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Leprosy Review

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LEPRA**

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Editorial

EPIDEMIOLOGY AND LEPROSY

Military metaphors and figures of speech come readily to the pens of leprologists dealing with the epidemiological aspects of their subject. We read of campaigns, and attacks (on the disease itself, on victims of mycobacterial aggression, and on the aggressor). We hear reverberating down the laboratory corridors and into the field of operations such exhortations as "seek and destroy", addressed indiscriminately to the drugs themselves and those who deploy them.

But leprosy is more than a chronic mycobacterial infection, and to control its ravages and prevent its spread will require more than a simple campaign to "seek and destroy". It is here that the science and practice of modern epidemiology comes into its own. In regard to leprosy, this cannot be merely a descriptive exercise, or an identification of infective agents and vectors; not even, or only, a predominantly experimental investigation in the laboratory—but an amassing, a study and an analysis of the multifactorial data concerned with the transmission and persistence of leprosy in a community, with the object of establishing and validating aetiological hypotheses leading to control and eventual eradication of the disease.

At once we plunge into a morass of ignorance, unproved assumptions, and sheer prejudice, and a reticence and ill-concealed shame that still characterize leprosy above all other diseases. We also must admit that the very crux of the leprosy problem—our lack of knowledge of the exact mode of transmission of the bacilli—continues to baffle and to challenge us. This obligate intracellular parasite of human tissue cells must, on occasion, leave its host, remain viable for an unknown length of time, and eventually be introduced by an unknown route into a human being—whether susceptible or not will depend on some little-understood genetic configuration. At once, unanswered questions are raised concerning extra-human reservoirs, vectors, healthy carriers, inapparent infections, and resistant extra-corporeal and viable infective agents. And in the larger setting, we face the need for precise definition of "close contact", and methods of appraisal of the risks of infection. The vague concepts of socio-economic status, poverty, overcrowding, nutrition, personal hygiene, level of public health, etc., can no longer be decisively invoked as relevant or determinant factors unless and until they earn some degree of scientific and experimental respectability.

Pragmatic methods of case-finding, early diagnosis and adequate treatment should—where local circumstances render the exercise practicable—show a definite reduction in incidence after some years. But in very few instances has such a happy event come to pass. And the overall cost of discovering a single case of leprosy may vary, in South America, from £30 to £6000. In other leprosy control schemes, such as the LEPRO programme in Malawi based on regular diagnostic and treatment circuits, costs may be lower, much lower, but whole-population-screening procedures or selective screening of high-risk or vulnerable groups, may

still be prohibitively expensive for a developing country. Effective and economic procedures have still to be worked out, if patients with incipient or early—and limitable and curable—infections are to be detected, with a minimal number of false-negatives (or false-positives). New studies are needed on all these points if leprosy is ever to be controlled effectively on a world scale.

Prevention is better than cure, it is true, but secondary prevention (i.e., rendering non-contagious every patient suffering from multibacillary leprosy), must eventually yield pride of place to primary prevention, by vaccination or chemoprophylaxis, or a combination of the two, coupled with—and most importantly—the application of those still unknown general principles that will assuredly become evident as the result of prospective epidemiological studies in typical populations exposed to different leprosy risks.

Is all this talk of epidemiology and leprosy an example of anxious concern with small and relatively unimportant fires while the whole of Rome is threatened with devastating conflagration—widespread malnutrition, to say nothing of nuclear holocaust and pollution? The sum total of human suffering caused by the ravages of leprosy is such that no scientific or humanitarian effort should be spared, in the context of all the other ills and threats to which the human race is exposed, to find out more, so that we may help the better. “The context” today means not only the other prevalent endemic diseases, but the whole gamut of nutrition and economics, of urbanization and industrialization. And leprosy detection and control must eventually be integrated into that comprehensive medical care to which every citizen has an inalienable right.

Meanwhile, we “soldier on”, and confidently await more adequate epidemiological insights and directives.

News and Notes

DAMIEN-DUTTON AWARD FOR 1971

The 1971 Damien-Dutton Award has been presented to Dr Chapman H. Binford at a ceremony at the Capitol, Washington, U.S.A. Many distinguished guests, representing the worlds of medicine, scientific research, and voluntary agencies, attended the ceremony itself and the Cosmos Club luncheon that followed.

The congratulations of all workers in leprosy go to Dr Binford on this well-deserved tribute to his outstanding contributions to leprosy research. As pathologist and Registrar of Leprosy to the Armed Forces Institute of Pathology in Washington, as an indefatigable worker and organizer in connection with the Leonard Wood Memorial and the International Leprosy Association, Dr. Binford has exerted a most commendable scientific and humanitarian influence on the direction of leprosy research over several decades.

AWARD TO DR C. K. JOB

The first award of the Dr Chandra Sahu Gold Medal has been made by the Hind Kusht Nivaran Sangh to Dr C. K. Job, Professor of Pathology at the Christian Medical College, Vellore, S. India, in recognition of his outstanding contributions to leprosy research in India. Dr Job's record of writing, teaching, and laboratory investigations in microbiology, histopathology, and electronmicroscopy have earned him the admiration of a wide circle of friends.

THE STAR, CARVILLE

With its issue of September-October, 1971, *The Star* attains its 30th anniversary. This attractive and well-illustrated magazine, published by the patients in the United States Public Service Hospital at Carville, Louisiana, now has a circulation of 37,000 and reaches 105 countries as well as every State in the U.S.A.

Over the years, Carville patients have through their magazine done much to promote knowledge and understanding of the disease from which they suffer. *Leprosy Review* sends its greetings and best wishes for the future.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE

Dr S. G. Browne, Chairman of the Editorial Board of *Leprosy Review*, was elected a Vice-President of the Royal Society of Tropical Medicine and Hygiene at the Annual General Meeting of the Society held on 17 June, 1971.

NATIONAL HEALTH COUNCIL, BRAZIL

Dr. Ernani Agricola, who is well known for his long service to leprosy, has been nominated by the Ministry of Health of Brazil to be the Vice-President of the National Health Council.

LEPROSY IN HONG KONG

For some little time past, it has been evident that leprosy was being tackled successfully in Hong Kong through a co-operative effort of Government and a voluntary agency, each supplementing the work of the other. The control of leprosy in this rather special and rather privileged and circumscribed area is now considered to be sufficiently advanced for the Government to issue a press release, on 16 June, 1971, in the following terms:

“Leprosy under control in Hong Kong—Government plans to phase out leprosarium”.

Plans for phasing out and eventually closing the leprosarium at Hay Ling Chau are now being considered by the Government.

Leprosy has now been brought under control in Hong Kong, thanks to well-planned care and control programmes conducted by the Leprosy Mission (Hong Kong Auxiliary) and the Medical and Health Department.

The general pattern throughout the world is to integrate leprosy treatment into normal medical services, as it is thought that the admission of patients into a leprosarium, as distinct from a general hospital, makes subsequent rehabilitation and integration into the community more difficult. For many years the Social Hygiene Services of the Medical and Health Department have been providing out-patient treatment for leprosy patients through their special “skin” clinics, and leprosy patients suffering from other diseases are already being treated in the public wards of Government hospitals.

The number of patients in Hay Ling Chau has been decreasing each year. Once there were 540 patients, today there are only 215, including 118 non-contagious patients who are admitted only for follow-up, observation, convalescence, etc.

By 1974, when the change is contemplated, it is estimated that there will be fewer than 80 patients needing continued institutional care while others can be treated on an out-patient basis.

For these 80 patients the Government plans to make available a special unit in the infectious disease block of the Lai Chi Kok Hospital now under construction on a promontory to the west of Lai Chi Kok bay. In this block there will be ample facilities for separating patients with different infectious diseases.

So far, more than 1000 people have been treated and discharged from Hay Ling Chau, and referred back to Government out-patient clinics for follow-up by Government.

“There is no danger to people who visit or live near a leprosy patient, as the disease is spread only by direct and continuous contact between one person and another over a long period of time, and modern and effective treatment renders the patient non-infectious within a short period of time,” a spokesman for the Medical and Health Department reiterated today. “The vast majority of people

have a natural resistance to the disease and are able to destroy the invading germs."

"The interest and concern shown by members of the community towards leprosy patients has been most encouraging," he said.

Since the opening of the leprosarium in 1951, about 40,000 local and overseas people, an average of 2000 a year, have visited Hay Ling Chau to meet and talk to patients. Students from a well-known local co-educational secondary school go to Hay Ling Chau each Saturday to help the younger patients with their lessons or join them in an afternoon of entertainment.

LEPROSY IN IRAN

While leprosy may not constitute a major health problem in Iran, energetic action must be taken if the disease is ever to be controlled. In a population of some 25 million, sparsely scattered for the most part in rural areas, the official estimate of the number of leprosy patients is about 6000, of whom 4456 are registered. The real prevalence, however, may be considerably higher if suspicions are confirmed that high rates are to be found among the nomadic tribes of Mongolian extraction in the north and west of the Caspian Sea, and among the settled villagers of Azerbaidjan to the east. The total figure may well prove to be over 20,000.

Family and village foci are apparently common, especially in those areas where roads and communications are poor and where medical facilities are minimal. The male/female ratio is said to be 3 : 1.

The attitude to leprosy varies from district to district; in some areas it is not unknown for victims to be driven from their villages, but in others the principle of domiciliary treatment is accepted.

There is a central dispensary in Tehran in the Nedjat Hospital where about 400 leprosy patients receive regular treatment (out of 1681 registered). The 2 main sanatoria are situated at Meched, about 1000 km east of Tehran, in which there are about 556 patients, and at Tabriz (with about 620 patients). In addition, an agricultural centre at Behkadeh provides ex-patients with the opportunity of living away from a hostile society that has rejected them.

One of the happier features of the health situation is the army hygiene teams, which attempt to control endemic diseases in the most out-of-the-way villages; plans are afoot for the inclusion of leprosy among the diseases they tackle.

An attempt to promote legislation for the compulsory segregation of all patients discovered to be suffering from lepromatous leprosy has proved abortive, there being insufficient accommodation in the two leprosaria to make such a procedure possible.

An active Leprosy Relief Association is in existence, in which Her Imperial Majesty the Queen of Iran takes a genuine interest. A French-Canadian team is shortly to begin work in Iran; Dr R. G. D. Garrigue (of the *Compagnie Internationale de Développement Rural*) has carried out a comprehensive survey of the leprosy problem in Iran and made recommendations.

Dr S. G. Browne recently visited Iran to lecture in Tehran and offer advice. The interest of the medical schools and their staff in Tehran, Meched and Tabriz should be enlisted in the investigation and control of the leprosy endemic in Iran, and medical students should be challenged with the need to do more for the sufferers from leprosy in the context of the developing health services.

Any doctor (English- or French-speaking) experienced in leprosy and wishing to co-operate in the Iran programme, is invited to write to:

His Excellency Dr A. H. Radji, Acting Director, *Bureau de l'Association d'Assistance aux Lépreux*, Avenue Derakhti, Koutche Naraghi 104, Tehran, Iran.

Or to:

Dr R. G. D. Garrigue, Maison Médicale de l'Ermitage, 60 Autrechès, France.

LEPRA AND THE EAST CENTRAL STATE, NIGERIA

The British Leprosy Relief Association (LEPRA), co-sponsor of the *ad hoc* Committee that has been meeting from time to time in London to consider how best to help co-operatively in meeting the leprosy situation in the East Central State of Nigeria, recently received a report from Mr Brian Wheatley, F.R.C.S., who had been conducting an on-the-spot enquiry into the situation on behalf of LEPRA and the *ad hoc* Committee. Mr Wheatley, whose services are underwritten by LEPRA, has been given the official position of Adviser in Leprosy to the East Central State Government. In this capacity, he has been able to secure a gift of vehicles from UNICEF for use in the State, and is currently reorganizing the leprosy control service, continuing and hastening the process of integration which was begun some years ago.

TRAINING IN OPHTHALMOLOGY FOR LEPROSY WORKERS

Two distinguished eye specialists, both experienced in the ocular manifestations and complications of leprosy, would like to place their expertise at the disposal of doctors and medical auxiliaries working in leprosy. Their offer was made, and accepted, at a recent meeting of the Executive Committee of LEPRA. Two principal ways of helping are suggested.

First, the specialists would welcome at their ordinary hospital clinics (in London and in Southend-on-Sea, Essex) any doctors from abroad who are interested in leprosy and who happen to be passing through Britain, or staying near London. They would be pleased to instruct these doctors in the recognition and management of the ocular complications of leprosy, including the use of the corneal microscope, the indications for medical dilatation of the pupil and for the local and systemic administration of corticosteroids, the operative technique of sector iridectomy, etc.

Second, where suitable financial arrangements can be made to cover travelling and other expenses, they would be willing to visit leprosy centres abroad with the object of instructing the medical and nursing staffs as mentioned above. In addition, reliable statistics on the prevalence and nature of ocular complications in leprosy could be collated during such visits. Contact should be made direct with either of these specialists:

Mr H. E. Hobbs, F.R.C.S., 46 Wimpole Street, London W.1,

or

Mr D. P. Choyce, F.R.C.S., 45 Wimpole Street, London W.1.

SECOND CONGRESS OF THE ASSOCIATION DE LEPROLOGUES DE LANGUE FRANÇAISE

This young and very lively Association held its Second Congress in the historic St. Louis Hospital in Paris from 8-10 September, 1971. The 76 participants came from a score of countries. Understandably, Metropolitan France was well represented, as well as Belgium, Switzerland, Italy, Israel, and Great Britain, while the happy professional relations persisting between France and French-speaking overseas countries were made evident by the presence of doctors from the West Indies, several African countries, and the Far East. The French Ministry of Health, the Order of Malta, ELEP, and the World Health Organization also took part in the proceedings. The International Leprosy Association was represented by its Secretary-Treasurer, who also is a *Conseiller Technique* to the French Association. The principal papers presented at the Congress and summaries of the discussions will be published in 2 issues of *Acta Leprologica*, by kind collaboration of the publishers, the Order of Malta.

After the opening ceremony the participants immediately began the scientific business of the meeting, with wide-ranging papers by Lechat and Labusquière, and detailed consideration of the state of the leprosy campaigns in Senegal, the Ivory Coast, Morocco, Guadeloupe, Vietnam, South India (Polambakkam), Tunis, Algeria, French Guiana and Syria. A long and useful session on therapy provided up-to-date information on clofazimine (Lamprene, Geigy), rifampicin and ethionamide, as well as summaries of recent work on dapsone and the long-acting sulphonamides. In the treatment of reaction in leprosy, thalidomide and the immuno-suppressive drugs were discussed, in addition to clofazimine.

A special session on Leprosy in Europe disclosed a far from reassuring picture of the disease in Italy and the Iberian Peninsula, and a changing pattern in Britain, France and Switzerland consequent on recent importations of leprosy. Recent work on attempts at cultivation of *Myco. leprae*, on skin reactions to different allergens, and on cell-mediated immunity was given prominence. The excellent surgical investigations of the French surgical teams in France itself and in Africa, and good operative results were reported by Metropolitan orthopaedic surgeons, ophthalmologists and rhinologists.

Receptions for the participants were given by the Order of Malta, both in Paris and at the Prieurie d'Osmoy. Professor Merklen, the President, was ably assisted in the organization of the Congress by Professor Cottenot, and by the Secretary General of the Association, Professor Basset. A general meeting of the Association was held during the Congress.

Obituary Notice

JAMES ARTHUR KINNEAR BROWN, C.M.G.
(1902-1971)

James Arthur Kinnear Brown, C.M.G., M.D., B.Sc., D.T.M. & H., died suddenly at Hale, Cheshire, on 28 September, 1971. The news of his passing, at the age of 69, will be received with real sadness by his friends in many lands; the cause of leprosy has lost a valuable and valued worker and advocate.

Born in Hull, Yorkshire, Kinnear Brown received his early education at Hymer's College in Hull, and entered the Faculty of Science of Manchester University, graduating B.Sc. with Honours in chemistry in 1924. He then turned to medicine, and qualified as a doctor in 1929, gaining the diplomas of M.R.C.S. and L.R.C.P., and the M.B., Ch.B. degrees of Manchester University. During this time he lived in Hartley College, in company with Methodist ministerial students. He was thus well known to two generations of men who subsequently were ordained to the Methodist ministry. He took the course in Tropical Medicine at the Liverpool School, gaining the D.T.M. & H. diploma in 1930.

Having married Hilda Kirkland, S.R.N., S.C.M., a ward sister at St Mary's Hospital, Manchester, the previous year, he left England with his wife in April, 1930, for Eastern Nigeria as a medical missionary of the Methodist Missionary Society. He served a 9-month apprenticeship at Itu Leprosy Settlement, a pioneer establishment organized by Dr A. B. MacDonald of the Church of Scotland. Kinnear Brown was then appointed superintendent of the embryo Owerri Native Administration Leprosy Settlement which the Church had been asked by the Government to establish. With characteristic vision and forthrightness, he declined the offer of a stretch of infertile and waterless land that had been a brickfield, and chose instead a densely-forested area to the north of Uzuakoli. The new settlement was officially opened in 1932. Within the next 4 years, thanks to real co-operation between everybody concerned, and to Brown's administrative ability, Uzuakoli became a well-organized and tastefully laid out settlement, where leprosy sufferers needing in-patient care could obtain it. At the same time, the foundations were laid for an extensive system of segregation villages: with the support and encouragement of local chiefs and their people, families containing a member suffering from leprosy were established in loosely-knit communities on fertile land. Treatment was provided by the newly-developed teams of leprosy aides. During his furlough in England in 1934, Kinnear Brown gained the M.D. degree of Manchester University, the subject of his thesis being Leprosy and Diet.

In 1937, he had to return to England for medical and domestic reasons. He was in general practice in Altrincham, Cheshire, for 14 years—covering the 1939-45 war. For his services in this capacity, he was made a Life Member of the British Red Cross.

In 1951, he returned to Africa as Senior Specialist, Leprosy, with the Uganda Government. He reorganized the existing leprosy settlements sponsored by

Christian missions, both Roman Catholic and Protestant, and ensured a happy working together of government and voluntary agencies. Dapsone was provided for all those needing it. He inaugurated a mass treatment campaign throughout Uganda, including 85 villages built by communal labour, and over 200 district clinics. He carried out extensive fact-finding surveys in Uganda and also in Kenya, and did the preliminary work for the investigation into the possible value of BCG vaccination in the prevention of leprosy, with which his name will always be associated. It was in 1960 that this latter project was inaugurated, under the aegis of the Uganda Government and the Medical Research Council, and with financial help from the Ministry of Overseas Development.

Meanwhile, he had—in 1951—been elected a Fellow of the Royal Society of Tropical Medicine and Hygiene, and—in 1957—a member of the World Health Organization Expert Committee on Leprosy. He was Honorary Lecturer in Leprosy at Makerere University Medical School, Kampala, and taught successive batches of Leprosy Assistants at Kumi, Uganda. In 1963 he had to resign his full-time appointment on health grounds, but was able to continue in an advisory and supervisory capacity as Honorary Consultant in Leprosy to the Uganda Government and representing the Medical Research Council. He was the principal author of the First and Second Reports on the BCG vaccination investigation, and was, indeed, engaged on the compilation of the Third Report when the end came.

For his outstanding work in Uganda, he was made a Companion of the Most Distinguished Order of St Michael and St George in 1967.

Kinnear Brown was the author of over 60 publications on his subject, and wrote a chapter in Trowell and Jelliffe's *Diseases of Children in the Tropics and Subtropics*. He was a member of the International Leprosy Association and a familiar figure at its Congresses.

Many folk in Nigeria and Uganda, as well as in England, will mourn his passing, and remember him as a conscientious and untiring worker, possessed of a keen enquiring mind, a flair for administration, and organizing ability of no mean order. Leprosy patients will be grateful to him for his kindness and keen concern for their welfare. He was a Christian gentleman who carried his ideals of selfless service into his daily work, whether it was diagnosis and treatment, or demonstrating and lecturing, or painstakingly arranging the details of a scientific investigation.

Our sympathy goes out to his widow in the sudden distress of bereavement, and to his married daughter and son.

Orthopaedic Appliances for Leprosy Patients

The Fixed Ankle Brace Walker^{*†}

LUTZ WOLLSTEIN‡

*Orthopaedic Tech. Master, Schieffelin Leprosy Research Sanatorium,
Karigiri, South India*

JOHN GIRLING

*Manager, Artificial Limb Workshop. Christian Medical College and Hospital,
Vellore, South India*

The authors describe an appliance, the FAB walker, that has been developed to confirm the proposition that if a plaster-of-Paris walking cast will heal a plantar ulcer, then an appliance that follows the principles of a PoP cast will prevent re-ulceration. The weight distribution principles of the PoP cast are described and how these principles are built into the FAB walker. Details are given of the specially shaped sole which allows the patient to walk with a normal gait, even though the ankle is fully immobilized. The step-by-step measurement taking and the procedures of making the walker are described. The types of foot deformities that benefit from the appliance are listed, as well as other advantages and disadvantages.

The main obstacle in the rehabilitation of leprosy patients with badly deformed feet is the continual recurrence of their plantar ulcers. The ulcers heal in a below-knee walking cast of plaster-of-Paris (PoP). Footwear is then given, but in most cases the patient returns to the clinic within 1 to 3 months with re-ulceration. This can be referred to as the "eternal circle of re-ulceration". If the patient's foot could be kept permanently in a PoP cast the re-ulceration would not occur. This was first stated by Price (1961), who wrote: "The recent observations of the effect of plaster casts does [*sic*], however, suggest an effective method of preventing recurrence of ulceration. It is based on the deduction that as the ulcer has healed while the cast was in position, it would remain healed if the cast was left on the limb indefinitely." Various designs of footwear have been developed that have partially followed the PoP design. This footwear has usually included a ridged sole, moulding of the inner sole, and some form of roll (Price, 1960; Ross 1962; Ward, 1964; Girling *et al.*, 1967). None of the designs has included a projection up the leg to immobilize the ankle. For many patients whose feet are not badly deformed this ridged footwear has been sufficient to

* Received for publication July, 1971.

