

PANELS AND ROUND TABLES

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The following pages carry condensations of the reports drawn up by the several Panels, Round Tables and Special Committees of the Congress. Many of the reports were much longer than the condensations here furnished. Those desiring the full reports may see them in the forthcoming *Transactions* of the Congress or secure them by writing to the Panel, Round Table or Committee Chairmen, whose names are printed in footnotes to the reports.

REPORT OF TECHNICAL COMMITTEE ON PATHOLOGY AND
EXPERIMENTAL TRANSMISSION¹

This report, prepared by members of the Round Table Group on Pathology and Experimental Transmission, summarizes discussions held by the group in Rio de Janeiro, Brazil, September 9-11, 1963. The members endorse the introduction of round table discussion groups as valuable, particularly in allowing time for discussion *before* the main Congress.

PATHOLOGY

Because pathology was included as a special subject for the first time at the VIIth International Congress of Leprology in Tokyo, it was reviewed broadly at that time by the Technical Committee on Bacteriology and Pathology. The present report deals more specifically with aspects of pathology in which progress has been made in the last five years or in which views expressed by the previous Technical Committee should be reiterated.

Practical application of pathology.—Histologic examination of biopsy material is an essential examination for the proper diagnosis, classification and prognosis of the disease and assessment of progress or regression of the disease in patients under treatment. Between the two polar groups of leprosy there is a wide spectrum of intermediate responses dependent on the host-parasite reaction. Histologic examination provides an essential picture of the host-parasite relationship and should be given at least equal weight with the clinical picture. In properly conducted chemotherapeutic trials it is important to select suitable cases, based on both histologic and clinical examination, in order to exclude, where possible, patients with more favorable prognoses. Because histology provides an overall picture of the cellular and bacillary elements, the examination can be used to assess *both* the lesion size (area of cellular infiltration) and the concentration of acid-

¹The Committee was composed as follows: Dr. R. J. W. Rees, *chairman*, Dr. H. M. Portugal, *secretary*, and Drs. M. Bergel, C. H. Binford, Y. T. Chang, K. R. Chatterjee, J. Convit, W. H. Feldman, W. A. Hadler, N. Nishimura, J. M. Robson, A. Serial, C. C. Shepard, F. F. Wilkinson, *members*.

fast bacilli. Combination of these two assessments in a so-called "histologic" index provides a more accurate assessment of the infection than the classic bacteriologic index. Thus a series of biopsy specimens taken from the same site or sites during the course of treatment can provide an additional important measure of progress. Pathologists are urged again to seek agreement on the application of this histologic index for careful assessment of progress of patients in chemotherapeutic trials.

Now that considerable evidence supports the view that irregularly stained bacilli are degenerate, report of the morphologic appearance (irregularly stained and solidly stained organisms) of bacilli in Ziehl-Neelsen-stained sections has added importance. It has obvious applications in recording progress in treatment in chemotherapeutic trials. More detailed knowledge of the proportions of irregularly and solidly staining bacilli in different types of leprosy, during reactions and in different sites in the body or in particular types of cells, would help in elucidating the pathogenesis of leprosy. Attention is drawn to the value of a simple histochemical test (Sudan III stain) on frozen sections from diagnostic biopsy specimens. Lipids are found in lepromatous and dimorphous lesions, but not in tuberculoid.

The Committee appreciated the recent contribution of Dr. Wade in sending to members of the Technical Committee and others a set of excellently prepared and stained slides illustrating the histopathology of 12 lesions of the "histoid variety of lepromatous leprosy." There was insufficient time to study the slides adequately, but the Committee urges those who received the slides to send their comments directly to Dr. Wade.

Recent advances in pathology.—1. Identification of "fuchsinophil" cells: This designation was given by Khanolkar to round and spindle-shaped cells containing acid-fast granules in sections stained by the Ziehl-Neelsen method. More recently it has been shown that these fuchsinophil cells are tissue mast cells commonly found in most tissues, including the dermis, of normal healthy subjects. Although the granules are acid-fast, they show also the characteristic metachromasia of mast cells.

2. Neuropathology: Leprosy holds a special challenge to neuropathology because it is the only mycobacterial infection in man involving nerves. Because, in fact, leprosy has a predilection for peripheral nerves, it is more than likely that research in the field of neuropathology will throw new light on the pathogenesis of leprosy. Advance during the last five years, based on careful observations (using light and electron microscopy) of human leprosy tissues and on experiments in animals, indicates that leprosy bacilli are found usually in the Schwann cells. These observations contradict the view of the pathogenesis of leprosy put forward by Khanolkar in which the nerve fiber is consid-

ered to be the site in which the bacilli multiply and in which bacilli travel along the nerve pathway in the axoplasm of the nerve fiber. Recent experimental studies in rats and man have shown that Schwann cells behave as phagocytes capable of ingesting not only neural debris but also foreign particles, such as carbon particles or mycobacteria, in their neighborhood. It is significant that Schwann cells have been shown to have general phagocytic activity as well as the well-recognized function of phagocytosing neural debris. The Schwann cells are most actively phagocytic at the time of nerve degeneration or regeneration. Since there is a physiologic turnover of nerves all the time, particularly in the skin, there will always be some Schwann cells in an active phase. Recent experiments (Weddell, Rees and Jamison, Pathogenesis of Leprosy, Ciba Symposium, No. 15, 1963, p. 3) on patients with leprosy have shown that activated Schwann cells have selective powers of ingesting mycobacteria; they are said to phagocytose heat-killed human leprosy bacilli actively, but not heat-killed rat leprosy bacilli. This observation is of such fundamental importance that it must be confirmed. In addition to these basic observations on the nerve-fiber-Schwann-cell complex in man and experimental animals, it is of interest that nerve involvement has been observed also in some of the experimental mycobacterial infections in animals following injection of *M. leprae*.

3. Application of electron microscopy: In addition to the value of electron microscopy for defining nerve involvement more precisely in leprosy, it is a valuable tool for examining the host-bacillus relationship at the cellular level. Recent studies suggest that the intracellular reaction to *M. leprae* differs in lepromatous and borderline patients and furthermore that degenerate bacilli predominate in Virchow cells.

