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Editorial

INTEGRATION

There are fashions in words, and in ideas. Some words emerge from the study, the laboratory or perhaps even the gutter, achieve a more or less transient popularity, and then disappear. Other vogue-words and phrases really fulfil a long-felt need and pass into the language, perhaps undergoing more than a little sea-change on the way. The "protagonists" seeking "parameters" of "psychosomatic disease" await the "psychological moment".

"Integration" is one of these vogue-words—a watchword that is in danger of becoming a mere catchword, a battle-cry that gets muted into a parrot-cry. We hear it in relation to leprosy and to leprosy control. We shall hear more of it in the future, because it does stand for something desirable and necessary. Integration must come, sooner or later. Leprosy cannot remain in isolation, "splendid" or not-so-splendid. And the leprosy services, the leprosy control programmes, must sooner or later become an integral part of any plan to deliver some kind of comprehensive medical care to the mass of citizens.

Sometimes, for various reasons—most of them non-medical—a leprosy programme has been the first impact of Western medicine on a non-Western rural population. It has tackled a considerable and obvious and neglected problem, a problem made worse by prejudice and ignorance. Historically, the compassionate care of the early days was at length supplemented by scientific therapeutics, and then by reconstructive surgery and rehabilitation. For various reasons, some good, some less than convincing, a separate leprosy service has developed, with its separatist outlook and traditions, its own staff structure, and its vested interests. An over-emphasis on one disease has undoubted drawbacks: while focusing attention on a grossly neglected human problem, it may have contributed in some measure to the perpetuation of the stigma, the aura of uniqueness, of leprosy; while ensuring that leprosy sufferers were at least offered treatment, it may have turned them into over-privileged citizens enjoying a degree of medical attention denied their neighbours who were suffering from pulmonary tuberculosis, or trachoma, or from some physical impairment resulting from an accident or disease other than leprosy.

In all too few countries integration proceeded quietly and unspectacularly, even naturally. A rural health service was in existence, and when the new anti-leprosy drugs became available, mass treatment was offered through the dispensaries and health centres to all leprosy sufferers. Social discrimination and medical "apartheid", fortunately, did not disturb this process. Integration became a *fait accompli,* because the possibility of any alternative was not entertained.

The present position is thus diverse and confused. Government planners and economists, costing their programmes and cheese-paring their estimates, are understandably chary of piecemeal schemes for separate diseases. Special campaigns may from time to time be necessary—for malaria or yaws, for trachoma

or trypanosomiasis; but health and nutrition and population control are but different facets of one indivisible problem—man in community.

Any new programme for disease control should take advantage of the new knowledge and the changing climate of opinion. Any new scheme for reconstructive surgery and rehabilitation, any plans for long-term care of the hopelessly disabled and handicapped, and any proposals for vocational therapy and sheltered workshops, should be broadly conceived so as to include those whose disabilities are due to leprosy. Similarly, in many instances those pioneering activities designed exclusively for leprosy sufferers might well cease to "discriminate" against those suffering from other conditions, such as congenital deformities, poliomyelitis, trauma (industrial or traffic accidents, or warfare), etc. The sheer size of the aftermath of leprosy may sometimes justify a special institution, but only in the context of approximately equivalent facilities being made available to the victims of conditions other than leprosy.

Admittedly, specialist advice and expertise must be readily available to governments that are faced with a sizeable leprosy problem. And there will always be a need for the devoted individual, be he research scientist or field worker, with restricted interests but deeper knowledge. Furthermore, as leprosy touches on (and oft-times illuminates) neighbouring branches of medicine and of science, the sheer fascination of the study of our specialty should captivate more and more the enquiring mind and the dedicated hand. But . . . the "one-track mind" is an anachronism today. There are other tracks, maybe parallel, often converging, and all of them important to the study and practice of leprosy and leprosy control in the community.

Governments and voluntary agencies have their parts to play in this inevitable integration of leprosy into the general health services. There are difficulties in the way, of course. Adaptation of buildings, in-service training of auxiliary workers so that by supplementary courses they become polycompetent; widespread education of the medical and nursing professions, political leaders, and the public at large in order to break down prejudice and undermine vested interests; the transformation of leprosy clinics into polyvalent dispensaries and health centres—in short, the "rehabilitation" of leprosy into the thinking and practice of all those concerned with the health of the community.

The voluntary agencies historically concerned with leprosy, and still in the forefront of the worldwide campaign against the disease, have a unique rôle in this process of integration. With their resources and attributes—of initiative, flexibility, and speed of operation—they might well pioneer in this, as they have in other directions. Any possible risk of loss of identity will be more than offset by the certainty of bringing more hope and better health to more people, including those suffering from leprosy. For the present, and for as long as the victims of this scourge suffer discrimination of many kinds and remain without treatment, there must be a continuing campaign to ensure that they receive a fair deal in the commendable efforts to plan integrated medical services.

News and Notes

"TROPICAL DOCTOR"

We give a warm welcome to a new quarterly. *Tropical Doctor* is published by the Royal Society of Medicine, with a grant from the Commonwealth Foundation. It is intended for the isolated medical worker in tropical countries, and hence would interest many of the readers of *Leprosy Review.* It will publish invited articles on the treatment, management, and prevention of diseases and conditions prevalent in tropical countries. These articles will, in effect, constitute a continuing course of postgraduate instruction especially directed to the practical needs of medical men and women working on their own in mission, government, and other hospitals in out-stations, dispensaries, and health centres in tropical countries.

News letters and unsolicited contributions will be published in so far as they bring to light, or provide helpful comments on, matters of common concern and interest. Original articles reporting research work will not, as a rule, be published in *Tropical Doctor*—adequate media already exist for this purpose—but short accounts of procedures and techniques that readers have developed or adapted will be welcomed.

The Editor is Dr. Hugh Clegg, who for many years edited the *British Medical Journal* with outstanding success. The Editorial Committee includes figures well-known in tropical circles. Leprosy is represented in the person of Dr. S. G. Browne. It is understood that forthcoming issues will include symposia on Skin Disease in the Tropics, and on Leprosy.

The "Notice to Subscribers" published in the first number of *Tropical Doctor* (January, 1971) is appended for the information (and action) of our readers.

Notice to Subscribers for *Tropical Doctor*

From 1 January, 1971 the annual subscription rate will be £3 ($8) post free in all countries, single copies will be 75p ($2). Remittances must accompany orders, and should be made as follows: (i) by banker's draft on London, in favour of *Tropical Doctor* and addressed to The Editor, *Tropical Doctor,* International Relations Office, Royal Society of Medicine, Chandos House, 2 Queen Anne Street, London W1M 0BR, England; or (ii) to National Westminster Bank Ltd., 250 Regent Street, London W1R 6AU for account of *Tropical Doctor*. The Royal Society of Medicine will consider concessionary rates of subscription for missionary societies and hospitals, and for university faculties and final-year medical students in developing countries. Enquiries about these should be addressed to the Editor.

"WORKSHOP" AT KARIGIRI, NOVEMBER, 1970

The first All-India Workshop on leprosy problems in India, held at Karigiri, South India, from 12 to 14 November, 1970, attracted 60 participants from Tamil Nadu State and beyond. The major expenses of the "workshop" were defrayed by a generous grant from the Social and Rehabilitation service of the Department of Health, Education and Welfare of the United States of America.

Unlike many such conferences, at which a surfeit of scientific presentations leaves little or no time for discussion, this workshop was so organized that participants had ample time and opportunity for tackling (in small groups) the real practical problems concerned with "Deformities in leprosy; implications, prevention and management".

At the Inaugural Function, a stimulating and challenging address was given by Dr. Paul Brand on the relative failure of much of the effort put forth in treating individual leprosy patients, medically or surgically, when considered in relation to the endemic as a whole. Despite the undoubted successes, little impression seems to have been made on the incidence of leprosy in South India or the prevalence of physical deformity and social stigma. Dr. Stanley Browne, deputizing at short notice for Dr. J. K. G. Webb, Principal of the Christian Medical College, Vellore, referred to the need to make leprosy academically and scientifically respectable in close co-operation with a teaching and treating medical faculty. Professor A. J. Selvapandian outlined the practical scope of the workshop sessions. Before setting the "workers" to "work" in the workshop, the Organizer (Dr. D. A. Ranney, Chief of Surgery at Karigiri) called on Dr. Stanley Browne to speak on "The Rôle of Rehabilitation in Leprosy Control".

For the following sessions, the same pattern was generally observed—a provocative paper or demonstration, and then a frank discussion on the topics prescribed, such as: (a) the problems involved in detection and management of the cases likely to develop deformities and those with early deformities; (b) evaluating the principles, methods, and materials of health education in the prevention of the deformities; (c) the need for trained personnel in medical and para-medical fields, and their training, placement, and utilization; (d) the problems involved in the availability, manufacture, and utilization of simple and practical appliances and devices in the prevention of deformity, and their management.

This workshop was, by common consent, most helpful and useful. Doctors and physiotherapists, social workers and prosthetists, laboratory technologists and occupational therapists, despite their diversity of outlook and activities, managed to discuss their common problems together and derive real help from their joint deliberations.

LEPROSY CONFERENCE AT ASKA, ORISSA, INDIA

The German Leprosy Relief Association (D.A.H.W.) and the Danish Save the Children Fund together sponsored an informal conference (a "Get-Together", they called it) of representative workers in voluntary-agency leprosy institutions supported in part by the German organization. They met at the headquarters of the Danish leprosy control programme at Aska, Orissa, from 14 to 18 November, 1970. The great majority of the participants were Indian, and included medical and para-medical workers and lay superintendents of leprosy hospitals, together with some expatriates working in these institutions. The invited guests were Dr. E. A. Blum and Dr. J. A. Cap, both World Health Organization leprosy consultants, and Dr. Stanley Browne.

Under the wise and genial chairmanship of Professor T. N. Jagadisan, the participants discussed the subjects raised by the speakers and the practical outworking of the exemplary Aska Leprosy Control Project. They saw the small

central hospital designed for treating the acute complications of leprosy, and visited typical "under-the-trees" leprosy clinics.

The WHO leprologists gave helpful papers on the control of leprosy and Dr. Browne spoke on "The rôle of voluntary organizations in leprosy control," and "The place of rehabilitation in a leprosy control programme". Mr. E. Ostergaard, the man who has inspired and encouraged the programmes at Pogiri and Aska, described the simple administration and financial structure of the Aska Project, emphasizing its low cost (23 Rupees per patient treated per year, including an average of 4 Rupees per patient for hospital care) and its reproducibility. So far, over 48,000 leprosy patients have been registered at Pogiri, and nearly 19,500 at Aska. The cost per head of the population in the area covered by the Aska control project, for the leprosy service alone, is about half a rupee per year (0.56 Rs.). About 40% of the leprosy patients in Orissa (population, 18 million) are being treated in the Aska project.

The three full days of conference, discussion, and observation brought home to the participants the fact that leprosy can be controlled in a given area with minimal dissipation of energies and money on organizational overheads.

XAVIER AWARD TO DR. O. W. HASSELBLAD

Dr. Oliver W. Hasselblad, President of American Leprosy Missions, Inc., was presented with the Xavier Award for his "outstanding zeal and devotion to the cause of Missions". The presentation was made by the Jesuit Seminary and Mission Bureau on 6 November, 1970. The Award was established in 1953 in honour of St. Francis Xavier, patron saint of Missions.

Dr. Hasselblad's well-merited award sets the seal on a lifetime of devoted service in India and, since 1959, in the many countries he has visited in the interest of leprosy sufferers.

LEPROSY IN LIBYA

Though not a serious public health problem in Libya, leprosy is responsible for much suffering. The prevalence is probably about 2 or 3 per 1000 of the population, and no area is exempt. In-patient treatment is provided at Birstamilad (near Tripoli), and a new hospital for leprosy sufferers is about to be brought into use at Barce (east of Benghazi) and near the new town that has been built to replace the old Barce, which was severely damaged by earthquake in 1963.

Dr. Stanley Browne recently conducted a survey of the leprosy situation in Libya, and made recommendations to the Libyan Government regarding a programme for leprosy control.

LEPROSY IN NIGERIA

The leprosy control programmes in two of the three states comprising the former Eastern Nigeria (South-Eastern and East Central) have been investigated recently.

Dr. O. W. Hasselblad made an extensive survey of the South-Eastern State at the invitation of the State Government, and made comprehensive recommendations for the reorganization of the leprosy service in his official report.

Dr. Stanley Browne toured the East Central State on behalf of the Christian Council of Nigeria and an *ad hoc* body brought together by The Leprosy Mission in London and representing all the voluntary agencies engaged in leprosy work in the former Eastern Nigeria before the outbreak of the war there. The leprosy service, which had been one of the most effective in Africa, is disrupted; the world-renowned Research Unit at Uzuakoli and the Settlement itself suffered extensive damage. The voluntary agencies are most desirous of co-operating with the Government in integrating a leprosy control service within the framework of endemic-disease control in the State.

LAMBARENE

Following a fact-finding visit of Dr. Stanley Browne to the Dr. Albert Schweitzer Hospital and *Village de Lumière* (village for leprosy sufferers) at Lambarene, certain proposals are before the international committee charged with the administration of the work. Generous benefactions have recently come from Swiss and American sources to help rebuild the *Village de Lumière*.

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Letters to the Editor

Dr. Brubaker's letter in *Leprosy Review* of April, 1970 (**41**, 2, 128) concerning the use of dapsone in Northern Nigeria raises some very important issues. I do think, however, it was the Government's policy to provide treatment only for those showing definite evidence of leprosy. There is, as is well known, a great desire on the part of the public to obtain dapsone for reasons I have not understood, and in the clinics where I began working there were many people who had no signs of leprosy. Some of these could be immediately discharged, but there was a considerable number who presented a dilemma. The description of the initial lesions at the time of the patient's first attendance was often scanty or absent and it was impossible to decide whether the person had ever had leprosy or whether genuine skin patches had disappeared with treatment. If these patients were discharged there was then a possibility of relapse because of inadequate therapy. I therefore adopted a very cautious approach and kept on treatment a large number of people, but obviously many of them probably had not the disease. This then was the reason for the large numbers of attenders reported in my paper, rather than a deliberate policy of chemoprophylaxis.

Similarly, in other parts of Northern Nigeria there were many people obtaining dapsone because leprosy attendants were too ready to accept them without adequate examination, and so Dr. Brubaker is quite right to argue that the decline in the disease could in part be due to the chemoprophylactic effect of the drug. However, I feel that the direct effect of dapsone in the leprosy patient is more important, particularly in those with multibacillary disease in which bacteria are rendered non-viable after a few months of therapy, thus preventing new cases from arising. The well-documented articles published in recent numbers of *Leprosy Review,* describing control projects where patients were closely supervised, have shown how successful this approach has been, and it was my intention also to advocate this in my paper. I too am strongly opposed to the haphazard distribution of dapsone tablets.

Faculty of Medicine,
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C. L. CRAWFORD

16 November, 1970

For many years the history of leprosy has suffered from the contradictory opinions expressed regarding the method of transmission of the disease. In India it used to be thought that there was no need to take special precautions in working with leprosy patients; I had to work cheek by jowl with an infective patient, looking down the same microscope. The wind of change then began to blow, and masks and gloves were worn.

A paper has recently been published (*Leprosy Review* (1970) **41**, 31 and 167) whose main contention is that skin-to-skin contact is a minor source of infection, and that the principal method of spread is *via* the nasal secretions. The skin-to-skin route, with the skin unbroken, is ignored. While it is true that a positive nasal smear indicates a greater possibility that *Myco. leprae* may be transferred from an infected person to a healthy one, yet it cannot therefore be inferred that the nasal route is the sole method by which a person can become infected. In the first place, how often, except in a case of diffuse lepromatous leprosy, is the skin intact? In the second place, bacilli can be detected in the sweat of a patient perspiring profusely. Further, bacilli can be found in the epithelial cells of the skin.

Therefore, while it is true that the nasal mucosa may, in many instances, be the chief route of infection, it is unwise to consider this as the sole source; by so doing, other possible routes are ignored, and an unwise policy may be advocated. I have been long enough in leprosy work, approaching half a century, to be very sceptical of statements that emphasize only one aspect of the transmission of the disease. I would emphatically stress that, while we give due importance to the nasal route of spread, we do not thereby ignore other possibilities.

Let us keep our feet firmly on the ground, and neither be unduly scared in regard to hypothetical routes of infection, nor nonchalant about methods of dissemination whose importance in the transmission of leprosy from the infective person to the susceptible individual cannot at present be readily determined.

20 February, 1971 R. G. COCHRANE

I should like to comment on two points in Dr. Cochrane's letter, which queries certain statements in my recent papers (Pedley, 1970*a, b*), first on the statement: "bacilli can be detected in the sweat of patients perspiring profusely".

If bacilli are indeed excreted in the sweat on to the surface of the skin, I should have expected, in a systematic search of an area of 813 sq cm of maximum infiltrated lepromatous skin in 24 patients, to have found a large number of *Myco. leprae,* since partly dried sweat would have been present in every case, leaving its solid contents adhering to the skin. As it was, only 28 bacilli were found by Composite Skin Contact Smears (C.S.C.S.), of which 25 were present on the face of 4 patients, in each of whom the nose-blowings were heavily infected (Pedley, 1970*b*). Two of these patients had been sweating profusely, for the weather was humid, and their faces were still clammy with perspiration when I made the examinations. Had I not first examined the nose-blowings, I might have concluded (wrongly) that the bacilli had been excreted in the sweat. The patients here dispose of their nasal discharge and sputum most unhygienically; one patient, whose nose-blowings were heavily infected, was seen to wipe the nasal discharge on to hand, forearm, face and thigh. From any of these contaminated areas, bacilli on the skin surface could doubtless have been demonstrated by the technique described.

In the 24 patients in my series (Pedley, 1970*b*) with untreated lepromatous leprosy, 18 showed large numbers of solid-staining *Myco. leprae,* together with many globi, in their nasal discharge. Bacilli would probably have been found in the nasal mucus of the remaining 6 patients had they been examined more than once, or had the nasal mucosa itself been examined. Thus, I conclude that in the

majority of patients with untreated lepromatous leprosy, enormous numbers of *Myco. leprae* may be present in the nasal discharge.

I admit that bacilli may be present in the sweat of patients with lepromatous leprosy, but before it is justifiable to conclude that bacilli found on the skin of the face had been deposited in the sweat, the nasal discharge must be examined (more than once, if necessary) for the presence of acid-fast organisms.

Second, Dr. Cochrane asserts that ". . . bacilli can be found in the epithelial cells of the skin". This is undoubtedly true, but it does not necessarily follow that these bacilli will emerge on to the skin surface. The likelihood of this happening may be doubted for the following reasons: if this were true, more than 28 bacilli on the area of skin examined would have been found; and the sections I have seen show that when intracellular organisms are present in an epidermal cell, the cell is situated deeply. In this layer, the cells are considerably flattened and the nucleus and cytoplasm appear to be disintegrating before being transformed into the horny layer.

It is, of course, possible that by the time the cell containing the bacilli reaches the surface of the epidermis, the acid-fast organisms will have disintegrated along with the nucleus and cytoplasm of the cell.

Leprosy Mission,
Tan Sen, Nepal

J. C. PEDLEY

11 March, 1971

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Obituary Notice

MAJOR-GENERAL C. K. LAKSHMANAN

(1898-1970)

Many people outside India, and many in India not connected with the Hind Kusht Nivaran Sangh, will be saddened to learn of the passing of Major-General Lakshmanan at the age of 72. For many years he had been closely connected with the Leprosy Control Programme of the Government of India, and served as a most understanding and gracious link between the Government and voluntary agencies concerned with leprosy in India. As Director-General of Health Services, he was (from 1954 to 1958) an *ex-officio* member of the governing body of the Central Leprosy Teaching and Research Institute at Chingleput and helped with his mature advice during the critical formative phase of its activities.

General Lakshmanan was educated in Madras and in London (at St. Bartholomew's Medical College and Hospital). He had a very distinguished career, first in the Indian Army and then in civil employment under the Central Government, rising eventually to the highest position. Both before and after his official retirement, he was often called upon because of his expert knowledge and wide-ranging sympathies.

It was during his years as Honorary Secretary of the Hind Kusht Nivaran Sangh (1958 to 1969) that he was brought into contact with leprosy workers throughout India and made many happy acquaintances with leprologists on the international scene.

Our deep sympathy goes to his widow and members of the family.

S. G. BROWNE

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Cataract in Leprosy: A Biochemical Approach*

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The possible rôle of phenoloxidase of *Mycobacterium leprae* in producing cataract in leprosy is discussed. It is suggested that diethyldithiocarbamate, a potent inhibitor of the enzyme, could be of value as a therapeutic agent.

