to alert ophthalmic professionals to ocular involvement and its consequences, and to engage trained ophthalmic workers in patient care and training of leprosy staff.

7.3 Grading of disabilities

At its previous meeting the WHO Expert Committee on Leprosy commented that the disability grading system formulated in 1970 (*29*) was "rather beyond the comprehension of primary health workers" (*1*). It is evident that no single system of grading will meet all requirements. A simple, three-grade (0, 1 and 2) system of classification is suggested below, primarily for collection of general data regarding disabilities and/or impairments.

7.3.1 *Hands and feet*

Grade 0: no anaesthesia, no visible deformity or damage.
Grade 1: anaesthesia present, but no visible deformity or damage.
Grade 2: visible deformity or damage present.

Each hand and foot is to be assessed and graded separately. "Damage" in this context includes ulceration, shortening, disorganization, stiffness, and loss of part or all of the hand or foot.

It may be noted that the proposed grades 0 and 1 are the same as the previous grades 0 and 1, respectively. However, the proposed grade 2 includes the previous grades 2 and 3.

If any disability found in the patient is due to causes other than leprosy, that fact should be noted.

7.3.2 *Eyes*

The following three-grade classification (Grades 0–2) is recommended:

Grade 0: no eye problems due to leprosy; no evidence of visual loss.
Grade 1: eye problems due to leprosy present, but vision not severely affected as a result of these (vision 6/60 or better; can count fingers at six metres).
Grade 2: severe visual impairment (vision worse than 6/60; inability to count fingers at six metres).

"Eye problems due to leprosy" include corneal anaesthesia, lagophthalmos and iridocyclitis. Each eye is to be assessed and classified separately.

If any disability found in the patient is due to causes other than leprosy, that fact should be noted.

7.3.3 *Overall grading of the patient*

It will often be necessary to provide information on overall disability grading for the patient. In that case, the highest leprosy disability grade for any part of the body will be taken as the overall disability grading of the patient.

7.4 Rehabilitation

There are many leprosy patients who, despite established disabilities, are still active and can be cared for in the community.

Rehabilitation of patients disabled by leprosy has two principal objectives:

—prevention of further deterioration in the patient's physical, social and economic situation; and
—restoration of the patient's level of economic independence and social status where necessary.

Priority should be given to those who are likely to be successfully rehabilitated. This is particularly important at the beginning of a rehabilitation programme when it is essential to demonstrate to the patients and the community alike that leprosy patients can be rehabilitated.

Three inter-related basic strategies are recommended for achieving the above objectives:

—access to the medical system through outpatient clinics and hospitalization for such needs as ulcer care and reconstructive surgery when appropriate;
—home care; and
—community-based rehabilitation (CBR).

It is recognized that rehabilitation could be mediated either through the leprosy service or through CBR.

CBR is a relatively unfamiliar concept to leprosy workers. It follows the same principles as community-based health care and has the same strengths and weaknesses.

Wherever CBR services, services for the prevention of blindness, or a fully developed community health care service exist, most rehabilitation needs of disabled/handicapped leprosy patients can be met through community services, provided that those working in the services have had appropriate training. Where CBR services do not exist, or community health care services are not developed, the

leprosy clinic staff should be encouraged to take the initiative in stimulating development of appropriate community-based services. Special provision will also have to be made for supplying protective footwear to leprosy patients with anaesthetic feet.

Community action to rehabilitate disabled leprosy patients should ensure that they are fully accepted as members of the community, that local community resources are made accessible to them, that responsibility is accepted for the development of additional resources for them, and that they are encouraged to participate in the decision-making activities of the community.

A detailed account of objectives, action and resources for community-based rehabilitation of leprosy patients is given in unpublished WHO document WHO/CDS/LEP/87.3, available from Leprosy, World Health Organization, 1211 Geneva 27, Switzerland.

Rehabilitation of severely disabled and handicapped leprosy patients is a difficult task. A decision should be taken as to which agency should be given this responsibility, and practical steps should be devised to implement that decision.

7.5 Social problems in leprosy

The importance of social and cultural factors in leprosy control, and the serious and sometimes catastrophic impact of these factors on individual leprosy patients are now generally recognized.

At one time, in efforts to prevent the spread of disease, patients were commonly isolated and relatively little attention was paid to their social problems. In fact, the practice of compulsory isolation helped perpetuate the stigma of leprosy in many countries. Since chemotherapy and domiciliary care have become the accepted methods of leprosy control, it is being increasingly recognized that the customs, culture, social attitudes and restrictive laws that still exist in some countries have a great impact on leprosy control activities as well as on the social and economic well-being of the patients.