† Sponsored by the Swiss Emmaus Association.

‡ A detailed illustrated manual describing the step by step manufacture of the FAB walker is obtainable from L. Wollstein, S.L.R.S., P.O., Karigiri, via Katpadi, South India.

prevent re-ulceration, but for those with more severely deformed feet this has not been the case.

The foot deformities which present the unsolved ulcer problems are: (1) The foot with the completely collapsed tarsal and metatarsal arch (the boat-shaped foot). (2) The grossly inverted or everted foot in which the plantar aspects of the foot are intact, but the ulceration occurs on the medial or lateral border. (3) The grossly absorbed foot, with constant high pressures on the forefoot because of imbalance of the dorsal to the plantar flexors. (4) The ridged arthrodized foot.

The footwear given so far to patients with these types of feet have not prevented re-ulceration. This paper describes a design of footwear incorporated into a brace that follows exactly the basic characteristics of the PoP walking cast.



Fig. 1. The fixed ankle brace walker.

This appliance is called the fixed ankle brace (FAB) walker (Fig. 1), and it has been used at the Schieffelin Leprosy Research Sanatorium, Karigiri, and the Christian Medical College and Hospital, Vellore, for the last 3 years. To date, over 100 of these appliances have been issued to patients, and a detailed long-term follow-up is being carried out. What has been observed so far is that the majority of the patients now using the FAB walker are at last free from ulcers, after having suffered many years with the "eternal circle of re-ulceration".

To understand the function of the FAB walker fully we must first of all look into the function and action of the below-knee PoP cast. When a patient has a plantar ulcer a thin dressing is applied over the ulcer, and his leg is put into a PoP cast. There is no microcellular rubber (MCR) in the cast to give moulding or to act as a shock absorber. It must be realized that in a below-knee cast all the weight is taken through the plantar surface of the foot, no weight-bearing being taken on the lateral or medial aspects of the leg. There is, however, one big difference. The pressures placed on the sole of the foot in a PoP cast are very different from those

normally taken while walking barefoot. While walking in the PoP cast there is very even distribution of pressures over the whole of the plantar surface during the entire weight-bearing phase. These pressures have been measured and are around 0.5 kg per cm² (7lb/in²) (Bauman *et al.*, 1963). It must also be realized that this intermittent pressure also comes on to the ulcer area, yet the ulcer heals. It may even be that controlled intermittent pressure on a wound encourages healing, the theory being that the intermittent pressures on the ulcer act as a pump for the blood supply. If an ulcer will heal with controlled intermittent pressures on it, then it will stay healed under similar controlled intermittent pressures. In addition to the even distribution of weight, the PoP cast prevents localized, high, oblique pressures resulting from deceleration (heel strike) and acceleration (push off). Further increase of inversion or eversion deformities of the foot are prevented, as well as further collapse of the tarsal bones (boat-shaped foot). The joints of the foot and ankle are completely immobilized.

A walking brace that has the characteristics of the PoP walking cast must necessarily have the following similar qualities: (1) An accurately hard-moulded sole to take the place of the moulded plaster sole in the PoP cast. (2) A method of immobilizing the ankle. (3) To compensate for the loss of ankle movement, some form of rocker bar must be given for the foot to roll over. In the brace this bar must give more stability for standing than does the narrow rocker bar of the PoP cast. (4) As the brace is intended to be permanent it must be cosmetically acceptable, taking into consideration all the cosmetic limitations that the deformed foot presents. To achieve this in a brace is not difficult. In fact by orthopaedic-appliance standards a simple appliance can be made which fulfils all these criteria easily.

Method of Fabrication of a FAB Walker

The patient's foot is first inspected for danger areas on the sole, i.e., hard scars, prominent bones, skin grafts, etc. These are outlined with an indelible pencil. Malleoli are marked in the same way. A strip of lead or leather is then put down the front of the leg and foot and a thin damp cotton stocking then pulled over it up to the knee. Foot and leg are wrapped in plaster bandage extending to 10 mm (3/8 in) below the head of the fibula. With the patient sitting and the foot in a plantar-grade position the foot is pressed against a sheet of soft foam rubber (Fig. 2). Care must be taken that the leg is at an angle of 90° to the floor. The plaster cast is then cut off with a knife, cutting down on to the lead or leather strip (Fig. 3); the indelible pencil marks will have been transferred to the inside of the plaster cast. The cast is now closed up with one more plaster bandage and filled with plaster cream. A holding and reinforcing rod is then sunk into the plaster; this rod must extend right down to the foot. When the plaster has set the bandage wrap is removed and the cast adapted.

The malleoli are built up with plaster by approximately 6 mm (¼ in). The tendon Achilles is built up 3 mm (1/8 in) and the toes built out by at least 25 mm (1 in). The forefoot shape is formed to give a cosmetic shape to the shoe while at the same time giving clearance for the toes. The danger areas on the plantar aspect of the foot are re-marked with indelible pencil (Fig. 4). When the cast is fully dried a thin cotton sock is pulled over it and painted with polyester resin; this is done to reinforce the cast. The marks on the plantar surface will show through the sock reinforcement. These areas are then built up with a layer of 6-mm cork



Fig. 2. Taking the plaster cast.

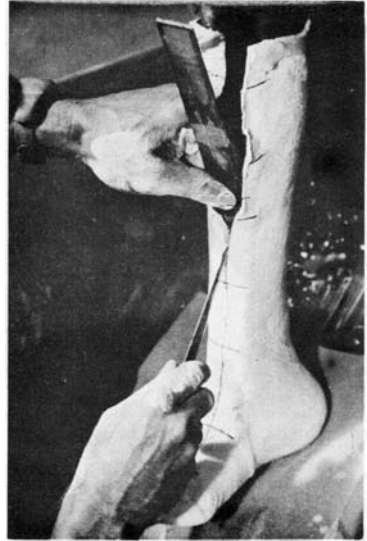


Fig. 3. Cutting off the plaster cast.

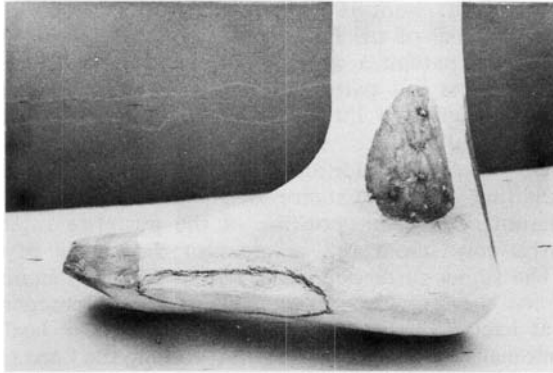


Fig. 4. The adapted plaster cast with the danger area marked.

sheet with the edges blending into the foot shape (Fig. 5). In the finished moulded sole the cork will be replaced by a 6-mm patch of 15 shore microcellular rubber; this MCR patch will accurately mould itself to the minute unevenness of the danger areas. It is not possible to produce such minute moulding in a plaster cast.



Fig. 5 The cast reinforced with a sock impregnated with polyester resin. The cork build-up over the danger area can be seen.

A vertical bisecting line is now drawn down the lateral aspect of the leg. Thin sole leather is blocked on to the foot, extending up the medial side in the area of the arch. If there is an inversion deformity the leather should also extend up the lateral side. The underside of the blocked leather sole is built up with cork sheet until it is level.

The moulded cork insole serves two purposes: (1) It forms an accurate firm mould to give even distribution of pressure to the patient's foot. (2) The underside is shaped so as to give the bottom shape to the sole of the boot. This bottom-sole shape of the boot is very important, as it has to serve the same function as the rocker bar of the PoP cast. At the same time it must also be so shaped as to allow the patient a smooth uninterrupted gait. Since the patient's ankle is immobilized, the gait pattern is controlled entirely by the bottom-sole shape. The sole is divided into three parts (Fig. 6) *viz.* (1) Impact-surface. (2) Stance-surface. (3) Toe-off-surface.

The line where the impact-surface joins the stance-surface is called the posterior fulcrum, while the line where the stance-surface joins the toe-off-surface is called the anterior fulcrum. The exact position of the posterior fulcrum and of the anterior fulcrum is very important, as are also the angles of the impact and toe-off-surface. The stance-surface must be flat to give firm standing ability. The impact-surface must curve upwards at an angle of 20° to compensate for lack of plantar flexion at heel strike and also to prevent excessive heel impact, as this would create a moment around the knee joint, forcing the knee into flexion. The posterior fulcrum will be 2 to 3 cm behind the lateral vertical bisecting line. The toe-off-surface must also slope upwards to compensate for lack of dorsiflexion. The angle of this must be at least 15° and the anterior fulcrum should be at, or just posterior to, the metatarsal heads. Care must be taken while building up the cork that the latter vertical line is at 90° to the stance-surface (Fig. 7). From the anterior view, the shank must lean slightly to the lateral (outer) side (Fig. 8); this will allow for the bowing of the lower leg.

When the cork build-up has been carefully checked, the edges of the moulded leather are trimmed and skived down to blend into the shape of the cast. A blocked leather shank gaiter is put on with a skived anterior overlap and the boot is then built over the foot and the cork sole (Fig. 9). The top edge of the upper of

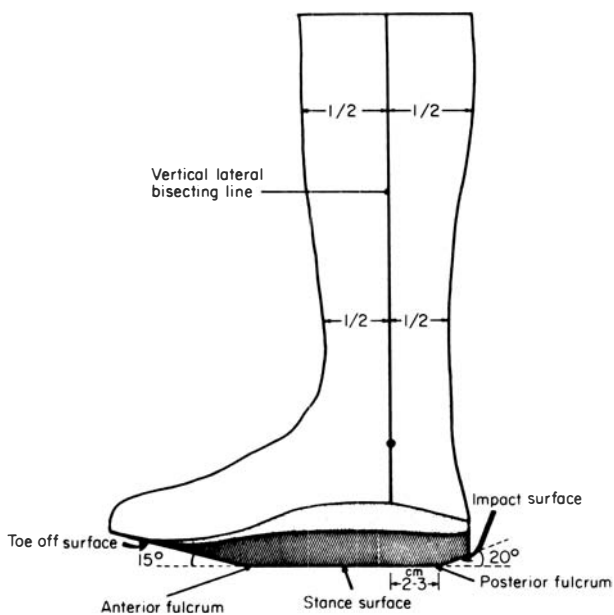


Fig. 6. A diagram of the position of the leather-and-cork insole.

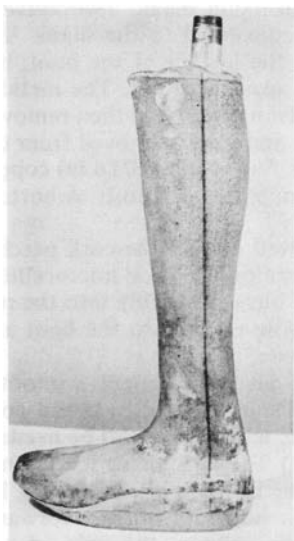


Fig. 7. A lateral view of the cast and finished insole.

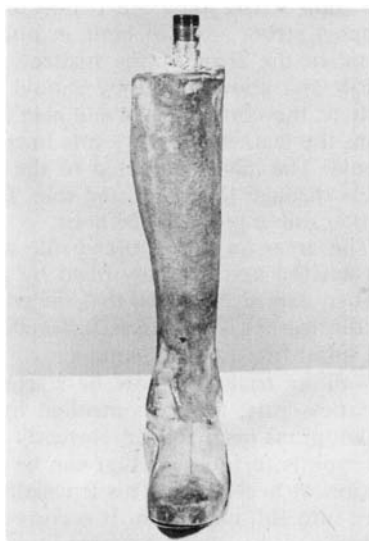


Fig. 8. An anterior view of the cast and insole ready to have the boot built over it.



Fig. 9. The boot and gaiter ready for the fixing of the metal brace.

the boot should overlap the distal edge of the gaiter by 13 mm ($\frac{1}{2}$ in). If this is not done there is the likelihood that a circumferential band of oedema will form in the area of the ankle. The boot is constructed up to the welting.

The metal side-bars are made from 20 mm $\times$ 3 mm mild steel strip. The vertical bars lie on both sides of the leg and the lower ends are bent in under the sole of the foot, where they are connected to a full length metal shank. Two anterior support struts are also bent in under the sole and connected to the shank. The metal in the areas of the malleoli should just clear the leather of the boot, but below and above this they should be lying snugly against leather. The metal is bent to the correct shape and held in place with rivets or bolts. It is then removed from the leather, all the joints brazed, and the boot and gaiter removed from the mould. The metal is riveted to the boot by three or four 4-mm ($\frac{3}{16}$ in) copper rivets through the shank and sole. The gaiter is held in place with bolts. A bottom leather sole is put into the boot.

The areas on the moulded sole which were hollowed out by the cork patches put on the cast are now filled by patches of 15-shore 6-mm thick microcellular rubber, care being taken that the edges of the rubber blend smoothly into the rest of the leather sole (Fig. 10). Finally, the moulded sole is put into the boot and the splint fitted to the patient.

Walking trials can now be started. The aim is to give the patient a smooth, effortless gait; this is controlled by the shape of the bottom sole. If the cork build-up has been shaped correctly very little, if any, adjustment will be needed. The points to look for that can be corrected are: (1) The knee being forced into flexion at heel-strike. This is usually compensated for by the patient locking his knee into full extension. It is corrected by moving the posterior fulcrum forward, which can be done by standing down the leather sole in the area of the impact-surface. (2) Patient not being steady at mid-stance phase. The stance-surface is not level or is at an angle so that not all of it is in contact with

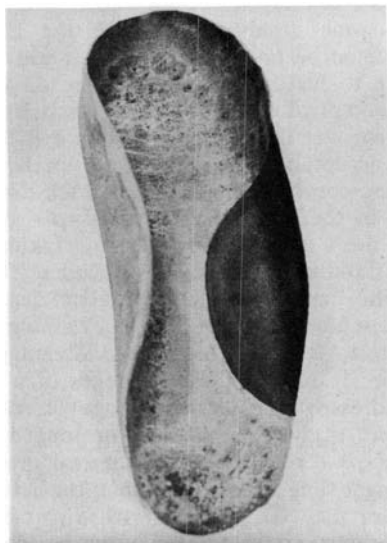


Fig. 10. The hard moulded insole with the 6-mm MCR in the danger area. The moulding in the arch can also be seen.

the ground. This is corrected by sanding down and applying leather to bring all the stance-surface into contact with the ground. (3) At heel-off the patient does not roll over the front part of the foot easily, so that the knee is forced back into extension; the patient will also bend forward at the waist in order to bring his centre of gravity further forward over the foot. This condition is caused by the anterior fulcrum being too far forward or the stance-surface being too high in the front. It is corrected by sanding down the leather sole. (4) At push-off the patient comes up on to the front section of the toe-off surface. This is due to the anterior angle being too low and the stance-surface not having been built up high enough to allow for the angle of 15° . Check and correct the angle of the toe-off surface. (5) The patient has a tendency to lateral instability. This condition is usually seen in a patient who has a fixed inversion of the foot. The cause is insufficient lateral build-out of the insole. At stance-phase the weight line must pass through the centre of the sole. To achieve this with an inverted foot the sole must be extended out on the lateral side; this should be done when building the cork insole. Lateral instability is difficult to correct at the fitting stage.

The patient wears the FAB walker in the fitting state for at least 8 h. The usual care has to be taken that there are no "shoe bites" caused by the new leather. At finishing, the sole has one layer of car tyre stitched and glued to it; care must be taken that the tyre is of even thickness. The leather gaiter is finished with some type of anterior fixing, e.g. lacing, buckles and straps, or Velcro straps. The gaiter is riveted to the side bars. The FAB walker is now finished.

This design of brace sounds as if it is very cumbersome and ugly, but this is not the case at all. Cosmesis is achieved by the boot and bracer very closely fitting the patient's foot and leg so that very little extra bulk is added to the patient's deformed foot. In the case of a shortened foot the forepart of the boot is extended to give the resemblance of a full-length foot.

There are naturally some disadvantages with the FAB walker, but while thinking about them it must be taken into consideration the limitations that the patient already has due to his deformed foot. The disadvantages are: (1) The brace and boot must be kept in good repair. (2) As it is made from leather and metal it is not suitable for wet framing, etc. (3) As it is footwear, in most Asian countries it will not be acceptable in the temple or kitchen. (4) If the patient has a plantar ulcer there is no room for bandages or thick dressings, unless space has been allowed for them in the accurately moulded sole. (5) The manufacture of the FAB walker is a fairly straightforward undertaking, but it still requires accuracy and the understanding of the basic principles. The manufacture should be entrusted only to the hands of a skilled technician. (6) The brace is not suitable for patients whose ulcers will not heal in a walking PoP cast.

On the other hand the FAB walker has several advantages, apart from keeping deformed feet ulcer-free. It has all the advantages of a PoP cast, in that it is removable—this is indeed essential for hygienic reasons. Another advantage is that the chronic ulcerated foot is given a chance of prolonged healing. This gives the surgeon an opportunity to review plans on surgical procedures. As is known, osteomyelitis needs a longer time for recovery than the actual healing of the ulcer.

The responsible patient may be supplied with a pair of additional sandals to wear for festive occasions where a full boot may not be acceptable. Other patients who are wearing sandals can be provided with a FAB walker. At the first sign of the formation of an ulcer the patient uses the brace—in other words he applies his own PoP. Such patients can also use the brace when they have long distances to walk. With the correct placement of the roll the patient's gait is nearly normal. This is regardless of muscle imbalance or muscle weakness in the foot or limited movement in joints. When a patient is wearing long trousers or a lungi it looks as if he is wearing a pair of shoes, whereas in actual fact he is wearing the equivalent of a PoP cast. As the FAB walker is made from leather and mild steel the cost is low, Rs. 30, £1.60, \$4 for materials and 30 h for fabrication is all that is needed. This money and time must be compared to the full cost of treating a deformed perpetually re-ulcerating foot.

For many patients the FAB walker has broken the circle of re-ulceration and so is the essential link to his rehabilitation.

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Treatment of Moderately Severe Erythema Nodosum Leprosum with Clofazimine—A Controlled Trial*

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The results of a controlled trial of clofazimine in the treatment of erythema nodosum leprosum in a small group of patients of various races give further confirmation of the value of clofazimine in the treatment of this complication of leprosy.

Introduction

It is beyond dispute that erythema nodosum leprosum (ENL) is one of the most serious complications of lepromatous leprosy. It frequently causes chronic discomfort and malaise, and as nerves are commonly involved there is the consequent tendency to develop more deformities. Some patients are unable to work for prolonged periods, and thereby a social problem is added to the clinical one. Hence the need for a non-toxic drug that requires minimal medical supervision, i.e., which is suitable for domiciliary use, and which enables the ENL patient to return quickly to work.

The riminophenazine derivative clofazimine (B 663, Lamprene (Geigy)) has serious claims for this purpose. First synthesized by Barry and collaborators (Barry *et al.*, 1957), it was shown by Browne and Hogerzeil (1962*a, b*) and then by numerous other workers to be highly effective in the treatment of lepromatous leprosy. Browne (1965*a*, 1966), observing that surprisingly few patients receiving clofazimine developed ENL, first reported on its possible anti-inflammatory properties, and this was subsequently confirmed experimentally by Vischer (1969). Since then this additional effect of clofazimine in suppressing ENL has been confirmed by many workers, including Hastings and Trautman (1968), Imkamp (1968) and Warren (1968). During the Ninth International Leprosy Congress in 1968 a group of workers, representing most centres with experience of the drug, met in London to discuss in detail its antimycobacterial and anti-inflammatory properties (Waters, 1969). The great majority of the reports confirmed that clofazimine possesses a clinically significant anti-inflammatory effect. However, at the Leprosy Research Unit, National Leprosy Control Centre, Sungei Buloh, the trial carried out by Pettit (1967), using 100 mg of the drug

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daily in very severe ENL, failed to confirm that clofazimine was of any significant value. Therefore we considered it important to carry out a further controlled trial, this time to assess the value of clofazimine in a higher dosage (300 mg per day) in treating somewhat less severe cases of ENL. The double-blind controlled trial here reported employed the methodology of Pearson and Vedagiri (1969) and is based principally on the premise that the effectiveness of a treatment in controlling ENL can be revealed by the concomitant reduction in the requirement of other anti-ENL drugs.

Organization of the Trial

GENERAL DESIGN

The trial was designed to assess the anti-inflammatory effect of clofazimine in treating moderately severe ENL, comparing its action with an identical placebo. All patients continued treatment with dapsone (4'4-diamino-diphenyl sulphone, DDS) throughout the trial, and in addition received clofazimine for a period of 4 weeks. The trial lasted 14 weeks, and was divided into 4 periods: (1) first control period (2 weeks), (2) first trial period (4 weeks), (3) second trial period (4 weeks), (4) second control period (4 weeks). Capsules containing clofazimine (100 mg) and placebo capsules were labelled A and B respectively, and the key as to which was which was kept in a sealed envelope; this latter was opened only after the results of the trial had been analysed. Patients were allotted randomly to treatment in the 1st trial period with capsules A or B in a dosage of 3 capsules daily. In the 2nd trial period the treatment was reversed, i.e., patients who had received capsule A in the first trial period received capsule B in the second trial period, and vice versa. The capsules were issued weekly in individual containers labelled only with the patient's name, number, and the week of the trial. Thus the doctor in charge did not know which of the 2 capsules each patient was receiving at any time during the 2 trial periods, and the patients were unaware that a placebo capsule was being used at any period of the trial.

