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WHO Expert Committee on Leprosy

Fifth Report

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WHO EXPERT COMMITTEE ON LEPROSY

Geneva, 19-25 October 1976

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WHO EXPERT COMMITTEE ON LEPROSY

Fifth Report

The WHO Expert Committee on Leprosy met in Geneva from 19 to 25 October 1976. The meeting was opened by Dr I. D. Ladnyi, Assistant Director-General, on behalf of the Director-General.

In welcoming members, Dr Ladnyi referred to the shortcomings of the available strategy for combating leprosy and the difficulty of determining when infectious cases are cured. He recalled the recent advances in leprosy research and the hopes they raised for improved leprosy control methodology in the future.

INTRODUCTION

Three resolutions have been passed in consecutive World Health Assemblies in 1974, 1975, and 1976¹ calling for improved leprosy control and intensification of research. Voluntary agencies engaged in technical cooperation are increasing their expenditure on leprosy work.

There are three main reasons for this return of leprosy to the forefront of world attention.

(1) Newly independent countries are increasingly realizing their responsibility for tackling the age-old problem of leprosy, which has largely ceased to exist in the industrialized countries.

(2) Leprosy research, principally in immunology, has made important advances in the past decade.

(3) It is now realized that the hopes raised over 30 years ago that leprosy could be controlled by the introduction of the sulfone drugs were overoptimistic.

Clinical diagnosis is indispensable in leprosy, and it is unlikely in the immediate future that tests will be developed that will replace direct patient-doctor contact. WHO and other bodies are intensifying the search for more active drugs or combinations of drugs to reduce the period of infectivity of patients and to prevent the much feared develop-

¹ WHO handbook of resolutions and decisions. Volume II, second edition, 1977, pp. 36-37 (resolutions WHA27.58, WHA28.56, WHA29.70).

ment of drug resistance. The discovery of new animal models, especially that provided by the armadillo, has enabled WHO to start a research programme for a specific skin test and an antileprosy vaccine.

The Committee has concentrated on the main problems most frequently encountered and has made suggestions for their solution. It has also tried to show how the modern concepts of health programme formulation and management can be applied to leprosy control. Many of the basic principles for leprosy control expressed in past Expert Committee reports remain valid, and the present report should be read in the light of them. In its deliberations the Committee was able to benefit from a working paper summarizing the views of 69 experts in leprosy, tuberculosis, and public health.

1. EPIDEMIOLOGY

1.1 Size of the problem

In 1970, the WHO Expert Committee on Leprosy¹ considered that the number of leprosy cases in the world had not greatly changed from that estimated in 1965, i.e., 10 786 000.

Although data are limited, it would seem that the reductions in numbers of cases effected by leprosy control measures may have been more than offset by increases in the numbers of cases arising as a result of the growth of population in the countries in which leprosy is endemic. Revised estimates from a number of the larger countries indicate that the total cases throughout the world may well exceed 12 million.

A large proportion of patients, both lepromatous and nonlepromatous, who have been detected too late or who have been inadequately treated, suffer from the results of motor and sensory deficit. In areas of high prevalence their numbers represent a major health problem. No detailed data are available on the effect of leprosy deformities on the socioeconomic development of communities, but in many areas leprosy can be considered as the major cause of physical handicap.

1.2 New evidence on the transmission of leprosy

Important evidence has been accumulating in recent years that clarifies some of the problems posed by the transmission of leprosy.

¹ WHO Technical Report Series, No. 459, 1970 (Fourth Report of the WHO Expert Committee on Leprosy), section 1.1.

At first sight this new knowledge may appear to imply that leprosy is more contagious than had been previously thought, but it cannot be too strongly stressed that the attack rate of leprosy among contacts and the epidemiological situation remain unchanged; only a few of the people exposed to infection develop clinical signs of leprosy.

Because of the low prevalence rate in endemic areas it was for long assumed that the disease was only feebly contagious and that prolonged intimate contact, especially skin-to-skin contact, was required for the successful transmission of *Mycobacterium leprae* from patients to others. However, a number of epidemiological observations—particularly the occurrence of leprosy epidemics—and many case-histories were difficult to explain on this hypothesis, which has been further challenged by the results of certain immunological investigations. These studies carried out both *in vitro*^{1, 2} and *in vivo*,³ show that immunological conversion has taken place in a large proportion of leprosy contacts. These observations provide a firmer basis for placing leprosy in the group of infectious diseases (which includes tuberculosis and poliomyelitis) in which the rate of transmission of the infecting agent is very significantly higher than the disease attack rate.

The discovery of the viability of the large numbers of bacilli emerging from the nasal mucosae of patients suffering from untreated lepromatous leprosy is very important. *M. leprae* may also be shed by such patients from lepromatous skin ulcers, in the milk of lactating mothers, and in much smaller numbers from the skin appendages. Nevertheless, both the precise mechanism of transmission and the portal or portals of entry of *M. leprae* remain obscure.

Airborne infection could explain some of the epidemiological findings. Early studies by Schäffer⁴ demonstrated that droplet infection was a distinct possibility by showing that active lepromatous cases could expel by speaking, coughing, and sneezing very considerable numbers of bacilli in a few minutes. Shepard⁵ proved that leprosy bacilli in nasal washings were viable on mouse foot-pad inoculation. Davey & Rees⁶ provided proof that *M. leprae* expelled in nasal blows may remain

¹ GODAL, T. ET AL. *International journal of leprosy*, **40** : 243–250 (1972).

² MYRVANG, B. *Acta pathologica et microbiologica scandinavica*, B, **82** : 707–714 (1974).

³ CONVIT, J. ET AL. *Bulletin of the World Health Organization*, **52** : 193–198 (1975).

⁴ SCHÄFFER, I. *Archiv für Dermatologie und Syphilis*, **44** : 159–174 (1898).

⁵ SHEPARD, C. C. *American journal of hygiene*, **71** : 147–157 (1960).

⁶ DAVEY, T. F. & REES, R. J. W. *Leprosy review*, **45** : 121–134 (1974).

viable for 1-2 days and occasionally for as long as 7 days. The hypothesis that leprosy is an airborne infection therefore deserves serious consideration. A significant proportion of mice rendered immunologically incompetent by thymectomy and irradiation and then made to inhale aerosols containing viable *M. leprae* subsequently developed evidence of leprosy infection in their tissues.¹

It has been assumed that *M. leprae* is unable to pass through unbroken skin, but cuts and abrasions are not uncommon. Though the number of bacilli reaching the surface of the skin may be small, it has been shown in mouse experiments that multiplication of *M. leprae* can be obtained after inoculation of very small numbers of bacilli. The entry of *M. leprae* via the skin therefore remains a definite possibility. Mechanical transmission by biting insects may also play a part. The part played by the ingestion of leprosy bacilli has not been clearly established.

Clinically, the first recognizable lesion may be located anywhere on the skin. Whether the site of the first skin lesion corresponds to the site of entry of the organism or whether it is the result of a generalized spread remains unknown.

Many studies have shown that contacts of tuberculoid cases have a much lower risk of developing leprosy than have contacts of proven lepromatous cases (70 % lower in a WHO leprosy/BCG trial).

The role of tuberculoid cases in the spread of the infection remains to be explained. A distinction should be made between the individual importance of a nonlepromatous case and the role of nonlepromatous cases in the transmission and maintenance of the disease in a population. While it is recognized that an individual nonlepromatous case represents a much reduced risk as compared to a lepromatous case, their large numbers in certain areas indicate that they could constitute a significant reservoir of infection. Thus the two types should be considered in relation to their relative proportions. This does not imply any assumption about the way in which tuberculoid cases could spread leprosy.

While it would seem extremely unlikely that polar tuberculoid patients and subjects with subclinical infection pose a real hazard, further research is needed to clarify the relative importance of the few lepromatous cases present in areas with a high prevalence of tuberculoid leprosy and to what extent borderline tuberculoid cases in reaction can discharge bacilli. The fact that low-resistant (BT) tuberculoid leprosy patients may show positive skin smears during reactions (although the bacilli

¹ REES, R. J. W. & MCDUGALL, A. C. *Journal of medical microbiology*, 10 (in press).

nearly always show degenerative changes) underlines the need for such investigations.

Untreated indeterminate leprosy may evolve into lepromatous or nonlepromatous forms or resolve spontaneously. Hence indeterminate patients form a potentially important group in the strategy of leprosy control. The Mitsuda reaction may assist in identifying those indeterminate cases that would tend to develop lepromatous leprosy.

The identification of subjects with subclinical infection (see section 4.2.2, p. 45) may provide important epidemiological information. In some epidemiological situations it may help in detecting infectious cases and possibly in delineating high-risk groups.

1.3 Information collected in leprosy control programmes

Leprosy control activities require the collection, analysis, and processing of various kinds of information for epidemiological and operational purposes.

Depending on the use to which it is put, the information collected can be classified as: (1) information concerning individual patients, (2) information of an operational nature, and (3) epidemiological information.

Individual information may be clinical (distribution of skin lesions, eye complications, development of paralysis, etc.), bacteriological, administrative, social, and economic. The purpose of collecting such information is to ensure that the patient receives the appropriate treatment and care in accordance with the stage of development of the disease. Some of this information may be suitable for analysis to provide quantified information.