Host and tissue preferences of pathogenic bacteria have been attributed to differences in nutritional conditions in different hosts and in different tissues within the same host. A case in point is the invasion by brucellae of certain tissues in pregnant animals, where erythritol is present (Smith, 1968). The human leprosy bacilli multiply at sites in the human body (e.g. skin and peripheral nerve) where metabolism of 3,4-dihydroxyphenylalanine (dopa) or its derivatives is important. Dopa is a precursor of melanin pigment, and of norepinephrine which is a neurotransmitter. *In vitro* studies have shown that *Mycobacterium leprae* rapidly oxidizes dopa and its analogues (Prabhakaran *et al.*, 1969).

Involvement of the eye is common in advanced cases of leprosy. Besides the nerves supplying different areas of the eye, various parts of the organ are invaded by the bacilli. Large numbers of *Myco. leprae* have been found in the cornea, iris, and the ciliary body. The ciliary body is gradually destroyed—a major cause of blindness in leprosy. Cataracts commonly develop and sometimes vitreous opacities (Choyce, 1964). It is interesting that dopa has been shown to be present in the iris and ciliary body (Pirie, 1968). Various lines of evidence suggest that the metabolism of dopa or its derivatives may be important in the multiplication of *Myco. leprae.*

The enzyme that oxidizes dopa or tyrosine to pigmented products is known as tyrosinase or phenoloxidase. It has been suggested that cataract formation in man is due to the action of quinones formed from dopa or tyrosine by the activity of tyrosinase (Srivastava and Nath, 1968). Homogenates of senile cataractous lenses were found to have tyrosinase activity; this activity could be inhibited by the addition of reducing agents (ascorbic acid or glutathione) to the homogenates. Normal lenses contained no tyrosinase. However, when inhibitory metabolites were removed by dialysis, homogenates of normal lenses also showed tyrosinase. It is likely that in old age a decrease in reducing agents activates tyrosinase of the

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lens. The quinones produced in the oxidation of dopa or tyrosine might form compounds with the lens proteins, leading to the cataractous condition. In the presence of tyrosinase the quinones also oxidize -SH groups of proteins to produce insoluble -S-S- proteins which cause opalescence in the cataractous lens (Srivastava and Nath, 1968).

Human cataractous lenses vary in colour from pale yellow to deep brown. The brown colour is associated with an insoluble protein in the lens. Cataractous lenses of naphthalene-fed rabbits contain brown proteins; these are compounds of lens proteins with naphthoquinone (Pirie, 1968). Dopa, as well as tyrosinase, occurs in areas of the eye such as the iris and ciliary body. It is likely that the brown colour of the human cataractous lens is due to compounds of lens proteins with quinones which are formed from tyrosine or dopa by tyrosinase. When homogenates of cattle lenses were incubated with a mixture of tyrosine, dopa and tyrosinase, the lens proteins gradually developed yellow and brown colours, and became black on prolonged incubation. Concomitantly, there was a loss of thiol groups from the proteins (Pirie, 1968).

Myco. leprae was found to oxidize dopa and several other phenolic compounds *in vitro* (Prabhakaran *et al.*, 1969). As a result, when leprosy bacilli invade the eye they could oxidize the dopa present, and so give rise to quinones. These quinones might interact with the proteins of the lens, leading to a cataractous condition. Thus, in leprosy there are 2 factors contributing to cataract formation: (i) the tyrosinase of the lens, and (ii) the tyrosinase of *Myco. leprae.*

It has been shown that tyrosinase activity present in homogenates of senile cataractous lenses could be inhibited by the addition of reducing agents like ascorbic acid and glutathione (Srivastava and Nath, 1968). As such, the administration of high levels of ascorbic acid might be expected to help alleviate the cataract in leprosy patients resulting from the tyrosinase of the lens. However, *in vitro* experiments have shown that the phenoloxidase of *Myco. leprae* is different from the tyrosinase of mammalian or plant origin, in the effect of reducing agents on the enzyme (author's unpublished results). The formation of quinone from dopa by the latter 2 enzymes was completely suppressed in the presence of ascorbic acid and glutathione; on the other hand, reducing agents had little effect on the oxidation of dopa to quinone by *Myco. leprae.* Therefore, it is likely that the administration of ascorbic acid may not prove to be completely effective in combating the cataract which directly results from invasion of the eye by *Myco. leprae.*

In this situation, a search for inhibitors which suppress tyrosinase of *Myco. leprae* is important. Non-toxic compounds which completely suppress tyrosinase of the leprosy bacilli would prevent the formation of quinone which causes the cataract. In our experiments, the most effective inhibitor of tyrosinase from different sources was diethyldithiocarbamate (DDC) (Prabhakaran *et al.*, 1969). This compound produced total inhibition of the enzyme in *Myco. leprae.* DDC has been successfully used in the treatment of Wilson's disease (hepato-lenticular degeneration) and in the case described improvement of the eyesight was also reported (Sunderman, Jr. *et al.*, 1963). DDC penetrates even intact *Myco. leprae* and suppresses its tyrosinase activity. A sulphone drug tested was less effective (Prabhakaran *et al.*, 1969). Moreover, although sulphone treatment sometimes arrests the progress of ocular leprosy, a cure rarely takes place. The above considerations indicate that DDC might be effective in preventing quinone-formation from dopa by *Myco. leprae* and thus help alleviate the cataractous

condition so common in leprosy. Our preliminary results on multiplication of *Myco. leprae* in the mouse footpad (to be published) also indicate that DDC, besides preventing quinone formation from dopa, might also lead to killing of the leprosy organisms.

Acknowledgements

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Epidemiology and Leprosy Control*

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Leprosy increasingly interests workers in other fields because of its growing relevance to their own work (for example, immunology). It may be helpful, therefore, to reconsider the rôle that modern epidemiological methods have to offer in leprosy control, primarily in research, but also on the service side.

Introduction

"Epidemiology" itself needs some definition in the context of leprosy. Hitherto, the word has often been loosely applied to clinical observations—for example, the alleged different sites of first lesions in children being related to their (infected) mothers' way of carrying them—or to the characterization of groups of patients who are often highly selected by virtue of being in hospital, or who volunteer for study. This usage, though formerly understandable, is no longer justifiable. Modern epidemiological methods involve eliminating as much bias as possible in identifying cases of a disease, and relating them to the population from which they are drawn. In practice, these precepts mean looking for cases outside hospitals as much as inside them, making every effort to find *all* the cases in a defined population, and obtaining the same accurate and comprehensive information about the unaffected, as well as the diseased members of the population.

The term "control" must also be defined. Leprosy control is currently most often used in the context of detecting and treating early but established disease. This usage fits into the classic concept of *secondary prevention. Primary prevention* aims at forestalling the development of clinical disease altogether by eliminating causes or by detecting individuals at particular risk (perhaps already with "precursor" disorders) and by protecting them as far as possible. (*Tertiary prevention,* for completeness, is concerned with controlling deterioration in severe, relapsing and disabling disease.)

Primary prevention is obviously the ideal. One of the very few studies of leprosy that has produced incidence figures from year to year (Vellut, 1969) has

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shown that in spite of a highly organized and intensive "control" programme designed to detect and treat early disease, the rate at which new cases appear is not declining. In other words, there is no evidence from Vellut's study that what is basically "a secondary prevention" approach is in fact "controlling" leprosy in the sense that it is making the occurrence of new cases of the disease any less frequent. Indeed, if very early cases are infectious, or if there is an infectious prodromal period (and evidence is accumulating that suggests this), one would hardly expect secondary prevention to make more than a partial contribution, at most, towards *eradication.* This it may do by rendering a limited proportion of established cases bacteriologically negative earlier than otherwise, but such patients will still have a great potential for infecting other people. For leprosy, no less than for any other disease, "prevention is better than cure", and eradication must ultimately depend on effective primary prevention, so that what is eventually improved—that is lessened or even abolished—is the individual's chance of coming into contact with the bacillus, rather than his chance of being detected, treated and made bacteriologically negative; this depends on reducing or eliminating the "prevalence pool" of infection.

This paper is an attempt to shift the emphasis on "control" of leprosy very much more into the field of primary rather than secondary prevention, and to discuss the difficulties and problems that would arise in the incidence studies necessary to do this.

Prevalence and Incidence

The *prevalence* of a disease is the proportion of a defined population affected at a given time; it is usually expressed as a percentage. The *incidence* is the rate at which new cases develop in the population, expressed usually as a percentage per annum. (This distinction is crucial, and is made here because frequently, as in parts of Cochrane and Davey (1964), "incidence" is used to describe "prevalence".)

Prevalence studies are relatively easy to mount, can usually be completed fairly quickly, and are generally reasonably inexpensive. Incidence studies, on the other hand, involve an initial prevalence study in order to identify established cases, which are then excluded from the subsequent follow-up; but this may not take place until several years later and therefore involves the costly process of keeping the population under review. (Incidence studies, based on documentary data, in which the initial examinations and/or follow-up have been carried out at some time in the past, are possible, and may reduce the problems and cost of keeping a check on the population; but the investigator is not usually in a position, as he is with on-going clinical studies, to decide on and to influence the kind of data collected at the initial examination. In addition, other problems concerned with defining and keeping in touch with the population may arise.)

There is always a large and stable "pool" of prevalence cases of leprosy in an endemic area. This has in the past provided an open invitation to easily available clinical material, since it was only necessary to go to a leprosy hospital in an endemic area to have the widest possible choice of all the clinical varieties of the disease for study—or, with a little more effort, to carry out a prevalence survey in the certain knowledge that it would not be long before an ample number of cases became available for further study. But in the first case patients in hospital are seldom, if ever, representative of the condition in question; in the second case the

very onset of a disease like leprosy often alters the general social and personal characteristics of those affected (i.e. the very attributes thought to be important in causation), so that what is being studied is the *results* of the disease and not (or only in a very limited sense) its *causes*. (Considerations of this sort form the standard epidemiological basis of work in, for example, ischaemic heart disease.) It follows that incidence, not prevalence, is the vital index in leprosy (as in most diseases), and more detailed reasons for this and their relevance to primary prevention are now discussed.

There are a number of reasons why modern field-study methods have so far been used to only limited purpose in leprosy, particularly where incidence is concerned. Paradoxically, however, and as is well known, the importance of epidemiology to leprosy was clearly recognized as long ago as 1933 by Doull *et al.* (1942) who clearly differentiated prevalence from incidence and discussed the advantages and disadvantages of these two indices in a way that, in the area of epidemiology, placed this group far ahead of workers, not only in leprosy, but in almost every other field. The subsequent history of this group's field studies, which will be discussed, high-lighted many of the difficulties the leprosy epidemiologist faces.

Importance of Incidence Studies

Leprosy is a chronic disease, though acute events such as reactions and certain types of neurological involvement frequently occur. It is also a disease of multiple aetiology in the sense that while exposure to the bacillus is a necessary cause, it is by no means sufficient for clinical infection; in highly endemic areas with a prevalence of 3% or more, and in spite of the fact that members of the indigenous population must be more or less exposed throughout their whole lives, vastly more do *not* develop clinical disease than *do*. Even of those living in families with a leprosy patient (lepromatous or otherwise), while running a higher risk than those in unaffected families, only a few develop clinical disease (Guinto *et al.*, 1954). Clearly, many other factors such as age, sex, ethnic group, socio-economic conditions and immunological status are involved in the development of leprosy. Finally, leprosy obviously has a prodromal pathological stage preceding its (usually rather gradual) clinical appearance, and definitions of onset therefore present a problem.

In these respects—i.e. chronicity, "multiple aetiology", difficulties of definition of onset, and long prodromal pathological phases—leprosy closely resembles many of the developed world's *non*-communicable diseases, notably ischaemic heart disease (which may even—we do not yet know—have a necessary but not sufficient "cause"). There can be little doubt that our (by now) quite considerable knowledge of the causes of the chronic non-communicable diseases has come chiefly from epidemiological studies, and, in particular, incidence studies. The great contribution of the epidemiological method to investigation of these diseases has arisen chiefly from the fact that it fulfils three functions, namely: (1) the study of *whole* populations, permitting useful comparisons between affected and unaffected groups; (2) epidemiology is the only discipline that can assimilate, process and analyse data that have been collected simultaneously on a very diverse range of variables—medical, social, demographic —that are thought to be of importance; and (3) the method has been well adapted, from the days when infectious diseases were its main concern, to deal

with long-term situations. Diversity of the data that need to be considered, and the importance of long-term study are, of course, two outstanding features of leprosy.

The methods that have been most fruitful in the chronic non-communicable diseases have been those of identifying likely aetiological *risk factors* that characterize *high risk groups,* i.e. particular groups within a defined population who show these risk factors. For example, the risk factors of raised blood pressure and plasma cholesterol level have been used to define a high-risk group of men whose individual chances of developing ischaemic heart disease within 5 years are, at 1 in 7, five times higher than the group in which neither of these risk factors is present (Morris *et al.,* 1966). In other words, the very real possibility of *predicting* the onset of ischaemic heart disease exists, with the obvious implications that this has for prevention; similarly, there is every reason to believe that the same approach would be valuable in leprosy.

These methods of prediction depend on two fundamentals: (1) the studies on which they are based must be incidence studies in which, as already indicated, information on variables thought to have an aetiological rôle is collected *before* the onset of the disease; and (2) that methods of analysis must be used which can indicate the contribution to prediction of each variable, independently of its *association* with the others. For example, living in a household where there is leprosy and a low socio-economic status are both thought to be important in determining the onset of new cases of leprosy. But do both these factors influence onset in their own right, or is it merely that they are often associated with one another, that is, that living in a leprosy household tends also to go with a low socio-economic position? A *multivariate technique of analysis* will give a weighting to each of these factors, so that the importance of each can be identified independently of its possible association with the other (or with others, if the example is made more complex and 10 or 12 variables are included). These methods of analysis enable, often for the first time, valid discussion of the possible separate causes of a chronic disease of multiple aetiology; in practice they usually demand access to computers.

In view of the general, but relevant, similarities between leprosy and certain chronic non-communicable diseases, there is really no doubt that incidence studies of leprosy that satisfy certain criteria (to be discussed) could reveal a great deal in the way of transmission and causation, and also indicate the priorities for preventive measures more clearly and objectively. Indeed, on the question of prevention, it is essential that high-risk groups be identified precisely before mass BCG and DDS prophylactic measures (Russell *et al.,* 1964; Wardekar, 1967; Brown *et al.,* 1968; Bechelli *et al.,* 1970) make it too difficult to do so.

Experience of Previous Incidence Studies

The reports from Cordova and Talisay, Cebu province, in the Philippines, provide the largest body of data from studies from a single source specifically set up to determine incidence (Doull *et al.,* 1942; Guinto *et al.,* 1954). This series began in 1933, when the first group of a defined population of 21,000 people was initially examined, and its prevalence cases identified (and excluded from further follow-up). The population was followed up at intervals until 1951, with a *mean* follow-up interval of about 15 years, when 275 *new* cases of leprosy (68

lepromatous and 207 non-lepromatous) had been identified, an annual incidence of only 0.09% for all types of the disease and of 0.03% for lepromatous leprosy. The final results were studied in relation to the variables initially recorded (which, systematically and comprehensively, were confined to age, sex and household exposure). The main finding was a confirmation that living in a household which included a leprosy patient (especially one with lepromatous disease) appears to increase the individual's chance of developing leprosy himself.

However, these studies drew attention to several serious problems. First, both prevalence and incidence cases (particularly the latter) were identified, it seems, by a mixture of physical examination and verbal recall, the relative importance of each method depending on which members of a family were available when the team called at any household. A physical examination for leprosy at a particular point in time—and leaving aside problems of observer variability and validity—gives information on those affected *at the time,* but not about those who may have had disease *in the past* and which had resolved and left no residual signs. Verbal recall does, theoretically, deal with the latter problem, but much depends on the informant's accuracy of diagnosis of himself and his family. In an endemic area, where fungal skin infections and other conditions requiring differential diagnoses occur, where taboos and prejudices about leprosy may be strong, and where spontaneous remissions and relapses are frequent, it is obviously too much to expect an (often) illiterate population to give valid answers.

It is not entirely clear from the published material, but it appears that in carrying out follow-up surveys the Philippines group relied more on physical examinations (versus verbal recall) than they had done at the initial examination. If this is so, it might partly explain the apparent (but possibly spurious) fall in incidence noted over the 15-year follow-up period. It seems likely that, at the first survey, many people reporting past disorders (especially of the skin) might have been diagnosed, on little evidence, as having had leprosy whereas the physical examination at the second survey would have provided an opportunity of making a more accurate differential diagnosis, and of excluding fungal infections, psoriasis, and other diseases sometimes mistaken for leprosy. Another reason for the possibly spurious fall in incidence is discussed later.

However, the mixing of verbal recall and physical examination, without applying one method uniformly, does emphasize a fundamental problem of all field studies (especially prevalence studies), namely, that of identifying those who have had acute, or relatively acute events, such as, in the case of leprosy, a hypopigmented patch that comes and goes (or is cured) in the interval between a first examination and subsequent follow-up, i.e. the "evanescent" cases. Obviously, a study that misses these is at fault, and ways of dealing with the problem are also discussed later.

There have been very few other *formal* studies of the incidence of leprosy. Some incidence rates, obtained chiefly from studies which have primarily been set up as "control" projects (again, in the sense of secondary prevention) or as prophylactic trials of BCG and DDS are shown in Table 1.

(Not included in the group of prophylactic trials are the studies of prevention by BCG in Uganda (Brown *et al.,* 1968) and by DDS in South India (Dharmendra *et al.,* 1965) as these were carried out on contacts of leprosy patients, i.e. high risk groups, and as such can give only limited incidence data referable to a whole population.)

In Table 1, studies no. 2 (New Guinea) and no. 3 (Nigeria) are based on small

populations and rather small numbers of new cases; the incidence rates may therefore well be subject to considerable random variation. The rates in studies 4 (Tanzania), 5 (North India), and 9 (South India) are estimates, as either the exact duration of follow-up is not stated or the exact numbers of new cases arising in a given period are not precisely known or clearly stated.

The main feature of these studies is that incidence rates are *very low,* though prevalence rates are high (the latter being the main index, according to present usage, of endemicity). If only lepromatous disease is considered, incidence rates are, of course, much lower.

It is important that one implication of the large numerical difference between the prevalence and the incidence of leprosy be realized in planning for primary prevention or for control, and that is that the temptation to make plans on the basis of much easily available prevalence data must give way to the difficulties of obtaining the much scarcer incidence data. The high prevalence of leprosy is mainly due to the fact that, unlike ischaemic heart disease for example, leprosy is rarely fatal, and that cure, when it takes place, does so very slowly. Thus, the prevalence "pool" once established (and this process is, of course, well described by Wade and Ledowsky (1952) for the island of Nauru), remains large, although the incidence "inlet" is small, because the "outflow" of cases due to death and cure is also small. Leprosy, in fact, is a "static" disease in the sense that very little occurs to disturb the basic composition and stability of the large prevalence "pool". (This situation can be contrasted with a "dynamic" disease like, for example, cancer of the bronchus, where the prevalence "pool" is always small and where death removes cases from it almost as quickly as incidence adds them.) Low incidence may of course be the result of incomplete case-finding, but in most of the studies cited in Table 1 it is most unlikely, as the published material makes clear, that this has occurred to any significant extent. But even if 25% of actual cases were missed, incidence rates would obviously still be very low.

Another important distinction made by considering incidence rather than prevalence is that between the relative load of lepromatous and non-lepromatous disease. Though there are, of course, wide geographical variations, most sources suggest that in a group of leprosy patients the proportion of those with lepromatous disease (i.e. on a *prevalence* basis) is about 25 to 35% of the total. Table 1, however, indicates that only 7% or so of new (i.e. *incidence*) cases are lepromatous. Lepromatous leprosy, in other words, is a *rare* disease in the sense that it develops in only a very small proportion of those who contract leprosy, of whatever type. It is *over*-represented in prevalence figures because its course is so prolonged and because cure is both slow and uncertain compared with tuberculoid disease. This fact only emerges, however, from incidence studies.

