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Reports of Committees

Committee 1: Advances in Experimental Leprosy

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1. INTRODUCTION

This report covers the five years since the last International Leprosy Congress. However, before reviewing these advances and their relevance to leprosy in man, it is necessary to consider, on the one hand, the contributions made from studies on experimental models in the successful fight against other infectious diseases and, on the other hand, the particular difficulties in developing any experimental models for studying leprosy. In no field of medicine has greater progress been made than with the infectious diseases, particularly those caused by bacteria but also some viruses. This progress in knowledge, whether on the microbiological, pathological, preventive or therapeutic side, has evolved, in the first instance, from studies on the cultivation and *in vitro* properties of the causative organisms and only subsequently on experimental animal models. Unfortunately, leprosy has remained an exception, because *Mycobacterium leprae* has still not been cultured *in vitro* and only since 1960 has an animal model been available. Therefore, once animal models were available for studying leprosy it was reasonable to assume that they would also be applicable to leprosy in man. In the first instance, the mouse footpad infection was systematically exploited and has enabled the same topics to be studied in leprosy as in other bacterial diseases affecting man. However, the mouse model had also to be adapted for studying the bacteriological characteristics of *Myco. leprae,* which for other bacteria are studied *in vitro*.

From these general and particular considerations the field of experimental leprosy has been developed and has rapidly advanced, all within the last 13 years, almost entirely based on animal models using the mouse and more recently, the rat and the nine-banded armadillo. Our report summarises the relevance, importance and suitability of these animal models in contributing to knowledge of leprosy in man.

2. ANIMAL MODELS

2.1. Mouse. Shepard in 1960 presented unequivocal evidence that infections with *Myco. leprae* could be transmitted to animals by showing that *Myco. leprae* multiplied locally when inoculated into the footpads of mice. This claim has been

fully substantiated on hundreds of strains of *Myco. leprae* in laboratories throughout the world. By applying standardized techniques the footpad infection has provided a sensitive and reproducible *in vivo* model for bacteriological studies on *Myco. leprae.* However, bacterial multiplication in the footpad is limited to increases of 100-fold and confined to the first 6-8 months following inoculation. Although *Myco. leprae* infections in other rodents, including rat and hamster, are similar to the mouse, practical reasons favour the mouse as the standard model.

In 1966 Rees introduced the immunologically suppressed mouse model on the assumption that multiplication was limited in the normal mouse by the development of immunity to *Myco. leprae* infection. Pure-line strains of mice are used (mainly CBA) and made immunologically deficient by adolescent thymectomy (T) followed by total body irradiation (900R), requiring syngeneic bone marrow replacement. In T/900R mice *Myco. leprae* continue to multiply beyond the 6-months period, giving eventual yields of bacilli 10-1000-fold higher than in normal mice. These observations in mice have been confirmed in other laboratories. To simplify the T/900R procedure, lead shielding of a limb, or T followed by 5 fortnightly exposures to 200R, has been used successfully. Both modifications avoid bone-marrow replacement and permit the use of outbred mice.

Thus two distinct mouse models were developed initially for bacteriological studies of *Myco. leprae.* Subsequently the models were exploited to study the evolution and pathogenesis of experimental leprosy throughout the animals' life-span (2-3 years), following inoculation of *Myco. leprae* locally into the footpad or ear, intraperitoneally or intravenously and, in limited experiments, animals exposed to aerosols or nasal drops.

2.2. Rat. Footpad infection with *Myco. leprae* in the intact rat is similar to the one in the mouse. In the neonatally thymectomized Lewis rat, however, the bacillary population reached levels 100-fold higher than in the intact animal. Following intravenous inoculation, spread to peripheral sites (footpad, ear, tail and nose) occurs. The advantage of these immunologically impaired animals is that they do not develop runting disease. Subtotal body irradiation appears to further depress their immunological capacity.

2.3. Armadillo. The nine-banded armadillo (*Dasypus novemcinctus,* Linn.), a primitive mammal, possesses some unique biological characteristics, which could make it a valuable animal model for leprosy research. Among the biological features particularly relevant to leprosy are: (a) low body temperature (32-35); (b) long life-span (12-15 years) and regular production of litters of monozygous quadruplets.

Kirchheimer and Storrs reported disseminated infection with *Myco. leprae* in an armadillo in 1971. Further results in the short period available have shown at autopsy that about a third of dermally inoculated armadillos become systematically and heavily infected before 37 months, In these animals the histology was of the human lepromatous type, including nerve involvement. In the other inoculated animals there was no evidence of infection, including some observed up to 42 months. In addition the two intravenously inoculated armadillos have developed disseminated infection within 30 months.

The evidence for the identification of the organism grown in the armadillo as *Myco. leprae* is based on: (1) Mouse footpad inoculation; (2) Failure to grow *in vitro*; (3) Lepromin testing; (4) Dopa-oxidase activity; (5) Pyridine extraction; (6) Histological picture and (7) Immuno-diffusion test.

3. CHARACTERISTICS AND CLINICAL IMPLICATIONS OF ANIMAL MODELS FOR RESEARCH IN LEPROSY

The main work and advances have come from the mouse models because they were first to be developed.

Unless otherwise stated, the succeeding report is based on the mouse model.

3.1. Bacteriological characteristics. The growth pattern and rate of multiplication of *Myco. leprae* (mean generation time 13 days) in the mouse footpad of normal and T/900R mice is completely reproducible for all primary isolates of bacilli from leprosy patients including drug resistant strains, or after serial passage in mice. These characteristics now form a basis for the identification of *Myco. leprae.*

Important recent applications of these criteria are:

(a) Monitoring the viability of *Myco. leprae* used to inoculate other animals and the identification of the acid-fast organism subsequently recovered.

(b) Identification as *Myco. leprae* of acid-fast bacilli in nasal discharges and their survival up to 1.75 days in discharges allowed to dry outside the body.

(c) Identification of *Myco. leprae* in various arthropods fed on leprosy patients or recovered from arthropods in the vicinity of cases with untreated leprosy.

(d) Monitoring *in vitro* attempts to cultivate *Myco. leprae.*

Until *Myco. leprae* are cultured *in vitro,* the only, but relatively small, laboratory source of *Myco leprae* has been from mice. Susceptible armadillos can now provide large yields of bacilli which will be of the greatest importance for future studies on *Myco. leprae.*

3.2. Clinical implications. Although there are small variations in the growth pattern of leprosy bacilli in mice, the same variations are seen in bacilli obtained from bacilliferous patients in different parts of the world. There is no evidence from these obervations that the geographical variation in the clinical form of leprosy is caused by variations in the virulence of different strains of *Myco. leprae.*

3.3. Chemotherapeutic applications. Very great advances have been made in chemotherapy entirely based on the mouse models and which are reported in detail by the Committee on Experimental Chemotherapy. However, it is important to make clear that drug-resistant variants (to dapsone and thiambutosine) have the same infectivity and pathogenicity in the mouse as sensitive strains. All studies on the significance and incidence of drug resistance in leprosy should be based on tests using the mouse footpad model. On the other hand, basic studies on the frequency of drug resistant mutants in populations of *Myco. leprae* could only be studied in highly susceptible animals with bacillary populations comparable to those found in man. The susceptible armadillo is the animal model most likely to provide this important information.

3.4. Pathological characteristics. A detailed picture of the pathology and pathogenesis of *Myco. leprae* infections in the mouse models has evolved from histological studies of tissues taken at regular intervals throughout the life-span of the animals (based on CBA mice). To correlate the histology with the bacteriology during the evolution of the infections, paired organs or tissues divided equally were used for the respective assessments.

The main findings are summarized:

(a) Although a lesion is first localized to the site of inoculation, systemic spread eventually occurs, with overwhelming evidence that it is haematogenous in origin,

since bacilli are found in the lining cells of capillaries haphazardly throughout the body. There are, however, sites of predilection, including the dermis of footpads, ears and tail, the nose, the testes and dermal and peripheral nerves. Although nerves become infected later than the other sites they are always involved by 20 months. The nose and testes are the sites most frequently and heavily infected. These same sites of predilection follow intravenous or intraperitoneal inoculation of *Myco. leprae.*

(b) The late cellular and bacterological patterns of response to *Myco. leprae* mimic those seen in human leprosy as defined by the Ridley-Jopling classifications. Thus by 20 months in the normal mouse, there is a well-developed epithelioid granuloma resembling BB to BT type leprosy and in T/900R mice the lesions resemble BB to LL type leprosy. Cellular changes in nerves mimic the complete spectrum of human disease from TT to LL.

(c) Nasal involvement, particularly in T/900R mice, is associated with positive nasal smears and histologically shows, unlike the dermis, the juxtaposition of the granuloma to the surface epithelium giving exit of bacilli to the exterior.

(d) Histological studies on immunological models have shown that established lepromatoid leprosy in T/900R mice changes to a BB or BT picture when the mice are given syngeneic lymphnode cells or thymus grafts. These changes are associated with an influx of lymphocytes into the lesions, destruction of bacilli, oedema and later collagen deposition. Similar changes are seen in nerves and are followed by destruction of axons.

(e) *Myco. leprae* has the same predilection for nerves in the mouse as in man, a characteristic shared by no other species of mycobacterium. Early nerve infections show bacilli in Schwann and perineural cells, later axons and perineural cells are destroyed and at both sites this is followed by deposition of collagen. Special studies have shown that leprosy neuritis in mice is associated with a defect in the blood-nerve barrier, since markers, such as trypan blue and ferritin, readily diffuse through the endoneural capillaries. This defect plus the destruction of the perineural sheath would seriously change the endoneural environment, thus diminishing nerve conductivity and also allowing the entry of macrophages and lymphocytes.

(f) In all the mouse models striated muscle fibres were frequently seen to contain bacilli. In human leprosy although smooth muscle such as arrector pili and dartos are frequently infected, striated muscle is less so.

Preliminary histological studies in susceptible armadillos also show the importance of haematogenous spread, including infection of nerves, nose with positive nasal discharges and most other sites common to man and mouse. In the armadillo the cellular picture at autopsy resembles LL type leprosy. However, in the armadillo, atypical sites, including the lung, are heavily infected, possibly because of lower body temperatures.

3.5. Clinical implications. The significance of these models for studying clinical leprosy is that they reproduce, or can be adapted to reproduce, many of the features of leprosy in man. They particularly provide models for studying early phases of the evolution and pathogenesis of leprosy that can never be undertaken in man. These features are of particular importance for studying the pathogenesis of leprosy neuritis and possible routes of infection via the lungs, nose or gastro-intestinal tract. Mice provide precise models for unravelling the immunological complexities of leprosy, bearing in mind that the majority of patients with leprosy are in the TT to BB range and these are the types of leprosy seen in

normal mice. The armadillo, on the other hand, may in addition provide models for studying innate susceptibility and resistance and their possible genetic bases.