Information of an operational nature is composite quantitative information used in the measurement of programme performance (e.g., detection rate, average interval between the onset of the disease and its detection, treatment coverage, treatment attendance rate, and relapse rate). It constitutes a measure of the efficiency of programmes but not a measure of their effectiveness. A programme may be conducted in a highly efficient manner but its effectiveness in solving the long-term problem of leprosy may still be low.

Epidemiological information relates to the size of the problem (incidence, prevalence) and to the impact of the action taken (reduction of incidence, reduction of prevalence). It permits the comparison of the leprosy problem with other health problems (determination of priorities), the surveillance of the development of the problem if no action is taken

(surveillance of natural incidence trends), the definition of **intervention strategies** (choice of methods), the assessment of **programme impact** (effectiveness), and the resulting modification of the measures implemented.

The justification for collecting these various kinds of information depends on their usefulness in decision-making. From this point of view, an item of information is valid and its collection is justified only if it leads to a decision.

Programme evaluation, based on information of an operational type, makes it possible to check constantly that activities are being carried out in conformity with the standards laid down for the chosen strategy. If the initial hypotheses that determined the choice of control procedures and the definition of the standards are assumed to be correct, strict adherence to these standards should produce the desired epidemiological effect.

By comparing the results obtained with those that could have been expected if no action had been taken, epidemiological surveillance makes it possible to assess the effectiveness of the strategies implemented and the appropriateness of the standards so that they can be adapted and modified whenever necessary.

1.4 Prevalence rates

Knowledge of prevalence rates is essential in order to assess the size of the leprosy problem. There are, however, inherent difficulties in comparing prevalence rates in different populations or under different conditions. These difficulties are discussed in the following paragraphs.

(1) The sensitivity of diagnostic criteria may vary according to detection procedures. As a result, in some areas patients with self-healing lesions may represent a significant proportion of the registered cases. This will also occur when surveys are repeated at close intervals. While detection and reporting of these cases is considered important, the diagnostic criteria and procedures of detection should be clearly stated in order to make rates comparable.

(2) The definition of inactive lepromatous patients must be given an end-point. Within the past decade, patients classified as lepromatous or borderline have been regarded as potentially a continuous source of infection. This means that all initially infectious cases are considered as "active" and are included in prevalence rates. Thus, no distinction is made between bacteriologically positive cases and those that are quiescent and of no immediate epidemiological or operational impor-

tance. Pending more research on the persistence of infectivity and additional data on relapses, consideration should be given to the possibility of excluding from prevalence data lepromatous and borderline cases that have remained persistently negative by standard methods of examination for 10 years or more. In the event of relapse and reactivation, they could be reincluded.

(3) The failure to distinguish clearly between active and inactive disease is another source of confusion in establishing and comparing prevalence rates. For operational purposes, a clear distinction should be made between active and inactive cases. It is recommended that the definition of inactive cases proposed by the WHO Expert Committee on Leprosy in 1970¹ be used.

(4) Time lag in releasing from control tuberculoid cases that fulfil the criteria recommended for release is another source of inaccuracy in assessing prevalence rates.

1.5 Incidence rates

The incidence rate is an accurate index of continuing transmission, but it is particularly difficult to ascertain retrospectively because of the imperfect histories given by patients and the tardy reporting of signs and symptoms. Serial surveys would have to be conducted annually to reveal most of the new cases, and this is clearly impracticable. However, annual surveys of a limited number of randomly chosen villages over a period of 5–10 years would allow reasonably accurate incidence estimates to be made. They would also provide correlations with case-detection rates and identify under the existing epidemiological conditions the proportion of persons who develop self-healing lesions. In practice, the majority of control programmes report case-detection rates.

1.6 The effect of control measures

Despite the undoubted value of the treatment programmes to individual sufferers from leprosy, the limitations of the control measures in ensuring that others will not become infected are evident from the continued appearance of new cases. Doubts about the efficacy of the treatment measures have been intensified by the recent findings that sulfone therapy cannot by itself ensure the total eradication of all viable

¹ WHO Technical Report Series, No. 459, 1970, section 2.15.

bacilli in the patient with lepromatous leprosy. Moreover secondary prevention must remain an imperfect tool in the control of leprosy transmission as long as it is not possible to identify infectious cases immediately they become a danger to others. In addition, serious operational problems are often encountered in carrying out control measures.

Nevertheless, there is substantial evidence that a significant decline of the disease in the community, shown not only by lowered prevalence rates but by reduction in incidence, is effected by present control measures, of which the main element is sulfone chemotherapy.

Two South-East Asian countries, Thailand and Burma, have maintained control projects for more than 15 years. Both projects have been the subject of useful assessments of what may be regarded as conventional specialized leprosy control programmes. Random sampling surveys conducted at 10-year intervals have shown significant reductions in the prevalence rates. In Khon Kaen Province, Thailand, the prevalence fell 70% from its initial (1962) level of 12.37 per thousand, and in central Burma there was a similar reduction from an initial (1963) level of 32.0 per thousand. Results from certain francophone African countries are comparable.

The data from the second surveys have confirmed the accuracy of the greatly lowered incidences suggested over successive years by case-detection figures. The latter are derived from school surveys, contact surveillance, and voluntary reporting by new patients. While these modes of detection have become more efficient over the years, the number of new cases recorded annually has fallen. An important factor in the epidemiological trends was the finding in both surveys that more than 75% of the estimated bacilliferous cases were under treatment (Khon Kaen, 76% ; central Burma, 90%). A considerable number of early tuberculoid cases have been found in such surveys, but many are likely to have been self-healing.

Clearly, despite deficiencies in operational procedures, a significant impact can be made on transmission. However, it would appear that in order to achieve a reduction in incidence it is necessary to treat (and render inactive) not less than a certain minimum proportion of the infectious cases. The proposal made by the WHO Expert Committee on Leprosy in 1966¹ and 1970² that 75% of lepromatous and borderline cases should be treated and rendered inactive appears to be valid.

¹ WHO Technical Report Series, No. 319, 1966.

² WHO Technical Report Series, No. 459, 1970.

1.7 Population-based studies

There is general agreement that random sampling studies of leprosy endemicity conducted at intervals of 5 or 10 years are extremely useful. Particular efforts should be made to study incidence rates.

The continued appearance of new leprosy cases with early and often transient lesions calls for a more diligent search both for undiscovered index cases and for the re-examination of bacilliferous patients supposedly under control, both within the family and among the extrafamilial contacts.

2. STRATEGY OF LEPROSY CONTROL

2.1 Overall approach

The first step in a control programme is to estimate prevalence by means of epidemiological surveys. Over the past 20 years or so, considerable progress has been made in this respect and much has been learned from random sample surveys in different parts of the world. As a consequence, it is now possible to estimate fairly accurately the extent of the leprosy problem in a given area or country. Those with higher prevalence levels require more intensive case-detection measures, ideally involving whole population surveys, while in areas of low disease prevalence active case-finding may be confined to a relatively small group of contacts.

Regardless of the method employed, the diagnosis of early leprosy is based on the recognition of certain clinical characteristics and therefore requires training and experience. In order to render more than palliative care, it is essential that cases be identified at an early stage. Advanced cases of leprosy are relatively easy to recognize, and it is these patients who are at the root of that aversion to and fear of leprosy that exists in many populations. The primary health worker, however, lacks a simple diagnostic aid for detection of early cases.

The primary health care approach may well be appropriate for the introduction of leprosy control with the active participation of the community. Such an approach integrates at the community level all the elements necessary to make an impact on the health status of the people, including preventive, promotive, curative, and rehabilitative health measures and community development activities. Primary health care workers would need to be adequately trained to make a tentative diagnosis of leprosy.

As community-based activities are developed, including those concerned with leprosy, they should be attached to the local health services, where such services are available.

2.2 Case-detection and bacteriology

The desirability of the diagnosis being confirmed by a doctor is recognized, but it is generally appreciated that auxiliaries after a reasonable period of training are capable of sound diagnosis based on the cardinal signs of leprosy. However, difficulty is experienced by many doctors and auxiliary health workers in the diagnosis of indeterminate leprosy. The Committee recommended the use of histamine tests in such cases.

The Committee expressed concern at the extremely low standards of the bacteriological examination techniques used in many leprosy control projects and stressed the need to improve them.

In programmes that have the operational facilities, at least one smear should be taken from all newly admitted cases, although for polar tuberculoid leprosy cases, when proper clinical recognition can be ensured, this requirement may not always be necessary.

When the diagnosis of multibacillary leprosy is suspected, smears should be taken from at least two sites—the edge of an active lesion and an earlobe. Where possible it would also be interesting to examine smears of nasal mucus from such cases.

There was agreement that the bacterial index remains the most practical bacteriological examination for use in the field, although different views exist on the practicability of recording morphological changes in the bacilli.

It must be realized that both the bacterial index and the morphological index represent minute samples of the total bacterial load, presenting merely an *indication* of what is happening. A negative bacterial index provides no proof of bacterial negativity, and a negative morphological index will give only an indication of the action of chemotherapy and (probably) of lowered infectivity.

2.2.1 Case-detection in urban areas

Leprosy in urban areas poses a special public health problem. For socioeconomic reasons, leprosy control in urban areas is more complex than that in rural areas. Effective control work in cities requires good coverage of the rural areas otherwise treatment opportunity for leprosy

may be an added attraction for the migration of patients into the cities from the villages.

