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No. 71

EXPERT COMMITTEE ON LEPROSY

First Report

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WORLD HEALTH ORGANIZATION

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SEPTEMBER 1953

EXPERT COMMITTEE ON LEPROSY

First Session

Rio de Janeiro and São Paulo, 10-19 November 1952

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- Dr. R. Chaussinand, Division of Communicable Disease Services, WHO (*Secretary*)
- Dr. Y. Biraud, Director, Division of Epidemiological and Statistical Services, WHO

The report on the first session of this committee was originally issued in mimeographed form as document WHO/Leprosy/16 Rev. 1, 20 April 1953.

EXPERT COMMITTEE ON LEPROSY

First Report¹

The Expert Committee on Leprosy met for its first session at Rio de Janeiro from 10 to 15 November and at São Paulo from 17 to 19 November 1952.

Dr. Arlindo de Assis, Director-General of the National Department of Health, welcomed the members of the committee on behalf of the Minister of Education and Health of Brazil.

Dr. Y. Biraud, as representative of the Director-General of the World Health Organization, thanked the Brazilian authorities for the invitation conveyed on their behalf by Professor Manuel Ferreira to the Fifth World Health Assembly for the committee to hold its first session in Brazil.

The committee elected Dr. H. W. Wade, Chairman, Dr. L. de Souza Lima, Vice-Chairman, and Dr. J. N. Rodriguez, General Rapporteur.

The committee further requested some of the experts to act as special rapporteurs for the sections of its report towards the preparation of which they had contributed basic papers: Dr. Dharmendra (section 1), Dr. E. Muir (section 2.1), Dr. N. Souza Campos (section 2.2), Dr. L. de Souza Lima (section 2.3), Dr. J. Lowe (section 3.1), Dr. R. Chaussinand (section 3.2 and section 4), Dr. H. W. Wade (section 5 and section 6).

1. EPIDEMIOLOGY

The epidemiology of leprosy varies in different countries, and may be, in different parts of the same country. The committee makes no attempt at a broad discussion of this subject. The present report deals with only

¹ The Sixth World Health Assembly adopted the following resolution:
The Sixth World Health Assembly

1. NOTES the first report of the Expert Committee on Leprosy;
2. THANKS the members of the committee for their work;
3. REQUESTS the Director-General to make arrangements for the collection of biopsy specimens from cases of leprosy, and for such specimens to be prepared and distributed through a suitable laboratory to histopathologists who might participate in their examination, and
4. AUTHORIZES publication of the report.

(Resolution WHA6.19, *Off. Rec. World Hlth Org.*, 48, 23)

one aspect of the subject, which has an important bearing on the policy of anti-leprosy control—namely, the infectivity of the different forms of leprosy.

1.1 “Open” and “Closed” Cases of Leprosy

From the administrative point of view, cases of leprosy may be divided into “open” and “closed” according to whether or not leprosy bacilli are detected by routine bacteriological examination of the skin lesions and/or the nasal mucosa by the slit method, which consists in making a small cut to the level of the dermis or sub-mucosa, and in scraping out a small amount of tissue pulp for the purpose of making smears.

According to this method of examination the “open” cases will include all the lepromatous and borderline cases, many of the tuberculoid cases in reaction, and a small, but varying, percentage of the cases of torpid tuberculoid and indeterminate forms (see section 4, page 19).

However, the failure to find leprosy bacilli by the routine bacteriological method in the “closed” cases does not indicate their total absence from the lesions, but only the extreme smallness of their number, since it is well known that if a careful search is made by appropriate methods, a few bacilli will be found in a fair proportion of such cases.

1.2 Evidence on the Greater Infectivity of Lepromatous Cases

As a result of their epidemiological studies, earlier workers such as Dehio and Hansen came to the conclusion that lepromatous cases of leprosy were far more infective than the tuberculoid and indeterminate cases. Most later work has confirmed this view and strong support for it has been provided by prolonged and extensive studies in Bengal, Indonesia, and the Philippines.

The intensive studies in the Philippines clearly brought out the marked differences in the attack rates of the disease among contacts of lepromatous and the tuberculoid and indeterminate forms of cases. In persons exposed to the cases of the lepromatous form the attack rate was found to be 6.23 per 1,000 person-years, while in those exposed to the non-lepromatous cases it was only 1.60. Thus the attack rates for those exposed to lepromatous cases were four times or more as high as for those exposed to tuberculoid or indeterminate cases.

Studies in a rural area in Bengal showed that, during a 7-year period, on an average one fresh case of leprosy arose per 3 families with a previous lepromatous case, per 20 families with a previous tuberculoid or indeterminate case, and per 40 families with no previous case of leprosy. This

would indicate that in persons exposed to contact with non-lepromatous cases in the household, the chances of appearance of the disease are much lower than in persons similarly exposed to lepromatous cases, though they are two times greater than in persons with no household contact of any kind.

The findings in Indonesia indicated that the morbidity rate in persons known to have been exposed to the lepromatous cases in the household was 7.77%, while in the case of persons known to have been exposed only to the tuberculoid or indeterminate cases in the family the rate was 0.7%. It was therefore concluded that the danger of house exposure to contact with a lepromatous case was well established. Further, the findings gave an indication of the importance of the influence of contact with lepromatous cases outside the family, with regard to the chance of contracting the disease by members of families with only tuberculoid or indeterminate cases.

1.3 Evidence on the Low Infectivity of "Closed" Cases

The idea of the low infectivity of the "closed" cases of leprosy is based on sound grounds: in these cases leprosy bacilli are so few that they are not found by the routine method of examination which involves cutting into the skin; and therefore they are not likely to be discharged from the patient's body, though a few of them are present deep in the corium and inside nerves. Further, as indicated above, this idea is supported by observations regarding the spread of leprosy among household contacts of lepromatous and non-lepromatous cases.

Findings in some recent studies in one centre have been interpreted by some workers as providing evidence on the infectivity of the non-lepromatous cases. There are three main findings which have led these workers to form this view: (1) when examined by the "clip" method, wherein a large piece of skin is removed for examination, a very large percentage of the non-lepromatous cases are found to contain leprosy bacilli in their skin lesions; (2) the incidence of leprosy among contacts of the lepromatous and the non-lepromatous cases was found to be similar; and (3) acid-fast bacilli (indistinguishable from leprosy bacilli) were found in the skin of about one-third of healthy contacts of leprosy patients of both kinds of cases.