4. CONCLUSIONS

The report summarizes the considerable advances that have been made in experimental leprosy using animal models in a period of only 13 years. Thus, animal models are proving to be as valuable in leprosy as they have been for studying other human infections. The particular merits of the various animal models available for studying leprosy are discussed.

References

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Committee 2: Advances in the Microbiology of *Myco. leprae*

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This report has been prepared by members of the Committee on Microbiology.

The report summarizes the progress made in the field of general microbiology of *Myco. leprae* during the past 5 year period since the 9th International Leprosy Congress in London in 1968. *Myco. lepraemurium* has been included in the review as an interim model for *Myco. leprae*. Progress has been made in four areas: cytology; metabolism; cultivation; and the identification of *Myco. leprae*.

1. CYTOLOGY OF *MYCO. LEPRAE*

1.1. Morphological Index (solid ratio). The utility of the morphological index (MI), based on the proportion of solidly staining *Myco. leprae* cells has been exploited particularly to follow the initial antimycobacterial drug action in patients during chemotherapy. The present MI does not distinguish the infectious from the non-infectious patient. No unified opinion has been formulated regarding the question whether the ratios of solid staining bacilli are associated with viability in the bacteriologic sense. Further studies appear necessary.

1.2. Pyridine-extractable acid-fastness. Myco. leprae in section or smears lose the property of acid-fastness, but not gram-positivity when extracted with pyridine. The acid-fastness of *Myco. lepraemurium, Myco. tuberculosis* and *Myco. intracellulare,* is not affected by this procedure. It has been suggested that a differentiation between *Myco. leprae* and other mycobacteria is possible by using Ziehl-Neelsen staining after extraction with pyridine. Further studies are needed with *Myco. ulcerans* and *Myco. marinum* from human lesions, with *in vitro* grown mycobacteria and with senescent populations of cultivable mycobacteria.

1.3. Electron microscopy. Studies with the combined use of electron microscopy and chemical and biological techniques were caried out. Miscellaneous information such as the band structure and peptido-glycolipid filaments on

the surface of *Myco. leprae,* chemical components of the cell wall of *Myco. lepraemurium* and the electron-transparent capsule-like outer zone around the bacilli were obtained.

As a significant discovery, the mycolic acids in the cell wall of *Myco. lepraemurium* were demonstrated to differ from corynemycolic or nocardic acids. The characteristic mycolic acid-arabinogalactan-murein in the cell wall of *Myco. lepraemurium* resembles that in other members of the genus mycobacterium such as *Myco. tuberculosis bovis* and strain BCG. The discovery of mycolic acid in *Myco. leprae* isolated from human tissues likewise indicates that this pathogen is a mycobacterium.

In the field of electron microscopy, further chemical and biochemical information would permit the interpretation of the relationship between structure and function or the physiologic state of *Myco. leprae.*

2. METABOLISM OF *MYCO. LEPRAE*

The extraordinary long generation time of 12-14 days in the mouse footpad has been regarded as one of the characteristics of *Myco. leprae.* No information is available to explain this slow rate of metabolism. One difficulty in metabolic studies on *Myco. leprae* is that of obtaining adequate supplies of cells and a second is that of collecting all the bacilli as suspensions without tissue contamination.

Fragmented reports have appeared indicating the presence of various enzymes in *Myco. leprae.* Among these, *o*-diphenoloxidase has been suggested to be unique to *Myco. leprae,* being distinct from plant and mammalian enzymes. Concentrates of *Myco. leprae* prepared from lepromatous material actively oxidized 3, 4-dihydroxyphenylalanine (DOPA) to pigmented products. This specific metabolic activity has been proposed as an identification test for *Myco. leprae.*

Ribulose diphosphate carboxylase activity was demonstrated in the supernatant from disrupted *Myco. leprae* collected from lepromatous tissues. It appears to be important if confirmed, because this enzyme occurs otherwise only in autotrophic bacteria and green plants.

Recent evidence has suggested an incorporation of tritiated thymidine into leprosy bacilli in cultures of human lepromatous macrophages. If the observation is confirmed, this is an important advance, because it implies that the organisms were synthesizing DNA. Further studies of this type are needed.

2.1. Metabolism of Myco. lepraemurium. Since the last congress, knowledge of the metabolism of *Myco. lepraemurium* increased dramatically. The major advance is in our knowledge that the overall energetics of the organism operate independently from those of the host. It has been demonstrated that *Myco. lepraemurium* contains a cytochrome-linked pathway for oxygen utilization. Due to the limited rate of terminal electron transfer, the assimilation and oxidation of exogenous substrates occurs very slowly and does not result in marked stimulation of oxygen uptake.

Experiments using isotope-labelled substrates and cell-free extracts of *Myco. lepraemurium* have confirmed the following facts:

(1) An extraordinarily slow rate of aerobic metabolism based upon a host-independent tricarboxylic acid (TCA) cycle. All enzymes of the TCA cycle were demonstrated, the pyruvate and α-ketoglutarate dehydrogenases being rate limiting. Although the TCA cycle may contain an alternative pathway at the

∝-ketoglutarate step, a conventional TCA pattern of isotopic distribution arose during substrate oxidation.
(2) There appears to be a lack of capacity to oxidize glucose, even though its incorporation into cellular material was established.
(3) Short-chain fatty acids, in contrast to medium-chain fatty acids, cannot be utilized for lipid synthesis.

Studies on energetics have been further advanced by the development of ultrasensitive methods for determining ATP (energy levels) in host-grown microbes. Host ATP has been eliminated and the quantitation of ATP refined to require only 1/60th the number of bacterial cells employed in the most sensitive methods hitherto available. The method has been applied thus far to demonstrate the potential losses of ATP during extraction, purification, prolonged refrigeration, and the growth potential of *Myco. lepraemurium* in cultivation studies. These methods have been designed to investigate the energetics of *Myco. leprae.*

3. CULTIVATION PROBLEM

3.1. Cultivation of Myco. leprae. Four cell-free systems have been described for the cultivation of *Myco. leprae in vitro.* These are: (a) a U-tube divided by a fine sintered glass membrane and using a conventional medium for mycobacteria, (b) an inorganic medium suitable for autotrophic bacteria, (c) semi-soft agar media, and (d) media enriched with substance of mycobacterial origin. These experiments have not been successfully repeated by other investigators.

Attempts at cultivation in cell cultures were carried out using cell lines of human origin, cell strains derived from human tissues, cell strains derived from animals, and mouse macrophages. No proliferation of the bacteria was noted.

Recently, evidence has been obtained regarding a limited multiplication of *Myco. leprae* within the macrophages derived from human peripheral blood cells. The applicability of the method is restricted by limited survival of the host cells. The majority of host cells did not survive beyond 60-80 days in most cultures.

3.2. Cultivation of Myco. lepraemurium. Extracellular growth of *Myco. lepraemurium* was obtained in cell-impermeable diffusion chambers implanted in the peritoneal cavities of mice. The generation time observed was 11 days. The division time was shortened to 8 days when macrophages were included in the chambers.

Noteworthy reports on the growth of *Myco. lepraemurium* in cell-free medium have appeared recently and reproducible results have been obtained by some other investigators.
(1) A pale yellow, R type macroscopic colony was produced on 1% egg-yolk solid medium after more than 3 months of cultivation at 37°C. Subcultures have been continued for 10-16 generations. Low plating efficiencies indicate a need for further studies.
(2) From 30-300 fold multiplication of *Myco. lepraemurium* (Hawaiian strain) was noticed at 30°C in Kirchner's medium containing calcium pantothenate, α-ketoglutaric acid, cytochrome *c* hemin and L-cysteine. Successive cultivation through serial transfer is required. Corroboration is desired in order to determine if specific growth factors are needed.

4. ADVANC S IN IDENTIFICATION OF *MYCO LEPRAE*

The WHO Expert Committee on Leprosy 1970 made a report on the identification of *Myco. leprae* as follows:

> "In all the cultivation work, it is important to prove the viability of the purported growth and to identify it by the methods now available (the inoculation of mouse footpad, lepromin test, enzymatic studies of DOPA oxidation, and serological identification of nodular extract antigen)."

The pyridine sensitivity and the specific *o*-phenoloxidase in *Myco. leprae* have already been described.

It has been observed that leprosy nodular extract (NE) contained at least two antigens which were differentiated from human serum proteins by the immunodiffusion test. One of these antigens was a heat-stable polysaccharide, and the other was a heat-labile protein which gave a single precipitation line with anti-NE serum absorbed with human serum. In as much as this antigen is highly specific for *Myco. leprae,* serological identification of *Myco. leprae* by the technique of immuno-fluorescence should become practicable with antiserum prepared against the antigen.

Committee 3: Advances in Experimental Chemotherapy

Members: C. C. Shepard *(Chairman)*; G. M. Ellard: L. Levy; V. A. Opromolla; S. R. Pattyn; J. H. Peters; R. J. W. Rees; M. L. R. Waters.

1. INTRODUCTION

Progress in the last decade in leprosy now allows the same topics to be studied in leprosy as in other bacterial diseases. They are:

(a) Screening of new drugs, and determination of minimal effective dosage (MED).

(b) Characterization of anti-leprosy activity: bactericidal, bacteriostatic, or bacteriopausal (prolonged bacteriostasis).

(c) Methods of measurement of drug in blood and tissue, and determination of minimal inhibitory concentration (MIC), pharmacokinetics including repository effect.

(d) Toxicity in relation to MIC.

(e) Metabolism of the drug.

(f) Short-term clinical trials to determine whether the drug is also active in man.

(g) Long-term clinical trials to determine whether the drug's activity continues to smear-negativity.

(h) Very-long-term follow-up to see if smear-negativity is maintained or if drug-resistant *Myco. leprae* eventually emerge.

These steps should be followed in the development of anti-leprosy drugs. Patients should not be deprived of standard dapsone (DDS) therapy in order to test compounds that have not been tested against *Myco. leprae* in animals or compounds that appear on the basis of results in animals to be clearly less efficacious than standard therapy.

