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LEPROSY REVIEW

VOLUME XXXVIII NO. 3 JULY 1967

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Book Reviews

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LEPROSY REVIEW

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The Association does not accept any responsibility for views expressed by writers. All communications re *Leprosy Review* and all subscriptions should be sent to the Editor.

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Editorial

We have ten papers from various parts of the world and we wish to welcome especially a paper from Japan, p. 135, by Sister Hilary Ross who formerly did such good work at Carville, U.S.A.

We have been very fortunate in having the

first annual report of the Lepra Control Project, Malawi, with the permission of Lepra and the Director of the Project, Dr. B. D. Molesworth, p. 200.

We draw attention to Dr. Meny Bergel's interesting discussion of Lysosomes on p. 189.

Ninth International Leprosy Congress

SEPTEMBER 16th-21st, 1968

Attention is drawn to the insert enclosed in this issue of *Leprosy Review* giving details of the arrangements for the Ninth International Leprosy Congress.

Cryoglobulinemia

SISTER HILARY ROSS*

Cryoglobulinemia is a common condition associated with an elevated serum globulin fraction. Relatively large amounts are found in patients with kala-azar, systemic lupus erythematosus, rheumatoid arthritis, periarteritis nodosa, etc. Cryoglobulins are present as a secondary phenomenon in specific disorders. Cryoglobulins may be considered as homogeneous proteins produced most probably by groups of plasma cells or lymphocytes in response to the antigenic stimulus of infection or inflammation, or they may arise as a result of spontaneous benign or malignant proliferation of these groups of cells as in myeloma and leukemia.

The particular characteristics of cryoglobulin is to precipitate or gel (or both) at serum temperatures below 37°C and to reverse these effects on being re-warmed to 37°C.

The spontaneous gelling of blood immediately on or during withdrawal into a syringe has at times been observed in leprosy patients with hypergammaglobulinema. (These observations were made in the sera of leprosy patients by the writer while on duty at the National Leprosarium, Carville, Louisiana, U.S.A.) The gelling is independent of clotting and the serum may form a precipitate on cooling. The name 'cryoglobulin' has been given to this coldprecipitable serum protein which, when first described, was shown to have the mobility and ultra-violet spectral characteristics of a gamma globulin and crystallized on cooling. In some instances of cryoglobulinemia gelling and precipitation occur in the syringe while the needle is still in the patient's vein. In these cases, warm the syringe to 38°C and take the blood in a warm room. More often the cryoglobulins precipitate at temperatures varying from 0° to 37°C over a wide variation of time. Cryoglobulins may be present as a scarcely visible turbidity, a marked flocculation or a viscid

gel. Antigenically this protein appears to be related to normal gamma globulin.

Precipitation of globulins in serum by cold must be differentiated from precipitation of protein in plasma, especially heparinized plasma. Fibrinogen readily separates from heparinized plasma when present in excess as in the case in most inflammatory disorders.

Commonly, in an erythrocyte sedimentation test performed when cryoglobulin is present, no sedimentation is found at 0°C, whereas at 37°C the sedimentation is very rapid—exactly the reverse of the sequence in the presence of cold agglutinins. The cryoglobulin precipitates at a low temperature and plugs the sedimentation tube so that the red corpuscles cannot form a sediment. This has sometimes led to the conclusion that the blood in these patients 'clots' instantaneously-an erroneous interpretation of a correct observation. There is no true coagulation since the pseudo-clot is easily soluble on warming the plasma or serum. The presence of cryoglobulin is certain when the pseudo coagulation is reversible with changes in temperature.

Cryoglobulins are only one type of blood protein with unusual physical properties and thermal characteristics. For example, C-reactive protein is cold-precipitable, pyroglobulins precipitate at 56°C; Bence Jones Protein precipitates at 45-50°C and the protein of amyloidosis has a high carbohydrate content⁴.

The precipitation of this globulin in the small vessels of the skin on cooling causes 3 types of lesions: (a) Raynaud-like syndromes with bluish discoloration of ears, nose and fingers, (b) purpura with oedema, and (c) the most severe type—ulcers and necrosis of the skin with little tendency to heal.⁹

^{*} Aitokuen, 1620 Nishihama, Wakayama Shi, Japan.

Mathews and Trautman² observed that many leprosy patients at Carville were intolerant to cold and led to the recognition of sensitivity to sudden temperature changes—but not necessarily cold temperatures, in a number of other leprosy patients. Exposures to such environmental changes have led to a variety of cutaneous manifestations including acrocyanosis, purpuric eruptions and ischemic necrosis. These workers observed that subsequent tests revealed that significant levels of cryoproteins were present in the sera of most patients with active lepromatous leprosy and dimorphous (borderline) leprosy. This protein was not observed in the sera of patients with tuberculoid leprosy.

For reasons which are unknown but which may be climatic, racial or related to differences in pathogenicity of *M. leprae*, leprosy presents clinical variations in different regions. Wade¹⁰ has stressed these differences. In the Philippines, for example, the lepromatous type comprises 40 to 50% of all known patients, a very much higher proportion than has been reported in Africa, China and India.

Spotted or diffuse leprosy of Lucio is a syndrome described by Lucio and Alvarado in Mexico in 1852 and later by Latapí¹. It is a diffuse lepromatosis with outbreaks of multiple necrotizing vascularities. At each site there occur frank necrosis of the capillaries and a secondary dermeopiderma necrosis.

According to most workers (Guinto *et al.*, Mauze, Mayama and our own work at Carville)^{4 3 5 7} the total proteins are normal or increased in the majority of leprosy sera. The quantity of albumen is usually moderately reduced, and in the writer's experiences at Carville, in one case complicated by amyloidosis, albumen was undetectable by ordinary chemical methods and poorly demonstrated by paper electrophoresis. There is a moderate hypergammaglobulinemia in many of the patients and obvious reversal of the albumen-globulin ratio.

There is less unanimity of opinion in regard to the quantity of the various globulin fractions in leprosy. The globulin increase may be a total increase of all of the globulin moities, or may be of a single fraction, or any combination of fractions. The most common occurence is the elevation in the gamma globulin region in active lepromatous patients. There is a definite tendency for the gamma globulin levels to increase with severity of the disease and with bacillary content of smears from the skin and mucous membrane. The next most common is a beta-gamma increase, then other smaller combinations occur in smaller numbers.⁴

It is known that the gamma globulin fraction is markedly elevated during Erythema Nodosum Leprosum reactions, more so than during non-reaction periods. This finding is usually attributed to a non-specific response to tissue damage although part of the gamma globulin fraction might represent antibody formation. As the erythema disappears the globulin fraction is lowered. In this reversible inflammatory state cryoglobulinemia subsides as the patient improves and the general protein pattern approaches the normal level.

Waldenström⁹ describes a number of conditions in which hyperglobulinemia is an important finding, such as viral infections, sarcoidosis, subacute bacterial endocarditis, etc. In the 'rheumatic' maladies or 'collagenosis' an increase in the gamma fraction is a common occurrence. Mathews and Trautman² state in substance that the notable resemblance of reactive episodes in leprosy to manifestations of collagen diseases may be more than coincidence. This resemblance does not end with the clinical manifestations. The presence in a significant number of leprosy patients of what the authors term cryoprotein, of rheumatoid factors, circulating thyroglobulin-antibody and biologically false positive serological tests for syphilis are additional factors pointing to a close relationship. However, of great importance is the fact that not only is leprosy a disease associated with many manifestations normally found in collagen disease but it is a disease for which an aetiologic agent is known.

Cryglobulins and purpura: A subject of frequent discussion is the association of purpura with the presence of serum cryoglobulin. This condition was first described by Lehmann and Fleming (cited by Waldenström⁹). Lerner *et al.* have investigated this condition and coined the name 'purpura cryoglobulinemica'. They consider it a sub-group of Waldenström's purpura Hyperglobulinemica.

ANALYSIS OF CRYOGLOBULINS

For the qualitative and quantitative analysis of cryoglobulins centrifuge the refrigerated sample at 4°C for one half to one hour, and pour off the supernatant serum. The lipid fractions float to the top. Wash the precipitate in normal saline, redissolve and precipitate overnight at 4°C. Usually 3 washings are required for an electrophoretically pure sample, otherwise other protein fractions remain absorbed in the precipitated protein. Washing leads to a loss of some cryoglobulin so that the exact quantitative determination may be difficult. Mathews and Trautman, in their fractionation of cryoprotein washed their precipitate with 10 washings of cold normal saline. This probably accounts for their albumen-like electrophoretic mobility of the cryoprotein since washing leads to a loss of cryoglobulin. Determine the mobility of the cryoglobulin by simultaneous electrophoresis (using a barbital buffer pH 8.6) of the whole serum, the washed cryoglobulin precipitate that has been redissolved in normal saline and the decanted supernatant serum. The mobility of the abnormal protein may be anywhere in between the beta and gamma bands or, exceptionally, in the alpha₂ region.

Most cryoglobulins have physical characteristics similar to normal gamma globulins. The sedimentation constant S_{20} lies between 6.0 and 7.8; the molecular weight is 160 200,000. Antigenically, these proteins appear to be related to normal gamma globulin. Some cryoglobulins have been isolated in crystalline needle, rhombic or cubic forms, suggesting that they have a greater degree of homogeneity and purity than normal gamma globulin. Normal gamma globulin has not been crystallized. Most cryoglobulins redissolve partly or completely on warming to 38°C and are soluble in normal saline.

Other than the report of Mathews and Trautman² this interesting field of cryoglobulins has not been studied in leprosy as far as the writer is aware. The currently available immunochemical and physiochemical data indicate that in the adult there are 3 major circulating immune globulins, Gamma-2, Gamma₁ A, and Gamma, M. Gamma-2 is the principal constituent of Cohn Fraction 11 and constitutes approximately two-thirds of the protein within the electrophoretically defined gamma area of serum. This boundary also extends through the beta and into the alpha₂ mobility region. It has been demonstrated by immunoelectrophoresis that all 3 immunological fractions are increased in the disease states associated with diffuse hypergammaglobulinemia, e.g., chronic infections, sarcoidosis and the collagen disease.⁶

The following information on the ultracentrifugation of serum proteins appears highly technical but is recommended.⁸ It was thought desirable to include it here for the benefit of those workers who may be interested in knowing that there is such a procedure.

For both clinical and research purposes the required differentiation of the protein macromolecular spectrum can be secured by the procedures of ultracentrifugation because they can be adapted to the physical characteristics of proteins of interest. Analytical ultracentrifugal procedures permit differentiation, characterization and quantitation of the serum protein fraction 'gamma globulins' (in the nomenclature of paper electrophoresis) into 3 different distinct protein classes:—

- (i) the class of 'true' gamma globulins with sedimentation constant of 7S;
- (ii) the class of macroglobulins with sedimentation constants S15 and higher (further characterized and quantitated by specific sedimentation constants found -15S, 21S, 24S, etc.);
- (iii) the class of proteins with sedimentation constants between S7 (gamma globulins) and S15 (macroglobulins) for which there is yet no class name.

Apparently cryoglobulinemia is a common condition with a raised serum globulin fraction,

but it must be properly investigated or it will be overlooked.

It would be of interest, at least qualitatively, to observe if this gelling phenomenon occurs on different populations with leprosy. If it is noted, perhaps some of the well equipped Research Centres for Leprosy could make a scientific study of this type of sera.

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Leprosy Field Logistics

Dr. M. J. MALLAC

Geneva, Switzerland

INTRODUCTION

It is no novelty to postulate that reports in general do actualise an accumulation of data, remarks and idiosyncrasies, rather than convey a *uniformity* of breadth and depth as regards the true dimensions of the leprosy problem in the field. Whereas this is almost unavoidable, yet it is also a truism to add that both the interest and value of a given system of reporting is directly proportional to the very way it is presented, to the very lucidity of its informations.

Although there are concerted views purporting to the whole magnitude of leprosy field work, no unifying system of reporting seems to enhance it so far, stock data not reflecting all the aspects of the picture since the endemicity of the disease varies from pocket to pocket and from belt to belt throughout the country. Besides, it would also be agreed that, from the point of view of epidemiology and control, the more minute the geographical breakdown, the clearer the nature of the problem, the firmer one's grasp over it.

With this in mind, the writer presents here an approach which, from want of a better term, bears the name of Leprosy Field Logistics as it embodies a fresh attempt at the national or mass campaign level and which, albeit not meant to replace field reports *per se*, nevertheless cuts through their variety and bulk in a direct, functional yet *visual* manner, aiming at the same time at a synthetic yet constructive evaluation of the problem on a yearly basis.

In effect, there is more in leprosy field work than the mere reporting of the total number of registered and treated patients per clinical type, sex and age group over a given period of time. There is more than the sorting out of patients within the demands of regularity of treatment. What are, for instance, the manpower and case-coverage? The work-load and expected case-load? The remaining coverage that can be reasonably expected from the present manpower? What is the overall balance for coverage? The full practical implications of case-finding, case-management and surveys?

COMPONENTS OF FIELD LOGISTICS

These have been worked out and based districtwise by the writer whilst on a recent WHO consultantship in Andhra Pradesh, India. In such a huge country—with its states, districts, taluks and blocks in that order—Leprosy Field Logistics could apply, for instance, state-wise at the National Leprosy Control Work; districtwise at the state level and, if necessary, taluk or block-wise at the periphery. Even for countries with much lesser densities of population, the writer advocates the division of field operations into a given number of zones to fit in the Leprosy Field Logistics whose basic components entail:—

> Organization and Communications Supervision and Co-ordination Manpower and Case-Coverage Case-Finding Surveys

Each component, with the exception of the first one, shows on the left hand-side a map of the area involved (in this case the state of Andhra Pradesh); a central table with the relevant statistical informations district-wise and where the use of 2 colours like red and green is highly desirable for attracting one's immediate attention to the very weak and weak aspects of the statistics respectively; on the right hand-side, finally, the pertinent remarks cut down to a functional minimum under: (i) Present Picture (brief summary of the main statistical informations); (ii) *The Problem* (implying the gaps to be filled), and (iii) *Achievements* (during the year).

ORGANIZATION AND COMMUNICATIONS

These indicate the distribution, type and number of the various anti-leprosy units at the periphery; their relationship to the centre; the staff position; the expected work-load and case-load respectively.

SUPERVISION AND CO-ORDINATION

These show the general pattern of the state per district per zone; the area and population involved; the breakdown of all anti-leprosy units per district per zone.

MANPOWER AND CASE-COVERAGE

Here, one has to reckon with the district population (DP), the population covered by all the anti-leprosy units (PC)—both Government and the Voluntary Agencies—and the percentage coverage involved. This is followed by: the *present* estimated cases per the Prevalence Rate of each district (EC); the number of registered (RC) and treated cases (TC); the attendance rate (AR) and the amount of uncovered cases (UC). With the known manpower (MP) and the expected case-load (CL) at hand, one is in a measure to work out the approximate expected number of new cases (ENC) through the aforesaid manpower and the overall balance for coverage (BC).

CASE-FINDING

Care is taken to sort out the way patients are found, i.e., whether they report on their own voluntarily—(V) or are detected through contact-tracing (CT), school surveys (SS), upon notification (N) or through other sources (OS).

CASE-MANAGEMENT

This is the bigger component of the Leprosy Field Logistics, unavoidably so. One would like to know the number of yearly new cases (YNC) and thus ascertain the Incidence Rate of the disease. Apart from the usual sex distribution and the various age groups (giving us the ratio male to female and the Child Rate), it is advisable to record the emigration rate (ER) per district. This is followed by the percentage of 'open' cases (OC), the difference of which indicating the percentage of 'closed' ones. It is also advisable to include the following rates pertaining to: relapse (RR), reaction (LR) of the lepromatous variety, disability (DyR), follow-up (FR) and death (DhR) as these are part and parcel of Leprosy Field Logistics. This section ends with the number of sign-free patients (SF) and those 'out of control' (OOC) during the year.

SURVEYS

Contact Survey: this shows the estimated number of contacts district-wise (EC) (in India, one has to reckon with an average of 5 members in the family). Of the total number examined throughout the year (TE) the leprosy rate (LyR) can be determined as well as the balance for coverage (BC).

School Survey: indicates the total number of schools district-wise (TS), the number surveyed (NS), the pupil population (PP), the number examined (NE). The leprosy rate (LyR) can be worked out accordingly as well as the balance for survey (BS) and for examination (BE).

Mass Survey: if this cannot be done once every 5 years or so during the course of the mass campaign—as it is time-consuming, expensive and limited, at the best of times, to about 70% of the population—sampling surveys would be indicated, both with the population involved (PI), the population surveyed (PS), the leprosy rate in question (LyR) and the balance for survey (BS).

There are 2 more components of the Leprosy Field Logistics which, although not included in this series, are worth considering:—

Budget: this can be worked out per antileprosy unit per district per zone so as to have a comparative idea of the per capita cost (PCC), quite an important item in a mass campaign. In effect, if the per capita cost is too high in relationship to the 'output' of a particular anti-leprosy unit, this would indicate either a lesser Prevalence Rate in the area than was thought or sheer inefficiency on the part of the workers. Evidence in favour of the former would lead one to cut down the staff or close down that particular anti-leprosy unit and integrate it with the general health services of the area.

Extension Programme: this is also an important item which ensures continuity of field work until full control of the spread of the disease is achieved. As part and parcel of the Leprosy Field Logistics it would, as a function of the above, show the proposed increase in the antileprosy units per district per zone, translated into the corresponding increase in manpower and the additional case-coverage.

CONCLUSIONS

Leprosy Field Logistics would appear to be the answer to the further strengthening of field activities since, owing to their respective components, the whole picture emerges; its latitude can be seen at a glance; its importance can be readily grasped. They may, furthermore, give the control measures a new direction, and probably a new structure fitted to the increasing demands of field work.