Leprosy control is closely linked with other measures that regulate urban planning and the general promotion of health. A limited drug-based approach will not be sufficient unless a community health programme with social, educational, and administrative measures for the improvement of the area is also encouraged. Leprosy control workers should become part of the municipal health services and collaborate with other community-level workers, e.g., teachers, social workers, welfare workers, and community leaders.

The three essentials of urban control activity are: case-detection through examination of schoolchildren and contacts of known cases and through the examination of shanty-town communities especially at risk; efficient outpatient treatment in convenient health centres and in all treatment institutions; health education of patients, families, teachers, social workers, and members of the medical profession.

2.3 Contact surveillance

The experience gained in contact surveillance in highly endemic areas, for example in Singu, Burma, is instructive for control strategy. The results obtained by routine methods of case-detection are set against the overall information provided by two surveys carried out in the WHO BCG trial area covering a population of 80 000 and separated by a 4-year interval. The estimated mean yearly incidence was 29.4 per thousand for household contacts of lepromatous cases and 5.9 per thousand for contacts outside the household. The risk of contracting clinical leprosy among household contacts of lepromatous cases is thus approximately five times greater than the risk among other contacts in this area; it is also three times higher than for household contacts of tuberculoid cases. Nevertheless, 80% of the cases detected in the 4-year period were derived from contacts outside the household. Therefore household contact surveillance with annual examinations fulfils the objective of early detection in a high-risk group and is obviously essential, but it yields only a small proportion of total new cases. It needs to be supplemented by other methods of case-detection, especially in highly endemic areas.

Apart from household contacts, other contacts are also subjected to varying degrees of risk. If such contacts can be defined and identified, they too should be kept under surveillance.

The Expert Committee considered that :

(1) contact surveillance of households with a lepromatous case should be maintained for a minimum of 10 years after the lepromatous case is bacteriologically negative ;

(2) ideally, contact surveillance in households with a nonlepromatous case should be maintained for 5 years from the time of diagnosis of the index case ; if this is impossible the contacts should be examined at least once.

2.4 Classification

The main relevance of the classification of leprosy patients to the strategy of leprosy control at present would be :

- (1) identification of infectious cases ;
- (2) identification of cases that may become infectious ;
- (3) identification of patients that are likely to develop deformity.

The Committee considered that the Madrid classification is precise enough to meet the essentials of the above requirements and at the same time simple enough to be used by auxiliary health workers. It recommended that the classification should continue to be used in leprosy control programmes.¹

The need was stressed for the identification and surveillance of tuberculoid patients with more than two lesions because of their risk of developing deformity and of patients with indeterminate leprosy because in the absence of treatment some of them might become lepromatous.

The Committee also recommended that more experience should be gained of the practicability of using the Ridley-Jopling classification² in leprosy control programmes. In some programmes, this classification could be added as subgroups, allowing medical officers to become familiar with its use.

2.4.1 Classification of disabilities

It cannot be stressed too strongly that deformity is not an inevitable or necessary part of leprosy. Its occurrence indicates some defect in the

¹ See WHO Technical Report Series, No. 319, 1966, section 1.3.

² RIDLEY, D. S. & JOPLING, W. H. *International journal of leprosy*, 34 : 255-273 (1966).

strategy of leprosy diagnosis and treatment. In a well conducted leprosy control programme, almost no leprosy patients on first diagnosis will be suffering from some deformity attributable to neglected disease.

The description of a patient's disabilities on registration for treatment is an important feature in leprosy control because further deterioration may be expected in the absence of preventive care. The WHO classification¹ proposed in 1970 was intended to provide a baseline from which a disability grading could be made to indicate treatment needs and to allow an assessment to be made of progress under treatment. It was understood by well trained workers, but appeared to be rather beyond the comprehension of primary health workers. It did not always contribute to the early recognition of potential damage but was perhaps useful for identifying patients for particular attention. The prevention and basic treatment of disabilities, which is based on the education of patients and the application of simple techniques, must be carried out by the local health services.

The grading of disabilities is useless unless the doctor or senior health worker indicates clearly to the auxiliary what measures are to be carried out. These measures will vary with the needs of the individual patients, the skill and knowledge of the auxiliary health worker, and the facilities provided by the health service. Ideally, the leprosy patient with disabilities should have access to all the rehabilitation services—including physiotherapy, reconstructive surgery, the provision of prostheses and protective footwear—available in an integrated programme to those whose deformity is due to trauma or to such diseases as poliomyelitis.

It would be instructive to reclassify a patient's disabilities at the time of his release from control.

2.5 Use of lepromin in leprosy control programmes

The Committee reiterated that lepromin is of no value in the diagnosis of leprosy. However, the lepromin test does have a limited place in leprosy control programmes because it may sometimes be of help in the classification of patients suffering from unstable borderline disease. It may also be of value in deciding the timing of the release from control of patients suffering from indeterminate leprosy, and it may provide guidance to the duration of surveillance required by contacts. Lepromin is further discussed in section 4.1.6, page 44.

¹ WHO Technical Report Series, No. 459, 1970, pp. 26-31 (Annex).

2.6 Therapy

Since the 1970 meeting of the WHO Expert Committee on Leprosy there have been major advances in the chemotherapy of leprosy. The blood plasma levels achieved in man with the major antileprosy drugs have been measured and the minimum inhibitory concentrations of all these drugs except clofazimine (the minimum effective dose of which is known) have been determined in mice. Rates of kill of leprosy bacilli by some of the drugs have also been studied by means of serial biopsies. Much wider experience has been gained in the treatment of lepromatous patients with rifampicin and clofazimine and in treating erythema nodosum leprosum (lepromatous lepra reaction) with thalidomide¹ and clofazimine.

2.6.1 *The use of antileprosy drugs*

The Committee took note of two major problems that have recently been identified—dapsons resistance and microbial persistence.

Since the last meeting of the Expert Committee in 1970, secondary dapsons resistance has become increasingly common throughout the world, occurring in lepromatous (LL) and borderline (BL) cases. Although only 2.5% of a group of such patients receiving regular high-dosage dapsons therapy in an institution developed sulfone resistance over a period of 20 years, an incidence of 3% per annum has been reported elsewhere in patients undergoing domiciliary treatment.² This would mean that of the latter group 30% would develop drug resistance within 10 years. In these circumstances a situation would be rapidly reached in which leprosy control would become ineffective.

The appearance of drug resistance seems to be related to very low initial doses and certainly to low-dose maintenance therapy and to irregular treatment. Sulfone resistance appears to develop in a stepwise fashion.

Sulfone resistance is of the greatest importance, not only to the patient but also to the medical services, because alternative drugs are more costly and may be more toxic than dapsons, and to contacts, because primary sulfone resistance might only slowly be recognized during an initial period on dapsons therapy.

¹ For drug safety reasons WHO does not assist countries or programmes in the purchase of thalidomide. Responsibility for the use of the drug must rest with the programme manager or hospital doctor. Thalidomide should be given to patients only after they have been fully informed about its possible teratogenicity.

² PEARSON, J. M. H. ET AL. *International journal of leprosy*, 44 : 140-142 (1976).

Proven primary sulfone resistance has not yet been reported although prima facie cases have appeared. Primary resistance may occur in any form of leprosy.

In order to prevent the emergence of secondary sulfone resistance, the Committee considered that the treatment of newly diagnosed cases of leprosy should be based on the following principles. Generally, dapsone should be commenced and maintained in full dosage, treatment should be continued regularly without interruption, and initial combined therapy should be given to lepromatous (LL) and borderline (BL, BB) cases.

There is now evidence that a significant proportion of relapses of lepromatous patients after cessation of treatment is due to the survival of a small number of viable leprosy bacilli—"persisters". This explains why lepromatous patients, who are unable to produce effective cell-mediated immunity against *M. leprae*, require such long periods of treatment before they can be released from control.

Dapsone remains the basis of treatment, in the recommended dosage of 6–10 mg/kg body weight per week.¹ This amounts to 50–100 mg daily in full-size adults, with correspondingly smaller dosages for children. If dapsone injections are preferred, the dosage is 300–400 mg twice weekly or 600 mg once weekly.

In bacteriologically negative tuberculoid (TT and BT) and indeterminate adult patients, a dose of 50 mg daily is sufficient.

The Committee considered combinations of drugs in relation to their toxicity, effectiveness,² cost, and availability. It favoured the combination of dapsone in full dosage with clofazimine in the dosage of either 100 mg daily or 100 mg three times a week, to be given to LL and BL patients for the first 4–6 months of treatment, to be followed by dapsone in unchanged dosage. An alternative regimen would be dapsone combined with rifampicin; it is tentatively suggested that the latter drug be given in the dosage of 300–600 mg daily for a minimum of 2 weeks. Pre-programme clinical toxicity studies are recommended. Other available combinations of drugs require further investigation in man (especially toxicity studies) before they can be recommended.

Secondary sulfone resistance should be suspected whenever a lepromatous or borderline patient receiving dapsone treatment relapses clinically and bacteriologically, solid-staining bacilli being found in the smears taken from the new active lesions. If such cases show no response to regular and supervised dapsone therapy within 3–6 months, dapsone

¹ WHO Technical Report Series, No. 459, 1970, section 2.5.