INTAKE

This consisted of 15 patients who were selected from among those living in hospital quarters and attending the clinic in the Leprosy Research Unit. They were of both sexes (10 males and 5 females) and of several races (9 Chinese, 5 Malays, and 1 Indian), while the age range was from 17 to 67 years, 6 being aged 17 to 20 years, 8 from 21 to 45 and one 67 years old). Clinically, they all had lepromatous leprosy. Histologically, they were graded lepromatous leprosy (LL) or indefinite lepromatous (LI) according to the classification of Ridley and Jopling (1966) as modified by Ridley and Waters (1969). All had received anti-leprosy treatment with dapsone for 2 to 3 years; 14 had suffered from ENL for a period of 1 to 2 years before admission to the trial, and 1 for 6 months. The ENL was severe enough to necessitate their attendance at the out-patient clinic regularly, but none of them had received any corticosteroids during the 3 months prior to admission to the trial. According to Waters' classification of the severity of ENL (Waters, 1963), 14 of them were graded 2+ and 1 graded 1+. During the trial they were left to carry on their usual daily activities, living in their quarters or dormitories; only 2 of them required admission to the hospital ward in this period.

PRELIMINARY INVESTIGATION

Before the beginning of the trial each patient underwent complete clinical examination for both the underlying leprosy condition and the severity and distribution of ENL, and coloured photographs were taken. A full urinary examination (including tests for dapsone) and white blood-cell counts (total and differential) were carried out. The chest was X-rayed if no radiograph had been recently taken, and unless previous reports were available, skin lesions were biopsied in order to confirm both the type of leprosy and that the reaction was definitely ENL. Smears taken from 6 sites (both ear lobes and 4 skin sites) were examined to determine the bacterial index (BI) and morphological index (MI), while the lepromin skin test (Mitsuda type) and the tuberculin test (using 1 t.u. of R.T. 23) were also performed, unless this had been done within 6 months prior to admission to the trial.

THERAPY

(i) *Dapsone*. All the patients were being treated with dapsone (DDS) by mouth, 12 receiving 100 mg, 2 of them 200 mg, and 1 patient 50 mg, all twice weekly. At the beginning of the trial the dose was standardized at 100 mg twice weekly for all patients and was left unchanged throughout the trial.

(ii) *Trial capsules A and B*. Patients were seen every day in the afternoon, except on Sundays. During the 2 trial periods the appropriate capsules were issued to them daily and swallowed at once in the presence of the doctor in charge (except that the Sunday capsules were issued on Saturdays).

(iii) *Other anti-inflammatory drugs*. All the patients were examined twice weekly to record the severity of ENL, and stibophen was prescribed at this time if and as required. Paracetamol was issued twice weekly to be taken freely by the patients. No other ENL drugs were prescribed during the trial.

ASSESSMENTS AND INVESTIGATIONS DURING THE TRIAL

Every day in the afternoon, except Sundays, each patient's temperature was taken and twice weekly the doctor in charge assessed the severity of the ENL. Every week the amount of stibophen prescribed for each case and the number of paracetamol tablets taken by the patient during the previous week were recorded. Once a month leucocyte counts (total and differential) and full urine examination were carried out.

Results and Comments

The results were analysed only after the end of the trial, the score being calculated according to the scheme shown in Table 1. It will be noted that in every case the higher the score, the more severe was the ENL. Results from only 10 of the patients were considered as the other 5 failed to complete the trial for social reasons, 4 because of absence for religious festivals and 1 because of urgent discharge on social grounds.

The overall results (total scores of all patients) are shown in Table 2. Comparison of the first and last columns shows that there was, on average, a slight improvement in the severity of the ENL at the finish as compared with that at the start of the trial—but the scores for all parameters during the period of clofazimine administration were markedly lower than those for the placebo

TABLE 1
Method of scoring of the assessments

Assessment	Score				
	0	1	2	3	4
ENL ^a	No	Mild	Moderate	Severe	Necrotic
Temperature	Below 99°F (37.2°C)	99°-99 ⁸	100°-100 ⁸	101°-101 ⁸	102° and above (38.9°C)
White blood-cell count	Below 10,000 per mm ³	10-14,000	14,100-18,000	Above 18,000	
Stibophen	The score comprises the number of ml prescribed in the appropriate time period				
Paracetamol	The score is the total number of tablets taken voluntarily by the patient in the appropriate time period				

^a Grading of ENL

- Mild = few or moderate number of lesions, indolent or slightly active, no discomfort.
- Moderate = moderate number of lesions, active with slight discomfort.
- Severe = very active lesions with marked discomfort and malaise.
- Necrotic = very severe ENL with pustule formation or necrosis of the lesions.

TABLE 2

Total scores of all cases for the 5 methods of assessment throughout each study period

Assessment	First control period (2 weeks)	Placebo period (4 weeks)	Clofazimine period (4 weeks)	Second control period	
				1st 2 weeks	2nd 2 weeks
Clinical severity of ENL	54	83	48	41	38
Temperature	22	34	19	22	19
White blood-cell count	5	10	3	4	4
Dosage of stibophen (ml)	100	186	80	80	90
Voluntary dosage of paracetamol (no. of tablets)	393	672	340	289	262

period. It should be noted that 7 of the 10 patients received placebo capsules first, while in 3 cases the clofazimine treatment came before the placebo (Table 3). This unequal distribution arose by chance as a result of the loss of 5 of the original 15 patients in the trial.

The results of the assessments of individual patients in the clofazimine and placebo periods are shown in Table 3. It is clear that in the great majority of patients the scores were markedly lower in the period of clofazimine treatment, i.e., clofazimine was substantially more effective than the placebo in controlling ENL.

In a few cases, however, the scores were somewhat higher in the clofazimine period. Case 10 showed more fever and required more stibophen; cases 4 and 7 recorded higher scores for fever; and case 2 was graded as suffering from more severe ENL. In each instance the additional scores were incurred during the first few days of clofazimine treatment, i.e., before the drug had become fully effective. This gradual development of the ENL-suppressive effect of clofazimine is shown clearly in the histogram (Fig. 1), which also shows that the activity of the drug persisted during the week after treatment had been stopped.

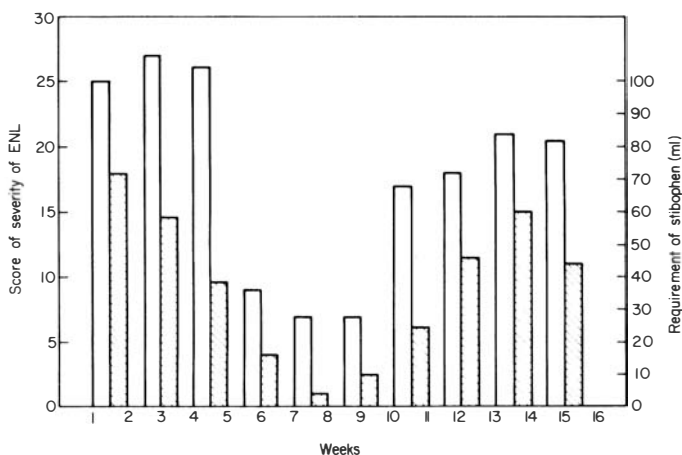


Fig. 1. Histogram showing the weekly scores (all patients) of the severity of the ENL, and of the stibophen requirements, for 10 weeks commencing 2 weeks before the clofazimine trial period and ending 4 weeks after stopping clofazimine. □, severity of ENL; ▨, stibophen (ml).

The scores for fever and the white blood-cell counts were all on the low side, reflecting the satisfactory degree of control of ENL achieved throughout the trial in these patients.

The results of the urine examinations were normal throughout the trial, and in 3 patients minor abnormalities (a trace of proteinuria and a few red blood cells) disappeared during the period of clofazimine treatment. In all cases, however, the urine became pink or red after 2 to 3 weeks of clofazimine medication, and retained a pink tinge for 2 to 3 months after stopping the drug.

The usual skin discoloration (Browne, 1965*b*), which occurs wherever clofazimine is given in this dosage in pale-skinned patients, became apparent after 2 to 3 weeks. It showed initially as a pink tinge, later becoming reddish. In the

TABLE 3

*Scores of individual patients during the trial periods of placebo and of clofazimine treatment
(For method of scoring see Table 1)*

Patient no.	Severity of ENL		Stibophen requirement (ml)		Paracetamol intake (tablets)		Fever		Total white-cell count	
	Placebo	Clofazimine	Placebo	Clofazimine	Placebo	Clofazimine	Placebo	Clofazimine	Placebo	Clofazimine
*1	2	1	0	0	0	0	3	0	0	0
2	5	9	16	8	32	26	8	2	0	0
3	13	5	24	6	84	54	0	0	1	0
4	12	6	28	0	54	33	0	1	3	1
5	10	5	12	0	104	35	4	0	2	1
*6	12	6	18	12	78	32	3	1	1	1
7	10	5	32	14	100	40	1	2	2	0
8	11	8	26	12	80	40	8	3	0	0
9	3	0	24	10	90	40	0	0	0	0
*10	5	3	6	18	50	40	7	10	1	0

* Cases 1, 6 and 10 received clofazimine in the first trial period, the remainder received the placebo first.

short period of this trial the blackish hyperpigmentation which commonly develops in skin lesions after prolonged treatment did not occur. The discoloration began to fade as soon as the drug was stopped, but took 2 to 3 months to disappear completely. In regard to side-effects, 2 patients (cases nos. 3 and 10) developed nausea, vomiting and epigastric discomfort during the trial; in both instances this turned out to be on the first day of the period of clofazimine treatment. Both patients were admitted to hospital, the capsules given in divided dosage, one 3 times a day, and the symptoms settled within 3 days.

Discussion

Despite the short period of treatment with clofazimine (4 weeks) the overall results reveal a clear preference, in each of the 5 parameters measured, in favour of the trial drug as compared with an identical placebo. Therefore we are able to confirm the anti-inflammatory action of clofazimine in the treatment of ENL. The majority of our patients experienced an increased sense of well-being while taking the drug, and this was reflected not only in the reduction of fever but more especially by the fact that every patient reduced his voluntary intake of paracetamol. Therefore we consider clofazimine will prove beneficial in helping ENL patients to resume normal life. Imkamp (1968) has already shown that with long-term clofazimine therapy many of her patients were able to undertake employment inside the Liteta Leprosarium in Zambia. No serious toxic effects were encountered in the trial here reported, although 2 patients developed mild gastro-intestinal symptoms which however rapidly settled with rest and the administration of the clofazimine in divided doses. The drug-induced pigmentation remains a considerable disadvantage in our light-skinned patients, but in general clofazimine appears to be the safest and most suitable domiciliary treatment of chronic ENL, provided the precautions suggested in the postscript to the report of the Working Party (Waters, 1969) are observed.

In this trial we studied patients with less severe grades of ENL than those reported by Pettit (1967) and the dosage of clofazimine was higher, being 300 mg as compared with Pettit's 100 mg daily. These factors amply account for the different results obtained in the 2 trials. Browne (1966), Imkamp (1968), Warren (1968) and others have shown that different patients require individually determined dosages of clofazimine to control their manifestations of ENL. However, the majority of patients hitherto reported have been controlled on 300 mg daily, whereas 100 mg has often proved inadequate (Waters, 1969).

This trial differs from the majority of others so far reported in that we did not stop simultaneous treatment with dapsone, but continued it throughout in a dosage of 100 mg twice weekly by mouth. The good response to clofazimine which we have shown casts some doubt on the importance of dapsone *per se* in the pathogenesis of ENL.

The method of study and scoring employed made it possible to detect more precisely the phenomena that have previously been noted qualitatively—namely, the time lag before clofazimine becomes effective (Browne, 1966), and the persistence of its activity after treatment is stopped (Williams *et al.*, 1965; Atkinson *et al.*, 1967). However the persistence was short-lived, lasting a few days only (and therefore is only partly demonstrated in Fig. 1, as the histogram is graduated in complete weeks), whereas excretion in the urine continued for 2 to 3

months after the intake was stopped. This would support Browne's suggestion (1966) that the anti-ENL effect of clofazimine depends on the circulating, rather than the tissue, drug levels, although this point requires further study. In this connection it is worth noting that in experimental animals the minimal inhibitory concentration of clofazimine for *Mycobacterium leprae* is very low (Shepard, 1969), whereas much higher dosage is required to display an anti-inflammatory effect (Vischer, 1969).

The trial was designed to be "double blind", but it ceased to be so the moment the skin discoloration appeared, i.e., 2 or 3 weeks after starting clofazimine. This eventuality was foreseen, and it appears to be an insuperable barrier to truly double-blind studies of this drug in the treatment of ENL. No placebo giving similar coloration is available, and the suggestion that the doctor in charge of the trial should wear dark glasses during examination of the patients has obvious drawbacks and was not adopted.

The general problems involved in designing trials of drugs active against ENL have been summarized by Pearson and Vedagiri (1969) and by Waters (1971) and need not be reiterated here. An additional point to be noted however is the length of time such trials require. The present study, involving only 4 weeks of clofazimine treatment, took 14 weeks to complete. It is reassuring therefore that the ENL of these patients showed only slight differences in average severity at the beginning as compared with that at the end of the study. This means that the benefit of clofazimine is unlikely to have been due merely to the natural history of the condition, which will always resolve in time provided anti-leprosy treatment is continued.

An incidental problem which we encountered was concerned with the patients' personal lives. For example 4 of the 5 patients lost from the study were excluded from the analyses because they required periods of leave to visit their homes during religious festivals. These occur frequently in a multiracial country such as Malaysia, and it is evident that social as well as medical factors should be considered in overall trial planning.

The results of this trial fully confirm the suitability of the method proposed by Pearson and Vedagiri (1969) for the study of drugs used in the treatment of mild and moderately severe ENL. This provides a reliable and sensitive technique for obtaining an accurate measure of the effectiveness of an anti-ENL drug, and it could be used to evaluate the many unproven compounds currently employed in the treatment of ENL.

Summary

In a controlled trial, designed to be double-blind, 10 patients suffering from moderately severe erythema nodosum leprosum (ENL) were studied for a total of 14 weeks. The trial was subdivided into an initial control period of 2 weeks followed by a first trial period of 4 weeks in which either treatment with clofazimine, 300 mg daily, or identical placebo capsules was prescribed, then by a second trial period of 4 weeks in which the treatment given (clofazimine or placebo) was the reverse of that in the first trial period, and concluded with a final control period of 4 weeks. Dapsone was given throughout in a dosage of 100 mg twice weekly.

The results, based on the clinical severity of the ENL, temperature, white blood-cell count, total dosage of stibophen prescribed, and total number of

paracetamol tablets voluntarily consumed by patients in each of the 4 periods, showed clearly that the ENL improved during the period in which clofazimine was given. Of the 10 patients, 8 did not develop any signs of clofazimine toxicity (2 developed mild gastro-intestinal symptoms for the first few days on clofazimine); they were able to carry on their normal daily activities and did not require any special medical supervision. It is concluded that clofazimine is an effective drug in the treatment of moderately severe ENL, and that it is suitable for domiciliary use.

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Forty-four Months' Experience in the Treatment of Leprosy with Clofazimine (Lamprene (Geigy)) *

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The author's experience in treating 123 patients with clofazimine is reported. Long-standing corticosteroid-dependent erythema nodosum leprosum (ENL) was adequately controlled after an average of 7 months of treatment with clofazimine. After an average of 16 months, recurrence of ENL was negligible. Early cases of ENL were easier to control. Patients with neuritis, and those with tuberculoid and borderline reactions and suspected dapsone resistance also responded favourably to clofazimine. A controlled trial over 2½ years indicated that while the addition of clofazimine to dapsone in the treatment of patients with lepromatous leprosy did not hasten bacillary clearance, the incidence of reactions was considerably decreased.

Introduction

A preliminary report of the results of the treatment of leprosy with clofazimine at Westfort was presented at a symposium held in London in 1968 (Waters, 1969) where previous observations of its efficacy both as an antibacterial and anti-inflammatory agent in leprosy were confirmed by numerous investigators. This report is an extension of these early findings and includes observations on 123 patients who received clofazimine for varying periods during 44 months. The dosage, duration of administration, and results of treatment with clofazimine are described under different headings, according to the purpose for which it was administered.

Erythema Nodosum Leprosum (ENL)

A total of 60 patients was treated. In the early stages only patients with severe long-standing corticosteroid-dependent ENL were included, but later patients with early, less severe forms of the reaction were treated as well. The purpose of the trial was to compare the duration of ENL and corticosteroid administration before and after treatment with clofazimine, the patients acting as their own controls. The patients were divided into 2 groups: (1) 31 with severe continuous ENL present for 4 months or longer, who had previously received prednisone in doses of 5 to 40 mg daily almost continuously, and (2) 29 with relatively mild ENL present for less than 4 months who had been given prednisone for short periods only, if at all. A further 6 patients with severe long-standing ENL who

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refused clofazimine for psychological reasons relatively soon after starting treatment, are included as an additional control group. The average duration of previous anti-leprosy treatment in the 3 groups was 36, 27 and 48 months respectively. At the start of treatment with clofazimine there were 9 patients with negative bacteriological smears in the long-standing corticosteroid-dependent group, 7 in the short-term ENL group, and 2 in the "control" group.

The initial dose of clofazimine was usually 100 mg daily, although some severe cases were started on 200 mg daily. The dose was increased by 100 mg daily at intervals of 1 to 2 weeks to a maximum of 400 mg daily according to the patient's response. It had been decided not to exceed this dose in view of possible gastrointestinal disturbance. When the ENL had improved, the dose of prednisone was gradually decreased and then stopped. In those patients in whom the dosage of dapsone had been decreased (or in rare cases, stopped) it was gradually increased until the routine dose of 300 mg weekly was again reached. ENL was considered to be under control when there were no, or only negligible, attacks and prednisone had been stopped. After the ENL had been under control for at least a month or more, depending on previous severity, the dose of clofazimine was gradually decreased and then stopped.

RESULTS

The average duration of ENL and prednisone administration, before and after clofazimine was started, the time needed for adequate control and the total duration of clofazimine administration are summarized in Table 1. At the time of writing, in 25 of the 31 patients in the group with severe long-standing ENL treatment with clofazimine had been stopped for periods varying from 1 week to 34 months, after an average treatment period of 16 months. In 6 of these patients, clofazimine was first stopped after about 8 months but had then to be restarted for ENL, which recurred within a few days to 7 months after clofazimine had last been given. In one exceptional case ENL recurred after an initial treatment period of 24 months. In the group of 29 patients with milder forms of ENL, the reaction at the time of writing is under control in all, but 15 are still receiving clofazimine and the total duration of treatment will therefore be longer than the present average of 5½ months.

TABLE 1
Results of treatment of ENL with clofazimine

Group	Previous ENL (months)	Previous prednisone (months)	Duration clofazimine (months)	Prednisone stopped (months)	Adequate control (months)
Long-standing corticosteroid-dependent ENL (31 patients)	20	17	16	4.75	6.75
Long-standing corticosteroid-dependent ENL—clofazimine refused (6 patients)	16	15	2.25	17	23+
Short-term ENL, not corticosteroid-dependent (29 patients)	2	0.5	5.5+	1.0	3.5

The maximum daily dose of clofazimine required was 100 mg in 9 cases, 200 mg in 9, 300 mg in 31 and 400 mg in 11 patients. Although the general tendency was for the patients with the milder ENL of more recent onset to respond to smaller doses, 3 of the patients requiring 400 mg were in this group. Patients who had in addition acute arthritis (5 cases) and ulcerating lesions of the erythema multiforme type (2 cases) were the most difficult to control and required systemic corticosteroids as well. Tibial pains following attacks of ENL did not appear to respond to clofazimine and were treated with anti-malarials and analgesics. In some patients the ENL became worse during the first few weeks of treatment, and 1 patient developed acute arthritis after 5 months of treatment while receiving 400 mg of clofazimine daily. Four patients developed neuritis while on low doses of clofazimine (100 mg daily and 300 mg weekly), one in the first month and the others after 10, 12 and 13 months of treatment, respectively, when the ENL was already under control. However, in 8 patients who had neuritis in addition to ENL from the start, the neuritis improved more quickly than the ENL.

At the end of the treatment period, the bacteriological index (BI) was negative in 24 of the 31 patients in the long-standing corticosteroid-dependent group and in 6 of the 29 patients in the short-term ENL group. Two patients died of amyloid nephrosis—one after 6½ months of treatment with clofazimine during which time the ENL improved but arthritis remained a problem, and the other 8 months after he had last had clofazimine which had been given for 7 months (see section "Laboratory Examinations" below).

Neuritis

Of the 13 patients (5 with lepromatous, 4 borderline, and 4 tuberculoid leprosy) who were treated with clofazimine for neuritis which had been continuous for an average of 2½ months, all but 4 had taken prednisone for an average of 1½ months with inadequate response. All had previously been treated with dapsone except for one with tuberculoid leprosy who was given only clofazimine from the start. Dapsone was continued in 7 of the patients treated with clofazimine, while in those at first treated with clofazimine alone dapsone was reintroduced and gradually increased to 300 mg weekly when the neuritis was under control. Of these patients, 8 had in addition either ENL, arthritis, or acute reactions in skin lesions. The dose of clofazimine was regulated in the same way as for ENL.

RESULTS

The average time needed for adequate control of the neuritis was 3½ months and prednisone was stopped after an average of 1½ months. The response in the different types of leprosy was similar. By the time of writing this report 9 patients had already stopped taking clofazimine for periods of 3 to 14 months, after an average duration of treatment of 9 months. Neuritis was under adequate control in the remaining 4 patients. So far neuritis has recurred in 2 of the 9 patients, 3 and 6 months respectively after clofazimine was stopped.

The maximum daily dose of clofazimine given was 100 mg in 1 case, 200 mg in 3, and 300 mg in 8 patients. In one of the borderline patients the dose was increased to 400 mg daily for an acute erythema-multiforme type of ENL after the neuritis had already improved. In 2 patients with tuberculoid leprosy acute

reactions in skin lesions and oedema of the hands and feet developed 2 months after starting clofazimine while taking 100 and 200 mg respectively daily. One of these patients developed bilateral foot-drop while taking 200 mg daily 4 months after treatment was started, but this improved remarkably during the next 6 months. An additional patient developed foot-drop one month after starting clofazimine, also while receiving 200 mg daily. The foot-drop improved within a month, but he later developed an acute reaction in skin lesions after the dose had been reduced to 100 mg daily. In view of the fact that more than half the patients in this neuritis group had additional reactions, the duration of clofazimine treatment may have been longer than otherwise required had they all had neuritis alone.