ON & COMMUNICATI







Present Prevalence Rate of Leprosy in mille per district per Zone



PRESENT

THE PROBL

ACHIEVEMENTS

4. CASE-FINDING

PRESENT PICTURE









5. CASE-MANAGEMENT

PRESENT PICTUR

6. SURVEYS



PRESENT

Advances in Leprosy Research

W. F. KIRCHHEIMER U.S.P.H.S. Hospital, Carville, La.

INTRODUCTION

In January, 1965, President Johnson and Prime Minister Sato of Japan agreed to undertake a greatly expanded programme of co-operation between the United States and Japan in the field of medical science. Their resolve was speedily implemented through the newly formed United States—Japan Co-operative Medical Science Programme. Primary emphasis of this Programme is on medical research on diseases of special concern to Asia. Leprosy is one of these. A joint panel of American and Japanese scientists found itself in complete agreement that the following areas in leprosy deserve special attention:—

- 1. Multiplication of the leprosy bacillus in:
 - (a) artificial culture media;
 - (b) cells isolated from man and other species;
 - (c) the intact animal.
- 2. Drugs against the leprosy bacillus, treatment of reactive episodes during the course of the disease, and drugs suitable for chemoprophylaxis.
- 3. Vaccination as a control method.
- 4. Certain aspects of the immunology of leprosy, including the pathogenesis of the reactive episodes.

During the last few years there were several occasions where advances made in these particular areas of leprosy research were reviewed where road blocks impeding progress were identified, together with singposts leading to new and promising approaches. Among these occasions were:—

The Leonard Wood Memorial Foundation (LWM)-John Hopkins University Symposium on Research in Leprosy, Baltimore, 1961.

- The VIII International Congress of Leprology in Rio de Janeiro, 1963.
- The LWM-Armed Forces Institute of Pathology Conference on Research Problems in Leprosy, Washington, 1965.
- The International Conference arranged by the Leprosy Panel of the U.S.-Japan Joint

Medical Science Programme, Tokyo, 1966. The major accomplishments brought to light, their extensions and applications, as well as emerging guiding concepts for future work, are the subject of this review.

This report, therefore, is selective and does not deal with all the aspects of leprosy. Excluded, for example, are the splendid efforts and advances made by Paul Brand and his co-workers in the use of physical and surgical methods in the prevention and management of deformities in leprosy. Also excluded is a detailed discussion of recent clinical drug trials.

It appears convenient to divide the subject into two major sections. Firstly, multiplication of M. leprae in artificial culture media, in cells isolated from man and other species and in the intact animal will be discussed.

This part of the discussion will point up some characteristics of the leprosy bacillus which now serve to identify it. It will illustrate on-going basic research, present-day application to experimental chemotherapy, active immunization, and epidemiology.

The second section concerns itself with hostresponses to infection, such as resistance and hypersensitivity. This part of the presentation establishes a theoretical basis for a better understanding of the different clinical and corresponding histopathological types of leprosy, and of newly evolving concepts of the pathogenesis of the reactive episodes and the urgent need for supporting them with experimental evidence.

SECTION I ATTEMPTS AT GROWTH OF *M. leprae* OUTSIDE OF ITS NATURAL HOST

At the Conference on Leprosy Research Problems in 1965 in Washington, D.C., the greatest amount of time was allotted to the cultivation problem of *M. leprae*. The keynote of the Conference seemed to be how incredible it was that in spite of all microbiological advances the leprosy bacillus stills fails to multiply in vitro. It is, of course, well known that successful cultivation of a microbial pathogen ordinarily precedes an increase in our understanding of the pathogenesis, epidemiology, treatment, and prevention of an infectious disease. It has been voiced repeatedly that progress in gaining a better understanding of leprosy has been hampered by the fact that M. leprae has not yet been grown in bacteriological culture media. (a) Attempts at Growth of M. leprae in Artificial Culture Media

Solution to the problem of growth of *M. leprae* in bacteriological culture media is now being approached directly by making additives to basal media, in the hope of supplying thereby the needed growth-factors. One reads or hears occasionally reports of success (Alexander-Jackson, 1961; Olitzky and Gershon, 1965; Nakayama, 1966), but in not a single instance were the claims supported by up-to-date criteria

It would not seem too promising to invest much time and resources in producing culture media by incorporating into a given basal medium chemical compounds selected at random. Obviously, the choice of candidate substances is legion, and mathematical considerations point up the vast number of different media which are possible by combining substances from even relatively small numbers of choices. Attempts at culture should be supported by rational working concepts. Lately, there has been increasing evidence that future additives to basal media will rely largely on components and co-factors which now have been revealed as important in the structure and function of mycobacterial cells other than M. leprae. (Morrison, 1965; Wheeler and Hanks,

1965; Hanks, 1965.) It seems that more direct evidence for suitable additives might result from metabolic studies with M. leprae. Due to lack of adequate amounts of material, no biochemical studies have been conducted until recently on M. leprae, and its metabolism remained completely unknown. This, in turn, has led to empirical methods being applied to cultivation of the bacillus and in chemotherapy of the disease. Now, however, it has been shown that the leprosy bacillus actively oxidizes 3, 4 dihydroxyphenylalanine (dopa) and that this enzymatic activity clearly distinguishes M. leprae from other mycobacteria, including Mycobacterium lepraemurium and microorganisms which at one time were thought to be the leprosy bacillus. (Prabhakaran, 1967, a. b: Prabhakaran and Kirchheimer, 1966.) This activity of *M*. *leprae* has been proposed by Prabhakaran and Kirchheimer (1966) as one of its identifying characteristics. A detailed investigation of the possible function of quinones produced by dopa oxidation as respiratory carriers is now under way in our laboratories. If dopa oxidation proves to be a key reaction in the respiration of *M. leprae*, rational approaches to artificial culture and anti-microbial therapy become possible.

(b) Attempts at Culture of M. leprae in Tissue Culture

Successful cell culture of M. leprae can be looked upon as a long step forward toward eventual independent growth of this microorganism. This topic is receiving major attention in several laboratories. The most encouraging results so far were reported in 1965 by Garbutt. Using monolayer cultures of human embryonic long cells, she obtained a 148.6 fold increase in bacterial numbers in 141 days. This corresponds to 7.1 bacterial generations, with an overall generation time of 17.4 days. In an additional experiment with 14 p f rat fibroblasts she obtained a cumulative bacterial increase of 1.62×10^6 fold, or 20.5 generations over 452 days, giving a generation time of 22.0 days. The general principles and methods used in these experiments were very much like the ones previously used by Garbutt, Rees and Barr (1962) and Rees and Garbutt (1962) in their successful attempts to grow M. lepraemurium in 14 p f rat fibroblasts. Methods used in our own experiments in Carville are similar to those used by the English workers. Human, other mammalian cells, and those derived from poikilothermic animals (rainbow trout) are maintained in such a form that they permit continuous cycles of cellular infection. An attempt is made to maintain the infected cells in media insuring multiplication at slow rates, to maintain favourable cell/bacteria ratios. In addition, substances are added to the cell culture medium, which might stimulate multiplication of the leprosy bacillus.

Among candidate agents which might be found useful for 'unblocking' *M. leprae* are: Diaminopimelic acid, mycobactin, RNA from various sources, gibberillic acid, -SH group donors like cystein, and more heterogeneous substances like sterile extracts of lepromatous tissue.

Evidence obtained from multiplication of M. leprae in the mouse foot-pad makes it appear likely that its growth temperature requirements might resemble those of $Myco-bacterium \ balnei$ and $Mycobacterium \ ulcerans$. On account of this possibility, incubation is at 33°C. and 37°C. Furthermore, it cannot be excluded that a relatively high pO₂ might be injurious to obligate intracellular parasites. This, of course, invites experimentation with gas phases of various composition, particularly some with increased p CO₂.

Up to this time, only small numerical increases were observed. For example, in cultures of human embryonic lung cells at 37°C., containing 10⁻⁴mg per ml of RNA from *Mycobacterium phlei*, there was a 3.2 fold increase of the bacteria in 108 days. Small numerical increases of the acid-fast bacteria were also noted by Chang and Neikirk (1965). Their cell cultures consist of mouse peritoneal macrophages, supplemented with L fraction of liver extract (Nutritional Biochemical Corp., Cleveland, Ohio) and ferric nitrate, maintained in a 5% CO₂-air mixture. (c) Multiplication of M. leprae in Experimental Animals

It is now well established that M. leprae multiplies in the foot-pads of mice (Shepard, Janssens and Pattyn, 1963; 1960, 1960a; Kirchheimer, 1964; Rees, 1964) and that maximum multiplication is limited to a narrow range of relatively low ambient temperatures (Shepard, 1965). The amount of multiplication and the location of the bacteria, following inoculation of several thousand leprosy bacilli into the foot-pad, is very typical and serves in distinguishing M. leprae from other mycobacteria, particularly M. lepraemurium. In contrast to the latter organism, M. leprae does not cause grossly visible changes of the injected foot, fails to invade adjacent or remote tissues, has a multiplication ceiling of a few million, and, as stated before, increased ambient temperatures depress its multiplication, which is not the case with *M. lepraemurium*. Recently, Rees (1965) has shown that in thymectomized, total body irradiated mice, kept alive with bone marrow transfusions, increased multiplication of the leprosy bacillus takes place in the foot-pad without, however, resulting in systemic infection. That the restricted multiplication of *M. leprae* in the foot-pad in all likelihood is due to immune intervention has been concluded from the observation that transfusion of thymectomized and irradiated mice with normal homologous lymphocytes re-establishes the former status, with respect to multiplication of the leprosy bacillus (Rees and Waters, 1966). Our own observation that multiplication of *M. leprae* in the foot-pad is depressed significantly in offsprings of vaccinated mice support an immunological explanation for the characteristic multiplication ceiling (Matsuo and Kirchheimer, 1966). Because of the quantitative and qualitative limitations of the mouse foot-pad model, search for more suitable experimental conditions is needed. In this connection it is noteworthy that Rees and Water (1965) noted a more generalized infection with *M. leprae* involving the foot-pads, ears, lymph nodes, striated muscles and tail skin in intravenous challenged thymectomized

and irradiated mice. In view of what was said before about the dopa oxidase activity of the leprosy bacillus, we are now contemplating trials with mice bearing melanomas.

Before summarizing some of the applications which were made of the mouse foot-pad model and some of the results of these endeavours, a third distinguishing characteristic of M. leprae must be added to its capability to oxidize dopa, and its multiplication pattern in mouse footpads. M. leprae seems to be the only known mycobacterium which fails to evoke grossly visible responses in the skin of leprosy patients with negative Mitsuda tests (McFadzean, 1962; Shepard and Guinto, 1963). Identification as M. leprae of an unknown mycobacterium failing to grow under ordinary conditions requires simultaneous intradermal injection of leprosy patients with the heat-killed mycobacteria and with standard lepromin. The leprosy patients must be so selected that there is a significant number of Mitsuda positive persons among them. In contrast to Mitsuda negative patients, these will respond with local reactions to the injection of leprosy bacilli.

(d) Application of the Mouse Foot-pad Model

The following is a list of applications which have been made of the mouse foot-pad technique:—

- 1. Experimental chemotherapy. Screening of anti-leprosy drugs. Detection of drug resistance.
- 2. Vaccination against M. leprae.
- 3. Stability of *M. leprae in vitro*.
 - Effect of wet-ice temperature on subsequent multiplication.
 - Effect of preservation at the temperature of liquid nitrogen on subsequent multiplication.
- 4. Epidemiology.

Role of arthropods in the transmission of leprosy.

The fact that M. leprae multiplies with regularity in the mouse foot-pad has provided an experimental *in vivo* method for testing the drug sensitivity of strains of leprosy bacilli from untreated and treated patients. Drug sensitivity has been assessed by comparing the yield of bacilli in the foot-pads of treated and untreated mice. The respective drugs are either fed in the diet or given by injection, ordinarily commencing on the day of infection (Shepard and Chang, 1964; Shepard, 1964; Pettit and Rees, 1964; Rees, 1966; Shepard, 1966; Shepard, McRae and Habas, 1966).

The principal results of these tests show:—

- 1. That all the accepted anti-leprosy drugs, including diaminodiphenylsulfone (DDS), the thiourea (Ciba 1906), the thiosemicarbazone (TBI), the 2 long-acting sulphonamides, Fanasil and Madribon, and the phenazine derivative B 663, more or less completely inhibit the multiplication of *M. leprae* in the mouse foot-pad.
- 2. That *M. leprae* is extraordinarily sensitive to DDS (Shepard, McRae and Habas, 1966). As little as 0.0001% of DDS in the diet of mice completely suppresses multiplication of *M. leprae* in their foot-pads. From the available findings Shepard (1966) estimated that the minimum inhibitory concentration of DDS for *M. leprae* is approximately 0.03 gamma per ml of blood.
- 3. That leprosy bacilli resistant against DDS occur (Pettit and Rees, 1964).

Multiplication of *M*. leprae in the foot-pad of mice has also been exploited for determining the efficacy of anti-leprosy vaccines (Shepard, 1965, 1966). The criterion for protection is reduction of multiplication of leprosy bacilli in the foot-pad of vaccinated, as compared to non-vaccinated mice. It has been shown that intradermal injection of 50 mcg. (dry weight) of BCG, Rosenthal, given one to two months prior to challenge reduces the final crop of leprosy bacilli by 50%. Much smaller amounts of the vaccine still have measurable effects. Answers to the question of the prophylactic value of BCG vaccination for the prevention of leprosy are being sought in mass trials in Uganda, Burma and New Guinea. The Uganda trial (Brown and Stone, 1966) included about 16,000 tuberculin-negative children, mostly under 10 years old and all in contact with leprosy. Half

of the children not vaccinated served as controls. The other half received freeze-dried BCG. One to three years after vaccination 89 cases of leprosy were detected among controls, but only 18 among vaccinated children. Evaluation of these findings, however, must take into consideration that only 8% of leprosy in Uganda is of the lepromatous type. To be certain that BCG vaccination is likewise effective in reducing the incidence of lepromatous leprosy, one must await the results of the trials from areas like Burma, which has a high incidence of lepromatous leprosy. Results from these fields trials in Burma and New Guinea will not be known for 2 or 3 years.

Shepard and McRae (1965) used the mouse foot-pad system to determine the effect of low temperatures and freezing on the infectivity of M. leprae. The keeping-quality of the leprosy bacillus is of special importance to leprosy research. This becomes understandable if one remembers the fact that competent research laboratories frequently are located far from the sources of supply of suitable material, which consequently must be shipped long distances. As measured by their subsequent ability to multiply in mouse foot-pads, leprosy bacilli in balanced salt solution containing 0.1% bovine albumin maintain viability for about 2 weeks at a temperature of 0°C. Freezing and storage at -60° C. does not seem to be a good way to preserve the leprosy bacillus. It is possible, however, to reduce the deleterious effect by including 10% of glycerin in the suspending medium prior to freezing. Experiments on viability of leprosy bacilli stored at the temperature of liquid nitrogen (-193°C.) are now under way.

At the VIII International Congress of Leprology (Rio de Janeiro, 1963) the members of the Panel on Epidemiology and Control expressed their opinion that the control of leprosy is closely dependent on the present state of knowledge concerning the epidemiology of the disease. They believe that a better understanding of the mechanism of transmission may bring about basic changes in our present method of control. The unsatisfactory state of knowledge of the mode of transmission of leprosy is pointed up by extant disagreements about the portal of entry of M. leprae into the human body. Recently, Weddell and his associates (1963) have cast doubt upon the belief in the prevalence of the dermal route of infection subscribed to by most leprologists. Furthermore, it is worth noting that not even the proponents of the hypothesis of dermal entrance are in agreement among themselves on the nature of the infecting event.

Some, like Khanolkar (1963), have stressed the necessity of persistent and intimate contact with human cases of leprosy in an infectious state. Dungal (1960,1961), on the other hand, comes out in favour of accidental infection by ectoparasites or parasites of the skin. One must agree with Spickett (1961) that a likely vector would have to be able to penetrate to the subepidermal tissues of man, the ordinary location of M. leprae, and in addition must be able to support the prolonged survival of the leprosy bacilli, particularly in its alimentary tract. Effective role as a vector also depends on biological characteristics of an arthropod such as feeding habits and length of survival, as well as on the behavioural characteristics of its host.

In the past, several workers (Muños Rivas, 1942; McCoy and Clegg, 1949; Spickett, 1961) have reported the occurrence of acid-fast bacilli in the alimentary tract of arthropods. Muños Rivas, for example, found 187 (11.4%) carriers of acid-fast bacteria among 1,627 fleas taken from places free of leprosy. At the time these reports were made, and in fact until recently, it was not possible to either identify these bacteria as M. leprae or prove their viability. In consequence, the significance of these findings for the transmission of leprosy could not be assessed. Fortunately, no such handicaps exist at the present time. Now, it is known that perhaps even as few as 10 viable leprosy bacilli, if injected into the mouse footpad, will multiply at this particular site, provided the ambient temperature of the animal quarters does not deviate much from 70°F (21°C). Additional methods for identifying mycobacteria growing in the mouse foot-pad as the leprosy bacillus have been discussed before. A research project, entitled 'The Role of Arthropods in the Transmission of Leprosy,' is now getting under way, in collaboration between the United States Public Health Service and The Jawaharlal Institute for Postgraduate Medical Education and Research, Pondicherry, India.

SECTION II

HOST RESPONSES TO INFECTION

It is a common observation that individuals exposed to leprosy bacilli may fail to develop readily detectable signs of infection. Others display partial resistance to the leprosy bacillus by supporting its growth in their tissues only with reluctance, or for a limited time. The tissues of some individuals, however, seem quite incapable of any effective resistance to the multiplication of the invaders and their progeny.

At the VIIIth International Congress of Leprology in Rio de Janeiro in 1963, there was an increasing readiness of workers in leprology to regard the various clinical and corresponding histological types of leprosy as an expression of the amount of host resistance. The 2 polar types of leprosy, tuberculoid and lepromatous, respectively, represent high and low degrees of resistance and stand at the ends of a spectrum encompassing all of the variations in resistance, expressing themselves as dimorphous (borderline) leprosy with varying amounts of mixtures of both forms.