In the view of this committee, the above findings have not produced conclusive evidence regarding the infectivity of the non-lepromatous cases. The interpretation of the various findings is subject to many fallacies:

(1) The finding of a few bacilli on meticulous search has to be interpreted with caution. There is obviously difficulty in accepting the view

that lepromatous and non-lepromatous cases are almost equally infectious, when one considers the enormous difference in the number of leprosy bacilli likely to be discharged from the two kinds of cases.

(2) For the purpose of ascertaining contact or lack of contact with a lepromatous case, only the presence of lepromatous cases in the household or in the immediate neighbourhood has been taken into account; the possible contact that the persons in a particular locality might have had with some lepromatous case in another locality or with some such cases who might have occasionally visited or lived there some time previously, has been ignored.

(3) There is no definite evidence that the acid-fast bacilli found in the healthy skin of some contacts are really leprosy bacilli; in the absence of conclusive evidence on this point, and in view of the fact that acid-fast bacilli, other than the leprosy bacilli, may sometimes be present in skin, these findings have to be interpreted with great caution.

The committee considers that "closed" cases of leprosy do not play an important role in the spread of the disease. Recent evidence to the contrary does not carry conviction. However, whatever interpretation is given to the finding of leprosy-like bacilli in the skin of contacts, such a finding is of sufficient importance to justify a further search for similar findings in other areas.

The recognition of a marked difference in the degree of infectivity of "open" and "closed" cases provides the basis of the widely practised policy of confining segregation to "open" cases. There is no adequate evidence to justify departure from this policy.

2. CONTROL

2.1 Basic Principles

Leprosy is not a disease apart; it is a general public-health problem in the countries where it is endemic.

Any measures which will raise the public-health standards are likely to help in the control of leprosy, whether they are directed against specific infections or infestations or concern the improvement of nutrition, sanitation or housing.

Specific leprosy control work must be undertaken by staffs working within the general framework of the health administration of a country, and must conform with the generally accepted public-health principles. Public health and not public fears and prejudices should determine the policy in respect to leprosy control.

The statement made at the Fourth International Congress of Leprosy in Cairo in 1938 is endorsed—namely, that the present conception of the transmission of leprosy is that it

“is an infectious disease spread principally by direct contact, and possibly by indirect contact . . . As with other infectious diseases, the aim is to discover cases as soon as possible in order to control the spread of infection to the community, and in order to give the patient the benefit of treatment”.

2.1.1 *Administrative methods and personnel*

It is obvious that the administrative methods to be adopted in leprosy control depend upon local circumstances, including the availability of suitable staff; they must fit into the general administrative organization of the national and local health services. Among factors that must be considered are the area to be covered, the population and its distribution, the degree of health consciousness of the people, and the means of communication and transport.

The most important factors are, however, the funds available and the possibility of securing personnel of the right type. While adequate salaries are necessary, only sympathetic and altruistic workers are likely to be successful in the relief and control of leprosy.

In some endemic countries special leprosy services exist only in a few administrative units, and most of the anti-leprosy work is organized by voluntary bodies. In countries where special leprosy services are found, there are wide differences in funds and personnel, so that it is difficult to set up generally applicable standards for leprosy control administration.

2.1.2 *Treatment as a control measure*

Modern treatment, which effectively reduces the infection in leprosy patients, and therefore their infectiveness, is regarded as the most potent generally applicable weapon now available in the control of the disease.

Treatment is the more effective when applied to early cases—a fact to be borne in mind in devising control policies.

2.1.2.1 *Dispensary.* That is why the dispensary system, as described below, aiming at the early detection and the early treatment of cases, is considered by the committee as the primary, essential element in the organization of leprosy control.

According to the density of the population, the leprosy incidence, the availability of medical and health resources, and the conditions of transport, the type of dispensary found preferable will be specialized or general, fixed or mobile.

The specialized local dispensary is located in the centre of an endemic area. It has various functions :

- (1) Detect cases and keep in touch with them and with all contacts (adequate records being kept of both cases and contacts in the area).
- (2) Treat cases which, under the regulations in force, are not treated in a leprosarium.
- (3) Arrange for the placement of patients in suitable types of leprosaria if, under the regulations in force, they should be isolated.
- (4) Select those cases for which domiciliary isolation may be permitted under the regulations in force, and carry out supervision of such cases.
- (5) Ensure follow-up treatment and surveillance of cases discharged by the leprosaria.
- (6) Arrange prophylactic measures for children born of leprosy patients, such as placement, temporary or otherwise, BCG vaccination, etc.
- (7) Carry out welfare work in families affected by leprosy.
- (8) Promote education regarding leprosy.

It may have to accommodate temporarily, for observation, for special treatment, or pending placement in an institution, certain patients or contacts ; it should in such cases have a few beds available for these purposes.

It should have an adequate staff of doctors, nurses, technicians, and welfare workers.

In certain areas, especially where the distribution of cases is sparse, or physicians are few, mobile units may be used to supplement stationary dispensaries.

In areas where the lack of resources, the sparcity of the population or low endemicity make special dispensaries impracticable or inadvisable, general dispensaries (health centres) and their staffs may be used to carry on, in a modified degree, the functions of the specialized dispensary.

A central dispensary with a well equipped laboratory, where the more elaborate examinations can be carried out, should co-ordinate the work of local and mobile dispensaries.

The work should, moreover, as far as possible, be co-ordinated with the general public-health activities in the area.

Treatment is of course a major function of the leprosaria as well as of the dispensaries.

2.1.3 *Isolation*

In theory, isolation of all infectious cases should break the chain of infection, and eventually result in the eradication of the disease. As a

matter of fact, many cases are infectious for years before they are diagnosed and isolated, and the fear of compulsory segregation makes patients hide their condition as long as they can, precisely during the period when it would be most curable. Consequently, institutional isolation alone has not given the results expected of it and has failed as a control measure even when applied rigorously and on an adequate scale.

Applied, however, with discrimination and in combination with education and effective treatment of all the cases, it retains an important place in the fight against leprosy.

In respect to isolation and from the administrative point of view, cases are to be divided into two classes: the infectious ("open") and the non-infectious ("closed"), even though it is recognized that there are different degrees of infectiousness. Only infectious cases need be subjected to some form of isolation, while all cases require treatment.