Acute Cutaneous Reactions

Eleven patients (6 with borderline and 5 with tuberculoid leprosy) who had acute swelling of skin lesions, accompanied in 6 cases by oedema of the face, hands and feet, were given clofazimine. Treatment was started within 1 to 4 weeks of the onset of the reaction. Dapsone had been stopped in 10 of these patients and the dose reduced in the 11th. Two patients had received prednisone for 1 week before clofazimine was started and in 4 prednisone was started at the same time as clofazimine. The dosage of clofazimine was similar to that given for ENL.

RESULTS

The average duration of clofazimine administration before the reactions were under control was 3 months in both borderline and tuberculoid patients. In the 6 patients who received prednisone, this was stopped after 2 to 5 weeks. Eight of the 11 patients were still receiving clofazimine at the time of writing, but all reactions were well controlled and it is unlikely that the present average time of administration, i.e. 6½ months, will be greatly exceeded. The maximum daily dose of clofazimine was 100 mg in 5 patients, 200 mg in 1, 300 mg in 4 and 400 mg in 1 patient. Treatment with dapsone was resumed once the reaction was under control, the dosage being gradually increased to 300 mg weekly while the dose of clofazimine was being decreased.

Suspected Dapsone Resistance

Dapsone resistance, which was diagnosed on the lack of clinical, bacteriological and/or histological response to standard treatment with the drug (300 mg weekly since 1966 and 600 mg weekly before then) was suspected in 6 patients with lepromatous leprosy who had previously received dapsone for 4 to 10 years. Clofazimine had so far been administered for 2 to 26 months in a dose of 100 mg daily to 4 of these patients and 300 mg weekly to 2. All 6 patients showed improvement in the bacterial index (BI) by the 7th month of treatment. In the patient who has had only 2 months of treatment so far, some flattening of lepromatous nodules has already been noted. In 2 patients with borderline leprosy who had not responded satisfactorily to treatment with dapsone for 2½ and 6½ years respectively, the BI became negative after a year of treatment with clofazimine, 100 mg daily, although the skin lesions took longer to clear. Treatment has been continued for 2 and 3 years respectively. Two patients with tuberculoid leprosy, who still had depigmented and slightly infiltrated macules

with histological evidence of activity after 3 years' treatment with dapsone, have been given clofazimine for 8 and 11 months so far, the first, an adult, receiving 100 mg daily and the second, a child of 10 years, 300 mg weekly. Improvement was noted after 3 months of treatment and the lesions have flattened and repigmented. All 10 patients continued to take dapsone.

Other Indications for Clofazimine

Of 2 patients with extensive lepromatous ulcerations and one with laryngeal involvement who were not responding to dapsone, all 3 improved considerably after clofazimine was given in addition in a dose of 100 mg daily. These 3 patients had had intermittent treatment with dapsone for 23, 24, and 17 years respectively, were still bacteriologically positive and could probably be classified as cases of dapsone resistance. The ulcers started to show improvement after 2 months and the laryngeal stenosis by the end of the 3rd month of treatment. Subsequently the BI has also markedly improved in all 3 patients.

Clofazimine was given instead of dapsone when it became necessary to treat a patient with lepromatous leprosy with vincristine and cyclophosphamide for an inoperable bronchogenic carcinoma. The sulphone was stopped, as previous observations (Davison *et al.*, 1964) indicated that it protects the bone-marrow from the leucopaenic effect of cyclophosphamide and could thus inhibit its anticancerous action. In the year prior to the patient's death from carcinoma the leprosy infiltrations and the BI improved steadily.

Another 3 patients with lepromatous leprosy were given clofazimine at their own request. The first, who had mild intermittent ENL and neuritis present for a year, became symptom-free after 4 months' treatment with 100 mg of clofazimine daily. He took 300 mg weekly for a further 14 months while continuing with dapsone, during which time he said that ulcers resulting from burns healed more rapidly than before he had taken clofazimine. The second patient had mild recurrent ENL and brawny oedema of the extremities. After 32 months' treatment with clofazimine, 300 mg weekly in addition to dapsone, there has been no recurrence of ENL but no demonstrable decrease in the swelling. He does not want to stop the clofazimine because he says he feels much better while taking it. The 3rd patient, who had been given thiambutosine for 1½ years as he regularly developed a rash whenever he took dapsone, requested clofazimine for neuritic pains and numbness of the extremities. After 8 months of clofazimine, 100 mg daily, his symptoms improved considerably. There was some objective improvement in the first 2 patients but subjective improvement was considerable in all, probably largely for psychological reasons.

Combination of Clofazimine and Dapsone in Lepromatous Leprosy

The purpose of this part of the trial was to ascertain whether the addition of clofazimine to standard treatment with dapsone would hasten clinical and bacteriological clearance in patients with lepromatous leprosy. It was started in 2 groups, each of 16 patients, all of whom had previous treatment with dapsone alone for an average of 8½ months. All patients had diffuse infiltration of the skin with strongly positive smears. Half of them had nodular lesions in addition. The patients were divided into 2 groups, equal as far as possible in regard to duration of previous treatment, lesion index (LI), bacterial index (BI), and morphological

index (MI).^{*} All patients received 300 mg of dapsone weekly and one group 100 mg of clofazimine daily in addition. At the start of the trial the LI, BI and MI values in the group given dapsone alone were 6.5, 3.25 and 1.5% respectively, and 7.5, 3.5 and 2.0% in the group receiving clofazimine in addition; 6 patients in each group had reactions, mainly in the form of ENL.

RESULTS

At the end of 18 months, 3 patients in the group given dapsone alone had severe reactions which were inadequately controlled by corticosteroids; they were removed from the trial as it was thought that treatment with clofazimine was warranted. Another 4 patients subsequently defected from the trial and by the end of 2½ years there were 10 patients left in the group receiving dapsone only, and 15 in the group on dapsone plus clofazimine. The MI was 0% in both groups by the end of 10 months. Subsequently until the end of the trial there were 2 patients in each group who had occasional intact bacilli. The reduction in the LI and BI in the patients remaining in the trial at the end of 18 months and 30 months are summarized in Table 2. At 22 months, 8 smears were counted to ascertain how examining more sites would affect the final results. The average BI was 5% higher when 8 sites were counted instead of 4, a difference which was not considered to be significant. From Table 3 it can be seen that whereas the number of patients with reactions decreased in the group receiving clofazimine, they increased in those given dapsone alone. If the 3 patients removed from the

TABLE 2

% reduction in LI and BI in lepromatous leprosy treated with dapsone and dapsone plus clofazimine

Group	Lesion index		Bacteriological index	
	18 months	30 months	18 months	30 months
Dapsone only	38	50	39	57
Dapsone plus clofazimine	45	52	47	58

TABLE 3

% ENL on treatment with dapsone and dapsone plus clofazimine

Group	Initial	18 months	30 months
Dapsone only	38	71	50
Dapsone plus clofazimine	38	19	27

^{*} These parameters were calculated as follows: LI: The sum of infiltrations, nodules and plaques or macules graded from 0 to 3 in 4 sites (face, ears, trunk and limbs); BI: The average of smears from 4 sites (ear, forehead, cheek and arm) graded according to the Dharmendra method from 0 to 4; MI: The percentage of solid, uniformly staining, bacilli of adequate length in each smear.

dapsone group at 18 months are included in the final analysis, the percentage of reactions in this group would be 60%, instead of 50% as given in the table. In the patients who still had reactions while taking 100 mg clofazimine daily, the dose was subsequently increased to control ENL.

SIDE-EFFECTS

Of the 123 patients treated with clofazimine 108 were Bantu, 8 Coloured, 5 White, and 2 Indian. All showed pigmentation varying from pink to very dark brown, almost black, being most marked in skin infiltrations and depending on the original skin colour, dose and duration of treatment. Marked conjunctival pigmentation was seen in only 5 patients, but 10 patients complained of pruritus, either generalized or confined to the face, without visible rash. In other cases pruritus was an early manifestation of ichthyosis, which was marked in 30% of patients receiving clofazimine. It was either generalized or localized to skin lesions or to the shins, appeared when the disease was resolving and subsequently desquamated. In 8 patients a rash developed during treatment, but this could not definitely be ascribed to clofazimine as it cleared with continued administration; in 5 of the 8 it took the form of non-specific, itching, follicular and papular eruptions mainly confined to the face, in 2 it appeared to be seborrhoeic dermatitis and in 1 erythema multiforme. Three patients developed a monilial perleche which cleared after 1 month's treatment with gentian violet. Three patients who were given clofazimine for ENL developed abdominal symptoms consisting of pain and either constipation or diarrhoea, severe enough to stop treatment. They had been treated for 12, 13 and 18 weeks respectively and the maximum daily dose was 300 mg in 2 cases and 400 mg in the 3rd. Weight loss was so marked in one patient that he was admitted to hospital. All routine investigations, including X-ray examination, were negative, but jejunal biopsy was not done; this patient recovered soon after clofazimine was stopped. Two of these patients subsequently tolerated clofazimine in reduced doses over several months while in 10 other patients who complained of transient abdominal pains and nausea in the early stages, treatment with clofazimine was not interrupted.

Laboratory Examinations

Blood cell counts, liver function tests, blood urea level and urinalysis were carried out only in the trial in which clofazimine was given in addition to dapsone to lepromatous patients; there was no evidence of any toxicity. By the end of the 2½-year period special investigations in the group receiving clofazimine showed fewer abnormalities than those in the group given dapsone alone. Indeed the haemoglobin level was higher, leucocytosis was reduced and serum protein electrophoretic patterns deviated less from the normal in the clofazimine-treated group.

Full post-mortem details are available in 2 patients who were treated with clofazimine for ENL and who died after developing a nephrotic syndrome with acute renal failure. The first had received clofazimine for 6½ months (maximum daily dose 300 mg) and died within a week of the last dose, while the second patient, who had had clofazimine for 7 months (maximum daily dose 200 mg) died 8 months after the last administration. In both cases the picture was that of healing lepromatous leprosy, with no demonstrable bacilli, and widespread secondary amyloidosis with marked renal involvement. In the first patient, who

died while still in a state of reaction, there was in addition marked renal tubular necrosis and small superficial ulcerations were found in the mucosa of the stomach and small bowel. In the second patient, who had last had clofazimine 8 months before death, frozen sections examined under polarized light revealed numerous crystals in the epithelial cells of the cortical tubules of the kidneys which resembled crystals of clofazimine, but these were not identified by further investigation. The bone-marrow was normal in both patients.

CLOFAZIMINE DURING PREGNANCY

Five patients took clofazimine during pregnancy, including the first trimester, but there was no sign of teratogenicity in any of the offspring. Post-mortem examination of 2 infants who died, one of prematurity and antemortem haemorrhage and the other of gastro-enteritis, showed no evidence of drug toxicity. None of the babies was hyperpigmented at birth. As all the mothers had lepromatous leprosy, none of the babies was breast-fed.

Discussion

In our patients with severe long-standing corticosteroid-dependent ENL, adequate control (i.e., attacks were negligible or no longer incapacitating and steroids were no longer required) was obtained after about 7 months of treatment with clofazimine. A further 9 months of treatment was necessary to prevent recurrence. In previously reported trials ENL was brought under control after shorter periods (Imkamp, 1968; Karat *et al.*, 1970; Languillon, 1970). Treatment for longer periods (up to 24 months) was however required to prevent recurrence in some patients (Atkinson *et al.*, 1967; Warren, 1970). Like Morgan (1970) we found that in a few patients with severe ENL the reaction became worse during the initial stages of treatment with clofazimine and that patients who were corticosteroid-dependent were slower to respond. It has been suggested that clofazimine should not be stopped while the BI remains high (Warren, 1970). This does not seem to be a reliable guide to the duration of treatment. In our patients with long-standing corticosteroid-dependent ENL who were treated for an average period of 16 months the BI naturally decreased during this period, but at the end almost a quarter of them still had positive smears. We have also seen patients in whom severe ENL has recurred for as long as 2 years after the BI became negative. In our patients with milder forms of ENL who were not corticosteroid-dependent, the BI did not change during the short treatment period of 3½ months in which the ENL came under control. It is of course impossible to tell whether the ENL in these patients would have run a shorter course even without treatment with clofazimine. Pettit (1967) found that clofazimine in a dose of 100 mg daily over a long period (14 months) had no anti-inflammatory effect in severe cases of ENL. Our findings in a trial over 2½ years in which lepromatous patients given clofazimine, 100 mg daily, in addition to dapsone were compared with patients treated with dapsone alone, indicated that while ENL was not completely suppressed on this dose, the incidence of ENL was considerably reduced. There is general agreement that the response of ENL to clofazimine depends on an adjustment of the dose to the severity of the reaction (Waters, 1969). So far, Gatti *et al.* (1970) are the only authors who have found that the incidence of ENL is higher on large doses (300 mg daily) than on smaller doses (100 mg daily). Of our 31 patients 4 with severe ENL were not adequately controlled on

clofazimine, 400 mg daily; only one of these patients was above average weight. Because our own experience and that of Atkinson *et al.* (1967) indicates that gastro-intestinal disturbances are readily reversible, we now give 500 mg of clofazimine daily when necessary. Dapsone was continued throughout the treatment period and our aim was to stop the clofazimine as soon as the ENL was under control. As clofazimine is excreted extremely slowly (Vischer, 1969), it was unexpected to find a few early recurrences of ENL after the close of a long period of administration of the drug. Other authors have had similar experiences (Atkinson *et al.*, 1967; Warren, 1970). In our patients neuritis was adequately controlled after an average of 3½ months of treatment with clofazimine. Two patients developed foot-drop while on the relatively low dose of 200 mg daily. Warren (1970) found recurrence of neuritis after many months of treatment with clofazimine; she ascribed this to the fact that the dose was not high enough. In her patients improvement in sensory and motor function appeared to be enhanced during treatment with clofazimine. Our impression is that patients with neuritis and acute cutaneous reactions in tuberculoid and borderline leprosy do better on clofazimine than on dapsone. We now start all patients with these presenting features on clofazimine alone in a dose of 100 to 200 mg daily. Dapsone is introduced gradually after several months when the reaction has been controlled. Browne (1965) found that the speed of bacterial clearance was slightly greater in patients who had been given dapsone in addition to clofazimine. In the earlier stages of our controlled trial on patients with lepromatous leprosy, those receiving clofazimine plus dapsone appeared to be doing better than those on dapsone alone, but clinical and bacteriological improvement was the same in the two groups after 2½ years of treatment. Skin pigmentation was seen in all patients given clofazimine and was initially objected to by a few young females, who however later accepted it. Transient rashes were encountered but none required cessation of treatment. Our findings are similar to those of Gatti *et al.* (1970), who found that the skin becomes xerodermic or frankly ichthyosiform as the lesions resolved. In a previous survey ichthyosis was found in 10% of all patients at Westfort (Schulz, 1965). During this trial marked ichthyosis was found in 30% of patients who received clofazimine. This higher incidence may be due to the fact that the ichthyosis is more visible as a result of hyperpigmentation or because the drug has a drying effect on the skin.

Clofazimine accumulates in the cells of the reticulo-endothelial system where it has been seen in experimental animals to be deposited in the form of crystals (Conalty and Jackson, 1962; Shepard and Chang, 1964; Vischer, 1969). Crystals have been found in the lamina propria of the jejunum and in the bone-marrow in patients treated for leprosy (Atkinson *et al.*, 1967). In 2 patients examined post mortem there were no pathological changes suggesting drug toxicity in any of the organs. The superficial ulcerations in the small bowel in the first patient were not associated with visible crystals and were ascribed to uraemia. Crystals, similar in shape to those of clofazimine, were found in the renal cortical tubules in the second patient. As the patient had last taken the drug 8 months before death, and as the crystals were present in epithelial cells rather than in association with macrophages, it is extremely unlikely that they were due to clofazimine. It has been shown in experimental animals that clofazimine is transmitted to a slight extent to the foetus via the placenta (Vischer, 1969). The lack of hyperpigmentation of the skin and of teratogenicity in infants born to our patients treated with clofazimine during pregnancy, suggest that transplacental transmission of the drug in the human subject is not of clinical significance.

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Leprosy in Bhutan: A Pilot Survey*

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The results of a pilot survey to determine the prevalence of leprosy in two districts of Bhutan showed the rates to be 13.4 per 1000 and 24.8 per 1000 respectively. The age of onset, lepromatous rate, and disability rate were found to be higher than in India.

Introduction

In 1964 the Royal Government of Bhutan invited The Leprosy Mission to co-operate in establishing a leprosy service. This work was begun in 1966 with the building of Gida Kom Leprosy Hospital and the carrying out of a preliminary exploratory survey (Berkeley, 1970).

In the planning of this leprosy service, two main problems were immediately apparent. The first was the absence of demographic data, as no national census had ever been taken, and there was no registration of births or deaths. The first census, in 1969, gave a total population for Bhutan of 1,034,774 (Royal Government of Bhutan, 1970). This figure will serve as a baseline for future demographic analysis, but it will be some years before the errors due to enumeration difficulties are eliminated.

The second problem was the lack of definite information regarding leprosy. Morbidity recording was introduced by the Directorate of Health Services in 1963, and each of the 27 government dispensaries throughout the country submits a monthly return of patients treated—with separate recording of gonorrhoea, syphilis, tuberculosis, leprosy, smallpox, malaria, goitre, helminthiasis, and diarrhoeal diseases. These records were examined over a 3-year period (1966-1968 inclusive), and it was found that for leprosy the total returns for the whole of Bhutan were:

1966-666 cases
1967-528 cases
1968-323 cases

These figures refer to the number of treatments given and not to the number of persons with leprosy; also, 76% of the total number was reported by 1 of the 7 administrative areas. These figures were thus of little use in the planning of a leprosy service.

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Objectives

The survey that forms the subject of this paper had 2 main objectives: (1) the investigation of the prevalence of leprosy and the various components of its variability; and (2) the development of field techniques and the training of paramedical workers. From the results, it was hoped that estimates could be made of the size of the leprosy problem in Bhutan, and an assessment obtained of the medical requirements in terms of hospital, clinic, and manpower resources.

METHOD

Administrative and geographical difficulties made it impracticable to examine a random sample of the population or of the villages. After discussion with the Director of Health Services, it was decided to undertake an extensive pilot survey.

Two administrative districts were selected, and a full survey of both districts carried out (Fig. 1). The basis of selection was one area (Paro District) where the Government believed that the prevalence of leprosy was low, and one area (Lhuntsi District) where leprosy was thought to be a serious public health problem. The main advantages of this fuller survey were (1) that the administrative officials of the district would be fully involved, (2) that a sampling frame could be constructed for use in future surveys, and (3) that the two selected districts would take into account racial differences that might have some bearing on prevalence rates. Although all Bhutanese are originally of Mongolian stock, those in Paro District (West Bhutan) are ethnically different from the people of Lhuntsi District (East Bhutan).

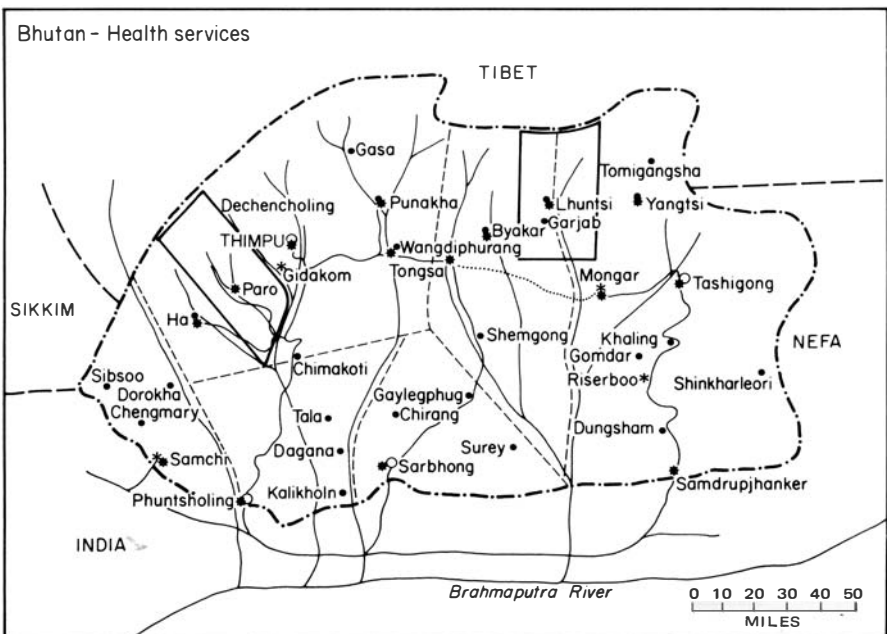


Fig. 1. Survey areas of Paro (West Bhutan) and Lhuntsi (East Bhutan) in boxes.

These two surveys were carried out in 1969, a similar procedure being followed in each case. The approval of the Government having been obtained, the Director of Health Services informed the district Dzongda (senior administrative official) of the purpose of the survey. About 1 month before the survey, a visit was made to the Dzongda and pamphlets left with him for distribution to village headmen. At the beginning of the survey, each village headman was informed of the expected date of survey of the villages under his jurisdiction. The survey team consisted of a staff of 3 trained members, who travelled from village to village. Communications were easier in Paro District, where no village was more than 2 days' walk from a road, than in Lhunsi District, where all the villages were 6 to 9 days' walk from a road.

Results

A total of 14,589 persons were examined in the two districts (Table 1). In Paro District, 79.9% of the population were examined, and in Lhunsi District 87.5%.

TABLE 1
Summary of population surveyed

	0-14 years		>15 years		
	Male	Female	Male	Female	Total
<i>Paro</i>					
Population	1326	1349	2667	3100	8442
Examined	1156	1244	1730	2619	6749
Percentage	87.2	92.2	64.9	84.9	79.9%
<i>Lhunsi</i>					
Population	1692	1590	2567	3092	8941
Examined	1530	1492	2026	2792	7840
Percentage	90.4	93.8	78.9	90.3	87.5%

The demographic difficulties previously mentioned account for some inaccuracy in these figures. The total population figures of each district were provided by the respective Dzongdas, and then checked with village headmen and with individual householders. There were some inconsistencies between these 3 sources of information, but these were not large enough to affect the survey percentages. It was noted that in Paro District only 64.9% of the adult male population were examined; this was partly due to the fact that a number of men were in South Bhutan, wintering their cattle.