Low incidence automatically requires large study populations. Clearly, it is desirable that a study of the incidence of leprosy should, in the follow-up period, produce a sufficiently large number of new cases for meaningful analysis of the least frequently occurring form of the disease. Assuming the need to relate the incidence of each form of leprosy to *at least* sex, 3 different age groups, and the presence or absence of household exposure, and if there are to be 5 new cases in each of the 12 cells of this analysis, then ideally 60 new cases of the least frequent form of the disease (whether this is lepromatous, indeterminate, or purely neural) will be needed. Some studies do satisfy this objective (which is meant to suggest an order of magnitude only, not to be a definitive target) in terms of lepromatous and non-lepromatous disease. But in study 3 of Table 1, Davey (1957) found

TABLE 1

Prevalence (rate %) and incidence (annual rate %) of all types and of lepromatous leprosy summarized from different reported studies

Study no.	Country	Date (approx.)	Population	Prevalence: all types*	Incidence:	
					all types*	lepromatous
1.	Philippines (Guinto *et al.*, 1954)	1933-51	21,791	1.9	0.09	0.03
2.	New Guinea (Russell *et al.*, 1968)	1962-68	5063	6.0	0.60	N.S.†
3.	Nigeria (Davey, 1957)	1941-55	3057	12.1	0.66	0.02
4.	Tanzania (Wheate, 1969)	1961-68	12,231,000 (approx.)	1.8	0.08	N.S.†
5.	North India (Lowe *et al.*, 1941)	1936-41	9561	4.4	0.15	0.03
6.	South India (Wardekar, 1967)	1964-66	20,000	3.1	0.70	0.05
7.	South India (Das, 1970; personal communication)	1968	437,231	1.7	0.12	0.01
8.	South India (Vellut, 1969)	1955-68	152,858	5.7	0.22	0.01
9.	South India (Suresh *et al.*, 1969)	1963-68	484,038	2.1	0.23	0.02
10.	Burma (Bechelli *et al.*, 1970)	1964-68	12,983	3.4	0.80	N.S.†

* Includes lepromatous disease.

† N.S.: Not stated, not available, or information not yet complete.

In general, figures are for all ages; original papers should be consulted for details. Data for studies 6 and 10 are drawn from control groups in prophylactic studies based on children and young adults. For further details see text.

only 2 new cases each of borderline and purely neural leprosy, so that if adequate numbers of these types were also required, the need for studying large populations becomes even more obvious.

Related to the number of new cases is the time during which these occur. In study 1 in Table 1 the Philippines group took 15 years to collect their 275 cases. Even today, with the most modern techniques of data-processing and wide experience of keeping checks on populations, not many centres can deal adequately with the problems involved in such long-term studies, particularly in the world's developing areas. Apart from practical difficulties, such as recruiting and keeping staff, and allowing for death and population movement, a 15-year period greatly increases the possible effects of extraneous influences. For example, the war in the Pacific, occurring as it did in the middle of the follow-up period of the Philippines studies, substantially altered, as the group readily admits, the balance between lepromatous and non-lepromatous disease in the area, though the mechanism of this is not known.

It is therefore clear, on the basis of low incidence and the desirability of a manageable follow-up interval, that if a study is to have the requisite numbers of new cases, especially of lepromatous leprosy, its population must be large. To obtain 100 new cases of lepromatous disease in 5 years, where the annual incidence of this form is, say, 0.02%, a study population of 100,000 persons is needed. If, as seems likely, the incidence of indeterminate and neural leprosy is lower than this, but also demands adequate numbers, the population would have to be even larger. In any case, it seems necessary to have populations of hundreds, rather than tens, of thousands available.

Planning to Study Risk Factors

The principles so far discussed and the studies reviewed have indicated that in order to study the independent effects of several variables that may be risk factors (1) incidence studies which elicit information on many different characteristics are necessary, and (2) large populations—of the order of hundreds of thousands—should be available for study.

These *general* statements can be made in spite of obvious differences in classification and nomenclature and of the undoubtedly real geographical and racial variations that make direct comparisons between the studies shown in Table 1 difficult.

On material so far published, however, only studies 1 (Philippines) and 10 (Burma) of Table 1 provide prospective information, over and above actual incidence rates, on more than one variable such as age, sex and household exposure (study 6 gives some rates by age). A study that is to provide material for defining risk factors and high-risk groups must collect systematic information on as many items as its organization can usefully manage and which are believed to be of aetiological importance. Age, sex, marital status, household exposure to leprosy, educational attainment, occupation, family size, some index of overcrowding, details of eating and sleeping habits and of important religious and cultural attributes are the kind of personal, social, and economic information that may be relevant and can usually be elicited fairly readily and comprehensively during an initial *ad hoc* census. Whether medical information such as the presence or absence of other disease, e.g. tuberculosis, or from skin testing, can also be gathered depends on the study's resources.

There are three main problems which arise from the studies reviewed in Table 1 that are particularly important. The first concerns the handling of "suspicious" or uncertain cases of leprosy discovered at the initial prevalence study. These should probably be considered as "definite" cases, and excluded from further study. Studies 1, 3, 5 and possibly 9 in Table 1 all describe falls in incidence rates with time that are quite likely to have been spurious. This was because "suspicious" and "doubtful" cases at the initial surveys were, for operational purposes, classed as *not* being cases of leprosy. These patients were then included in the follow-up; clearly many of them really did have leprosy when first seen and this became certain within a fairly short period. Incidence rates initially, though not so much towards the end of the follow-up period, were therefore artificially inflated, and tended to suggest that incidence was declining with time. Later observations, however, have not confirmed such a decline (Lechat, 1969; Vellut, 1969).

A second specific point of organization concerns methods of case-finding; the same method should be used at both the initial and follow-up examinations, and the reasons for this have already been touched on. A physical examination by a doctor or a para-medical worker (and in the latter case, confirmation of all suspect cases by a doctor) is preferable to verbal recall on the part of the patient. This is certainly true, without any qualification, for the follow-up examination. At the initial examination, the physical findings may need to be supplemented (but not replaced) by some questioning to elicit a history of episodes of prior spontaneous remission or cure, without residual signs, of earlier lesions; but the interpretation of these answers should be very cautious, and should be related to the cultural and educational status of the group studied. In fact, the only sure way completely to eliminate the need for verbal recall by individuals or their relatives at the prevalence survey would be to base a study on babies initially examined at birth, and then followed-up. But such a study would be impracticable on the grounds of the very long follow-up periods needed.

The third point arises over the need not to miss new, but short-lived, spontaneously healing or "evanescent" cases that might come and go between the initial and follow-up surveys; these may form an important part of the spectrum of clinical leprosy. Related to this, it is also obviously desirable to know the form in which new cases *first* occurred; for example, if a certain proportion of indeterminate cases later become lepromatous it is clearly much more valuable to detect these cases in their early indeterminate form and then to know that they alter, than simply to find them when they have settled into an unequivocally lepromatous form, with no knowledge that they started off otherwise. There are two main ways of dealing with these problems. The first (and in theory the best) is to follow-up the whole population by frequent examinations at, say, 6- or 12-monthly intervals, so that early lesions are more likely to be found; but this method involves a tremendous amount of work for the follow-up team, and few centres could provide the necessary facilities. The second method, if the *whole* population cannot be re-surveyed at short intervals, is to concentrate resources on following up a fairly large part of it after 6 or 9 months (depending on how long the most short-lived "evanescent" case is thought to last). The absolute number of "evanescent" cases likely to be found *at any particular point in time* is not likely to vary very much. At 6 or 9 months after an initial survey, this number can be related to a defined part of the total population, and it is likely that it represents all, or most, of the "evanescent" cases that have newly developed *in that particular group.* After a 5-year follow-up interval, however, the *same* number of

cases cannot be used to calculate the incidence of "evanescent" disease, nor related to the whole population, as an unknown number of such cases will have occurred and resolved in individuals who can no longer be identified.

Discussion

There would naturally be many problems in setting up incidence studies to define risk factors and high-risk groups. "Control" in terms of primary prevention does, however, depend on this kind of approach, and there is a growing number of centres where it could already usefully be studied in this way, as is evidenced by most of the studies shown in Table 1 and by the increasing number of large-scale approaches organized by, for example, the World Health Organization (Bechelli *et al.*, 1966, 1970), which has also actively encouraged the interest of epidemiologists who are not primarily engaged in the leprosy field (Newell, 1966). The need for large study populations can be helped by considering joint studies at several different centres, and by workers in leprosy collaborating with those interested in other diseases—an approach which may also make it easier financially, as well as offering the chance to collect additional, relevant medical data. Besides information on incidence and risk, studies of the sort suggested could contribute to knowledge of transmission, and could form a basis for studies of space- and time-clustering, which have proved themselves useful in other fields (Knox, 1963; Pike *et al.*, 1967).

It is important that a scientifically established basis for "control", i.e. primary prevention, be established in terms of risk factors and high-risk groups, *before* wide-scale prophylaxis has been introduced with the consequent inevitable distortion of the natural history of the disease. Most centres that could undertake the necessary studies already have "control" programmes in progress, aimed at early diagnosis and treatment of established cases, i.e. secondary prevention (and provision of a service, whether the main approach be primary or secondary prevention, is of course, mandatory). But the use of DDS in these programmes for *therapeutic* purposes has its main effect on the very large prevalence "pool". It is true that treating established cases may, by reducing the numbers of those who are bacteriologically positive, have an effect on the supply of new cases, but this effect is likely to be slow and small in an endemic area with a large prevalence "pool". This therapeutic effect will in any case be far less than interfering directly with the "in-flow" of new cases which, as demonstrated, is so small that any reasonably effective prophylactic measure, bearing as it does directly on incidence, will probably have far-reaching effects, certainly in statistical terms. Obviously both prophylactic and observational studies are needed at the present time, but any one centre can probably deal with only one of these approaches. Much patience and a careful weighing up of ethical considerations are necessary, but we need to know far more about the aetiology and transmission of leprosy, and about which are the high-risk groups, before we can risk spoiling the opportunities for further important observational studies.

Finally, there could be important subsidiary benefits of a clinical and service nature from studies of the kind suggested. First, population-based data of interest to the physician, surgeon, physiotherapist, bacteriologist and others, might become available. It would not be difficult or very costly, once the initial data were on magnetic tape, to extend them in time and in scope and to add additional clinical, social, and pathological data, if not on the whole population, certainly on

selected and intensively studied parts of it. In other words, the way would be open for workers in disciplines other than epidemiology, and with different interests, to base their research on defined populations, thus adding substantially to the meaning and interpretation of their results. *Ad hoc* studies of almost any kind—clinical, social, or immunological—would be greatly assisted by the availability of defined groups or samples and the information already stored about them. Secondly, the whole question of assessing the value of "control" programmes, and of evaluating what, if anything, they are achieving would be greatly facilitated.

Summary and Conclusions

Leprosy "control" must become increasingly concerned with *primary prevention* (that is, the prevention of disease in those hitherto unaffected). *Secondary prevention,* or the detection and early treatment of established cases must naturally continue as a service, but is unlikely to contribute much towards the ultimate eradication of leprosy.

Primary prevention depends on being able to predict, more precisely than at present, "high-risk groups", towards which prophylactic measures can be especially directed. The ability to predict will come only through incidence (rather than prevalence) studies, which will be concerned with a much wider range of social, economic, demographic and medical variables than has so far been attempted. Multivariate techniques of analysis should be available. There is every reason to believe, from analogies with the epidemiological study of chronic non-communicable disease, that this approach would be fruitful in the leprosy field.

The incidence of leprosy is very low; lepromatous leprosy, in particular, should be regarded (on an incidence basis) as a rare disease. Large study populations (of the order of hundreds of thousands) are ideally needed for epidemiological studies of leprosy; work to date indicates that the obstacles to surveys on this scale are not insuperable.

Three particularly important methodological problems—namely uniformity of case-finding methods, the handling of "suspicious" cases, and the detection of "evanescent" cases—need especial consideration.

"High risk group" studies should be undertaken before the possible widespread introduction of prophylactic measures makes it difficult to carry them out properly.

Useful subsidiary benefits to clinical, pathological and social studies of leprosy would arise from the epidemiological approach discussed.

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An Internally-controlled Double Blind Trial of Thalidomide in Severe Erythema Nodosum Leprosum*

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A double-blind, internally-controlled, clinical trial of thalidomide in severe, chronic, histologically-proven erythema nodosum leprosum (ENL) is reported. A total of 10 adult male patients were admitted to the trial, all of whom were receiving continuous treatment with steroids and whose minimum daily requirement just to suppress the reaction was in no case less than 15 mg of prednisolone or 18 international units of corticotrophin. The trial was divided into 4 equal parts (of either 4 or 6 weeks' duration) consisting of an initial control period, first and second trial periods, and a final control period. Throughout the trial all patients received DDS, 100 mg twice weekly; thalidomide, 300 mg daily, was given during one trial period and identical placebo tablets during the other. As judged by the reduction in their steroid requirements, 9 of the 10 patients showed a very significant improvement while they were receiving thalidomide, although 7 subsequently relapsed after stopping the drug. There was no dose-for-dose relationship between thalidomide and prednisolone. Two patients developed a mild allergic dermatitis.

Introduction

Since the discovery by Sheskin (1965*a, b, c*) that thalidomide has a beneficial effect on lepromatous lepra reactions, a number of communications have been published confirming the value of the drug in suppressing erythema nodosum leprosum (ENL). However, with the notable exception of the series reported by Sheskin and his colleagues (Sheskin, 1965*a, b*; Sheskin and Convit, 1966, 1969; Sheskin and Sagher, 1968) most of the studies have been uncontrolled.

In South-east Asia ENL is particularly common, developing in more than 50% of lepromatous patients within a year of their beginning anti-leprosy treatment (Waters *et al.*, 1967); frequently the reactions are severe. Therefore it was considered important to assess more precisely, by means of an internally-controlled double-blind trial, the effect of thalidomide in patients with well-defined lepromatous leprosy, suffering from severe, histologically-proven ENL. Only those patients whose reactions required at least 15 mg of prednisolone

* A brief account of this trial was presented at the Ninth International Leprosy Congress, London (Waters, 1968).

† Request for reprints should be sent to this address.

or 18 international units (IU) of corticotrophin (ACTH) daily for control of symptoms were admitted to the trial. Additional objectives included an assessment of the rate at which steroid dosage could be reduced in such patients after the introduction of thalidomide treatment, and whether in ENL there was any dose-for-dose relationship between steroids and thalidomide.

After this study was initiated, a second double-blind trial was carried out of the effect of thalidomide on less severe ENL; the results were earlier reported by Pearson and Vedagiri (1969).

Materials and Methods

INTAKE AND PRELIMINARY INVESTIGATIONS

Ten adult male patients aged 19 to 56 were admitted to the trial (Table 1). Post-menopausal females were also considered suitable, but none were available at the time of intake; of the 10 patients 6 were ethnically Chinese, 2 Malay and 2 Southern Indian. Clinically, all were lepromatous; histopathologically, 5 were pure lepromatous (LL) and 5 were indefinite lepromatous (LI) (Ridley and Jopling, 1966; Ridley and Waters, 1969). All were suffering from histologically confirmed, moderately severe or severe chronic ENL, 2 patients being graded ++++, 7 +++ and 1 ++/+++ (Waters, 1963). All required treatment with steroids, the average daily dose (9 patients) being 28 mg prednisolone (range 15 to 52.5 mg); 1 patient (no. 8), probably the mildest case of the 10, was receiving corticotrophin in an average dose of 20 IU daily. The duration of the ENL at time of intake varied from 9 months to 3½ years; that of steroid therapy averaged 12 months (range 1 to 23 months). All the patients were receiving dapsone (DDS) in various doses; the duration of anti-leprosy treatment ranged from 1 year 8 months to 3 years 10 months. Details of the cases are presented in Table 1.

Each patient was admitted to the Leprosy Research Unit wards, and spent the period of the trial in hospital. Pre-trial investigations included complete clinical examination, urine testing, X-ray of chest (unless performed within the previous 6 months), weight of patient, haemoglobin estimation, and white blood cell and differential cell counts. At the clinical examination, both the state of the lepromatous leprosy and the nature and distribution of the ENL lesions were noted, and colour photographs were taken. Unless previous reports were available, skin biopsies were performed to confirm the type of leprosy, and also that the reaction was indeed ENL. Smears were taken from both ears and from 4 skin sites, and the Bacteriological Index (BI), using Ridley's logarithmic scale, and the Morphological Index (MI) (Waters *et al.*, 1967) were determined. Intradermal tests were performed with lepromin (Wade-Mitsuda type) and tuberculin (1 TU of RT 23), unless they had previously been carried out within 6 months of admission to the trial.

THERAPY

All patients were standardized on 100 mg of DDS twice weekly by mouth, and this dose was left unchanged throughout the trial. In addition, all received either prednisolone (9 patients) or corticotrophin (1 patient) in daily doses designed to be just sufficient to suppress the reaction. Each patient was seen daily (except on Sundays) by the author, and the minimum dose of steroid was prescribed which it was estimated would control fever and reduce the number and frequency of ENL lesions to acceptable levels. In general, worsening of the symptoms was treated by

TABLE 1

Clinical details of the 10 patients admitted to the trial

Patient no.	Age	Race[a]	Classification of leprosy[b]	Smears		Severity of ENL[e]	Duration (months) of		
				BI[c]	MI[d]		Leprosy treatment	ENL	Continuous steroid treatment
1	34	C	LI	4.3	0	+++	46	42	15
2	51	C	LL	3.3	0	+++	30	25	15
3	32	M	LI	4.3	0	++++	23	9	9
4	21	C	LL	4.2	0	+++	22	20	9
5	27	C	LI	3.2	0	+++	38	33	15
6	19	M	LL	4.7	0	++++	30	26	23
7	44	I	LL	3.5	0	+++	44	27	14
8	56	C	LI	4.0	0	++/+++	26	18	14
9	51	C	LI	5.0	1	+++	20	17	2
10	28	I	LL	4.2	0	+++	24[f]	26[f]	1

[a] C = Chinese; I = Indian; M = Malay.

[b] LL = Pure lepromatous; LI = Indefinite lepromatous (Ridley and Jopling, 1966; Ridley and Waters, 1969).

[c] Bacteriological Index (Ridley's logarithmic scale).

[d] Morphological Index.

[e] Graded according to Waters (1963).

[f] This patient was treated for leprosy from 1952 to 1957; data of relapse uncertain, as are treatment details between 1957 and 1966.

raising the daily dose of prednisolone, but this was sometimes supplemented by giving one or a small number of corticotrophin injections. Whenever symptoms improved, the dose of steroid was reduced.

Thalidomide was supplied in 100-mg tablets, coded "B". Placebo tablets of identical appearance were labelled "A". The code was not revealed to anyone in Malaysia until after the trial was completed. During the appropriate periods of the trial (*vide infra*) either 1 thalidomide or 1 placebo tablet was given 3 times daily. All tablets were taken in the presence of nursing staff.

Stibophen was not given to the trial patients (unless they were receiving neither steroids nor thalidomide). Mild analgesic drugs such as aspirin and paracetamol were freely prescribed when symptomatically indicated.

ORGANIZATION OF THE TRIAL

(a) *First series.* Sixteen weeks schedule. The trial was designed to consist of 4 separate but continuous treatment periods of 4 weeks each, as follows:

Period 1. Weeks 1-4.	First control period, no added treatment.
Period 2. Weeks 5-8.	First trial period; tablet "A" or "B" given 3 times daily.
Period 3. Weeks 9-12.	Second trial period; tablet "B" or "A" given daily (reverse of Period 2).
Period 4. Weeks 13-16.	Final control period; no added treatment.

A series of sealed envelopes was prepared, containing the letter "A" or the letter "B" by random distribution. The decision whether a patient received tablet "A" or "B" throughout Period 2 (and vice versa in Period 3) was made according to the letter given in the next envelope in the series. The envelope was opened by the Leprosy Research Unit worker not running the trial, and he and the Unit Secretary dispensed the appropriate tablets, a week's supply at a time, to the ward in a bottle labelled only with the patient's name, number, and study number. At no time throughout the trial did the doctor-in-charge know who was receiving tablets "A" or "B", and the nursing staff and patients were not aware that 2 different tablets were being used.

(b) *Second series.* Twenty-four weeks schedule. Patients nos. 1 to 9 were all admitted to the 16-week trial schedule. However, after the intake of patient no. 9 it was realized, from a sequential analysis of the results, that the prednisolone requirements of patients receiving the active (presumed thalidomide) preparations were still falling at the end of the 4-week period and had not reached a base-line level. Therefore a second study, similar to the first study but consisting of 4 consecutive 6-week periods was devised as follows:

Period 1. Weeks 1-6.	First control period.
Period 2. Weeks 7-12.	First trial period.
Period 3. Weeks 13-18.	Second trial period.
Period 4. Weeks 19-24.	Final control period.