The degree of isolation of infectious cases necessary, the methods of securing it and the amount of compulsion to be applied, vary in different countries and areas, and in a given area will depend upon the patient and his environment.

Where leprosy is not endemic and the disease shows no tendency to spread, notification with whatever surveillance is deemed necessary may be sufficient in addition to treatment.

2.1.3.1 *Compulsory isolation.* In many countries where leprosy is highly endemic but where resources are inadequate for institutional treatment, obligatory segregation may be impossible.

In such a case, however, it may be found advisable for the health authorities to retain powers of compulsory isolation, to be applied when necessary and possible.

Even in endemic countries where the resources are adequate, compulsion should only be applied when persuasion fails and to cases considered by the competent authorities to be a danger to the community.

Compulsory isolation of infectious cases in institutions has, in spite of its theoretical advantages, very serious disadvantages. It often breaks up the family and leaves the dependants unprovided for.

Fear of this, and still more of an indefinite stay in a leprosarium, and even of the stigma of having been in one, leads patients to conceal their disease and to remain without treatment, and makes them a danger to their contacts.

The more effective modern treatment giving better chances of recovery calls for a reconsideration of existing practices regarding compulsory isolation. While the rule of isolation of infectious cases may still be retained,

the method of applying the rule may be modified so that the patient may be attracted to come forward earlier for treatment.

Prompt discharge of the patients from the leprosarium as soon as they are non-infectious may have a similar psychological effect. In addition, the beds thus freed in the leprosaria would be available for infectious cases.

The change would bring the practice regarding leprosy more into line with that used in tuberculosis, a much more infectious and more often fatal disease, and contribute to the disappearance of the unreasoning horror attached to leprosy.

In many cases, where dispensary follow-up and treatment is not available, patients may have to be kept under institutional treatment during a longer period of negativity to lessen the danger of relapses and of a return of infectiousness.

Three forms of isolation may be envisaged : in the home, in institutions, and in special villages.

2.1.3.2 *Domiciliary isolation.* This is suitable for the patient who can be isolated effectively in separate quarters inside or adjacent to his house and can be treated locally ; steps being taken to ensure that contact is avoided with relatives and others, particularly with children.

2.1.3.3 *Isolation in leprosaria.* This is indicated in the more severe and infectious cases. As treatment is prolonged and most patients are able-bodied and as occupational therapy is of particular value in treatment, the most useful form of leprosarium is the farm colony with agriculture and various industries in which patients may find suitable and congenial work, and live a life as nearly normal as circumstances permit.

In establishing a leprosarium, four main points should be kept in view : (1) the site must be healthy ; (2) it must have an adequate water supply ; (3) it should have an abundance of land suitable for agriculture and horticulture ; and (4) it should have good communications so as to facilitate the bringing in of supplies, allow of access to specialized treatment, and permit visits of relatives. The old idea that leprosy is so infectious that patients must be segregated in a distant place is one to be deprecated.

2.1.3.4 *Asylum.* For the permanently crippled patient in whom active disease may have died out but who has no means of support outside, a special infirmary or asylum may be desirable either as an annex to a leprosarium colony or as a separate institution. Such an institution must have adequate medical services.

2.1.3.5 *Village settlement.* Another method used in some countries is the establishment of leprosy patients in segregation villages or hamlets, these being built by the villagers, with or without outside aid, and inhabited

by infectious cases from one or more villages. Proper arrangements for treatment must, of course, be made. Such an institution may constitute a valuable auxiliary to the leprosarium in the control of leprosy.

2.1.3.6 *Hospitals.* Hospitals or hospital wards reserved for leprosy cases may be of service for the temporary treatment of cases needing hospitalization for special medical and surgical treatment. They may be independent institutions, or they may be attached to a leprosarium or to another medical institution.

2.1.4 *Early diagnosis*

The isolation of known infectious patients, and the treatment of others in dispensaries are not sufficient to control leprosy—a disease which is usually infectious long before it is recognized. Among the chief sources of danger are unrecognized infectious cases. Such cases can, however, be detected by a wisely planned survey. The survey should, where possible, involve a house to house canvassing.

Among some primitive peoples under tribal rule a compulsory round-up and immediate examination of the total population has been found possible. But as a rule compulsion leads to concealment and defeats its own object.

A method successfully adopted in some countries is first to win the confidence of the patient by dispensary treatment, and then to follow him up to his village and examine contacts. This examination should be repeated at regular intervals.

The examination of schoolchildren, followed by the examination of home contacts of cases found, constitutes a useful complement to the other methods.

By such methods a survey is gradually completed, while at the same time treatment is arranged for all cases found, and instruction is given to patients, relatives, and neighbours on the nature of leprosy and on how infection may be avoided by isolating infectious cases. Such isolation may be domiciliary in suitable cases, but where possible the more infectious cases should be persuaded to enter a leprosarium.

2.1.5 *Protection of infants and children*

The opinion is generally held that in endemic countries leprosy is more commonly acquired during infancy and childhood than at later ages. Special care should therefore be taken to prevent contact of infants or children with infectious relatives, either by isolating the patients or by removing the children.

In some countries healthy children born of leprous parents are removed to a preventorium or similar institution. In other countries such facilities are not available.

In order to allow proper intellectual and emotional development of healthy children, it is undesirable to keep them longer than necessary in special institutions ; wherever placement in suitable healthy families cannot be procured, it should be arranged for in ordinary children's institutions. In the latter case, they should remain under the discreet supervision of a leprosy specialist.

Prophylaxis by means of BCG in infants and children is described in section 2.2 (page 13).

2.1.6 *Welfare work*

The sufferer from leprosy and his dependants are particularly entitled to the sympathy and care of the community, and every plan for the control of leprosy should include an efficient welfare scheme.

2.1.7 *Educational methods*

One of the main difficulties in controlling leprosy is the ignorance of the public regarding the nature of the disease. Public opinion ranges from callous indifference to panic, and the patient and his relatives are often subjected to barbaric cruelty.

All medical students and nurses should be taught the essentials of leprosy so that they may be able to recognize the disease.

In endemic countries every means should be employed to educate the public and particularly the patient and his contacts.

Much can be done by co-operation with educational authorities, and in endemic countries elementary teaching on leprosy should form part of the instruction in schools.