2. DRUG SCREENING AND CHARACTERIZATION OF ANTI-LEPROSY ACTION

2.1. Experimental model. In the absence of significant growth of *Myco. leprae in vitro*, all work must be done in animals. Most research has been done in the mouse model. This infection is very consistent. Genetically uniform mice are readily available and easily maintained in standard conditions. Hence, the mouse continues to be the animal of choice. Other animals may be useful when particular findings must be checked in another species. For studies requiring larger populations of *Myco. leprae*, the thymectomized-irradiated mouse, the neonatally-thymectomized rat and the armadillo may provide suitable animal models.

2.2. Methods of study. The continuous method of drug administration (from the day of infection to the end of the experiment) reveals whether a drug is active against *Myco. leprae*. The kinetic method (administration of drug during a limited period, beginning early in the logarithmic phase of growth of bacilli), determines whether a drug produces bactericidal, bacteriostatic or bacteriopausal effects. Administration of drugs in graded dosages allows the MED and MIC to be determined.

2.3. Results of drug screening and characterization. With these methods, more than 200 drugs have been tested. Only a few have exhibited bactericidal (or bacteriopausal) activity and these few appear to include most of the drugs of real promise in leprosy. These drugs include:

(a) DDS and other sulphones giving rise to DDS in the gut or in tissues.

(b) Rifampicin. The related antibiotic streptovaricin is distinctly less active.

(c) Clofazimine (B 663) and another phenazine dye, B 1912.

(d) Long-acting sulphonamides. These compounds appear to have MIC's close to toxic blood levels in man.

(e) Ethionamide. In the dosage apparently required to man, gastrointestinal distress is frequent.

2.3.1. MIC of DDS. This was found to be 0.01 to 0.001 μg/ml (microgramme/ml) in the mouse, corresponding approximately to an oral dosage of 1 mg a day in man. This finding in mice led to the introduction of treatment with acedapsone (DDADS), which releases DDS at a steady rate of 2.5 mg daily, following injections of 225 mg every 75 days. The therapeutic efficacy of this regimen and that of 1 mg oral DDS given daily, confirmed these predictions. It needs to be emphasized that this study of 1 mg daily was carried out to compare the MIC of DDS in mouse and man, and not to evaluate, or encourage, very low dose DDS therapy as a practical therapeutic regimen.

2.3.2. Bactericidal effect of rifampicin. The curves of blood concentration in the mouse and in man are very similar, and studies of the anti-*Myco. leprae* effect of per-kilo dosages in mice have been predictive of the results in man. With the kinetic method in mice, rifampicin, was found to produce as much bactericidal effect in a few days as DDS in a few months. Bactericidal rates for these two drugs in man appear to be the same as in the mouse.

2.3.3. Clofazimine. Studies of the MIC of clofazimine have not been practical because the drug is very unevenly distributed in the tissues; thus, blood and tissue levels may not accurately reflect the concentration of drug in the immediate environment of the organism.

2.3.4. Demonstration of drug-resistant *Myco. leprae*. The mouse provides the only method of proving drug resistance. DDS-resistant *Myco. leprae* have been demonstrated in mice from some patients who have relapsed on prolonged DDS

therapy. By contrast, DDS-sensitive organisms have been isolated from relapsed patients who have, in fact, stopped taking the drug. Studies have shown that 1 to 10% of sulphone-treated patients eventually undergo relapse caused by DDS-resistant *Myco. leprae.* Combinations of anti-leprosy drugs appear to offer the most promise for the prevention of these relapses. Thiambutosine- and thiacetazone-resistant *Myco. leprae* have been isolated from patients who have relapsed after therapy with these drugs.

3. PHARMACOKINETICS AND METABOLISM OF DRUGS

Comparative studies of the pharmacology of drugs in the mouse and man are necessary for understanding their anti-leprosy actions.

3.1. DDS. In man there are great individual differences in the rate of DDS elimination. The half-life (T ½) of the drug varies from 5 to 50 h. Among patients with relapses caused by DDS-resistant *Myco. leprae,* there is a significant excess of persons with very short half-lives. Since it is not possible to determine the T½ of all patients, regimens need to be designed so that they will take care of patients with shorter T½. Fifty mg DDS daily would ensure blood levels continuously well in excess of the MIC, whereas 350 mg once weekly (the same total dosage) would not. For this reason, it is insufficient to describe dosage merely in terms of the total weekly intake.

The only metabolite of DDS found in human blood is monoacetylated DDS (MADDS). Humans have been found to be genetically polymorphic in their acetylation capacities, resulting in rapid and slow acetylators. Rapid acetylators have higher ratios of MADDS/DDS in their plasma, but do not eliminate DDS more rapidly, so *a priori* one would not expect the acetylator status to affect the response of leprosy patients to DDS. Nevertheless, some studies, but not others, have suggested an excess of rapid acetylators among patients with relapses caused by DDS-resistant *Myco. leprae.*

3.2. Rifampicin. Pharmacokinetic studies of rifampicin are complicated because the half-life of rifampicin varies with drug concentration and because blood levels tend to decrease after the patient has been receiving the drug for several weeks.

3.3. Clofazimine. Similar studies with clofazimine have not been possible because the drug is accumulated in the tissues.

TRIALS IN MAN

4.1. Background. Applications of experimental chemotherapeutic findings to man has been inadequately understood. For a better understanding, the bacterial populations in human leprosy have to be considered (Table 1). A lepromatous patient with a Bacterial Index (BI) of 4+ (Ridley) and a Morphological Index (MI) of 10%, may be estimated to have 10^{11} *Myco. leprae* in his body, of which 10^{10} are viable. For example in line 3 of the table, after 1 to 3 months of DDS treatment, the MI is less than 1%, so that the number of viable *Myco. leprae* is less than 10^9. If mouse inoculation is negative, the number of viable organisms is less than a hundredth of its original value and may be estimated to be less than 10^8. With each decrease of the BI by 1 unit, the corresponding numbers of bacilli fall to a tenth of the prededing value (decrease by one exponent). When the BI is less than 2+, measurement of the MI or inoculation of mice with standard numbers of bacilli is not possible, so that measurement of the proportion of viable bacilli is impossible. Consequently it is not technically possible with present procedures to

TABLE 1

Estimated number of Myco. leprae *in typical lepromatous patients at various times during response to regular DDS therapy*

	Findings			Interpretation	
	BI	MI	Mouse inoc[b]	Total *Myco. leprae*	Viable *Myco. leprae*
1 Untreated	4+	10%	Pos	10^{11}	10^{10}
2 Dapsone 1-3 mths	4+	1%	N.D.[c]	10^{11}	10^{9}
3 1-3 mths	4+	< 1%	N.D.	10^{11}	$<10^{9}$ [d]
4 1-3 mths	4+	< 1%	(Pos)[e]	10^{11}	10^{8}
5 1-3 mths	4+	< 1%	Neg	10^{11}	$<10^{8}$
6 *ca.* 1 year	3+	< 1%	N.D.	10^{10}	$<10^{8}$
7 *ca.* 1 year	3+	< 1%	Neg	10^{10}	$<10^{7}$
8 *ca.* 2 years	2+	< 1%	Neg	10^{9}	$<10^{7}$
9 *ca.* 2 years	2+	< 1%	Neg	10^{9}	$<10^{6}$
10 *ca.* 3 years	1+	N.P.[f]	N.P.	10^{8}	$<10^{7}$ [g]
11 *ca.* 5 years	0	N.P.	N.P.	$\leqslant 10^{7}$	$<10^{6}$ [g]
12 Required for cure					0?

[a] When carried out according to the specifications described for "solid ratios" so that the proportion of "solid" bacilli is the same as the proportion of bacilli infective for mice.

[b] When 1×10^{3} to 1×10^{4} bacilli are inoculated.

[c] Not done.

[d] For example, $<10^{9}$ means that the number may lie between 0 and 10^{8} (inclusive).

[e] Weakly positive (long incubation period and irregular results in mice), indicating that the number of viable *Myco. leprae* is near the limit of detectability.

[f] Not possible.

[g] Since it is not possible to determine the MI with a BI of less than 2+, the estimate of viable *Myco. leprae* is based on the supposition that not more than 10% of the total are viable. This does not imply an increased number of viable *Myco. leprae*.

estimate the number of viable *Myco. leprae* present in the body at any number less than 10^{9}. These considerations allow one to understand how there can be many viable bacilli present in the body if treatment is stopped after the MI has reached baseline values and infectivity for mice can no longer be demonstrated. To explain relapse in a patient, it is clearly not necessary to assume that non-solid bacilli have become viable. Similarly, in a patient with negative smears, it is not necessary to assume that non-acid-fast viable forms of *Myco. leprae* exist, since there could be as many as 10^{6} typical, viable but undetected *Myco. leprae* present in the body. The survival of living *Myco. leprae* during treatment appears to occur by two mechanisms. One, which is not unusual with other drug-bacteria combinations, is the survival of a small fraction of drug-sensitive bacilli in the continued presence of the drug. Such bacilli do not multiply, and since they are dormant or metabolically inactive, they remain relatively insensitive to the drug, until they resume normal metabolism. Moreover, the location of the bacilli in the tissues may be important, and some believe the location of *Myco leprae* in nerve or muscle favours their survival. Because of the large numbers of bacilli present, factors affecting even a very small fraction of the population of *Myco. leprae* become important.

The second, unrelated, mechanism of survival of *Myco. leprae* is drug-resistance. A small fraction of bacilli is genetically insensitive to the drug and can multiply in its presence. Again, because large numbers of bacilli are present in lepromatous leprosy, a small resistant fraction may constitute a large number of bacilli.

4.2. Clinical trials. In the treatment of leprosy, distinct differences exist between (a) the rate of loss of viability and (b) the rate of disappearance of acid-fast bacilli. Nearly all drugs that have been tried in leprosy were selected on the basis of their ability to carry out process (a), and such drugs do not affect process (b). During early treatment, (a) is much faster than (b).

Except for special studies in relapsed patients, all trials should be carried out in previously untreated lepromatous patients.

4.2.1. Short-term trials. These are carried out to confirm in man laboratory results of the anti-*Myco. leprae* effect of a drug. Two criteria may be applied:

(a) Measurements of the MI. These provide immediate results, but are difficult to standardize between laboratories, and are technically demanding.

(b) Mouse inoculations. They provide firm evidence of bacterial viability, are more sensitive than measurement of the MI, but they require greater investment of personnel and facilities, and results are available much later. Mouse inoculations may show more rapid bactericidal effect than do MI measurements, probably because changes in bacterial morphology may lag by perhaps two weeks behind loss of ability to multiply, a difference particularly evident with rifampicin.

Short-term trials may now be limited to a period of 6 months, or even much less, depending upon the regimen. The BI changes little in this period and is therefore of no value in such trials.