As a result, many leprosy programme managers are becoming directly involved in efforts to improve the social and economic conditions of patients through public health education and other activities. In addition, there is no doubt that the use of improved technologies such as multidrug therapy and reconstuctive surgery, added to the possibility of cure, is producing positive changes in public attitudes to leprosy and leprosy patients. Further, social

scientists have recently begun to make significant contributions to the basic understanding of social and cultural factors in leprosy.

Much remains to be done, however. As a sound basis for further progress, thorough analysis of existing situations is necessary. Quantifiable parameters must be used to define the impact of social, cultural and economic factors on leprosy transmission and control and upon the well-being of individual patients. The information thus obtained needs to be applied in a systematic way to permit the design and implementation of specific, cost-effective and acceptable measures to improve leprosy control and benefit the patients. This requires the combined efforts of many people, including social scientists and experts in clinical leprosy and leprosy control.

8. LEPROSY CONTROL

The strategy for leprosy control continues to be based on the secondary prevention approach, involving early detection and chemotherapy for all cases of leprosy, in order to halt transmission of the disease in the community and prevent disabilities. Correct classification of the patient, regularity of treatment, and improved case-holding are critical for the success of multidrug therapy.

8.1 Formulation of a leprosy control programme

This aspect was extensively covered in the Fifth Report of the Expert Committee and the views therein are endorsed (*1*).

Implementation of multidrug therapy requires more careful planning in terms of infrastructure and operations than does dapsone monotherapy. Planning should ensure periodic clinical and bacteriological assessment of cases, availability of drugs, and their timely distribution.

8.2 Components of leprosy control

8.2.1 *Health education*

The basic aims of health education activities are to promote acceptance of the programme, dispel the social stigma of leprosy and seek the participation of the community in facilitating self-reporting by patients. Case-holding is central to successful treatment, and

successful treatment is the best means of demonstrating the value of health education. Imaginative selection of appropriate health education media and materials for the community makes the input cost-effective.

8.2.2 *Case detection*

Case detection is an integral component of leprosy control programmes, although active case detection is justifiable only when treatment facilities are adequate to meet the resulting increased workload. A variety of rapid methods for identifying leprosy in the community have proved to be just as useful in case detection as house-to-house total population surveys and far less time-consuming (*5*). Programmes should promote self-detection through health education, as self-reported patients generally attend more regularly for treatment. Where multidrug therapy has been adequately implemented, it has been found that self-reporting by patients increases significantly. This is welcome as many of these cases present early, which helps to prevent deformities. During the implementation of multidrug therapy, treatment activities should receive priority over large-scale, intensive active case detection.

8.2.3 *Contact surveillance*

Of the various methods of active case detection, contact surveillance is the one for which there is some epidemiological justification. It is probably more useful in areas of low and moderate endemicity, where there is greater clustering of leprosy cases. In general, contact surveillance is well accepted by the population.

Throughout multidrug therapy it is recommended that patients' contacts be examined at least once a year. After completion of therapy, contacts of multibacillary cases should be examined for an additional five years and those of paucibacillary cases for two years, at yearly intervals. Contacts should also be educated to report any signs or symptoms of leprosy that appear.

8.2.4 *Case-holding*

More vigorous efforts are necessary to ensure regularity of drug intake, particularly in multidrug therapy. The ability of multidrug therapy to prevent rifampicin resistance depends upon the regularity

with which patients take their unsupervised daily doses of dapsone and clofazimine. Compliance with the self-administered component of the regimen must therefore be improved by health education and motivation, and be monitored by looking for the characteristic clofazimine discoloration, making tablet counts and, possibly, performing spot tests for dapsone in urine (*27*).

An efficient treatment service will itself have a significant impact on case-holding, but this can be further improved by an effective retrieval mechanism for defaulters. It must be remembered that the success of chemotherapy is determined as much by operational as by technical factors.

8.2.5 *Supervision*

In view of the complexity of implementing multidrug therapy and the necessity of applying it with acceptable regularity, supervisory activities are an essential component of any such therapy programme. Adequate transportation facilities are necessary for effective supervision.

8.2.6 *Logistics*

The supply to peripheral treatment centres of sufficient quantities of the three essential antileprosy drugs to ensure complete and uninterrupted courses of multidrug therapy for all groups of patients, and the storage of those drugs, are logistic problems requiring particular attention. Such factors as shelf-life of the drugs (especially rifampicin and clofazimine) must be taken into account when advance orders are placed, and support facilities such as transport and gasoline supplies must be adequate to the task.