2.1.8 *Role of voluntary organizations*

While the control of leprosy is primarily a responsibility of governments, voluntary organizations have in the past done much to relieve sufferers from leprosy and there are parts of the campaign in which their enthusiasm and devotion in this work are of immense value. Accredited and properly supervised societies of this nature should be encouraged and helped as far as possible.

2.1.9 *Research*

There are many leprosy problems still to be solved by both laboratory work and field investigation, and every control programme and special campaign against the disease should be planned and carried out with these problems in view.

2.2 Possible Prophylaxis by Means of BCG

The committee considers that there is strong circumstantial evidence that in healthy persons, a "naturally" occurring positive lepromin test indicates relative immunity to leprosy, and that the prognostic value of the lepromin test in cases of leprosy has long been firmly established.

There is strong evidence also that naturally acquired tuberculous infection frequently makes the lepromin test positive.

Further, it considers that it is firmly established that in lepromin-negative healthy persons the administration of BCG will make the lepromin test positive in a high proportion of cases. It is possible but not proved that this artificially induced lepromin positivity indicates a relative immunity to leprosy.

Studies of oral administration of BCG made in several countries, and particularly in Brazil, have shown that with this mode of administration, preliminary tuberculin testing is not indispensable. This finding might simplify the wider use of BCG if the preventive value of this vaccine were confirmed, especially as BCG vaccination is accepted as innocuous and as beneficial in protecting against tuberculosis.

Though there is indirect evidence of the protective value of BCG against leprosy, the committee could not justifiably recommend it officially as a control measure until adequate large-scale trials had been conducted. The importance of the subject demands that such trials be carried out according to pre-established plans, and that they be properly co-ordinated with tuberculosis services.

The committee therefore strongly recommends that such trials of the value of BCG, particularly given by mouth, be undertaken with suitable controls, and statistical evaluation. In such investigations consideration should be given, inter alia, in a selected endemic area to population factors, lepromin- and tuberculin-rates, and the incidence of leprosy. Adequate comparable controls for the population categories submitted to oral BCG vaccine should be provided, as should the regular checking of the lepromin and tuberculin reactions.

The committee considers that the investigations should include the determination of the optimum dosage of BCG to secure a positive lepromin test without incident; the methods of administration; the standardization of the lepromin antigen and criteria for its application; comparison of the lepromin and tuberculin tests; and the relationship of tuberculin allergy and the lepromin reaction. Further study should be made of the incidence of leprosy in vaccinated and non-vaccinated persons, in leprosy contacts, and in tuberculosis patients.

2.3 Mass Campaign in Limited Areas

In recent years, national and international organizations have developed mass campaigns directed at controlling certain communicable diseases under conditions where routine methods have not been successful. The committee therefore considered that in certain endemic areas where routine measures of leprosy control had had only meagre results it was desirable to envisage the possibility of "mass control measures in limited areas". The committee noted that the long incubation and comparatively long treatment of the disease did not favour such a method of control. It felt, however, that these handicaps should not prevent health administrations from concentrating efforts against leprosy with the object of achieving control in selected, limited, highly endemic areas within a period of action of at least 5 years.

The measures thus to be applied could include the following :

(1) intensive sulfone treatment of all known cases, efforts being made to detect unknown cases by systematic surveying of the population, and to attract concealed cases by doing away with compulsory segregation ;

(2) BCG vaccination of the whole non-leprosy population, or, if this cannot be achieved, at least of contacts, and of children and adolescents (oral administration being used if preliminary tuberculin skin testing is not practicable) ; and

(3) as far as possible, improvement of the bodily resistance of the whole population (including leprosy patients) through improvement of its dietary (additional vitamins, etc.), and mass treatment of common infectious and parasitic diseases (malaria, hookworm, intestinal parasites, etc.).

The committee recommends that in order to give experimental value to this attempt at mass control, control areas be selected as closely comparable as possible to those in which the concentrated attack on leprosy is staged, but without such an attack being made there, and that evaluation of the leprosy situation be made in both types of areas after a period of 5 years.

3. TREATMENT

3.1 Therapeutic Efficacy of Various Drugs

3.1.1 *Sulfone treatment*

Modern treatment with the sulfones, properly organized and supervised, now constitute one of the most important measures of control of the disease.

3.1.1.1 *General.* This committee is unanimous in the view that sulfone treatment is greatly superior to previous forms of treatment, though some workers continue to use chaulmoogra (*Hydnocarpus*) oil as a supplement to sulfones.

While almost all cases of leprosy show a response to sulfone treatment, the clinical response is slow in some, and the bacteriological response always slower. The response to treatment cannot be speeded up by giving exceptionally high doses of sulfone. It is possible that the usual doses of all the sulfones now used are already unnecessarily high.

It is recommended that treatment and observation in cases of all forms should be continued for at least one year after all clinical activity has disappeared and bacteriological findings (by standard methods) have become negative. This often takes several years. Even when these conditions have been fulfilled, the advisability of after-treatment has to be considered.

Sulfones are believed to be bacteriostatic; they appear to prevent multiplication of the bacilli and thus slowly reduce the intensity of the infection to a level at which the protective mechanisms of the body can control it. It is doubtful whether the infection is eradicated; relapse is therefore possible.

Data on relapse rates after the cessation of sulfone treatment are scanty; accurate assessment of the danger of relapse is not yet possible. Some workers even recommend that sulfone treatment at reduced doses be continued indefinitely.

While the necessity for this recommendation has not been clearly demonstrated, it presents, in many countries, no difficulties with forms of treatment now available. In some circumstances, however, it may be difficult.

The development of sulfone resistance in leprosy bacilli is a matter not open to direct study. There is no clear clinical evidence that it occurs.

Since the use of sulfones started eleven years ago, the results of leprosy treatment have greatly improved. The treatment has been found of great value in active cases of leprosy in all forms.

3.1.1.2 *With complex sulfones.* Disubstituted, monosubstituted, and other sulfone derivatives have given good results. No one group of these derivatives has been generally found to be superior to other groups, and no one derivative has been generally found superior to others. Individual workers still have their preferences. Furthermore, some patients appear to respond better to one derivative, and others to another derivative.

The general principles of sulfone therapy, the different derivatives in use at that time, and their doses and methods of administration are discussed in the report of the Fifth International Congress for Leprosy, held at Havana, Cuba, in 1948.