4.2.2. Long-term trials ("5-year trials"). These are carried out to determine whether a drug's activity continues until smear negativity and clinical and histological quiescence are reached. Not many patients on standard DDS treatment reach this stage within 5 years. For practical reasons, these trials usually need to involve commitments by appropriate organizations to ensure long-term continuity. Mouse inoculations are particularly helpful when treatment failure is suspected, in which case tests of drug-sensitivity provide crucial information. Measurements of the MI, if they can be performed reliably, may provide the first indication of treatment failure.

4.2.3. Very-long-term studies. Because of the very long generation time of *Myco. leprae,* a complete picture of the therapeutic efficacy of a drug cannot be obtained unless patients are followed for very long periods, perhaps for the rest of their lives. Therefore leprosy services that successfully practise very long-term follow-up of lepromatous patients can provide invaluable information on the final efficacy of regimen. As pointed out, smear-negativity does not signify that the patients is free of bacilli, but rather that the number of bacilli in the body is less than 10^7. The minimal number of viable *Myco. leprae* needed to cause a relapse in a lepromatous patient may be very small, since such a patient would not be expected to possess immunity against *Myco. leprae.* Therefore, treatment may need to be continued indefinitely. In these studies, it will be essential to determine whether relapse is caused by drug-sensitive or drug-resistant *Myco. leprae.* Experience with sulphone therapy has shown that such relapses may occur 5 to more than 20 years after the commencement of treatment.

5. CONCLUSIONS

The application of the mouse model has at last placed the chemotherapy of leprosy on an objective bacteriological and pharmacological basis. It has provided sensitive procedures for the assessment of new drugs, the response to treatment, and the detection of drug-resistance. It has also led to clarification of the theoretical basis of long-term and very-long-term clinical trials. These are difficult and expensive to carry out, but without them the final value of a regimen cannot be determined.

Committee 4: Advances in Immunopathology

Members: O. G. Skinsnes *(Chairman)*; T. Godal; M. Abe; C. K. Job; J. H. M. Pearson; D. S. Ridley; M. Ulrich; R. S. Weiser *(By correspondence)*.

Since the last Congress panel report in 1963, great strides have been made in the understanding of the immunopathology of leprosy. These advances, however, have been possible because of the great amount of pathologic information available from the work of the past century which has given direction to and formed a basis for the application of newer techniques and hypotheses in immunopathology generally.

Leprosy still remains clinically and histologically the best characterized infectious disease which covers the range from a stage of effective immunity at one end to a state of profound immunologic deficiency towards the infectious agent at the other.

Although advances in animal transmission of *Myco. leprae* have contributed significantly to the understanding of pathogenic mechanisms in leprosy, recent progress in basic medical research has provided methods by which it has become feasible to study in detail the host parasite interaction in the leprosy patient himself. This fact makes it increasingly important to establish and support laboratories in leprosy-endemic areas where immunopathological studies may not be undertaken on materials from leprosy patients. Such studies may not contribute to our understanding of disease processes in leprosy and related diseases but also give a lead to better care and control of the disease.

1. CLASSIFICATION

The classification adopted by the Sixth International Congress, Madrid, still seems operative, adequate and in conformity with new developments in understanding. Essentially, this classification recognized the two polar immunopathologic expressions of leprosy as "tuberculoid" and "lepromatous" with an interlying spectrum of variable manifestations, termed "borderline" (dimorphous) in place of the previously adopted "intermediate" and a category designated "indeterminate" of use particularly in early cases where the eventual classification characterization is not clear. This classification has been neatly summarized and correlated with its clinical, immunologic and morphologic expressions [*Lepr. Rev.* (1962), **33**, 119-128; *Int. J. Lepr.* (1966), **34**, 255-273] with the convenient code designations of TT, BT, BB, BL and LL added.

It is recommended that this system of classification and notation be generally used, and for ease of communication that this system be utilized in publications.

It is recognized that some workers and groups of workers feel that on occasion additional designative terms are necessary. It is suggested that when such are used, their relative position in the classification scale be stated and they be clearly defined either in terms of the full scale of immunopathologic and microbiological characterizations now used in classification, or, if they be used for clinical convenience, that this be stated. For reference purposes it is recognized that both the "Lucio" and the "histoid" expressions of leprosy are unexplained variants at the lepromatous end of the classification scale and it is desirable that these terms be retained and used appropriately.

The term "lazarine" leprosy has historical associations with both ulceration seen in "Lucio" leprosy and otherwise seen, often in association with debilitation. It is recommended that, since the cause of ulceration in "Lucio" leprosy is recognized to be vascular thrombosis with dermal infarcation, that the designation "Lucio phenomenon" be retained for this manifestation and the term "lazarine" be reserved for complicating ulcerative manifestions, particularly as associated with debilitation.

2. HISTOPATHOLOGY IN LEPROSY

The use of the biopsy for the diagnosis and classification of leprosy is well established. The significance of neural involvement in leprosy has long been recognized and is increasingly coming to the fore. It is urged that no histopathologic report on skin biopsies relating to the possibility of leprosy be regarded as complete or acceptable unless mention is made of evaluation of nerve involvement. It is of importance that all biopsies include full thickness of the dermis to provide inclusion of adequate cutaneous nerve samples.

3. MEASUREMENT INDICES IN LEPROSY

3.1. Bacteriologic Index (BI). The BI in use is of proven value. Variations in the standards employed in different laboratories impair its usefulness as a comparative measurement. Nevertheless, its standardized use in the form of log scale increments is recommended.

3.2. Morphological Index. This index, expressed as the percentage of solid form bacilli among the total counted, has come to be generally used as a measurement of the percentage of viable organisms present, and therefore as a measure of therapeutic response. Variations in its performance and in staining related thereto in various laboratories precludes its usefulness as a precisely comparative measure. The statistical confidence interval [*Int. J. Lepr.* (1971), **39** 857-862] is considerably greater when 100 bacilli are counted than when 200 are the basis of enumeration. The difference appearing when 200 is less significant and it seems reasonable to suggest, in balance, that the counting of 200 bacilli gives a more valid percentage whereas the counting of 400 is probably not worth the extra time and effort required. In patients in relapse it is important to utilize one or more of the most active lesions.

3.3. Histopathologic Index (HI). Also known as the Biopsy or Numerical Index. Based on the examination of an acid-fast strained paraffin section cut at 5 μm thickness, this assay utilizes the Bacterial Index system of bacterial concentration combined with an assessment of the proportion of the specimen occupied by bacilliferous lesion. Under controlled conditions it is more accurate than the slit smear index and has proved its value in research. It has not generally found a place in the routine management of patients.

4. SIGNIFICANCE OF VISCERAL LESIONS

The presence of bacillemia in leprosy postulated by the First International Leprosy Congress and subsequently demonstrated by a number of workers has recently been shown to be virtually continuous in untreated lepromatous leprosy. The circulating bacilli have been shown to be, in part at least, viable.

Significant morphologic evidence of leprous lesions in visceral organs, most particularly the liver, spleen, adrenal glands, bone marrow and lymph nodes has also been long available. More recently, however, biopsy studies have reiterated and extended the recognition that the visceral lesions essentially reflect the morphologic characteristics of the immunopathologic skin lesion type including episodes of lepra reaction. Such studies have also demonstrated that viable *Myco. leprae* are present in lepromatous leprosy in the liver and bone marrow, and it is therefore to be expected that they are present also in other areas of deposition. Though morphologic evidence suggests that these lesions may be viable evidence is not conclusive and that the presence of viable bacilli in these organs, though it may be supportive of this conclusion, can also be interpreted as merely the presence of recent haematogenous bacillary deposition.

Laryngeal lesions, at one time not infrequent and troublesome enough to require tracheostomy, have virtually disappeared under sulphone therapy. In contrast, nasal lesions, though also responsive to sulphone therapy, have increasingly been noted as a probable source of discharge bacilli for the spread of leprosy.

The nasal lesions in untreated lepromatous patients infiltrate cartilage and bone which form the framework of the nose, resulting in its collapse and deformity in some of them. Infection by secondary organisms may hasten this process of destruction. Similarly in the small bones of the hands and feet specific leprous osteomyelitis may be responsible for the bone erosion. But in this instance, more than often invasion by secondary organisms is responsible for loss of tissue, including bones. There are also the superimposed vascular alterations following nerve paralysis which create a complex pathogenic process. In addition, factors such as disuse atrophy, pressure atrophy etc., combine to produce the severe deformity that may be seen in these patients.

The involvement of the eye in lepromatous patients is a serious complication. There is infiltration of the iris, ciliary body, sclera and episclera by macrophage leproma. During the reactive phase there may be infiltration of the iris and cilary body by neutrophils with fibrinous exudate into the anterior chamber resulting in loss of vision. Anaesthesia of the cornea and lagophathalmos due to paralysis of the 5th and 7th cranial nerves respectively found in all forms of leprosy, may lead to corneal ulceration and ultimate loss of the affected eye.

5. PATHOLOGY OF NERVE INVOLVEMENT IN LEPROSY

Peripheral nerve involvement is a characteristic finding in all forms of leprosy, although the nature of the lesion varies depending on the type of this disease. In lepromatous leprosy the predominant picture is the invasion of the nerve by a large number of organisms which are present in perineural cells, Schwann cells and intraneural macrophages. There is also intraneural proliferation of all collagen and oedema. Inflammatory response bacillary antigen both intra- and peri-neurally and the nerve parenchyma is replaced by tuberculoid granuloma which in some instances may even caseate and form an abscess. *Myco. leprae* are demonstrable

with difficulty. In borderline leprosy the appearances are very variable, depending on the exact type of the disease.

Further, the nerve involvement is generalized in lepromatous and borderline leprosy and localized to one or few nerves in tuberculoid cases. However, the route of entry of organisms into the nerves is still a matter to be elucidated.

The onset of paralysis is slow and insidious in lepromatous leprosy, taking several years, and may improve under effective chemotherapy. In tuberculoid leprosy, however, the onset is comparatively rapid and usually irreversible. In borderline cases also the nerves are rapidly damaged and very severe and rapidly developing paralysis can occur in the presence of reactions.

The mechanism of destruction in the tuberculoid part of the spectrum is a delayed type hypersensitivity reaction to bacterial antigen in the nerve parenchyma. In lepromatous leprosy, although the presence of a large number of organisms ultimately causes much destruction, the exact pathogenic sequence of events is yet unclear. The reactions which may complicate all forms of leprosy commonly contribute to further damage.

Nerve damage is often permanent and disabling, and therefore of paramount practical importance in leprosy. Advances in the prevention and management of nerve damage are only possible as a result of increased understanding of the various mechanisms involved. Further research in this field therefore deserves high priority.