EXPERIMENTAL TRANSMISSION

The members of this Round Table Committee are favorably impressed by recent progress in the field of experimental transmission of *M. leprae*. At present some of the results obtained in different laboratories using different conditions or species of animals do not agree. It is believed that the more progressive and extensive experimental infections in animals need to be investigated further and particularly to be confirmed more consistently and in different laboratories, before finally being accepted as caused by the human leprosy bacillus. Nevertheless the Committee considers that the definite infection produced in the footpads of mice is presumably a human leprosy infection, particularly since it has now been reproduced consistently in several different laboratories and with *M. leprae* derived from patients all over the world.

In order to maintain progress in this most important field, to encourage exchange of data and materials, and to stimulate others to

undertake this type of work, the Committee recommends that the International Leprosy Association set up a working Committee on Experimental Transmission.

APPENDIX

The members of this group considered it of the greatest importance at the present stage of transmission studies to summarize their views regarding problems and methods in animal transmission experiments and criteria for assessing successful claims. Procedures are recommended as follows:

Inoculum: Suspension of M. leprae from man.—(a) Take biopsy specimens from untreated, smear-positive patients (to include all types of leprosy from lepromatous to reactional tuberculoid, classified, if possible, clinically and histologically). Biopsy specimens should not be taken from ulcerated lesions.

(b) Prepare suspensions of bacilli from biopsy specimens and inoculate them into animals as soon as possible (if delay is unavoidable, keep tissue in wet and *not* dry ice). Prepare suspensions in saline or albumin-saline. Compare suspensions of bacilli prepared with and without separation of human tissue by differential centrifugation.

(c) Count the number of acid-fast bacilli in suspension (Hanks and Hilson and Elek methods) in order to inoculate animals with known numbers of bacilli and compare large and small inocula. Make a differential count of the proportion of uniformly and irregularly staining bacilli.

(d) Culture suspensions on types of media suitable for isolating mycobacteria and incubate for not less than 3 months at 2 temperatures, 37°C and 30°-34°C. Culture suspensions in the untreated state and also after decontamination by a method used for treating sputum. (If culture-positive mycobacteria are isolated they should be identified and inoculated into animals.)

Choice of animals and plan of animal experiments.—(a) Present results suggest the use of the mouse and hamster, but as many different species of animals as possible should be compared. The use of very young animals is recommended. Because of the slow development of human leprosy, animals with a long life span should be tried. It was particularly recommended that an attempt be made to inoculate a colony of young chimpanzees and follow these by annual biopsy throughout their life span. Where possible a study should be undertaken comparing results in different strains of inbred and pure-line mice. Although every route and site of inoculation should be studied, particular attention should be paid to colder sites, i.e., ear, footpad and testis. (In order to compare results in different centers the animals' house temperature and the type of diet should be recorded.) In addition to the use of normal animals, the effect of hormones, diet (par-

ticularly including pro-oxidant diets), x-irradiation and any other alterations that might increase susceptibility to infection, should be studied.

(b) The series of animals should include: (1) animals inoculated with living bacilli; (2) animals inoculated with heat-killed bacilli; (3) uninoculated normal animals;² (4) animals modified by special diets, etc., divided into two groups, receiving living and heat-killed bacilli, and (5) standard diagnostic animals, i.e., rabbit and guinea-pig.

Investigation of bacteria isolated from animals.—(a) Count the total number of acid-fast bacilli harvested from the animal or particular site of inoculation and determine the proportion of uniformly and irregularly stained bacilli.

(b) Culture bacilli isolated (as under *Inoculum* (d) above).

(c) Prepare a standard type lepromin (integral and/or Dharmendra type) from the bacilli harvested from the animals and compare with a similarly prepared human lepromin in patients with tuberculoid and lepromatous leprosy. The tests should be carried out and read "blind." (The "animal" and human lepromins should be adjusted to contain the same number of acid-fast bacilli. Since the "animal" lepromin will contain animal tissue antigen, it is possible that this foreign antigen will produce a skin reaction in man. It may be necessary therefore to skin-test with a "lepromin" prepared from normal tissue or add normal animal tissue to the standard human lepromin.)

(d) Make enzymatic studies.

(e) Make serologic studies.

Histologic examination of animal tissues.—This study should be undertaken by a histopathologist trained in leprosy, who should look not only for alterations similar to those in man but also for unusual findings, particularly those recurring in animals. Histologic examination should be carried out routinely on all animal tissues (Zenker-type fixative recommended, and staining by H and E and Ziehl-Neelsen methods, using Wade modifications). If tissues have to be sent away, formalin fixative should be used.

Because acid-fast bacilli have been found associated with nerves in a number of recent experimental leprosy infections, nerves should be observed and where possible a special study should be undertaken using light (including silver staining) and electron microscopy. Because in man leprosy is the only mycobacterial infection known to involve nerves, and although it is stated that murine leprosy does not affect nerves, the Committee recommends that this question be reinvestigated in murine leprosy.

Response of experimental infection to drugs.—The pattern of response to antimycobacterial drugs in infected animals should be studied

²These groups are of great importance because normal stocks of mice and hamsters have been shown to harbor noncultivable ("murine leprosy type") mycobacteria.

as a means of (1) identifying the organism and (2) screening new antileprosy drugs.

Interpretation of results.—All the above studies are undertaken in order to determine how far experimental leprosy infection resembles the infection in man and to exclude where possible any other known mycobacterial infection, particularly the noncultivable murine leprosy infection. It is important to include adequate controls, and positive results should be accepted only if they are consistent and reproducible.

REPORT OF THE ROUND TABLE ON BORDERLINE AND INDETERMINATE LEPROSY¹

The clinical and histologic manifestations of leprosy are determined by the resistance of the individual to the infection. High resistance determines the tuberculoid, and low resistance, or its absence, the lepromatous picture. These types constitute the two "poles" of leprosy (or the polar types generally considered to be stable). Between these two "poles" are those patients whose resistance is intermediate and unstable.