3.1.1.3 *With the parent sulfone (DDS)*. It was long believed that DDS (di-aminodiphenyl sulfone) itself was too toxic for use in human beings. Experience in thousands of cases of leprosy in several countries for a period of over four years, has shown this belief to be erroneous, provided the dose is suitably regulated.

General experience has shown that the small doses of DDS in use have a therapeutic action which is in general no less than that of the larger doses of the DDS derivatives in use.

DDS has many advantages : its cost is very low ; its administration is very simple ; it is usually given orally but can, if desired, be given by injection ; daily administration is unnecessary ; weekly or bi-weekly treatment is widely used. In regions where patients live away from treatment centres, administration is also carried out twice monthly by injection of a suspension of DDS in oil in order to prolong the action of the drug.

For these reasons, in most circumstances, and particularly in large-scale work or mass treatment, DDS is of great value. For such work the dosage should in general be lower than in the treatment of patients under continued observation.

The doses of DDS used by different workers vary. The following régimes have been used with success in adults :

- 100 to 200 mg given orally once a day
- 200 to 400 mg given orally twice a week
- 300 to 600 mg given orally once a week

For children, the dose should be suitably adjusted to the body weight.

Doses higher than these should not be used in routine treatment. Moreover, treatment should be started at levels considerably lower (about one quarter) than the dose ultimately attained, and the increase should be gradual and last several weeks.

3.1.2 *Treatment with thiosemicarbazones*

The drug most often used has been *p*-acetamidobenzaldehyde thiosemicarbazone (TB 1/698). This has been used on a small scale for three years and on a larger scale for two years in several centres. A final assessment of its value in leprosy is not yet possible. Most reports have been favourable, but one has been unfavourable.

Compared with sulfones it has advantages and disadvantages. It is sometimes better tolerated and causes fewer reactions. Its disadvantages are the need for daily or twice-daily treatment, and the greater possibility of liver damage, of an acute agranulocytosis, and of drug fever.

Such effects are seen mainly during the first two months of treatment, during which period close medical supervision is therefore needed.

Thiosemicarbazone is therefore considered unsuitable for large-scale or mass treatment.

It provides a very useful alternative treatment for patients who are or who become intolerant to sulfones, or who do not respond adequately to sulfone treatment.

3.1.3 *Other therapeutic agents*

3.1.3.1 *Streptomycin*. Evidence so far available does not suggest that streptomycin will play a major role in the treatment of leprosy. Some workers have thought it of value in certain acute phases of leprosy. Toxic effects have been common in some trials and rare in others. Experiments now in progress should give more information on the value in leprosy of streptomycin alone and in combination with other agents.

3.1.3.2 *Iso-nicotinyl hydrazide (INH)*. Experience so far has been confined to a few centres, and covers limited periods. The results on the whole are not favourable to this agent as a basic treatment for leprosy; it may be, however, of some value in the acute phases of the disease. Further studies of its action when given alone and in combination with other agents are in progress.

3.1.3.3 *ACTH and cortisone*. Several workers have shown that acute and sub-acute manifestations of leprosy (e.g., reaction, neuritis, iritis) can be rapidly relieved or suppressed by giving these hormones, but the relief does not usually persist when the treatment is stopped. In some centres it has been found that the final result is often an aggravation of the acute symptoms and of the underlying disease. These hormones should be used with caution.

Instillation of cortisone drops into the eye, or sub-conjunctival injections, have been found of value in leprosy eye inflammation, and injections into nerves in cases of severe neuritis.

ACTH and cortisone have been found of great value in the treatment of the occasional severe reactions (dermatitis, hepatitis, etc.) to sulfones.

3.1.3.4 *Other agents*. Several other therapeutic agents are now under trial. None calls for special comment in this report.

3.1.4 *Supplementary treatment*

Chemotherapy constitutes only part of the treatment of leprosy patients. Supplementary treatment should include the use of measures aimed at minimizing disability caused by leprosy (e.g. leprosy eye affections need careful treatment and sometimes surgery) as well as measures to improve the general physical, nutritional, and psychological condition of the patients, and to remedy complicating infections and infestations.

In addition, various forms of local treatment of the lesions may be useful. Certain applications to the skin lesions (e.g., trichloroacetic acid, and carbon dioxide snow) or injections of mild irritant fluids into the lesions (e.g., chaulmoogra or other oils) may, quite apart from any specific action, accelerate the disappearance of lesions or make them less obvious.

3.2 Physiotherapy, Surgery, and Orthopaedics

Although considerable advances have been made in chemotherapy during the last eleven years, leading to a more favourable prognosis of leprosy, the problem of contractures and mutilations due to neural lesions is far from being solved.

Experimentation on a larger scale seems necessary in order to establish in an incontrovertible manner the real value of physiotherapeutic, surgical, and orthopaedic procedures in leprosy.

Concerning the effect of physiotherapy, certain workers have brought about improvement in contractures of the extremities, but others have obtained only disappointing results.

Surgery should be given a larger place in all institutions caring for leprosy patients. Early surgical intervention might often prevent a permanent disability. Tendon transplantation seems to be suitable for many patients suffering from paralysis of the small muscles of the hand involving only reducible deformity. However, until now this intervention has been carried out on a relatively small number of leprosy patients.

Investigation of new operative methods, particularly in neurosurgery, should also be encouraged.

Cosmetic surgery and orthopaedics, the use of which in leprosy raises no special problems, might be employed more extensively.

The committee considers that information on the value of the best methods of physiotherapy, surgery, and orthopaedy applicable to leprosy patients is yet too limited. To obtain information on these subjects, an intensive study is necessary in suitable centres in countries where adequate clinical material is available. This study should be carried out by staffs devoting their whole time to this work.

The committee considers that the perfecting of various simple and effective techniques which could be generally recommended would be of immense service and would considerably decrease the number of cripples among patients who can be rehabilitated and are undergoing chemotherapy.

However, from the practical view-point, it would be necessary to bear in mind during such research that only measures making moderate demands as regards staff and equipment could be applied in the majority of leprosy control centres.

4. CLASSIFICATION

The criteria which bear on the classification and subgrouping of leprosy cases are (1) clinical, (2) bacteriological, (3) immunological, and (4) histopathological. Existing systems of classification differ with respect to the priority given to certain of these criteria.