6. REACTIONS IN LEPROSY

A "reaction" in leprosy is regarded as a hypersensitivity phenomenon and does not include phenomena associated with the simple extension or regression of the infection. Biopsy studies are of value in elucidating whether or not such a reaction is taking place and for determining its nature. On occasion biopsies are essential.

Two types of reaction are well recognized, namely *erythema nodosum leprosum* (ENL) in lepromatous leprosy, and reversal reactions in borderline leprosy. ENL is associated with the infiltration of neutrophils as in the Arthus reaction. Necrosis and ulceration may follow. The presence of immune complex deposits have been reported in ENL lesions, together with alterations of complement levels in serum. Confirmation is awaited, but the precise nature of ENL remains to be fully elucidated. Reversal reactions are associated clinically and histologically with an increase of cell-mediated immunity which can be demonstrated by lymphocyte function tests. In experimental animals reversal reactions can be precipitated by the injection of syngeneic lympoid cells.

A number of other reactions are liable to occur and lack of fundamental knowledge precludes their classification. These include:

(a) Reactions in tuberculoid leprosy which are presumably an expression of delayed hypersensitivity;

(b) Reactions in borderline leprosy associated clinically and histologically with a downgrading within the immunological spectrum or with no change in immunity, though the results of lymphocyte function tests are variable;

(c) Reactions in lepromatous leprosy which vary in form from a simple localized neutrophil infiltration or necrosis in a hyperactive nodule to severe ulcerating lesions associated with thrombosis and dermal infarction in the "Lucio phenomenon". The relation of these lepromatous reactions to ENL remains to be determined.

Further studies of lepra reactions are regarded as important. It is recommended

that the most promising approach is a controlled longitudinal study with combined clinical, histological and immunological observations before, during and after the period of reaction. A further possible means of advance lies in the study of the antigenic structure of *Myco. leprae* since the antigenic components involved in the reactions are not yet determined. Two polysaccharides designated *beta* and *delta* have been demonstrated and a protein antigen able to elicit delayed type hypersensitivity has been isolated.

A most serious and possibly fatal sequel of severe lepromatous leprosy is the development of renal lesions, including amyloidosis. It is not yet clear to what extent this is due to ENL or to other forms of reaction. It is urged that renal biopsies on selected patients should be included in studies of reaction where facilities permit; and that the kidneys of patients who come to necropsy following reaction should be made available for study.

7. LEPROMIN

The following antigenic preparations of *Myco. leprae* appear at present to be used in the study of delayed (skin) hypersensitivity to *Myco. leprae* [*Bull. Wld Hlth Org.* (1973), in press]:

(a) Suspension of whole autoclaved homogenized leproma ("integral" lepromin).
(b) More purified bacillary suspensions ("bacillary" lepromin).
(c) Non-coagulated soluble bacillary proteins ("leprolins").
(d) Defatted and disrupted bacillary suspension ("Dharmendra antigen").

While lepromin containing whole bacilli elicits both an early (Fernandez) reaction (48-72 h) and a late (Mitsuda) reaction (3-4 weeks) "leprolins" and Dharmendra antigen elicit mainly an early reaction and none or a weak late reaction.

The early reaction indicates existing hypersensitivity to the injected antigens. The late reaction, on the other hand, allows sufficient time for the test subject to become sensitized by the injected antigens. Thus, the late reaction may not only measure existing delayed type hypersensitivity, but perhaps also provide information about the test subject's capacity to initiate and/or amplify the response to the injected antigens. The high incidence of late lepromin positive individuals in leprosy non-endemic areas is in agreement with this view. The late reaction, therefore, does not indicate whether a subject has previously been exposed to *Myco. leprae* or not. Its primary importance appears at present to be limited to the determination of prognosis in leprosy patients. Further information about the lepromin reaction may be found in a recent WHO Report [*Bull Wld Hlth Org.* (1973), in press].

It is recommended that in publications relating to their use, the type of antigen used and the nature of the reaction measured should be clearly specified.

It is urged that, if current reports of massive *Myco. leprae* proliferation in the armadillo continue to show validity, efforts be made to develop and utilize this source of bacilli for the preparation of standardized lepromin and leprolin that could be made universally available.

8. THE USE OF BCG IN THE IMMUNOPROPHYLAXIS OF LEPROSY

In the absence of additional information, this panel echoes the recommendation of the WHO Expert Committee on Leprosy [*Fourth Report, WHO Tech. Rep. Series No. 549,* (1970)] to the effect that it is premature to recommend the

general use of BCG vaccination and that final recommendation be postponed until the results of the controlled studies in progress achieve definitive evaluation.

9. IMMUNE RESPONSIVENESS IN LEPROSY

The concept of a host-determined immunologic spectrum in leprosy has received steadily increasing clinical and pathologic support during the last decades to the point where leprosy today stands forth as a unique immunopathologic disease model. The immunologic support for this concept was initially based on delayed hypersensitivity skin testings. More recently a considerable number of other immunological methods recently applied in studies on humoral and cellular immune responsiveness in leprosy include:

9.1. Humoral immune responsiveness

(a) Quantitative examination of serum immunoglobulin levels.
(b) Semi-quantitative determination of antibody production to TAB (typhoid-paratyphoid A and B) after active vaccination.
(c) Presence of anti-mycobacterial antibodies in serum by fluorescent antibody and gel precipitation techniques.
(d) Detection of antibody-coated bone marrow derived lymphocytes (B-cells) by immune fluorescence.

9.2. Cell-mediated immunity

(a) Delayed skin sensitivity to microbial antigens such as PDD and "artificial" antigens such as dinitrochorobenzene and picryl chloride.
(b) Detection of sheep red cell rosette forming lymphocytes (T-cells).
(c) Blastoid transformation of peripheral blood lymphocytes. This may be measured by morphologic examination of stained lymphocytes or more quantitatively by uptake of radioactive thymidine in such cells.

Substances used to stimulate lymphocytes may be divided into three categories:

I. Non-specific mitogens such as phytohaemagglutinin.
II. Antigens not related to *Myco. leprae.*
III. Antigenic preparations derived from *Myco. leprae.*

(d) Production and release of molecular mediators (lymphokines) from sensitized lymphocytes. These may be monitored by various techniques, including migration inhibition of autologous, homologous or heterologous phagocytes.

It should be noted that the last two groups of tests cannot *a priori* be judged as measurement of cell-mediated immune responsiveness as humoral immune responses can influence the results of these tests.

While the findings suggest that humoral immune responses are unimpaired in leprosy patients, there is increasing evidence of a depression of cell-mediated immunity in certain categories of such patients. The degree of depression appears to increase continuously from the TT to the LL end of the spectrum. Circulating antibody to mycobacterial antigens, on the other hand, increases towards the lepromatous end of the spectrum. In addition to this immunological imbalance in lepromatous leprosy which is specific to *Myco. leprae,* a non-specific depression of cell-mediated immunity has been reported in various studies. In contrast to the specific depression which does not recover as a result of anti-leprosy chemotherapy, the non-specific depression may become reduced by treatment.

10. MACROPHAGE FUNCTION IN LEPROSY

Most tissue macrophages are derived from blood monocytes. In the tissues, macrophages can adopt a wide variety of morphological forms. The resulting pleomorphism is well exemplified in leprosy where macrophages may appear as epithelioid, multinucleate, histiocytic or foamy cells. This differentiation and this influx into tissues appears to take place as a result of various stimuli, including products of activated lymphocytes.

Some laboratories have reported a lack in the capacity of lepromatous macrophages to lyse autoclaved *Myco. leprae* while other groups of workers have been unable to substantiate this finding.

Whether the deficiency of macrophages in lepromatous leprosy to dispose of the leprosy bacillus and its lipid degenerative products is a defect in the macrophage population *per se* or due to lack of stimuli from other cells, is not yet clear.

It would appear that the eventual solution to the problem will involve the concepts and techniques of both immunopathology and cell enzymology.

Committee 5: Advances in Epidemiology

Members: M. F. Lechat *(Chairman)*; P. B. Arcuri; J. A. Cap; Z. Castellazi; R. A. Feldman; R. S. Guinto; T. W. Meade; S. K. Noordeen *(Unable to attend)*; J. Walter.

1. INTRODUCTION

The Committee feels that there have been few major advances in the epidemiology of leprosy in the past five years. This report therefore deals mainly with suggestions for future work, after a brief initial review of recent developments.

2. ADVANCES IN PAST 5 YEARS

2.1. Analysis of data. There has been much work in many areas of the world on the statistical analysis of data on diagnosed cases of leprosy. However, much basic information is still wanting (especially in the absence of the ability to idemtify persons infected with *Myco. leprae*), on the characteristics of individuals, households and communities that are associated with the transmission of leprosy.

2.2. Control

(i) A number of studies have been indicated that the treatment of lepromatous and borderline cases has significantly reduced the subsequent incidence of leprosy in household contacts, especially children.

(ii) Some evidence from active control programmes suggests reductions in prevalence which might be expected eventually to influence incidence rates. However, long periods of intensive chemotherapeutic control and careful evaluation will be needed before it can be generally accepted and agreed that widespread falls in incidence have been achieved.

(iii) The need to clarify what is meant epidemiologically by "control" has become increasingly clear. The term does not include the treatment of cases presenting sporadically to clinics, etc. "Control" includes attempts to reduce

prevalence by the systematic treatment of existing cases in the programme area, and, finally, to reduce incidence. The interactions of epidemiology and control need to be continually reviewed.

2.3. New laboratory techniques with epidemiological implications. Recent developments in other disciplines (e.g. immunology, bacteriology) may well offer epidemiologists the prospects of being able to detect infection by *Myco. leprae,* as well as clinical manifestations of leprosy, and of studying host-parasite relationships more effectively than hitherto. At present, however, these possibilities have not been fully tested and validated in the field, and it is hoped that steps to do so will soon be taken.

3. FUTURE WORK: SUGGESTIONS

3.1. Population-based studies

(i) Prevalence studies, characteristic of the bulk of current epidemiological studies in leprosy, should, in certain instances, be extended to, or re-planned as, prospective incidence studies, with the necessary follow-up investigations. Since it is not possible to detect infection epidemiologically, such studies will have to be based on newly arising clinical cases.

(ii) The main objective of work of the sort proposed is the identification of risk factors whose modification or use may contribute to the control of the disease.