The population structure of the two districts showed the following age distribution:

	0-4 years	Total under 20 years	20 years and over
Paro	9.3%	36.7%	63.3%
Lhunsi	12.5%	43.5%	56.5%

This may be compared with India, where 15% of the population are in the 0-4 years age-group and 50% are under 20 years (Gopalan, 1969).

AGE AND SEX

A total of 285 cases of leprosy were found during the survey—90 in Paro District and 195 in Lhuntsi District. The distribution of these patients by age and sex is shown in Table 2.

Only 9 children under the age of 15 years were found to have leprosy; 2 of these were said to have developed the disease before the age of 5 years. The age of onset was taken as the patient's present age minus the duration of signs or symptoms of leprosy. In 36 cases, leprosy was stated to have been first recognized at over the age of 50 years.

TABLE 2
Age and sex of leprosy patients

Age (years)	Male	Paro Female	Total	Male	Lhuntsi Female	Total
0-4	0	0	0	0	0	0
5-9	0	0	0	0	2	2
10-14	2	2	4	2	1	3
15-19	2	0	2	5	1	6
20-24	4	4	8	13	6	19
25-29	7	9	16	10	8	18
30-34	8	5	13	9	13	22
35-39	6	2	8	15	9	24
40-44	6	0	6	15	9	24
45-49	4	3	7	12	9	21
Over 50	13	13	26	30	26	56
Total	52	38	90	111	84	195
0-14 years = 4.4%			0-14 years = 2.7%			
15-49 years = 66.8%			15-49 years = 68.7%			
Over 50 years = 28.9%			Over 50 years = 28.8%			
Mean age = 30 years			Mean age = 29.25 years			

CLASSIFICATION

The classification of the cases of leprosy, based on clinical criteria, is shown in Table 3.

TABLE 3
Classification of leprosy cases

	Paro				Lhuntsi			
	M.	F.	Total	%	M.	F.	Total	%
Lepromatous	27	17	44	47.0	39	22	61	31.3
Dimorphous	13	10	23	25.6	52	52	104	53.4
Polyneuritic	1	1	2	2.2	1	0	1	0.5
Tuberculoid	4	10	14	15.5	19	10	29	14.8
Indeterminate	7	0	7	7.8	0	0	0	0.0
Total	52	38	90		111	84	195	

It was found that the proportion of cases of tuberculoid leprosy was only 15% in both districts. The largest groups were the men with lepromatous leprosy in Paro, and men and women with dimorphous leprosy in Lhunsi. The lepromatous rates were 6.8 per 1000 in Paro, and 7.8 per 1000 in Lhunsi.

The lepromatous and dimorphous leprosy prevalence rates are shown in Table 4. The sex ratio (M : F) for lepromatous leprosy in both districts was 2.2 : 1.

TABLE 4
Lepromatous and dimorphous leprosy prevalence rates

Classification	Cases	Population	Prevalence (per 1000)
<i>Paro</i>			
Lepromatous	{ Male 27	2886	9.4
	{ Female 17	3863	4.4
Dimorphous	{ Male 13	2886	4.5
	{ Female 10	3863	2.6
<i>Lhunsi</i>			
Lepromatous	{ Male 39	3556	11.0
	{ Female 22	4284	5.5
Dimorphous	{ Male 52	3556	14.6
	{ Female 52	4284	12.1

This gives a sex ratio (M : F) for lepromatous leprosy in both districts of 2.2 : 1.

CLASSIFICATION AND AGE AT ONSET

Classification was related to age at onset of leprosy (Table 5); 9 cases were omitted from this table, as these patients were uncertain about the age at onset. The patients with polyneuritic and indeterminate leprosy were not included in the Table, since there were only 9 of them. It was found that the modal age of onset is in the 25-29 years age-group in Paro, and in the 20-24 years age-group in Lhunsi.

DISABILITY

Disability was recorded and graded according to the World Health Organization (WHO) method of classification (WHO, 1960). In Table 6 only the disabilities of hands and feet are considered, as these relate to the ability to be self-supporting.

In Paro District, 2 patients (2.2%) were blind in one eye and in Lhunsi District 5 patients (2.6%) were blind in one eye. This compares with the finding that approximately 1% of the general population of Bhutan are blind in one eye (Berkeley, 1969).

The large number of patients in Lhunsi with disability of Grade 4 or 5 was noted—32.8%, as compared with 23.9% in Paro—and this is particularly in those with dimorphous leprosy.

CONTACT

All patients were questioned regarding their contact with known cases of leprosy, either in the family or in the village. The replies are shown in Table 7.

TABLE 5
Classification and age at onset

Age (years)	Lepromatous			Dimorphous			Tuberculoid		
	M.	F.	Total	M.	F.	Total	M.	F.	Total
<i>Paro</i>									
0-4	0	0	0	0	0	0	0	0	0
5-9	0	1	1	0	1	1	0	0	0
10-14	1	2	3	0	1	1	1	1	2
15-19	4	1	5	2	2	4	0	2	2
20-24	4	3	7	1	0	1	0	0	0
25-29	5	5	10	3	2	5	0	0	0
30-34	2	1	3	2	0	2	0	1	1
35-39	5	0	5	1	1	2	0	2	2
40-44	2	1	3	0	0	0	0	2	2
45-49	1	1	2	1	0	1	0	1	1
Over 50	1	2	3	2	2	4	0	0	0
Total	25	17	42	12	9	21	1	9	10
<i>Lhuntsi</i>									
0-4	0	0	0	0	1	1	1	0	1
5-9	1	1	2	2	4	6	0	3	3
10-14	1	1	2	4	5	9	5	1	6
15-19	2	4	6	8	8	16	1	1	2
20-24	3	4	7	11	11	22	3	2	5
25-29	7	1	8	5	5	10	3	0	3
30-34	9	3	12	9	4	13	2	0	2
35-39	8	3	11	5	3	8	1	2	3
40-44	1	0	1	3	1	4	0	0	0
45-49	0	2	2	1	2	3	0	0	0
Over 50	7	3	10	4	8	12	3	1	4
Total	39	22	61	52	52	104	19	10	29

Considering that there is very little social ostracism of the leprosy patient in Bhutan, it is perhaps surprising that in Paro more than half the patients acknowledged no known contact. Twice as many of the patients in Lhuntsi gave a history of family contact, when compared with those from Paro District.

PREVIOUS TREATMENT

Only 87 of the patients in the two districts had ever had any treatment for their leprosy; 69% of patients had at some time been to either Gida Kom Leprosy Hospital, Kalimpong Leprosy Hospital, Garjab Leprosy Clinic or a Government dispensary, though in many cases this had been some years previously and for only one attendance.

Discussion

From this survey it was found that the prevalence rate for leprosy in Paro District was 13.4 per 1000 and in Lhuntsi District it was 24.8 per 1000. (This compares with India, where a "high" prevalence rate is taken as over 5 per 1000,

TABLE 6
Classification and disability grading

<i>Paro</i>	Grade 0-1				Grade 2-3				Grade 4-5			
	M.	F.	Total	%	M.	F.	Total	%	M.	F.	Total	%
Lepromatous	12	7	19	22.5	10	4	14	16.7	3	4	7	8.4
Dimorphous	3	1	4	4.9	4	4	8	9.6	5	4	9	10.7
Tuberculoid	1	5	6	7.1	3	1	4	4.8	0	4	4	5.8
Total				34.5%				30.7%				23.9%
<i>Lhuntsi</i>												
Lepromatous	18	10	28	14.6	10	6	16	8.3	10	6	16	8.3
Dimorphous	17	18	35	18.3	18	7	25	13.0	17	27	44	23.0
Tuberculoid	11	7	18	9.3	4	2	6	3.1	2	1	3	1.5
Total				42.2%				21.7%				32.8%

TABLE 7
History of contact

<i>Paro</i>	Family			Village			Not known		
	M.	F.	Total	M.	F.	Total	M.	F.	Total
Lepromatous	3	6	9	9	7	16	15	4	19
Dimorphous	2	2	4	4	0	4	7	8	15
Tuberculoid	1	0	1	1	3	4	2	7	9
Total			17.8%			30%			52.3%
<i>Lhuntsi</i>									
Lepromatous	13	11	24	19	6	25	7	5	12
Dimorphous	13	24	37	26	20	46	13	8	21
Tuberculoid	6	6	12	3	3	6	10	1	11
Total			37.4%			39.4%			23.3%

such areas being found mainly in eastern parts of India and between them accounting for about three-quarters of the total leprosy in India.) If these rates are applied to the estimated total population of Bhutan, there could be about 11,000 cases of leprosy in the country.

It is interesting to note that the age of onset of leprosy is apparently later in Bhutan than in many other countries, where the majority of patients show the first manifestations of leprosy before the age of 20 years (Cochrane, 1964). When this is taken in conjunction with the age-structure of the population, it would appear that the main emphasis in future survey work should be on school-leavers and such organized groups as police, monks, the army, and the labour force. The male : female sex ratio of 2 : 1 for lepromatous disease in the population aged 20-39 years would appear to indicate a potential source of spread of the disease, since it is men in this group who are likely to be found in the organizations mentioned above, or moving about the country in the course of their normal agricultural and trade customs.

Job (1965) has stated that in India lepromatous leprosy accounts for 13 to 15% of cases and in China it is thought to be about 40 to 45% of the total cases. From the survey figures here reported, it is seen that the corresponding figures are 47% for Paro and 31.3% for Lhuntsi. This would support the view that people of Mongolian extraction are more likely to develop lepromatous leprosy than inhabitants of India. The large number of patients with dimorphous leprosy in Lhuntsi would account for the high disability rate seen in that district.

Estimates of the frequency of disabilities vary considerably—from 10% in Burma (Mallac, 1962) to 29.2% in Bombay (Chodankar, 1962)—and are related to the pattern of the disease and the standards of medical care in different countries. In this survey a high rate of disability was found. About 54% of patients had some degree of disability (Grade 2-5), and of these, half were severely disabled (Grade 4-5). If these figures apply to the whole of Bhutan, there may be about 3000 people (about 1% of the adult population) who are so disabled that they are unable to support themselves.

It is encouraging to find that nearly 70% of the leprosy patients who were seen had at some time or other sought treatment. This would seem to indicate a willingness to accept modern methods of treatment, but the sporadic attendance

at clinics reveals the need to organize some kind of education and follow-up of all cases. To some extent this would mean the creation of leprosy clinics, but there are already Government Health Service dispensaries throughout Bhutan where treatment could be given. With this in view, a handbook on the diagnosis and treatment of leprosy has been circulated to all Government Medical Officers and Compounders (1970), and a simple pamphlet in both English and Bhutanese produced for general distribution.

This survey has provided the basis for certain recommendations regarding the organization of a leprosy service in Bhutan. The magnitude of the problem in Bhutan can be appreciated when one considers the thinly populated, mountainous region and the scarcity of trained doctors and auxiliaries. The present survey facilitated the training of medical auxiliary staff in leprosy work, and enabled various forms and procedures to be tried in the field.

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Leprosy in Peru^{*}

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Introduction

The appalling earthquake in the Huaraz area to the north of Lima in 1970 brought Peru into the headlines and stimulated massive financial aid from many countries of the world—not least from Great Britain, which raised over a quarter of a million pounds. Following this disaster, many individuals in voluntary and other agencies came to see medical and social problems in Peru for the first time, and when the emergency settled down it was therefore hardly surprising that various requests should be made for help in the public health field. By a curious chain of circumstances involving an internationally famous entertainer, an ophthalmologist, and a Peruvian army general, the British Leprosy Relief Association (LEPRA) was approached with a view to finding someone to go to Peru and assess the leprosy situation in the country.

The author was given this task, and the present paper describes impressions gained during a 4000-mile tour of the main areas and centres of leprosy work.

Background Information

Peru has a population of approximately 13 million, and a total area of 1,280,219 km²; after Brazil and Argentina, it is the third largest country in South America. The government is a military dictatorship, with the army in control of all aspects of life in Peru, but with civilian advisers at many levels. The budget of the Ministry of Health appears to be adequate to maintain services, without however allowing of much expansion and development. The physical geography of Peru is indeed extraordinary, and has an important effect on medical services. The country may be roughly divided into a long arid, rainless strip along the Pacific coast on the west; this merges into the Andes, running more or less the length of Peru, which in turn merge into the vast jungle area to their east and north-east, stretching to the Brazilian and Columbian borders. The contrast in climate, altitude, people, living conditions, and vegetation in these areas is almost beyond description.

It is difficult to identify the racial origins of the Peruvians; to a visitor, most of the people one meets appear to be of mixed blood and describe themselves as “mestizo”. In addition it is usually stated that there are around 46% of “pure Indian stock”, and these are Indian tribes living in the mountains and jungles,

^{*} Received for publication July 1971.

some of them not yet fully contacted by outsiders, and with hundreds of different sub-groups and languages. Their origin seems open to dispute; the word "Indian" is of course a misnomer. Perhaps around 1% of the total population is of Chinese, Japanese, or pure European origin. There are 2 or 3 main "Indian" dialects but the national language is Spanish, and English has very little use.

Objectives of the Visit

The opportunity of sending someone to Peru was of particular interest to LEPR, since in September 1970 a decision had been taken to extend its activities and aid to the international field, funds having been previously allocated only to projects within British Commonwealth areas. The fact that Peru had asked for help was thought to be important, and it was considered worth while to send someone to report on the practical possibilities of helping with leprosy control in a Spanish-speaking country, under a dictatorship, and at a considerable distance from London. OXFAM in England and the World Health Organization (WHO) in Geneva were able to supply information and contacts which proved of great value, and as events turned out the whole visit was greatly helped by the widespread interest and co-operation received in Peru itself.

Prevalence

The following sources need to be considered: (a) The WHO Guide to Leprosy Control (1966) gives the registered number of cases of leprosy as 2808 (0.24 per 1000) and the estimated number as 7000 (0.61 per 1000), based on a total population of 11,511,000; (b) however, more recent information from WHO states that at 31 December, 1968, a careful examination of the relevant clinical histories revealed an "active list of patients" of only 1347. Based on a population of 12,520,917 this would give a prevalence of 0.11 per 1000; (c) a report entitled "Information about Leprosy" by Neyra Ramirez, Chief of the Peruvian National Programmes against tuberculosis, leprosy and smallpox (Ministry of Health, Lima, July 1970) gives an *accumulated* total, starting from the year 1900, this figure being 3432.

Clearly many of these sufferers must now be dead, and others completely lost sight of. In others again the disease must surely be clinically and bacteriologically inactive and no longer in need of drug treatment or supervision. On this present visit it was not possible to get definite figures for the percentage of active/inactive cases, but Dr Neyra's belief is that approximately 2400 of the above 3432 are still "on the books", attending clinics and receiving treatment with dapsone.

Various other publications indicate a prevalence of significant cases of somewhere between 2000 and 3000. It is the present author's impression that about 3000 is a reasonable figure for known cases, and that the WHO estimate of a further 4000 still to be found (giving an estimated prevalence of about 7000) is supported by findings at the present time.

Incidence

Consecutive figures were not available, but in the year 1966, 98 new cases were notified in Peru, and figures for subsequent years have been of the same order

Lepromatous Rate

From the 98 cases in 1966, 25 were classed as lepromatous, i.e. 25.6%. However, the classification of the others raises some doubt as to the terminology used; 28 (28.6%) were classed as tuberculoid, 43 (43.9%) as undifferentiated, 1 as "dimorphous" and 1 as unclassified.

Distribution of Leprosy by Areas

For all practical purposes, leprosy in Peru occurs only in the Departments of Loreto (a vast area in the north-east quarter), San Martin and Amazonas (adjoining Loreto on its western border and in the north central part of Peru), and in Apurimac (that is, towards the southern third of the country). To say categorically that it does not occur in the numerous other departments is of course open to the usual arguments that a thorough search has not been made, that medical workers are not aware of the disease, etc., but in fact these arguments apply equally well to areas where leprosy continues to occur. The coastal strip is virtually free; cases diagnosed in Lima have almost invariably come from the interior. The population of Lima is now about 2 million, but on this visit no evidence was forthcoming for a case actually arising in Lima. The mountain range has very few of the notified cases, and the tropical, watery Department of Loreto is undoubtedly the most important source of leprosy in Peru; taken together with the adjoining departments of Amazonas and San Martin, it can be said that over 90% of all cases come from this region. It is the opinion of Dr Neyra Ramirez in the Ministry of Health that leprosy in the endemic areas mentioned above is still in a state of "increase and expansion"; that in the mountains the disease is tending towards self-limitation; and that in the coastal strip cases occur only in persons from other regions. The undoubted focus of leprosy towards the south, in the Department of Apurimac, is difficult to explain. The registers give about 130 cases for the whole Department at the present time, but there is some evidence to suggest that there were many more in recent years.

The Leprosaria of Peru

At one time there were three leprosaria in the country, but two are now officially closed and only one remains in use.

(a) *Guia Leprosarium, Lima*. This leprosarium in the city area continues to receive patients and is the only one remaining open for new admissions. Built originally for cases of plague, the general appearance and facilities have fallen below expected standards, and in the very near future it is planned to close it and receive patients at one of the general hospitals in the area.

(b) *Huambo Leprosarium*, in the Department of Apurimac, was closed about 5 years ago, and all patients are now treated as out-patients.

(c) *San Pablo Leprosarium* is in the extreme north-east corner of the country, where the Amazon enters Brazil, and is quite near the border. Though it is now officially closed and no longer available for the admission of patients, there are in fact about 400 patients still in residence who are cared for jointly by Ministry of Health staff and mission sisters. San Pablo was founded in 1933, and by 1955 had about 780 patients; it was closed for admissions from 1967, and the

present policy of the Ministry is to treat all leprosy patients as out-patients from the outset, and to treat complications in general hospitals.

In 1968, Dr Masayoshi Itoh visited San Pablo and his report (AMRO-0504/D) for WHO) describes the extent of disability among the patients he examined. He found over 87% of them had disability of Grade III and to be in need of surgical treatment and/or intensive physical rehabilitation. Since then it may well be that matters have deteriorated; it is the present author's impression that several hundred people are in need of an almost massive programme of mental and physical rehabilitation if anything worth while is to be achieved.

Ministry of Health Policy on Leprosy Control

In the Peruvian Ministry of Health, measures against tuberculosis, leprosy and smallpox are combined under one programme and under one doctor. Since 1967 it has been medical policy to treat all leprosy patients, wherever possible, as out-patients from the outset, and to use clinics, jungle dispensaries, local and general hospitals and all medical staff for the diagnosis and treatment of this disease. Very full and practical details have been circulated from the Ministry in a well-thought-out handbook entitled *Normas y procedimientos para los programas de control de tuberculosis y lepra*, which gives detailed instruction for the diagnosis, notification, treatment and prevention of leprosy in the field. In every department of Peru there is a doctor who is appointed by the Ministry of Health in Lima to be responsible for campaigns against tuberculosis, leprosy and smallpox, and there is usually at least one senior medical assistant (auxiliary) with administrative, if not clinical, experience in these fields to assist him. It appears to be a matter of chance rather than design if these departmental doctors have had experience in, or are interested in, leprosy. Many of them commented that mountains, rivers, rains and bad roads made out-patient leprosy control a theoretical possibility in Lima, but an impossibility in their own areas. The original diagnosis may be made by medical assistants (auxiliaries) in remote areas, and they are all trained in the performance of the histamine skin test and in the taking of skin (not nasal) smears, which are dispatched to the local departmental hospital, or to Lima, for examination.

Treatment and Prevention

Dapsone is the Ministry of Health standard drug, in a dosage of 100 mg weekly for adults, appropriately less for children. "Reactors" to dapsone, using the term very generally, are changed to Thiambutosine (CIBA, 1906) for a maximum of about 18 months. Thalidomide is used with a frequency characteristic of South America, mainly for lepromatous reactions. Warnings about the teratogenic hazards have been issued from Lima, and from now on it is likely that thalidomide will be kept by and issued from the Ministry only. Chemoprophylaxis for selected contacts at risk is also official policy, in a dose of 100 mg weekly for adults, and 50 mg weekly for children—but only in areas where supervision at a hospital or by an experienced medical assistant is possible. BCG inoculation has been practised for many years in Peru, using a syringe, not the Heaf gun, and on a wide, virtually indiscriminate scale without prior tuberculin testing. This campaign has been greatly advanced by WHO through the Organización Panamericana de Salud, which has supplied materials and organized teams for

smallpox vaccination in most parts of Peru. The Ministry of Health has wisely taken the opportunity to perform BCG inoculation on the other arm, and in some departments it is thought that a very high degree of population coverage has been attained. Taking the whole country over, however, the present figure for those vaccinated with BCG is probably about 50%.

Tuberculosis in Peru

The Ministry figures indicate a prevalence of 1.5% (i.e., 15 per 1000), and both in Lima and elsewhere all doctors interviewed were unanimous that tuberculosis presents a larger problem than leprosy at the present time. No figures were obtained for prevalence. A control programme is integrated, as noted above, with leprosy and smallpox; X-ray facilities are available in most areas, but the chief method of diagnosis and assessment of tuberculosis is direct sputum examination. The general impression gained was that in Peru this disease is better understood and diagnosed than leprosy, and that within the budget and personnel allowed, campaigns are proceeding reasonably well.

Conclusions

Though numerically not a large one, Peru has a continuing and significant leprosy problem. At senior levels in the Ministry of Health there is a great deal of enthusiasm and expertise; and a commendable programme of leprosy control, following principles laid down by WHO, has been drawn up and widely circulated throughout the country. Particular emphasis has been given to the out-patient diagnosis and treatment of leprosy and to its acceptance and handling by general medical services at all levels. This policy began in 1967 after many years of work based on remote leprosaria, and the change may well account for the fact that today the leprosy service in Peru finds itself very short of experienced personnel at "leprosy control officer" or "senior medical assistant" grade to supervise field work over such difficult terrain.