The question would now arise as to the kind of mechanism to which different individuals owe their particular degree of reistance to the leprosy bacillus. At the Congress, the members of the Sub-Committee on Immunology of the Panel on Bacteriology and Immunology expressed the opinion that native and acquired resistance to mycobacterial infections have not been shown to be due to or associated with antibody or antibody production. They stated, furthermore, that native resistance may depend in part on factors unfavourable to the reproduction of M. leprae. Native resistance, in the opinion of the members of the sub-committee, becomes rapidly fortified by acquired resistance. The latter was said to consist primarily of an improvement in the natural capacities of mesenchymal cells to digest mycobacterial cell walls and to hydrolyze their proteinaceous components. They added that acquired resistance to mycobacterial disease seems analogous to induced formation of enzymes. It is, of course, reasonable to assume that the extent to which individuals might respond with adaptive enzyme formation is genetically determined. There is so far no experimental support for this hypothesis as far as leprosy is concerned. In experimental tuberculosis, however, it has been shown that mononuclear phagocytes of rabbits genetically resistant to tubercle bacilli had greater metabolic activity on certain substrates than the same cells of susceptible animals (Allison, et al., 1963). In particular, cells from resistant animals showed a greater ability to break down glycerophosphate and Beta-hydroxybutyrate. Both of these substances are linked to the scheme of lipid metabolism. Lipids, of course, are an integral and predominant part of tubercle bacilli and some of these like, for example, the 'cord factor' may play a role in virulence. This increased metabolic activity of mesenchymal cells might, therefore, be of importance for explaining increased resistance against tubercle bacilli. Note must, however, be taken of the recently demonstrated fact that antibodies against antigens of the leprosy bacillus, identified as immunoglobulins, are present in the serum of patients with lepromatous and tuberculoid forms of leprosy (Merklen, et al., 1963). There are indeed indications that the resistance or the susceptibility to the disease may be related to immune phenomena. As was pointed out earlier, in the mouse foot-pad, at least multiplication of M. leprae seems to be limited because classic immune mechanisms are being invoked. Furthermore, there are several reports of abnormalities in the serum proteins in leprosy, particularly abnormalities of the immunoglobulins (Nudenberg, 1965). Matthews and Trautman (1965) demonstrated the presence of cryoglobulin in the sera of all 39 individuals with lepromatous

leprosy who were not receiving corticosteroids and in 16 out of 29 who were at that time under treatment with corticosteroids. This finding. associated with an increase of globulins in the gamma zone and the seeming lack of proper defence mechanisms, becomes extremely important in view of the usual association of crvoglobulins with immunologically incompetent paraproteins (Grabar and Burtin, 1964). Evidently, the antibodies found so far are not connected with resistance to the disease, since they prevail in people who do not exhibit a satisfactory immunological response. In the absence of a demonstration of protective antibodies, a study of the structure of the antibodyactive fragment of the immunoglobulins is the only possible approach to a study of immunological differences between apparently resistant and susceptible subjects.

An important and in many respects enigmatic aspect of leprosy is the pathogenesis of the reactive episodes. The need for clarification of the mechanism of these reactions was clearly recognized and expressed by the Panel on Leprosy Reactions of the VIIIth International Congress of Leprology (Rio de Janeiro, 1963). In the opinion of the majority of leprologists these reactions are allergic manifestations to mycobacterial antigens. The significance of mycobacterial antigens as possible sensitizing agents can, of course, not be denied. Yet it would seem best not to dismiss the possibility that, in some instances at least, other antigens might have engendered the hypersensitive state and, therefore, are capable of eliciting reactions at a later date. Some theoretical considerations support the assumption that autosensitization may take part in the pathogenesis of lepra reactions. For instance, the enhancing action of mycobacterial bodies on the antigenicity of other substances is well known and has been widely exploited experimentally in the form of Freund's adjuvant. One can well imagine that in leprosy mycobacterial bodies may exert a similar effect on tissue components which might have undergone some alterations during the prolonged course of the disease. In addition to support derived from theoretical considerations,

the following observations have been interpreted as suggestive of 'auto-immune' involvement: false positive serological reactions with lipoidal antigens, occurrence of antithyroid antibody, rheumatoid factor, antinuclear antibodies, and cryoglobulins (Cochrane, 1964;, Matthews and Trautman, 1965).

SUMMARY AND CONCLUSIONS

1. Research in the areas of cultivation of M. *leprae* chemotherapy, chemoprophylaxis, vaccination and of the immunology of leprosy is being accelerated under the auspices of the U.S.-Japan Co-operative Medical Science Programme.

2. The renewed attempts at cultivation in artificial culture media are guided by newly evolved concepts. Attempts to culture the leprosy bacillus in cell culture have provided some encouraging results.

3. The typical multiplication pattern in the mouse foot-pad, the distinctive reaction pattern of Mitsuda positive and negative individuals to intradermal injection of leprosy bacilli and its unique enzymatic activity distinguish *M. leprae* from other mycobacteria.

4. The mouse foot-pad system is being employed for the study of various aspects of leprosy like drug action, efficacy of vaccines, environmental effects on bacterial survival, and certain epidemiological aspects.

5. Modern immunological techniques need to be employed to further the understanding of resistance and the role of hypersensitivity.

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Priscol in the Prevention and Management of Leprotic Lagophthalmos

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Lagophthalmos is not an uncommon ocular complication of leprosy. It often poses a serious threat to the eye on account of the exposure and accompanied corneal anaesthesia. Incomplete closure of the lids invariably leads to keratitis, corneal ulceration and ultimate blindness.

The incidence of lagophthalmos in leprosy varies in different types of the disease and from country to country. Loutfley (1937) reported 17% incidence of lagophthalmos in sanatorium patients in Egypt. Doul's (1959) analysis of 202 patients in Hynkyns gave a figure of 5% and 11% for tuberculoid and lepromatous types respectively. In our leprosy patients the incidence of lagophthalmos seems to be approximately 3%, a figure significantly lower than the earlier reports. But considering the high incidence of the corneal complications associated with leprotic lagophthalmos, its early correction should be considered necessary.

Presently, the popular mode of treatment of lagophthalmos of any etiology has been tarsorraphy of the outer canthus. In more severe cases tarsorraphies of both the canthi have been practised. Although these procedures successfully prevent the exposure keratitis, they functionally and cosmetically give poor results.

Glazenow (1955) suggested the introduction of fascia lata graft in the lower lid with the object of giving better function and cosmetic results. Such an operation does not impart any movement to the upper lid. Gills and Millard (1957) described temporalis transplant as a suitable procedure for obtaining lid closure in lagophthalmos. Subsequently many workers reported encouraging results with this technique, but due to intricacies in the operation the technique is not popularised.

Therefore, it seems that none of the available techniques for the management of lagophthalmos is ideal. There is a vital need for the newer methods of treatment of lagophthalmos caused by peripheral facial palsy specially of leprotic origin. Recently, Mathur and Saxena (1965), Mathur (1965) and Mathur *et al.* (1966) reported good response by intraneural priscol in the treatment of leprosy deformities. Encouraged by their observations, we have used priscol in the management of leprotic lagophthalmos. The present report covers our preliminary observation on this aspect.

CASE REPORT

R.R., male, aged 32 years, attended the Bhowalka Eye Hospital, Banaras Hindu University, Varanasi, with the complaint of inability to close the left eye for the past 7 years. He was a leprosy patient for the last 18 years and had been receiving anti-leprosy treatment for the last 8 years.

On Examination: The left palpebral aperture was wider and the eye was prominent. Patient had infra-nuclear type of facial paralysis on the left side resulting in ectropion of the left lower lid and marked lagophthalmos (Fig. 1). The left eye had mild conjunctivitis and the left cornea had a faint cresentic opacity near the inferior limbus. The corneal sensation was slightly impaired. The other structures of the eye were normal. The right eye had no ab-



FIG. 1a Showing wide left palpebral aperture with slight ectropion of the left lower lid.



FIG. 1b Showing lagophthalmos of the left eye.



FIG. 2 Showing residual lagophthalmos after priscol therapy. 160 Leprosy Review

normality. Besides these ocular anomalies, he had loss of sensation, deformities and contracture of all the fingers of both the hands which showed improvement on local intraneural priscol therapy.

He was given a weekly injection of priscol 1 ml. by the following technique: Localisation of temperomandibular joint was done by asking the patient to open his mouth. A point 1 cm. below the position of the condyle was selected and with the help of a stout needle 4 cm. long, 0.5 ml. of priscol was injected. The needle was then directed and moved 1.5 cm. towards the stylo-mastoid foramen and 0.25 ml. of the solution was injected. Now the direction of the needle was changed towards the outer canthus of the eye and the remaining 0.25 ml. of priscol was infiltrated along the course of the branches of the facial nerve as they fan over the malar bone.

After 6 injections, there was marked symptomatic improvement in the patient's condition. The epiphora and conjunctivitis disappeared. The patient appreciated the return of the lacity in the taut left upper lid, which had facilitated the blink reflex. The lid lagging was comparatively less marked. A further course of 6 injections was repeated and it significantly helped the patient in closing the left eye, although slight lagophthalmos persisted (Fig. 2).

The patient was followed after the termination of priscol therapy for a further period of 6 months. There was neither a recurrence of ectropion of the left lower lid nor any improvement in the lid closure function.

COMMENTS

Lagophthalmos in leprosy results from involvement of the motor branch of the facial nerve to the orbicularis oculi muscle either isolated or as a part of more extensive degeneration of the peripheral branches of the nerve. This degeneration of the nerve has a close relationship with vascular constriction generally manifested by the disease. The choice of priscol in prevention of degeneration of the nerve or its regeneration is obvious, as it has a local vasodilatory action and thus it improves the blood supply of the ischaemic nerve bundles (Mathur *et al.*, 1966). Systemic administration of priscol has no value in the treatment of lagophthalmos. The present patient received as many as 18 intraneural injections in the upper limbs resulting in improvements in the degrees of deformities but no improvement was noted in his lid closure activity. Therefore local priscol therapy was attempted for the correction of the lagophthalmos.

It is evident from the foregoing case report that injections of priscol in the neighbourhood of the main facial nerve have improved function of the eye lids and cosmetic appearance of the patient, the patient's annoying epiphora disappeared and he could close the lids to a greater extent. The residual lagophthalmos in the present patient can be explained as irreparable damage done by the prolonged ischaemia caused by the long-standing disease. One may, therefore, expect complete recovery in a case of peripheral facial palsy where priscol therapy is instituted without allowing any time for paraneural or interneural fibroblastic proliferation, which in turn results in greater vasoconstriction and ultimate irreparable nerve degeneration.

Recently authors (Nema *et al.*, 1967) have studied the topical effect of priscol in nonleprotic facial palsies of less than one year of duration where B_1 and B_{12} therapy failed to be effective. The experience gained in the treatment of such patients is sufficient to conclude that improvement is more rapid and recovery of paralysis is more complete if priscol is locally administered in the neighbourhood of the facial nerve without losing much valuable time. It is, however, suggested that all patients of paralytic lagophthalmos should be subjected to local priscol injections before submitting to more intricate and less rewarding surgical procedures.

SUMMARY

Various available surgical techniques for the correction of lagophthalmos are reviewed. A medical treatment with local priscol injections in the neighbourhood of facial nerve was found to be encouraging in a patient of leprotic lagophthalmos. It has been suggested that all patients of paralytic lagophthalmos of recent onset should be subjected to priscol therapy before submitting them for intricate and less rewarding surgery.

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Streptomycin and INAH in the Treatment of Leprosy

A Preliminery Communication

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Since the introduction of DDS (Diameno-Diphenyl Sulphone) in 1941¹ as a specific treatment for the various types of leprosy, there has been a revolution in the thinking of physicians engaged in the treatment of leprosy. DDS brought new hope and offered, for the first time, definite possibility of cure for the leprosy patient. However, the initial therapeutic enthusiasm has gradually begun to wane with the realisation that DDS is no longer the 'wonder drug' it was hoped it would be. The main limitations of DDS are the slow clearance of bacilli² and hence the need for prolonged treatment; and the tendency of DDS to produce progressive neurological deficit and to precipitate reactive phases of the disease in all types of leprosy except the indeterminate group.^{3 4 5} Hence the search for a new drug that is likely to be able to clear the bacilli quickly and at the same time be free of sideeffects continues. To date no such drug is available.

Davison⁶ reported on a limited trial of Streptomycin and INAH in lepromatous leprosy and found the improvement on bi-weekly treatment with this combination comparable to that on DDS in relation to lepromatous infiltrations and nodules. Dreisbach and Cochrane⁷ conducted a trial of the combination of streptomycin and INAH (Isonicotinic acid hydrazide) in leprosy and concluded that this had a limited value in the management of leprosy except in patients with mucosal involvement (nose and larynx). We have been attracted to the use of streptomycin and INAH in leprosy both because this combination effectively combats infection by another mycobacterium, and because of the relatively short time taken for 'sputum conversion' to occur even in patients with fairly advanced pulmonary tuberculosis. We were also struck by the rapid improvement in clinical and bacteriological status of patients with lepromatous leprosy and tuberculosis when they were treated with a combination of daily injections of 1 g. of streptomycin along with 300 mg. of INAH orally. This prompted us to undertake a prospective study of the use of combination of streptomycin and INAH in various types of lepromatous leprosy. This report is in the form of a preliminary communication.

MATERIAL AND METHODS

Schieffelin Leprosy Research Sanatorium in Karigiri, South India, is situated in an area endemic for leprosy. Being a research institution, leprosy patients with various complications come to this hospital from all over the country. There are just over 14,000 patients on the register. Sixteen to 17% of the patients have lepromatous leprosy. Twenty-five typical lepromatous leprosy patients were included in the trial. The age-sex distribution of the sample studied is shown in Table 1.

	TAE	LE l	
	Sample	Studied	
Age	Male	Female	

(years)	Male	Female	Total
<15	4		4
>15	15*	6	21*
Total	19*	6	25*

* 2 patients had 2 courses of treatment with Streptomycin and INAH, making a total of 27 trials.

Patients chosen were those who were intolerant of DDS and were liable to recurrent attacks of erythema nodosum leprosum (ENL) and/or acute neuritis (acute painful enlargement of nerves). Some patients had advanced lepromatous leprosy, some others had lepromatous laryngitis with hoarseness of voice and some had severe involvement of nasal mucous membrane as judged by complaints of difficulty in breathing due to blocking of the nose, epistaxis and/or collapse of the nasal bridge. Some of the patients had acute lepromatous skin ulceration. Table 2 shows clinical findings at admission to this trial.

Clinical	Findings	at	Admission	to	Therapy
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Male	Female	Total
10	3	13
5	1	6
1	-	1
3		3
1		1
1	2	3
21	6	27
	Male 10 5 1 3 1 1 21	Male Female 10 3 5 1 1 - 1 - 1 2 21 6

Routine skin smears were taken once a month in most cases according to the slit skin method and read on a 0 to 6 scale of Ridley.⁸ The initial bacteriological index on this scale is indicated in Table 3.

TABLE 3 Bacterial Index at Start of Therapy

Bacterial Index	Male	Female	Total
1—	4	1	5
2	4	2	6
3 -	6	1	7
4—	6	2	8
5—	1	-	1
Total	21	6	27

RESPONSE TO TREATMENT

The change in bacteriological index (B.I.) during the period on treatment with streptomycin and INAH is depicted in Table 4. Of the 27 trials, in 25 there was significant improvement in B.I. In one case there was no change and in another there was an increase of 0.13 from 1.37 to 1.50.

TABLE 4 Change in Bacterial Index during Streptomycin/INAH Regime

Decrease in Bacterial Index	Male	Female	Total	
< .5	2	1	3	
.5—	7	2	9	
1.0—	2	1	3	
1.5	3	1	4	
2.0—	3	1	4	
2.5 -	1		1	
3.0 -	1	<u></u>	1	
Total	19	6	25	

In over 90% of the samples under study, there was a decrease in B.I. There was no noticeable sex difference in the response to treatment.

The change in B.I. in relation to the duration of treatment is shown in Table 5.

Duration Months 3			3-		6-	
Decrease in Bacterial			S	ex		
Index	M	F	M	F	M	F
< .5	1		1	1		
.5—	1		4	1	2	2
1.0—	1	1	1			
1.5 -	1	1	2			
2.0 -			2		1	1
2.5 -					1	
3.0—	1					
Total	5	2	10	2	4	2

TABLE 5 Change in Bacterial Index according to Duration of Therapy

The change in B.I. according to initial pretreatment B.I. is shown in Table 6.

TABLE 6 Change in Bacterial Index according to Initial Bacterial Index

Decrease in	Initial Bacterial Index				
Bacterial Index	1—	2—	3—	4—	5-
< .5	1	2			
.5—	3	2	2	2	2
1.0—		2	1		
1.5 -			2	2	
2.0—			1	3	
2.5 -				1	
3.0—					1
Total	4	6	6	8	1

From Tables 5 and 6 it is obvious that the maximum response occurred in this sample between 3 and 6 months. Further, it is seen that the higher the initial B.I., the more rapid and greater is the fall in B.I. (Fig. 1—scatter diagram.)

The patient in whom there was no change in B.I. had hoarseness of voice which improved rather dramatically while on trial. But the treatment had to be stopped at the end of 30 days because of onset of vertigo and unsteadiness of gait. The one patient who showed a small rise in B.I. had chronic eyrthema nodosum which continued during treatment with streptomycin and INAH and hence the treatment was stopped at the end of 2 months.

CLINICAL RESPONSE

The change in B.I. in relation to clinical findings at initiation of treatment is presented in Table 7.

It appears as though patients with erythema nodosum leprosum (ENL) show lesser improvement in B.I. compared to those who did not have ENL. The best response is seen in those with lepromatous nodules as well as those with acute leprous skin ulceration.⁹ (Photographs: Figs. 2, 3, 4, 5.) In addition, the cosmetic results in these patients are very gratifying. The changes in B.I. in patients with nodules and acute ulceration is emphaised through Table 8.

TABLE	7

Change in Bacterial Index in relation to Clinical Findings at Initiation of Treatment

Condition	Change in Bacterial Index									
	< .5	.5—	l—	1.5—	2—	2.5-	3—	0	+0.13	Total
Erythema Nodosum Leprosum	3	2	2							7
ENL+Neuritis		5			1					6
ENL+Ulceration					1					1
$\mathbf{ENL} + \mathbf{Tuberculosis}$		1						1	1	3
Neuritis + Ulceration							1			1
Ulceration		1		2						3
Nodules only				1		1				2
ENL+Nodules			1	1	2					4



FIG. 1 Scatter diagram showing initial bacterial index and change in bacterial index during treatment with Streptomycin and INAH.