BORDERLINE LEPROSY

Definition.—The Round Table agrees with the statement of the Madrid Congress that the borderline (dimorphous; intermediate; bipolar) group comprises a variety of cases between the tuberculoid and lepromatous types, and is of the opinion that the position occupied by any borderline case in the spectrum between tuberculoid and lepromatous leprosy depends on the host-parasite relationship, or, in other words, on the resistance of the patient to the infection.²

Onset and evolution.—Borderline leprosy may start as borderline leprosy or may develop from the indeterminate group. It develops rarely from the tuberculoid type or the lepromatous type under treatment. The development may occur acutely or more gradually. It is generally agreed that it is an unstable form of leprosy, and although some cases remain borderline throughout their course, others move toward the lepromatous "pole" of the spectrum or toward the tuberculoid "pole."

Clinical description.—The question of resistance being fundamental, some cases will occupy a position nearer the tuberculoid "pole" of the spectrum, some nearer the lepromatous "pole" and others in between. Hence a wide range of clinical manifestations may be encountered. The Round Table does not propose to describe all of these, but wishes to draw attention to some characteristic clinical features. One type takes the form of an oval or circular area of normal or hypo-

¹The Round Table was composed as follows: Dr. R. D. Azulay, *chairman*, Dr. W. H. Jopling, *secretary*, and Drs. R. G. Cochrane, F. Contreras, Dharmendra, T. Imaeda, J. R. Puchol, W. F. Kirchheimer, K. Kitamura, F. Sagher, L. de Souza Lima, *members*.

²Drs. Contreras, Puchol and Imaeda do not agree with the use of the words "dimorphous" and "bipolar."

chromic skin, sometimes atrophic, surrounded by a band of raised skin of variable width and irregular shape. The edge limiting the circular area is clearly marked, giving a "punched-out" or "Swiss cheese" appearance, whereas the outer edge tends to flatten and fade into the normal skin. These lesions vary in number, size and location, and some degree of anesthesia can be found in them. Plaques may simulate those of tuberculoid or of lepromatous leprosy, the edges being well defined in some parts and indistinct in others. They are frequently succulent and of shiny appearance; their color may vary widely. Skin lesions usually have an asymmetric distribution. The ear lobes are often involved, sometimes unilaterally. Edema of the extremities may be present. Peripheral nerve involvement may occur; if present it gives rise to sensory disturbance of the extremities, with or without palpable thickening of the affected nerves. There may be muscle weakness, with or without wasting.

Bacteriology.—Skin lesions are usually bacteriologically positive, the degree of positivity depending largely on the position of the case in the above-mentioned spectrum. Globi are few or absent. The nasal mucosa may be negative for bacilli.

Histology.—The histologic appearance also depends on the position of the case in the spectrum. An incomplete and loosely arranged tuberculoid structure may be found, the main feature of which is the epithelioid cell. Usually there is a clear but narrow subepidermal zone. A not fully-developed lepromatous structure may be present, with large numbers of histiocytes, many of which may contain lipid (vacuolated) cells, but in contrast to lepromatous leprosy there is a variable amount of cellular infiltration of cutaneous nerves.

Immunology.—The lepromin test (Mitsuda) is generally negative. When positive it is never strongly so. It may vary between negative and weakly positive during the course of the disease ("oscillatory phenomenon").

Prognosis and response to treatment.—The prognosis is more favorable than in lepromatous leprosy and the response to treatment is more rapid.

INDETERMINATE LEPROSY

Definition.—This is a form in which early leprosy usually manifests itself. It may evolve to any other form of the disease, but sometimes continues unchanged or even regresses.

Clinical description.—Indeterminate leprosy presents clinically with hypochromic and/or erythematous macules. These vary in number, size and location, and frequently show some impairment of sensation. The borders may or may not be well demarcated. Palpable thickening of peripheral nerves is not likely to be encountered in the early stages.

Bacteriology.—Bacilli are usually absent on routine examination, and, when present, are few.

Histology.—This shows scattered nonspecific histiocyctic and lymphocytic infiltration, with some concentration around skin appendages and neurovascular bundles. Isolated bacilli may be found within cutaneous nerves.

Immunology.—The lepromin test may be negative or positive.

REPORT OF THE PANEL ON LEPROA REACTION¹

Definition.—In a broad sense the word "reaction" comprises all acute and subacute manifestations of leprosy. Leprologists are aware of the damage left by reactions in other forms of leprosy, but consider as more frequent and important the acute and subacute episodes in lepromatous leprosy.

Classification.—The Madrid Congress classified reaction as follows: (A) Leprea reaction, (B) Erythema nodosum. This Panel is of the opinion that the true lepra reaction is erythema nodosum and that the so-called "lepra reaction" of the Madrid Congress should be called "lepromatous exacerbation." It is recognized that there are objections to these terms, but it is suggested that, in view of their long and customary usage, they be retained until improvement in the state of our knowledge makes it possible to adopt a rational nomenclature.

It is proposed, therefore, to distinguish the following:

1. *Leprea reaction* (lepromatous).—An acute or subacute clinicopathologic syndrome that appears during the chronic course of lepromatous leprosy, with systemic symptoms and local lesions in the skin and other organs. The lesions are related to varying degrees of vasculitis of an inflammatory, nongranulomatous nature, which are produced by some mechanism of hypersensitivity whose pathogenesis needs to be clarified. Leprea reaction presents a variety of clinical and histologic manifestations, which are broadly distinct, but which frequently occur in combination (e.g., erythema nodosum necroticans).

(a) Erythema nodosum:—Disseminated and painful nodosities, which appear in sites apparently not affected previously by the lepromatous process.

(b) Erythema multiforme:—The typical appearance is of flat and extensive reddish lesions in "cocarde."

(c) Erythema necroticans:—(Lucio phenomenon). Multiple red and painful capriciously-shaped spots with a tendency to dry or bullous necrosis. This cutaneous lesion of lepra reaction is more common in diffuse lepromatous leprosy, but may appear in the nodular form.