The committee agrees unanimously that the basic criteria of primary classification should be clinical, comprising the morphology of the skin lesions and neurological manifestations. Indispensable in connexion with the clinical criteria is the bacteriological examination of smears of skin lesions and the nasal mucosa.

In the scientific study of cases full use should be made of the immunological criterion (the lepromin test), and of the histopathology of the lesions; these factors are involved in the determination of certain of the subgroups which it may be desirable to establish for certain purposes.

The histological examination, of importance in the diagnosis of the form of leprosy and consequently in the prognosis, should not govern the primary classification except in case of definite error in the clinical determination (e.g., the form designation of a case regarded as tuberculoid should be changed to lepromatous, or vice versa, if definitely indicated, but in either contingency the lepromin test should afford confirmatory evidence). In the indeterminate form, the histological findings may serve to separate, as subgroups, the pre-lepromatous cases on the one hand and the pre-tuberculoid cases on the other hand, but such cases should not be transferred from the indeterminate form until so required by further clinical developments.

Cases should be classified according to the findings at the time of the examination. They may or may not present evidence, by history or objective stigmata, of a previous form or phase of evolution, and sometimes these features are significant with respect to present classification.² The evidence obtainable may indicate a likelihood of change to another form or phase in the future evolution of the disease, but that factor does not affect the form determination until such a change actually occurs.

From one point of view, leprosy cases might be divided into two categories: lepromatous and non-lepromatous. The lepromatous form is distinguished particularly by a specific histopathology not found in any other disease, whereas the structural changes of the forms which constitute the non-lepromatous category are not distinctive, whether they be tuberculoid, simple chronic inflammatory, or more complex.

² For example, it may be known, or be evident from existing stigmata, that a case in which the skin lesions are simple macules was previously tuberculoid; such a case should be classed as residual tuberculoid and not as indeterminate.

4.1 Primary Clinical Classification

The committee recommends that four forms or classes of leprosy be recognized in primary classification. These are briefly defined as follows :

4.1.1 *Lepromatous leprosy*

A malign form, especially stable,³ strongly positive on bacteriological examination, presenting more or less infiltrated skin lesions, and negative to lepromin. The peripheral nerve trunks become manifestly involved as the disease progresses, habitually in symmetrical fashion, and often with neural sequelae in advanced states.⁴

4.1.2 *Indeterminate leprosy*

A benign form, relatively unstable, seldom positive on bacteriological examination, presenting flat skin lesions which may be hypopigmented, erythematous, or hyperpigmented, with a reaction to lepromin variable from case to case. Polyneuritic manifestations may develop in cases which have persisted in this form for long periods. The indeterminate form consists essentially of the "simple macular" cases and comprises those cases previously known as "maculo-anaesthetic". Cases of this form may evolve toward the lepromatous form or the tuberculoid form, or may remain unchanged indefinitely.

4.1.3 *Tuberculoid leprosy*

A benign form, relatively stable, infrequently positive on bacteriological examination, presenting erythematous skin-lesions which are elevated, marginally or more extensively, and almost always positive to lepromin. Sequelae of peripheral nerve involvement may develop in a limited proportion of cases. This frequently appears to occur as a result of extension from or through cutaneous nerve branches rather than of systemic dissemination, and consequently it is often asymmetrical and unilateral. This form of the disease can be subdivided as follows :

4.1.3.1 *Minor tuberculoid*. Skin lesions are only slightly to moderately elevated, often only at the margin or even a part of the margin, usually

³ The word "stable" implies stability as regards the form, not the degree, of the disease.

⁴ Furthermore, the lepromatous cases are regularly negative to lepromin, whereas the others for the most part react positively to the test, as do many normal persons. Other distinctive features of the lepromatous form are the abundance of bacilli in the lesions and the relative resistance of the cases to treatment.

"Borderline" cases are almost always strongly positive with respect to bacilli and negative to lepromin, but they are distinct from the lepromatous cases in their clinical appearance, do not have the specific histopathology, and, as a rule, respond better to treatment.

with irregularity of the surface. The condition tends to be relatively superficial, and palpable enlargement of cutaneous nerves associated with the lesions is infrequent.

4.1.3.2 *Major tuberculoid*. Skin lesions are often smooth of surface but more markedly elevated and thickened than the minor variety, the affected zone usually broader; the more recent lesions may show only partial central recession or no recession; because of the degree of the condition in the deeper levels of the skin, manifest extension in the associated cutaneous nerves is relatively frequent and marked.

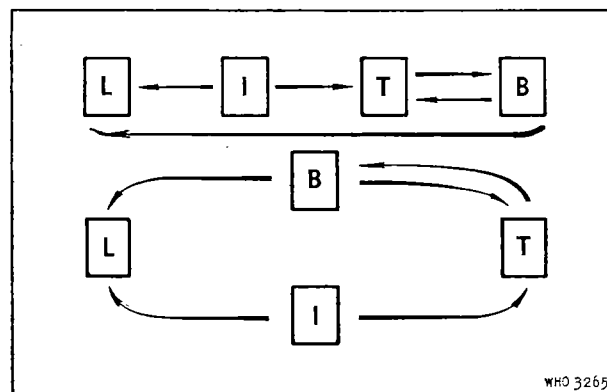
4.1.3.3 *Reactional tuberculoid*. Infiltrated lesions of active, succulent appearance, without central retrogression, develop abruptly from major tuberculoid lesions or from lesions of lesser degree (minor tuberculoid or even indeterminate), or on sites not previously involved. In some cases, more or less numerous and widely scattered, metastatic, small nodules may appear. The lesions of the peripheral nerves become marked, and necrosis, and even abscess formation, may occur. Coincident with an increase in the number of bacilli, the response to lepromin may decrease and even disappear temporarily. With repeated reactions, such cases may evolve to the borderline form.

4.1.4 *Borderline leprosy*

A malign form, very unstable, almost always strongly positive on bacteriological examination, generally negative to lepromin. This form frequently arises from the tuberculoid form as a result of repeated reactions, and sometimes evolves to the lepromatous form.