It was therefore decided to advise LEPROA that while giving serious attention to the plight of 400 patients with "burnt-out" leprosy in San Pablo Leprosarium and also to the provision of certain basic items of equipment and transport, the most important priority was the training of suitable Peruvian nationals for leprosy control work in the field. This is now being followed up, with the possibility of sending candidates for training to Mexico or some other South American centre. Both in the short-term and long-term it would seem that the provision of training in leprosy work is by far the best contribution LEPROA can make towards the problem in Peru.

Acknowledgements

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Histoid Variety of Lepromatous Leprosy*

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Histoid lesions seen in 15 patients at Ankaful Leprosarium, Ghana, over a period of 7 years are described. Some of the earlier observations made by other workers on this interesting variety have been confirmed. The significance of this type of lesion, as far as it is known at present, is discussed.

Introduction

The histoid variety of lepromatous leprosy was first described by Wade in 1963. In the latter part of the same year, Wade sent collections of sections from histoid lepromatous cases to various centres and our interest in this interesting variety which was aroused at that time has been maintained. Since 1964, we have seen 15 patients with the histoid type of lesion, and in this report we present a few salient observations, some of which have earlier been mentioned by other workers, on this interesting variety of lepromatous leprosy.

Materials for Study

The 15 cases mentioned above occurred in a total patient population of 960 seen since 1964 at Ankaful Leprosarium. All 15 cases were confirmed by histopathological and bacteriological studies.

Of these, 9 were relapsed cases, while the remaining 6 had not previously received any specific antileprosy treatment. It should be noted here that while these 15 cases conformed to the characteristic features of histoid lepromatous leprosy, 10 more cases showed only early histoid features either clinically or histopathologically or in both.

In 3 of the latter 10 cases the clinical features underwent regression, while in the remaining 7 cases the subsequent biopsies showed only isolated areas of early histoid features which were overrun by the general picture of lepromatous pathology. These were taken to be stages, caught in the initial transformation into the variety. For the purposes of this report these 10 cases are not included.

CLINICAL FEATURES

The essential clinical features noted could be divided into 4 main types: (1) Subcutaneous nodules—these are separate nodules which are not tender. They grow primarily by expansion and tend to expand upwards and to become attached to the dermis. (2) Deeply fixed cutaneous nodules. These are derived from the subcutaneous nodules. Their tendency is to soften, rupture and ulcerate

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on the top, and finally heal with superficial scarring. (3) Superficially placed cutaneous nodules. These are primarily cutaneous lesions, are protuberant and pearl-like in appearance, and occasionally become pedunculated. (4) Histoid plaques or pads. These are seen over bony prominences, especially around the elbows and knees.

CHARACTERISTICS OF HISTOID LESIONS

- (a) Many young histoid nodules were found to be transient in nature (Rodriguez, 1969).
- (b) In long-standing cases the different varieties of lesions mentioned above were seen in the same patient. This was particularly observed in relapsed cases (see Fig. 1).
- (c) In the majority of our cases, characteristic lepromatous infiltration was largely limited to the face and ears, leaving the back and extremities as areas prone to the formation of histoid nodules. In some cases the infiltration was minimal and the isolated histoid lepromata looked seemingly innocent.
- (d) Involvement of the nasal mucosa was far less than would be expected (Price and Fitzherbert, 1966) and there was no involvement of the eye except for the formation of pannus in one case.
- (e) Trophic disturbances in the limbs, such as dyskeratosis, atrophy of the nails, and hyperpigmentation following chronic venous and lymphatic stasis, were minimal in the histoid cases.

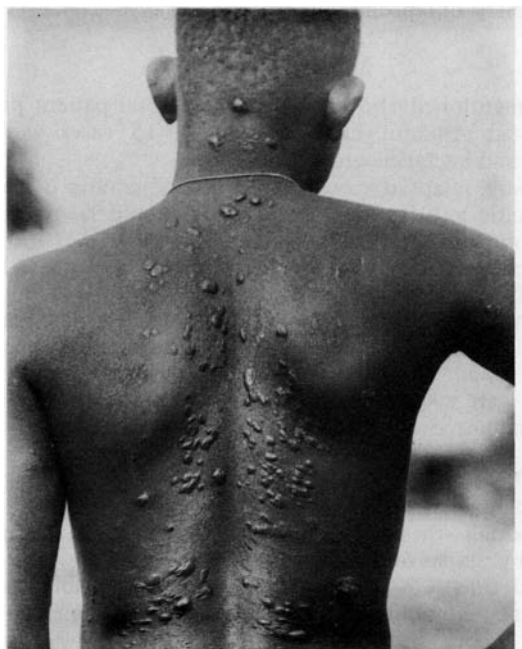


Fig. 1. Subcutaneous nodules, deeply fixed cutaneous nodules, superficial cutaneous nodules and plaques in a lepromatous patient.

- (f) Erythema nodosum leprosum, the frequently seen subacute reaction in lepromatous leprosy, was not seen in any of the histoid cases.

BACTERIOLOGY AND HISTOPATHOLOGY

It was observed in skin smears that the large number of leprosy bacilli were grouped in dense "bundles", and that the "globus" formation was rarely seen. Also the average size of the bacilli was observed to be larger than usual. Wade (1963) commented that the absence of "globus" formation may perhaps be explained on the ground of some local peculiarity of metabolism of the bacilli in the environments obtained, whereby they fail to produce the glial substance essential to the formation of the globus which occurs in the ordinary leproma.

The typical histoid nodule presents histopathologically a picture of intertwined whorls and bands of spindle-shaped cells, together with areas which are entirely composed of large, round histiocytes massed with bacilli (see photomicrographs Figs 2 and 3). These constitute what Wade (1963) described as "histoid habitus". In Wade's modification of Fite stain, the bacilli show deep purple staining which in places gives the appearance of an amorphous mass of pigment completely overlapping the identity of the cells in which they are contained. The cellular

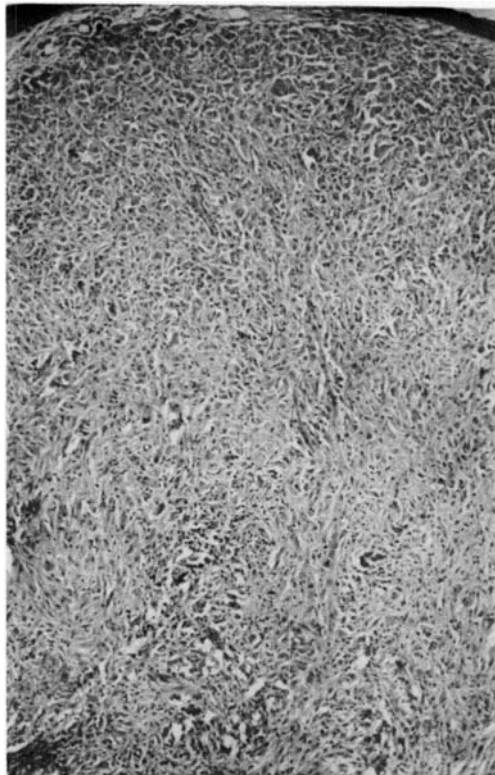


Fig. 2. Lepromatous leprosy. Section of the skin shows predominantly histiocytic infiltration. Histiocytes show a downward pattern of distribution which gives a whorled appearance. (H & E $\times 60$)

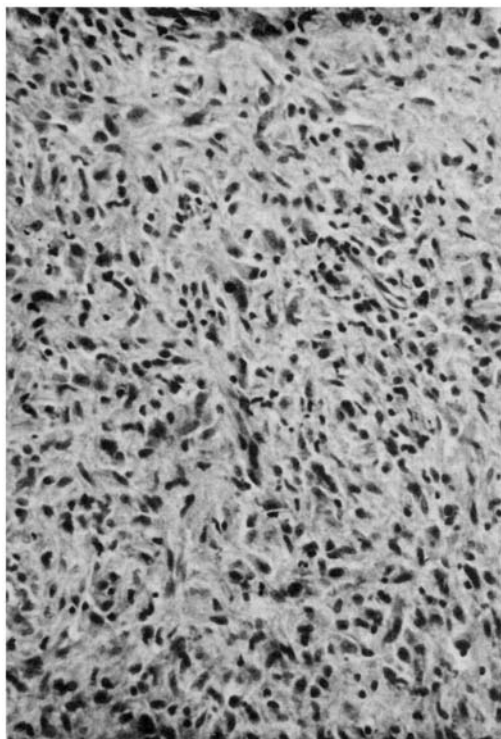


Fig. 3. Lepromatous leprosy. Section of the dermis showing histiocytes distributed in whorled fashion. (H & E $\times$ 300)

infiltrate itself seems to expand and push out the collagen matrix to form a pseudocapsule. These nodules are well vascularized but contain no nerve twigs. The interesting feature which Wade described as "contaminating tuberculoid foci" was observed in some of our cases where in isolated areas the epithelioid cells and lymphocytes constituted a small focus within the predominantly histiocytic infiltration.

It was observed that these areas contained few or no bacilli in Wade-Fite staining. The other interesting feature, which was mentioned by Wade (1963) and has been confirmed in the present study, is the alteration in the stainability of the bacilli in such "contaminating foci". When sections were cut from a paraffin block the bacilli in the sections, made a few years later out of these blocks, showed a "defatting" effect and were found to be smaller and fewer in numbers. The exact mechanism of this is not understood.

SIGNIFICANCE OF HISTOID LESIONS

The appearance of histoid lesions certainly indicates a highly active lepromatous process. This type of lesion is associated with drug resistance against dapsone (Pettit *et al.*, 1966). It is thought that this type of lesion is caused by a

mutant variety of *Myco. leprae* (Rodriguez, 1969). We do not know details of this supposed mutation—for example, whether it is a genetic or a phenotypic adaptation, or both. The fact that histoid leproma are seen in relapsed cases, especially in a post-sulphone period, indicates that an increased incidence of such lesions poses a considerable epidemiological problem. What is the mechanism of formation of such single tissue-element infiltrate composed entirely of, spindle-cell tissue or histiocytes? These lesions are not at all ascribable to the “fibrosis” of ordinary lepromata (Wade, 1963) and they are very different from the inflammatory granulomata seen in the ordinary lepromatous case.

Lever (1961) holds that in the skin the adventitial cells around a blood vessel, which normally develop into fibroblasts, may under pathological conditions, produce histiocytes. Petit *et al.* (1966) conjecture that in leprosy an acute increase in the number of bacilli might cause these adventitial cells to act as host-cells for bacilli, retaining some fibroblastic properties though not producing any large amount of collagen. Such cells differ somewhat from the normal reticulo-endothelial host cell and so modify the attributes of the granuloma.

The significance of the “contaminating tuberculoid foci” in the histoid lesions is not entirely clear. Melamed *et al.* (1964) view this as evidence of a transitional phase borderline reaction in its evolution to lepromatous pathology. Pettit *et al.* (1966) consider that these contaminating foci as examples of tissue reactivity which could be elicited even in a pure lepromatous (LL) lesion.

The histoid variety of a lepromatous lesion can be easily missed or misdiagnosed, especially where the luscious shiny isolated nodules are not accompanied by discernible infiltration elsewhere in the body. To pathologists, these nodules may masquerade as nodular subepidermal fibrosis, xanthoma, fibrosarcoma, or keloid. The diagnosis can of course be clarified by acid-fast staining and Mallory’s aniline blue staining for collagen. To the clinician, especially in West Africa, histoid lesions of lepromatous leprosy may bear a resemblance to an onchocercal nodule, keloid, warts, Kaposi’s sarcoma, or neurofibroma.

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Nerve Enlargement in Relation to Classification of Leprosy*

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While certain details of the pathogenesis of nerve involvement in leprosy are rather obscure, it is well known that peripheral nerves are damaged at certain sites of predilection. The nerves become enlarged and tender and exhibit a varying consistency on palpation. Although the changes are due essentially to the presence of *Myc. leprae* in the nerve, the consistence of the enlarged nerve depends on the amount of oedema and cellular infiltration within the nerve and of fibrosis in the sheath or in the nerve itself (Browne, 1963). Superficiality, repeated trauma, constricting bands, lower temperature, and a greater temperature variation (Brand, 1959) have all been suggested to explain the apparently complex pathogenesis of nerve involvement in leprosy. Not only truncal nerves but also cutaneous nerves, which are normally difficult or impossible to palpate, may become so enlarged as to be easily palpable and sometimes visible. Occasionally nerve abscesses may be encountered.

From the detailed studies of peripheral-nerve enlargement reported by Chatterji (1933, 1936) at the Calcutta clinic, it was obvious that he was dealing mainly with the tuberculoid type of leprosy. Murdock (1949), following an intensive study, documented the frequency and distribution, without reference to classification, of peripheral-nerve enlargement in 117 leprosy patients and compared his results with those of Chatterji. Browne (1965), in an interesting paper, reported some less common neurological findings made over a period of 28 years and covering a large number of patients.

The present prospective study was undertaken to obtain more precise information with regard to the pattern of clinical manifestations, and of the frequency and distribution of enlargement of the cutaneous and truncal nerve in the various types of leprosy.

Patients and Methods

A total of 540 leprosy patients were chosen by stratified random selection from 41 peripheral clinics of the leprosy control programme undertaken by the Schieffelin Leprosy Research Sanatorium, Karigiri. Of these, 130 patients were classified as having indeterminate leprosy, 130 tuberculoid, 130 lepromatous, and 150 borderline leprosy. The classification of the type of leprosy was determined by the usual clinico-bacteriological criteria employed for this purpose; both male

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and female patients were included in the study. All the patients were receiving antileprosy treatment at the time of assessment. Patients in acute lepra reaction and those with quiescent leprosy were excluded.

The study was conducted by means of repeated visits to all peripheral clinics over a period of 6 months and was based on the patients who were attending the clinic at the time of the visit. Special forms listing all the cutaneous and truncal nerves in the head and neck, trunk and upper and lower limbs were used in the course of the clinical examination, which consisted in careful inspection and palpation of the nerves. Palpation in each was done across the course of the nerve and compared with that on the opposite side. It was sometimes necessary to distinguish an enlarged nerve from an enlarged lymphatic gland or leprotic nodule. Skin lesions and the areas surrounding them were palpated to detect nerve enlargement. In addition, cutaneous and truncal nerves were routinely palpated at the usual levels where they are subcutaneously placed, and any pain or tenderness was recorded. Particular attention was paid to the consistency of enlarged nerves, which were classified as hard, soft, and beaded or node-like. In a few cases where a nerve abscess was suspected, surgical exploration was undertaken by one of the authors (D.A.R.). Fibrosis of the nerve and paralysis when present were noted. In all cases the patient's age, sex, duration of the disease, and treatment received were recorded (Table 1).

Results

Table 1 shows the number of male and female patients studied in each group. It also records the group's average age and the duration of disease and treatment according to classification.

In Table 2, the nerves that were found enlarged on palpation in 130 patients with indeterminate leprosy are recorded. The consistency of the nerve and its association with any skin lesions, pain and tenderness, fibrosis, or paralysis are shown where present. Table 3 shows the results in the 130 patients with tuberculoid leprosy. The frequency of unilateral and bilateral involvement of nerves and the consistency of the nerve is noted. The relationship of nerves to skin lesions, pain, tenderness and paralysis is also recorded.

Table 4 records the findings on examination made of the cutaneous and truncal nerves of 130 patients with lepromatous leprosy. The consistency of the nerve

TABLE 1
Age, sex, duration of disease and treatment according to classification

Classification	Male	Female	Total	Average duration of disease (years)	Average duration of treatment (years)	Average age of patients (years)
Indeterminate	76	54	130	2.8	1.7	14.4
Tuberculoid	76	54	130	3.3	2.3	22.3
Lepromatous	85	45	130	7.3	3.0	31.4
Borderline	96	34	130	5.1	2.9	28.0

No significant difference in nerve involvement was noted between male and female patients in any of the groups studied.

TABLE 2
Indeterminate leprosy

Nerves	Unilateral		Bilateral		Hard		Enlargement Beaded		Soft	
	No.	%	No.	%	No.	%	No.	%	No.	%
<i>Head and neck</i>										
Greater auricular	4	3.1	1	0.8	2	1.5	—	—	4	3.1
<i>Upper limb</i>										
Lat. antebrach. cut.	3	2.3	4	3.1	7	5.4	—	—	4	3.1
Ulnar	23	17.7	15	11.5	20	15.4	—	—	33	25.4
Radial	1	0.8	—	—	—	—	—	—	1	0.8
Ulnar cutaneous	6	4.6	—	—	1	0.8	—	—	5	3.8
Radial cutaneous	12	9.2	3	2.3	3	2.3	—	—	15	11.5
<i>Lower limb</i>										
Lateral popliteal	15	11.5	14	10.8	20	15.4	—	—	23	17.7
Musculo-cutaneous	10	7.7	—	—	5	3.8	—	—	6	4.6
Posterior tibial	5	3.8	4	3.1	12	9.2	—	—	2	1.5
Totals	79	—	41	—	70	—	—	—	93	—

TABLE 3
Tuberculoid leprosy

Nerves	Enlargement															
	Unilateral		Bilateral		Hard		Beaded		Soft		Skin lesion		Tenderness		Pain	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
<i>Head and neck</i>																
Supratrochlear	2	1.5	1	0.8	1	0.8			3	2.3	4	3.1				
Supraorbital	1	0.8			1	0.8					1	0.8				
Infraorbital	6	4.6	1	0.8	2	1.5			6	4.6	8	6.2				
Upper division (F)	3	2.3	1	0.8	3	2.3	1	0.8	1	0.8	5	3.8				
Greater auricular	16	12.3	13	10.0	27	10.8	2	1.5	13	10.0	41	31.5				
Smaller occipital	1	0.8	1	0.8	1	0.8			2	1.5	3	2.3				
Cervical cutaneous	1	0.8	—	—	—	—			1	0.8	1	0.8				
<i>Upper limb</i>																
Dorsal antebrach. cut.	4	3.1	2	1.5	8	6.2					6	4.6				
Med. antebrach. cut.	4	3.1			3	2.3			1	0.8	4	3.1				
Lat. antebrach. cut.	34	26.2	20	15.4	56	43.1			18	13.8	53	40.8	1	0.8		
Ulnar	39	30.0	40	30.8	65	50.1	2	1.5	29	22.3	72	55.4	2	1.5	2	1.5
Median	10	7.7	2	1.5	12	9.2			3	2.3	11	8.5				5 3.8
Radial	5	3.8	2	1.5	8	6.2			3	2.3	7	5.4	1	0.8		1 0.8
Ulnar cutaneous	21	16.2	6	4.6	23	17.7			9	6.9	28	21.5	1	0.8		
Radial cutaneous	34	26.2	27	20.8	54	41.5	2	1.5	28	21.5	73	56.2	2	1.5		
<i>Lower limb</i>																
Lateral popliteal	29	22.3	33	25.4	67	51.5			25	19.2	92	70.8			1 0.8	1 0.8
Musculo-cutaneous	20	15.4	12	9.2	32	24.6			12	9.2	44	33.8				
Sural	1	0.8	1	0.8					3	2.3	3	2.3				
Posterior tibial	6	4.6	9	6.9	20	15.4	1	0.8	3	2.3	22	16.9				
Totals	237	—	171	—	383	—	8	—	160	—	478	—	7	—	2	—

(1) Ulnar nerve abscess

TABLE 4
Lepromatous leprosy

Nerves	Enlargement											
	Unilateral		Bilateral		Hard		Beaded		Soft		Skin lesion	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
<i>Head and neck</i>												
Supratrochlear	3	2.3	3	2.3	2	1.5			7	5.4		
Supraorbital	3	2.3	9	6.9	1	0.8			20	15.4		
Lacrimal	3	2.3							3	2.3		
Infraorbital	7	5.4	6	4.6	2	1.5			18	13.8		
Upper division (F)	1	0.8							1	0.8		
Greater auricular	24	18.5	43	33.1	26	20.0	1	0.8	80	61.5		
Smaller occipital	1	0.8							1	0.8		
Greater occipital			1	0.8					2	1.5		
Supraclavicular	7	5.4	2	1.5					11	8.5		
<i>Upper limb</i>												
Dorsal antebrach. cut.	6	4.6	2	1.5	6	4.6			4	3.1		
Med. antebrach. cut.	6	4.6	2	1.5	6	4.6			4	3.1		
Lat. antebrach. cut.	31	23.8	34	26.2	49	37.7	1	0.8	33	25.4	3	2.3
Ulnar	16	12.3	95	73.1	84	64.6	3	2.3	110	84.6	2	1.5
Median	3	2.3	15	11.5	2	1.5			29	22.3	1	0.8
Radial	11	8.5	4	3.1	10	7.7			9	6.9	2	1.5
Ulnar cutaneous	28	21.5	30	23.1	26	20.0			56	43.1		
Radial cutaneous	21	16.2	84	64.6	69	53.1	1	0.8	103	79.2	2	1.5
<i>Lower limb</i>												
Lateral popliteal	23	17.7	89	68.5	88	67.7			110	84.6	2	1.5
Musculo-cutaneous	34	26.2	30	23.1	36	27.7			58	44.6	2	1.5
Sural	4	3.1			2	1.5			2	1.5		
Posterior tibial	27	20.8	41	31.5	43	33.1			66	50.8	2	1.5
Totals	259	—	490	—	452	—	6	—	727	—	16	—

TABLE 5
Borderline leprosy

Nerves	Enlargement																				
	Unilateral		Bilateral		Hard		Beaded		Soft		Skin lesion		Tenderness		Pain		Fibrosis		Paralysis		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
<i>Head and neck</i>																					
Supratrochlear	3	2.0	2	1.3					7	4.7	4	2.7									
Supraorbital	6	4.0	6	4.0	1	0.7			17	11.3	7	4.7									
Lacrimal	4	2.7	4	2.7					12	8.0	6	4.0									
Infraorbital	10	6.7	6	4.0	2	1.3			20	13.3	10	6.7									
Mental	2	1.3							2	1.3	2	1.3									
Upper division (F)	5	3.3	1	0.7	2	1.3			5	3.3	6	4.0		1	0.7				3	2.0	
Lower division (F)	3	2.0							3	2.0	1	0.7									
Greater auricular	25	16.7	41	27.3	31	20.7	6	4.0	70	46.7	16	10.7		2	1.3						
Smaller occipital	3	2.0			2	1.3			1	0.7	3	2.0									
Curvical cutaneous	2	1.3							2	1.3	1	0.7									
Supracalvicular	3	2.0	3	2.0	2	1.3			7	4.7	2	1.3									
<i>Upper limb</i>																					
Dorsal antebrach. cut.	5	3.3	5	3.3	10	6.7			5	3.3	11	7.3									
Med. antebrach. cut.	7	4.7	2	1.3	5	3.3			6	4.0	8	5.3									
Lat. antebrach. cut.	43	28.7	34	22.7	62	41.3			47	31.3	22	14.7									
Ulnar	26	17.3	96	64.0	73	48.7	1	0.7	134	89.3	35	23.3	6	4.0	2	1.3	8	5.3	8	5.3	
Median	10	6.7	17	11.3	7	4.7			35	23.3	11	7.3	4	2.7	1	0.7	2	1.3	3	2.0	
Radial	10	6.7	6	4.0	6	4.0			17	11.3	11	7.3	3	2.0							
Ulnar cutaneous	39	26.0	28	18.7	28	18.7	2	1.3	65	43.3	24	16.0	2	1.3	1	0.7					
Radial cutaneous	42	28.0	73	48.7	57	38.0	3	2.0	128	85.3	36	24.0	2	1.3	1	0.7					
<i>Lower limb</i>																					
Lateral popliteal	29	19.3	94	62.7	59	39.3			134	89.3	25	16.7	4	2.7	2	1.3	3	2.0	3	2.0	
Musculo-cutaneous	36	24.0	41	27.3	25	16.7			88	58.7	24	16.0		2.0	2	1.3					
Sural	3	2.0	3	2.0					9	6.0	8	5.3									
Posterior tibial	30	20.0	38	25.3	33	22.0			71	47.3	14	9.3	4	2.7	2	1.3					
Totals	346	—	500	—	405	—	12	—	885	—	287	—	28	—	14	—	13	—	17	—	
Rt. ulnar abscess (1) Beaded																					

Rt. ulnar abscess (1) Beaded

Hard nerves, unilateral involvement and association of enlarged nerves with skin lesions were abscessed in the borderline-tuberculoid group. Soft nerves and bilateral involvement were seen in the borderline-lepromatous group.

and the frequency of unilateral and bilateral involvement of these nerves are shown. Pain, tenderness, fibrosis, paralysis, and the association of enlarged nerves with skin lesions are also recorded. Lastly, Table 5 shows the results in the 150 patients with borderline leprosy. Patients with borderline-tuberculoid, borderline-borderline, and borderline-lepromatous were included in this group. The number of nerves thickened unilaterally and bilaterally, the consistency of the nerves, and the association of the nerves with skin lesions, pain and tenderness, as well as fibrosis and paralysis are recorded.