Patient no. 10 was entered for the 24-week trial only; in addition, patients nos. 1 to 7, who had completed the first trial schedule, were admitted to the second, 24-week, schedule. Once again, random selection was used to decide whether tablet "A" or "B" was given first. Patient no. 8 was omitted because by the end of the 16-week schedule, his ENL had so improved that he no longer satisfied the admission criteria. Patient no. 9 was also omitted, in this case because his ENL

had been so variable and unstable that his prednisolone requirements showed wide fluctuations during the 16-week trial; furthermore, for social reasons he wished to be discharged from hospital.

The same personnel were responsible for the second schedule as for the first, the same investigations and assessments were carried out, and the same methods of analysis were used in both studies.

INVESTIGATIONS AND ASSESSMENTS DURING THE TRIAL

The temperature of each patient was taken routinely, 5 times daily. The severity of each patient's reaction was noted daily (except Sundays) by the author. At the end of each week a summary of the week's clinical findings was made, together with an overall assessment of the severity of each patient's ENL. Full leprosy examinations were carried out at the end of each 4- or 6-week trial period, and complete clinical examination at the end of the trial schedule.

Patients were weighed every week. Haemoglobin estimation and white blood cell and differential counts were normally performed fortnightly. Urines were checked weekly for albumin, and laboratory urinalysis was carried out every 4 weeks.

ANALYSES

The analyses compare the 4 treatment periods in each patient. In both schedules, there were 2 effective control periods (the first and either the second or the fourth); thalidomide was given during either the second or the third period, and the subsequent period (either third or fourth) demonstrated the speed at which the effects of the drug subsided after its withdrawal. The assessments were made on the total dose of steroid prescribed, the temperature, the clinical condition, and the white blood cell count.

The principal assessment was based on the total dosage of steroids prescribed per week in each period; for uniformity of presentation, this has been expressed in mg of prednisolone. Aqueous corticotrophin, given in small supplemental doses to patients receiving oral prednisolone, has been converted in the analysis at the arbitrary rate of 2 IU of corticotrophin to 1 mg of prednisolone. Prednisolone given by injection has been scored, milligram for milligram, as equivalent to oral prednisolone; hydrocortisone given by injection has been scored on the basis that 5 mg of the drug was equivalent to 1 mg of prednisolone, and 1 mg of betamethasone was considered as equivalent to 8 mg of prednisolone (these 3 drugs were all given to patient no. 1 during a very severe exacerbation of his ENL). For the one patient (no. 8) who received corticotrophin only, dosage is expressed in international units of corticotrophin and no notational conversion to prednisolone has been attempted.

The highest temperature recorded each day for each patient was scored as follows:

Temperature below	99° F (37.2° C)	= 0
Temperature from	99 to 99.8° F (37.2 to 37.7° C)	= 1 point
	100 to 100.8° F (37.8 to 38.2° C)	= 2 points
	101 to 101.8° F (38.3 to 38.8° C)	= 3 points
	102 to 102.8° F (38.9 to 39.3° C)	= 4 points
	103 to 103.8° F (39.4 to 39.9° C)	= 5 points
	104° F (40° C) and over	= 6 points

Daily temperature points were added together to give weekly aggregate scores.

The weekly assessment of the severity of each patient's ENL could not be graded according to our previous scale (Waters, 1963), as this was dependent on steroid dosage unmodified by other drugs. Therefore, in this trial the severity of the ENL was scored according to the following criteria:

Grade 0: no new ENL lesions; no evidence of active reaction or neuritis.
Grade 1: very mild; relatively sparse, scattered ENL papules; temperature below 99° F (37.2° C).
Grade 2: mild ENL; fairly numerous but discrete ENL papules occasional mild fever.
Grade 3: moderate ENL; widespread ENL papules; moderate general malaise, with fever to approximately 102° F (38.9° C); alternatively, pustular or necrotic ENL with little or no fever.
Grade 4: severe ENL; widespread ENL papules, which may be necrotic or pustular, associated with marked general malaise and high fever to approximately 103° F (39.4° C).
Grade 5: extremely severe ENL, very ill patient with continuous high fever over 103° F (39.4° C); necrotic or pustular ENL, often with coalescing lesions; very severe malaise and prostration.

Although subjective, these assessments were all made by the same worker, and it was possible to achieve consistent and uniform scoring.

The total white blood cell counts were not scored, but the actual figures were examined to see if they bore any obvious relationship to the giving of thalidomide.

Results

SIXTEEN-WEEK STUDY

Steroid requirements. The weekly steroid requirements for all 9 patients admitted to the 16-week schedule are shown in Table 2, and those for 1 representative patient (no. 4) are illustrated in Fig. 1. Patients nos. 2, 4, 7, 8 and 9 received thalidomide in Period 2 (weeks 5 to 8), whereas patients nos. 1, 3, 5 and 6 received the trial drug in Period 3 (weeks 9 to 12).

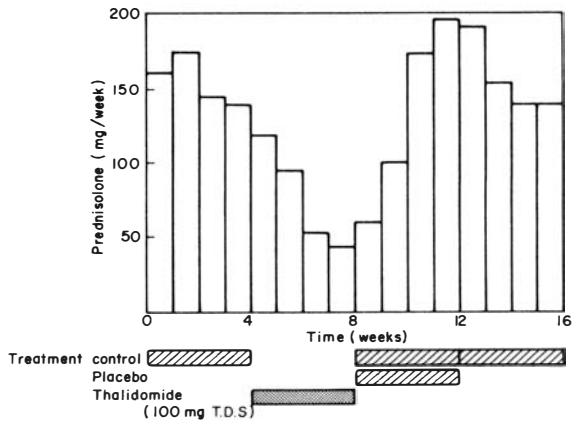

Fig. 1. Effect of thalidomide (300 mg daily for 4 weeks) on prednisolone dosage in severe chronic erythema nodosum leprosum. Double-blind trial, 16-week schedule; patient no. 4.

TABLE 2

Total weekly steroid dosage prescribed for each of the 9 patients in the 16-week trial schedule

Patient no.[a]	Total weekly steroid dosage (expressed in mg of prednisolone[b]) in trial week no.:															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
2	135	123	105	140	140	98	75	48	70	83	105	105	105	95	124	135
4	161	175	145	140	118	93	53	43	58	100	173	196	190	153	140	140
7	105	103	100	105	88	58	30	6	13	16	25	235	173	170	164	158
8	110	147	147	161	168	85	6	0	0	6	18	25	0	0	0	0
9	175	190	215	223	306	375	393	405	363	363	335	310	208	155	140	140
1	210	183	170	509	798	1073	620	660	830	605	840	650	520	843	710	860
3	390	490	400	350	325	393	485	460	395	290	200	155	153	153	171	195
5	175	190	210	175	170	118	135	268	226	125	80	33	63	98	105	183
6	175	170	176	201	200	210	210	200	160	103	98	80	100	181	194	210

[a] Patient nos. 2, 4, 7, 8 and 9 received thalidomide during weeks 5 to 8; patients nos. 1, 3, 5 and 6 during weeks 9 to 12.
[b] Patient no. 8 received only corticotrophin; his figures give total weekly corticotrophin dosage (in international units).

During Period 1 (first control period) the weekly steroid requirements of 8 of the 9 patients remained remarkably steady, not varying individually by more than 32%. In only one patient (no. 1) was a significant change observed. Towards the end of the 3rd week his ENL became much more severe, his steroid requirements rose rapidly and the skin lesions were no longer ENL papules but resembled erythema multiforme. By the beginning of the 5th week he was slightly jaundiced, grossly anaemic, and dangerously ill. Because of the deterioration from +++ to extreme ++++ ENL, his results cannot be analysed with confidence in the 16-week schedule. However, his ENL stabilized at the severe level, and he was subsequently admitted to the 24-week schedule. The control analysis may also be extended to include Period 2 (for patients nos. 3, 5 and 6) or Period 4 (for patients nos. 2, 4, 7, 8 and 9), even though some residual effect of the thalidomide is detectable in the latter period; in particular, patient no. 8 no longer required daily steroid therapy. For patients nos. 2, 3, 4, 5, 7 and 9, the greatest variation in weekly steroid requirements in the appropriate 2 periods was 56% (in patient no. 5, in whom a determined attempt to lower the daily steroid dose while he was receiving the placebo resulted in a sharp, if short-lived, exacerbation of his ENL).

When the steroid requirements for these 8 patients (i.e. omitting patient no. 1) are analysed for the whole 16 weeks, it is seen that 7 made a dramatic response to thalidomide. All except patient no. 9 showed a progressive fall in steroid dosage while receiving the trial drug, although in only 2 cases (patients 7 and 8) was it possible completely to stop prednisolone and/or corticotrophin before the end of the thalidomide period. Table 3 compares the average weekly dose of steroid prescribed during the 4 weeks immediately preceding treatment with thalidomide, with the total steroid prescribed in the 4th (final) thalidomide week. With the exception of patient no. 9 the steroid requirements fell by more than 60%, and the dosage prescribed in the 4th thalidomide week was very significantly less than the lowest weekly steroid total during the preceding period. Patient no. 9,

TABLE 3

Sixteen-week schedule: average weekly steroid dosage in the 4 weeks preceding thalidomide therapy compared with total steroid dosage prescribed in the 4th week on thalidomide

Patient no.	Average weekly steroid dosage[a] in the 4 weeks preceding thalidomide therapy[b]	Total steroid dosage[a] prescribed in the 4th week after commencing thalidomide[c]	Percentage fall in steroid requirements
1	788	650	18
2	126	49	61
3	416	155	63
4	155	43	72
5	173	33	81
6	205	80	61
7	103	6	94
8	141	0	100
9	201	405	−101

[a] Steroid dosage expressed in mg of prednisolone, except for patient no. 8 which is given in international units of corticotrophin.

[b] Weeks 5 to 8 for patients 1, 3, 5 and 6; weeks 1 to 4 for patients 2, 4, 7, 8 and 9.

[c] Week 12 for patients 1, 3, 5 and 6; week 8 for patients 2, 4, 7, 8 and 9.

however, showed a marked increase in steroid requirement throughout Periods 2 and 3; at the same time his ENL increased in severity from +++ to ++++, with ulceration of skin lesions and liquefaction of axillary lymph nodes; but he began to improve again from week 11 onwards, and Period 4 closely resembled Period 1.

When thalidomide was stopped at the end of the appropriate period, 6 of the 7 patients who had responded to the drug relapsed significantly and for a time required steadily increasing doses of steroid. However, the precise pattern of relapse varied. Some patients, e.g. nos. 4 and 7, after 3 weeks off the drug temporarily required steroids in excess of the Period 1 dosage, whereas Patients 2 and 3 were still well below their control-period prednisolone dosage 4 weeks after stopping thalidomide. Patient no. 8 had only a mild relapse, requiring no more than occasional injections of corticotrophin and his ENL stabilized at a less severe level (++ instead of ++/+++).

Other analyses. The total temperature scores (sum of the 28 daily scores) and the total clinical scores (sum of the 4 weekly-assessment scores) for each of the 4 periods are given in Table 4.

TABLE 4

Sixteen-week schedule: total temperature and clinical scores for each of the four 4-week periods

Patient no.[a]	Total temperature score[b] for period no.				Total clinical score[c] for period no.			
	1	2	3	4	1	2	3	4
2	4	3	12	6	5½	3	4½	5½
4	3	9	23	2	5	3½	5½	3½
7	1	5	26	3	4½	3½	8½	5
8	26	5	14	2	6½	2½	4½	4
9	18	31	4	5	10	12	10	7
1	32	77	24	56	8½	17	10½	13½
3	42	17	2	14	9	7½	3½	6
5	0	26	1	16	4	6½	3	5½
6	4	0	0	3	7	6	3	6½

[a] Patients nos. 2, 4, 7, 8 and 9 received thalidomide in period 2; patients 1, 3, 5 and 6 in period 3.

[b] Temperature score derived from maximum daily temperature (1 point for every degree, or part of degree Fahrenheit above 98°F).

[c] Clinical score—total of the 4 weekly clinical scores in each period.

Although the aim in the trial was to adjust the steroid dosage as rapidly as possible according to the needs of the individual patient, in practice there was usually a 24-h delay between the onset of a relapse and the raising of the prednisolone (or corticotrophin) intake. Similarly, when steroid requirements were falling, there was a slight delay in the cutting of dosage. Therefore it is not surprising that the clinical and temperature scores tended to be low in the period during which thalidomide was prescribed, and tended to be high in the subsequent period in which most patients relapsed. But these figures also reflect the greatly improved control of ENL achieved with thalidomide. The one exception was patient no. 9; even patient no. 1 improved slightly, according to these 2 assessments, while he was receiving thalidomide during Period 3.

Regular fortnightly white blood cell counts were undertaken for patients nos. 1 to 8, and the majority of results, except those for patient no. 8, showed a polymorphonuclear leukocytosis. Considerable fluctuations occurred throughout the trial, but generally the white cell counts fell while patients were receiving thalidomide. However, in only 4 patients were the lowest counts during the period of thalidomide treatment lower than the lowest recorded during the other 3 periods of the trial.

SECOND SERIES: 24-WEEK SCHEDULE

Eight patients (nos. 1 to 7 and no. 10) were admitted to the 24-week study, which for the first 7 patients began 11 weeks after they had completed the previous (16-week) schedule. On admission, 2 (nos. 1 and 3) were graded ++++, 1 (no. 6) was +++/++++, and the other 5 were graded +++. All 8 patients were given prednisolone orally as their principal steroid, all received occasional injections of corticotrophin, but at various times during the 24 weeks patient no. 1 also received prednisolone and hydrocortisone by injection and betamethasone by mouth.

Throughout the 6 weeks of Period 1 the severity of the ENL remained remarkably constant in all 8 patients, both clinically and in regard to steroid requirements. Therefore the results from all 8 have been accepted for analysis, the methods used being similar to those in the 16-week schedule. The results obtained from the 24-week study fully confirm the value of thalidomide in severe ENL.

Steroid requirements. The steroid requirements for the 8 patients admitted to the 24-week schedule are shown in Table 5, the dosage for 1 representative patient (no. 4) being illustrated in Fig. 2. Patients nos. 2, 4 and 5 received thalidomide in Period 2 (weeks 7 to 12) and patients nos. 1, 3, 6, 7 and 10 in Period 3 (weeks 13 to 18).

During Period 1 (weeks 1 to 6), no patient showed a variation in steroid requirement of more than 25%. Indeed in 4 of the 5 patients who received placebo in Period 2, the greatest variation recorded during the whole of the the first 12 weeks (Periods 1 and 2 combined) was 30%. This emphasizes the remarkable chronicity and stability of their reactions. However, patient no. 10

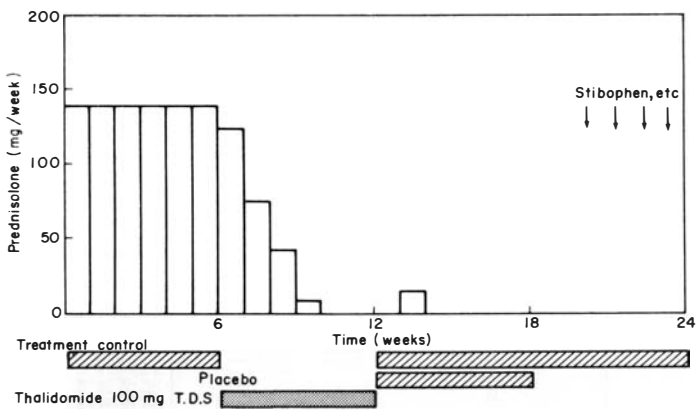

Fig. 2. Effect of thalidomide (300 mg daily for 6 weeks) on prednisolone dosage in severe, chronic erythema nodosum leprosum. Double-blind trial, 24-week schedule; patient no. 4.

TABLE 5

Total weekly steroid dosage (expressed in mg prednisolone) prescribed for each of the 8 patients in the 24-week trial schedule

Patient no.	Control period[a] before thalidomide (average weekly requirements and range)	Total weekly steroid dosage (expressed as mg prednisolone) in each trial period: Thalidomide period[b]; weekly totals for weeks 1	2	3	4	5	6	Post-thalidomide period[c] weekly totals for weeks 1	2	3	4	5	6	Final control period[d] (average weekly requirements and range)
2	154 (140-165)	130	93	84	70	50	53	95	96	105	105	105	105	110 (105-111)
4	140 (140-140)	123	75	44	8	0	0	0	13	0	0	0	0	0
5	150 (140-175)	140	78	21	0	0	0	0	0	0	0	0	0	23 (0-50)
1	1032 (970-1160	1140	690	580	598	485	365	350	485	659	1083	790[e]	400[e]	
3	305 (270-350)	280	185	138	100	66	53	53	63	123	160	[f]	—	
6	177 (173-190)	155	103	83	63	60	61	79	161	175	180	165	160	
7	144 (140-150)	110	101	105	83	44	30	19	113	140	140	200	200	
10	207 (130-255)	103	45	20	0	0	0	0	0	0	0	0	0	

[a] Patients 2, 4 and 5 = weeks 1 to 6; patients 1, 3, 6, 7, 10 = weeks 7 to 12, when they were receiving placebo.
[b] Patients 2, 4 and 5 = weeks 7 to 12; patients 1, 3, 6, 7, 10 = weeks 13 to 18.
[c] Patients 2, 4 and 5 = weeks 13 to 18, (when they received placebo); patients 1, 3, 6, 7, 10 = weeks 19 to 24.
[d] Patients 2, 4 and 5 only (weeks 19 to 24).
[e] Patient 1 recommenced thalidomide at the beginning of week 23.
[f] Withdrawn from trial at week 23 for neurosurgery.

showed a marked fall in his prednisolone dosage in weeks 11 and 12, and therefore the significance of his subsequent results must be viewed with some reserve.

During their 6 weeks on thalidomide, all 8 patients showed a dramatic fall in their prednisolone requirements (see Table 5). It proved possible to stop steroid therapy completely in 4 patients, and the requirements of 2 others (nos. 1 and 3) were still falling at the end of the 6 weeks. However, the steroid requirements of nos. 2 and 6 stabilized, albeit at a low level, after 5 and 4 weeks respectively. Moreover, the weekly steroid requirements of patient no. 1 fell by approximately 670 mg of prednisolone, whereas those of patients nos. 2 and 6 fell by only 100-120 mg. Therefore thalidomide was effective in all 8 patients (although the severity of the ENL may also have been decreasing naturally in patient no. 10), but its effectiveness, when given in a standard dose of 300 mg daily, varied from patient to patient and bore no dose-for-dose relationship with prednisolone.

After stopping thalidomide all the patients except no. 10 relapsed to a lesser or greater degree. As judged by their steroid requirements, patients nos. 2, 6 and 7 relapsed within 1 week, nos. 1, 3 and 4 during the 2nd week, but patient no. 5 not until the 9th week after ceasing thalidomide treatment.

The speed and severity of the relapse varied from patient to patient. Thus, patient no. 1, who at the end of the 6 weeks on thalidomide had become almost free of ENL, steadily deteriorated; by the end of the 4th week off the drug he was acutely ill again, and approximately 160 mg of prednisolone daily failed to control the reaction. It was therefore decided, almost as a life-saving measure, to break the trial protocol, and during weeks 23 and 24 he received the same trial tablet as he was given during Period 3. Patient no. 6 reverted to his control-period steroid requirements within 3 weeks, as also did patient no. 7. However, a week later the latter developed bilateral foot-drop and therefore his steroid dosage was again increased, this time to above his pre-thalidomide control level. Patient no. 2 stabilized after 3 weeks at a lower steroid dosage than in the control period. Patient no. 3 also appeared after 4 weeks to be stabilizing at a lower dosage; however, he had suffered from ulnar neuritis before commencing thalidomide, which recurred in week 17 (when, under thalidomide his prednisolone had been cut to only 20% of his control requirements), and again in week 19 soon after stopping thalidomide. In week 22 the neuritis became much more severe, and therefore he was withdrawn from the trial. Patients nos. 4 and 5 appeared to have relatively mild relapses, which could be controlled by stibophen, i.e. their ENL had improved from Grade +++ to Grade ++. Patient no. 4 remained unchanged throughout the remainder of the trial; however, patient no. 5 suffered from a recurrence of ulnar neuritis, and was treated with corticotrophin from weeks 21 to 24. Subsequently he underwent an ulnar fasciculotomy. Only patient no. 10 had such mild ENL (Grade +) that no further treatment with either prednisolone or corticotrophin was required throughout the remainder of the trial.

Other assessments. As in the 16-week study, the temperature and clinical assessment totals tended to be lower during the period in which thalidomide was prescibed. This was most marked with patient no. 1, in whom very severe, inadequately-controlled ENL was well controlled by the trial drug. The development or recrudescence of neuritis after stopping thalidomide in 3 of the 8 patients is especially noteworthy.

As before, the white blood cell counts were variable, but in most patients fell during thalidomide treatment and rose again once treatment with the trial drug ceased.