(iii) The factors studied should cover all the attributes likely to be relevant to the onset of leprosy in the groups under study, i.e. probably need to include a wider range of constitutional and environmental variables, including information on intercurrent diseases, than has generally been the case so far. Because the incidence of leprosy is low, projects of this sort require very large numbers and long follow-up periods, which need to be related to the endemicity of leprosy in the study areas.

(iv) Strict attention must be paid to the development and use of standardized criteria and procedures so that the results of different studies may usefully be compared.

(v) Clear distinctions must be drawn between case-finding (the detection of established as well as new cases) and incidence, in order to avoid possible confusion (especially in the early stages of a prospective study) as to whether incidence is really changing or not.

(vi) In addition to observational studies, opportunities afforded by on-going field surveys for epidemiometric model building and computer simulations of onset and natural history should be taken.

(vii) Population-based studies of the sort suggested are likely to pay dividends in other ways, by providing sampling frames for the collection of biological material, the conduct of clinical trials, and for a range of other purposes.

(viii) Field research programme should take full account of the medical requirements of all diagnosed leprosy patients.

(ix) The need for large study populations presents problems, especially in countries where skilled and semi-skilled manpower and other resources are limited. However, the experience and achievements of groups who have attempted large scale studies make it clear that these can be carried out. In addition, individual investigators or small teams who can carry out well-planned epidemiological studies of particular problems, especially where exceptional conditions or opportunities exist, should be encouraged.

4. INTERNATIONAL CO-ORDINATION: VOLUNTARY AGENCIES

The role that international bodies such as the World Health Organization and voluntary agencies can play in contributing to the general co-ordination and comparability of large-scale, long-duration studies and of smaller undertakings requires special emphasis.

Committee 6: Therapy

Members: J. Languillon *(Chairman of meeting)*; K. Ramanujan *(Chairman by correspondence)*; J. Barba-Rubio; J. C. Gatti; N. Torsuev *(By correspondence)*; A. B. A. Karat *(By correspondence)*; J. R. Trautman.

"It has been said that it is now a practical proposition to control leprosy in this generation and eradicate it during the next. All that has to be done is to ensure that an adequate number of the correct pills pass down the throat of patients for a significant length of time" (Walker, 1973).

1. TREATMENT OF UNCOMPLICATED LEPROSY

1.1. Diamino-diphenyl-sulphone (DDS). The parent sulphone, DDS, continues to hold sway as the drug choice in the management of uncomplicated leprosy; its low cost and infrequency of the emergence of sulphone resistant cases, when given in conventional doses, are its special features. Its slow bacteriostatic action and the consequent necessity to administer it over long periods of time and its inability to quickly clear the body of bacilli are some of its inherent drawbacks.

Under DDS therapy, even after the complete disintegration of bacilli in the skin, intact bacilli have been reported to be still present in smooth muscle and superficially located striated muscle (Leiker, 1971), liver, bone-marrow and lymph nodes. This may perhaps explain why relapses tend to occur even while the patient continues on the drug.

Unanimity has not been reached with regard to the optimum effective dose of DDS, frequency of administration of the drug, its relationship to the occurrence of reactive states and continuation of treatment after attainment of the inactive state, but the Committee recommends treatment of lepromatous cases for life.

1.2. Other drugs. Less effective bacteriostatic agents such as thiambutosine, streptomycine and thiosemicarbazone are used less frequently in the treatment of leprosy.

Long-acting sulphonamides have the advantage of weekly administration by the mouth. Some leprologists claim to have obtained good results with these drugs particularly in tuberculoid forms of the disease and its complicating neuritis. However, since serious and even fatal complications have followed the use of these drugs in the treatment of other diseases, the drugs should be used with caution in mass leprosy campaigns.

1.3. Clofazimine. A notable advance in the therapy of leprosy was the demonstration of the activity of clofazimine against *Myco. leprae.* The drug has bacteriostatic as well as anti-inflammatory properties.

The initial reports of Browne bearing out the anti-inflammatory properties of clofazimine (Browne, 1965) were followed by the demonstration of the

anti-mycobacterial activity by Pettit, Rees and Ridley (1967) in the human and Shepard (1969) in the mouse footpad. The extensive clinical experimental studies of Ross and his colleagues established the efficacy of clofazimine in sulphone-resistant cases. Clofazimine has established its value in the treatment of lepromatous leprosy but its high cost and the easy availability of the safe effective and cheap DDS militate against its use in the treatment of uncomplicated lepromatous leprosy.

1.4. Diacetyl-diamino-diphenyl-sulfone (DADDS). An initial short-term trial with this drug in the Philippines (Shepard, Tolentio and McRae, 1968) and a subsequent longitudinal clinical trial in New Guinea (Russel *et al.*, 1971) and Micronesia (Sloan *et al.*, 1971) have yielded satisfactory results. Although the initial reports are encouraging about the therapy on schedule in underdeveloped areas, the possiblity of the emergence of sulphone resistance, occurrence of relapses and the possible danger that this preparation may perpetuate a reactive state in cases in which the drug has triggered such a state have to be borne in mind.

1.5. Rifampicin. The newest entrant into the therapy of leprosy is a very potent antibiotic. Rees and his colleagues, after establishing its efficacy in mouse footpad infection with *Myco. leprae,* used the drug in active and sulphone-resistant lepromatous cases (Rees, Pearson and Waters, 1970) and found it effective, It is expected that the rapid killing of *Myco. leprae* would prevent the slow release of intracellular antigens of *Myco. leprae* and thus eliminate or markedly reduce the incidence of complications of immunocomplex deposition such as ENL. Although no toxic effects have been reported by these workers, there have been conflicting reports about its hepato-toxicity and the occurrence of thrombocytopenia (Proust, 1971). In view of its high cost and limited availablity, it would be wise to restrict its use to selected cases.

2. COMBINED THERAPY

Concurrent administration of drugs such as thiambutosine, long-acting sulphonamide, thiosemicarbazone, clofazimine and rifampicin along with DDS have been tried in the treatment of leprosy with a view to obtaining a synergistic effect and also to prevent the development of sulphone resistance. The results of the trials are not uniform—some found the combined treatment better than DDS alone, while others did not notice any substantial difference.

3. TREATMENT OF COMPLICATIONS ASSOCIATED WITH LEPROSY

3.1. Reactions in leprosy. With the advent of sulphone therapy, the incidence of the reactive states has been on the increase with the manifestations becoming more severe and serious.

The first major breakthrough in the management of reactive states in lepromatous leprosy was the introduction of corticosteroids (Roche *et al.*, 1951). Although this drug dramatically relieves the agony of severe reactions, the attendant undesirable side effects and drug dependence pose serious therapeutic problems.

The indication for the use of corticosteroids in the management of the distressing complications associated with leprosy has declined with the introduction of thalidomide (Sheskin, 1965). The effectiveness of thalidomide in controlling the acute exacerbations in lepromatous leprosy has been confirmed.

In Dimorphous and RTL reactions, it is reported to be much less effective. The major drawback of this drug is its teratogenic effect when administered to pregnant women.

While the concensus of opinion amongst workers is that the drug produces a spectacular effect in acute lepra reaction, there is no unanimity regarding the effect of the drug in neuritis, ocular and joint manifestations. In many instances these complications respond more readily to corticosteroid therapy possibly because of its more generalized anti-inflammatory effect.

In recurrent lepra reaction, a maintenance dose of 50 to 100 mg/day of the drug is reported to keep the reaction under control. Further experience with the drug has shown that under its protective cover, steroid-dependent cases can be weaned from steroids and sulfone-sensitive cases continued on treatment with DDS.

With Browne's report of a possible anti-inflammatory action of clofazimine in lepromatous leprosy, a new hope opened up for lepromatous patients who were subjects of recurrent necrotising reaction. The controlled clinical trials of Karat *et al.* (1970) confirmed the beneficial effects of the drug in lepra reaction. Similar reports have also appeared from Hastings, Warren and Trautmman and many others. However, the beneficial effect of clofazimine takes as long as 8-12 weeks and sometimes high dosages, to become manifest, and hence in severe cases with necrotizing lesions it will be necessary to combine clofazimine with corticosteroids or thalidomide until the acute phase is controlled. The significant improvements in the general health of these severely ill patients have been well documented.

While it is not effective in quickly controlling the acute reactive states, clofazimine has been observed to suppress not only the recurrent reactive episodes, but also permits withdrawal of steriod in steroid-dependant cases. Also it increases a tolerance to DDS in sulphone-sensitive cases while simultaneously exerting a benificial effect on the disease process. Long-term studies are necessary to determine whether once the reactive states are controlled and the patient is able to take DDS in adequate doses, clofazimine can be withdrawn. It is a matter for serious consideration whether this drug could be safely used in cases of recurrent severe lepra reaction with overt renal involvement.

4. SULPHONE RESISTANCE

The occurrence of drug resistance, one of the anticipated outcomes of chemotherapy, has now been established in lepromatous cases (Pettit, Rees and Ridley, 1966) on DDS therapy. Inadequate dosage and irregular treatment appear to be contributing factors. This condition poses serious therapeutic problems. Clofazimine and rifampicin either alone or in combination with DDS (or other drugs such as thiambutosine and ethionamide) have been found to be effective in the management of these cases. However, emphasis should be laid on the prevention of this clinical state by adequate DDS therapy.

5. CHEMOPROPHYLAXIS IN LEPROSY

Chemoprophylaxis using DDS orally (WHO, 1970) and DADDS (Walker, 1973) has been found to yield satisfactory results. The value of chemoprophylaxis in the prevention of the development of lepromatous leprosy, its duration, the optimum dose and the frequency of adminstration are yet to be determined.

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Committee 7: Leprosy Control

Members: L. M. Bechelli *(Chairman)*; M. L. Brubaker; C. Estrada Silos; P. Kapoor; M. R. Labusquiere; E. Rasi; H. Sansarricq; C. M. J. Vellut.

Despite substantial and sometimes even striking gains in many fields of leprology, progress in leprosy control has not kept pace—mainly because of the present unavailability of an ideal drug or specific vaccine. Control continues to focus on the patient or those more prone to develop leprosy. The population at higher risk is known, but the means to protect it are not yet available or still under study, and active drugs are badly needed to make a greater impact on the load of infectiousness. Hopefully, the preparation of a specific vaccine and/or the obtaining of favourable results in chemoprophylaxis can make primary prevention possible. The prevalence and duration of leprosy, plus its unique characteristics and socio-economic implications, call for special priority in public health programmes and in research.

Because there was no major breakthrough necessitating special changes in the guidelines and methodology of leprosy control, the relevant reports prepared by the Committe of Leprosy Control (Rio, 1963) and by the WHO Expert Committee on Leprosy (1966 and 1970) are generally valid today. Therefore our

attention will be focused only on certain aspects of control which need more emphasis or represent an addition to the previous guidelines.