² SHEPARD, C. C. *International journal of leprosy*, 44 : 135–139 (1976).

resistance is considered to be confirmed clinically, and the patient should be referred to the leprosy control doctor. Where facilities are available, drug sensitivity testing in the mouse foot-pad is recommended.

In the treatment of dapsone resistance, combined drug therapy should be instituted. The suggested combination is 600 mg of rifampicin *daily*¹ with 100 mg of clofazimine daily. It is tentatively suggested that combined therapy should be given for a duration of 2-3 months and that thereafter treatment should be continued indefinitely with clofazimine.

In areas where irregular very-low-dosage dapsone treatment has been a feature, many lepromatous (LL) and borderline (BL) patients will be incubating dapsone resistance. Experience in Malaysia and Ethiopia has shown that raising the dapsone dosage alone (but continuing monotherapy) only delays, but does not prevent, clinical relapse. Investigations are continuing in order to assess the value of giving at least one and preferably two other drugs, in addition to increasing dapsone dosage and the regularity of treatment.

While good guidelines for tackling the problem of dapsone resistance have been obtained both from studies carried out on series of sulfone-resistant leprosy patients and by analogy with the chemotherapy of tuberculosis, no data have been obtained that help in solving the problem of microbial persistence. Persisting *M. leprae* have been isolated from patients treated for 5 years with rifampicin,² for 6 years with clofazimine, and for 10-12 years with dapsone. The effect of initial combined drug therapy with dapsone and rifampicin on the subsequent development of persisters is being investigated in previously untreated lepromatous patients.

2.6.2 Problems in the treatment of reactions

Most reactions seen in leprosy control schemes belong to one of two main types, namely, erythema nodosum leprosum (lepromatous lepra reaction) and reversal reaction. The former occurs in lepromatous (LL) and small numbers of borderline (BL) patients; the latter is related to an increase in specific cell-mediated immunity and occurs in borderline (BT, BB and BL) leprosy usually soon after chemotherapy has been started. Reactions in TT leprosy are probably akin to reversal reaction.

Although these reactions can easily be distinguished clinically, they are frequently misdiagnosed.

¹ Because of the known toxic effect of rifampicin when the drug is taken intermittently, daily treatment is strongly advocated.

² REES, R. J. W. ET AL. *International journal of leprosy*, 44: 159-169 (1976).

Treatment of erythema nodosum leprosum. The Committee recommended that mild erythema nodosum leprosum (ENL) should be treated in the field. If there is any nerve tenderness, the affected limb(s) should be rested. Analgesics should be given as required, and the patient should be seen regularly by the leprosy worker at least once every two weeks. In particular, the eyes should be checked at each visit to ensure that the patient is not developing iridocyclitis.

ENL is graded severe if there is high temperature and general malaise ; if the skin lesions become pustular and/or ulcerate ; if the nerves become painful or if loss of nerve function develops ; or if there is evidence of iridocyclitis, orchitis, joint swelling, or persistent albuminuria. The patient should be referred immediately to hospital, analgesics being given as required for the journey.

In general, the antileprosy treatment should be continued unchanged. Drugs available are steroids, thalidomide, and clofazimine. Prednisolone rapidly controls ENL but requires continuous and often increasing dosage ; steroid toxicity and dependence have been frequently seen. Thalidomide is relatively inexpensive and has few toxic effects. The contraindication of thalidomide in outpatients derives from its teratogenicity. Clofazimine takes 4-6 weeks to exert its full effect. In very severe ENL, even at dosages of 300 mg daily (a dose level that should not usually be maintained for longer than about 3 months), clofazimine may not be as effective as steroids or thalidomide, and it may not be accepted by light-skinned patients.

Treatment of reversal reactions. The Committee recommended that, in mild reactions, the antileprosy treatment be continued unchanged. Analgesics should be given as required. If there is nerve tenderness, the affected limb(s) should be rested. The patient should be seen at least once every two weeks and asked to return immediately if the reaction becomes more severe.

In severe reversal reactions, especially those in which there is nerve pain and tenderness or loss of nerve function, the patient must be referred immediately to hospital. Analgesics should be given as required. Painful nerves should be rested and the affected limb supported in a splint if necessary. In hospital, dapsone treatment should in general be continued unchanged ; and treatment should be started with prednisolone. The initial dosage is usually 10 mg three times a day, although individual patients will vary in their dose requirements. Provided that patients can be seen monthly by a doctor and have responded well to therapy, they may be sent home at about the end of the second month, if necessary

on a small dose of prednisolone, which should be continued until the reaction subsides.

Experts particularly concerned with field programmes consider that in general the attention given to reactions in the field is not satisfactory.

To effect an improvement it is considered necessary to provide better training in the recognition of reactions so that field workers may be able to undertake appropriate and early action. It is also necessary to organize a better system for the referral of cases to hospitals and institutions. Wherever possible, local district hospitals should be involved in the management of many of these acute cases.

2.7 Release from control of inactive cases

No changes are proposed in the criteria for the release from control of inactive cases.¹ The Committee strongly recommended that inactive tuberculoid and indeterminate cases be promptly released when they meet the criteria. This action is not only in the interest of the patients but has an important bearing on operational efficiency and would release resources for other activities of the programme.

2.8 Relapse

The earliest possible detection of relapse is important both to the individual patient and to the leprosy programme. Relapse may be due to the reactivation of the disease because of inadequate treatment (resulting in the multiplication of persistent organisms), to the emergence of drug-resistant bacilli, or possibly to reinfection in patients incapable of producing a sufficient degree of cell-mediated immunity.

The clinical signs of relapse—whatever the cause—are similar. Their appearance is usually preceded, perhaps by several months, by evidence of bacillary multiplication in the dermis and perhaps also in the nasal mucosa. Hence the importance of examining smears from patients treated for multibacillary forms of leprosy on every occasion when they return for control after clinical and bacteriological inactivity has been attained and whether or not they are still taking antileprosy drugs.

Whenever relapse is suspected, the auxiliary should immediately inform his supervising officer, who will take urgent steps to establish its cause. A distinction should be drawn between clinical relapse and bacteriological relapse in lepromatous patients who have been bacteriologically negative for a time. A distinction should also be made between

¹ WHO Technical Report Series, No. 459, 1970, section 2.15.

the finding of a very small number of fragmented leprosy bacilli in the smears of a patient who has recently become smear-negative (a finding explicable on the basis of random sampling) and the reappearance of significant numbers of leprosy bacilli, including solid-staining bacilli, resulting from the renewed multiplication of *M. leprae*.

2.9 Prophylaxis by BCG and chemoprophylaxis

In Uganda, among intrafamilial child contacts, the protective value of a single dose of BCG was reported to be as high as 80%. In a trial in Karimui, Papua New Guinea, in which the whole population received repeated BCG vaccination, the protection achieved was 43%. In the WHO antileprosy BCG trial in Burma, to which the whole child population was admitted and in which (unlike the situation in Uganda) there has been no significant decline in the incidence of leprosy in the control group, the vaccinated group showed a protection rate of about 15%. Moreover it is noteworthy that 10 histologically confirmed multibacillary cases were diagnosed during 1974–75 in the Burma trial. Three were found in the vaccinated group (1 L, 1 BL, 1 BB) and 7 in the control group (2 BL, 1 BB, 3 L, 1 B). The fact that infectious forms have now appeared in the vaccinated group indicates the limited value of this measure. However, it is not clear whether any protection should be expected more than 5 years after vaccination.

It is considered that the position taken by the WHO Expert Committee in 1970 and restated at the International Leprosy Congress, Bergen, Norway, in 1973—that it is not yet possible to recommend BCG as a specific prophylactic measure for the prevention of leprosy—must be upheld. However, taking into account the protective values of BCG vaccination found in the Karimui trial in Papua New Guinea, the Mandalay area in Burma, and the Uganda trial,¹ the Committee recommended that programme managers should ask the vaccination services to apply BCG vaccination to areas known to have high prevalence rates of tuberculoid leprosy. This would take advantage of the protective effect that BCG may have against tuberculoid forms of leprosy owing to its possible enhancement of resistance, whether specifically or non-specifically. Vaccination cannot be regarded as an alternative to active case-finding. Those responsible for the planning and evaluation of control measures and who use BCG vaccination are requested to follow up detection rates carefully for periods of at least 10 years and to publish the results.

¹ WHO Technical Report Series, No. 459, 1970, section 3.2.1.

There is evidence from trials in India, Kenya, the Republic of Korea, and the USSR that the prolonged administration of dapsone to a child exposed to leprosy infection within the household will considerably reduce the risk of his subsequently developing the disease. The results from a WHO-assisted prophylactic trial in the Philippines are less convincing. The uncontrolled variables, such as the infectivity of the index case, the duration and degree of contact, and the unknown immunological susceptibility of the subjects, render comparisons difficult.

In certain circumstances, there may be a limited place for the administration of prophylactic dapsone. However the administrative, financial, and medical problems (including the slight but definite incidence of drug toxicity) must be borne in mind, especially when treatment is being given to perhaps only one in five leprosy sufferers. Moreover, there is uncertainty about the duration of the proposed prophylactic regimen, and it is not known whether an individual contact would take treatment regularly. In view of all these factors, the Committee could not recommend the use of dapsone as a prophylactic in large-scale control programmes.