Discussion

Since the earliest lesions of leprosy usually constitute the indeterminate group, and also because many of the patients were children, the average age was distinctly lower and the duration of the disease and of treatment shorter in this group than in the other three groups (Table 1). There was also a relative infrequency of nerve enlargement in the indeterminate group, only one or a few nerves being involved in each patient. Although 34 nerves were routinely examined in each case enlargement was recorded only in the 9 nerves listed in Table 2. The nerve enlargement was discrete, was just perceptible on palpation, with the consistency varying from hard to soft; pain and tenderness were not elicited in any of the nerves examined. This confirms the accepted view that thickening of peripheral nerves is usually not detected in the early indeterminate group of leprosy, although later some of the nerves may be found enlarged. It may be assumed that even though acid-fast bacilli may be found within the nerves, the bulk of the nerve parenchyma remains unaffected at this stage of the disease (Iyer, 1965). Another interesting finding was that cutaneous nerves supplying the area in which skin lesions are situated were not found to be enlarged. It seems appropriate to comment on the particular involvement of the ulnar nerve and the lateral popliteal nerve even at the stage of indeterminate leprosy. In addition to such factors as superficiality, temperature, constricting bands and trauma already mentioned, it was observed by Sunderland (1953*a*, 1953*b*) that the ulnar nerve behind the medial epicondyle of the humerus and the lateral popliteal nerve behind the neck of the fibula are composed of few and larger funiculi with little connective tissue between them. On the basis of the variation in the relative number of funiculi and amount of connective tissue in different nerves, and also along the course of a particular nerve, it is apparent that nerves or segments of nerves which are composed of only a few, but large, funiculi will have a much larger proportion of the nerve affected than those with the same number of funiculi destroyed but whose funiculi are smaller and more numerous. Furthermore, the thinness of the interfunicular connective tissue would render the nerve more vulnerable to extraneural trauma, as well as allowing the transmission from one funiculus to another of pressure and possibly even bacteria. Also, since nerves which have few funiculi tend to have a greater proportion of their blood supply more superficially placed, such nerves are more vulnerable to trauma. These factors may combine to allow the adverse influences of trauma and infection to operate and so make the nerves particularly vulnerable to damage.

The characteristic feature in the group of 130 patients with tuberculoid leprosy (Table 3) was the enlargement of cutaneous and truncal nerves supplying the area in which skin lesions were situated. This feature was marked in most of the nerves examined in the head and neck and the upper and lower limbs. Enlargement of

branches of the facial and trigeminal nerves was in all cases associated with skin lesions on the face. One or more cutaneous branches and one or more truncal nerves were observed to be associated with a single skin lesion. Sometimes a nerve supplying a small lesion was grossly hypertrophic while that supplying an extensive lesion was found to be only slightly thickened. Other features were that only a few nerves were involved in each patient and that the involvement was more frequently unilateral than bilateral and depended to a large extent on the distribution and number of skin lesions, the neurological pattern being determined by the asymmetrical distribution of a few skin lesions. As may be expected with tuberculoid leprosy, where the cellular reaction to paucibacillary infection in nerves is vigorous, the consistence of the nerves was mostly hard. Tuberculoid leprosy is a form of disease in which the body defences are adequate and in which attempts are made to localize the disease. Since the bacilli are also located in the nerve, the reaction takes place within the nerve. This is probably an antigen-antibody disorder confined to nerve tissue (Iyer and Desikan, 1968), the *Myco. leprae* being the antigen which provides the trigger enabling an immune response to be adjuvated and to take place rapidly (Weddell *et al.*, 1963). Therefore nerve involvement in tuberculoid leprosy may be considered a delayed hypersensitivity reaction, with *Myco. leprae* merely acting as an adjuvant. Other agents, traumatic or toxic, acting on nerve tissue may also be precipitating factors in determining this nerve damage (Browne, 1965).

In the softer nerves the absence of tenderness may be due, to some extent, to the effect of therapy. Some beaded enlargement was encountered. One beaded ulnar nerve was surgically explored and found to contain an area of softening. In this group of patients with tuberculoid leprosy there was little relation between nerve thickening and paralysis.

In all the patients with lepromatous leprosy many nerves were found to be enlarged, and more nerves were involved bilaterally than unilaterally (Table 4). The consistence was recorded as soft in 727 nerves, compared with 452 nerves which were felt to be hard. A few beaded nerves were encountered, but none were surgically explored. Although pain and tenderness were present in some of the nerves examined in both upper and lower limbs, paralysis was noted in only one ulnar and two median nerves. The average age, duration of the disease and of treatment were also proportionately greater in this group. It has been demonstrated by Job and Desikan (1968) that bacilli are found throughout the course of the nerve but are particularly abundant at those sites where the nerves are placed subcutaneously. As cellular infiltration of the nerves is generally minimal the clinical evidence of damage is generally late, that is, from the third year onwards (Browne, 1965). An epidemiological study by Srinivasan (1965) showed that deformities were generally more frequent in lepromatous than in non-lepromatous leprosy. It was suggested that in a systemic disease like lepromatous leprosy, where there is a haematogenous spread of the infection, more nerves are likely to be involved with, in consequence, a greater likelihood of nerve damage. In addition to non-paralytic deformities that are likely to occur during lepra reaction (Furness *et al.*, 1968) a significant increase in neurological deficit was also recorded (Karat *et al.*, 1969) in a group of patients with recurrent and/or chronic erythema nodosum leprosum (ENL) as compared with a control group without reactions. The unrestrained multiplication of *Myco. leprae* within the reticulo-endothelial cells in the anergic type of leprosy seems to suffer no limitations except those imposed by some little understood need for proximity to

the surface of the body. There is a polyneuritis and nerves are enlarged at sites where they are superficial, suggesting that their involvement may be temperature-dependent.

In the borderline group of 150 patients, the characteristics of nerve enlargement represented an admixture of those seen in tuberculoid and lepromatous leprosy. In these cases 23 different nerves out of a total of 34 examined were found to be enlarged in the head and neck, trunk, and upper and lower limbs (Table 5). Whereas 500 nerves were enlarged bilaterally, only 346 showed unilateral enlargement. A soft consistence was recorded in 885 nerves, 405 nerves felt hard, and 12 beaded on palpation. Although 287 enlarged cutaneous and truncal nerves were found to be associated with skin lesions, this was less than the 478 nerves found to be associated with skin lesions in tuberculoid leprosy (Table 3). Unilateral involvement, hard nerves and some relation of nerve involvement to skin lesions were observed mainly in the borderline-tuberculoid group in this study, while bilateral enlargements and soft nerves were noted in patients with borderline-lepromatous. An abscess was found during surgical exploration of a right ulnar nerve in a patient with borderline-tuberculoid leprosy. Pain and tenderness were present in several nerves in the upper and lower limbs and face. Paralysis was more frequent in borderline leprosy than in any of the other groups studied.

In none of the groups studied did there appear to be any relationship between nerve enlargement and paralysis. Sherron (1945) has stated that about one-third of a nerve can be divided without producing demonstrable motor or sensory deficit. Sunderland (1945), following studies made by intraneural tomography, observed that owing to reassortment of fibres in progress in the proximal portion of the nerve and to the fibre composition of funiculi at high levels, the injury may involve those bundles which contain only a few fibres of some or all of the branches, so that the resultant loss of function may not be detected clinically. These reasons explain in part the normal function of infected, enlarged nerves in leprosy. Although local tenderness has been known to persist in some enlarged nerves after clinical and bacteriological arrest of the disease, its marked infrequency in the groups studied can be attributed only to effective therapy.

Summary

A group of 540 leprosy patients, of whom 130 had indeterminate leprosy, 130 tuberculoid, 130 lepromatous, and 150 borderline disease, were examined by inspection and palpation to study the pattern of clinical manifestations and frequency and distribution of cutaneous and truncal nerve enlargement according to classification.

A relative infrequency of nerve enlargement was recorded in the group with indeterminate disease, only one or a few nerves being involved in each patient. The nerve thickening was discrete, just perceptible on palpation, with a consistence varying from hard to soft. The particular predilection for involvement of the ulnar and lateral popliteal nerves, even at the indeterminate stage, is discussed.

The characteristic feature of the tuberculoid group was the enlargement of cutaneous and truncal nerves supplying the area in which the skin lesions were situated, the neurological pattern being determined by the asymmetrical distribution of a few skin lesions. The nerves were felt to be mostly hard. The

opinion is expressed that the nerve enlargement is probably a delayed hypersensitivity reaction, with *Myco. leprae* merely acting as an adjuvant.

Many nerves were involved in lepromatous leprosy. The involvement was predominantly bilateral rather than unilateral, while the consistence of the nerve was felt to be soft. The unrestrained multiplication of *Myco. leprae* at sites of predilection where such sites are superficial suggests that nerve involvement in lepromatous leprosy is temperature-dependent.

In the borderline group, the characteristics of nerve enlargement represented an admixture of those seen in tuberculoid and in lepromatous leprosy. Hard nerve enlargements, unilateral involvement, and association of nerves with skin lesions were noted in the borderline-tuberculoid group, while bilaterally involved soft nerves were seen in the borderline-lepromatous group. Nerve enlargement was most frequent in this latter group of patients.

No significant difference in nerve involvement was noted between male and female patients in any of the groups studied.

In none of the groups studied did there appear to be any relationship between nerve enlargement and paralysis. Some reasons for this discrepancy are suggested. The marked absence of pain and tenderness in the nerves was probably due to the effect of treatment.

The duration of disease and of treatment was longest in the group of patients with lepromatous leprosy, and shortest in the patients with indeterminate leprosy.

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Exacerbation of Dimorphous Leprosy Apparently Due to BCG Vaccination*

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A patient whose dimorphous leprosy was clinically and bacteriologically quiescent after 4 years of treatment with dapsone, experienced a sudden reactivation of the skin lesions a month after receiving BCG vaccination, together with a slight increase in evidence of peripheral nerve damage. The reaction subsided spontaneously, dapsone treatment being continued at the same dosage as before. No other treatment was given.

The factors suspected of precipitating episodes of acute exacerbation in lepromatous and dimorphous leprosy are many and varied: any intercurrent disease, a raised temperature (from whatever cause), smallpox vaccination, a change in the hormonal state, and mental stress are among these factors. In the patient who is the subject of the following report, BCG vaccination apparently acted as the exciting cause of clinical reactivation of dimorphous leprosy lesions that had been quiescent for some time.

CASE REPORT†

The patient was a female, 35 years of age, born (of British parents) in India, where she had remained, except for short visits to Britain, until 1965. She was married and had one child (born in 1964).

The first leprosy lesion was noticed by the patient in 1960, on the right thigh. It was diagnosed as a mycosis and treated with various fungicidal ointments. It disappeared while she was pregnant, but returned after parturition, becoming larger and more obvious. A year later, a similar lesion appeared on the right cheek. In 1965, "dimorphous leprosy" was diagnosed on clinical and histological grounds. A section of skin from the lesion on the thigh showed a "dense infiltrate of foamy cells in the superficial dermis. . . . Many *Myco. leprae* present".

Clinical examination at this time revealed extensive annular lesions extending from the right buttock to the outer aspect of the middle-third of the right thigh. The inner border was well defined, but the outer margins faded imperceptibly into the adjacent normal skin. The colour of the actual lesions was coppery (Figs 1-3).

On the right cheek, left arm, and over the left hip small discrete hypopigmented macules, with erythematous margins, were present. Over the lower parts of both legs were numerous small and slightly raised erythematous

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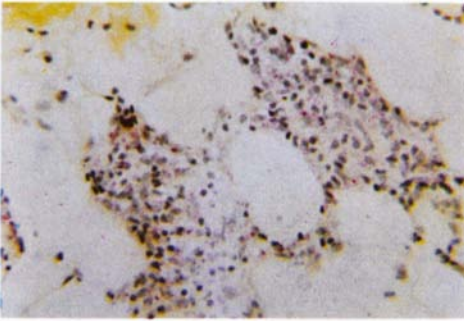
† This case was previously referred to in Wright, F. J. (1971) *Scott. Med. J.* **16**, 209.



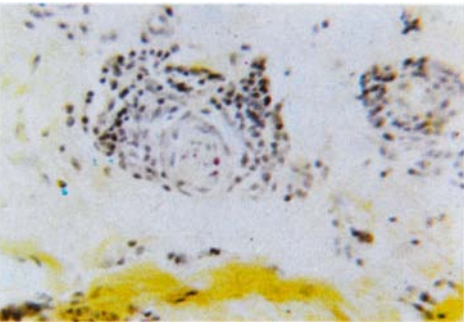
Fig. 1. Original appearance of right thigh.



Fig. 2. Right thigh after reaction to BCG.



(a)



(b)

Fig. 3.(a) and (b). Histological appearance of lesions in sections from right thigh and left leg after reaction to BCG.

lesions. No sensory loss was detectable in these areas. In the area enclosed by the ring-like lesion on the right thigh there was some loss of tactile sensation and of thermal appreciation and pin-prick. The peripheral nerves showed no abnormality.

TREATMENT

The lesions responded rapidly to small doses of dapsone, and the bacterioscopic findings were very satisfactory, only a few granular organisms remaining recognizable after 6 months' treatment. Treatment with dapsone was continued for a total of 4 years. By this time no trace of the skin lesions could be detected, and the only abnormalities discovered were a small area of residual skin anaesthesia on the right thigh, and enlarged dorsalis pedis nerves on both feet.

FURTHER HISTORY

The patient's husband having been diagnosed as suffering from pulmonary tuberculosis, the patient was tested twice with tuberculin (Heaf) and was found to be negative.

On 15 January, 1970, she was given BCG vaccination in the left deltoid region. On 15 February, 1970, the lesion on the right cheek re-appeared as a red ring, and the skin over the right thigh and leg (at the sites of the former lesions) became red and raised. The patient noticed tingling in the left foot. Clinical examination 4 days later confirmed these findings: the lesions seen were very similar to the appearance noted 4 years previously. There was no increase in the area or degree of sensory loss in the skin.

LABORATORY FINDINGS

Examination of the blood disclosed no abnormality. The erythrocyte sedimentation rate was 3 mm after 1 h.

TREATMENT

The patient continued taking dapsone by mouth in a dose of 100 mg twice weekly. The paraesthesiae on the outer side of the left foot persisted, but no sensory loss was at first demonstrable by standard tests.

HISTOLOGICAL REPORT

"Cellular infiltrate along some of the neurovascular pathways in the deep and middle dermis . . . cells are histiocytes, lymphocytes and a few plasma cells. A few small clusters of irregularly staining acid-fast bacilli in the arrector pili muscles . . . no evidence of bacillary viability" (specimen rather shrunken).

FURTHER PROGRESS

By 9 June, 1970 the skin lesions had almost completely faded, and on 24 November, 1970 only a faint trace of them remained. Superficial sensory loss over a small area on the outer side of the left foot persisted and the skin over the dorsum of the 4th and 5th left toes now showed a similar pattern of sensory loss.

Book Reviews

WHO Expert Committee on Leprosy: Fourth Report. WHO Techn. Rep. Ser. No. 59, Geneva, 1970. 31 pp. Price 30p; U.S. \$1.00, Sw. fr. 3. (Sales agent for U.K.: H.M. Stationery Office.)

This report will be read and pondered with interest in ministries of health in many countries and by leprosy workers the world over. Like previous reports, it attempts to assess the present situation in regard to leprosy, to appraise progress, and to provide useful data for planning control measures.

The number of patients diagnosed and registered during the past quinquennium (500,000) is about half the expected total. This is one of the figures submitted with "many reservations", and reflects the incomplete nature of the returns from countries where leprosy is most prevalent. [The statement that "even in areas of very high endemicity . . . it is unlikely that the prevalence rate will exceed 50 per thousand" is open to challenge, and is refuted by findings from several "areas" in Africa and Asia.] It is concluded that "the prevalence now remains at approximately the same level" in 1970 as in 1965 [which would suggest, in view of the increasing population, that the total number of patients is greater].

The Committee is of the opinion that, because of the risk of relapse of patients with lepromatous leprosy, and the proportion of such patients harbouring bacilli, it is necessary to ensure by regular treatment that at least 75% of patients with multibacillary disease must be rendered bacteriologically negative if a reduction in incidence is to be achieved. The point is made that dependence on auxiliary staff opens the way to either under- or over-diagnosis of leprosy under field conditions.

In the matter of therapy, the Committee (with perhaps undue caution) asserts that there is no "established alternative" drug to dapsone when intolerance to that drug occurs. The Committee recommends that where treatment is given into the patients' hands, reports should indicate "regularity of attendance" rather than "regularity of treatment".

Unexceptionable comments are made on the training of auxiliary staff and on health education. The observation is made that, although 5 years have elapsed since the Third Expert Committee Report was published, some countries still have not developed a suitable system for collecting and reporting the necessary statistics regarding leprosy. The modified criteria for "released from control" are appended *in extenso*: "A leprosy patient without any sign of clinical activity and with negative bacteriological findings should be considered as an 'inactive' case. Once inactivity is achieved, *regular treatment* should be continued for varying periods of time before the patient is 'released from control' (r.f.c.). These periods should be 1½ years for tuberculoid leprosy, 3 years for indeterminate, and *at least* 10 years for lepromatous and borderline cases. Since data on relapses after r.f.c. are scarce, it is advisable and important to continue the follow-up of lepromatous cases but without treatment; some leprologists consider that this should be done for life."

The section on research provides a useful summary of recent and projected work. One important observation refers to the Morphological Index, and reads as follows: "Because of its limits of sensitivity, however, it is not a suitable procedure for distinguishing the infectious from the non-infectious patient, even when performed under optimal conditions by highly experienced investigators." (This assertion will be received with mixed feelings by field workers and by public health administrators, who were hoping that the experimental evidence concerning viability of *Mycobacterium leprae* could be utilized in positive recommendations of control measures.)

Recommendations for future research into the cultivation of the causative organism, into drugs and immunology indicate the lines of future investigations. The vexed question of the value of BCG vaccination in the prevention of leprosy is adequately summarized, and the conclusion is reached that it is premature to recommend the widespread use of BCG vaccination for this purpose. The standardization of lepromin has now achieved general consensus; stocks should be made from lepromin yielding 160 million bacilli per ml. The following criteria are recommended for the late (Mitsuda) lepromin reactions: 0 = no reaction; $\pm$ = induration less than 3 mm; + = nodule of 3 to 5 mm; ++ = nodule of 6 to 10 mm; and +++ = nodule larger than 10 mm or with ulceration. The letter "U" should be added to the size to indicate ulcerations.

The paragraph on recent advances in the immunology of leprosy indicates the progress made in recent years, and mentions the isolation of a protein antigen that is apparently specific for *Mycobacterium leprae*. An indirect fluorescent antibody technique, employing smears from *Mycobacterium lepraemurium* as antigen, is reportedly giving consistent results in sera from persons with leprosy.

The section on chemotherapy and chemoprophylaxis summarizes accepted views on the sulphones, the long-acting sulphonamides, clofazimine, and acedapsonone. Regarding thalidomide, the Committee recommends that for the present the drug should "be used only for strictly investigative purposes under proper conditions of observation and control". The studies in chemoprophylaxis are referred to briefly, with mention of the need to determine the optimum dose of drug needed and the duration of administration. The gaps in our knowledge of epidemiology and transmission, and of genetics, are emphasized in a concluding section.