There are definite indications that where an effective case-detection and case-holding programme has been developed the total number of patients and the annual detection of new cases has been reduced. It also appears that with such programmes larger proportions of early, non-deformed patients are detected who can be easily treated, helping ultimately in reducing the quantum of infection in the community. There is, however, a good number of new cases in spite of efficient work. This requires epidemiological investigation and also the need to find ways and means to improve present methodology.

1. MEDICAL MEASURES

1.1. Case-finding. To control leprosy it is essential to diagnose the early cases prone to develop lepromatous leprosy and the early lepromatous cases; this requires good training and experience of the relevant staff. For such diagnosis bacteriological examination should be done on all patients.

In the surveillance of contacts, the criteria recommended by WHO Expert Committee (1966) should be adopted. School surveys are useful in highly endemic areas.

Mass survey is an important method for case detection. In non-hyperendemic areas it has limited value. In such areas the most effective and practical case-finding method is contact tracing, not only limited to household contacts.

The above methods of case detection should be supported by health education and where possible, by multiple purpose surveys.

Where mass surveys are undertaken, they should be multipurpose, as performed in several countries, and advantage should also be taken for health education in leprosy and other diseases. In this way, such surveys would be relatively less expensive and yield better results and public acceptance.

1.2. Out-patient care. Irregularity of treatment continues to be one of the most important drawbacks in control, in spite of the efforts to prevent it. The cause of absenteeism should be investigated by social and behavioural scientists.

Efforts should be made to take the treatment to the patients, near their homes, even if this must be done once a month. Advantage should be taken during the visit for health education and contact examination and other activities including prevention of disabilities of comprehensive medical care.

1.3. In-patient care. Facilities for temporary hospitalization for acute illness must be provided. However, institutional isolation of infectious cases, even temporary, is no longer recommended.

1.4. Medical rehabilitation. Prevention and treatment of disabilities by simple physiotherapeutic methods merits greater attention and should be part of the out- and in-patient care. Reconstructive surgery should be undertaken in general rehabilitation centres, surgical and orthopaedic services, including university hospitals.

1.5. Release from control. This should be a continuing activity to avoid inflation of the prevalence and of keeping patients under control for a longer time than needed, thus increasing the work load and expenses.

1.6. Protection of the healthy population with special reference to contacts and children. The Committee noted with great interest the findings so far reported by the groups investigating the preventive effect of BCG in Uganda, Karamui and Burma. Similar interest was shown in the chemoprophylaxis trials.

In view of the findings so far available from these trials, the Committee considers it premature at this stage to recommend BCG vaccination or chemoprophylaxis as a regular part of the leprosy control measures. Further research is still needed in these important subjects.

2. HEALTH EDUCATION

Although it is most important to remove fear and irrational behaviour about leprosy, it still seems that health education is too often a neglected subject in most countries. The attitude of the medical and health workers is often the first stumbling block. Health education is a most important aspect of leprosy control and should be given high priority.

With regard to terminology and approach, all aspects of culture and language call for attention. To be effective and create a positive feeling for action, health education must be in a language people understand.

The cause of prejudice should be investigated to develop a better methodology for overcoming it.

3. TRAINING

In spite of all the emphasis given to this crucial measure, in a number of countries leprosy training for medical officers is neglected. Initial training and refresher courses and in-training should be conducted regularly for the various types of workers. Refresher courses should be repeated at regular intervals. Seminars and symposia should be frequently organized for all levels of workers.

Training in leprosy for undergraduate and postgraduate students is not receiving adequate attention, for which the leprosy campaign suffers. The efficiency of the teaching and learning processes should be evaluated.

4. ADMINISTRATIVE MEASURES

4.1. Planning. Many projects have not yet established quantitatively defined objectives for the different activities. Each project should have realistic objectives, feasible with available resources, and defined in terms of quantity, areas and time. When defining objectives in quantitative terms, special attention should be given to the following priorities: treatment and follow-up of infectious and indeterminate patients and surveillance of contacts of the infectious patients.

Control measures, specialized or integrated, should aim at reaching a country-wide coverage within the shortest possible time.

4.2. Quantification of the problem. Data collection. The data available on the prevalence in many countries do not represent the real situation, because the case-finding has not reached the desired level and sometimes because the number of patients released from control is small, thus inflating the rates. More realistic figures and baseline information are required for planning and evaluating programmes.

A uniform definition of terms is a basic requisite in a system of leprosy statistics: the information collected should allow comparisons between the various areas of the country and also between different countries and continents.

4.3. Integration. The principle of integration of leprosy control activities into the general health services is widely accepted, as are the difficulties recognized in

achieving it. One of the questions is how to prepare the polyvalent personnel both at medical and paramedical level.

Complete integration may not be feasible at the present time in many countries, however desirable it might be. If integration is attempted too soon. the leprosy work will be the first to suffer most.

> "Full integration will be attained only as a result of a long drawn-out process and for this reason countries should be encouraged to take the first step as early as practicable . . ." (WHO Expert Committee on Leprosy, 1970),

after appropriate training and motivation of all the staff concerned. It should be started and studied in a pilot test area. Where feasible, leprosy control programmes should be combined with other control programmes.

4.4. Evaluation. Constant evaluation should be carried out in all projects, especially where control work has been undertaken for 10 years or more, or in areas that appear to have achieved a reduction in incidence and prevalence.

Detection of a large number of early cases the success of the programme, but does not necessarily mean that leprosy is increasing. Detection of such benign cases and subsequent early release from control reduces the prevalence rate, apparently indicating that leprosy is being controlled. However, this does not mean that the source of infection has been removed from the community and further control measures must be continued.

4.5. Supervision. In most countries, adequate supervision by medical officers and senior auxiliary staff is lacking or is unsatisfactory. It is essential that such supervision be provided and exercised for all activities connected with leprosy control.

5. OPERATIONAL RESEARCH

The Committee notes with interest the efforts to develop techniques which can be useful in the detection of the high risk groups. Subjects relevant to immediate and/or long-term public health action should preferably be chosen and should include test runs of optimum solution given by the epidemiometric model. Efforts should continue to develop an epidemiological model to provide forecasts of the impact of the programmes on the natural course of leprosy and its control.

Studies should also be undertaken regarding the methodology to be applied in urban leprosy control.

Studies on reactivation and relapses are needed to determine the criteria and length of treatment required for releasing patients from control.

6. RESULTS THAT MIGHT BE EXPECTED FROM THE PRESENT CONTROL METHODS

Where the methodology is currently and persistently applied and where there is co-operation of all concerned and where there has been motivation of the population, it can be expected that there will be an increase of early benign cases, a decrease in the number of disabilities, a slow and progressive decrease of infectious cases and finally a gradual fall in the detection rate. The whole thing is such a long process that it requires a long time to achieve the end result. This prospect can only be improved by intensifying research.

Committee 8: Rehabilitation

Members: O. W. Hasselblad *(Chairman)*; J. J. Arvelo; P. W. Brand; M. I. Bly; A. E. Carayon; T. N. Jagadisan; S. Karat; R. O. Manzi; J. M. Mehta; W. F. Ross; A. Samy; K. Saikawa; N. Hasselblad *(Secretary)*.

1. INTRODUCTION

We must begin by pointing out an anomaly in the use of the term "Rehabilitation" in relation to leprosy treatment. By tradition all those aspects of patient care which relate to the prevention of physical disability have been grouped under "Rehabilitation" along with corrective surgery and other definitive rehabilitation techniques, managed by a surgeon and his staff, while the treatment of the disease itself has been managed by specialists in leprosy control. The result has often been that when a rehabilitation team is not available, the physician in charge of the control project has felt that techniques related to the management of disabilities are not considered to be his responsibility. Thus patients are deprived of aspects of *primary patient care* which might have saved them from progressive crippling deformity and social, economic, psychological and vocational disability.

We wish to emphasise that the special techniques that have been developed to prevent physical disability are absolutely basic to the medical care of every patient who has suffered peripheral nerve damage, whether or not a definitive Rehabilitation Team is available. Appropriate techniques can be carried out without expensive equipment or specialized personnel. The essentials are extra time spent by the auxiliaries on each patient and additional expenditure on such devices as protective and therapeutic footwear.

The extra cost is compensated for by the improved cost-effectiveness that results from better attendance of the patients who will recognize that trophic ulcers are healed and that felt needs met, beyond which personal experience and that of their neighbours teaches it could not be accomplished by medication alone.

Conversely, the ultimate cost of caring for the totally disabled patient whose disability has not been prevented, is many times more than the very small amount saved by withholding the care which should have *prevented* the disabilities. That the public and governments are deeply conscious of the burden of this cost of caring for the totally disabled is demonstrated by the large sums of money collected and provided for their care whether in or out of institutions as compared to the amount budgeted for the control of the disease.

Moreover the continuing accumulation of newly disabled patients from among the ranks of patients treated in mass campaigns is regarded by new patients as evidence of failure of control programmes. Failing to care for the patient as an individual becomes a valid reason for discontinuing treatment.

To ensure that staff, responsible for control of leprosy, assumes full responsiblity for techniques of disability prevention, it is essential that new dialogue be instituted between physicians in charge of control programmes and those specialists in rehabilitation who have been mainly concerned with the problems of disability. It is not sufficient to state that the responsibility must be transferred; there is a great deal of experience that needs to be communicated and every opportunity for such communication must be taken advantage of.

The total care of leprosy p ıtients may thus be considered under these headings:

1.1. Primary patient care. The large majority of patients need no other care than this, and prevention of disability should be carried out by all staff of the leprosy control programme.

1.2. Rehabititation. Patients with substantial established disability require a planned programme to restore maximum ability to function as self-respecting and respected persons. Frequently vocational training and counselling is required to discover means of self-support consistent with their residual abilities. Many of these activities require specialized trained personnel.

1.3. Social welfare. Given relatively limited resources, it is not feasible to attempt rehabilitation of all disabled patients. For the totally disabled it must be accepted that permanent provision for their care be made, consistent with human dignity and decency. In principle the creation of segregated facilities for whatever reasons, for patients whose disabilities arise from a particular disease such as leprosy, must be deprecated. Such facilities may have served a useful function in the past but their continued existence perpetuates a public image that leprosy is a disease apart and its victims are to be excluded from the life of the community. In addition, the influence of any type of categorical segregation facility on the patients themselves is almost always dehumanising and unjust.