In 3 patients with hoarseness of voice due to lepromatous laryngitis, there was rapid improvement in voice which was noticeable from two weeks of initiation of treatment. Similar dramatic response was seen in another patient with acute lepromatous necrotising lymphadenitis.¹⁰ In this patient the septicaemic, swinging temperature came down to normal in a few days, the tenderness and swelling of lymph glands and hepatosplenomegaly cleared up in 2 weeks time.

Of the 25 patients, 21 had erythema nodosum

TABLE 8
Changes in Bacterial Index in
Nodular and Ulcerated Patients

Change in Bacterial Index	Nodular	Ulceration		
< .5	_	-		
.5		1		
1.0—	1	_		
1.5—	2	2		
2 0—	2	1		
2.5-	1	-		
3.0	-	1		
Total	6	5		

leprosum on admission. All of them gave a history of recurrent episodes of ENL and had become intolerant of DDS on account of recurrent ENL. While on treatment with streptomycin, 4 of these 21 patients developed further crops of ENL. However, except in one of them the ENL episodes were mild, not necessitating interruption of treatment with streptomycin and INAH. In one of them, treatment had to be discontinued at the end of 2 months because of the persistence of fairly severe ENL. It is of interest to note that the rest of the 20 patients were able to tolerate other specific anti-leprosy drugs better at the end of the course of treatment with streptomycin and INAH and are, at the time of reporting, found to be maintaining the progress they had shown while on trial.

Though 7 patients had acute painful peripheral neuritis due to leprosy at admission to the trial, in all of them the peripheral neuritis settled down with relief of pain and no further progression of neurological deficit as judged by sensory charts and the motor assessments of muscles supplied by the affected nerve. This particular result is worth emphasising. While on trial, no patient developed fresh peripheral neuritis and in none was there progression of neurological deficit.

SIDE EFFECTS

Of the 27 trials in 25 patients, 3 developed disturbance of vestibular function as evidenced by complaints of vertigo and demonstration of unsteadiness of gait and incoordination. In all of them, the symptoms and signs cleared up within a few days of cessation of treatment with streptomycin, the longest duration of vertigo being 3 weeks from cessation of treatment.

DISCUSSION

The change in B.I. in these patients while they were on non-streptomycin period is depicted in Table 9.

TABLE 9	
Change in Bacterial Index du	ring
Non-Streptomycin/INAH Re	gime

	Duration Months					
$<\!3$	3—	6—	9—	12—	Total	
_	3	-	1	2	6	
	3	3	1	-	7	
1	1			_	2	
22	1	1	-	4	28	
23	8	4	2	6	43	
	<3 - 1 22 23	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	

This picture is strikingly different from the one showed for streptomycin and INAH period in Table 5. None showed decrease below 2 units of B.I. despite treatment over one year.

For purposes of comparison of the action of streptomycin and INAH with that of the standard anti-leprosy drug, DDS, a random sample of the charts of 60 lepromatous patients on DDS 600 mg per week (given as 100 mg o.d. for 6 days) was studied in retrospect. The changes in B.I. while on this dose of DDS is shown in Fig 6 (scatter diagram) in relation to the initial B.I. Comparing this with Fig. 1, which shows the change in B.I. while on streptomycin and INAH, the merits of treatment with the latter are self-evident. While a drop in B.I. of 2 units or more has occurred within 6 months of treatment with streptomycin and INAH in a significant number of patients, similar changes in B.I. while under DDS therapy takes a year or more.

It has long been known that though DDS may kill the bacilli rapidly as judged by the rapid change in morphological index of leprosy


 $\begin{array}{c} {\rm FIG.~2} \\ {\rm Nodular~lepromatous~leprosy~before~treatment~(on~20.8.66).} \end{array}$



FIG. 3 Same patient as in Fig. 2, after 84 days of treatment with Streptomycin and INAH (on 14.11.66).



FIG. 4 Showing acute lepromatous skin ulceration before treatment (on 7.12.65).



FIG. 5 Same patient (on 6.1.66) 30 days after treatment with Streptomycin and INAH.



FIG. 6

Scatter diagram showing initial bacterial index and changes in bacterial index according to varying durations of treatment with 100 mg DDS once a day, 6 days a week.

bacilli in patients under DDS therapy, the clinical improvement of the patient does not correspond to the bacteriological index. In other words, the clearance of leprosy bacilli in patients on DDS treatment is a slow process and takes many years. (Personal observation.) This state of affairs is in striking contrast to the effect demonstrated here with streptomycin and INAH. One of the reasons for rapid clearance of bacilli in patients on streptomycin may be the bacteriocidal effect of streptomycin as compared with the bacteriostatic effect of DDS. The mode of disposal of dead leprosy bacilli by the body merits further study. The findings with streptomycin and INAH treatment in leprosy closely parallel those in pulmonary tuberculosis. CONCLUSIONS

From the data presented so far, it appears as though the maximum benefit occurs in those with nodular leprosy and acute leprous ulcers in terms of drop in bacterial index. The improvement in patients with hoarseness of voice, acute leprous lymphadenitis and acute leprous peripheral neuritis are also worthy of note. The reduction in the incidence of ENL and the improved tolerance of anti-leprosy drugs among lepromatous leprosy patients subject to recurrent ENL following a course of treatment with streptomycin and INAH are other useful features. SUMMARY

1. Therapeutic trial of daily intramuscular injection of 1 g. of streptomycin sulphate along with 300 mg. of INAH orally in 25 patients with typical lepromatous leprosy is presented.

2. A significant reduction in bacteriological index was noticed in all except 2 patients.

3. Maximum drop in B.I. occurred in those with nodular lepromatous leprosy as well as in those with acute leprous skin ulceration.

4. Significant clinical improvement was noticed in the voice of patients with hoarseness due to lepromatous laryngitis; in acute leprous peripheral neuritis and in acute necrotising lepromatous lymphadenitis.

5. Of 21 patients who on admission had ENL and a history of recurrent ENL, only 4 developed ENL while on trial. In 3, the ENL was mild and in one patient ENL was severe enough for the trial to be suspended.

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Histological, Bacteriological & Immunological Differences between the Bacilliferous Forms of Leprosy in Chinese

(with a note on the histological features of the paucibacillary forms)

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A clearly demarcated classification of the various forms of leprosy is not only intrinsically desirable, but is essential for comparable analysis of studies of patients in different parts of the world. Classifications based solely on clinical features have led to arguments and confusion, probably because of wide pigmentary and somatic differences between various peoples; for example, borderline leprosy in the Far East has been described as being nearer to lepromatous leprosy in its clinical features than is the case in Africa (Browne, 1963). However, when the histological picture of skin lesions of untreated patients is analysed, features can be found to identify the various forms of leprosy. Ridley and Jopling (1962, 1966) have fully described and tested an acceptable 5-form spectrum of leprosy, in addition to the indeterminate form. Histological, clinical, bacteriological and immunological studies amongst Chinese leprosy patients have led independently to the recognition of an almost identical 5-form spectrum. These studies were initiated in 1961. A pilot study of more than 100 skin biopsy specimens revealed that in Chinese patients a classification based on the histological features of a skin biopsy specimen correlated more closely to the subsequent clinical course than a purely clinical classification. Clearly distinguishable histological pictures were identified that corresponded to different forms of leprosy whose clinical course under treatment was markedly different from each other. The 5-form classification found in Chinese patients was

included in the protocols of a study of leprosy bacilli in the nasal mucosa, and the statistically significant differences between the bacilliferous forms are reported here. Classification based on the biopsy of a skin lesion is also the method adopted at the U.S.A. Leprosarium at Carville, Louisiana (Shepard, 1960).

The importance of distinguishing evenly stained forms from irregularly stained forms of M. *leprae* in routine skin and nasal smear preparations was recognised many years ago by workers in West Africa (Davey, 1958, 1959; Browne, S. G., personal communication).

Following the suggestion of Waters and Rees (1962) that the percentage of evenly stained, morphologically normal forms of M. *leprae* should be calculated in routine Ziehl-Neelsen preparation, the term 'Morphological Index' was adopted (Goodwin, 1963), and has been accepted (Pettit and Rees, 1964, Browne, 1965).

It would appear necessary for the next International Congress of Leprology to consider a detailed classification and also the nomenclature of various forms. To enable the full range of histological features that characterise each of the forms to be appreciated, this study in Chinese leprosy patients is reported. Slight modifications or additions to the Ridley and Jopling classification may be considered. Inasmuch as the nomenclature of the intermediate forms of leprosy is still in a transitional period,

Note: Much of this study formed part of the work for a thesis for the degree of M.D. of Cambridge University.

it may be useful to mention that in this study in Chinese patients the terms 'atypical lepromatous' and 'atypical tuberculoid' were used for the BL and BT forms of Ridley and Jopling. Although BL presumably is the sigla of Borderline Lepromatous, it is not clear that the BB form of Ridley and Jopling is a similar sigla of Borderline Leprosy.

MATERIALS

This report is based on a detailed study of 187 unselected Chinese leprosypatients admitted to the Hong Kong Leprosarium of the Leprosy Mission between May 1962 and May 1964 and treated there. The course of treatment was accompanied by a group of tests repeated serially. Because treatment in the Leprosarium was primarily for bacilliferous patients, very few patients at the tuberculoid end of the spectrum were studied. Three tuberculoid leprosy out-patients were studied.

The patients consisted of 136 males and 54 females, with ages ranging from 7 to 76 years.

METHODS

(a) Bacteriological. Every patient on admission to the Leprosarium was subjected to a group of tests for *M. leprae* in the skin and nasal mucosa. The whole body surface was examined for leprosy skin lesions and 6 sites were selected to ensure complete coverage of the body. These sites included one of the ear-lobes, the face, the back or chest, one arm, one leg and one buttock. At each site a leprosy lesion, if possible, was selected and the test made at the edge of the lesion. The skin lesion selected was that which was expected to have the greatest density of leprosy bacilli, and when randomly selected patients were multiply sampled, it was confirmed that skill in selecting the most bacilliferous lesion had been attained.

The nasal mucosa was sampled on both sides of the nasal septum. The mucosa was swabbed clean with dry cotton wool. The tip and edge of the nasal scraping instrument or knife were pressed firmly on to the mucosa and drawn backwards and forwards in a line of about 8 mm. until a trace of blood exuded. The tissue was transferred to a slide and spread as a 'smear' to obtain uniform thickness. Skin and nasal smears were stained by the Ziehl-Neelsen method modified by the use of 3% hydro-chloric acid in 95% alcohol for decolorisation (Davison, 1960; Padma, 1964).

The density of bacilli in skin and nasal smears was graded from 0 to 6 according to the logarithmic method of Ridley (1964). The average of the 6 skin sites was taken as the skin Bacterial Index (B.I.), and the average of the 2 nasal smears as the Nasal Bacterial Index (N.B.I.).

Patients in whom leprosy bacilli were found in the nasal mucosa were subjected to serial tests in the skin and nasal mucosa at 3-month intervals until nasal leprosy bacilli could no longer be found, or until May 1964 if nasal bacilli were still present.

(b) The Morphological Index. Using a powerful light source and a magnification of $\times 1250$, 100 to 200 individual bacilli in each skin and nasal smear preparation were examined and the percentage of evenly stained, morphologically normal leprosy bacilli in a preparation was estimated.

From the 6 skin smear sites the average percentage was calculated, and taken as the skin Morphological Index (M.I.). In the smears from the 2 slides of the nasal septum the average percentage of evenly stained, morphologically normal bacilli was taken as the Nasal Morphological Index (N.M.I.). The Morphological Index is affected more than the Bacterial Index by variable selection of sampling sites and it is desirable that a definite set of sites should be universally accepted, so that B.I. and M.I. estimations by different workers may be more comparable. The M.I. and N.M.I. were estimated in patients admitted from March, 1963.

(c) Histological. From every patient on admission a biopsy specimen was taken from the edge of an active, usually raised skin lesion. The specimen was fixed in Ridley's Formol-Zenker fixative (Ridley, 1957). One section was stained with haematoxylin and eosin, and one by the Ziehl-Neelsen method modified by the use of 10% sulphuric acid for decolorisation.

In 2 patients who exhibited markedly different skin lesions in different areas of the body, biopsy specimens from each of the 2 different lesions of each patient were found to contain basically similar histological features.

Ridley and Jopling (1966) reported that in biopsy specimens from a pair of lesions it was the exception to find any different classification features between the 2 lesions.

In Chinese patients the following features were notified for classification purposes:—

Lepromatous

The epidermis is usually thinned, and the rete pegs, or ridges, are flattened. In the subepidermal region of the dermis there is a thin zone that is free of inflammatory cells, in contrast to the rest of the dermisin which many collections or even sheets of inflammatory cells are seen. The inflammation is composed primarily of histiocytes, and macrophages with a characteristically foamy cytoplasm or 'soapbubble' appearance. These cells contain large numbers of leprosy bacilli and often globi. In heavy infections bacilli may be seen between the cells. In the granulatomus infiltrate plasma cells may be seen, and also varying numbers of lymphocytes. In untreated patients who have had the disease for many years, atypical giant cells, with vacuoles and a basophilic cytoplasm may be seen. Nerves in the skin exhibit perineural inflammation, but their architecture is relatively unaltered. In long-standing cases the nerves may show hyaline degeneration. Leprosy bacilli are seen in the nerves. Fig. 1 shows some clinical and histological features of a patient with lepromatous leprosy.

Atypical Lepromatous

The histological picture is basically similar to that in lepromatous leprosy, but there are the following differences:—

The sub-epidermal zone may be entirely free of inflammatory cells, or may contain a few inflammatory cells, but they are not as dense as in the rest of the dermis. The inflammation is more



Fig. 1

Lepromatous leprosy skin lesion (Patient No. 1552). The epidermis is thinned and the rete pegs are flattened. There is a thin sub-epidermal zone which is relatively free of inflammatory cells, in contrast to the subjacent dermis in which the normal tissue is almost entirely replaced by inflammatory cells.

Н&Е

 $(\times 160)$

markedly focalised and there may be large numbers of lymphocytes, and fewer histiocytes may have a foamy cytoplasm. There may be a very few epithelioid cells. The nerves may show some intraneural inflammation. The number of leprosy bacilli seen may be relatively high, but there are not many globi, and there may be relatively few bacilli. Figs. 2 and 3 show clinical and histological features of patients with a typical lepromatous leprosy.

Borderline

The sub-epidermal zone usually contains a few inflammatory cells, but it is suggested that the pathognomonic features of borderline leprosy among the Chinese are that in the dermis there are both bacilli-laden, often foamy, histiocytes and also follicular groupings of epithelioid cells with one or more Langhan's type giant cells and surrounding lymphocytes. Often the inflamma-



FIG. 2 Atypical lepromatous leprosy skin lesions on the left arm and face (Patient No. 1565). The lesions exhibited no sensory loss. Smear bacterial density: arm 4, face 5. Photograph taken on admission, 12/7/63. The biopsy site is marked on the arm.

B.I. 3.8, M.I. 2%, N.B.I. 0, N.M.I. 0%.



FIG. 4

The left knee and thigh of a borderline leprosy patient (No. 1544) showing multiple nodular lesions. Biopsy site marked faintly on the medial side. The lesions exhibited no sensory loss. Smear bacterial density 2. B.I. 2.2, M.I. 1%, N.B.I. 0, N.M.I. 0%.



FIG. 3

The dermis of a skin lesion of an atypical lepromatous leprosy patient (No. 1565), in which is a large collection of lymphocytes and a few histiocytes.

H & E $(\times 120)$ (This picture is what was described for the similar form of leprosy by Ridley and Jopling (1962).)



The dermis of a borderline leprosy skin lesion (Patient No. 1544), in which is a large follicular grouping of epithelioid cells with a few surrounding lymphocytes, also a Langhan's giant cell.



F1G. 6

Right thigh of atypical tuberculoid leprosy patient (No. 1564). The skin lesion consists of a large macule with central hypopigmentation and peripheral satellite lesions. The lesions exhibited sensory loss, to touch and pin-prick. Smear bacterial density 1. Biopsy site marked. Photograph taken on admission, 12/7/63.
B.I. 1, M.I. 0%, N.B.I. 0, N.M.I. 0%.



Skin lesion of atypical tuberculoid leprosy patient (No. 1564). The sub-epidermal region contains less inflammatory granuloma than the underlying dermis. The dermis contains focalised epithelioid cells and some lymphocytes.

H & E $(\times 30)$ (These features are the same as those described for the same form of leprosy by Ridley and Jopling (1962).)



Thigh of tuberculoid leproxy patient with macular lesion. The lesion was anaesthetic. Patient No. OP 787. Photograph taken 30/1/64. B.I. 0, N.B.I. 0.



F1G. 9

tion is markedly follicular, especially if there is no leprosy reaction, and often there are large numbers of lymphocytes. The nerves show perineural and intra-neural inflammation. Varying numbers of leprosy bacilli are found, but often very few bacilli are seen. Figs 4 and 5 show the clinical and histological features of a patient with Borderline leprosy.

Atypical Tuberculoid

Inflammatory cells are present in the subepidermal region in many parts of the section. In the dermis are epithelioid cells which may be focalised or diffuse with Langhan's giant cells and some lymphocytes. Nerves are usually extensively infiltrated with inflammatory cells. A very few leprosy bacilli may be seen. Figs. 6 and 7 show the clinical and histological features of a patient with atypical tuberculoid.

Tuberculoid

Inflammatory cells are found in the subepidermal zone, and they may infiltrate the basal layers of the epidermis. In the dermis there are follicular groupings of epithelioid cells, with Langhan's-type giant cells and surrounding lymphocytes. The architectures of the nerves is usually entirely disrupted by intra-neural inflammation. No leprosy bacilli are seen. Figs. 8 and 9 show the clinical and histological features of a patient with tuberculoid leprosy.

Indeterminate

Inflammation is not marked, and neither epithelioid cells nor foamy histiocytes are seen. There are scattered foci of lymphocytes round the nerves and other skin appendages, with a small number of leprosy bacilli present, especially in the nerves. Fig. 10 shows the histological features of a patient with indeterminate leprosy.

(These criteria for indeterminate leprosy are the same as those subsequently delineated by the VIIIth International Congress of Leprology, Rio de Janeiro Congress, 1963.)



Skin lesion of indeterminate leprosy patient (No. 1643). There are a very few, very small collections of chronic inflammatory cells, with intraneural A.F.B. Biopsy taken on admission, 6/3/64.