The problem of irregular treatment is overcome by the use of acedapsone. Russell and his co-workers¹ have shown that, in a circumscribed community in which the disease was endemic, the risk of developing leprosy was reduced to zero by the regular administration of the drug for 3 years. However, a small number of new cases began to appear when the prophylactic regimen was completed. Two of these cases were child contacts of a dapsone-resistant patient. Furthermore, as acedapsone produces only low serum concentrations of dapsone (50 ng/ml), the attendant risk of the emergence of sulfone-resistant bacilli in those receiving the drug cannot be ignored.

3. THE FORMULATION AND MANAGEMENT OF A LEPROSY CONTROL PROGRAMME

It is possible to demonstrate the efficacy of some well organized national leprosy control programmes, which have supported a sustained effort for one or two decades. On the other hand, the progress in many other leprosy control programmes has been disappointing, mainly because of failure to define the true magnitude of the problem or to

¹ RUSSELL, D. A. ET AL. *International journal of leprosy*, **44**: 170-176 (1976).

provide a true estimate of the level of the human and financial resources required, and the period of time for which they were required, to attain the programme objectives.

Before embarking on renewed efforts in leprosy control, governments should first decide on the priority to be assigned to leprosy within their other public health commitments. This decision has to be based on a realistic appreciation of the magnitude of the problem as well as on the resources required to achieve a solution.

Therefore the planning and programming of leprosy control measures are essential. And since countries afflicted by leprosy have many other public health problems, it is very important that leprosy activities be combined as much as possible with other health activities in order to improve the cost/effectiveness ratio of the leprosy programme.

Criteria that have to be considered in assigning leprosy its correct priority include not only its prevalence and incidence but also in leprosy disease its life-long duration, the disabilities it causes, the subsequent family and social problems, the prejudice against the leprosy patient and his or her family, as well as the amount of human suffering.

Since the proper training of all categories of personnel involved is the main factor on which the quality of a leprosy control programme will depend, due consideration must be given to the training requirements at all stages of the planning and programming process. In view of the critical importance of this process in the development of a sound leprosy control programme, those responsible for such a programme should be trained in planning and programming techniques.

3.1 Aims and objectives

The general aims of leprosy control are to protect the healthy population, to bring about a reduction of the infection in the human reservoir by effective chemotherapy, and to provide adequate early treatment for all detectable cases, so avoiding the possible disabling sequelae of the disease.

In leprosy control there are three basic principles.

(1) Coverage of the whole country should be a general objective, although varying prevalence rates may justify the fixing of priorities by area.

(2) Resources should be allocated over a 20-year period, if a significant impact on the disease is to be made, particularly in view of the chronicity of the disease and the limited effectiveness of present strategies.

(3) Control measures should be developed as an integral part of the general health services, which should be strengthened as necessary, and where a health service is being introduced into any area leprosy control measures should form part of the programme from the beginning.

Leprosy control measures should provide for an intensive health education programme in the community, the development of a system of active case-finding aimed at early diagnosis and treatment, and the promotion of a system of surveillance of persons at special risk in order to maintain a constant assessment of the leprosy situation in the endemic area.

Goals must be expressed quantitatively in terms of time and results and should relate to specified areas.

3.2 Problem identification and quantification

The size of a country's leprosy problem may remain unappreciated for a long time. Attempts to estimate the total number of cases will require wide-ranging investigations of the records of hospitals, health care units, and medical agencies and assiduous questioning of local government officials and village leaders. The results of such inquiries may direct attention to areas where more detailed investigations should be undertaken. School surveys or child surveys are valuable in areas of high prevalence.¹

Random sampling surveys of an area can provide very useful baseline epidemiological data, permitting estimates of overall prevalence and age-specific rates.

Case-finding programmes are often less effective than might be expected. Random surveys in a number of countries have shown that even in apparently good case-finding programmes as many as 75% of cases may remain undetected.

The four commonly used indicators for delineating the nature of the endemicity in a given area are :

- (1) the overall prevalence rate,
- (2) the lepromatous prevalence rate,
- (3) the proportion of the different forms of leprosy,
- (4) age-specific rates.

¹ BECHELLI, L. M. ET AL. *Bulletin of the World Health Organization*, 48 : 502-503 (1973).

3.3 Planning and programming

In essence, programme and project formulation provides a logical process for ensuring a full examination of the current epidemiological, operational, and administrative problems. It also enables a plan to be devised to meet and satisfy these problems. The process is shown diagrammatically in Fig. 1 and 2. It is shown as a linear step-by-step process, but in fact it tends to be rather more circular ; as the planner works along the process he must continually refer back to and modify the operational methods of earlier stages to ensure attaining the objectives of the plan. The inherent objectives of this type of programme/project formulation are :

- (1) to relate the programme or project objectives positively to the leprosy problem ;
- (2) to ensure that the planned objectives and targets are consistent with available resources ;
- (3) to provide a management plan that relates the operational activities to the technical strategy for attacking the problem of leprosy control ;
- (4) to provide a mechanism for monitoring the progress of the plan.

In some countries where new control programmes or extensions of programmes are being planned it would be desirable to develop an operational preprogramme study in a limited area, to evolve a suitable organization for control measures in the context of the local epidemiology, stage of development of the health services, and the available resources and manpower.

Since any effective plan will be spread over a number of years, it is imperative that it should be regularly reviewed in the light of changing circumstances. This will allow periodical and appropriate modifications to be made so that the plan can function continuously as an effective managerial guide throughout its duration.

3.3.1 *Resources and constraints*

In the short- and long-term planning of a leprosy programme, divers constraints may be encountered.

One of the most important of these is the attitude of the individual patient and the community to leprosy. The degree of stigma varies greatly in different cultures and is largely associated with the physical deformities occasioned by leprosy. No programme for leprosy control, however well conceived, that fails to take cognizance of these attitudes

Figure 1
Concept formulation

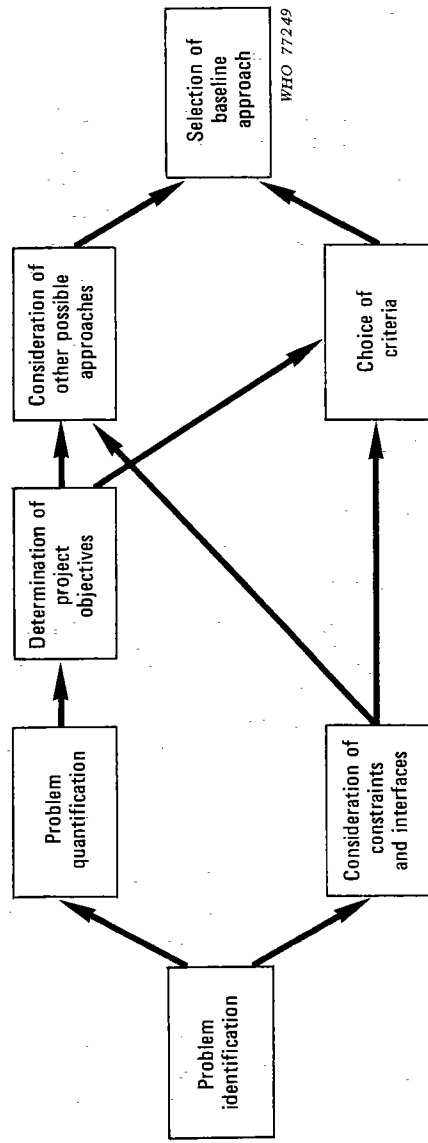
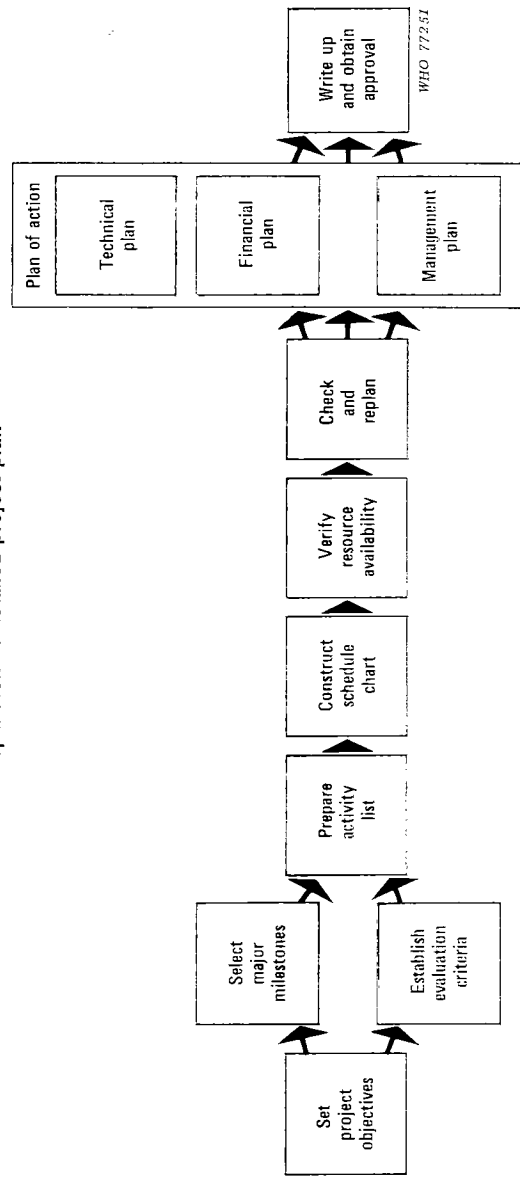


Figure 2
Preparation of detailed project plan



and beliefs will be successful in the long run. It is most important to obtain the informed support of doctors, health administrators, and community leaders. National voluntary organizations may render valuable help in this direction, and village health committees may take a lively interest in leprosy patients, accepting them, and encouraging them to take treatment regularly.