8.2.7 *Monitoring and evaluation*

Each country should have a well developed, uniform and simple information support system for monitoring the operational and epidemiological aspects of leprosy control programmes.

The essential indicators, defined by the WHO Study Group on Epidemiology of Leprosy in Relation to Control and listed in their report, are practicable and should be within the capabilities of most health services (*3*). The same report contains an extended list of indicators which are also practicable for programmes with well developed information systems.

The OMSLEP Recording and Reporting System (*28*) is a method of using the basic data from individual records and registers for analysis of the effectiveness of leprosy control programmes. It can be adapted to the specific information systems used in various countries, it provides for comparisons between countries and it can be implemented using traditional methods of information retrieval as well as microcomputers. Software and instruction manuals are available.

A routine system of quality control should be established for the collection of data. It should cover sample checks on diagnosis and classification of leprosy, smear examination, and individual treatment records.

8.2.8 *Manpower training*

Experience has shown that considerable training and retraining are necessary to implement the relatively new approaches to leprosy control and patient care that have been recommended. In addition, successful integration of leprosy into the basic health services necessitates training for the staff of those services: even in endemic countries, few doctors or other health staff receive training in leprosy at medical school. Implementation of training on the required scale demands a systematic approach, an appropriate strategy and a thorough command of the technology of training itself on the part of those responsible.

The approaches to training should include the following elements:

(1) A plan of action for training should be developed at national level, based on the endemicity of the disease, the strategies chosen for leprosy control and the work to be done to fulfil these strategies. Consideration should be given to providing appropriate basic training for medical and paramedical professionals who are likely to have contact with patients. Other professionals, including schoolteachers, who can have a significant influence on public attitudes to the disease, should receive appropriate training in leprosy health education.

(2) A task-oriented strategy is strongly recommended for leprosy training. Detailed analyses of tasks in leprosy have been prepared for workers in primary health care (unpublished WHO document

WHO/CDS/LEP/86.3)[1] and for work in the field of disability prevention and rehabilitation (unpublished document WHO/CDS/LEP/87.3).[1] A general analysis of tasks relevant to leprosy control is also available (unpublished document WHO/CDS/LEP/86.2).[1]

(3) Much of the training currently given in leprosy is focused on the acquisition of knowledge. In the development of specific learning objectives for training, appropriate attention should be given to the need for trainees to acquire knowledge, attitudes and skills relevant to the work to be done. It is the main responsibility of the trainer to identify the essential knowledge and to define the standards of performance that are necessary to complete the prescribed tasks appropriately.

(4) Training programmes and teaching materials should be developed or selected that are appropriate for the trainees and relevant to the tasks for which they are being prepared. Consideration should be given to the use of newer approaches such as self-instruction through reading, video programmes and problem-based learning. Emphasis should be placed on achievement of appropriate standards of performance, especially in clinical skills.

Evaluation of the effectiveness of training is crucial.

One of the most important aspects of training in leprosy is the distribution of all available literature and other teaching materials to those who need them.

8.3 Leprosy control through primary health care

In almost all countries where leprosy is endemic, leprosy control activities were started as vertical programmes. Over the past decade the specialized, vertical services have been increasingly integrated into the general health services, most commonly by progressive transfer of direct responsibility for leprosy control activities to the general health service staff.

The rationale for this policy is that optimal health care, including that for leprosy patients, should consist of comprehensive, continuous and integrated care, which is best delivered through multipurpose, decentralized health services. Integration also ensures the widest possible coverage of patients for leprosy control.

Integration of leprosy control into the primary health care system does not imply that all specialized elements should disappear from

[1] A limited number of copies of this document are available to interested persons from: Leprosy, World Health Organization, 1211 Geneva 27, Switzerland.

the health services. Indeed, in many countries where integration has been implemented, elements such as technical supervision, referral of patients, drug supply and financing have necessarily remained specialized.

Depending on local conditions (e.g., prevalence of leprosy, training of the various levels of health staff), each country should decide at which level (national, regional, district) of the primary health care system such specialized support should be available.

Integration of a vertical leprosy control programme into a primary health care system requires careful and adequate planning in advance, and step-by-step introduction. Gradually it should expand to cover the whole country, with realistic targets being set to prevent unnecessary delay. To facilitate the process of integration, some countries prefer to start it only when coverage by multidrug therapy is complete, while others find it more convenient to start integration with the initiation of the multidrug therapy programme.

Most vertical programmes have detailed reporting systems which the specialized staff appear to handle adequately. After integration, however, the reporting system will have to be adapted to meet the new needs.