H & E (×64) B.I. 3.5, M.I. 0%, N.B.I. 2, N.M.I. 0%.

(d) The Lepromin Test was performed with Dharmendra-type lepromin (Dharmendra, 1941) standardised against lepromin from The Leprosy Research Unit, Uzuakoli (by kindness of Dr. S. G. Browne). The reading of the lepromin reaction was done by measuring with calipers the diameter of the infiltration which could be palpated at an interval of 21 days after the injection (Lowe and McNulty, 1953; Leiker, 1961). The reading was recorded in millimetres. A reading of 2 mm. or more was regarded as a positive reaction. (145 patients were included in the analysis of this test.)

RESULTS

In 48 of 50 lepromatous patients (96%), in 13 of 18 atypical lepromatous (72.3%) and in 7 of 15 borderline patients (46.6%) leprosy bacilli were found in smear preparations from

TABLE 1

7		Lepromatous		Atyp	nical Leprome			
l'reatment = (months)	No. of Patients	Range of B.I.	Mean B.I.	No. of Patients	Range of B.I.	Mean B.I.	t	p
0	50	2.8-5.5	4.30	18	0.5-4.5	3.12	5.46	< 0.001
3	76	2.3 - 6.0	4.16	40	0.3 - 5.0	3.07	6.813	< 0.001
6	64	1.7 - 5.5	3.69	20	0.3 - 4.5	2.37	5.696	< 0.001
9	48	1.7 - 5.3	3.38	8	1.0-3.0	2.20	3.806	< 0.001

A comparison of the density of leprosy bacilli in the skin and nose in the different forms of leprosy 1A Lepromatous and Atypical Lepromatous Leprosy—B.I.

1B Atypical Lepromatous and Borderline Leprosy-B.I.

T	Atyp	nical Leprom	atous		Borderline			
Treatment - (months)	No. of Patients	Range of B.I.	Mean B.I.	No. of Patients	Range of B.I.	Mean B.I.	t	p
3	40	0.3-4.5	3.07	17	0.3-4.8	1.70	4.419	< 0.001
9	8	1.0-3.0	2.20	2	0.3-1.0	0.65	2.768	< 0.05

1C	The Nasal	B.I.	in L	epromatous a	nd Atvo	ical Lei	promatous I	Leprosv
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Treatment		Lepromatous			pical Leproma			
(months)	No. of Patients	Range of N.B.I.	Mean N.B.I.	No. of Patients	Range of N.B.I.	Mean N.B.I.	t	p
3 6	76 64	0-6 0-5	$2.53 \\ 1.88$	40 20	0-4 0-20	$\begin{array}{c} 0.85\\ 0.60\end{array}$	$6.500 \\ 4.267$	${<}0.001 \\ {<}0.001$

the nasal mucosa. The difference between the incidence in lepromatous and atypical lepromatous patients is statistically significant at the 2% level (X²=5.63). The 2 lepromatous patients in whom nasal leprosy bacilli were not found, both had a history of the disease of less than one year.

A comparison of the density of leprosy bacilli before and during treatment in the different forms of leprosy, both in the skin and the nose (Table 1) reveals highly significant differences between lepromatous and atypical lepromatous leprosy, and between atypical lepromatous and borderline leprosy. The difference between the number of patients sampled at 0 and 3 months is due to the fact that some patients prior to admission had received a few weeks of anti-leprosy treatment. After 6 and 9 months treatment, the patients sampled were those that had a positive N.B.I. at the previous sampling.

The mean skin Morphological Index after 3 months treatment in 41 lepromatous patients was 7.06% and in 19 atypical lepromatous patients was 2.67%, the difference being significant at the 5% level.

Of 29 untreated lepromatous patients, 15 had a positive N.M.I., with 9 patients having an N.M.I. between 40 and 80%. However, only 2 out of 15 untreated atypical lepromatous patients had a positive N.M.I.—the highest being 10%.

The lepromin reaction in all the 78 lepromatous patients was negative, but of the 38 atypical lepromatous patients, 4 (10.5%) had a positive lepromin reaction. This difference is significant at the 2% level (X²=5.37). Of 26 patients with borderline leprosy, 15 (47.6%) had a positive reaction, the difference between this percentage and that in atypical lepromatous leprosy being significant at the 0.1% level (X²=14.27).

DISCUSSION

A form of leprosy intermediate between borderline and tuberculoid has been suggested by Currie (1961), Leiker (1964), Cochrane (1964) and Pfaltzgraff (1967); and a form between lepromatous and borderline has been recognised by Waters and Rees (1962). The 5-form spectrum of Ridley and Jopling (1962) is supported by the present study in Chinese patients, among whom statistically significant differences both bacteriological and immunological, have been found between lepromatous, atypical lepromatous and borderline leprosy.

All the lepromatous patients were found to have a negative lepromin reaction and in all but 2, those with a history of less than one year, nasal leprosy bacilli were found. This is similar to details in the report of Shepard (1960) of 34 patients in the U.S.A., when a positive lepromin reaction was always associated with an absence of nasal leprosy bacilli, and all the lepromatous patients in whom nasal bacilli could be found exhibited a negative lepromin reaction.

Shepard also gave details of 14 lepromatous patients in the Philippines. Two patients exhibited a positive lepromin reaction and no leprosy bacilli were found in nasal washings; but in 2 others, with a very small positive lepromin reaction of 1 mm. diameter, some nasal leprosy bacilli were found. This observation might be explained by the fact that the 4 patients with a positive lepromin reaction were not suffering from pure lepromatous leprosy, and the findings in Chinese patients suggest that such patients might have been suffering from atypical lepromatous leprosy. The most reliable basis for recognition of the intermediate forms of leprosy would appear to be the histological picture of an active untreated skin lesion (Currie, 1961; Ridley and Jopling, 1962). The clinical features of the intermediate forms are also delineated by Ridley and Jopling (1966). They report the different rates of fall of the Biopsy Index in the different forms of leprosy, and in Chinese leprosy patients the rate of fall of the Bacterial Index has been found to be markedly different in lepromatous, atypical lepromatous and borderline leprosy. These facts illustrate the prognostic value of the 5-form classification.

SUMMARY

Statistically significant differences, both bacteriological and immunological, between 3 bacilliferous forms of leprosy in Chinese patients are reported, the form intermediate between lepromatous and borderline leprosy being termed atypical lepromatous leprosy. This classification is based primarily on the histological features of an active untreated skin lesion. The relevant features are delineated both for the bacilliferous forms and also for tuberculoid leprosy and the form intermediate between borderline and tuberculoid which is termed atypical tuberculoid leprosy. This independent discovery of a 5-form spectrum, almost identical to that of Ridley and Jopling (1962, 1966) supports the need for recognition of such a Classification.

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The Significance of Mycobacterium leprae in the Nasal Mucosa, with special reference to Chinese Leprosy Patients

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INTRODUCTION

The nasal mucosa as a convenient site for bacteriological sampling in leprosy patients has enjoyed varying popularity during the last 70 years. Following the observations of Arning (cited by Lancet, 1886), Goldschmidt (1891) and Koch (1896) that acid fast bacilli, presumably M. leprae, could be found in the nasal passages of leprosy patients, great emphasis was placed on examining the nasal mucosa in the diagnosis of leprosy (Sticker, 1897; Jeanselme and Laurens, 1897). This opinion remained prevalent (Manson-Bahr, 1954) and is still widely held (Marshall, 1964). However, the fact that leprosy bacilli can be found in leprosy skin lesions whenever they are found in the nose, and in many patients when they cannot be found in the nose was reported from Hawaii (Brinckerhoff and Moore, 1909), the Philippines (Gomez, 1923), India (Dharmendra and Sen, 1948) and Vietnam (Chaussinand, 1955). These studies and others (Ryrie, 1948; Maxwell and Kao, 1952; Browne, 1966) also refute the suggestion of early workers that the nose is the site of the initial lesion in leprosy. In the absence of skin or nerve lesions of leprosy the finding of acid fast bacilli in the nose is of highly doubtful significance (Karlinski, 1906; Johnston, 1917).

Scraping of the nasal mucosa is a more successful method of obtaining leprosy bacilli than swabbing the mucosa (Lowe and Christian, 1932). Samples from the nasal mucosa must be carefully taken and adequately decolourised to avoid confusion that could be caused by mycobacteria other than M. leprae (Cochrane, 1947a) or even diphtheroid organisms (Goodwin, unpublished data). The possibility that mycobacteria other than M. leprae are frequently present in the nose of leprosy patients is discounted by the studies of Shepard (1960, 1962) who reported that acid fast bacilli found in large numbers in nasal washings would not grow on artificial media or in tissue culture, but mouse foot-pad inoculation with acid fast bacilli from nasal washings resulted in lepromatous granulomata. A bacillary lepromin antigen prepared from mouse foot-pads produced the same reaction in leprosy patients as standard human lepromin (Shepard and Guinto, 1963) indicating that the bacilli obtained from the nose were M. leprae.

Conflicting reports of the comparative value of sampling leprosy skin lesions or the nasal mucosa, to determine the weight of infection and for reliable bacteriological assessment of response to chemotherapy, are probably due to ethnic variations. In Congolese and Nigerian patients the density of leprosy bacilli in the nose is usually greater than the density in skin lesions, and leprosy bacilli persist for a longer period in the nose than the skin (Browne, 1959; Davey, 1959). By contrast, rapid disappearance during chemotherapy of nasal leprosy bacilli, with bacilli persisting in skin lesions has been found in patients in the U.S.A. (Byers and Wolcott, 1954), in Morocco (Rollier, 1959), in Vietnam (Chambon and Pestel, 1960), in East Africa (Allan, 1961), in Russia (Torsuvev et al., 1962), in India (Ram, 1963) and in South America (Opromolla, 1966).

Note: This study formed part of a thesis accepted for the degree of M.D. of Cambridge University.

The importance of distinguishing evenly stained forms of M. leprae in scraped incision smear preparations from the skin and nasal mucosa was recognised many years ago by workers in West Africa (Davey, 1958, 1959; Brown, S. G., personal communication). The observation that irregularly stained leprosy bacilli are almost certainly non-viable (Rees and Valentine, 1962) is supported by mouse foot-pad cultivation studies of *M. leprae* (Shepard and McRae, 1965). Following the suggestion of Waters and Rees (1962) that the percentage of evenly stained, morphologically normal forms of M. leprae should be calculated in routine Ziehl-Neelsen stained preparations, the term 'Morphological Index' was adopted (Goodwin, 1963), and has been accepted (Pettit and Rees, 1964; Browne, 1965).

This study in Chinese leprosy patients includes an analysis of the incidence, density and morphology of leprosy bacilli in the skin and nose in the different forms of leprosy before and during anti-leprosy chemotherapy, together with an investigation into the relation of the length of history of the disease and the lepromin reaction to bacilli in the nose. A spectrum of 5-forms of leprosy was identified in 1961 and written into the protocols of this study. This classification, based on histological features of a skin lesion, is almost identical to that of Ridley and Jopling (1962, 1966). Statistically significant differences, both bacteriological and immunological between the various forms, support the validity of this classification (Goodwin, 1967).

MATERIALS

A detailed study was made of 187 unselected Chinese leprosy patients admitted to the Hong Kong Leprosarium of the Leprosy Mission between May 1962 and May 1964 and treated there. Every patient on admission was subjected to a group of tests for *M. leprae* in the skin and nasal mucosa. Patients in whom leprosy bacilli were found in the nasal mucosa were sampled at 3-month intervals until nasal leprosy bacilli could no longer be found, or until May 1964 if nasal bacilli were still present. The patients

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consisted of 136 males and 54 females, with ages ranging from 7 to 76 years.

METHODS

(a) Bacteriological. The whole body surface was examined for leprosy skin lesions and 6 sites were selected to ensure complete coverage of the body. These sites included one of the ear-lobes, the face, the back or chest, one arm, one leg and one buttock. At each site a leprosy lesion, if possible, was selected and a scraped incision (Wade, 1935; Cochrane, 1964) made at the edge of the lesion. The dermal tissue obtained was spread on a slide as a 'smear' to obtain uniform thickness. The nasal mucosa was sampled by scraping on both sides of the septum, the mucosa first being swabbed clean (Browne, 1966). Skin and nasal smears were stained by the Ziehl-Neelsen method modified by the use of 3% hydro-chloric acid in 95% alcohol for decolourisation (Davison, 1960; Padma, 1964). The density of acid fast bacilli in skin and nasal smears was graded from 0 to 6 according to the logarithmic grading of Ridley (1964). The average of the 6 skin sites was taken as the skin Bacterial Index (B.I.) and the average of the 2 nasal smears as the Nasal Bacterial Index (N.B.I.).

(b) The Morphological Index. Using a powerful light source and a magnification of $\times 1250$, 100 to 200 individual bacilli in each skin and nasal smear preparation were examined and the percentage of evenly stained, morphologically normal leprosy bacilli in a preparation was estimated. From the 6 skin smear sites the average percentage was calculated, and taken as the skin Morphological Index (M.I.). In the smears from 2 sides of the nasal septum the average percentage of evenly stained, morphologically normal bacilli was taken as the Nasal Morphological Index (N.M.I.). The M.I. and N.M.I. were estimated from March, 1963.

(c) Histological. From every patient on admission a biopsy specimen was taken from the edge of an active, usually raised skin lesion. The specimen was fixed in Ridley's Formol-Zenker Fixative (Ridley, 1957). One section was stained with haematoxylin and eosin, and one by the Ziehl-Neelsen method modified by the use of 10% sulphuric acid for decolourisation. The histological features identified to distinguish each of the 6 forms of leprosy have been fully described (Goodwin, 1967). In addition to the recognised forms of lepromatous, borderline, tuberculoid and intermediate leprosy, the form intermediate between lepromatous and borderline was termed 'atypical lepromatous' leprosy, and the form intermediate between borderline and tuberculoid leprosy was termed 'atypical tuberculoid'.

(d) The Lepromin Test. Intradermal inoculation of 0.1 ml. of standardised bacillary lepromin antigen (Dharmendra, 1941) gave rise to a variable induration, which was measured 21 days after inoculation (Lowe and McNulty, 1953; Leiker, 1961). A reading of 2 mm. or more was regarded as a positive reaction. (145 patients were included in an analysis of this test.)

(e) Assessment of the duration of the disease after treatment. Because of the social stigma associated with leprosy in the minds of Chinese, the first recognisable manifestation of the disease leaves a profound impression in the patient's memory (Maxwell and Kao, 1952). Detailed questioning accompanied by examination was conducted by the author and a Chinese doctor.

RESULTS

(i) The incidence of M. leprae in the nose. In all untreated patients with lepromatous, atypical lepromatous and borderline leprosy, M. leprae could be found in the skin. In 47 of 50 lepromatous patients (96%), in 13 of 18 atypical lepromatous (72.3%) and in 7 of 15 borderline patients (46.6%) leprosy bacilli were found in smear preparations from the nasal mucosa. The density of leprosy bacilli in skin lesions (the B.I.) in the 15 patients with no nasal leprosy bacilli, was on average 1.84, with a range of 0.2-4.7. In the 3 patients with tuberculoid leprosy, bacilli were found neither in the skin nor in the nose. After 18 months chemotherapy, leprosy bacilli were not found in the nose of any patient with atypical lepromatous leprosy and in only 32% of lepromatous patients, while bacilli could be found in skin lesions in 100%

of patients with both forms of leprosy. In 37 lepromatous patients at the time when the Nasal Bacterial Index (N.B.I.) was 0 the skin B.I. was on average 2.73, and in 15 atypical lepromatous patients the B.I. was 2.25.

(ii) The value of nasal sampling in assessing bacteriologically the severity of the disease process. The superiority of skin sampling is demonstrated by an analysis of the density of leprosy bacilli before and during treatment in the different forms of leprosy (Table 1). (The difference between the numbers of patients sampled at 0 and 3 months is because some patients prior to admission had received a few weeks chemotherapy. After 6 and 9 months treatment the patients sampled included only those who had a positive N.B.I. at the previous sampling.) In lepromatous and atypical lepromatous patients nansal tests gave a false impression of the success of chemotherapy.

(iii) The Lepromin reaction, and the duration of the disease. In all the lepromatous patients the lepromin reaction was negative, but 10.5%of 38 atypical lepromatous patients had a positive reaction. A correlation was evident between the density of nasal leprosy bacilli and the size of the lepromin reaction. All patients with a density index of nasal bacilli (N.B.I.) greater than 3.0 had a negative lepromin reaction, while in patients with a moderate lepromin reaction of 2 mm. to 6 mm. a low N.B.I. was found; and when the lepromin reaction was greater than 6 mm. the N.B.I. was 0. Inasmuch as a positive lepromin reaction indicates a relative tissue immunity and an ability to localise the infection, it would appear that the nasal mucosa is parasitised when the infection is disseminated. Such a dissemination would be expected to be more frequent the longer the duration of the disease before treatment. This is supported by the observations that among the lepromatous patients the only 2 who had no nasal bacilli had a history of less than one year, and the greatest density of nasal leprosy bacilli was in patients with the longest history (Table 2). The density of the bacilli in the skin was unrelated to the duration of the disease.

TABLE 1

Α	comparison	of the	e densitv	of le	prosv	bacilli	in	the	skin	and	the	nose	before	and	during	treatment

	Traction	No. of	Skin	<i>B.I.</i>	N.B.I.		
	(months)	Patients	Range of B.I.	Average B.I.	Range of N.B.	I. Average N.B.I.	
	0	50	2.8 - 5.5	4.30**	0-6	2.85**	
	3	76	2.3-6.0	4.18	0-6	2.53	
	6	64	1.7 - 5.5	3.69	0-5	1.87	
Lepromatous	9	48	1.7 - 5.3	3.38	0-5	1.43	
-	12	41	1.2-4.7	3.18*	0-4	1.36*	
	15	24	1.3-4.2	3.02	0-4	1.46	
	18	14	0.3 - 4.5	2.86	0-3	1.50	
	21	7	1.3-4.2	2.64	0-2	1.26	
	0	18	0.5-4.5	3.12**	0-5	1.58**	
	3	40	0.3-5.0	3.07	0-4	0.85	
Atypical Lepromatous	6	20	0.3 - 4.5	2.37*	0-2	0.60*	
• •	9	8	1.0-3.0	2.20	0-2	0.62	
	12	4	0.3 - 2.7	1.62	0-1	0.50	
	15	2	0.2-3.2	1.70	0-2	1.00	
	0	15	0.2-4.5	1.99	0-5	1.07	
Borderline	3	17	0.3 - 4.8	1.70	0-4	0.80	
	6	6	0.8 - 2.3	1.35	0-3	1.50	
	9	2	0.3-1.0	0.65	0-1	0.50	

 \ast The difference between the Average B.I. and N.B.I. is significant at the 0.1% level.