Toxic effects of thalidomide. The only important toxic effect was a mild allergic dermatitis which developed in 2 patients, nos. 4 and 5. The irritant rash appeared after 20 and 13 days respectively of thalidomide in the 16-week schedule; it recurred during the 24-week schedule, 9 and 2 days respectively after recommencing thalidomide treatment. Both patients developed eosinophilia. The rash was easily controlled with antihistamine drugs, and both patients considered that the improvement in their ENL resulting from thalidomide more than compensated for the slight discomfort of the sensitivity rash.

Patient no. 10 made no complaint of a rash, but perifollicular thickening of his skin was noticed while he was receiving thalidomide, and he developed a marked eosinophilia after 4½ weeks on the drug. Patients nos. 6 and 8 also suffered from transient rashes and eosinophilia while receiving thalidomide, but these were not undoubtedly related to the drug.

One patient complained of constipation and 2 of giddiness (although in 1 of the latter cases this was quite clearly unrelated to thalidomide). Interestingly enough, no patient complained of sleepiness during the 16-week schedule; however, 2 immediately complained of being sleepy within 24 h of recommencing the drug at the beginning of the appropriate periods in the 24-week schedule. The urine tests gave no evidence of any toxic effect on the kidney.

Discussion

There have been all too few controlled clinical drug trials of the treatment of established erythema nodosum leprosum (ENL). This is partly due to the difficulty in designing such trials; in many patients, ENL is either episodic or else it varies considerably in severity over short periods of time. However, it has been realized for a number of years that severe, chronic, steroid-treated ENL may remain remarkably constant in severity, and that the individual steroid dosage required just to suppress the symptoms of ENL may change only marginally over a period of many months. Recently 2 careful studies have been published (Pettit, 1967; Hastings and Trautman, 1968) in which this observation was used in the assessment of the effectiveness of clofazimine (B 663, Lamprene) in the treatment of ENL, and one of these was internally controlled, i.e. each patient acted as his own control. But as clofazimine discolours the skin and urine, a "double-blind" design could not readily be used. In the trial now reported, a complete double-blind design was introduced. Indeed the clinician in charge of the patients, who was responsible for prescribing the daily steroid dosage, was not even aware who was receiving tablet "A" (the placebo) or tablet "B" (the trial drug). Only the time of change-over from one tablet to the other was known, but it is doubtful if this produced any significant bias.

The results emphasize how essential careful patient-selection is. Thus, patient no. 9, although he had suffered from ENL for 17 months, had received continuous steroid therapy only for the 2 months before starting the trial. It was found that he was undergoing rapid and large changes in his steroid requirements, and in subsequent follow-up, extending over 2 years, the severity of his ENL has repeatedly waxed and waned. Therefore it is not surprising that he failed to show any improvement while receiving thalidomide. This experience suggests that patients must have been on continuous steroid treatment for a minimum of several months before they may be judged stable enough for inclusion in this kind of study.

The initial control period, included primarily to measure the average weekly steroid requirements before giving the trial drug, should help to confirm the stability of the ENL. However, even a patient (e.g. no. 1) who appears to be stable over a long period may suddenly develop a very significant change in his reaction severity which must be detected if the trial results are to be interpreted correctly. For this reason a final control period, following the trial drug period, is essential. In this way any change in a patient's steroid requirements over the whole period of the trial may be detected, whether resulting from natural alteration with time of the severity of the ENL, or from a prolonged effect of the trial drug outlasting the actual period in which it was prescribed. In addition, the final control period will reveal the rate of relapse on cessation of the trial-drug treatment. As it may be expected that different drugs will affect ENL at different rates, it is important to choose trial periods of sufficient duration to demonstrate the full effect of the drug under investigation—with thalidomide, 4-week periods proved slightly too short. On the other hand, it is equally important that the total length of the trial must not be so great that significant natural variations in the severity of ENL occur in a high proportion of the patients. Pilot trials, carried out before the controlled trial, should give the necessary guidance on the first of these points.

The results here reported have confirmed that an alteration in steroid requirements was the most significant and objective method of assessing the effect of a drug on severe ENL. Assessments based on clinical signs and symptoms, including temperature and white blood cell counts, gave confirmatory evidence of the value of thalidomide but were less decisive. For this reason, drug-trials in mild ENL (untreated with steroids) are more difficult to design, and more subjective types of assessment have to be used. When the present study was completed at the Leprosy Research Unit, Sungei Buloh, a further double-blind, internally-controlled trial of thalidomide was performed in patients suffering from less severe ENL. In the latter study, Pearson and Vedagiri (1969) presented a method of assessment and analysis based principally on the clinical severity of the ENL, but which also took into account the stibophen and paracetamol requirements of patients during the different trial periods.

Even though the clinical diagnosis of severe ENL is usually simple, in this study histological confirmation was obtained in every case. This was to ensure that all the reaction patients formed a homogeneous group, and also that as far as possible any controversy over classification was avoided. Indeed histology appears to be essential in any study of the effect of drugs on reactions in leprosy (Pearson and Vedagiri, 1969).

The present results confirm that thalidomide has an undoubted effect on ENL. Nine out of 10 patients showed moderate or marked improvement while they were receiving the drug. However, no dose-for-dose relationship with prednisolone was discovered. This was perhaps only to be expected. Although there is considerable evidence that thalidomide possesses immunosuppressive properties (Hellmann *et al.*, 1965; Turk *et al.*, 1966; Murphy *et al.*, 1968), its mode of action is still not clear (Mouzas and Gershon, 1968) but would appear to be different from that of prednisolone and similar corticosteroids, and may be related to its action as a folic acid antagonist (Köhnlein *et al.*, 1969). Moreover, Convit *et al.*, (1967) have shown that patients who have not received steroids respond within 48 h to thalidomide whereas patients already receiving steroid undergo a sharp relapse of their ENL of up to 2 weeks' duration if the steroid is withdrawn at the same time as thalidomide is first given.

Thalidomide was found not only to have a good effect on the general signs and symptoms of ENL and the skin lesions but also on ENL neuritis, although 3 patients developed a marked relapse of their neuritis once thalidomide was withdrawn. Sheskin *et al.* (1969) have carried out motor conduction velocity studies in patients with lepromatous lepra reactions (ENL). These demonstrated a dramatic improvement in the function of nerves affected by ENL neuritis as a result of treatment with thalidomide. This is particularly important as, in the past, small numbers of non-leprous patients were reported to have developed neuropathy (predominantly a sensory peripheral neuritis) after intake of thalidomide (Fullerton and Kremer, 1961). No neurotoxic effects of thalidomide have been reported to date in lepromatous patients, and it is considered that the drug's undoubted beneficial action in established ENL neuritis completely outweighs any slight theoretical risk of neurotoxicity.

Although confirming the efficacy of thalidomide in ENL, the current study does not define the optimal dosage of the drug. In order to have as few variables as possible in the trial, the intake of DDS was standardized throughout, a dosage of 100 mg twice weekly being chosen, as the majority of patients were previously receiving this dose. We have discussed elsewhere (Waters *et al.*, 1967; Waters, 1968) our reasons for preferring to continue effective anti-leprosy treatment without interruption in lepromatous patients suffering from ENL. Similarly, a standard dose of 300 mg of thalidomide daily was used throughout the trial. On this dose, some patients were able to stop steroids completely, and their reactions were very adequately controlled; other patients stabilized on smaller doses of steroids, but prednisolone could not be completely withdrawn during the 4- or 6-week trial drug period. Therefore it is assumed that different patients require different minimum dosages of thalidomide just to suppress the signs and symptoms of ENL, in the same way as they require different minimum dosages of prednisolone. But whether in the treatment of ENL the minimum suppressive dosage of a drug is necessarily the optimal dosage is open to doubt. The use of prednisolone in ENL has been governed by the ready and approximately dose-related development of steroid toxicity. Apart from its teratogenic effect, thalidomide appears to be a far less toxic drug than prednisolone. In many ENL patients a dosage in excess of the minimum suppressive dose may be safely given. ENL is known to be an immune complex disease resembling the experimental Arthus phenomenon (Wemambu *et al.*, 1969). The precise aetiology of the steroid-sensitive relapsing nephrotic syndrome of childhood is not known, and caution is necessary in comparing it with ENL. However, it may be relevant that Barratt and Soothill (1970) have shown that in a controlled trial of cyclophosphamide given during steroid-maintained remission, a significant reduction was obtained in the incidence of relapse of the steroid-sensitive nephrotic syndrome. Therefore the possibility should be considered that in treating ENL greater long-term benefit may be obtained either by giving maintenance thalidomide in higher than minimum suppressive dosage, or by giving a combination of reaction-suppressing drugs.

Sheskin's introduction of thalidomide in the treatment of ENL is without a doubt a notable advance, and it is possible to assess the value of the different methods now available for the management of severe reactions. It is suggested that there are 3 principal alternatives, namely: (1) DDS plus steroids (usually prednisolone); (2) DDS plus thalidomide; (3) clofazimine. The first regimen suffers from the well-known disadvantages of steroid toxicity. However, it may be

used in the majority of patients of all ages and both sexes. Steroids are very quick-acting immunosuppressives, and prednisolone is both cheap and universally available. Thalidomide is also fast acting, toxic effects are few, and the majority of patients suffer either no, or only minimal, side-effects. In our experience, sleepiness has been only a minor problem. The 2 cases of allergic dermatitis were both mild and could be controlled with anti-histamines, and we have not observed any evidence of "thalidomide neurotoxicity". But in our opinion the drug should never be given to pre-menopausal females. Indeed, because of the risk of its teratogenic effects, most leprologists consider that thalidomide should only be used under stringent conditions in well-controlled medical centres, a frustrating situation when such a cheap and otherwise relatively non-toxic drug is available.

As far as toxicity is concerned, clofazimine (Lamprene) is the safest of the 3 alternatives. Few toxic effects have been reported and no serious side-effects have been seen at the Leprosy Research Unit during 6 years' experience with the drug. Unlike the other 2 regimens it is considered that clofazimine may be safely used in domiciliary practice. It has been shown to be effective in ENL in many patients in many parts of the world. However, it acts more slowly on ENL than either prednisolone or thalidomide (it is anti-inflammatory but not immunosuppressive) and even in very high dosage may not always control the most severe reactions (see Working Party, 1969). In addition, in high dosage in light-skinned patients it causes marked pigmentation, and when Pettit (1967) used smaller doses (100 mg daily), which gave a more acceptable degree of discoloration, he found that severe ENL was not controlled. Therefore it is concluded that the treatment of severe ENL must be decided on the individual patient's circumstances. But with the recent introduction of both thalidomide and clofazimine the situation is greatly changed, and the outlook for ENL sufferers is correspondingly improved.

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Relapse in Lepromatous Leprosy*†

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The investigation based on a follow-up study of 125 lepromatous cases living in their natural environment and followed up for about 6 years, showed a relapse rate of 3.22% per year. It was also found that all the relapses occurred among those who, after becoming negative, either were very irregular in taking treatment or sought no treatment. The risk of relapse was found to decrease progressively with the number of years that passed after the patients attained a bacteriologically negative state.

Introduction

The term relapse is derived from the Latin word "relapsus", and according to Dorland's medical dictionary it means "return of the disease after its apparent cessation". The main difficulty is not in understanding this definition, but in how to define apparent cessation (or subsidence) particularly in a disease like leprosy. In lepromatous leprosy it has become the practice to base cessation of the disease on bacteriological negativity. The situation is even more difficult in non-lepromatous leprosy. Further, unless relapse is qualified so as to indicate whether it occurred under treatment or not, it is not fully meaningful. Similarly, risk of relapse calculated without reference to the period of exposure to risk, as is often done, gives an incorrect picture.

Review of Past Work

Published well-documented data on the rate of occurrence of relapse in leprosy are not many, to the extent that we do not know clearly at present the risk of relapse a patient runs under various conditions such as, the patient's original clinical and bacteriological status, the regularity of treatment during the active phase of the disease, the continuation of treatment and its regularity after he becomes bacteriologically negative, the patient's age and sex, and the stress factors faced by the patient. Erickson (1950), in a study of 33 arrested cases from Carville which he followed-up for periods ranging from 6 months to 5 years, found a relapse rate of 45% (5 out of 11) among patients who discontinued

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sulphone treatment after becoming negative, and 4.5% (1 out of 22) among patients who continued treatment. Lowe (1954), on the basis of a follow-up of 139 lepromatous cases from Eastern Nigeria, reported a relapse rate of 10.8%, the period of follow-up ranging from a few weeks to 5 years (average 22 months). Rodriguez (1959) has reported on relapse in the Philippines both among sanatorium cases and out-patients discharged earlier from sanatoria. From his figures the relapse rate for in-patients works out at 4.5% for 3½ years (46 out of 1027) under conditions of irregular treatment; for out-patients the rate was 3% (3 out of 101). The relapse rate was highest among those who had been negative for 6 months to 2 years, and lowest among those who had been negative for more than 2 years. The rate was also low in the first 6 months of negativity. He has also compared his relapse rates of 3 to 4% in 3½ years in the sulphone era with relapse rates observed earlier among chaulmoogra-treated negative lepromatous cases. He had found that in the period of chaulmoogra treatment the relapse rates ranged between 30 and 40% among those completing the first 5 years of negative period while by 10 years, the rate reached 75%. Quagliato *et al.* (1961), working with cumulative coefficients, found that the cumulative probability of suffering a relapse during the first 3½ years was 18.9%, whereas for the first 6½ years this figure was 26.4%. They also found that the relapse rates for cohorts of patients discharged between 1949 and 1952 was higher than that for cohorts of patients discharged between 1953 and 1959. From the figures provided by the authors the relapse rate works out at 8.4% per year for those discharged between 1949 and 1952, and 6.3% per year for those discharged between 1953 and 1959. Torsuev *et al.* (1965) reported 45 relapses among 187 patients followed-up for up to 18 years (crude relapse rate 24.1%), and considered that the relapses were due to various factors, such as inadequate or prematurely discontinued treatment, long intervals between courses of treatment, over-treatment with large doses of sulphones, and other factors such as intercurrent diseases, physical strain, or abuse of alcohol. Recently, Quagliato *et al.* (1968), on the basis of a retrospective study of 807 lepromatous cases registered between 1946 and 1968, reported that the 5-year cumulative relapse rates ranged between 7.7 and 14.4% for lepromatous cases of different types under regular treatment; while the rates for those under irregular treatment ranged between 10.9 and 28.4%. Similarly the 10 years and over cumulative relapse rates in patients under regular treatment ranged between 19.6 and 27.8% for different types of lepromatous cases, and for those under irregular treatment the figures ranged between 45.0 and 62.4%. Basto and Barbosa (1968) reported a relapse rate of 20% in about 9 years for lepromatous cases under treatment.

From the various figures quoted above it can be seen that it is very difficult to compare one set of figures with another, as the different studies are based on different methods of calculation and different assumptions. However, from a review of the above 10 studies the following general inferences can be drawn. (1) Relapse is a common feature in lepromatous leprosy. (2) Patients with negative lepromatous disease who discontinue treatment or are irregular in taking treatment run a higher risk of relapse, which may range between 1 to 6% per year under different conditions, whereas those who continue treatment run a much lower risk, which may range between 0.5 to 2.5% per year. (3) The risk of relapse decreases with the passage of time (although cumulative relapse rates will show increase with passage of time). (4) Well established and more extensive disease tends to relapse more often than less extensive.

Materials and Methods

The present investigation of relapse was possible because of a chemoprophylaxis study in Chingleput Taluk (S. India) conducted by the Central Leprosy Teaching and Research Institute at Chingleput, where a number of patients with lepromatous leprosy, who served as index cases for the study, have been regularly followed up both clinically and bacteriologically for about 6 years, and whose treatment status in most cases was also known. The patients were examined every 6 months; several of them were bacteriologically negative and the disease clinically inactive even at the start of the study. A large number who were positive at the start of the study later became negative as the result of treatment. Most of those who became negative during the study period or were negative at the start remained negative subsequently, but a few did become bacteriologically positive again. The length of time for which patients remained negative before becoming positive again varied from 6 months to 5 years. Cases showing negative smears only for a short period may not necessarily be inactive and therefore their subsequent positive status may not necessarily indicate relapse; at any rate we have so far no standard criteria for declaring a case as a case of relapse. In the absence of such criteria we have defined relapse, for the purposes of the study, as the reappearance of acid-fast bacilli (AFB) in skin smears from lepromatous patients who had been negative continuously for 3 years or over, as determined by at least 6 consecutive skin smear examinations performed at half-yearly intervals; the skin smears were taken at 6 sites and examined by standard methods. The number of lepromatous cases which remained negative for 3 years or more and are included in the study was 125. However, the periods of follow-up of these 125 cases were not uniform, as they ranged from 6 months to 2½ years. Therefore, the analyses in the study were based on the calculation of person–years of follow-up, thus giving due weighting to the varying period of follow-up; the relapse rates are calculated per 100 person–years, which is the same as per cent per year.

Results

The total period of observation of the 125 cases was 279.5 person–years, and the number of relapses among them, by our definition was 9, thus giving a relapse rate of 3.22% per year. When the data are analysed according to regularity and continuation of treatment after becoming negative, it is found that there was no relapse among those who took regular treatment, and that all the relapses occurred among those who either were very irregular in taking treatment or completely neglected to have treatment. The relapse rates are about the same whether the patients were taking treatment irregularly or were completely abstaining from taking treatment. Table 1 shows the relapse rates by treatment status.

Relapse occurred most frequently in the second year of follow-up. In the first and second half-years of the follow-up study, there was no relapse; in the third half-year the relapse rate was 10.3% per year, in the fourth half-year it was 11.9% per year, and in the fifth half-year the rate was only 0.9% per year. Thus the risk of relapse for lepromatous cases appears to decrease considerably 5 years after attaining negativitiy. All but 13 of the lepromatous cases studied were in males, and all the relapses occurred in male patients. Also, all but 2 of the patients were

TABLE 1

Relapse in lepromatous leprosy by treatment status

Treatment status	No. of cases	Person-years of follow-up	No. of relapses	Relapse rate % per year
Regular (51 to 100%)	43	98.5	0	0.00
Irregular (5 to 50%)	50	114.5	6	5.24
Absent (Less than 5%)	25	52	3	5.77
Not known	7	14.5	0	0.00
Total	125	279.5	9	3.22

adults, and all the relapses occurred among the adults. As the numbers studied are small it is not possible in this group to make age or sex comparisons.

Discussion

Although the study is not based on a very large number of cases, it has the distinct advantage of a repeated, intensive, and near-complete follow-up of a group of patients with lepromatous leprosy living in their natural environment. The relapse rate for those not taking regular treatment works out at 5.2% per year; this figure is similar to the findings in other studies. The complete absence of relapse among those taking regular treatment was, however, unexpected. In an earlier study (Neelan and Noordeen, 1970) based on routine follow-up of lepromatous patients treated in a mobile treatment unit, we had found that even under regular treatment after becoming bacteriologically negative, there was still a small risk of relapse, to the extent of 0.7% per year (Table 2); on the other hand, in the same study the risk of relapse for those who took irregular treatment was about 4½ times greater, the rate being 3.2% per year. Thus there is no doubt that irregular treatment or cessation of treatment after becoming negative increases the risk of relapse in lepromatous leprosy. Further, the risk of relapse progressively decreases as years pass. In the earlier study we had also found that the risk of relapse was very low after the 6th year of attaining bacteriological negativity and this risk was not affected by whether the patients took treatment regularly or irregularly. This suggests that probably 6 years of treatment, after a case of lepromatous leprosy becomes negative, may be adequate and that the present procedure of advising life-long treatment for lepromatous cases may not be necessary.

Conclusions

From our study it can be concluded that relapse is a serious problem in lepromatous leprosy, particularly if regular treatment is not taken after becoming bacteriologically negative. However, it also appears to be unrealistic to ask patients with lepromatous leprosy to take life-long treatment, particularly when

TABLE 2*

Relapse in lepromatous leprosy by treatment status and period of follow-up

Treatment status	1 to 3 years			3 to 6 years			Over 6 years			Total		
	Person-years	No. of relapses	Relapse rate	Person-years	No. of relapses	Relapse rate	Person-years	No. of relapses	Relapse rate	Person-years	No. of relapses	Relapse rate
Irregular	48.5	7	14.4	154	12	7.8	494	3	0.6	696.5	22	3.2
Regular	97.5	0	0.0	314.5	3	1.0	1085.5	7	0.6	1497.5	10	0.7
Total	146	7	4.8	468.5	15	3.2	1579.5	10	0.6	2194	32	1.5

* From Neelan and Noordeen—Relapse in leprosy (under publication).

we know that the risk of relapse decreases with passage of time, and that there is some indication that the very low risk of relapse in later years may not be influenced by treatment status. The problem is particularly serious in centres where large numbers of patients are treated, as for example in leprosy control units. Further work on this problem is suggested.