Geographical constraints such as limited resources, a tropical climate, and poor communications may make it difficult to give assistance to important population groups. Where the distribution of leprosy is uneven or in pockets, it may be a problem to allocate resources to the different areas covered by a national leprosy control programme.

Legislative constraints may exist in some countries and the Committee wished to reaffirm the statements made in the fourth report,¹ which should be given serious consideration by governments: "Any special legal measures that might increase prejudice against leprosy and prevent early cases from presenting themselves for diagnosis and treatment should be abolished". It was the Committee's view that "no special legislation is necessary and that the legal measures applicable to chronic communicable diseases should also be applied to leprosy".

Interfaces

There are numerous possibilities for technical cooperation between governments and multilateral, bilateral, intergovernmental, and voluntary agencies. Besides the national resource allocations such as manpower and finance, international agencies such as UNICEF may cooperate in providing material assistance, particularly in the form of drugs, equipment, and possibly transport, in response to government requests. Other sources of funding may be sought from international and bilateral agencies, as well as voluntary bodies, for particular needs. The contributions to leprosy control made by voluntary agencies may represent a most important resource, especially when they support ambulatory services. The search for additional resources from voluntary organizations within the country should be encouraged.

Role of voluntary bodies in national leprosy programmes

In a number of countries, voluntary agencies make an important contribution to the care of leprosy patients. A large proportion of leprosy

¹ WHO Technical Report Series, No. 459, 1970, section 2.12.

patients at present being taken care of are treated through voluntary agencies. Of recent years, the activities of voluntary agencies have been steadily extended to leprosy control with systematic case-finding, early diagnosis, and conscientious ambulatory treatment. There is now a general appreciation among voluntary agencies seeking to help leprosy patients that their action should be an integral part of, or closely coordinated with, government programmes.

With their flexibility and initiative, voluntary agencies are able to introduce new approaches in leprosy treatment and control in the light of their concern for the social components of the disease. Full advantage could be taken of their training experience, literature, and inpatient facilities both in general hospitals and in hospitals specially catering for leprosy sufferers.

Voluntary agencies can provide a valuable contribution to the development of the general health services, especially in the early stages of development of rural and urban health facilities. An already established voluntary agency hospital, which is fulfilling the functions of a district or local hospital, may provide some primary health services, including leprosy control, for an area designated by the health authorities. The mode of organization and cooperation would need to be worked out locally.

Voluntary agencies can frequently initiate and develop certain aspects of an antileprosy service, e.g., specialized physiotherapy units, workshops for prostheses, and re-education centres for handicapped patients—which some governments cannot fully provide at present. These, however, should: (1) be developed as part of the facilities for all suitable patients, (2) not become so elaborate or expensive that they cannot be incorporated into the government's programme if and when desirable, and (3) serve as training centres wherever possible.

Continuous consultation between the health authorities and voluntary agencies should be encouraged.

In the light of present-day insistence on the need for primary health care, voluntary agencies could continue to provide experience and facilities for the training of community workers.

It is suggested that in the present climate of change, when national health authorities are developing long-term plans for basic health services with some simple form of comprehensive primary care at the village level, it would be appropriate for voluntary agencies to seek to pattern their own services on those of the government.

3.3.2 Selection of programme delivery

Situational analysis

The consideration of alternative approaches to the delivery of the leprosy programme depends on a careful situational analysis. The information should include : (1) detailed descriptions of the geographical features of the area of operations, (2) demographic statistics such as population distribution and age and sex distribution ; (3) data on the health situation, such as the morbidity of the most prevalent diseases and the general structure of the health services and coverage of the population, and (4) a summary of the nature and extent of nongovernmental services, general practitioners, voluntary agencies, and local healers to whom the people resort.

Operational procedures

Case-detection. In considering case-detection, an appreciation of the feasibility and acceptability of each method is essential, together with a careful assessment of its costs in terms of money, personnel, and other resources.

In all areas where leprosy is endemic, the disease should be detected by active methods of case-finding. It should be recognized that in most parts of the world case-detection will be performed by auxiliary workers, whether or not the diagnosis is confirmed by doctors.

The possible methods of case-finding include total population surveys, selective surveys, contact surveys, and school surveys.

Total population surveys should ideally be made in areas of high prevalence. However, in those areas where it is possible to create awareness of the disease and of its treatment, organized and well chosen health education programmes should be undertaken to encourage voluntary reporting.

In all areas in which leprosy programmes operate, contacts should be regularly examined. School surveys should also be carried out periodically to detect early cases, especially in areas in which prevalence in children is thought to be high.

Treatment delivery. A situation in which patients are required to maintain treatment for many years may lead to a loss of motivation, especially to attend a clinic regularly, and the problem is further compounded by the risks of developing sulfone resistance if treatment is inadequate or irregular.

An associated grave problem in leprosy control is unsupervised self-administered therapy in countries where the health infrastructure is rudimentary.

Three main issues are involved in treatment delivery—whether to treat selected cases or to provide treatment for all ; how to improve the attendance of patients for treatment ; and whether to introduce supervised or intermittent treatment. No obvious and standard solution to these issues is possible under the great variety of field conditions prevailing in developing countries. However, those responsible for leprosy control activities must be aware of the problems and must work out the most suitable methods of ensuring the utmost regularity of treatment. Some practical suggestions are made in the following paragraphs.

(1) In the selection of cases, priority should be given to the regular treatment of bacteriologically positive cases.

(2) The improvement of patient attendance at treatment centres depends to a large extent on health education, which is crucial to the whole problem of leprosy control. Nevertheless it would be unrealistic to expect leprosy patients in endemic areas to have a higher sense of concern over treatment than that displayed by patients under treatment for a chronic condition (e.g., diabetes) in industrialized countries. The following operational factors that could contribute to improvement are advocated :

- involvement of all general health units in treatment ;
- greater use of voluntary workers at village level to provide support to patients ;
- better supervision of the basic worker who is responsible for primary leprosy care ;
- more frequent clinical reviews by doctors or senior supervisors ;
- fixed clinics with mobile workers ;
- full primary health care for leprosy patients ;
- timely release from control of those patients who no longer need treatment ;
- provision of simple rehabilitation ;
- provision of training centres for all levels of leprosy control programme staff ;
- provision of laboratory facilities for the monitoring of drug ingestion by the testing of random urine samples for the presence of dapsone.¹

¹ ELLARD, G. A. & GAMMON, P. T. *Leprosy review*, 45 : 224–234 (1974).

(3) The question of directly supervised or intermittent therapy is subject to the following considerations. In the chemotherapy of leprosy with dapsone, the serum levels are maintained satisfactorily by daily oral administration of the drug. In some programmes patients have been required to attend a treatment centre once or twice weekly so that the tablets can be administered directly. Some doubt is expressed about giving a once-weekly oral dose but twice-weekly treatment has experimental support. In some areas efforts should be encouraged to organize a weekly clinic for the lepromatous cases in which the main dose of dapsone (say 200–400 mg) is given under supervision on the day of the visit and a smaller dose (say 200 mg) is administered during the week by the patient himself.

Where operational limitations prevent the patient being seen more than once every two or three months, intermittent treatment by the injection of 225 mg acedapsone at 75-day intervals is justified, together with daily oral doses of dapsone (6–10 mg/kg body weight per week) administered by the patient himself.

General health services, specialized services, and combined services

The value of integrated services is unquestioned. However, in many countries leprosy control has developed separate operational structures with specialized personnel, and the fusing of leprosy control with other services is fraught with difficulties, which are less administrative than attitudinal. Since leprosy control does require an active case-finding programme, special provision may have to be made initially for uni-purpose or multipurpose staff to engage in leprosy case-detection.

In some countries it may be convenient and economical to use specialized field personnel to undertake combined programmes of tuberculosis or other disease control programmes and leprosy. These combined programmes would be aimed at the eventual integration of all activities with those of the general health services. In such situations the fundamental need would be the training of health workers capable of handling multipurpose programmes.

3.4 Implementation and management

3.4.1 Manpower training and deployment

When a country has a leprosy problem, all professional and auxiliary staff in their basic training should be given an understanding of the disease. The implementation of a disease control scheme will call for more specialized knowledge.

It is important to appreciate that as staff are being prepared to participate in leprosy control, which has long-term goals, they should be able to expect eventually a permanent place within the general health service. The recruitment of doctors for technical and supervisory services represents a more difficult problem, although the overall direction of the project should have the technical guidance of a doctor with specialized training.

It is essential to fix the case load of the leprosy control worker according to the local situation. Workers should be able to fulfil the targets set annually for contact surveillance, the examination of school-children, and health education. In setting targets, it is assumed that patients are seen on average once a month, even though the actual frequency of attendance must be decided by the individual patient's needs.