** The difference between these 2 means is significant at the 1% level.

TABLE 2

The relation of the duration of the disease to the density of skin and nasal leprosy bacilli in lepromatous leprosy

Duration of Disease	No. of Patients	Range of B.I.	Average B.I.	Range of N.B.I.	Average N.B.I.
Less than 1 year	7	2.8-4.7	4.0	0-4	2.0
1-4 years	25	3.7 - 5.5	4.84	1-5	2.94
5-10 years	12	3.0 - 5.0	3.97	1-4	2.50
More than 10 years	6	3.8 - 5.5	4.63	3-6	4.16

(iv) The nasal mucosa as a source of viable leprosy bacilli. The percentage of evenly stained, morphologically normal bacilli in nasal smears (the N.M.I.) ranged from 40% to 80% in 9 lepromatous patients, while the percentage in skin smears (the M.I.) was never greater than 30%. Of 73 patients with normal bacilli in the skin or nose, 43 (58.8%) had such bacilli in the skin alone. Only 2 out of 15 atypical lepromatous patients had evenly stained bacilli in the nose, the highest being 10%. Evenly stained bacilli persisted for a longer time in the skin than the nose (Table 3). (v) Reappearance of nasal leprosy bacilli. Of 24 patients who consented to nasal sampling for 12 months after nasal bacilli had disappeared, 18 patients continued to respond to chemotherapy as shown by a fall in the B.I. and in these patients no nasal bacilli were found. In the remaining 6 patients the skin B.I. rose temporarily and nasal bacilli reappeared; but with a later fall of B.I., nasal bacilli could not be found.

(vi) A comparison of the effect of Dapsone and Thiambutosine on nasal leprosy bacilli. Of 49 lepromatous patients who could be sampled for 18 months, 35 were treated with Dapsone



The effect of treatment on morphologically normal leprosy bacilli in the skin and the nose in 32 lepromatous patients

and 14 with Thiambutosine. After 12 months treatment nasal bacilli were found in 54.3%of the Dapsone group and in 57.2% of the Thiambutosine group. After 18 months the percentage with nasal bacilli in the Dapsone group was 28%, but in the Thiambutosine group was 43%, confirming previous reports that some patients may develop resistance to Thiambutosine after 12 months treatment.

DISCUSSION

In Chinese leprosy patients leprosy bacilli were found in the nasal mucosa in relation to the severity and length of duration of the disease. In pure lepromatous patients with a history of longer than one year, leprosy bacilli were found in every patient. A high incidence of nasal leprosy bacilli in patients with a longer history was reported by Rogers and Muir (1925), who found that 68% of established patients, but only 37% of early patients had nasal bacilli. In 600 lepromatous patients in India, Cochrane (1947b) found nasal bacilli in 100% of very advanced patients, 85.9% of moderately advanced patients and in only 36.8% of early patients of the disease. In the Philippines, 35children with early leprosy had bacilli in skin lesions, but only 40% of the children had bacilli in the nose (Solis and Wad, 1925). The earliest sign or symptom of leprosy has been variously found to be an area of anaesthetic skin (Gomez, 1923), skin macules or a thickened nerve (Ryrie, 1948) and neuritic symptoms (Maxwell and Kao, 1952). These reports support the proposition that in most patients the nasal mucosa is the site of multiplication of leprosy bacilli at a later date than the skin or nerves.

In many Chinese patients with borderline and atypical lepromatous leprosy, *M. leprae* could be found in skin but not in the nasal mucosa. Thus skin lesions and not the nose should be sampled for bacteriological confirmation of the diagnosis of leprosy. Nasal tests may have a value in indicating whether the disease process has become disseminated; and it was in patients with a greater tissue immunity, as evidenced by a positive lepromin reaction, that nasal leprosy bacilli were rarely found.

For the apparently conflicting reports from different countries of the incidence of *M. leprae* in the nose of leprosy patients, three reasons are suggested, the most probable reason being that there is a geographical or racial variation in the pattern of leprosy and nasal lesions in different countries. Secondly, the significance of the duration of the disease in relation to the incidence of nasal leprosy bacilli may not have been realised; if many early patients of leprosy were included in a study, a lower incidence of nasal leprosy bacilli might be found. The third reason is that patients with atypical lepromatous leprosy, who are shown by this present study to have a lower incidence of nasal leprosy bacilli, may be included in the figures for lepromatous leprosy.

In Chinese patients in lepromatous, atypical lepromatous and borderline leprosy, the average density of bacilli in the skin was found to be significantly higher than the average density in the nose, both before and during treatment. The observation that nasal leprosy bacilli disappear after a shorter period of treatment than bacilli in the skin has been reported from all countries, except West Africa, and has been found in the Anglo-Indian type of patient in England (Goodwin, unpublished data). Skin lesions and not the nasal mucosa should be sampled for a bacteriological assessment of the response to chemotherapy. However, nasal leprosy lesions when they do occur, may be of great importance in the spread of leprosy. Leprosy bacilli in the nose are probably spread to the environment more easily from the nose than from the skin, and in Chinese patients the percentage of evenly stained, presumably viable leprosy bacilli in the nose can be much greater than the percentage in the skin. This has been briefly reported in Nigerian patients (Browne, 1966).

In only a very few patients with atypical lepromatous or borderline leprosy were evenly stained bacilli found in the nose.

Evenly stained bacilli persisted for a longer period in the skin than in the nose, in contrast to observations in Nigerian patients (Browne, 1966).

'Elimination of nasal scrapes is recommended.' This statement was recorded by the panel on Bacteriology at the VIIIth Internal Congress of Leprology in September, 1963 (Rio de Janeiro Congress, 1963). However, the force of the recommendation was weakened by the preceding sentence which stated: 'In routine examination, work can be saved by recalling that ear lobes, the nasal mucosa and margins of active lesions are the sites more frequently and strongly positive, and the last ones to become negative during therapy.' This grouping together of the nose and skin lesions in one generalisation would seem to be confusing, in the light of this report and the others mentioned in this paper. In West African patients, nasal tests may be of great value, but in patients in other countries nasal tests are probably of less value than skin tests. It is agreed that nasal tests should lie more in the province of the research worker.

SUMMARY

187 Chinese leprosy patients were studied during the period May 1962 to May 1964. A 5-form spectrum of classification based primarily on the histological features of an active skin lesion was adopted. Leprosy bacilli were found in scrapings of the nasal mucosa in relation to the duration and severity of the disease. In many borderline and atypical lepromatous patients. especially in those with a positive lepromin reaction, few or no nasal leprosy bacilli were found; but in all patients with other forms of leprosy, M. leprae were found in skin lesions. The density of leprosy bacilli in the skin was significantly greater than the density in the nose in all forms of leprosy before and during treatment. Skin lesions and the nasal mucosa should be sampled for bacteriological confirmation of the diagnosis of leprosy, and for assessment of the response to chemotherapy. Nasal tests may have greater value in West Africa than other countries. The nose can be a potent source of infection, as a higher percentage of presumably viable bacilli can be found in the nasal mucosa than in the skin, in Chinese leprosy patients.

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Lysosomes—Their Relationship with Vitamin E and Leprosy

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INTRODUCTION

Leprosy is an infectious disease probably due to 'organic susceptibility'. Immunological studies of the disease have shown that, in the pair bacillus-host, the latter seems to be the main factor in its pathogenesis.

Therefore it will be interesting to investigate the biological, biochemical and immunological conditions that prepare the organic susceptibility which facilitates or impairs the growth of M. leprae. This paper is a partial attempt to unveil the pathogenic mechanism of the leprosy infection through modern knowledge on lysosomes.

LYSOSOMES

Lysosomes were discovered by De Duve in 1955, and the CIBA Foundation dedicated a symposium¹ to them. They are subcellular cytoplasmic organelles which enclose hydrolytic enzymes, mainly acid phosphatase, with only one membrane. These corpuscles are formed by enzymes, lipids, peptides, aminoacids, nucleotides, metals, etc.; they are found in most animal cells, especially in liver, kidney, spleen, intestine, leukocytes, macrophages, etc.

The enzymes contained in the lysosomes are of the hydrolytic type; they act mainly in acid pH and show their activity on biopolymers. These enzymes are generally proteases, phosphatases, glycosidases, etc.; the most important enzymes isolated were: acid phosphatases, cathepsin, ribonuclease, arylsulfatase, betaglucuronidase and beta-galactosidase. The activity of the acid phosphatase is especially important as it indicates the lysosomic enzymatic complex.

Lysosomes are formed by 2 elements: the membrane and the hydrolytic enzymes contained inside it. The membrane differs from that of other subcellular corpuscles as mitochondria—with double membrane—because of its simple structure. This single membrane of lipoproteic nature acts as a barrier between lysosomic enzymes and substrates. Thus the enzymes remain inactive as long as the lipoproteic membrane is untouched.

It has been proved lately that lysosomes are involved in the mechanism of morphologic changes, catabolic disorders, autolytic processes, necrosis, and infections and inflammatory processes, etc. They initiate intracellular digestion and a great number of catabolic processes, being therefore connected to the pathogenesis of several morbid processes. They would be mainly connected with phagocytosis and the destruction of alien substances.

LYSOSOMES AND VITAMIN E

The lipoproteic nature of this single membrane in the lysosomes suggested a relationship between these corpuscles and the compounds connected with the auto-oxidation of lipids such as Vitamin E—well known biological antioxidant—as the attack of subcellular particles is generally initiated through their membranes.

Damage of the lysosomic membrane and lysosomes themselves were connected to the conditions which cause auto-oxidation of lipids, such as irradiation peroxides, systems that form free radicals, vitamin E deficiency, etc.

Experimental studies^{2 3 4} have shown that these conditions damage the lysosomic membrane. Besides these, other alterations as osmotic pressure, pH, detergents, freezing, etc., cause the previously mentioned damage.

These studies led to experiences on nutritional Vitamin E deficiency and muscular dystrophies in relation to lysosomes.

Tappel *et al.*⁵ have shown that in muscular dystrophies, genetic as well as nutritional ones, caused by Vitamin E deficiency, there is a high proportion of lysosomic enzymes originated in the macrophages, in direct relationship to the catabolic processes of the muscle. These, in turn, are evidenced in histological manifestations of muscular disorganization and excretion of products of tissular degradation. Lysosomic alterations have also been shown to occur in other alterations caused by Vitamin E deficiency, such as encephalomalacia in chickens. Homogenates of chicken brains in chickens with Vitamin E deficiency and symptoms of encephalomalacia show important increase in lysosomal activity.

The explanations of these facts would be as follows: Vitamin E deficiency causes an increase in peroxidation of lipids, damaging cells and its subcellular components, among which lysosomes are counted. As these are broken, lysosomal enzymes are freed, and they alter cells causing an invasion of macrophages and muscular catabolism.

On the other hand, Desai *et al.*² have shown that the lysosomes isolated in rat livers are extraordinarily labile to the auto-oxidation produced by systems that form free radicals, such as linoleate emulsions, ultra-violet radiation, and gamma radiation.

Sawant *et al.*⁶ have proved that irradiation frees lysosomal enzymes in *in vitro* systems such as arylsulfatases, beta-glucuronidase, acid phosphatases and ribonucleases.

In conclusion, both peroxidation and irradiation cause selective damage on the lipoproteic membrane of lysosomes through the activity of the free radicals generated by the mentioned systems.

LYSOSOMES AND LEPROSY

The electronic-microscopic study of the leprosy cell allowed the discovery by Yamamoto, Imaeda and Nisihura^{7 8 9 10} of subcellular elements called 'opaque droplets' or 'opaque bodies'. The histochemical study of these elements identified them as lysosomes. At this stage of knowledge on these subcellular corpuscles, study of their connection with the histogenesis, pathogenesis and chemotherapy of leprosy was started.

Cytochemical techniques show clear evidence of the existence of acid phosphatases in those 'opaque droplets' that Brieger and Allen¹¹ identify as lysosomes.

The lysosomes, in the appearance of a thin granular substance, are found in the leprosy cell around the leprosy bacillum. They are also found in other infections, such as those by tuberculosis bacillus and staphylococci.

Chemotherapy with DDS and similar compounds alters the contents of this lysosomal substances, in the sense that administration of such chemotherapy increases the contents.

It was also seen that bacilli disintegrate in that substance of abundant hydrolytic enzyme content. When bacterial disintegration occurs a foamy structure appears around the lysosomal substance.

The lysosomal activity of the leprosy cell has also been connected with the clinical evolution of leprosy patients, with the degree of ease with which the leprosy bacillus develops, and with the natural immunity to this disease.¹²

Karat¹³ suggests that DDS acts through the lysosomes, which, by freeing hydrolytic enzymes, kill the M. *leprae* and help the removal of bacillar rests.

Recent experiences tend to show that Schwann cells are rich in lysosomes and immunity to leprosy rests partially in them. There can also be a connection between the lack of response to the antileprotic chemotherapy and the deficient content of lysosomes in the cells or the decrease or inhibition of lysosomic activity that occurs in certain cases.

Interpretation of these facts is as follows: lysosomes are subcellular corpuscles with a lipoproteic membrane, very sensitive to autooxidation processes which have the important function of destroying *M. leprae*. Therefore any element that tends to protect the lipoproteic membrane and also the lysosome, indirectly helps destroying *M. leprae*. That is the case of the biological antioxidants, potent inhibitors of auto-oxidation, and of DDS, biological antioxidant with Vitamin E-type of activity, as shown by Bergel.

VITAMIN E AND LEPROSY

In 1951 Bergel¹⁴ made the first complete description of the possible relation between leprosy and Vitamin E. Later on, this investigator carried out many experimental trials^{15 16 17 18 19 20} which have confirmed this type of relation. Other authors have also confirmed^{21 22 23} part of these trials.

Of this series of experimental trials, the most important facts that show the connection between Vitamin E and leprosy are summarized below: (a) development of M. leprae inoculated in rats and mice under prooxidant and severely prooxidant diets; (b) biological antioxidant activity, manifested as anticeroid activity, of chemotherapeutic antimicrobial agents, especially antileprotics. Bergel²⁴ has proved the biological antioxidant activity-similar to that of Vitamin E-of the DDS, both in vitro and in vivo, which would be due to the presence of its 2 free amino groups in position 1-4; (c) therapeutic activity of a great number of biological antioxidants as those already mentioned and of Vitamin E. It has also been established that prooxidant diets favour the development of experimental infections caused by other mycobacteria as BCG, M. tuberculosis Vallee, M. fortuitum Penso, etc.25

COMMENTS

This reveals the importance of lysosomes in the pathogenesis and cure of leprosy and also the important role of antioxidants, especially Vitamin E in the protection of the lipoproteic membrane of lysosomes. An increase in the biological oxidations through the formation of free radicals destroys the lipoproteic membrane of lysosomes and therefore they cannot destroy M. leprae, which develops freely and originates the disease. The administration of DDS and other biological antioxidants, by impairing autooxidant processes would protect the lipoproteic membrane of lysosomes increasing therefore the defensive capacity of the organism against

M. leprae. Hence, the antileprous chemotherapy acts on M. leprae indirectly through the lysosomes. In this sense it differs from antituberculosis chemotherapy which, according to Rist, acts directly on M. tuberculosis.

This confirms the fact that leprosy needs a special biological susceptibility for its development, which is conditioned by the lysosomal activity. This explains why M. leprae experimentally inoculated does not develop in normal animals under normal conditions, as Bergel has sustained.

SUMMARY

This is a review of the experimental facts that connect lysosomes with leprosy and Vitamin E. Leprosy infection develops in an auto-oxidant susceptibility which favours destruction of the lipoproteic membrane of lysosomes. Lysosomes, due to their destructive activity of M. leprae, represent one of the natural mechanisms of defence against leprosy infections.

The antileproty activity of the sulfones and other antileprotics would be indirect and through its biological antioxidant capacity which protects the lipoproteic membrane of lysosomes, natural agents of destruction of M. leprae.

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Physical Therapy in the Management of Recent Paralysis in Leprosy

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A common feature of recent paralysis in leprosy is the presence of infiltration by inflammatory exudate and oedema in the affected nerve which causes ischaemia in the nerve.¹ Partial ischaemia causes a neuropraxia or impairment of nerve conduction without Wallerian degeneration. When blood flow returns, conductivity of the nerve is restored to normal. If the ischaemia progresses to complete loss of blood supply or lasts for a long time, then the nerve is destroyed and the paralysis becomes irreversible. Loss of conductivity of a nerve nearly always precedes nerve destruction. It has been observed that this stage may last for a short while or extend over a period of months and be followed by recovery.

This paper outlines the principles of physical therapy used in recently paralysed muscles in leprosy and explains the methods employed to preserve the physiological properties of the muscles and prevent atrophy and deformity during the stage of paralysis, and the techniques used to re-educate and strengthen muscles during the recovery phase. It must be emphasised that physical therapy in these cases is supplcmentary to adequate and proper medical care under the supervision of a physician.

MATERIAL

This study was conducted on a group of 36 patients in whom the duration of paralysis ranged from 4 days to 6 months: 12 presented with lateral popliteal paralysis; 7 with radial paralysis; and 17 with final paralysis. Their duration of treatment ranged from 5 weeks to 5 months. All patients continued to be under medical treatment during their period of physical therapy. At Schieffelin Leprosy Research Sanatorium specific anti-leprosy treatment is stopped in all patients who are found to have recently developed neurological deficit and appropriate anti-inflammatory drug is introduced, the choice of which depends upon the clinical condition of the patient.

ASSESSMENTS

The following assessments were made on each patient and repeated at regular intervals.

- 1. The Manual Muscle Test using the international 1 to 5 scale was recorded periodically on a form to facilitate quick and accurate reviews.
- 2. Sensory Test. Both tactile and pain sensations were tested and recorded on maps of the extremities at regular intervals.