4.1.5 *Schematic representation*

The relationships of these four forms may be represented by either of the two following schemes :



4.2 Subclassification and "Administrative Classification"

The committee has not felt it necessary or desirable to go into details of the subgrouping of cases in a report intended primarily for health administrators. It notes with satisfaction that the next congress of the International Leprosy Association, to be held in Madrid, Spain, in 1953, will deal further with the matter of classification from the point of view of the clinician. The committee also learns with satisfaction that it is proposed to reprint in an early issue of the *International Journal of Leprosy* certain basic documents pertaining to the so-called "South American classification" in order to pave the way for consideration of subclassification at the forthcoming congress at Madrid. It would, however, call attention to the so-called "administrative classification" set up by the Leonard Wood Memorial Conference held in Manila, Philippines, in 1931 and reiterated by the congress at Cairo in 1938, according to which cases are classified without regard to clinical form as "open" and "closed" (or infectious and non-infectious) depending upon whether they are bacteriologically positive or negative by the standard method of examination of the skin lesions and nasal mucosa.

5. IMMUNOLOGY

The lepromin test, as an indicator of the reactivity of the skin to the presence of leprosy bacilli and hence of resistance, has assumed an important role in the study of leprosy cases with respect to classification and prognosis, and of contacts and others with respect to probable resistance to infection. It is being used more and more widely, and extension of its use in practice should be encouraged.

At the same time, since the introduction of sulfones in therapy, a difficulty has arisen in that it is becoming increasingly less easy to obtain suitable lepromatous lesions with which to prepare the antigen for the test. For this reason, if for no other, it is of much importance that the technique of preparing lepromin should be improved so as to obtain the highest possible yield of the essential element of the antigen—the bacilli of the lepromatous lesions—without introducing any other undesirable feature. It is also highly desirable to arrive at a method of preparing the antigen which, besides being economical of the bacilli, would eliminate so far as possible the non-essential elements of the lesion-tissue used and would permit more accurate standardization of the bacillary suspension than is feasible with the classical Mitsuda suspension, and would also have minimal undesirable effects in strongly reactive cases.

The Mitsuda antigen can be standardized only approximately, by taking certain precautions to be considered shortly. In recent years there have been introduced, by Fernandez and by Dharmendra, two methods of preparing refined bacillary suspensions containing minimal quantities of tissue elements, the final products being made up by weight.

In the Fernandez technique, the bacillary element of the leproma suspension is first floated by centrifuging after increasing the specific gravity with sodium chloride, following which the specific gravity of the supernatant fluid is lowered by the addition of alcohol and the bacilli are deposited by centrifuging. In this method an unduly large proportion of the bacilli is lost in the processing, and in practice it is little used.

In the Dharmendra technique, the bacilli are first separated from the tissue by means of chloroform, taking advantage of the polarity affinity which acid-fast bacteria have for this substance. Then, after evaporating off the chloroform, the residue—a mixture of bacilli and soluble lipids—is taken up in ether and the bacillary bodies are deposited by centrifuging, the supernatant ether solution of lipids being discarded. With preparations of these “defatted” bacilli—which for the most part are rendered non-acid-fast in the process—the nodules produced in the late reactions are usually smaller than those obtained with the classical antigen in the same cases. On the other hand, it is claimed that the early reactions are usually stronger.

Because the Mitsuda type of lepromin has been used for many years, is employed very widely, and is relatively well understood, and because its preparation is simple and can readily be effected where electric power and centrifuges are not available, it is the consensus of opinion among the committee that its use can be recommended. This is said, however, without prejudice to the use of the Dharmendra antigen by those who prefer it, but with the recommendation that in publications they should specify that their findings were obtained with it.

It is the opinion of the committee that further investigations should be made with the Dharmendra antigen, and perhaps with variants of it, and with other preparations in comparison with the classical Mitsuda antigen, preferably improved.

5.1 Preparation of the Mitsuda Antigen

The original description (Hayashi) of the preparation of the Mitsuda antigen was very brief, and it is probable that practice in this matter varies considerably.

Apart from that, it is wasteful because much of the suspension is lost in the wetting of the gauze filter and a great deal of bacillary material is

lost in the discarded tissue residue. It is recommended that consideration be given to the several features of the following technique :

(1) For each batch of lepromin, lesion-tissue from several cases should be used, and reliance should not be placed alone on a tissue such as the ear lobe. The purpose of this "pooling" of material is to compensate for possible antigenic deficiencies of material from one or more cases by inclusion of material from others which may be more favourable.

(2) Each specimen used should be incised and a bacteriological smear examined, to ensure that only those which contain abundant bacilli will be used. Those poor in bacilli should be discarded.

(3) All tissue extraneous to the actual lesion mass should be trimmed off and discarded. This includes subcutaneous fat and loose connective tissue, as well as the epidermis if the lesion is a cutaneous nodule or infiltration, and the skin itself if it is removed with a subcutaneous nodule and is not involved in the lesion.

(4) It is probably preferable to weigh the tissues to be used before they are heated. (A material loss of weight occurs in the heating, whether that be done by boiling or by autoclaving, and whether it be done in saline solution or without it.)

(5) The trimmed tissue is heated either at boiling temperature or by autoclaving. The latter form of sterilization is to be used if the tissue is to be shipped to a distant laboratory for processing.

(6) The heated material is ground fine in a mortar with gradual addition of saline up to 20 ml per gram of tissue.

(7) The material is then filtered. Filtration is best done through a single layer of the finest mesh bolting cloth of silk, or preferably of nylon, the latter having no capillary attraction for water. (This process avoids the loss of a great deal of tissue suspension which occurs when highly absorbent multiple layer cotton gauze filters are used.) The nylon fabric is applied, provision being made for a pouch, to a wire ring made to fit the funnel to be used. The suspension is worked through by gentle scraping with a spatula. The nylon filter, properly cleaned, can be resterilized and used repeatedly.

(8) The residue left on the filter may be returned to the mortar, reground for some minutes, suspended in fresh saline, and put back into the same filter. (In this way 20 ml of saline per gram of tissue can be used in the first instance and 10 ml per gram in the second instance, thus obtaining 50% more of the final preparation than when the tissue pulp is not reground.)

(9) 0.5% of phenol is added to the filtered suspension which is then distributed in the desired containers, which are sealed and reheated to ensure sterility, although asepsis is practised throughout.

5.2 Reading of the Reactions to Lepromin

To be considered separately are (1) the classical late reaction, or Mitsuda phenomenon, a productive lesion which generally attains its maximum after two to three weeks, and (2) the early or Fernandez reaction, which is comparable to the response to tuberculin.