Special training needs to be arranged for laboratory workers and assistant physiotherapists working in the field. Schools of medicine, nursing and public health are encouraged to incorporate the subject of leprosy control into their teaching programme.

3.4.2 *Supervision*

Supervision entails regular monitoring and control of the operational output, i.e., of the critical activity provided by the service. For instance, the project manager is responsible for seeing that the project objectives are achieved on time and within the budget. Activity managers (intermediate supervisors) are responsible for the timely fulfilment of individual activities and will need to undertake regular field visits.

The range of programme supervision, according to the level of the supervisor, stretches from logistics (such as drug provision, transport requirements, and maintenance of equipment) to the proper management of patients and their treatment. Regular annual clinical reviews of each patient's progress should be an essential function of senior field officers.

Another important activity is health education, although it has no measurable characteristics that allow operational (output) targets to be fixed. The best measures of success of the health education programme will be the high regularity of patients for treatment and the close correspondence of the case-detection rates (and attendance for treatment) and the true incidence ascertained by surveys.¹

¹ See also : WHO Technical Report Series, No. 459, 1970, section 2.9.

3.4.3 Expenditure

The economics of primary health care, including leprosy control, is determined by the benefit to the "consumer"—the patient and the healthy population to be protected—and by the service costs.

For the measurement of costs, expenditure can be subdivided into capital expenditure on facilities and durable goods (such as vehicles) and recurring expenditure on personal services, salaries, training activities, etc.

Care should be taken to ensure that lower costs do not mean loss of quality or the reduction of effectiveness of a programme below a critical level. Technical advances in many instances imply increased costs which have to be balanced against increased effectiveness. This, in leprosy, applies particularly to the use of new and expensive drugs and drug combinations.

3.5 Evaluation measurements

3.5.1 Milestones and output targets

A milestone is a critical event that signals the completion of one or more sequences of activities or permits the commencement of a new sequence. Examples of milestones are: "project budget approved", "case estimate completed", "required transport available", and "a specified number of primary health care workers have received training in leprosy control activities".

Milestones must be a built-in feature of the plan from the outset.

Operational targets may be on case-detection activities, on treatment regularity, or on the monitoring of bacteriological smears. An example of such a target might be the statement: "Registration of 50% of the estimated lepromatous and borderline cases and of 20% of the estimated tuberculoid and indeterminate cases by the end of the second year. At the end of the fifth year—75% of lepromatous and borderline, 50% of tuberculoid and indeterminate. At the end of the tenth year—85% of lepromatous and borderline, 60% of tuberculoid and indeterminate."

The determination of such targets must go hand-in-hand with the initial resource allocation and may be feasible in a defined area only. Another example of an operational output target is: "The criterion of regular treatment is the taking of 75% or more of the treatment prescribed."

3.5.2 Monitoring of bacteriological smears

The organization of an efficient service for the taking of slit skin smears and their processing is a necessity for a leprosy control service.

Routine smears of bacteriologically positive cases performed annually should be mandatory.

Arrangements should be made for the regular training and supervision of laboratory workers and for the checking of their equipment by senior staff preferably from public health laboratories.

3.5.3 *Operational indicators*

The strategy for leprosy control, as recommended by the WHO Expert Committee and the International Leprosy Congress, may be summarized as follows :

- (1) earliest possible detection of the largest possible number of patients ;
- (2) proper treatment (early, regular, adequate, and of sufficient duration) of the greatest possible number of patients.

Patients with the lepromatous form, who have a higher transmission potential, are regarded as the priority target group for the application of these procedures.

There are a number of indices for evaluating the efficiency of programmes based on these principles. The following indices are recommended, taking into account a review by Bechelli and Martínez Domínguez.¹

(1) Coverage and intensity of detection ; early detection. The extent (completeness) of case-finding involves two factors—the proportion of the population actually reached by case-finding activities (coverage rate) and the intensity of case-finding within this segment of the population (detection rate). The population reached by case-finding activities may be limited geographically or restricted to specific population groups (children, contacts, workers, etc.). In all cases, a knowledge of the size of the population covered is needed to calculate these rates.

Unless thorough pilot studies are available for use as a reference, it is not possible to know how complete the case-finding is. The detection rate is therefore mainly useful in equivalent epidemiological situations—e.g., for comparing the “ yield ” of activities in different sectors of the same region during successive periods or in different population groups. It will be particularly useful for evaluating staff performance.

The detection rate is expressed in relation to a given period of time such as a year or in exceptional cases the duration of a specific operation.

¹ BECHELLI, L. M. & MARTÍNEZ DOMÍNGUEZ, V. *Bulletin of the World Health Organization*, **42** : 631–634 (1970).

It is useful to compare the yield of the different case-finding methods employed (e.g., routine examination of entire population, passive case-finding, examinations in schools, examinations in dermatology clinics). The mode of detection of each patient should therefore be recorded. The detection rates per population group can also be derived from this information.

The average interval between the onset of the first symptoms and signs and the detection of the case is difficult to assess, except in the case of mass routine examinations conducted at short intervals. The *disability rate among new cases* permits an indirect assessment of the delay in detecting the disease by providing a measure of the number of old cases that escaped case-finding. In an efficiently conducted programme no new case with irreversible disabilities should be detected and a thorough investigation should be made of any newly found disabled case.

The *proportion of cases with single lesions* among the newly detected cases of tuberculoid leprosy provides an important indication of early detection.

The proportion of lepromatous subjects among the total number of patients detected is interesting to follow over the years. During the first few years of a leprosy control programme this proportion is generally high and then gradually declines.

(2) Treatment. The *treatment coverage rate* should approach 100% ; all active patients registered should be located and signed on at a treatment centre.

The *treatment attendance rate* refers to the percentage of treatment sessions attended by the patient in one year. Criteria of attendance were defined in the fourth report of the WHO Expert Committee on Leprosy.¹

The *annual treatment defaulting rate* indicates the number of patients who default from treatment each year in relation to the number of patients under treatment. This rate requires the definition of defaulting from treatment in terms of the number of sessions missed, whether consecutive or not. The annual treatment resumption rate shows the number of defaulting patients who resume treatment each year. The denominator, which relates to the number of patients not under treatment, is often difficult to determine.

The *dose administered as a percentage of the dose prescribed* provides an indication of the efficiency of treatment activities.

¹ WHO Technical Report Series, No. 459, 1970, section 2.6.

The *annual inactivation rate* relates to the number of treated patients who become clinically inactive each year, according to the definition of inactivity given in the fourth report of the WHO Expert Committee on Leprosy.¹

The *annual bacteriological conversion-to-negativity rate* reflects the number of bacteriologically positive patients who have become bacteriologically negative during the year.

The *annual relapse rate* refers to the proportion of inactive patients under surveillance who present a reactivation of the disease during the year. Care should be taken to define the denominator of patients at risk of relapse, since the selective inclusion or exclusion of certain categories of patients such as those lost sight of, dead, or at special risk may bias the rates.

3.5.4 *Epidemiological evaluation of leprosy programmes*

Incidence, or the number of new cases occurring during a given period (generally one year) in relation to the population, is the only index for measuring the efficacy of the measures taken, i.e., the reduction of transmission.

The continued occurrence of new infections in children is of great epidemiological significance as it indicates continuing transmission of the disease. In such cases it is useful to separate the incidence rates for children and adults.

Changes in prevalence are only indirectly indicative of the impact of a programme on the epidemiological situation. However, the total number of patients to be treated needs to be known for planning and organizational purposes.

Leprosy control activities should be based on an information system permitting :

- (1) evaluation of the efficiency of the programme within the context of established strategies and norms ;
- (2) evaluation of the effectiveness of leprosy control methods with regard to the reduction of the problem from the epidemiological viewpoint and, if appropriate, from the social and economic viewpoints ;
- (3) evaluation of the efficacy and productivity of certain programme components, e.g., results of therapy and identification of high-risk groups in order to increase case-finding rates.

¹ WHO Technical Report Series, No. 459, 1970, section 2.15.

The information collected should be simple and capable of leading to decisions (strengthening of compliance with the norms, increase in activities, change of strategy, adjustment of norms, shift of priorities, etc.). It should be of a kind that can be collected directly by the staff responsible for health activities at the peripheral level, who are not necessarily specialized in leprosy.

At present there is a need in many control programmes for evaluation of the existing epidemiological situation. The Committee recommended that such evaluation be undertaken by means of sample surveys that include an assessment of the numbers of still undetected cases of leprosy.

4. RESEARCH

4.1 Review of some recent advances

Important areas of progress made during the past five years have been referred to earlier in this report. They may be summarized as follows.

(1) The identification of two major problems related to chemotherapy, namely, dapsone resistance and microbial persistence (see section 2.6.1).

(2) The establishment of rifampicin as a potent antileprosy drug.

(3) The indication, from new evidence, that nasal discharge from lepromatous patients represents an important source of infection and that immunological conversion takes place in a large proportion of leprosy contacts (see section 1.2).

(4) The development of an epidemiometric model. Such models may be of value as tools for planning and in evaluation of control programmes. The present model reveals the long duration needed before the impact of a control programme on disease incidence can be observed.¹ Other areas in which important progress has been made are described in the following paragraphs.