2. *Lepromatous exacerbation.*—This term applies to a rapid ex-

¹The Panel was composed as follows: Dr. F. Latapi, *chairman*, Dr. D. S. Ridley, *secretary*, and Drs. J. Ramos e Silva, A. R. Mercier, J. H. Frenken, D. Peryassu, A. Aguirre de González, C. Sisirueá, C. K. Job, E. A. Carboni, J. G. Tolentino and J. Terencio de las Aguas, *members*.

tension of lepromatous lesions, with possible appearance of new ones of the same nature.

HISTOLOGY

1. *Lepra reaction*.—This includes the three forms of erythema listed above. Characteristics of the first two of these, which are histologically similar, is the focalized accumulation of polymorphonuclear leucocytes in the dermis or subcutaneous tissue. The lepromatous granuloma, usually small, is regressive, with much foamy degeneration. The dermis is otherwise normal. In erythema nodosum necroticans extensive polymorphonuclear leucocytic infiltration sometimes proceeds to abscess formation. It is more diffuse than in other types of lepra reaction. Capillaries frequently show endothelial swelling and sometimes necrosis. Toward the end of the reaction there is an increase of plasma cells. Edema is a prominent feature of this reaction. The dermis shows evidence of collagen and elastic damage, with fibroblastic increase. In the Lucio phenomenon polymorphonuclear leucocytic infiltration is intense, and diffuse or multifocal. The reaction is characterized by vasculitis, the vessels affected being of larger caliber than in necrotizing ENL. The dermis is not much affected.

2. *Lepromatous exacerbation*.—The reaction is mild. There is some edema. The dermis shows a slight increase of fibroblasts. The lepromatous granuloma differs from that of lepra reaction. It is active, with an increase of histiocytes and young macrophages.

BACTERIOLOGY

1. *Lepra reaction*.—Bacilli are usually few in the areas of polymorphonuclear infiltration. In the surrounding lepromatous foci the number of bacilli is comparable to that in the nonreacting lepromatous lesions. The bacilli are already granular before the onset of the reaction.

2. *Lepromatous exacerbation*.—There is an increase in the number of bacilli in the lesions at the time of the reaction, and an increase in the percentage of solid-staining forms.

PATHOGENESIS

The acute and subacute episodes are closely linked with the immunologic process, which in turn determines the various clinical forms of leprosy. Disturbance of the immunologic equilibrium may precipitate an acute attack, with the appearance of disseminated lesions. The disease itself may become better or worse. Several factors may disturb the equilibrium between the host and the bacilli. Physical and mental stress, endocrine imbalance, intercurrent infections, and specific anti-leprosy therapy, are some of the more important ones. Some investigators believe that acute and subacute episodes are part of the natural

history of the disease and independent of external factors. It is suggested that intensive research in immunology be undertaken to elucidate the pathogenesis of this complex process.

TREATMENT

With the various factors liable to intervene in the pathogenesis of lepra reaction in mind, rational therapy should be designed mainly to eliminate or interfere with the constant or repeated action of the determining or "trigger" causes referred to above. Treatment should be conditioned in each case by the severity of the reactional episodes. To this end, therapy will be directed as follows:

(a) Basic general treatment, intended to control systemic symptoms. Emphasis is laid on the restoration, by means of blood transfusion, of the blood picture, which is nearly always disturbed by a severe lepromatous reaction.

(b) Symptomatic treatment, especially designed to act on the acute, focal or regional manifestations, such as ocular, neural, articular, testicular and visceral reactions. In such cases it is advisable to call in the corresponding specialists for consultation.

In the circumstances indicated above, as in others not specified, benefits can be secured by the use of the antimonials, certain antibiotics, the antimalarials, antihistaminics, etc. Only when acute attacks are severe can the administration of corticoids or ACTH be considered, and then only under strict medical control. The Panel advises against their routine use.

Specific treatment of leprosy should be maintained, lessened or stopped altogether, according to the severity of the reactional state.

PROPHYLAXIS

The Panel makes the following recommendations:

1. Every patient, before specific treatment is started, should be submitted to a comprehensive clinical examination. The presence of any intercurrent affection of a general nature (infectious, metabolic, hormonal) or local nature (septic foci, parasitic, etc.) should be determined. A record should be made of the nutritional state, and also of any stress that might disturb the patient's psychosomatic balance.
2. A detailed laboratory examination, especially of blood and serum, should be made.
3. Specific treatment should not be started until the patient is found to be in good condition.
4. Initial doses should be minimal, and the effective dosage reached only after a suitable period.
5. Periodic clinical and laboratory examinations should be made as frequently as required in each particular case.
6. The inconvenience of iodide medication should be borne in mind.

REPORT OF THE PANEL ON THERAPY¹

In presenting this report, the Panel on Therapy states at the outset that in spite of much good work at various centers on several new drugs, there is no spectacular progress to record in the therapy of leprosy since the last Congress. No one drug seems to be outstanding in its action, or likely to supplant dapsone on the grounds of therapeutic efficacy, cost or ease of administration.

1. *Sulfone therapy. Dapsone (DDS).*—The Panel considers dapsone as still the drug of choice in sulfone therapy for general use in active leprosy. Its well-known advantages and disadvantages have been stated in previous reports. The Panel wishes, however, to draw attention to the following points:

(a) *Slow therapeutic action:* The main shortcoming of dapsone is its slow effect (clinical, bacteriologic and histologic) in the serious forms of leprosy. This is probably related to such factors as the essential chronicity of the infection and long generation time of *M. leprae*. While dapsone may produce bacterial negativity and clinical arrest in lepromatous leprosy in from three to six years, up to 50 per cent of patients in some countries may still be bacteriologically positive at the end of that time. Whatever their proportion to the total number of patients who respond satisfactorily, these "persistent positive cases" constitute a therapeutic challenge. Poor absorption from the intestine for one reason or another is a possible explanation, but bacterial resistance may occur. Further investigation is required. Moreover, the removal of nonviable acid-fast debris may be abnormally protracted in some patients, and the tissues in others may be persistently hypersensitive to acid-fast material.