It is highly desirable that uniformity be attained with respect to both the recognition of positivity and the grading of the degree of these reactions. Measurements should preferably be made with calipers. When the reaction lesions are elongated or irregular the longest and shortest diameters are measured and averaged. The findings are recorded to the nearest millimetre.

5.2.1 *Late reaction*

Recognition of positivity of this reaction depends in part upon its morphological characteristics and appearance of activity, and not alone on size, so that it is sometimes justifiable to record as positive a reaction which, by strict application of the usual size-scale, would be classed as doubtful.

The results of the reaction may be expressed simply as negative, doubtful, and positive, or for special purposes, with grades of positivity.

Simple reading

Negative (—): lack of evident response, or slight infiltrations, without definite appearance of activity, and less than 3 mm in diameter.

Doubtful (\pm): elevated infiltrations measuring from 3 to 4 mm in diameter, without unequivocal characteristics of activity, provided that lesions of this size which present definite evidence of activity may be classed as positive.

Positive (+): nodular lesions of active nature larger than 4 mm in diameter.

Graded reading :

Negative (—): as above

Doubtful (\pm): as above

One-plus positive (+): reaction larger than 4 mm and up to 7 mm in diameter, without ulceration.

Two-plus positive ($\dagger\dagger$): reaction lesions larger than 7 mm and up to 10 mm in diameter, without ulceration.

Three-plus positive ($\dagger\dagger\dagger$): reaction lesions with ulceration, or those larger than 10 mm without ulceration.

5.2.2 *Early reaction*

The basic criteria of positivity of the tuberculin and other analogous reactions should be applied to the Fernandez reaction to lepromin: (a) the reaction should be regarded as positive only when both erythema and perceptible infiltration are present (erythema alone and also erythema extending beyond the area of infiltration should be disregarded); and (b) the reaction should be read only after 48 hours, more fleeting reactions being evaluated at most as doubtful. Erythematous responses, without definite infiltration, may sometimes be observed even in lepromatous cases, and in other cases they must be considered highly equivocal. Reactions which subside within 48 hours are also equivocal, granting that in some proportion of cases the later Mitsuda reaction may follow. Many positive reactions show more or less subsidence after 72 hours, although strong ones will persist for that length of time and may even fail to subside before the late reaction begins to develop.

Grading (48 hour reading) :

Negative (—) : absence of reaction, or erythema without infiltration, or erythema with infiltration not larger than 5 mm in average diameter.

Doubtful (\pm) : erythematous reaction with an area of infiltration larger than 5 mm but not exceeding 10 mm in average diameter.

One-plus positive (+) : reaction with an area of infiltration larger than 10 mm but not exceeding 15 mm in average diameter.

Two-plus positive (++) : reaction with an area of infiltration larger than 15 mm but not exceeding 20 mm in average diameter.

Three-plus positive (+++) : reaction with an area of infiltration larger than 20 mm in average diameter.

6. SIGNIFICANCE OF HISTOPATHOLOGICAL EXAMINATIONS

In recent years much emphasis has been placed on the histopathological findings in biopsy specimens from leprosy patients. In large part such examinations are made in connexion with the classification of cases and the question of prognosis connected therewith. They are also made to ascertain the changes of structure which occur in the lesions of patients who are improving under treatment, or who present reactional conditions which may at times result in change of form.

In most instances the histopathological picture is clear-cut and unequivocal, conforming to one or another of the well-established kinds of

lesions of this disease. At times, however, especially in cases whose clinical features depart from those of the more readily recognizable forms, the histopathology is atypical, or mixed and confusing. In such instances the interpretation of what is seen depends to a considerable degree upon the personal judgment of the individual examiner, and it may be that the techniques employed in preparing the sections for examination may influence his findings.

In short, the histopathological determinations are not necessarily absolute or infallible, as for example those of a chemist may be. Experiences have been cited of materially different descriptions, and even form-diagnoses, rendered by different examiners dealing with identical specimens. There is reason to believe that the personal factor in this matter is not fully appreciated, especially by clinicians who depend upon the findings of the histopathologist in the classification of their cases.

How frequently, and in precisely what ways, individual examiners might differ in their findings of given cases, especially the "problem" cases, cannot be said. It is the opinion of the committee that it would be eminently worth while to investigate this matter by arranging with a limited number of histopathologists working in leprosy to report their findings on a number of identical specimens, and that such a project should be provided for.

Subject to such modifications as might be indicated when the project is developed, the following would be the essential features of the plan:

(1) Specimens of proper kinds and of adequate size would be obtained from two or more sources. For the project, probably not less than 12 specimens should be used. They should be prepared by the same method, for which Zenker fixation would be preferred. (Details regarding fixation, hardening, and preparation for mailing would be supplied.)

(2) The specimens should include some from (*a*) indeterminate, (*b*) frank lepromatous, and (*c*) clinically tuberculoid cases (both quiescent, or "torpid", and reactional), and finally (*d*) several from the problem kind variously called "borderline", "transitional", "dimorphous", etc. The lesions would have to be so selected, and the specimens of such size, that the entire series of sections to be made would show essentially the same condition.

(3) These specimens would be sent to the WHO Secretariat, which would arrange for their processing. Each would be accompanied by a summary statement of clinical findings, including the bacteriological examinations of smears and, if possible, the lepromin test. These records would be kept strictly confidential, for the later use of the evaluating authority, and would not be supplied to the examiners. (Forms for the clinical data would be supplied.)

(4) From the Secretariat, the specimens, identified only by numbers or letters, would be sent to a laboratory where they would be embedded in paraffin, sectioned serially, and mounted on slides.

(5) A set of, say, five slides from each specimen, identified only by the symbols given by the Secretariat, would be then sent to each participating laboratory or pathologist. Except for perhaps one slide of each such set, they would be unstained so that the participants might employ the techniques to which they are accustomed.

(6) The reports of each participant should include summary descriptions of the histopathology, the findings of the examinations for bacilli, and histological diagnoses as definite as might in the opinion of the examiner be justified.

(7) The evaluating authority, after receiving these reports, would undertake an analysis which would be communicated to the participants and would be published in such form and way as might be deemed best.

(8) The number of participants could not be very large, since the number of sections that could be made from each specimen would be limited, but they should be representative.

The committee requests the Director-General to make arrangements for the collection of the necessary specimens and, with a suitable laboratory for the preparation and distribution of the sections, and with the histopathologists who might participate in their examination.