4.1.1 *Transmission to experimental animals*

The mouse foot-pad infection remains the most convenient method for the screening of new drugs against *M. leprae* and the laboratory

¹ LECHAT, M. F. ET AL. *Bulletin of the World Health Organization*, 51 : 361-373 (1974).

detection of drug resistance. However, the mouse cannot generate large quantities of *M. leprae*. The discovery of the armadillo as a species highly susceptible to *M. leprae* infection has complemented the mouse in this respect. However, the use of the armadillo has not obviated the need for more studies to achieve *in vitro* cultivation of *M. leprae*.

Stringent precautions should be taken in laboratories in which work is carried out on infected armadillos.

4.1.2 *Mechanism of host resistance to intracellularly growing bacteria*

Immunity to intracellular parasites like *M. leprae* depends on cell-mediated immune mechanisms. The carriers of this immunity are thymus-dependent lymphocytes (T-cells). However, T-cells themselves are not able to kill the parasite directly but act through another host cell, the mononuclear phagocyte (macrophage). At least two mechanisms are involved in this cell-to-cell collaboration—macrophage activation and macrophage mobilization. This concept may explain why in leprosy the degree of host resistance is generally reflected by the content of lymphocytes in the lesions while the leprosy bacillus resides inside macrophages. It is also in agreement with the finding that when macrophages in lepromatous patients are activated locally by nonleprosy antigens they also reveal increased elimination of *M. leprae*.

4.1.3 *Classification for research purposes*

For various research purposes, such as drug trial programmes, there is a need for detailed histopathological examination and classification. The Ridley-Jopling classification, which corresponds to the degree of host resistance to *M. leprae*, would appear to be the most suitable for research purposes.

4.1.4 *Nature of the immunological defect in lepromatous leprosy*

The defect in cell-mediated immunity shows specificity to antigens of *M. leprae*. The defects so far observed have been located in the T-cell compartment of the immune system. The origin of the defect remains unknown. The sole involvement of genetic factors seems unlikely. The possible role of environmental factors needs clarification.

4.1.5 *Genesis of tissue damage*

Adverse effects of immune responses to *M. leprae* appear to play an important role in the development of tissue damage. In tuberculoid and

many borderline leprosy patients, cell-mediated immunity plays a major role in nerve damage. In erythema nodosum leprosum the deposition of immune complexes in the tissue appears to be involved. The mechanism of the slowly progressive nerve damage in lepromatous leprosy remains largely unknown; histologically, these lesions are degenerative in nature.

4.1.6 *Lepromin*

In view of the worldwide shortage of readily available leprosy-infected human tissues, studies have been carried out with lepromin derived from tissues of infected armadillos. The studies indicate that armadillo-derived lepromin gives results similar to human lepromin. Although there is no evidence that "crude" armadillo lepromin produces adverse effects, the Committee considered that, since more refined preparations can now be made, their use in future studies should be encouraged.

4.2 Recommendations for future research priorities

Leprosy control remains hampered by gaps in knowledge about the epidemiology of the disease, by limitations in the available control measures, and by logistic difficulties. Research at all levels therefore remains a component of high priority in the overall antileprosy strategy.

The Committee noted with satisfaction the renewed interest in research in leprosy and the initiative taken by WHO in this field at both central and regional levels, and it recommended that appropriate mechanisms should be set up to ensure optimum coordination at country, regional, and central levels. Moreover, in discussing possible ways of improving the effectiveness of leprosy control programmes, the Committee noted the need for closer coordination of research efforts at basic, epidemiological, and operational levels. This requires an increase in the research potential of countries in which leprosy is a problem.

4.2.1 *Chemotherapy*

In view of the threat posed by the emergence of dapsone resistance and the low number and high costs of alternative drugs the Committee made the following observations.

(1) Research on the development of antileprosy drugs should be strengthened by seeking the cooperation of research institutes and the pharmaceutical industry.

(2) There is an urgent need for controlled clinical trials of combined chemotherapy in multibacillary leprosy—both short-term trials to establish the toxicity of the regimens and long-term trials to study (a) the incidence of drug resistance developing on different regimens and (b) whether rates of persisters can be reduced by any drug combinations, thereby allowing the period of chemotherapy to be shortened (see item 4 below).

(3) There is an urgent need for controlled clinical trials of combined chemotherapy in confirmed cases of dapsone resistance in order to establish the most effective regimens.

(4) Nonlepromatous patients represent a large workload in leprosy control programmes. The duration of treatment needed in such patients remains virtually unknown. If short-term effective drug regimens could be found, they would be likely to have a very significant impact on the morale of patients and their regularity of treatment, as well as on the cost/effectiveness of control programmes.

(5) The most effective methods of detecting early relapses, especially those due to dapsone resistance should be established—i.e., the relative importance of clinical examination, bacteriological examinations (including examination of nasal mucus), and histopathology.

The Committee welcomed the initiative being taken by WHO in establishing a special programme in this research area and expressed its appreciation of the memorandum¹ published by members of the Committee on Experimental Chemotherapy of the tenth International Leprosy Congress, which was held in Bergen, Norway, in August 1973.

4.2.2 Immunology

Vaccine development. The use of the armadillo as a species susceptible to *M. leprae* may be of assistance in the search for an effective antileprosy vaccine since it will provide large quantities of *M. leprae* for immunological investigations (e.g., immunochemical characterization, experimental sensitization) and taxonomic studies.

However, the Committee noted that research in this area is unlikely to provide a specific antileprosy vaccine in the immediate future in view of the number of stages involved in the development of such a vaccine.

Development of immuno-epidemiological tests. The ability to obtain mycobacteria from the armadillo provides new opportunities for devising

¹ *Bulletin of the World Health Organization*, 53 : 425-433 (1976).

methods of detecting immune responses to *M. leprae* under field conditions. It is hoped that practical tests will result from the various lines of investigation at present being pursued, but the specificity and sensitivity of the tests await clarification.

Immunotherapy. Various approaches to immunotherapy have recently been pursued in leprosy.

The induction of a cell-mediated immune response to *M. leprae* in treated lepromatous leprosy remains an important goal, since this may well be the only way of enabling such patients to control microbial persistence, allowing a safe release from leprosy control.

The results reported have been of a preliminary nature and are to some extent conflicting. Promising results have been obtained with thymosin in enhancing resistance to mycobacterial infection in T-lymphocyte-depleted mice. However, these results cannot be extrapolated directly to clinical leprosy.

The Committee recommended that much further work should be undertaken and welcomed the interest shown in immunotherapy by many investigators.

Microbiology. The *in vitro* cultivation of *M. leprae* remains a target that, if reached, would be likely to have a strong impact on most areas of leprosy research and ultimately on control. The Committee recommended that investigators in this field should use the present available methods for identification of *M. leprae*.

Epidemiological and operational research. These two areas of research are closely related and are therefore considered together. It should be recognized that data collection for research purposes usually provides little information unless the data collection system is designed to answer specific questions. There is a need for simple standard forms to be used by the primary health worker. The kind of information needed in specific areas of epidemiological and operational research is summarized below.

(1) Epidemiology of dapsone resistance. It would be useful to know the size of the problem in different parts of the world and the factors that influence the emergence of dapsone resistance—e.g., irregularity of treatment, dose of dapsone given. These factors should, if possible, be quantified in practical terms. The relative infectivity of sulfone-resistant lepromatous patients as compared with untreated sulfone-sensitive ones should be measured.

(2) Epidemiology of multibacillary leprosy. It is important to determine the proportion of persons with lepromatous leprosy who

discharge bacilli before they develop clinical signs of the disease. Further information from different areas of the world is needed on the effectiveness of the detection and treatment of early leprosy (especially of indeterminate leprosy) in reducing the incidence of lepromatous cases.

(3) Epidemiology of reactions. Reactions represent an important mechanism of nerve damage and thus of deformity. More precise information is needed both on their pathogenic mechanisms and on the early signs of severe reactions in order to permit their early diagnosis and treatment before significant nerve damage has been caused. More information is also required on the impact of the early detection and treatment of leprosy on the subsequent incidence of reactions.

(4) Surveillance of contacts. Contacts of index cases of leprosy represent a high-risk group. Further statistical support is required on the length of time they should be kept under special surveillance after the index case has been put on treatment.

(5) Epidemiology of immunodeficiency to *M. leprae*. In view of the present limitations of knowledge in this field (see section 4.1.4), epidemiological studies on the role of genetic and environmental factors are needed.

(6) Transmission. The Committee stressed the need for further information on the transmission of the disease and noted that epidemiological investigations relating to cases imported into nonendemic countries may provide important information, as secondary cases appear to be exceedingly rare in such countries.

(7) Identification of high-risk groups. Epidemiological studies should be directed at the identification of high-risk groups. Risk-factor studies would be facilitated by the development of specific diagnostic tests.

4.2.3 *Development of simplified technology for leprosy control programmes*

An attempt should be made to develop standard techniques for bacteriological examinations, etc., that will allow proper comparison to be made between different programmes.

With regard to the morphological index (see section 2.2), more reliable methods should be developed for assessing the proportion of

viable organisms in smears. Simpler methods for analysing urine for dapsone content are also required, and there is a need for methods applicable in the field for the detection of immunological conversion to *M. leprae*.