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Evaluation of Leprosy Control Programmes: Some Suggestions for Operational and Epidemiological Assessments *†

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With existing agents and methods, the object of leprosy control projects is to reduce progressively over a period of many years the morbidity of leprosy to a level at which it no longer presents an important public health problem. The achievement of this objective depends on several measures, administrative, medical, social and legal, and on health education and training of personnel.

The assessment of a leprosy project should therefore be concerned with all the measures applied in the control of the disease. In this note we shall deal only with the medical measures. Moreover, to limit the length of the paper, we shall suggest only the assessment measurements without considering the interpretation of results which may derive from the evaluation: also we shall not discuss the actions or measures which could be pertinent after the assessment. We shall stress that in the interpretation of results, in the choice of the best strategy to reach the objectives, and in the action to be taken after evaluation, all the local factors should be taken into account.

The evaluation of the medical measures should be concerned with the operational aspects of the project (*operational assessment*) and with the trend of the disease under the influence of the control measures, often associated with other factors (*epidemiological assessment*).

For both types of assessment it is indispensable to have the relevant base-line information, and for the former it is necessary to know whether or not the programme has quantitatively defined objectives and also to know the priorities adopted. In each country or area the measurement indicators to be selected, and the interpretation of the findings, should be considered in the light of these elements. In fact, to consider only one of these factors, in control programmes with quantitatively defined objectives, the assessment at central level or in each unit is more easily done by comparing the achievement in each activity (cases to be diagnosed, treated, etc.) with the target proposed for monthly, quarterly or annual periods.

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* Prepared for a meeting on Assessment Measurements of Leprosy Control, convened by the Indian Council of Medical Research, 28 July-1 August, 1969.

† Reprinted from *Bull. Wld Hlth Org.* (1970) **42**, 631-634 by kind permission of Chief, Technical Publications, WHO.

It should be stressed that this report is intended to give general guidance on operational and epidemiological assessments applicable on a global basis but useful for adaptation to the actual situation existing in any given country. A few countries, with good recording systems, would be able to utilize the indicators suggested, while at the other extreme there are countries in which only a certain number of these indicators could be selected. Each country should, in fact, choose appropriate indicators.

Base-line Information for Evaluation

For evaluation purposes it is essential to have information* on:

(1) Characteristics of the area, including geographical, climatic, socio-economic and cultural conditions, communications, etc.

(2) The population, age and sex composition and rural/urban distribution.

(3) Health situation and health services structure.

(4) Leprosy service structure, technical policy, priorities.

(5) Characteristics of leprosy endemics, known prevalence, number of registered cases and their classification, age and sex distribution in the rural and urban areas before the start of the project. Prevalence should have been estimated; if not it should be estimated in order to establish targets.

The most reliable method of estimating prevalence is by a random sampling survey. However, as this is very expensive, the prevalence is generally estimated by taking into account information readily available in the area concerning known cases and the proportion of lepromatous (L) + borderline (B), indeterminate (I) and tuberculoid (T) cases. With this information the specific prevalence rates (sex, age, each form of leprosy) should also be estimated. Bechelli and Martínez Domínguez (1966) made a proposal for the estimation of prevalence taking into account the findings of the WHO Leprosy Epidemiological Team. Estimates should be adjusted in the course of the campaign, taking into account the data collected.

(6) Resources: (a) budget for health and leprosy service (for in-patients and for out-patients); (b) health services in the area and co-operation in leprosy control; (c) leprosy service personnel and their training: number of doctors (full-time and part-time);† number and kind of paramedical personnel; number of social workers; administrative personnel; others (drivers, porters, etc.); (d) facilities for medical assistance to leprosy patients—number and capacity of sanatoria and/or facilities for temporary hospitalization; dispensaries, skin clinics, treatment centres, mobile units, etc., and their location; laboratory facilities; (e) training facilities; (f) transport facilities; (g) equipment; (h) other possible resources (number of practitioners working in the area, voluntary agencies and their activities).

Operational Assessment

When assessing the operational aspects of a project the first thing to establish is

* Details are given of information which can be useful for programming and evaluating leprosy control projects in: Bechelli, L. M. (1966) *A Guide to Leprosy Control* (unpublished document available, on request, from Leprosy, World Health Organization, Geneva, Switzerland).

† Estimated workload for each category of personnel.

whether the programme includes quantitatively defined objectives. If there are quantitative objectives, at central or at unit level, it is easy to assess the development of the programme by comparing the estimates at the beginning of the year for each activity with their accumulated monthly projections.

In countries where the leprosy projects do not have annual targets, the evaluation can be undertaken by using several measurement indicators. These can also be considered for the first group of countries, to complement the assessment of targets.

In the light of the above, every project should have quantitatively defined objectives, as stressed initially by the Pan American Sanitary Bureau/WHO Regional Office for the Americas (1963) at the Leprosy Seminar held at Cuernavaca and in unpublished papers prepared for that seminar by R. Huerta and F. Pereda and later again by the WHO Expert Committee on Leprosy (1966). Guide-lines for establishing yearly timetables are given in these papers and documents.

Timetables should be prepared taking into account the resources, targets and priorities adopted in the programmes (treatment and follow-up examination of L + B cases, surveillance of their contacts, and treatment of indeterminate cases).

For an assessment it is also essential to know whether the control project has adopted a system of priorities and if a target has been fixed for the proportion of L + B cases to be detected and treated in a certain period of time.

The priorities recommended by the WHO Expert Committee on Leprosy (1966) are as follows: "Countries with limited budgets, only a few physicians, and facing other serious problems, should treat first of all the lepromatous and other infectious cases and the indeterminate lepromin negative. They should keep child household contacts, especially of infectious cases, under surveillance and try to help patients in the prevention of disabilities. Means and personnel should be concentrated on the infectious cases and their contacts, particularly children.

"At the other extreme, countries with adequate budgets and good leprosy services, whether or not integrated in the public health services, should diagnose and treat as early as possible *all* patients, maintain surveillance of *all* contacts, prevent disabilities, rehabilitate *all* patients with deformities, and examine certain population groups, in particular, children."

Several measurement indicators can be suggested:* they will enable an operational assessment to be made of certain activities. In listing these indicators we have adopted the classification of leprosy recommended by the WHO Expert Committee on Leprosy (1966).

CASE-FINDING

(a) Contact tracing (annual examination):

(i) proportion of contacts examined yearly; (ii) proportion of contacts of L + B cases examined yearly. The same for contacts of I and T cases.

(b) Proportion of cases among persons referred or reported by physicians and others as possible patients, and proportion of L + B, I and T cases detected.

(c) Proportion of cases among persons who spontaneously requested examination, and proportion of L + B, I and T cases detected.

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* The numbers used as numerators and denominators for obtaining the proportions and/or rates are also of interest for appraising the development of the projects.

(d) Proportion of leprosy cases in skin clinics and proportion of L + B, I and T cases detected.

(e) Proportion of leprosy cases in school surveys and proportion of L + B, I and T cases detected.

(f) Proportion of leprosy cases detected in the examination of recruits, workers and others, and proportion of L + B, I and T cases detected.

(g) Proportion of leprosy cases in mass surveys, and proportion of L + B, I and T cases detected.

(h) Proportion of registered cases in relation to the estimated total number of cases. (No. of L + B cases detected up to . . ./no. of estimated cases at the end of this period) x 100.

(i) Proportion of cases wrongly diagnosed.

(j) Proportion of cases incorrectly classified.

TREATMENT

(a) No. of patients under treatment in the year/no. of patients requiring treatment in the year* x 100.

(b) No. of patients of L + B under treatment in the year/no. of patients of L + B requiring treatment. The same for I and for T patients.

In (a) and (b), consider if treatment is regular (patient conforming to at least 75% of the recommended number of attendances†) or irregular (less than 25%, 25 to 50% and 51 to 74%).

INACTIVITY‡

(a) Percentage of inactive leprosy cases in relation to the total no. of cases (related to regular and irregular treatment).

(b) Percentage of L + B inactive cases (related to regular and irregular treatment), if possible by cohorts. The same for I and T cases.

REACTIVATION§

(a) Proportion of reactivations related to treatment (regular or irregular).

(b) Proportion of reactivation of L + B patients. The same for I and T patients.

CASES RELEASED FROM CONTROL

(a) Proportion of patients released from control related:
(i) to total no. of patients under treatment; (ii) to total no. of inactive cases.
Study of cohorts is preferable.

(b) Proportion of L + B related:
(i) to total no. of L + B patients under treatment; (ii) to total no. of L + B inactive cases.

The same for I and T cases.

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* Number of patients registered excluding those released from control, dead or emigrated.

† Regular treatment is defined as follows: "A patient conforming to at least 75% of the recommended number of attendances should be considered to be attending regularly" (WHO Expert Committee on Leprosy, 1960).

‡ A leprosy patient without any sign of clinical activity and with negative bacteriological examination should be considered as an "inactive case" (WHO Expert Committee on Leprosy, 1966).

§ When an inactive case again presents active lesions and/or bacterial positivity.

RELAPSE* (OF CASES RELEASED FROM CONTROL)

(a) Proportion of cases relapsed related to the total no. of patients released from control.

(b) Proportion of relapsed L + B related to the total no. of L + B patients released from control. The same for I and for T patients.

SULFONURIA TEST

(a) Proportion of leprosy patients with positive sulfonuria test in relation to total no. of patients supposed to be under treatment.

(b) Proportion of L + B patients with positive test in relation to the no. of L + B patients supposed to be under treatment. The same for I and for T patients.

FOLLOW-UP EXAMINATIONS (AT LEAST ONCE A YEAR)

(a) Proportion of patients examined yearly (or every 6 months) related to the no. of patients requiring treatment.

(b) Proportion of L + B patients examined yearly (or every 6 months) related to the no. of L + B patients under treatment. The same for I and for T patients.

OUT-OF-CONTROL CASES†

(a) Proportion of leprosy patients out of control (related to the total no. of patients requiring surveillance).

(b) Proportion of L + B patients out of control (related to the no. of L + B patients requiring surveillance). The same for I and for T patients.

ANNUAL PROPORTION OF DISABILITIES IN NEWLY REGISTERED PATIENTS (RELATED TO EACH FORM OF LEPROSY)

RATIO OUT-PATIENTS/IN-PATIENTS AND THE RATIO OF THE COST PER PATIENT YEAR IN-PATIENT/OUT-PATIENT

Cost analysis concerning in-patient and out-patient care is therefore needed, if possible with regard to the main activities.

Epidemiological Assessment

It is known that the best possible indicator for an epidemiological assessment is the annual incidence rate. However, reliable rates can be obtained only in research projects with an excellent coverage of the population surveyed; in leprosy control projects it is very difficult to get reliable figures for incidence.

For this reason, the annual rate of newly registered cases and their classification are mainly used to evaluate the epidemiological trend. Because of the limitations of antileprosy drugs and of the lack of a vaccine to prevent the disease (the studies on BCG are still in progress), it is not possible to expect a considerable reduction of this rate after a few years of control work. Consequently one has to multiply the indicators to be able to recognize any epidemiological improvement.

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* Once inactivity is achieved, full treatment should be continued for different periods of time before the patient is released from control. These periods should be 1½ years for tuberculoid, 3 years for indeterminate and 5 years for lepromatous and borderline cases.

† When a case released from control again presents active lesions and/or bacterial positivity.

These indicators should be appraised in connexion with some of those used for operational assessment: in fact, some of them may be used for both the operational and the epidemiological assessments.

Furthermore, good epidemiological achievements reflect, to a variable extent, the success of the operational measures. While we should have an evaluation of the operational measures in short periods (every 3 or 6 months or even monthly) the epidemiological assessment should be made after long periods, preferably after 5, 10 and more years.

The following indicators—related to age (mainly below 15) and sex when pertinent—are suggested for the epidemiological assessment:

(1) Annual incidence rates or annual rates of newly registered cases.

(2) Forms of leprosy of annually and newly registered cases (proportion and rate).

(3) Items (1) and (2) related to selected groups of population (contacts, schoolchildren, soldiers, etc.): (a) attack rate among contacts examined yearly; (b) attack rate among contacts of L + B patients examined yearly. The same for contacts of I and T patients; (c) proportion of newly registered contacts examined yearly and attack rate; (d) proportion of newly registered contacts of L + B patients examined yearly and attack rate. The same for contacts of I and T patients; (e) proportion of L + B, I and T cases detected in (a), (b) and (d); (f) attack rates and proportion of L + B, I and T cases detected in cohorts of contacts of L + B, of I and T patients.

(4) Prevalence rate.

(5) Prevalence rates in selected groups of population (contacts, schoolchildren, soldiers, etc.).

(6) Proportion of bacteriologically negative cases among L + B patients under treatment (by cohorts).

(7) Proportion of L and B, I and T cases rendered inactive* (by cohorts).

(8) Reactivation (already considered under operational assessment).

(9) Proportion of cases released from control† related to (a) patients under treatment and (b) patients under treatment + out-of-control cases.

(10) Proportion of relapses related to each form of leprosy, mainly L + B cases.

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* "Out of control", "absentee", "lost sight of" and other terms have been used for registered patients who have not been under control for 2 or more years (WHO Expert Committee on Leprosy, 1966).

† Criteria for inactivity and release from control should be given.

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Plaster Casts*

GRACE WARREN

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A step-by-step description is given of a method of applying a plaster of Paris walking cast that can be performed by one technician with minimal assistance.

Plaster of Paris walking casts are recommended for the treatment of foot ulcers in leprosy. They are also an essential part of the treatment of tarsal-bone disintegration in leprosy. To be effective, a cast must be strong, light, and well fitted so that it does not rub and cause an abrasion which, because of anaesthesia, may remain unnoticed until a deep ulcer has developed. Since a plaster applied to an oedematous leg or foot becomes loose as the swelling subsides, steps should be taken to reduce swelling before the walking plaster is applied.

Introduction

A simple method of applying a walking cast developed by the staff at Hay Ling Chau is here described in the hope that it may interest medical orderlies and other field workers. Alternative appliances for enabling the patient to walk are also available.

Method

1. POSITION

(a) The patient lies face down on the couch with the knee of the affected side held at 90° of flexion. This means that the leg is not being supported on the horizontal plane and so reduces the risk of isolated pressure spots being caused by the assistant inadvertently pressing on the wet plaster (Fig. 1).

(b) The ankle and foot are easily controlled. (1) The patient can hold the foot correctly himself, in a good position. (2) Finger-tip pressure on the toes will maintain an anatomically normal foot. (3) If the foot arch needs much moulding, a strip of cotton bandage may be passed across the arch and pulled by the assistant to exert downward pressure on the arch while the assistant pushes the forefoot plantarwise. The combined action will give maximum arch moulding while the plaster is moulded over the bandage (Fig. 1). (4) Where there is marked heel inversion because of contracting soft tissues, an assistant forcibly moulds the foot until sufficient plaster is applied to hold the foot in the desired position. (5) If the metatarsals or phalanges are damaged, it may be advisable to use adhesive plaster and/or small splints to straighten the toes, and thus enable healing to proceed in a position of function.

N.B.: In most leprosy patients, it is important to apply the plaster with the

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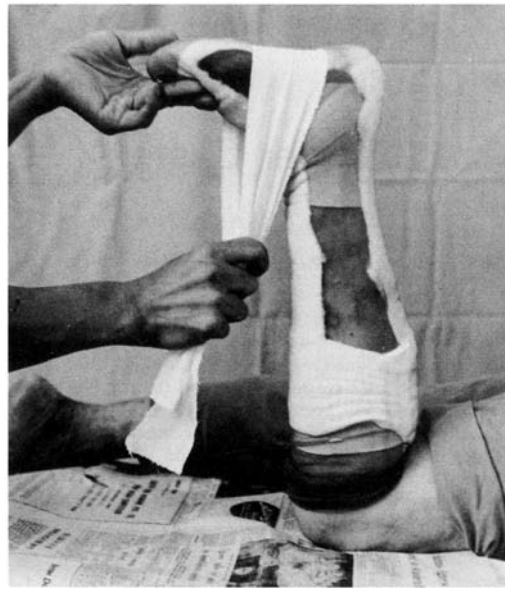

Fig. 1. The patient lies face downward on the plinth with the affected foot prepared for plastering. The position of the foot is held by use of a cotton bandage as described under Position (b) 3.

foot at right-angles to the leg, or even slightly dorsiflexed. If the plaster is applied while the foot is in plantar flexion, contracture of the tendo Achilles may occur, especially if the dorsiflexors of the foot are weak. Furthermore, the foot should be kept slightly everted (and not inverted), and the toes should be straight.

2. SKIN PROTECTION

Adequate protection must be provided at any points subject to pressure or friction, such as the front of the ankle and the upper end of the plaster, that is, near the knee. (a) Elastoplast has proved an excellent material, in that it moulds to the contours of the limb and does not move. A figure-of-eight bandage protecting the malleoli and the front of the ankle, combined with a cuff at the proximal limit of the plaster, is adequate. The upper limit of the plaster is determined by the patient's habits: if squatting is part of his way of life, the cuff needs to be lower than is usual. (b) Orthopaedic felt is satisfactory as a protector. (c) Rolls of cotton wool may be used, but care must be taken that the application provides a uniform layer that is not too thick and will not allow movement of the whole plaster. A combination of 2 or more of these "pressure point protectors" is probably best. (d) Old nylon stockings provide an excellent substitute for tubular stockingette; indeed they are in some ways preferable, since being already shaped they do not wrinkle in front of the ankle. Also the intact stocking toes keep dust and dirt from the ulcerated area.

At Hay Ling Chau, the routine for a plaster application is as follows:

(1) Elastoplast is applied around the ankle as a figure-of-eight. (2) A circular

cuff is made of the same material at the level of the upper edge of the plaster. (3) A nylon stocking is rolled on and pulled up over the knee. (4) A layer of wool is applied along the sole and 3 in (7.5 cm) up the back of the leg to protect the heel (which is very vulnerable to pressure), carried over the tibial ridge, and over the Elastoplast at the level of upper edge of the plaster. (5) A second nylon stocking put on over the wool holds this firmly in position. (6) The position is checked and maintained—(as described in Section 1). (7) Plaster of Paris is then applied. (8) A cuff of nylon stocking and wool is turned down over the proximal edge of the wet plaster. This provides a nice cuff and helps to reduce rubbing at the proximal end of the plaster.

3. PLASTER APPLICATION

(1) A back slab of 8 to 10 layers of 6-in (15-cm)-wide plaster bandages is made, big enough to reach from the toe tips to the proximal (upper) edge. After being soaked, rubbed in and smoothed on a flat surface it is then applied carefully, moulded well on to the arch of the foot and round the heel and the tendo Achilles to ensure a good fit.

(2) A 3- or 4-in (7.5- or 10-cm) bandage is soaked and applied to the ankle and arch area to hold the foot and heel in position. If a cotton bandage is used to hold position (as described in 1, b, 3 above) this is not removed till the plaster is dry, but it can be worked around and later cut.

(3) A 6-in (15-cm) bandage is then soaked and applied proximally to give good support and fit around the calf, to form the upper limit of the plaster, and to complete the leg.

(4) When the plaster is dry enough to maintain the desired position of the foot, any moulding can be removed and the plaster completed by further 4- or 6-in bandages. It is important when applying the plaster to the toes that they be plantarflexed. Care must be taken that in applying the plaster the fifth toe is not extended at the metatarso-phalangeal joint.

(5) The proximal edge of the cast is smoothed off and the stocking or stockingette turned over to provide a smooth edge.

(6) The plaster must be completely dry before walking is allowed. This takes at least 24 h. If possible, the walking appliance should be applied only after the plaster is dry to ensure that the patient does not walk too soon.

4. WALKING APPLIANCE

(a) Bohler-type walking irons should be used for any patient with osteoporosis or tarsal-bone disintegration of the talus and/or ankle joint to minimize compression of the ankle region. A simple metal walking iron can be made by a local metal worker. Double cross bars on the long side pieces are desirable and these pieces should be malleable in order to fit the cast well (Fig. 2). The total weight of the iron must be considered in selecting a suitable metal or it may be so heavy that the patient cannot walk.

(b) Wooden or rubber rockers can be applied to the foot. Wooden ones can be made from a wooden packing case by a jobbing carpenter as shown on the diagram (Fig. 3), and shod with car tyre or made like the Karigiri shuffle board described by Ross (1962).