(b) *Duration of treatment:* Previous Congresses have given general guidance, and there has been no great departure from former practice. There is now, however, a greater readiness to advise that treatment continue for life, after clinical and bacteriologic arrest of lepromatous or borderline disease, with half the standard therapeutic dose. After arrest of the disease, regular bacteriologic examinations are advocated as the best and earliest means of detecting relapse.

(c) *Dosage:* In an attempt to reduce the incidence of neuritis and all types of reaction, many workers have been using a smaller initial oral dose, and a lower maximum dose than has been recommended in the past. Although the Panel believes that each area individually must decide its own optimum dosage schedule, it is to be noted that many workers have obtained excellent results with 25 mgm. twice weekly initially, rising to a maximum of 200mgm. twice weekly. For mass

¹The Panel was composed as follows: Dr. S. G. Browne, *chairman*, Dr. M. F. R. Waters, *secretary*, and Drs. A. M. Alonso, A. Baccaredda-Boy, J. Barba Rubio, R. A. Brechet, T. F. Davey, J. C. Gatti, G. Pérez-Suárez, J. Aguiar Pupo, W. O. Opromolla, R. Rollier, A. T. Roy, K. F. Schaller, S. Schujman, M. S. Silva, *members*.

treatment by medical auxiliaries, different dosage schedules are not recommended for the different types of leprosy, although the Panel would add that the initial dose should be small and increments made slowly.

(d) Injectable repository dapsone: Various preparations that give adequate blood levels for two weeks are in general use, but as yet no suspension of dapsone for injection once every four weeks has been forthcoming.

(e) Prophylaxis: There is insufficient evidence at this stage to advise either on the efficacy of the prophylactic use of sulfones or on the advisability of giving sulfones prophylactically.

2. *Thiambutosine (DPT, Ciba-1906)*.—This drug has gained widespread acceptance as a useful alternative to dapsone, although the development of resistance after two years has been reported from many countries. It has proved useful in particular in patients intolerant to dapsone. An injectable preparation is under investigation.

3. *Ditophal (Etisul)*.—This continues to evoke contradictory comments. The consensus, however, would seem to be that while ditophal has an undoubted action in leprosy when given alone (though resistance may develop), its addition to standard dapsone therapy for a longer or shorter time, in an untreated or a treated patient in stationary condition, does not generally result either in more rapid clinical or bacteriologic improvement than with dapsone alone, or in material shortening of the total length of treatment required. Notwithstanding good reports from some centers, ditophal has not received consistent acclaim. Its odor is generally a disadvantage and its cost makes it an uneconomic drug when its use is not followed by definite shortening of the period of treatment. Local dermatitis and generalized cutaneous hypersensitivity precipitated by its use vary in incidence from negligible to very high. Where the clinical forms of leprosy are most severe, opinions concerning the drug are least commendatory. Its future sphere of usefulness may well be limited.

4. *Long-acting sulfonamides*.—These have been studied now for five years. Early reports indicated that sulfamethoxypyrazine (also known as sulfamethoxy pyridazine) gave uniformly good results in small series of patients with tuberculoid leprosy, but that bacteriologic improvement in patients with lepromatous leprosy was not consistently good. More recently, other long-acting sulfonamides have been tried at a few centers, and preliminary reports covering up to two years suggest that these compounds may have a definite place in antileprosy therapy. Mention may be made of acetylsulfamethoxypyrazine (acetyl-Kelfizine, or 11,589 R.P.), and Ro 4-4393. In lepromatous leprosy, their action seems to be comparable to that of the sulfones. No adverse side-effects have been reported to date, and the incidence of drug-induced reaction is not greater than with the sulfones. According to some

workers, but not to others, the action of these drugs in tuberculoid leprosy may be more rapid than that of the sulfones. Expanded trials are indicated in this promising series of drugs. While those at present under trial cannot be expected to replace dapsone in mass therapy, the advantages of a drug given orally, once a week, are evident.

5. *Other drugs.*—(a) Diaminodiphenyl sulfoxide (DDSO) has been found too nephrotoxic for general use. (b) Thiacetazone (thiosemicarbazone, TB-1): in certain hands thiacetazone continues to give satisfactory results, although emergence of drug resistance must be borne in mind. (c) Streptomycin and isoniazid (INH, isonicotinic acid hydrazide): insufficient new information has been gained during the past five years for any addition to be made to the last Congress report. (d) B-663, a rimino-compound (*aposafranin*), has given good results both alone and in combination with dapsone in a small series of patients. Further trials are indicated. (e) Rifamycin: this drug has been studied in a very few patients only. Further reports are required before it can be evaluated. (f) Vadrine, cycloserine, kanamycin, and many other compounds reported on by different centers may, for various reasons, have a limited sphere of usefulness, but none appears to be sufficiently promising to be recommended for widespread use.

6. *General considerations.*—A therapeutic agent capable of several diverse actions is required in leprosy. This ideal agent should be rapidly bactericidal, facilitate the clearance and removal from the body of nonviable acid-fast material, and minimize or abolish the pathologic effects of the presence of living or dead acid-fast material in the tissues. Several drugs are either bactericidal to *M. leprae* in approximately nine months, or prevent their multiplication, but all workers are agreed that this desirable result is not equivalent to clinical cure of leprosy. The main kinds of leprosy for which such an agent is urgently required are the long-standing lepromatous, the severe and rapidly-advancing lepromatous, the reactional tuberculoid, the reactional borderline, and all kinds of leprosy characterized by severe neuritis. Perhaps the concurrent use of more than one agent will eventually be the answer to the problem.

7. *Bacteriology.*—The Panel considers that uniformity in expressing the bacterial index is desirable in all reports of therapeutic trials. Some members were of the opinion that a logarithmic scale such as Ridley's should be studied with a view to its eventual adoption. Meanwhile, members of the Panel are strongly of the opinion that all reports should include information concerning the morphology of *M. leprae* as seen in smear preparations made according to standard techniques, expressing as percentages "normal solid-staining rods" and "non-solid forms" of all kinds.