PHYSICAL THERAPY

Since neuropraxia in leprosy may last for a long time, it is necessary to prevent atrophy and deformity and prolonged overstretching of the paralysed muscles during the period the nerve is not functioning. Attempts must be made to initiate a response from these muscles as early as possible so that function can be quickly restored.

The paralysis was therefore treated in 2 phases:—

- (a) the expectant phase in which signs of recovery were not yet present; and
- (b) the re-educative phase in which recovery had already begun.

PRINCIPLES OF PHYSICAL THERAPY

(a) In the Expectant Phase

1. To prevent contractures due to muscle imbalance and to retain mobility of the joints.



F1G. 1 Simple 'S'-shaped splint with soft rubber covering for wrist support and allowing free finger movements.

2. To prevent atrophy of the muscles.

3. To prevent prolonged overstretching of the paralysed muscle and to retain the denervated muscle in an adequate nutritional state until re-innervation.

The methods to implement these principles were:-

- (i) Passive Movements. These movement were used to prevent contractures that may arise in joints due to muscle imbalance and disuse. In radial paralysis passive movements were used daily for the joints of the wrist, fingers and the thumb. In lateral popliteal paralysis the ankle joint and the small joints of the foot were put through full range of movements.
- (ii) Massage. Light effluerage and finger kneadings were used for muscles of the face to increase circulation in the facial muscles, and to maintain them in good



FIG. 2

Standard foot-drop spring. The spring and buckles are adjusted to prevent excessive dorsiflexion.

> nutritional state until recovery of function occurred.

- (iii) Electrical Stimulation. When there is a neuropraxia of a motor nerve, impulses from the brain fail to pass the site of the lesion to reach the muscles supplied by the nerve. Contractions of the muscles were therefore obtained by a faradic stimulus applied below the site of the lesion. Treatments were given twice a day. Since these contractions closely simulate voluntary contractions they help to preserve a sense of movement and prevent atrophy that may be caused by disuse of the muscles.
- (iv) Splinting. Splinting was used to prevent prolonged overstretching of the paralysed muscle which would damage its physiological properties of elasticity, extensibility and contractility and retard re-

194 Leprosy Review covery. Splints were also employed to prevent adaptive shortening of the antagonist muscles and to allow functional use of the limb. Patients with a radial paralysis were provided with an 'S' shaped splint which maintained the wrist in dorsiflexion while allowing free movements of the fingers (Fig. 1). Lateral popliteal paralysis was treated with a dorsiflexion shoe spring during the day (Fig. 2), which allowed functional use of the limb for walking, and a posterior slab to hold the foot at 90° during the night. Sagging facial muscles were strapped with adhesive plaster to prevent prolonged overstretching and were removed only during exercise periods.

(b) In the Re-educative Phase

1. To develop motor awareness and voluntary response.

2. To strengthen progressively the affected muscles by resisted exercises which were specific for the paralysed group.

3. To restore full function of the affected muscles by skilled, co-ordinated movements.

Since contraction is the only means by which muscles regain their normal function it is essential to obtain a response as soon as possible from the muscles affected by paralysis. Besides, the longer the muscles remain inactive the greater will be the tendency for disuse atrophy. Therefore, when the acute phase of the lesion had subsided, reactivation of the motor unit was undertaken and proved possible except where there had been destruction of axons. In patients in whom the demands made on the neuromuscular system by voluntary effort were insufficient to elicit the maximal responses required for contraction and rapid re-development of muscles, methods designed to stimulate or augment the demand for activity were instituted:-

 (i) Facilitation techniques. The techniques of proprioceptive neuromuscular facilitation¹ which rely mainly on the use of the stretch stimulus to initiate tension within paralysed muscles through the stretch receptors and muscle spindle mechanism, were used to initiate contraction in recovering muscles. Resistance and stretch were applied manually to muscles working to perform patterns of movement in patients with radial and lateral popliteal paralysis. The stretch stimulus was also applied to facial muscles to obtain contraction of these muscles.

(ii) *Exercises*. Once the power of contraction was gained active exercises were used eliminating gravity, and were progressed to exercises against gravity. When muscle fatigue was noticed in weak muscles, periods of rest were given during the performance of the exercise. When a muscle was able to perform a movement against gravity and was graded 3, exercises against resistance were commenced to hypertrophy the muscle. At this stage support, passive movements, assisted active movements and artificial means of maintaining circulation were gradually discontinued.

Resisted exercises for radial, lateral popliteal and facial paralysis were given manually. Weights were used at a later stage as a means of resistance in lateral popliteal paralysis.

Co-ordination was improved by repetition of an exercise so that exercises and activities which at one time required concentration and much effort became, with practice, more or less automatic in character and function of the limb was improved.

Occupational therapy played an important part in the management of recovering nerve lesions in leprosy. Exercises were made more interesting and dexterity was improved in the performance of movements. Work in the department was directed towards the skills necessary for the patient's previous occupation.

RESULTS

A total number of 36 patients were treated: 7 with radial paralysis; 12 with lateral popliteal paralysis; and 17 with facial paralysis. All 5 lepromatous patients with paralysis showed recovery. In the tuberculoid type 12 out of a total of 16, and in the borderline type 11 out of a total of 15, recovered. The total percentage of recovery was 78%.

The average duration of paralysis among those who failed to recover was 5 months. Patients whose average duration of paralysis was 2.75 months, recovered.

This series is too small to permit valid generalisation, though it would substantiate the clinical impression that the chances of recovery in paralyses in leprosy are related to the type of leprosy and the duration of paralysis before institution of adequate and supervised medical treatment and physical therapy.

TABLE 1 Recovery according to Classification

Classification	Numbers Treated	Numbers Recovered
Lepromatous	5	5
Tuberculoid	16	12
Borderline	15	11
TOTAL	36	28 (78%)

 $$T_{\rm ABLE}\ 2$$ Duration of Paralysis and Duration of Treatment

	Patients Recovered	Patients Not Recovered
Average Duration of Paralysis	2.75 months	5 months
Average Duration of Treatment	2.25 months	4 months

SUMMARY

1. The patho-physiology of nerve lesions in leprosy is briefly described.

2. The principles and methods of physical therapy during the expectant phase and the re-educative phase are described and discussed.

3. The clinical results in 36 patients with recent onset of peripheral nerve paralysis (radial 7, lateral popliteal 12, facial 17) treated at the Schieffelin Leprosy Research Sanatorium are presented.

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The Course of Leprosy in an immigrant population in the Netherlands

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INTRODUCTION

Shortly before Indonesia became independent, those Ambonese who were in the Dutch-Indonesian Army or who for other reasons feared repercussions, were offered facilities to move, together with their families, to the Netherlands.

Because of shortage of houses in post-war Netherlands, and because it was generally believed that the sojourn in Holland would not be of long duration, a number of camps were allocated to the immigrants. Most Ambonese preferred the camps to houses outside, in order to preserve their culture and pattern of life, rather than face the risk of becoming absorbed by the foreign community.

After a number of years it became clear that return to Indonesia had to be postponed. Many men had found work outside the camps, some families had moved to houses outside, but the great majority continued to live in the camps.

After 1958, however, the authorities actively suggested and facilitated the transfer to private houses. Many people responded, but others refused the transfer for fear of losing their identity and especially for fear that their children would lose the desire to return to the home land. After 1960, however, the number that left the camps markedly increased and at present only some rather small camps remain.

On arrival a large proportion of the immigrants were young people, unmarried or with a family of only one or a few small children. Many of the former married soon. The birth rate in these families was high. The death rate in children was low. Between 1951 and 1958 the population increased from about 13,000 to about 18,000. Camps and houses became heavily populated, if not crowded, with young children.

THE COURSE OF LEPROSY

At present a total of 37 Ambonese leprosy patients are registered, a prevalence of about 2 per 1,000. In only 10 patients, however, the symptoms of the disease were already present on arrival, a prevalence of only 0.8 per 1,000. In the first 5 years after arrival 23 new patients appeared. In the second 5 years period only 4 more new patients were found. In the last 5 years no more new patients were found. It appears that the incidence of the disease increased markedly soon after arrival, but that thereafter a rapid decrease occurred. At present the disease is rapidly disappearing completely in the Ambonese.

CHANCE OF INFECTION

Of the 37 patients, 9 are lepromatous, 15 are intermediate and 13 are tuberculoid. Of the patients with an intermediate form of leprosy, several were temporarily bacteriologically positive in routine examinations. The number of open patients seems to be high enough for at least some spread of the disease in the community.

Some patients were temporarily hospitalised in general hospitals or in a small leprosy sanatorium. They lived, however, for considerable periods in the camps while they were still positive. Several others were never hospitalised.

The average number of house contacts was high. House contact was not limited to the family proper but included many members of the extended family.

§ Medical Adviser on Leprosy of the Gastmann Wichers Foundation at Rotterdam and of the Dermatological Department of the Universities at Amsterdam and Utrecht. The average age of contacts was low. In a survey in one of the camps it was found that 20% of the inhabitants were children below the age of 5 and 40% were between 5 and 15 years old. The houses frequently were rather over-crowded.

It seems that the conditions for spreading of the disease were very favourable.

COURSE OF LEPROSY IN INDO-EUROPEAN IMMIGRANTS

The course of leprosy in part European immigrants corresponds with the findings in the Ambonese. Of 245 patients registered since 1946, 184 already had signs of the disease before arrival. In the 61 other patients the first signs were noticed in 49 patients in the first 5 years after arrival and in only 12 patients in the second 5 years after arrival (Table 1). Ambonese. In this close community it is difficult to conceal the signs of the disease for a long time. More advanced patients would be noticed and become known to the local physicians, who often are Ambonese themselves. Co-operation between camp physicians and the treatment centre at Rotterdam has always been excellent. The great majority of patients were registered and treated in this Centre and practically all patients treated elsewhere are known.

The families of all known patients have been examined annually. Very few new patients have been found in these families. In 1960 an intensive survey in one of the camps was carried out. In 832 people no new patients were found. It is believed that practically all leprosy patients in the Ambonese are known.

In Indonesia risk of infection existed not only within the group but also outside, by contact

TABLE 1 Relationship between onset of disease and time of arrival in the Netherlands

Onset before arrival								Onset after arrival					
No. of years :	10 +	8-9	6-7	4-5	2-3	0-1	1-2	3-4	5-6	7-8	9-10		
Ambonese	0	1	1	0	1	7	9	14	3	0	1*		
Indo-Europeans	53	11	15	17	40	48	32	17	6	4	2		
Total	53	12	16	17	41	55	41	31	9	4	3		

* In this patient some evidence of an earlier initial lesion was found.

DISCUSSION

The question may be asked if the figures truly represent the course of the disease in the Ambonese. Because leprosy is feared, hiding of patients would be likely. In the first years after arrival some patients came forward for treatment after considerable delay. After it became more widely known, however, that compulsory segregation was not practised, effective treatment free of charge was available, that social assistance was given to patients and that they did not need to fear interference with their daily occupation, most patients came forward voluntarilv and attended for treatment regularly. Defaulters were, usually without great difficulty, persuaded by the social worker to resume treatment. Leprosy is well known by the marked increase in the incidence of leprosy in the first 5 years after arrival in the Netherlands, therefore, is somewhat unexpected. One would expect a decrease. In Indonesia leprosy patients frequently were not allowed to stay in the military camps or they left the camps on their own initiative. In the Netherlands, patients remained in the camps. It is unlikely, however, that this is the reason for the increase. Because of the long incubation period, one would expect an increase in the second 5 years period after arrival and not so soon after arrival. It is more likely that the temporary increase has to be explained by the unusual circumstances before departure. The people were concentrated in a number of camps, frequently under rather

with members of other population groups. The

unfavourable condition, and they were transported on ships that were very crowded. The transmission rate probably was higher than usual shortly before departure and during the voyage.

The marked decrease in the incidence of leprosy that followed the temporary increase cannot easily be explained by the factors influencing the epidemiology of leprosy that are usually mentioned, e.g., isolation, improved hygiene, etc. The climate in the Netherlands has not changed essentially since the time that leprosy was endemic. Tuberculosis cannot have been the main factor as the incidence of tuberculosis decreased in the Netherlands. The use of more and of thicker clothes may have reduced the incidence of patients infected outside the family, but does not offer an explanation for the fact that the incidence of new patients in children in families with infectious parents has been so low.

In our opinion a factor of major importance is that most patients were treated in a reasonably early stage of the disease and that they have attended regularly. Lepromatous patients may remain bacteriologically positive for many years under treatment, but the percentage of morphologically intact bacilli rapidly decreases after regular, adequate treatment. Such patients probably are much less infectious or even noninfectious under European conditions. So far only one patient with leprosy, a man who has never visited an endemic country and who had no known contact with patients in the Netherlands, has been discovered (Beek, 1961).

The immigration of numerous leprosy patients in non-endemic countries in Europe at present creates some difficulties. The experience in the Netherlands is reassuring. There is no need for restrictions, provided the medical practitioners have a working knowledge of leprosy that enables them to suspect leprosy in an early stage of the disease.

In order to render the patient less contagious in the shortest possible time, and to reduce the chance of disability, patients should be treated by experts or at least be treated under the supervision of experts. Central registration of patients is needed for following the trend of the disease. If treatment is free, some social assistance is offered and no restrictions are enforced on patients, the great majority will come forward voluntarily. Defaulters, however, should be traced and persuaded to start or to resume treatment. In our experience only exceptional patients are persistently non-co-operative. Such patients doubtless are a danger, although under European conditions they are not a great danger.

Even in such cases the use of compulsion is as a rule not a remedy. Direct or indirect force results in a greater number of patients that report only in a more advanced stage of the disease or abscond from treatment.

The findings also are encouraging for mass treatment campaigns in endemic countries. Such campaigns, however, become really effective only if serious attempts are made to get the great majority of patients on treatment in an early stage and regularly and if the treatment is adequate.

SUMMARY

The incidence of leprosy decreased rapidly in Ambonese and Indo-European immigrants already in the second 5 years after arrival in the Netherlands, despite conditions that seemed favourable for spreading of the disease. The main reason for decline of leprosy is the regular treatment of patients which rendered patients less or non-infectious even while they were still bacteriologically positive.

Early and regular attendance should be encouraged by offering patients facilities. Restrictions forced on patients result in nonco-operation and have an adverse effect.

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This is the first full year of work on the Project. During 1965 Dr. G. Currie was seconded by the Government of Malawi to institute the work and by the end of the year had been joined by Mr. Drake, Survey Officer, and Mr. Eldon as Administrator. Accommodation had been acquired for the Senior Staff with the purchase of a block of flats in Blantyre and a great deal of preliminary planning of the Project Headquarters had taken place.

Excellent co-operation from all concerned was forthcoming and the Project received a great deal of publicity. Some equipment, particularly the first 2 land rovers, had arrived and work amongst the patients could begin.

All existing clinics in the region were visited and the leprosy work taken over with the co-operation of the Medical Assistants in charge. Attendance at clinics was very poor and mostly irregular; of 5,000 registered less than a half ever showed up, and about a quarter with any regularity.

It was impossible to do any case finding as the staff required did not exist.

At the beginning of 1966, Dr. Molesworth, the permanent Director, arrived and for the 3 months had the invaluable advice and assistance of Dr. Currie before he left for the United Kingdom in April. Also m January the first 3 Medical Assistants reported for training. Later in the year the second batch reported, now making a total of 6. In September, Miss Dean, S.R.N., and Miss Arnold, A.M.I.L.T., arrived from the United Kingdom; Miss Dean to be the Sister i/c of the new wards and Miss Arnold of the Laboratory work. Extra drivers and clinic attendants were also recruited.

PROJECT HEADQUARTERS

After much further discussion the contract was approved and work began on the site in the grounds of the Queen Elizabeth Hospital on 8th August. The buildings consist of 2 blocks: administration, laboratory, operating theatre and out-patients in one, and ward accommodation for 40 acute patients in the other. The blocks are connected to each other and to the Queen Elizabeth Hospital by covered ways.

On October 20th the foundation stone was unveiled by Dr. H. Kamuzu Banda, First President of Malawi, a great honour for LEPRA and the occasion was very well attended. Dr. Banda in his address called upon all walks of life to co-operate with the Project.

Work on the building has gone well with only minor hold-ups and the roof was on just before the rains began; work on the interior is now going ahead and we should be in occupation early in 1967.

TERRAIN

The centre of our region is occupied by the Palombe Plain with the rivers in the northern part running west to east into Lake Chilwa which forms the north-eastern boundary. In the southern part of the plain the rivers work southwards to join the Ruo River, but wander about considerably and very inconveniently before finally reaching it. The south-east corner is occupied by the Mlanje Massif, nearly 10,000ft., where the Ruo River rises and flows west forming the southern boundary until it reaches the edge of the Cholo ridge and turns away south. From here north to Blantyre is hilly country at about 5,000ft., large tea estates, very deep valleys with villages scattered on opposing sides and very poor roads. From Blantyre northwards the ridge continues to the Zomba Massif, 40 miles away, and the Project area includes the scarp and the southern and eastern edges of Zomba as far as Domasi about halfway up the eastern side. From Domasi east and south is plain continuous with the Palombe plain bounded on the east by Lake Chilwa, difficult country again because of the intersecting rivers heading for Lake Chilwa. Main roads are good but once on side roads the going becomes progressively worse and may become impassable after heavy rain; mere trickles in the morning being impassable torrents by afternoon and bridges there last week are no longer present. Some of the tracks are only passable by bicycle or on foot. The heavy rains are from December to March.

In this area live over a million people according to the 1966 census, mostly engaged in agriculture of some form or fishing around Lake Chilwa; villages as such hardly exist, houses are widely scattered and names on maps are only approximate and the actual village is often some miles away.

From the ridges to the plain is a fall of some 2,000ft.

The distribution of patients through the area shows a heavy concentration in the Mlanje region and this continues northward around the shore of Lake Chilwa to reach Domasi and the end of the Project area. Working westwards across the Palombe Plain is a very sparsely inhabited area of swamp land, but west of this again the concentration rises and continues up the eastern slopes of the ridges which form our western border. In the south-west, in the Cholo area where we have not yet penetrated, there seems anyway no falling off in numbers; it is also an area where onchocerciasis is endemic. North and west of Blantyre, after a drop to the Shire River Plain of some 1,500ft., there is an area at the foot of the scarp with certainly as much leprosy but seemingly a complete indifference to it. This is the area of our Friday run from Blantyre.