The incorporation of leprosy control into the curricula of medical and paramedical schools is essential for the successful integration of leprosy control into the primary health care system. Systematic management training is needed for intermediate-level health service managers in order to ensure adequate planning, monitoring and evaluation of integrated programmes.

The operational combination of the vertical control programme for leprosy and that for tuberculosis should not be taken as integration. Basically, such combined programmes are subject to the same limitations as are vertical control programmes for leprosy alone.

8.4 Urban leprosy control

There is a general notion that leprosy is primarily a disease of rural areas, but in many countries the prevalence of leprosy is just as high in urban areas. Integration of urban control activities with primary health care should receive particular attention.

Leprosy control in urban areas poses special problems, including the high level of social stigma, the mobility of the population, poor compliance with treatment, multiple registration of patients,

difficulties with active case detection, and self-reported cases coming from outside the urban area. Existing control strategies, particularly for using multidrug therapy, have therefore to be modified for urban areas. The following initiatives are expected to improve the quality of urban control programmes:

—active involvement of all available facilities, urban health centres, dispensaries and hospitals (skin clinics) in case-detection and treatment after appropriate training of the personnel;
—orientation of private medical practitioners in leprosy control strategies, multidrug therapy regimens and reporting of results;
—supply of antileprosy drugs to participating private practitioners;
—involvement of peripheral health workers in the retrieval of defaulters from treatment;
—optimal use of the media to increase community awareness of leprosy services;
—development of a cross-notification system to trace patients migrating within and outside the urban area;
—creation of, and publicity for, referral centres; and
—periodic review of programme activities with the participating agencies.

8.5 Financing leprosy control programmes

Even though multidrug therapy requires the use of rather expensive drugs, the relatively short treatment periods and the efficacy of the therapy make it more cost-effective than prolonged dapsone monotherapy. Once the accumulated cases have received a course of multidrug therapy, the total programme cost, particularly the drug cost, will be substantially reduced because of the reduction in the caseload.

In budgeting for the multidrug programme, a substantial sum should be allocated for the training of personnel, updating of the registry, and clinical assessment of every known case for assignment to the appropriate regimen, increased supervision and monitoring, and health education of the community.

The total cost of multidrug therapy, at least at the initial stage of implementation, is probably much greater than most national governments can reasonably allocate, and additional financial support from contributing agencies will be required. Optimal use of national resources needs careful planning with priorities being set for

the various activities within leprosy control programmes and in the context of other health programmes.

8.6 Role of nongovernmental organizations (NGOs) and other contributing agencies

It is important to accept the principle that health care of the people is the prerogative of the people themselves and the responsibility of national governments as their representatives. The role of external NGOs should therefore be to support the efforts of national governments and national NGOs.

The main role of national NGOs is to advocate leprosy control activities and to promote community participation in the national control programmes. Because of their flexibility, NGOs are uniquely placed to experiment with novel solutions to problems which, if successful, could later be incorporated into government programmes.

One area of work that is readily open to NGOs is rehabilitation of leprosy patients and social and economic support for the patients' families, which governments often find it difficult to undertake. The capacity of the NGOs to organize social measures to relieve human suffering, and their sensitivity and responsiveness to the needs of the people, render them most suitable for these activities.

In the past, in a number of countries, external voluntary agencies played an important role in initiating leprosy work, and treatment of many leprosy patients is currently being supported through these agencies. In recent years, voluntary agencies have steadily extended their activities to leprosy control, based on multidrug therapy, and their contributions represent a most important resource.

The Committee strongly advocates effective coordination between national governments, national and international NGOs and other international contributing agencies to ensure optimum utilization of available resources for better leprosy control.

9. RESEARCH NEEDS

In the past two decades of leprosy research major advances have been made in such areas as chemotherapy, immunology, and molecular biology; the new tools that have emerged as part of this progress have enabled better leprosy control. In this context, the

contribution by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) has been substantial. Notwithstanding the above, there is considerable need to strengthen field research in countries where leprosy is endemic, particularly in such areas as validation of new technology, evaluation of its relevance to disease control, and development of approaches to its cost-effective application. Many endemic countries afford considerable opportunities for highly significant field research, oriented towards better leprosy control, in such areas as epidemiology, health systems research and assessment of health technology. With this in mind, priority areas for research are listed below. (It should be pointed out that no relative priorities are implied by the order of these research projects.)

9.1 Epidemiological research

The following priority areas of epidemiological research were identified:

(1) Investigation of subclinical infection using immunological tools.

(2) Identification of possible specific environmental factors, and comparison of infection rates in population groups with different exposure and disease attack rates among the infected, could lead to a better understanding of the dynamics of the infection and of the disease.