REPORT OF THE PANEL ON EPIDEMIOLOGY AND CONTROL¹

In order to meet space limitations a selection of topics has been made by the Editor, from the detailed Report submitted by the Panel. Its Chairman, who advised the Editor in the difficult matter of selection, has emphasized the value of the full report for all interested in leprosy control. The full report will be made available on request as indicated in the statement preceding this series of panel and committee reports.

EPIDEMIOLOGY

The epidemiology of leprosy deals particularly with relationships between the prevalence of leprosy or its various forms and determinants such as host factors or ecologic conditions, which may affect either exposure to infection or resistance to the disease. Through such knowledge it is possible to develop and test sound measures for its control. Control implies definitions, measurements, and research.

1. DEFINITIONS

(This paragraph emphasizes the importance of clear definition of terminology, screening methods and procedures of diagnosis.)

2. MEASUREMENTS

(Prevalence and incidence rates as applied to leprosy are defined. Methods to obtain prevalence data by total population surveys, sampling surveys and selective surveys are dealt with extensively, with special consideration for the biases and pitfalls encountered for the derivation of such information in leprosy. With regard to the ratio of lepromatous to the total number of patients, emphasis is laid on the fact that this ratio can be misleading and must always be followed by the prevalence rate for lepromatous leprosy. Other measurements are mentioned, and some other types of measurements which should be developed are enumerated.)

3. RESEARCH

Epidemiologic research in leprosy is considerably hampered by our present lack of fundamental knowledge. The fact that *M. leprae* has not yet been cultivated nor routinely transmitted to animals has prevented experimental study of the agent factors involved in the spread of the disease. Host-factors are difficult to investigate because of the absence of bacteriologic, serologic or skin-test methods for detecting latent or possibly nonapparent infections. The length of the

¹The Panel was composed as follows: Dr. M. F. Lechat, *chairman*, Drs. B. D. Molesworth and A. Salazar Leite, *secretaries*, and Drs. E. Agricola, D. A. Akintonde, L. M. Balina, L. M. Beehelli, C. M. Brusco, W. M. Cantidio, O. Diniz, E. H. Hermans, C. Kettanurak, J. A. Madeira, M. Orusco, F. E. A. Rabello, H. Sansarricq, A. Saul, *members*. Drs. J. M. de Barros and R. Huerta, *observers*.

silent period before clinical onset, makes it often impossible to single out simple environmental factors.

Under these circumstances prospects for epidemiologic investigations in leprosy are heavily dependent upon achievements in the corresponding fields of microbiology and immunology. It is anticipated that extension and speeding-up of research in these fields will provide the epidemiologist with new baselines and new tools. In the present state of knowledge, certain special problems should be studied.

1. *Genetics.*—Several observations suggest a possible role of genetic factors in the susceptibility or resistance of individuals and populations to leprosy or to the lepromatous type of the disease. The possibility of a genetic mechanism should be studied with respect to (a) leprosy itself, (b) polar types of the disease, (c) the occurrence of lepra reaction in lepromatous leprosy, (d) reactivity to tuberculin associated with nonreactivity to lepromin, and (e) the nonconversion of the lepromin reaction after BCG.

These problems could be studied in twins, in families, and in populations. In each case, they will require joint planning by a statistician, an epidemiologist, a geneticist and a leprologist, for they call for highly elaborate methods of sampling and statistical interpretation. For twins' study, a world central registrar of twins with leprosy should be setup, eventually with the help of WHO. Studies of familial aggregation should be undertaken or expanded in areas where good demographic and clinical records have been available for several generations.

Methods of population genetics should be applied to leprosy. Studies of genetic polymorphisms associated with leprosy and with its manifestations should be expanded and coordinated, in order to proceed in various parts of the world among patients and controls to a large screening of the genetic markers known at present. The development of micro-methods for field use, shipment or storage, has radically modified and enlarged the scope of possible investigations, and should be used largely in leprosy. Cooperation with serum banks should be sought, and blood samples collected and deposited for future investigations, since new methods will be made available and new genetic markers discovered.

2. *Lepromin reaction.*—(*Problems deserving further attention in this field are enumerated.*)

3. *Attack rates among household contacts.*—Attack rates among household contacts should be studied and compared in different parts of the world, wherever reliable data are available, keeping as a model of such investigation the studies of Doull and his colleagues in the Philippines. Life-table methods may be used, and other epidemiologic methods could be designed eventually after consultation with mathematicians.

Special attention should be given to attack rates among contacts with respect to the type of leprosy in the index case. A point of particular importance is the role of tuberculoid cases in transmission of the disease in areas of the world where open cases constitute only a small proportion of the cases.

4. *Urbanization.*—(*Urbanization provides opportunities to study environmental factors.*)

5. *Limited foci.*—

6. *First lesions.*—

7. *Arthropod vectors.*—The possible role of insects in the transmission of leprosy has been long neglected. More data are needed on the cultivability of acid-fast bacilli found in various insects, and on the relative frequency of such findings in insects associated with cases of leprosy as compared to those found in other places.

8. *Carrier stage.*—

9. *Spontaneous healing.*—

10. *Association of disease.*—

11. *Deformities.*—(*Application of epidemiologic methods to the study of deformities is recommended.*)

12. *Lepra reaction.*—

13. *Nutrition.*—

14. *Miscellaneous.*—The various factors that may influence the epidemiology of leprosy are so numerous that here only a brief list is given of factors for which data are available or could be obtained. These include: (a) prevalence and type of leprosy in relation to race, climate, altitude or living conditions, (b) information regarding relapses after treatment, (c) possible role of tuberculoid cases in the transmission of leprosy, (d) influence of puberty, pregnancy, severe illness, change of conditions or menopause on the development and evolution of leprosy, and (e) modification in the epidemiology resulting from changes in control policies such as the replacement of compulsory segregation by outpatient treatment.

CONTROL

Because of its long duration and the deformities it causes, leprosy constitutes a severe burden for the affected individual as well as for the community. In many countries, it is only one of the major health problems. Consequently it must be dealt with in coordination with other public health programs. Among these programs, however, it deserves a high priority.