(c) For patients with bilateral foot lesions, or others for whom stability when standing may be a problem, a flat sole can be made on the plaster. Care must be taken that the plane of the sole is at 90° to the tibial line and that the foot is not

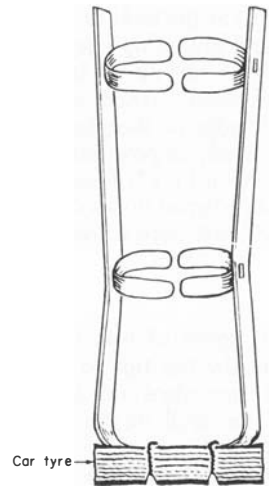

Fig. 2. A Bohler type walking iron made by a local metal worker and shod with car tyre.

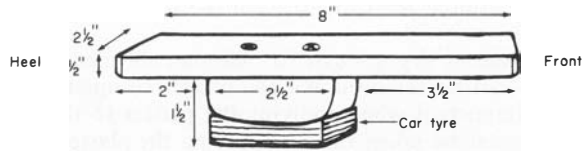

Fig. 3. A wooden rocker (showing dimensions) shod with car tyre.

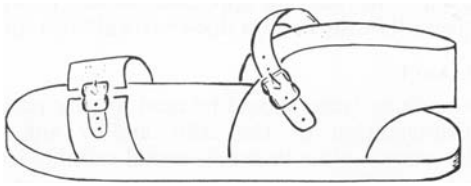

Fig. 4. Rubber-soled sandal with canvas straps and buckles to wear over a plaster cast.

forced into eversion or inversion. The sole is built up with plaster and smoothed off with a flat board. When it is dry the patient is provided with a sandal with a rubber or leather sole and adjustable straps that can fit over the plaster (Fig. 4). In wet weather a plastic bag can be used between the sandal and the plaster. These flat plasters have proved very useful and effective, especially in the elderly and less active patients and those in whom both feet need treatment at the same time (Fig. 5).

Fig. 5. Sandalled plaster casts on a patient with bilateral foot lesions.

Comments

The use of walking plasters may cause osteoporosis, the degree of decalcification being proportional to the length of time the plaster is worn. Any foot that has been in plaster for 6 weeks or more should be observed carefully for several weeks after removal of the plaster. Unsupported and unrestricted ambulation should not be allowed at once, as the development of tarsal-bone disintegration following the use of a walking plaster is a very real possibility.

Early treatment of lesions due to tarsal-bone disintegration can result in complete recovery in an undeformed position. On the other hand, neglect may result in a grossly deformed foot and much disability.

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Prosthetics in Leprosy *†

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This paper deals with the implications for amputation of the lower extremity of the patient with Hansen's disease, the preparation of the prosthesis, and the care of the stump. Particular attention is given to the making of a hard socket to prevent breakdown of the skin of the stump. Inexpensive methods of producing useful and acceptable prostheses are described.

Introduction

The management of amputees suffering from leprosy (Hansen's disease) offers a fascinating challenge to the prosthetist as well as to the orthopaedist who does the amputation and follows the care and fitting of the stump. The knowledge gained and practised regarding patients with Hansen's disease can be carried over into use for any amputee with sensory paralysis of the lower extremities. This is especially true in the case of paraplegia and spina bifida.

As an orthopaedist I will not try to tell the prosthetist how to make an artificial limb. However, there are a few points that we have observed which may be of help, or which may stimulate further study. One of the best monographs on the subject of orthopaedic and prosthetic appliances for leprosy is that written by J. A. E. Gleave, published by the United Nations Organization (Gleave, 1968). Most workers devise their own short cuts and simplifications, but all have not been published. By far the majority of leprosy patients in India who have undergone amputation go without the benefit of prostheses. Some of the reasons are the cost, the lack of prosthetic facilities available, unsatisfactory fitting followed by rejection of the limb, and the psychology of a begging community who get more alms by displaying grotesque deformities—the amputee leaves his prothesis at home when he goes out to beg. In this paper we will deal with our management of some of these difficulties.

Pathology

Any type of leprosy may result in loss of sensation, and the problem of fitting a prosthesis is the same. The loss of sensation creates a host of problems, such as

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† This study was partly sponsored by the Social and Rehabilitation Service, U.S. Department of Health Education and Welfare.

ulceration due to trauma and pressure. The ulcer gradually becomes deeper and involves the bone and joint, causing an osteomyelitis or septic arthritis. The disease may also cause cystic areas in the small bones of the extremities with resulting collapse and deformity (Job, 1963; Lechat, 1962; Paterson, 1961). Finally the loss of sensation in the joint may produce a Charcot-type joint which gradually disintegrates and becomes literally a "bag of bones". The unhappy plight of the leprosy patient in India contributes to his neglect of his wound (Figs 1, 2). The infection which follows may destroy the extremity so that it cannot be salvaged. The orthopaedist's primary rôle is to prevent complications arising from the involved extremity. Many papers and monographs (Fisher, 1955; Girling *et al.*, 1967; Walkey *et al.*, 1965) have been written on the care of the feet for healing of the ulcers with proper footwear. Where the main problem is motor paralysis corrective surgery by tendon transfers, arthrodeses, and/or bracing are very satisfactory, both in the feet as well as the hands (Fritschi and Brand, 1957).

When the condition has progressed beyond the stage of a cure of the ulcer and the infection of bones and joints, then amputation must be resorted to. It is our policy to do the least amputation possible. The general principles of avoiding the Chopart amputation (Fig. 3), and amputation through the lower third of the tibia are generally adhered to. Toes may be removed and we are sometimes amazed to see how many years a patient will walk around on a mid-tarsal or Chopart-type stump.

The rest of this discussion will be devoted to our findings with the Syme's and more proximal amputations.

Methods

SYME'S AMPUTATION

Wherever possible, if the foot has to be amputated, a Syme's amputation is done. Good normal skin under the calcaneum is a prerequisite for this procedure. We have found, however, nearly as much difficulty in providing a prosthesis for this type of stump as for a below-knee amputation. Because of this, we insist on a very carefully fitted patellar tendon-bearing prosthesis, distributing the weight as evenly as possible over the patellar tendon, the upper part of the leg, and the end of the stump itself. Any spurs that develop under the end of the stump will predispose to ulceration. Pressure on any scar or this portion of skin of the leg must be avoided.

BELOW-KNEE AMPUTATION

Whenever possible, the usual below-knee amputation is performed, leaving a stump 5 to 6 in (12.5 to 15 cm) long. An attempt is made to get a synostosis formed between the distal end of the tibia and fibula, as this gives a more stable stump. Immediate-fitted prostheses have occasionally been used, although in the event of pre-existing infection this usually cannot be done. The immediate-fitted prosthesis has not been very successful in our hands, owing to the breakdown of anaesthetic skin. We strongly feel that wherever possible, the knee-joint should be saved as a bent knee; end-bearing prosthesis may be provided. Even when the stump is too short for a patellar-tendon-bearing prosthesis, a good weight-bearing

Fig. 1.

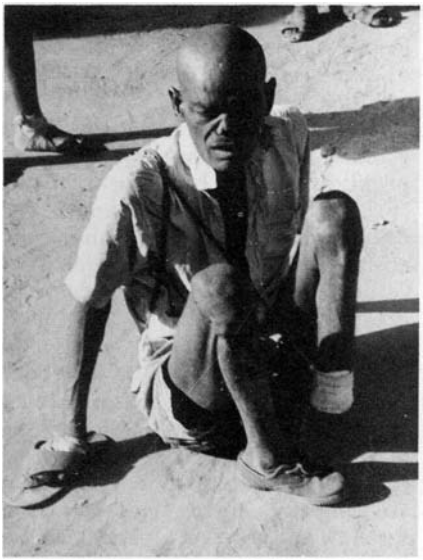


Fig. 2.

Fig. 3.

Fig. 1. The leprosy patient's unhappy plight.
Fig. 2. An artificial limb would enable this man to walk.
Fig. 3. Chopart-type amputation with resultant deformity (note left hand tied to crutch.)

surface remains. The only prerequisites are that the patellar tendon with the tubercle be intact and the skin healthy. Through-knee or standard above-knee amputations may also be used.

PREPARATION OF THE PROSTHESIS

The initial step in the preparation of the prosthesis is a thorough examination of the skin and stump for pathological changes, oedema, and other symptoms (MacGregor, 1962; Pfaltzgraff, 1963). Only when it is ascertained that there are not apparent conditions that will lead to breakdown of the skin later on, is work on the socket begun. The patellar-tendon-bearing socket (Ross, 1963) is used in our institution whenever possible. The main departure from it that we are studying, and which we wish to present here, is the use of the hard socket instead of the soft socket. Our reasons for this are as follows: A collection of moisture next to the skin of any patient with total anaesthesia, such as paraplegics and leprosy patients, predisposes to breakdown of the area. For example, a rubber macintosh under the sheet on which a paraplegic is lying will generate heat, causing a collection of moisture and the breakdown of the skin into decubitus ulcers. Rubber and leather lining in a soft socket creates an ideal environment for the collection of moisture and the breakdown of the skin of the stump. The one exception is microcellular rubber used for the "chapple" or shoe of the patient with leprosy. This is acceptable because there is no problem of the collection of moisture on the surface and the sole of the foot is the normal weight-bearing area of the body. The hard socket is similar to the walking-boot cast which is generally accepted as the treatment of choice for ulcers on the plantar surface of the foot of a leprosy patient. In the preparation of this cast, no lining is used under the plaster. A small amount of sheet wadding or cotton and stockingette are all that are needed. Following this principle in the making of the socket for the prosthesis, we make a plastic socket with no lining other than the patient's stump sock. We feel that this hard socket will prove ideal for the patient with leprosy, especially if a porous plaster is used or a few holes are drilled in the socket (Fig. 4).

END-BEARING PROSTHESIS

When the stump is too short, or in too poor a condition, or when the patient has a fixed contracture, a patellar-tendon-bearing prosthesis is not practical. In these cases a simple end-bearing prosthesis can easily be made with a leather bucket and ordinary hinge-joint for the knee (Fig. 5). The patient starts right off walking when this is applied as it affords good control. Full pressure can usually be put on the end of the stump without fear, as usually there is no anaesthesia over the knee and patellar tendon itself.

ABOVE-KNEE PROSTHESIS

Where through-knee or above-knee amputations have been carried out the usual fitting, as in any other above-knee type, may be done. For our above-knee prostheses we use total contact quadrilateral plastic sockets with a belt. There is no vacuum for suction, and the patient wears one or 2 stump socks.

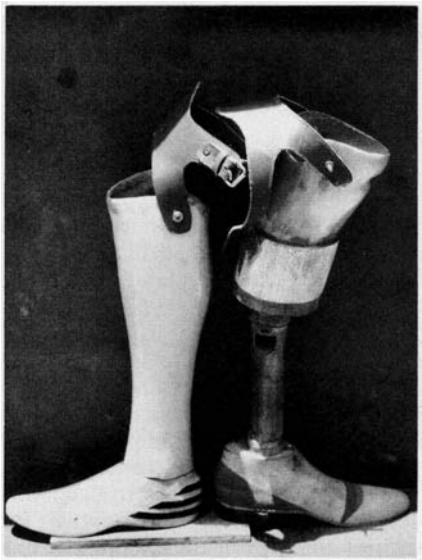


Fig. 4.

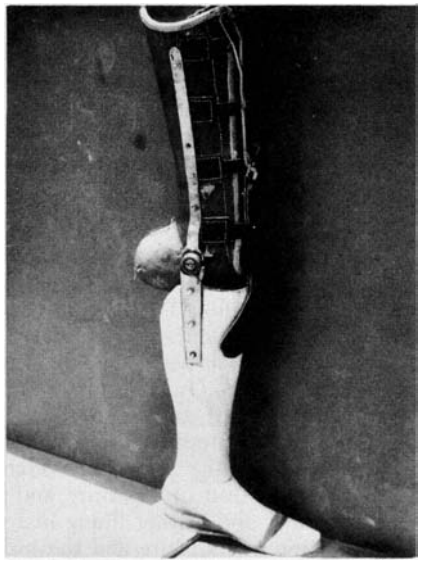


Fig. 5.

Fig. 4. Hard socket. Foort-type alignment shin. Rubber and wooden solid-ankle-cushion-heel feet.

Fig. 5. Knees bearing prosthesis before finishing.

COSTS

One of the major problems in providing an artificial limb for the leprosy patient is that neither the patient himself nor the sponsoring agent can afford the cost of supply. Keeping this in mind, we have the following suggestions to make:

(1) *Plastic.* We have had good results with the polyester resins. They are generally much cheaper than epoxy resins. In our institution the cost of plastic for a below-knee prosthesis is about $2.00. Technicians can be trained in a much shorter time to use plastics than is required when only wood is used.

(2) *Wood.* With the use of plastic prostheses, wood does not play the important rôle that it did in the older type of prostheses. Any light wood of the area can be used.

(3) *Shin.* We have recently been making a Foort-type shin assembly (Foort and Hobson, 1965; Radcliff and Foort, 1961) with wedged discs entirely out of bamboo (Fig. 6). The cost of this item is negligible.

(4) *Bicycle knee joints.* In searching for a knee-joint of good quality steel, we found that the front hub of a bicycle is the average size for an adult knee. It comes complete with axle, ball bearing, etc., of very good steel. The cost is 56 cents in our area. This joint with a simple platform and a pipe for the shin (Figs 8, 9 and 10) fastened to the foot, gives an above-knee prosthesis that can be easily aligned. This is covered with a very thin shell of plastic for below the knee, and the usual plastic covering above the knee. The bicycle hub can also be inserted into a shaped knee block (Fig. 8). (Named after Barkat Masih, our prosthetist who designed the block.)

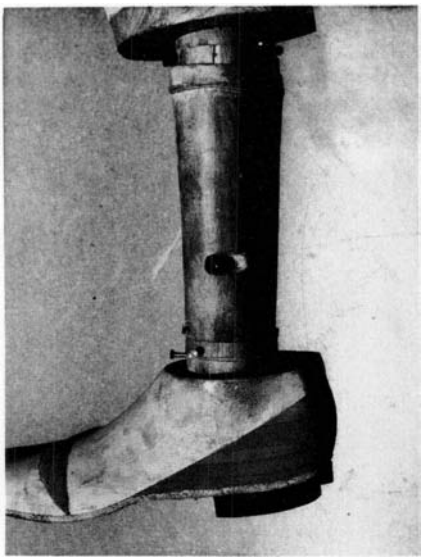


Fig. 6.

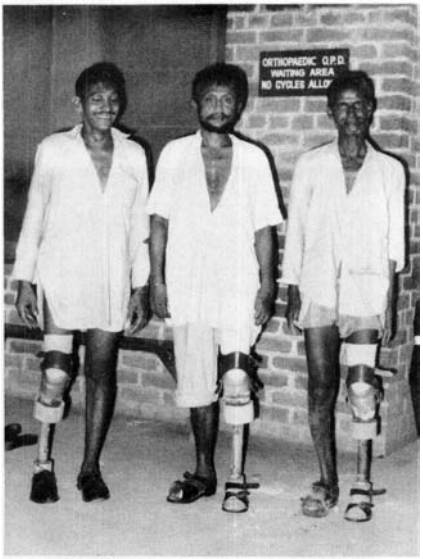


Fig. 7.

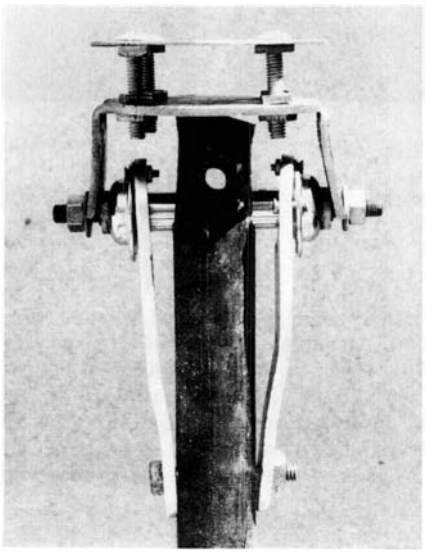


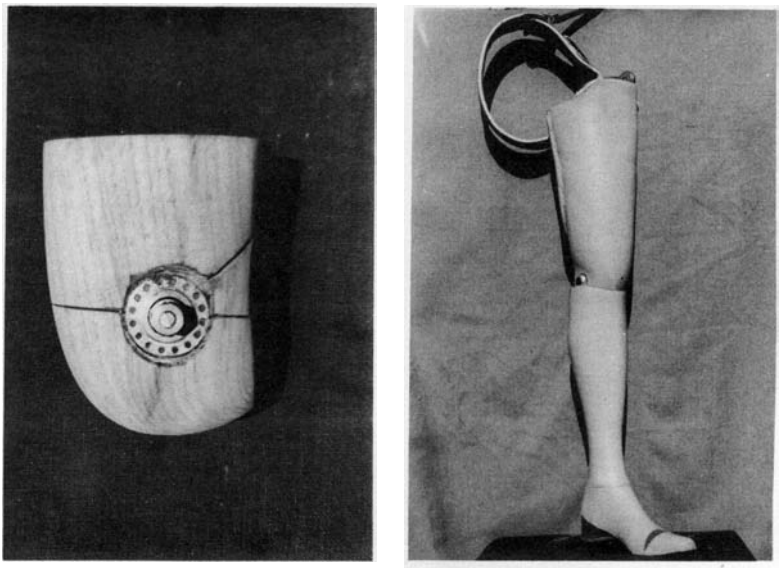
Fig. 8.

Fig. 6. Foort-type shin, using bamboo. Wooden type solid-ankle-cushion-heel foot.

Fig. 7. Three limbs on trial using Foort-type bamboo shin.

Fig. 8. Knee joint using front hub of bicycle and alignment platform.

5. *Foot.* We use the cobbler's shoe form to make a solid-ankle-cushion-heel foot. We insert rubber for the toe break and make a rubber heel as in the conventional solid-ankle-cushion-heel foot (Fig. 9). This again is very inexpensive and eliminates the problem of the solid-ankle-cushion-heel feet made of inferior rubber which frequently fractures.



(a) (b)

Fig. 9. (a) Barkat knee joint, using bicycle hub in knee joint. (b) Completed limb using bicycle knee.

The use of these simplified materials do not detract from the function of the prostheses and yet provide very inexpensive ones. In our area the cost amounts to about $10.00 to $13.00 (£4 to £5) for either a below-knee or above-knee prosthesis, complete with foot. Everyone prefers to look normal and the application of a foot as described here adds $2.00 or less to the cost of the limb. Any sort of a chapple or shoe can be used (Fig. 10). On occasion a rounded wooden block is used in place of a foot, but this is more difficult to align and is also unsightly.

CARE OF THE STUMP

It should be pointed out that more than the usual care must be given to the stump. The skin, the stump sock, and the socket must be absolutely clean. Any redness means that the prosthesis should immediately be removed and not used until the skin is healed and any defect in the socket has been corrected (Ross, 1963).

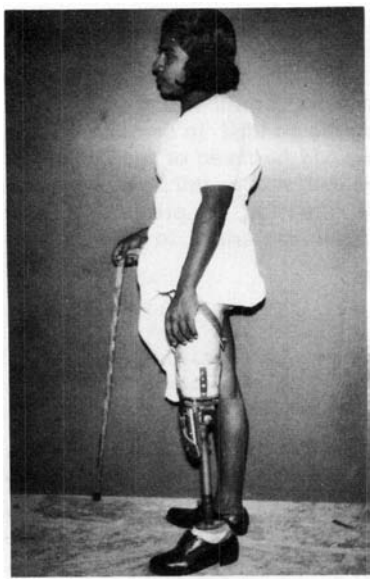


Fig. 10.

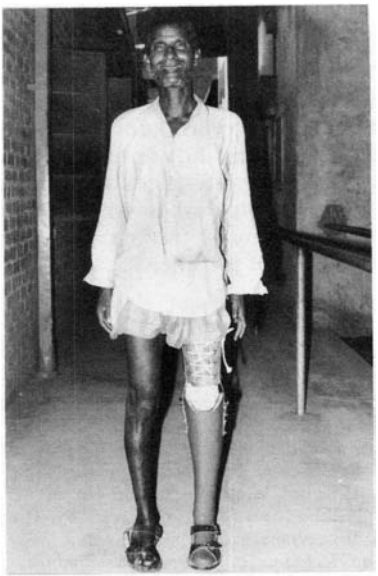


Fig. 12.