(3) Analysis of the trends of different epidemiological parameters (such as age, sex, type-specific incidence over time and for successive cohorts, sex and type ratios, age at detection) which might be valuable in developing prediction indicators for long-term monitoring, especially in situations of declining incidence.

(4) Studies on the epidemiology of disability, in order to define the risk factors associated with early lesions of different types, and with different environmental or cultural characteristics.

(5) The application of epidemiological modelling to the prediction and simulation of various control methods, namely immunization and chemotherapy.

9.2 Operational research

A multidisciplinary approach using methods developed in health systems research should help to assess, optimize and evaluate the following:

(1) Integration of leprosy control into general health services in the context of primary health care.
(2) Transfer of new technology for management, information systems and screening methods.
(3) The best use of resources in relation to effectiveness of leprosy control.
(4) Community participation, in particular for case-detection and case-holding.
(5) Extension of community-based rehabilitation to the care of leprosy patients with deformities, disabilities and handicaps.
(6) Development of simple and standard methodologies for assessing the magnitude of the leprosy problem.

9.3 Social and economic research

Priority needs in the area of social and economic research include studies directed towards assessing the social costs of leprosy, improving awareness of leprosy, enhancing compliance with treatment, increasing family and community support for leprosy patients, and improving the motivation of health providers towards leprosy. The role of such research in improving the utilization of available health technology for leprosy control should not be underestimated. However, it is important to ensure that the research is multidisciplinary and goal-oriented. It should be recognized that, although most of the results are site- or culture-specific, they can provide an insight into issues of wider significance.

9.4 Clinical and chemotherapy research

The following priority areas of clinical and chemotherapy research were identified:

(1) Studies on occurrence of rifampicin resistance.
(2) Study of BT patients similar to BB in their response to multidrug therapy, occurrence of reversal reactions and relapses and the management of these conditions.

(3) Study of quiet nerve paralysis, its frequency, pathology and management.

(4) Development of reliable and sensitive *in vitro* methods for screening of new drugs.

(5) Development of multidrug regimens of shorter duration. One question that remains to be answered is that of the duration of treatment required to kill the relatively few bacilli (assumed to be present in each patient) naturally resistant to rifampicin.

(6) Development of new methods or drugs for preventing and controlling leprosy reactions and nerve damage.

(7) Study of the relationship between *M. leprae* persisting after multidrug therapy and the occurrence of late relapse in multibacillary leprosy.

(8) Trials to study the possible impact of fluoroquinolones in enhancing the therapeutic effects of the current multidrug therapy regimens.

(9) Studies on means of accelerating bacterial clearance in multibacillary leprosy.

(10) Studies on metabolism of *M. leprae*.

9.5 Immunology research

The following priority areas were identified for immunological research:

(1) Development and evaluation of sensitive immunological tools for the identification of *M. leprae* infection.

(2) Evaluation of the protective value of the killed *M. leprae*-based vaccine.

(3) Development of a second generation vaccine based on *M. leprae*-specific antigens or epitopes.

(4) Studies of immunopathological aspects of leprosy, including immunological deficit, reactions and nerve damage.

(5) Studies to evaluate immunotherapy in the management of multibacillary leprosy.

10. CONCLUSIONS AND RECOMMENDATIONS

The major conclusions and recommendations of the Committee are summarized below.

(1) Leprosy continues to be a major public health problem, although the clinical profile is changing for the better.

(2) An operational definition of a case of leprosy has been recommended by the Committee.

(3) Certain clinical problems, such as quiet nerve paralysis, need greater attention.

(4) Significant progress is being made in the fields of immunoprophylaxis, molecular biology of *M. leprae* and development of new drugs.

(5) Drug resistance will continue to be a serious problem unless multidrug therapy is used routinely.

(6) The multidrug therapy recommended by the 1981 WHO Study Group on Chemotherapy of Leprosy for Control Programmes has so far performed very well in terms of efficacy, acceptability and feasibility. The Committee endorses the recommendations of the Study Group on multidrug therapy with a slight modification to the definition of paucibacillary leprosy.

(7) The importance of prevention and management of disability is emphasized in the light of available and feasible technology. The WHO disability grading system has been redefined.

(8) The introduction of multidrug therapy has increased the need for proper planning and evaluation of leprosy control programmes and the appropriate integration of leprosy control into primary health care.

(9) Task-oriented training is the key to proper implementation of leprosy control.

(10) Efforts in several areas, including chemotherapy, immunology, epidemiology, socioeconomic and operational research, should continue in order to develop better tools and methods for leprosy control.

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