Control of leprosy has as its objective the progressive reduction of its morbidity, in such a manner that it no longer constitutes a public health problem. Its far-reaching goal is eradication of the disease. It implies activities following three lines, viz., prevention, early detection, and treatment. Rehabilitation is a necessary complement.

Measures to meet these objectives may be grouped under six headings: (1) administrative, (2) medical, (3) training of personnel, (4) health education, (5) social, (6) legal. Research to improve and to adapt these measures continuously is needed.

One must realize, however, that in many circumstances there is a gap between what should be done and what can be done. Leprosy control is inseparable from the development of other health activities and of the potential of the whole nation. Difficulties may also be encountered as a result of previous leprosy campaigns, leading to the necessary acceptance of facilities, personnel and even methods not in accordance with present conditions or new concepts. In such cases, it is sometimes necessary to cope with the situation as it stands, making the best possible use of it and modifying it progressively, rather than to seek drastic changes.

1. ADMINISTRATIVE MEASURES

(General principles of public health must be applied to leprosy control. Special consideration is given to gradual integration of the leprosy campaign with general public health activities.)

2. MEDICAL MEASURES

The principal weapon of the antileprosy campaign is still chemotherapy with sulfone drugs. Regular and prolonged sulfone treatment, generally over several years, reduces infectiousness in the majority of cases. It follows that if a considerable proportion of bacteriologically positive patients are treated, the disease will decline. Sulfones, however, do not arrest the progress of deformities once these are initiated, and appropriate action must be taken to prevent and correct deformities. For special cases, or in particular situations, other chemotherapeutic drugs are valuable.

Other means, either of a preventive or therapeutic nature, such as a rapidly effective bactericidal drug, are urgently needed. If these means should become available, they would probably change our present approach and lead to a modification of the measures outlined in this report.

At present, therefore, in many countries, and as a result of the large number of patients and limit of resources, control implies mass treatment by a form of sulfone therapy that can be administered safely and with standard methods by auxiliary workers supervised by highly qualified medical personnel. DDS administered either by mouth or by repository injections fulfills those requirements. The primary problem thus becomes largely a logistic one: (a) to make the optimal use of medical facilities, budget and personnel in order to detect and to treat a maximum number of patients, especially those who are bacteriologically positive or likely to become positive, (b) to detect and treat pa-

tients early enough in the course of the disease, (c) to apply therapy when it is most effective, (d) to prevent the onset of deformities, and (e) to secure regular attendance of the patients in a regimen of treatment prolonged over several years. Medical measures therefore are threefold: (a) case finding, (b) treatment, and (c) protection of healthy population with special reference to contacts.

Measures must be adapted to the region under consideration. To do this, the importance of a preliminary survey is stressed. The leprosy campaign should start first by a pilot project in a selected area. The pilot project should serve to adapt general principles of leprosy control to the local situation, in prospect to future development, as well as to train personnel. Expansion of the work to other areas should be progressive and systematic, in keeping with the development of the local health services.

Control measures must be corrected continuously and adapted as the campaign progresses and more experience is gained. Efficient control, therefore, implies evaluation of the results. Built-in methods of evaluating results are mainly a matter of local conditions, and their use cannot be generalized at present. As a matter of principle, however, one should seek simplicity and avoid undue multiplication of forms and reports, whose only result is to harass the worker in the field and yield loose information. A few accurate facts are better than a large number of inaccurate ones. It is obvious that cooperation from any available adequate sources, in terms of medical facilities or manpower, governmental or voluntary, will be sought following the lines laid down by the leprosy service.

(a) *Case finding.*—(*Methods of case finding are described.*)

(b) *Ways of treatment.*—In all cases detection must be followed by treatment, either by the surveying team, or through referral to a leprosy treatment unit. If a multistep procedure is used for detection, with preliminary screening by auxiliary workers, treatment should not be withheld pending confirmation of the diagnosis. Emphasis should be placed on the necessity of early, regular and prolonged treatment. The possibility of reactions and other complications should be anticipated.

(1) *Outpatient care:*—Depending on the stage of development of the local health services, outpatient care should be carried on by fixed health centers, mobile units or both. There should be an adequate number of such facilities, the number and distribution being related to the prevalence of the disease in various regions. Treatment centers should be conveniently accessible and so located as to serve the largest number of patients.

Fixed centers staffed and equipped for general public health services, such as health centers, rural polyclinics and dispensaries, should be adapted progressively to carry out all functions essential to the

antileprosy program and integrated in their basic activities of preventive and curative medicine. Leprosy functions include at least the recognition, treatment and follow-up of patients. Whenever and wherever possible they should extend to include examination of contacts, application of simple techniques of rehabilitation, surveys for leprosy in the local population, home nursing and social work. In countries where dermatologic clinics are well developed, these may collaborate to perform leprosy activities.

Wherever necessary, fixed centers should be supplemented by mobile units. Advantage should be taken of mobile teams to launch other health activities, in such a manner that the mobile unit will constitute a nucleus for developing integrated services later.

(The subsequent paragraphs in this section deal with prevention of deformities, rehabilitation of outpatients, management of acute complications, and problems of attendance for treatment.)

(2) Inpatient care:—Indiscriminate and compulsory isolation for leprosy is condemned. The following principles apply:

(a) Up-to-date facilities for inpatient care are necessary for those in acute reactional phenomena, resistant to routine treatment, intolerant to drugs, or in need of reconstructive surgery and other rehabilitation measures. Construction of small units may be advisable. These facilities should be located near, tied in or better integrated into a general hospital, in order to benefit from the services of various specialities.

(b) In countries with already existing adequate facilities, the most infectious cases could be induced to enter sanatoria on a voluntary basis. The period of hospitalization should be temporary, and only sufficient to effect clinical regression and to reduce infectiousness. A prolonged series of negative smears should not be required for discharge. A rapid turnover of patients in sanatoria, with early transfer to outpatient treatment, will reduce the chance of social atrophy due to institutionalization. Due consideration should be given to the care of burnt-out cases, and indigent and irremediable invalids. Care should be taken, however, that patients of this category, and even more that of reluctant negatives, do not jam the existing facilities. These sanatoria form also the centers for research, for training of professional personnel of all grades, and for special surgery. A large part of the activities must be directed to rehabilitation.