1.4. Comprehensive community health planning. The management of leprosy is severely handicapped by community social attitudes. The methodology of management has tended to place the patient at risk in regard to his self image and that of his community which should be supportive of his welfare. Informed studies reveal that the majority of patients prefer the risk of disability to segregation and alienation from home, community and whatever margin of economic security he has been able to maintain. The patient is always a person in relationship. New forms of health care delivery systems need to be examined which will include the treatment of leprosy among other priority health needs of the community and not as a separately vertically structured programme.

2. PRIMARY MEDICAL CARE

Primary medical care, so far as prevention of disability is concerned, begins with the attempts to prevent damage to the peripheral nerves. This depends, in the first place, on health education directed toward the patient to make him constantly aware of early danger signs and that he be prepared to report such signs to the auxiliary worker, even in the absense of neuritic pain. From the time of diagnosis the patient must learn to actively participate in his own treatment and prevention of disability. Equally important is the alertness of the medical auxiliary to understand early danger signs and to act promptly as they appear. The treatment may then consist of the use of anti-inflammatory drugs, splintage of affected parts, and in selected cases, decompression of swollen nerves or constricted blood vessels by surgical intervention. This sequence of monitoring events and timely intervention is the ultimate responsiblity of the supervising physician who alone can insure an inter-relationship of confidence between patient and auxiliary worker.

Primary medical care includes the prevention of *progressive* disabilities. Thus it is important that the physician aims to cater for all complications which may lead to disability, to give immediate and effective care using the most feasible methods that will enable the patient to return to normal activity as quickly as possible.

It is important to recognize that effective treatment for 90% of the complications related to eyes, anesthesia and paralysis, is simple, inexpensive, and

can be administered by specifically trained auxiliary medical workers in peripheral clinics or at home. These methods have been tested and found successful in domiciliary based leprosy control programmes. The auxiliary medical worker can be trained and motivated to offer such services adequately and effectively under the supervision of a physician who himself has had adequate training and who cares. In practical terms this approach means:

(1) Health education directed towards securing the patient's full participation in the methods of prevention of disabilities progressing from early danger signs of complications.
(2) Immobilization of limbs with even minor injuries, wounds and ulcers.
(3) Simple care of early eye complications.
(4) Provision of protective footwear including suitable modifications as indicated.

Essential to the delivery of primary medical care is the adequate training of physician and auxiliary medical worker in order to fulfil their decisive responsibilities. International training centres are now available where physicians can be exposed to both didactic teaching and active demonstration programmes in which management and prevention of disability is an integrated element in routine treatment. Several centres nationally and internationally situated, offer similar training opportunities for various categories of auxiliary medical workers. However, essentially it is the responsibility of the trained physician or supervisor to provide in-service training for those for whom he is responsible. Training is a continuous process in which every level of worker must be involved through refresher courses, training programmes designed to up-grade the standard of performance, and most important of all is the need for constant interaction between the supervised and supervisor.

3. REHABILITATION

Rehabilitation is the process of being involved in assisting the handicapped individual to reach his "maximum potential for normal living, physically, psychologically, socially, vocationally." However, before a patient is referred to a rehabilitation service, it must be insured that he has passed through the services of *primary medical care,* regardless of the degree of disability when first seen by a physician or auxiliary medical worker. The physician responsible for primary care must first fulfil his responsibilities in his own area of competence. Rehabilitation is a specialized activity requiring advanced skills on the part of those engaged in it.

Reconstructive surgery which has formed a large part of previous reports of this panel, is not considered in detail this year. This is not to minimize its importance, but to emphasize that it should not ordinarily be considered part of the responsibility of the leprosy control team. This is a special discipline which requires years of training. The surgeon who undertakes such training should ordinarily use his expertise for reconstructive surgery of any deforming disease including leprosy. Ideally, rehabilitation services should be integrated in order to make the maximum use of skilled manpower available.

In areas of high leprosy endemicity there may be a place for a full-time leprosy surgeon, but rarely for a physician who is a part-time surgeon.

Similarly, in Vocational Rehabilitation, it is not ideal for a physician or even a social worker to undertake to train patients for the skills required to become self-supporting in their future life. This is a field for vocational counsellors,

industrialists, agriculturalists, engineers, business men, marketing specialists, and placement officers. Such experts may often be persuaded to give part time service voluntarily to assist in this important and even decisive activity in successful rehabilitation.

In the area of the specialized skills of physiotherapy and occupational therapy, training in the management of disabilities arising from leprosy is also required. However, it is a sufficiently narrow field that it has been proven practicable to use technicians who are trained by qualified therapists, and who then devote their whole time to the physical problems of leprosy including the mobilization of stiff joints and splintage of injured limbs, re-education after surgery and the special training of patients to work without damaging their hands and feet.

Every leprosy control and rehabilitation programme also needs a shoemaker. With training and experience such a skilled individual may make a most valuable contribution and should be regarded as a full member of the professional team.

Many disciplines are required in leprosy rehabilitation. It is imperative that personnel be recognized for the particular skill they can bear as a member of a team. Mutual respect among members of the team is of primary importance to insure that the patient remains the object of the care offered rather than the exercise of professional prerogatives.

We recognize that full integration is impractical at this time but as a first step, all centres that are able to offer comprehensive rehabilitation services to leprosy patients should accept a proportion of those with disabilities arising from causes other than leprosy. Centres which have so far excluded leprosy patients should similarly be encouraged to accept a proportionate number of such cases. This is not a simple matter, however. Few general rehabilitation workers and medical personnel have had experience in dealing with the problems posed by patients with anaesthetic limbs. Special training of all grades of staff will be required to enable them to adapt their skills and basic techniques to the needs of leprosy patients. It is particularly advocated that medical universities and teaching hospitals realise the importance of ensuring that both student and staff are exposed to the rehabilitation needs of leprosy patients.

4. SOCIAL WELFARE

We recognize that substantial numbers of leprosy patients are so severely disabled that rehabilitation is not a practical possiblity. They are, nevertheless people, and have a basic human right to live with dignity and self-respect. They need care. Their needs are often primarily social and thus are deserving of the best possible social welfare service that the community in which they live can provide, equal in every way to services offered those whose physical, social and economic disabilities derive from other causes. Facilities designed for the care of only those whose disabilities arise from leprosy are to be deprecated. There is evidence to suggest that serious disadvantages arise in attempting to care for the totally and permanently disabled in institutions primarily meant for the short term care of medical and surgical complications of patients requiring primary medical care and definitive rehabilitation services.

The social welfare services ought to be integrated, providing for the needs of those whose disabilities arise from causes other than leprosy as well as those whose disabilities do arise from leprosy. Ideally these severely disabled patients should be cared for in their own families. Where homes cannot be found or where

families cannot accept the patient, substitute families should, if possible, be provided.

In this connection we have considered alternate uses for the traditional type of leprosarium or sanatorium.

(1) A gradual phasing out of the segregated facilities and the development of Leprosy Hospitals as the base hospitals for leprosy control programmes.
(2) Such institutions may become hospitals that offer general medical services if in an under-served area.
(3) Some may assume the responsibility for providing specialized care of the permanently disabled, regardless of the cause of disability.
(4) Where there is a general hospital in the vicinity of the leprosarium, the hospital activities including short-term care of leprosy complications should be integrated with the general hospital. In some instances additional facilities will be required to become an integral part of the hospital and sharing all facilities for patient care.

5. COMPREHENSIVE COMMUNITY HEALTH PLANNING

It is well to recognize that in many communities, attitudes toward leprosy patients are unsatisfactorily conditioned by the presence of severely disabled patients who are non-productive and hence a costly burden to the community. Attitudes are also conditioned by outmoded methods of leprosy control that segregate the patient and isolate his care from the public health services offered to the community for other diseases.

There is evidence to suggest that the provision of good, primary medical care that includes leprosy treatment and management, helps to change public attitudes. Prejudicies fade away when the public observes that the medical profession accepts responsibility for the care of the leprosy patient as any other. Community attitudes will also be favourably influenced when it is observed that the leprosy patient may continue as a self-respecting contributing and thus, respected member of the community.

In addition, a systematic approach to Health Education in the community is important. This is necessary in order to ensure that the desired changes in attitudes actually take place. This will involve a careful diagnosis of the situation, preferably by social scientists with special training in this field. There will be particular emphasis on the discovery of beliefs in the community about the causation of the disease, their specific attitudes to leprosy and those whose lives have been interrupted by it, their specific attitudes toward deformity. Only through such in-depth understanding can it be expected that health education methods will be devised to alter attitudes. Leaders of community opinion will be identified and special efforts directed toward them. This must begin with the medical and auxiliary medical professions.

Diagnosis will be followed by the definition of specific measurable goals. Planning is necessary and the advice of specialists in education should be sought to determine the most suitable means of bringing about measurable changes in attuitudes.

The use of trained volunteers for the actual execution of the programme should be explored as should the possibility of using carefully chosen leprosy patients as health educators.

Into all such health education programmes should be built means of evaluation to determine effectiveness and to determine needs for effective methods.

6. SUBJECTS FOR FURTHER INVESTIGATION

(1) The problem of neuropathy.
(2) A systematic and widely acceptable approach to the training of staff.
(3) Operational research to evaluate the methods in use for the health care delivery systems to leprosy patients.
(4) Social anthropology and patient psychology studies as a basis for a better understanding of the patients' viewpoints in order to develop better patient health education.
(5) Study of comprehensive Community Health Planning projects into which leprosy treatment has been integrated to determine whether they offer more efficient means of case-finding and case-holding as well as the prevention of social and vocational dislocation.
(6) Surrounding or in the vicinity of many leprosy institutions, communities of discharged patients have settled. In other instances there are selfmade communities, citizenship in which is determined only by having had a direct or indirect association with leprosy. In many instances the members of the community will have become socially and economically marginalized by a long term stay in a leprosy institution. How may the development of such communities be prevented? What practical methods may be used to restore individuals and families into normal community life?

7. RECOMMENDATIONS

(1) That arrangements be made for further exchanges between personnel involved in leprosy control and rehabilitation so as to define more effectively the role of primary medical care and the prevention of disabilities in leprosy control programmes.
(2) That the International Leprosy Association be requested to include a combined meeting of panels on Leprosy Control and Rehabilitation in the next Congress.
(3) The problem of peripheral neuropathy is of sufficient importance to warrant the arrangement of a separate section to discuss this subject at the next Congress and that the International Leprosy Association be so requested.
(4) To foster a wider dissemination of information concerning advances in management and research of leprosy, voluntary agencies are encouraged to provide subscriptions to the major leprosy journals for medical universities throughout the world.