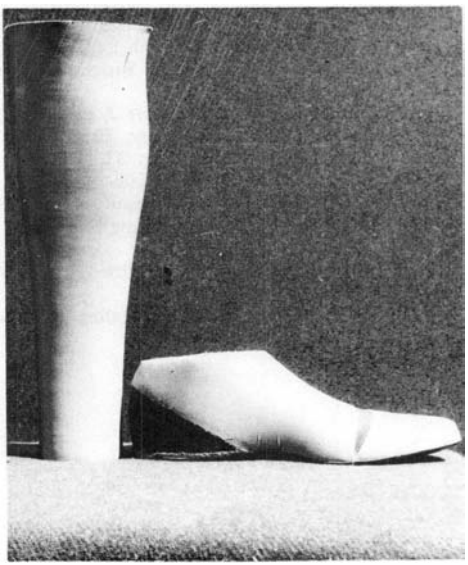


Fig. 11.

Fig. 10. Bicycle knee joint on trial.

Fig. 11. Plastic shell for shin. Wooden foot solid-ankle-cushion-heel type covered with plastic.

Fig. 12. A leprosy patient walks out. Note chapple of microcellular rubber on right.

Conclusion

Careful amputation should be carried out on the patients suffering from Hansen's disease. Application of a prosthesis requires careful fitting. Any factor that might lead to breakdown of the stump should be avoided. In certain climates, such as extremely hot or humid areas, studies should be made of the use of the hard socket in preference to the soft socket lined with rubber and leather. As cost is always a factor, wherever leprosy patients are cared for, the prosthetic centre should continually search for inexpensive local materials to use in the manufacture of prostheses.

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Abstracts

1. **Patterns of sensory loss in lepromatous leprosy**, by T. D. SABIN and J. D. EBNER. *Int. J. Lepr.* 1969, **37** (3), 239-48.

At Carville, Louisiana, U.S.A., the authors compared thermographs depicting skin temperature patterns of normal subjects with the configuration of sensory loss to pinprick in a series of patients with lepromatous leprosy, and found that the pattern of sensory loss tends to involve the cooler skin surfaces earliest and then progresses on the basis of relative skin temperature. Thus the limbs are affected first—the dorsa of feet, the lateral aspects of legs, and the dorsal aspects of hands and forearms—whereas the scalp, axillae, intergluteal fold and the inguinal areas are all warm regions that tend to show normal sensation even in far advanced cases.

W. H. Jopling

2. **Double-blind controlled clinical trial of clofazimine in reactive phases of lepromatous leprosy**, by A. B. A. KARAT, A. JEEVARATNAM, S. KARAT and P. S. S. RAO. *Br. Med. J.,* 1970, Jan. 24, 198-200.

A double-blind controlled trial in 24 patients with lepromatous leprosy in reaction showed that clofazimine (B 663, Lamprene) successfully controlled erythema nodosum leprosum and had a useful effect in preventing recurrence once the reaction had been controlled. The dosage of clofazimine was 100 mg 3 times a day, and the authors consider the drug to be safer and more effective than prednisolone. The only side-effect was red/black skin pigmentation, and the patients were willing to accept this in return for relief of symptoms.

W. H. Jopling

3. **Dapsone-resistant *Mycobacterium leprae* in a patient receiving dapsone in low doses,** by S. G. BROWNE. *Int. J. Lepr.,* 1969, **37** (3), 296-301.

A Nigerian man, aged 35 years, suffering from advanced lepromatous leprosy, was treated at the Oji River Leprosy Settlement. The patient's Morphological Index (MI) was 35% initially and the Bacterial Index (BI) 3.3 (maximum 4). Dapsone 50 mg was given twice weekly for 52 months, each dose of the drug being swallowed in the presence of a doctor or a leprosy worker. After 6 months treatment, the MI was 0% and after 35 months "even fragmented bacilli and acid-fast dust were no longer to be seen" in skin smears. After 52 months, small fleshy papules appeared on the skin of the arms and the lumbar region. The histological picture was granulomatous tissue crammed with *Mycobacterium leprae,* 80% of which were morphologically normal. "There was no suggestion of any defect in intestinal absorption" (of dapsone). Apparently normal skin, earlobes and nasal mucosa "remained free from bacilli". Tissue from one of the papules was injected into the footpads of mice receiving dapsone in their diet. Multiplication of *Myco. leprae* was found in 10 out of 12 footpads of mice receiving dapsone 0.006% in their diet, and 6 out of 12 footpads of mice receiving 0.025% dapsone.

The significance of this case history is discussed, including its relevance to field work by medical auxiliaries. Dapsone given in a "low-dose regimen facilitates treatment. . . . On balance, then, the risk of the emergence of resistant strains is most probably outweighed by the undoubted advantage of a reduced rate of complications" (of low dose dapsone). [The rate of excretion of dapsone varies widely and may be very rapid. Now that the minimum inhibitory concentration of dapsone for *Myco. leprae* is known approximately, a rational discussion of

dapsone dosage and treatment intervals in relation to maintaining satisfactory anti-bacterial blood levels would have added to the value of this paper. That alternative low dosage regimens are rational, such as 10 or 25 mg daily, 50 mg thrice weekly or 75 or 100 mg twice weekly, should be more widely known.]

C. S. Goodwin

The following 3 abstracts are reprinted, with permission, from *Trop. Dis. Bull.,* 1970, **67**, 10:

4. **Die Verbreitung der Lepra in Spanien und die seit 1948 durchgeführten Bekämpfungsmassnahmen** by E. H. FINK. (Prevalence of leprosy in Spain and control measures since 1948). *Ztschr. Tropenmed. Parasit.,* 1970, **21**, No. 2, 135-46.

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

"By assessment of epidemiological and clinical data a general account of leprosy prevalence in Spain is given as it has evolved since a campaign to eradicate this disease was started in 1948:

"About 5000 leprosy patients are registered with the Health Authorities in Madrid; more than 1200 of them are considered sufficiently treated and cured, and more than 500 show acid-fast bacilli on bacterioscopic examination. These cases are distributed over four endemic areas, namely (arranged in the order of decreasing importance) Andalusia, the Levant Provinces from Alicante to Barcelona, the Canaries, and Galicia, a region north of Portugal. Since the prevalence of active cases has not shown any striking changes during the last 10 years, a consolidation phase—as defined by WHO criteria—has probably been achieved. Nevertheless, eradication of leprosy in Spain is not to be expected in the immediate future as indicated by the annual incidence. During recent years, an increasing number of early cases, i.e. within 1 or 2 years after the first clinical manifestations, have been detected.

"The institutions taking part in the campaign and their activities are described. Despite the low infectivity of leprosy, exchange of information between the Public Health Authorities of neighbouring European states is recommended. This would also confer advantages on those patients moving from one country to another as far as uninterrupted medical care is concerned."

5. **Nodular vasculitis-like lesions as the initial manifestation of leprosy**, by O. CANIZARES and R. ANDRADE. *Derm. Int.,* 1969, **8**, Nos. 2/4, 50-56.

This is a description of a Puerto Rican woman with skin lesions similar to the erythema nodosum leprosum (ENL) seen in lepra reaction, together with oedema of feet, lower legs and hands. These clinical signs first appeared 9 months previously, when she was pregnant, the lesions at that time being confined to the legs but later extending to other parts such as the skin of thighs and forearms. Macules on the trunk were diagnosed as tinea versicolor. There were no neurological signs; smears from the lesions and from nasal mucosa were negative for acid-fast bacilli, and the lepromin test was negative. Biopsies from the lesions showed a diffuse inflammatory infiltrate consisting of histiocytes, many of them vacuolated, a few lymphocytes and fewer plasma cells, together with large numbers of bacilli—the typical features of lepromatous leprosy. The sections showed no evidence of vasculitis. The authors conclude that the erythematous nodular lesions marked the onset of the patient's leprosy—a very rare phenomenon.

[Skin lesions which are bacilliferous on biopsy *always* provide positive smears, and the fact that the authors failed to demonstrate bacilli in smears raises serious doubts with regard to their technique.]

W. H. Jopling

6. **Ethambutoli en el tratamiento de la lepra. Resultados del tratamiento de 20 pacientes durante 12 meses,** by A. SAUL and R. BARCELATA. (Ethambutol in the treatment of leprosy. Results of treating 20 patients for 12 months) *Derm. Revta Mex.,* 1969, **13,** No. 2, 152-60. English summary.

Ten adult men and 10 women suffering from leprosy were treated with ethambutol in a single daily dose of 800 mg per day. Sixteen patients who had the lepromatous form of the disease were treated for 12 months; 3 with the tuberculoid form and 1 with the dimorphic form were treated for 6 months. Seven of the patients had received previous treatment with dapsone. The evolution of the disease ranged from 1 to 20 years. Improvement of the lepromatous lesions, such as disinfiltration of the lesions, flattening and necrosis of nodules and healing of ulcers, was seen after 15 to 30 days. After 12 months, the authors considered that there was clinical cure in 4 of the patients with lepromatous leprosy, improvement in 3 and relapse in 5. Smears remained positive in 9 patients at 12 months. The 3 patients with the tuberculoid form had lost all their lesions at 6 months, and the dimorphic patient appeared to be cured at 12 months. No lepra reaction or side-effects were observed. Since 5 of the patients with the lepromatous form, who were initially much improved, began to show active lesions again after 9 months, it is possible that the bacilli had become resistant to the drug. Accordingly, it is recommended that ethambutol should be combined with dapsone and that further trials should be made.

F. Hawking

The following 2 abstracts are reprinted, with permission, from *Trop. Dis. Bull.,* 1970, **67,** 11:

7. **Hallazgo de bacilos ácidos resistentes en la pulpa dental da pacientes leprosos,** by R. CESPEDES and B. MEONO. (Acid-resistant bacilli in the dental pulp of patients with leprosy) *Acta Méd. Costarric.,* 1970, **13,** No. 1, 105-10.

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

"Eighty-two biopsies from active Hansen's disease removed from dental pulp were studied.

"Ten patients had invasion of the pulpar tissue by acid resistant bacilli with important histopathological changes.

"We emphasize the fact that finding the bacilli in the dental pulp also implies the possibility of finding the bacilli in the dentine with the corresponding histopathological alterations."

8. **Preservation of sensation in a cutaneous vascular malformation in lepromatous leprosy,** by T. D. SABIN. *New Engl. J. Med.,* 1970, **282,** No. 19, 1084-5.

After discussing the evidence for the view that in lepromatous leprosy the cooler areas of the skin contain the greatest numbers of leprosy bacilli and have the most marked sensory loss, the author describes the case of an adult male who commenced treatment for lepromatous leprosy in 1952. By 1967 smears and biopsies become bacteriologically negative but by this time the patient had developed extensive sensory loss, together with weakness of the intrinsic muscles of both hands. However, on testing the hands for sensory loss, it was noted that there was a small island of preserved sensation on the palm of the right hand exactly where he had a congenital capillary vascular malformation. A thermograph demonstrated that this area was strikingly warmer than the surrounding skin. The hypothesis is put forward that during the active phase of the disease the warmth of this area was sufficient to create a relatively unfavourable site for multiplication of leprosy bacilli, thus sparing the intracutaneous nerve endings and networks.

W. H. Jopling

The following 4 abstracts are reprinted, with permission, from *Trop. Dis. Bull.*, 1970, **67**, 12:

9. **Leprosy in the Bible,** by S. G. BROWNE. 20 pp. 1970. London: Christian Medical Fellowship.

In this scholarly study of leprosy in the Bible, the author deals with the Old and New Testaments separately. After quoting from the Old Testament he makes it clear that leprosy was quite unknown in the lands of the Bible at the time of Moses and the patriarchs, and the word *tsara'ath* did not stand for a disease but rather for a social ill characterized by visible skin blemishes, engendering fear and requiring ritualistic cleansing. In the translation of the Old Testament from Hebrew into Greek—the Septuagint—the word *tsara'ath* is replaced by *lepra,* a word representing a generic concept of scaliness and containing no essential idea of ritualistic uncleanliness or defilement. The words *leprosy* and *leprous,* as they appear in the Bible today, are derived from the Vulgate—Jerome's translation of the Septuagint into Latin. Turning to the New Testament and the references to *leprosy* in the Gospels, it is probable that some of these refer to true leprosy, as the disease "certainly existed in Greece, Italy and north Africa at the time of our Lord", but no positive help comes from archaeological findings in Palestine. Finally, the author discusses the present-day role of the Christian missionary in leprosy work, and he suggests that Christ's command to His disciples to "cleanse the leper" be broadly interpreted as "Seek the outcast, the underprivileged, all those who suffer because of society's attitudes. Help them in all ways. . . ."

W. H. Jopling

10. **Prikaz dva novootkrivena slučaja lepre dijagnostikovana u infektivnoj klinici u Beogradu, sa osvrtom na problem lepre u našoj zemlji,** by M. PETROVIC and N. ANDELKOVIC. (Two newly discovered cases of leprosy diagnosed at the clinic for infectious diseases in Belgrade and general aspects of the leprosy problem in Yugoslavia) *Glasn. Zav. Zdrav. Zašt. SRS.,* 1969, **18**, No. 5, 31-45.

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

"In the period 1919 to 1967, 120 cases of leprosy have been reported, 55 of which with fatal issue (lethality 45.8%). The most important focuses of leprosy in our country are in Bosnia, Montenegro and Serbia.

"From 1945 to 1967, 8 cases and another 2 in 1968, were reported in Serbia. During the investigation of leprosy areas in Sandzak, in June 1968, 3 further cases were discovered. Of the total of 13 cases reported in the Socialist Republic of Serbia 10 are males (76.9%) and 3 (23.1%) females.

"Nine cases are from the interior of Serbia, 2 from the Autonomous Province of Vojvodina and 2 from Kosovo. Of the first 9 cases, 4 are from the surroundings of Prijepolje, 1 from Sjenica and 1 from Nova Varos.

"The 2 cases described in this paper are of lepromatous (open) type of autochthonous leprosy. The clinical diagnosis has been confirmed by isolating the *M. leprae* in body secretions and by histopathological findings.

"The source of infection in these cases has been in the family; the focuses of leprosy in our country have subsisted through intrafamilial infection in districts where hygienic and general living conditions are poor.

"The problem of leprosy has not yet been solved in Yugoslavia. The occurrence of even a few cases of the lepromatous type of disease in a region must be considered as a health problem and measures should be taken to assure its solution."

11. **A study of epidermal melanocytes in the hypopigmented patches of leprosy,** by A. NAYAR and C. K. JOB. *Indian J. Med. Res.,* 1970, **58**, No. 2, 187-93.

This investigation was undertaken to determine whether the hypopigmented lesions in leprosy

could be attributed to "a diseased melanocyte system". From 10 patients with indeterminate or tuberculoid leprosy who had flat, hypopigmented, skin macules (group I), and from 10 patients with dimorphous [borderline] or "major tuberculoid" leprosy who had raised "infiltrated", hypopigmented skin lesions (group II), skin biopsies were taken, one from the hypopigmented lesion and one from the "symmetrically opposite side of the body, where the skin showed no obvious change". Epidermal sheets were prepared and stained with buffered dopa solution.

The number of melanocytes in normal skin from the upper and lower limbs varied from 700 to 1885 per mm^2 and from the back, chest and abdomen from 1026 to 2131 per mm^2. In 7 of the 10 patients in group I there was a decrease in the number of melanocytes in the hypopigmented skin compared with the control one, in 5 of these the decrease being statistically significant, and the number ranging from 596 to 1368 per mm^2. In group II in 6 of the 10 patients there was a reduced melanocyte population in the hypopigmented skin lesions, 4 of these showing a statistically significant decrease with numbers ranging from 523 to 962 per mm^2. In 6 of the 20 patients there was an increase in the number of melanocytes, 3 of these being statistically significant. Variations in the intensity of staining of melanocytes, their size, length of dendrites and branching are described and illustrated in 8 microphotographs. No consistent pattern was observed.

The authors conclude that "the majority of the lesions studied showed a reduction in melanogenic activity", and suggest that this is of "etiological significance in the pathogenesis of hypopigmentation in leprosy".

C. S. Goodwin

12. **The sensitivity to dapsone (DDS) of *Mycobacterium leprae* from patients with and without previous treatment**, by C. C. SHEPARD, L. LEVY and P. FASAL. *Am. J. Trop. Med. Hyg.*, 1969, **18**, 2, 258-63.

The sensitivity of these strains of *Mycobacterium leprae* was determined by inoculating 5×10^3 bacilli into the footpads of mice and then administering dapsone in the diet from the day of infection. The amount of dapsone in the diet was 0.0001% and this quantity is calculated to give concentrations in the blood and tissues of 0.02 μg/ml, which is x 100 that present in man on standard doses of the drug. Four months after the day of infection, the number of bacilli in homogenates of the pads of the untreated mice was compared with the number in the treated animals and, if necessary, the counts were repeated at intervals of 2 to 3 months.

All of 11 strains from untreated patients and 6 from patients who had received some treatment with dapsone multiplied in treated mice at a much slower rate than in untreated ones, and these strains were regarded as dapsone-sensitive. By contrast, 15 isolates from 10 patients who had been treated with sulphones for 11 to 20 years (some having started treatment with either sodium glucosulphone or sodium sulphoxone) were regarded as dapsone-resistant, because they grew at approximately the same rate in the treated mice as in the untreated ones. The authors suggest that treatment with the diamino-subsituted forms of dapsone may have contributed to the development of this resistance.

S. R. M. Bushby

13. **Nerve abscess in leprosy**, by K. K. KUNDU. *Bull. Calcutta Sch. Trop. Med.*, 1968, **16**, 131.

A patient suffering from lepromatous leprosy, untreated and of 7 years' duration, presented with peripheral paraesthesiae, widespread enlargement of superficial nerves, and two soft swellings in the right median nerve. The pus evacuated after incision under local anaesthesia contained numerous non-cultivable acid-fast organisms. Histopathological examination of the skin and nerves revealed typical changes characteristic of lepromatous leprosy.

S. G. Browne

14. **Deux cas d'abcès lépromateux aigus du nerf cubital. (Two cases of acute lepromatous abscess of the ulnar nerve)**, by A. CARAYON, J. LANGUILLON, L. MAYDAT, I. FAYE and M. BOURGES. *Bull. Soc. Méd. d'Afrique Noire,* 1969, **14,** 659-661.

The authors describe two examples of acute and localized softening of the ulnar nerve (pseudo-abscess) occurring in patients with histologically-confirmed lepromatous leprosy. In the first, from three separate areas of softening, "pus" containing numerous acid-fast organisms was evacuated, the patient's high temperature falling to normal after the operation. In the second case a single area of softening was seen, in the nerve lodged in the epitrochlear tunnel; the "pus" contained many acid-fast organisms.

In the first patient, the nerve changes occurred during an acute exacerbation; in the second case the "abscess" appeared during a clinical relapse some 20 years after apparent cure.

S. G. Browne

15. **Absorption and excretion of ^{35}S dapsone in dermatitis herpetiformis,** by J. O.'D. ALEXANDER, E. YOUNG, T. McFADYEN, N. G. FRASER, E. P. DUGUID and E. M. MEREDITH. *Br. J. Derm.* 1970, **83,** 620-631.

The possibility that dapsone might be concentrated in inhibitory amounts in the lesions of leprosy, and particularly in the vicinity of *Myco. leprae,* was investigated and reported by K. R. Chatterjee and R. K. Poddar in a paper entitled "Radio-active tracer studies on uptake of diamino-diphenyl-sulphone by leprosy patients" (*Proc. Soc. exp. Biol. Med.* (1957) **94,** 122).

In the present paper Alexander and his colleagues, investigating the metabolism of dapsone in patients suffering from dermatitis herpetiformis, and using modern radiochromatographic techniques, report studies that are of interest to leprosy workers.

They found that the concentration of tagged dapsone was similar in the lesions studied to that in the normal skin; dermatitis herpetiformis, in contrast to leprosy, is an acute disease, characterized pathologically by an early eosinophilic leukocyte reaction progressing to a mild chronic inflammatory infiltrate which heals in a fortnight. However, there was a concentration of isotope in the papillary layer of the upper corium (an area often primarily affected in bacilliferous leprosy), but not in the papillary capillaries. The authors found no evidence that any local concentration of dapsone was necessary for its observed efficacy.

In comparing the isotope findings with chemical estimations of dapsone levels in the serum, the authors found that the latter were less consistent and less reliable than the former. There was considerable individual variation in the serum levels, a fact that may be correlated with the occurrence of cyanosis and methaemoglobinaemia unrelated to the dose given.

The rapid excretion of dapsone indicates a half-life of about 72 h, but the remaining measurable quantity often demonstrable in the serum may be therapeutically effective in the individual patient.

S. G. Browne

Erratum

Lepr. Rev. **41** (4), p. 223

In the title of the paper by Ellard *et al.* Sulphadimethozine should read Sulphadimethoxine.

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