Leprosaria should be adapted to perform these functions. The construction of new large institutions is positively not recommended. Hospital facilities should coexist with outpatient treatment and should be complementary, but efforts at hospitalization should not be permitted to drain the budget and the efficiency of out-patient treatment centers, which form the core of leprosy control.

(c) *(This paragraph deals with segregation villages or agricul-*

tural colonies for leprosy patients, as found in various parts of the world.)

(d) *Protection of the healthy population with special reference to contacts and children.*—(1) *Removal of children.*—In many countries experience has shown that to remove an infant from its mother increases the mortality. The separation of a baby from its leprous parents is therefore not generally recommended and leprosy must be taken as a calculated risk and other methods of protection attempted. A temporary separation, however, can be considered where adequate creche facilities or willing relatives exist, until such time as the parent is negative. Psychologic trauma is so important that the period should be reduced to the minimum. There is no need of special institutions for children of leprous parents, but, when institutional care is necessary, they should be admitted to establishments for general child care.

(2) *BCG.*—There is evidence that BCG may anticipate the conversion to positivity of the lepromin test in children and that with or without BCG there is a group of poor or slow responders in whom the lepromin reactivity cannot be achieved. Field studies are necessary to determine whether that anticipation is useful to individuals not yet exposed to *M. leprae* and whether it may prevent leprosy in contacts and in those who are persistently lepromin-negative. This study is difficult because of the relatively low incidence of leprosy and of the need of following up the studied group for some years.

At the same time research should be continued to determine the relation between intensity of lepromin reaction and age, with oral and intradermal BCG, influence of larger doses, the behavior of individuals or other age-groups, especially 0-6 months and adults, the effect of BCG in children and adults previously exposed to *M. leprae* or not and persistently lepromin-negative, and the eventual need of revaccination. There is urgent need to continue research on the preventive value of BCG in leprosy and these studies are strongly recommended.

(3) *Chemoprophylaxis.*—Some research has been carried out on chemoprophylaxis, but there is not yet a definite conclusion on its value as a preventive measure. Chemoprophylaxis trials are very important to ascertain whether it might be useful or not for household contacts, and what should be its duration and the best dosage.

As data confirming or refuting the effectiveness of either or both methods of protection (BCG and chemoprophylaxis) are as yet insufficient, no recommendations can be made. It is hoped that the trials now in progress may lead to a definite conclusion.

3. TRAINING

(This section deals with the training to be given for different categories of personnel engaged in leprosy control, with special attention to paramedical workers.)

4. HEALTH EDUCATION

(Methods of health education as applied to leprosy control are reviewed.)

5. SOCIAL MEASURES

Although noticeable progress has been accomplished in the last several years, erroneous concepts regarding the disease continue to impose harsh and unjustifiable penalties upon the leprosy patient and his family. The obligation of society to render assistance, education, medical care and social help is complementary in public health.

(Different types of assistance are considered. Special problems are given attention: admission of leprosy patients in general hospitals when affected by other diseases, mental patients suffering from leprosy, prisoners, and the right of education for children with leprosy.)

6. LEGAL MEASURES

Leprosy must be classified among other transmissible diseases, and special legislation directed to the disease should be abolished. In the meantime, where extravagant legislation is not yet repealed, the application of existing laws must be brought into line with present knowledge. Reporting of the disease to the health department, however, is a necessity and should be required on the part of the physicians or other professional personnel in charge. The importance of professional secrecy in doctors and auxiliaries is stressed.

Indiscriminate compulsory segregation is an anachronism and must be abolished. Discretionary authority, in certain circumstances, could be given to health officials to require isolation of lepromatous patients discharging bacilli in those instances in which sulfone therapy is neglected or ineffective. The only desirable compulsory measure is the medical examination for transmissible diseases.

On the international level, special attention should be paid to nomadic populations, especially when campaigns are unequally developed on two sides of a border.

7. RESEARCH IN PUBLIC HEALTH METHODS

The control of leprosy is closely dependent on the present state of knowledge concerning the epidemiology of the disease. For example, a better understanding of the mechanism of transmission may bring about basic changes in our present methods of control. There is, however, another type of research directly related to the procedures of control. This may be called research in the field of management and administration of public health.

Evaluation of the best methods for integration of leprosy control in general public health activities is one example. Combination of a leprosy campaign with other health campaigns is advantageous, but not

all measures are likely to yield the same returns and to display the same efficiency. The possible psychologic effect of one-shot, fast-acting campaigns, such as a dramatically effective yaws campaign, on the cooperation of patients in the same community engaged in a treatment of long duration such as that for leprosy should be studied.

The problem of poor attendance for treatment, and of the very high rate of drop-out, should be studied on a large scale. There seem to be different patterns of drop-out; they should be identified, their cause found, and remedies proposed. The relationship between methods employed for giving the drugs and the cooperation of the patients, should be stressed.

Methods for training paramedical personnel require special consideration, in order to develop teaching methods to stimulate their interest, promote their initiative, and prepare them in a practical way for the task that faces them.

Choice of the best strategy for detection of the maximum number of cases with resources available, as well as the organization of outpatient treatment, including allocation of time, budget and personnel, location of the clinics, determination of areas of priority, and fixation of mobile teams' itineraries and schedules, could benefit by methods developed in the field of operational research and system analysis.

Leprosy control should take advantage of the collaboration of specialists from other disciplines, not only epidemiologists, biostatisticians and health educators, but also psychologists, cultural anthropologists, economists, management scientists and research analysts.

It is hoped that researches on these problems will be conducted during the next few years, eventually under the auspices of WHO, and results made available for the IXth International Congress.

At present, the whole body of measures recommended against leprosy is directed mainly at recognized patients. With progress of knowledge in microbiology and epidemiology, leading to better understanding of the ecology of *M. leprae* and its transmission among populations, and with progress in therapy and the possible development of immunizing agents, it is hoped that more rational and better control of leprosy will be achieved.