It is unfortunate that the Chilwa shore area is the most difficult to cover adequately. The frequent deep and, in the wet, impassable drifts running west to east make direct progress in the north/south direction a matter of constant back tracking, while at the southern end of the lake north of Mlanje we just have not yet penetrated.

Around Blantyre and its suburbs is an area from which few patients come forward or come once and are lost. Urban populations are always difficult and although patients exist here as elsewhere, we have not yet the staff to mount such a difficult case finding operation. For instance, apart from those attending the Queen Elizabeth Hospital, out of 130 registered patients only 30 have attended and even fewer with adequate regularity. Many patients come as work becomes available and drift away when it ceases. Somewhere in Blantyre/Limbe one could expect at least 1,500 patients.

MOBILE TREATMENT UNITS

During the year 3 Mobile Treatment Units were started, based on Blantyre, Mlanje and Zomba. The villages in each of the areas from which the known patients came were plotted on a map with indicators for the numbers involved. The villages were then located and visited and the Headmen concerned had the objects of LEPRA explained to them and their help enlisted. Patients from the existing clinics were then informed when and where treatment would be available at the nearest point to their village where the circuit passed. Finally the circuit was put into operation and with minor 'teething troubles' has worked well, so that by the end of December, 1966, 2,806 patients were receiving their treatment with a regular attendance figure of 60%, but sometimes dropping well below this, depending on the local conditions, weather and brewing mainly.

Each team consists of a Driver, a Clinic Attendant with a bicycle and a Medical Assistant who is in charge. Where patients cannot be reached by Land Rover the Clinic Attendant is put down and cycles across country giving treatment, while the Land Rover goes round visiting its own patients and picks him up at the end of his run.

It will be seen from the description of the terrain that constant modifications are necessary as roads become impassable or are again open, but on the whole the scheme is working satisfactorily and certainly a far greater number of patients are reached with greater regularity than was ever achieved hitherto and this will increase.

ABSENTEES

Absentees from the original clinics were attempted to be found and Tony Drake did a great deal of work trying to trace them. At first lists were prepared and sent by post to Health Assistants and Village Headmen concerned, for those named to be rounded up, but very few in fact were. Then personal preparatory visits and explanations were tried but with very little more success and so this method of case finding was abandoned, the work and time involved was far too great for the results obtained.

CONTACTS

Following the abandonment of attempts to trace absent patients, the emphasis was changed to the examination and recording, village by village, of the contacts of known leprosy patients working along treatment runs. All those contacts under 20 years of age were given BCG, by the end of the year 3,503 contacts had received BCG and a total of 4,931 examined, with the discovery of 123 new patients; a rate of 2.5%.

This method, though far more satisfactory, still has a loophole which is that quite obvious but unknown (to us) patients do not get seen as they may not be a contact of a known patient. This has been found quite often. It seems reasonable, therefore, that in a country with a leprosy prevalence of probably 2% everyone should be regarded as a contact and examinations, village by village, of the whole population will be the answer. Now staff is trained this can be undertaken, again working along the general run of a mobile unit in order to ensure immediate treatment of the patients This is very slow work with widely discovered. scattered houses instead of compact villages, and to obtain a nearly complete coverage often many visits are necessary.

Two schools were surveyed and, in conjunction with the American Peace Corps Unit, tested for reactivity to several mycobacterial antigens, Lepromin, PPD Sibert Tuberculin, a Scotochromogen, Kansasi and Avian. The results showed an incidence of leprosy of 1.5%. It was also apparent that by 15 years old nearly all the children were reacting to all the antigens used, but 2 children with tuberculoid leprosy were only positive to lepromin. It would appear that some antigen outside those used was sensitising the population.

Nearly all also showed one or more nerves to be thickened by standards met in other parts of the world.

STATIC CLINICS

There are dispensaries or hospitals where treatment was available before the start of our Mobile Units. By the end of the year all but 9 had been included as a treatment point in one of the runs. Those that remain are visited once a month but continue to give treatment until such time as we can truly absorb them. These are the 3 urban dispensaries other than the Queen Elizabeth Hospital in Blantyre, The Mission Hospital at Nguludi, 14 miles out, and a group of clinics around Cholo, a large area we have not yet penetrated, Namadzi which lies between Blantyre and Zomba and Kalinde to the south of Lake Chilwa and north of Mlanje.

MALAMULO LEPROSARIUM

This leprosarium is in the extreme south-eastern corner of our area and is run by the Seventh Day Adventists. There are about 300 inmates and some 500 out-patients under treatment. Their co-operation with the Project is excellent and during the year this has been our only means of admitting patients for hospital treatment.

Leprosaria at Utale and Likwenu are just outside our area, both are very helpful to us and, lacking doctors, are grateful for such visits as we can give them, though these are inevitably very infrequent.

The help and co-operation we have received in every phase of the Project from all we have come in contact with makes an enormous difference and we are very grateful for it. In addition to the staff mentioned we had with us during his long vacation from university, Mr. Henry de Lotbiniere. He was stationed at Mlanje and with the Medical Assistant there did a first class job in finding villages and plotting possible Land Rover runs. His work was very valuable and enabled us to get the Mlanje runs under way well ahead of schedule.

TRAINING

Training this year has been limited to our own group of Medical Assistants and could really be better described as in-service training since time for set lectures became shorter and shorter as the case load increased. The Medical Assistants have been quick to learn and are proving their value. Every opportunity has been taken to lecture groups of nurses, health assistants, peace corps workers or to show patients at clinical meetings.

PUBLICITY

During the year the Project has received a great deal of publicity, Dr. Currie's O.B.E., Dr. Molesworth's arrival, Dr. Currie's departure, Mrs. Morton's visit and, of course, the splendid coverage the Foundation Stone unveiling received. There have been several articles and broadcasts on our aims, and progress and, of course, the LEPRA Land Rovers with their red lettering are probably almost our best advertisement plus the fact that the word is spreading that there is now regular and effective treatment. This brings new patients and also, alas, very old and hopeless ones for whom we can do little, a grim relic from the past.

Talks have been given at chiefs' courts, to assemblies of Headmen and to gatherings of anyone interested in areas where we are working. This interest has been very genuine and has resulted in practical help.

The Lions Club in Lilongwe presented a McArthur microscope and extra fittings for it were presented by Dr. McArthur himself. This is proving very valuable in field work and its value will increase as the work expands.

The siting of the LEPRA Centre in Blantyre brought to light that there was considerable apprehension that this would bring many patients of leprosy to town. An article and a broadcast to answer this have been published but I feel this will only die down when people become accustomed to the idea through familiarity.

REHABILITATION

The problem here was whether the Government of Malawi were to sponsor a comprehensive scheme or whether LEPRA should 'go it alone' on a reduced scale. Pending a decision on this point nothing could move in spite of a great deal of talk. In June the Governor General, Sir Glyn Jones, called a meeting of all possible interested parties to investigate ways and means. This was followed by a second meeting a month later and a committee was formed of which Dr. Molesworth was elected Chairman. The point on which everything depended was that, while voluntary organisations were fully prepared to do their utmost to provide the capital and equipment, a firm undertaking from the Government was necessary with regard to the running expenses. This was a long time in coming but was finally obtained at the very end of the year, thus giving the scheme the go-ahead.

FIGURES

During the year 1,512 new patients were found, bringing the total to date to 2,148.

Detailed charting was carried out on about 3,500 new and previously treated patients.

Contacts examined	4,931	
New patients discovered in this		
group	123	(2.5%)
Children and Adolescents (under		
20) without signs of leprosy		
receiving BCG	3,503	
Total Patients under Treatment:		
By Mobile Treatment Units	2,806	
By Leprosarium in the Project		
Area I.P	273	
O.P	517	
By existing Clinics not yet in-		
cluded in our Mobile Treat-		
ment runs	488	
	4.004	
	4,084	
	the second second	

On the Land Rover Circuits the number of patients per mile travelled are as follows:—

Blantyre	M.T.U.	 2 patients per mile
Zomba	M.T.U.	 2 patients per mile
Mlanje	M.T.U.	 3 patients per mile

The pattern of leprosy in the area shows a lepromatous rate considerably higher than expected, especially if Borderline patients are included in the figure; almost 30% in the Zomba area and 20%-25% in Mlanje and Blantyre. On a percentage breakdown the figures are:—

L.M.	14.6%
L.F.	10.0%
N.L.M.	30.7%
N.L.F.	44.7%

There has been remarkably little erythema nodosum leprosum, our standard dosage for lepromatous adults being 100 mg dapsone daily. This refers to the Mobile Runs only. ENL is, of course, more frequent in leprosarium patients. Intolerance to DDS is also very rare.

Neuritis is a more frequent complication mostly responding rapidly to corticoid drugs. It is a matter of conjecture whether the relative frequency of neuritis is in any way associated with the finding of thickened nerves in the general population.

Unfortunately burns, blisters and their complications are only too common. Open fires and a complete disregard for heat producing some horrible accidents. It is very difficult to teach patients that the ability to pick up hot things is not an advantage.

General dermatological patients inevitably come our way, in fact the Mobile Units carry a compound ointment for fungal and scabies infections, which is very popular and also good propaganda. Apart from these 2 obviously common ailments we see a lot of psoriasis, lichen planus, allergies, porphyrias, lupus erythematous and various vitamin deficiencies; these latter are very common towards the end of the dry season and before the new crops are ready. They also produce some very difficult differential diagnoses. SUMMARY

In the Project area some 4,000 patients are now under active treatment, of these 2,806 are covered by the Mobile Treatment Units.

 $3{,}500$ patients, new and old, have been recorded in detail.

Case finding has been started.

4,931 contacts have been examined with a 2.5% leprosy incidence.

3,503 apparently uninfected contacts under 20 years of age have received BCG.

Headquarters buildings was begun August 8th and is nearing completion.

Malawian staff have been recruited and trained.

In 3 of the 4 quadrants of the area a reasonable degree of control has been established.

Abstracts

1. Maharashtra Medical Journal, Vol. 13, No. 1, April, 1966, and No. 2, May, 1966, Special Number on Leprosy in 2 parts, Poona, India.

These issues contain valuable contributions to leprosy in the following papers:—

PART 1: Mycobacterium leprae, by S. G. Deodhare.

Genesis of Early Lesion, by K. B. Niphadkar and R. V. Ranade.

Clinical Diagnosis of Leprosy, by N. Figueredo. Differential Diagnosis and Pitfalls in the Early Diagnosis of Leprosy, by A. C. Parikh. Classification of Leprosy, by N. Figueredo.

The Ocular Manifestations of Leprosy, by A. D. Patwardhan.

Drug Treatment of Leprosy, by R. Ganapati. Physiotherapy in Leprosy, by Miss K. B. Kothare.

- Deformity in Leprosy, by N. H. Antia and M. H. Keswani.
- Complications of Leprosy and their Treatment, by K. K. Koticha.

Epidemiology of Leprosy, by N. D. Katdare. Leprosy—A Social Point of View, by R. K.

Mutatkar.

Leprosy Work in India and Maharashtra, by M. S. Mehendale.

PART 2: Leprosy—Its Diagnosis, by K. Ramanujam.

Certain Aspects of Early Forms of Leprosy, by C. G. S. Iyer.

Bacteriology of Leprosy, by C. S. Swaminathan.

Prevention of Deformities, by S. M. Mukherjee. Epochs in our Fight against Leprosy, by P. Mohamed Ali.

Education of the Public, by D. Chakrabarti.

Epidemiology of Leprosy, by S. K. Noordeen.

Neuritis in Leprosy, by Shriniwas Ranade.

Skin—A Versatile Armour and an Immunologic Mirror, by Sharat C. Desai.

The papers are in English, with a few translations into Marathi, and would be well worth studying in the original. The journal is to be congratulated on its work for leprosy.

The following abstracts are reprinted with permission from *Trop. Dis. Bull.*, 1967, **64**, 3:

2. Improvement of the Growth of Mycobacterium leprae in vitro and Isolation of Pure Cultures in a Selective Medium, by A. L. OLITZKI. Harefuah, Jerusalem, 1966, Oct. 2, 71, No. 7. (In Hebrew 199-202. English summary 202.)

The English summary appended to the paper is as follows:—

'1. *M. leprae* grew in 8 subcultures during a period of 15 months on the medium described previously (see this *Bulletin*, 1966, **63**, 411, 765). In addition to the extract of *M. smegmatis* (No. 2) growth was improved by human foreskin-extract, 0.5% glycerol and 0.05% Tween 80.

'2. *M. leprae* was isolated 12 times in 15 repeated examinations from the auricular skin of patients. In order to inhibit the growth of the non-mycobacterial flora, 0.01% malachite green was added. In 12 auricular skin examinations of patients the results obtained microscopically and by culture were negative.

'3. From 4 patients (3 microscopically negative and 1 positive) acid-fast bacteria were isolated which were identified as "rapid growers".

'4. Preliminary skin tests with cultured M. leprae showed stronger reactions in patients to the cultured bacteria than the conventional lepromin antigens.'

3. Impaired Delayed Hypersensitivity in Patients with Lepromatous Leprosy, by D. S. WALDORF, J. N. SHEAGREN, J. R. TRAUTMAN and J. B. BLOCK. Lancet, 1966, Oct. 8, 773-6. (17 refs.)

In view of conflicting evidence on the ability of patients with leprosy to develop delayed hypersensitivity, 34 such patients were tested for the development of hypersensitivity to 2,4-dinitrochlorobenzene (DNCB). DNCB was chosen as the allergen because it induces delayed hypersensitivity in over 90% of normal people and previous contact with it is unlikely. Only 4 of 17 patients with lepromatous leprosy but without erythema nodosum leprosum could be sensitized to DNCB. In all other groups (lepromatous leprosy with ENL, dimorphous leprosy and inactive leprosy) the response was not significantly different from that of the control group. Several patients in the non-reacting lepromatous group, in whom sensitization to DNCB was depressed, were tuberculin positive. This suggested that delayed hypersensitivity, which developed before the onset of leprosy, would persist despite the later state of anergy.

D. S. Ridley.
4. Electromyographic Studies in Leprosy and Dermatomyositis, by K. C. KANDHARI and V. N. SEHGAL. Dermatologia Internat., Philadelphia, 1965, Apr.-June, 4, 2, 96-101, 6 figs. (24 refs.)

'Electromyographic studies were conducted on 37 patients with leprosy and 3 patients of dermatomyositis. Results obtained were compared with 23 normal controls. Five of the leprosy patients showed a complete nerve lesion with isoelectric recordings, even on muscular contraction, while others showed a partial nerve lesion with a specific mixed pattern, with polyand biphasic waves. Dermatomyositis patients showed a specific pattern of their own. The significance of these findings in the prognosis for such cases is discussed.'

 The Facial Nerve in Leprosy, by N. H. ANTIA, S. C. DIVEKAR and D. K. DASTUR. 1. Clinical and Operative Aspects (ANTIA, DIVEKAR and DASTUR). Int. J. Lepr., Wash., 1966, Apr.-June, 34, 2, 103-17, 8 figs. 2. Pathology, Pathogenesis, Electromyography and Clinical Correlations (DASTUR, ANTIA and DIVEKAR). Ibid., 118-38, 16 figs.

1. 'Detailed clinical features, surgical observations, and gross morphologic findings are reported for 11 patients with polyneuritic leprosy, who presented with lagophthalmos with or without weakness of other facial muscles.

'All patients showed greater or lesser areas of anesthesia in the distribution of the maxillary division of the trigeminal nerve.

'An extensive operative exposure, electric stimulation and biopsy of the affected nerve branch were possible as measures preliminary to surgical repair of the palsied eyelids. 'In no 2 patients was the pattern of facial nerve branching identical; different forms of dichotomizations and anastomoses were encountered.

'In accord with the clinical impression, the zygomatic branch of the facial nerve was found most affected and invariably unresponsive to electric stimulation; it was the one biopsied, and the biopsy specimen included the surrounding tissues.

'Adhesions, and frequently compression of the zygomatic branches in the surrounding tissues, which appeared fibrosed, were observed.'

2. 'Electromyographic findings in 7 and histopatholige observations in 11 patients, and correlation of these with the clinical and operative observations reported in our first paper, have been presented here on patients with lagophthalmos due to leprosy.

⁽Preoperative electromyographic observations on the orbicularis oculi, the frontalis and orbicularis oris in 7 of the patients, revealed increased latency of conduction and abnormal muscle activity in the form of reduced interference patterns, giant single unit patterns and polyphasic potentials.

'A chronic inflammatory and fibrosing neuritis of varying severity and duration was observed in all patients. Granulomatous reaction was noted in 3.

'The greater involvement of distal rather than proximal parts of the nerves to the orbicularis oculi was noted in a number of patients, and suggested the possible ingress of infection in this motor nerve from the sensory branches of the maxillary nerve anastomosing with the zygomatic branch of the facial nerve. The role of secondary factors operating upon the facial nerve branches in the bony zygomatic region is discussed.

'There was a good correlation in 8 of the patients between the clinical, the electromyographic, the operative electric stimulative and histopathologic findings. This was more evident in severely affected patients with single unit activity in which correspondingly severe nerve damage was evident structurally.'

Book Reviews

Elementos de Leprología Experimental (Rudiments of Experimental Leprology) by MENY BERGEL, Director del Laboratorio de Investigaciones Leprológicas, E. Zeballos 3411, Rosario, Argentina, 90 pages, 32 illustrations.

This booklet examines the methods used in experimental leprology and described the various techniques for the inoculation of M. leprae. Examples of standard investigations are described and the conclusions summarised. The author also gives general rules to be followed in clinico-therapeutic experiments for the evaluation of new compounds on human leprosy. Tables and useful data for investigations in experimental leprology as well as general bibliography are added. The booklet has been carefully prepared and merits study in the original. There are general summaries in Spanish, French, English and German.

- All Things Made New, by A. D. ASKEW, price 2s., The Leprosy Mission, 7 Bloomsbury Square, London, W.C.1.
- The Field is the World. The Report for the Year 1966, price ls., The Leprosy Mission, 7 Bloomsbury Square, London, W.C.1.

These 2 booklets give a comprehensive and very interesting report of the work of The Leprosy Mission and are recommended.



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World Health Organization Technical Report Series 1966, No. 319.

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