This Fourth Report of the Expert Committee provides a useful summary of the generally accepted views on leprosy, and will be referred to as an authoritative and serious pronouncement on the major aspects of the disease.

S. G. Browne

Health and the Developing World, by John Bryant. Ithaca and London: Cornell University Press. 345 pp. Price \$10.00; £4.75.

This book should be required reading of everybody having to deal in any way with problems of health and disease in the developing world. It would be of great and salutary interest to all workers in leprosy, but particularly to those who have any say in the formulation of policy and in its implementation. The proverbial isolation of the leprosy worker will sooner or later have to yield before economic, social, and medical pressures. Reading this book will both prepare him for the inevitable changes, and help to make him an active participant in accelerating and welcoming them.

Dr Bryant marshalls in eye-catching and convincing array all the statistics and tabulated information required for an appraisal of the health situation in the countries of the Third World and for the formation of a judgement on the trends now apparent. Throughout the argument, he spares no punches—for the dead-hand of western-orientated teaching in the new medical schools, for the insistence on curative medicine in sophisticated surroundings for the favoured few, for the uneconomic yield in terms of cost/effectiveness of much foreign aid and many teaching programmes. He notes that leprosy at first attracted only the voluntary agencies, and that their help, for the "outcast" sufferers from leprosy could not keep pace with the "never-ending demand". He expatiates at length on the place and function of the medical auxiliary (perhaps retrained and up-graded) in any scheme for the delivery of some kind of health care to rural communities, and criticizes the widespread professional opposition to their deployment, especially where doctors and medical services generally are concentrated in the big towns.

Dr Bryant considers that no single country in the developing world can afford to seek out and treat all those suffering from tuberculosis or leprosy. Perhaps some problems that share common causes or have some common elements, such as tuberculosis and leprosy, might profit from a single programme of detection, treatment, and prevention. A programme of BCG

vaccination, inexpensive and practicable, might well point the way to effective control of both diseases. He does not see how countries with severely limited budgetary resources can embark on a programme entailing a series of specialized divisions pursuing particular problems or specific diseases. As an example of ill-considered spending, he cites the example of a country that allots the disproportionately high sum of 5% of its national budget to leprosy, but fails to bring any kind of treatment to over 90% of leprosy sufferers. The reason?—an instance of institutional as opposed to ambulatory treatment. The recurrent problem is to disburse severely limited resources so as to obtain the maximum possible benefit. While admitting that “some of the most important reforms in the fields of health and education are of necessity social reforms”, Dr Bryant advances weighty arguments to support his main thesis that despite all obstacles, the way to health in the developing world would be made less difficult by more knowledge, more goodwill and more co-operation. Leprosy workers would re-echo these sentiments.

S. G. Browne

Handbook of Leprosy, by W. H. Jopling. London: William Heinemann Medical Books Ltd. Price £1.15.

This little book of 91 pages, with 4 pages of coloured plates and several black-and-white photographs and diagrams, should prove a useful introduction to leprosy for doctors and nurses. The author expresses the hope that medical assistants will find in it the help they need in the diagnosis and management of leprosy. Dr Jopling gives a very readable account of the practical aspects of leprosy, combining his descriptions with some up-to-date observations on advances in the bacteriological and immunological investigation of this intriguing disease.

The pages devoted to treatment contain much good advice from a clinician who is constantly confronted by the problems he describes. His tribute to the invaluable work of the medical auxiliary will be re-echoed by anybody connected with a leprosy control scheme anywhere in the world.

S. G. Browne

Memorandum on Leprosy Control, by Stanley G. Browne. London: OXFAM, LEPR, The Leprosy Mission.

Here is a brochure of 27 pages that will prove of value to all concerned with leprosy. Written largely in non-technical language and intended primarily for the guidance of OXFAM Field Directors, Committees, and Headquarters Staff in examining requests for financial assistance, it should prove very useful to those who put forward the requests, and in fact to all engaged in organizing or taking part in schemes for leprosy control.

The brochure summarizes the generally accepted principles of leprosy control, and includes sufficient technical details to indicate the scientific basis for the rather dogmatic assertion printed on the title page: “if existing knowledge about leprosy were conscientiously and persistently applied, the disease could be controlled in our generation and eradicated in the next”.

The brochure was prepared for, and approved by, the Medical Panel of OXFAM. It is issued jointly by OXFAM, the Leprosy Relief Association (LEPRA) and The Leprosy Mission. Copies of the English edition are available free to medical and senior paramedical personnel concerned in leprosy work. Requests should be addressed to:

The Editorial Department,
The Leprosy Mission,
50 Portland Place,
London W1N 3DG.

Translations into French, German, Spanish, Italian, Dutch and other languages are in active course of preparation. Details may be obtained from:

Dr. S. G. Browne, O.B.E.,
57a Wimpole Street,
London W1M 7DF.

Leprosy in Five Young Men, by George J. Hill. Boulder, Colorado: Colorado Associated University Press. February, 1971. Price \$8.00

This book provides a fascinating record of a most detailed investigation of 5 Mexican leprosy patients who voluntarily submitted to a whole battery of tests at the National Institutes of Health, Bethesda, Maryland, U.S.A. It thus provides a summary of the bacteriological, biochemical and immunological findings in typical patients, 4 of whom had lepromatous leprosy and the other near-tuberculoid leprosy. One's respect for the high standards of the investigators is matched by admiration of the co-operation of the "human guinea-pigs" who endured the succession of procedures and tests, the results of which are tabulated in this account.

Many of the investigations reported are of academic interest only; others are of genuine pathological importance. *Myco. leprae* is to be found almost anywhere in the human body, and it persists at out-of-the-way sites for long periods. (The brain and cerebro-spinal fluid appear to have escaped the probing curiosity of the Bethesda team.)

One important omission impresses the reader: that is, any informed and detailed discussion of the morphology of *Myco. leprae* as seen in the material examined. Another point: the bacillary content of the lepromin used; and the significance of late (Mitsuda) skin reactions of less than 5 mm in diameter.

This book should stimulate the investigation in depth of patients with other forms of leprosy, and the use of techniques (especially serological techniques, and those of immunofluorescence) now becoming available. There must still be "more light and truth to break out" from leprosy, and we thank Professor Hill for permitting us to share something of the scientific fascination of the work of the distinguished team of which he was so enthusiastic and competent a member.

S. G. Browne

Leprosy, by S. G. Browne. Basle: Geigy 1970. 78 pp. Illustrated. (*Documenta Geigy: Acta Clinica*, No. 11)

This is a distillate of the knowledge acquired during a professional lifetime devoted largely to leprosy work, research and teaching, and as such is "heady" wine supplied in a small container. Publishers of medical books and papers will wince at the sight of this magnificent array of colour photographs—100 in all!

Those engaged in the study and management of leprosy will have good reason to be grateful to the author and to Geigy Ltd. for giving them such an authoritative and stimulating guide.

W. H. Jopling

Abstracts

The following 26 abstracts are reprinted, with permission, from *Int. J. Lepr.*, **37**, No. 4 and **38**, 1-4.

1. **Primeras manifestaciones clinicas en la lepra. Experiencia personal (Primary clinical manifestations of leprosy. Personal experience)**, by EGEA BUENO. *Actas Dermosifilog.*, 1968, **59**, 477-486.

Interrogation of patients is of relatively little value in the recognition of initial lesions in leprosy. To determine these as precisely as possible, periodic examination of family and dwelling contacts of patients is essential. The lesions the author has observed most frequently are liprides and achromic macules. These are followed by zones of anaesthesia, and in smaller proportion diffuse infiltrations of the face and later extensive bacilliferous involvement. Finally there are cases in which the only manifestation of the disease is the presence of *M. leprae* in the nasal mucosa—a good reason for not abandoning bacilloscopy in the examination of contacts.

Author's Summary

1. **Temperature-linked sensory loss. A unique pattern in leprosy**, by T. D. SABIN. *Arch. Neurol.*, 1969, **20**, 257-262.

A unique pattern is described of sensory loss in the arm in lepromatous leprosy patients, sparing the palm and antecubital fossa, with concomitant dense loss of sensation over the dorsum of the hand and forearm. Determination of sensory thresholds and skin temperature at multiple sites suggests that the relatively cool areas show the most marked sensory loss. It is suggested that in advanced lepromatous leprosy destruction of fine cutaneous nerve endings occurs earliest in relatively cool areas of the skin, leading to a pattern of sensory loss unique to this disease. Attention to this pattern would permit diagnosis of lepromatous leprosy when there are no skin lesions or when a patient has become bacteriologically inactive.

From Author's Summary

- Résultat du traitement spécifique de la lèpre par les sulfamides retards à l'Institut Marchoux (Results of specific treatment of leprosy by long-acting sulfonamides at the Marchoux Institute)**, by J. LANGUILLON. *Acta Leprol.*, 1969, N.S. **34-35**, 45-56.

Since 1958, 490 leprosy cases have been treated at the Marchoux Institute by orally given long-acting sulfonamides, including sulfamethoxypyridazine (Sultirene), sulfamethoxydiazine (Madribon), sulfamethiodiazine (Kiron), Depovernil, acetylmethoxypyrazine (Acétylazide) and sulforthomidine (Fanasil). Dosages of the first 4 of these were 750 mg every 2 days, and the last 2 respectively 2.50 g and 1.50 g weekly. Among 235 tuberculoid cases of a type recognized as prone to self-healing, practically 100% cure occurred within 3 years. In lepromatous cases Sultirene gave the best results within 5 years (89%). In practical mass treatment Fanasil proved preferable. No toxic reactions were observed with the sulfonamides.

From Author's Summary

4. **Chirurgie directe des gros troncs nerveux dans la lèpre (Direct surgery of the great nerve trunks in leprosy)**, by A. CARAYON. *Acta Leprol.*, 1969, N.S. 34-35, 65-91.

We are now in a position to respond to problems feared by Paul Brand in 1966. This work, which should be repeated and controlled by others, in the fight against the habitual failure of medical and orthopaedic treatment in nerve deficits is supported by new documents, and justification of direct nerve surgery. That work, endowed today with effective methods and without danger, gives a reasonable proportion of success if one limits it to strictly selected cases. It has gained the right of choice in the treatment of leprotic disabilities, and its application should be extended with earlier indications. In the face of the motto "without using the knife at all" we believe that direct surgery of the leprotic nerve is now an indispensable link in "preventive rehabilitation".

From Author's Summary

5. **Cell walls from *Mycobacterium tuberculosis* (BCG) as vaccine against *Mycobacterium leprae* infections in mice**, by C. C. SHEPARD and E. RIBI. *Proc. Soc. Exp. Biol. Med.*, 1968, 127, 517-521.

Cell walls from BCG were prepared by the method of Ribi *et al.* (*Bull. Hyg.* 41 (1966), 1146). After lyophilization, 100 mg of the preparation were mixed with 0.48 ml 7-*n*-hexyloctadecane and suspended in 40 ml saline containing 0.2% Tween 80; the mixture was then heated at 65°C for 30 min, and was referred to as the oil-treated vaccine. A similar vaccine was also prepared but without the treatment with oil. Groups of CFW mice were vaccinated either intravenously or intradermally with the oil-treated vaccine, with the vaccine without oil-treatment, or with viable BCG, and after 34 days the mice were inoculated in the foot pad with 5×10^3 *M. leprae*. At 6 months, when the count in unvaccinated control mice had reached more than 10^6 bacilli, the number of bacilli in the vaccinated mice was determined and again 3 months later; these counts were made on pools of up to 8 mice. The results showed that intradermal vaccination with the oil-treated cell wall preparation gave less protection, as judged by depression of multiplication of the leprosy bacilli, than did intravenous vaccination, and that at 6 months the degree of protection was similar to that produced by viable BCG, although at 9 months, it was somewhat inferior. Cell walls without treatment with oil afforded no protection. Local induration from the intradermal vaccination was less with the oil-treated cell wall preparation than that produced by the viable BCG vaccine; the enlargement of the draining lymph glands was also less. Intravenous injection of the oil-treated vaccine and the viable BCG produced pulmonary nodules with a peripheral zone of macrophages.

From abstract by S. R. M. Bushby, Trop. Dis. Bull., 1969, 66, 307-308.

Erythema nodosum leprosum: a clinical manifestation of the Arthus phenomenon, by S. N. C. WEMAMBU, J. L. TURK, M. F. R. WATERS and R. J. W. REES. *Lancet*, 1969, ii, 933-935.

Granular deposits of immunoglobulin and complement were found by fluorescence microscopy in the dermis of lesions from patients with erythema nodosum leprosum. In some cases the deposits apparently also contained soluble mycobacterial antigen. The distribution of these deposits corresponded with the areas of polymorph infiltration. It is suggested that erythema nodosum leprosum is a manifestation of the Arthus phenomenon. In a few of the patients studied the level of the third component of complement in the serum was raised.

Authors' Summary

7. **Osteo-dental alterations and anomalies in children suffering from leprosy**, by R. P. G. MIRANDA. *Publ. Centro Estudos Leprol. (Parana)*, 1969, 9, 17.

The work of Møller-Christensen and other authors on osteo-dental alterations in adults with lepromatous leprosy has been confirmed. A case of 12 years' duration in a 41-year-old man is described, with absence of upper incisors, bone rarefaction, destruction in the anterior region of the maxilla increasing the nasal opening, and absence of the nasal spine. In leprosy children these characteristic alterations were not seen, although slight changes in the region of the roots of the upper incisors suggested their commencement. It is believed that typical changes require a longer time for their development.

E. R. Long

- Evaluation of the earlobe in leprosy. A clinical and histopathological study**, by R. E. MANSFIELD, M. A. STORKAN and I. S. CLIFF. *Arch. Dermat.*, 1969, 100, 407-412.

Biopsy of the earlobe in leprosy patients has revealed histopathologic findings and acid-fast bacilli of a diagnostic nature, substantiating, on a histologic basis, the use of the earlobe as a site for useful clinical information. The best correlation of clinical appearance and histopathologic findings in the earlobes is found in patients with lepromatous leprosy. In most instances skin smears and biopsies of earlobes of leprosy patients appear to provide similar information. The systemic form of leprosy reaction was reflected in the earlobe histopathologic findings. Positive histopathologic findings in dimorphous leprosy patients could not be predicted.

From Authors' Summary

- Deux cas d'inefficacité antiréactionnelle de la thalidomide dans la lèpre (Two cases of antireactive ineffectiveness of thalidomide treatment of leprosy)**, by F. P. MERKLEN and F. COTTENOT. *Bull. Soc. Fr. Dermat. et Syphilig.*, 1968, 75, 738-739.

A case of major tuberculoid leprosy with reactional exacerbation in an African patient yielded on the first occasion to a daily dose of 400 mg of thalidomide, but a second attack, with ulceration, was not modified after 6 weeks of the same treatment. A second African case, of lepromatous type, in neuritic and febrile reaction did not yield after 10 days of the same treatment, but was improved by 3 blood transfusions.

P. Harter

10. **Human leprosy in normal mice**, by R. J. W. REES, A. G. M. WEDDELL, E. PALMER and J. M. H. PEARSON. *Br. Med. J.*, 1969, 3, 216-217.

It has now been shown that normal mice can be used as models for studying the early stages in the development of leprosy. Inoculation into the footpads of mice of as few as 10^4 leprosy bacilli leads to infections which spread to distant sites via the bloodstream and after 2 or more years give rise to granulomata and neural damage at the sites of inoculation. Where the tissue response had fully developed it reproduced exactly the histologic features of human leprosy in the borderline range.

Authors' Summary

11. **Correlation with results of mouse footpad inoculation**, by L. LEVY, P. FASAL and L. P. MURRAY. *Arch. Dermat.*, 1969, 100, 618-620.

The morphologic appearance of *M. leprae* in acid-fast stained sections of skin biopsy specimens from patients with lepromatous leprosy has been found to correlate well with the infectivity of

the specimen for the mouse. Viable *M. leprae* were demonstrated in 15 of the 16 patients with previously untreated lepromatous leprosy. Ten of 38 specimens obtained early in the course of dapsone therapy of previously untreated patients were found to contain viable *M. leprae*; viability of the organisms was found to be much reduced in 5 of these 10 specimens. By contrast, of 15 specimens obtained during dapsone therapy from 5 patients proven to harbour dapsone-resistant *M. leprae*, 14 were demonstrated unequivocally to contain viable organisms.

Authors' Summary

12. Cell-mediated immunity in patients with leprosy, by J. L. TURK and M. F. R. WATERS. *Lancet*, 1969, *ii*, 243-246.

Fifty per cent of patients with lepromatous leprosy could not be sensitized to 2,4-dinitrochlorobenzene (DNCB). However, 10 DNCB nonreactors could be induced to show delayed hypersensitivity to keyhole-limpet haemocyanin (KLH). Failure of cell-mediated immunity is, therefore, not absolute. This is confirmed by the finding of small numbers of small lymphocytes in the depleted paracortical areas of lymph nodes from these patients. No difference could be found in the lymph nodes of DNCB reactors and nonreactors, a fact consistent with the nonspecific failure of cell-mediated immunity being relative. It is concluded that induction of DNCB sensitivity is a relatively weak indication of cell-mediated immunity as compared with KLH. In leprosy, nonspecific loss of cell-mediated immunity, as evidenced by loss of ability to be sensitized with DNCB, is probably secondary to the infiltration of the paracortical areas of lymph nodes with histiocytes, rather than a primary event leading to the development of the lepromatous state.

Authors' Summary

13. Cellular immunity in infectious diseases (Editorial). *Lancet*, 1969, *ii*, 253-255.

The role of cell-mediated immunity (CMI) in leprosy has lately attracted great interest, much of which has been stimulated by the work of Rees and his co-workers, who found that a disease similar to lepromatous leprosy could be produced in experimental animals only after a general depression of CMI by thymectomy and deep X-irradiation. Under these conditions *M. leprae* could be induced to disseminate widely throughout the tissues as in the human disease. The possibility therefore arose that lepromatous leprosy could develop in man as a result of a general deficiency in CMI, similar to that seen in babies with congenital aplasia of the thymus. Job and Karat recorded a delay in heterologous skin-graft rejection for as long as 70 days in patients with lepromatous leprosy. An additional phenomenon which has been associated with a deficiency in CMI is an impairment in lymphocyte function, which can be demonstrated by a decreased ability of these cells to be transformed into blast cells in culture by phytohemagglutinin (PHA). Impairment of transformation of lymphocytes by PHA has been shown to parallel the inability of patients to be sensitized with contact sensitizers, such as DNCB in Hodgkin's disease, sarcoidosis, and primary biliary cirrhosis as well as leprosy and congenital thymic aplasia. It seems that inability to be sensitized to DNCB, or a deficiency in the response of lymphocytes to PHA may reflect only a relative depression of CMI insufficient to make the patient more susceptible to infection. That impairment of contact sensitivity does not demonstrate a complete inability of the patient to develop CMI is clear from a paper by Turk and Waters (see preceding abstract). Patients with lepromatous leprosy who could not be sensitized with DNCB could be induced to develop hypersensitivity reactions to a more powerful antigen—haemocyanin. Failure of CMI in leprosy is probably directed at first specifically against *M. leprae*. The failure of immunologic response does not, however, affect humoral antibody production, since these patients can have a high concentration of antimycobacterial antibodies in their serum and they may have a chronic "serum-sickness"-like disease (erythema nodosum leprosum) due to deposition of immune complexes, formed

between antigen and antibody, in their tissues. Nonspecific impairment of CMI would then be a secondary rather than a primary event, and it would be the result of the replacement of those parts of the lymphoid tissue where lymphocytes proliferate during the development of a cell-mediated immune response by histiocytes containing mycobacteria. These cells probably drain down to the central lymphoid organs from the peripheral tissues where they are present in large numbers. The evidence suggests that lepromatous leprosy develops in patients with an intrinsic constitutional defect. Conceivably a primary inability of the cellular immune mechanisms allows the infective agent to gain a foothold in the tissues. The organism then proliferates to such an extent that a state of specific immunologic tolerance develops. This state, however, affects cellular immune processes only, leaving humoral antibody-producing mechanisms intact. Evidence so far indicates that the tests used, such as the development of DNCB sensitivity, reflect a secondary rather than a primary defect in CMI, and more sensitive tests will have to be found to discover the cause of the initial defect which allows the organism to proliferate in the first place.

14. **BCG vaccination in mycobacterial infections**, by R. J. W. REES. *Br. Med. Bull.*, 1969, 25, 183-188.

Immunization against mycobacterial infections has been directed mainly against tuberculosis, as representing the most serious of these infections. Although BCG vaccination has been available since 1921, it has taken 40 years to establish beyond doubt its efficacy against tuberculosis. Evidence is now accumulating which indicates that BCG may also be of value in protecting against other mycobacterial infections, including leprosy (Uganda, New Guinea and Burma trials), and *M. ulcerans* infections (Uganda trials). This would be consistent with the wide range of common antigens shared by many species of mycobacteria. It is the appreciation of these immunologic features of mycobacteria that during the last decade has helped to unravel the complexities surrounding vaccination against mycobacterial infections.

Author's Summary

15. **An unusual form of lepromatous leprosy**, by S. KUNDU and S. GHOSH. *J. Indian Med. Ass.*, 1969, 52, 566-578.

Two cases of lazarine leprosy, a form not infrequent in Latin America, were detected in the Leprosy Research Department, School of Medicine, Calcutta. In each case the disease was fulminant, with unusually severe signs and symptoms, and both patients died. The authors note that the disease is in general progressive and the trend is toward fatality even though a patient may at first appear in good health.

E. R. Long

- Skeletal muscle changes in leprosy: their relationship to changes in other neurogenic diseases affecting muscle**, by P. SLOTWINER, S. K. SONG and P. J. ANDERSON. *J. Path.*, 1969, 97, 211-217.

The report is based on biopsy studies of 4 leprosy patients (3 females and 1 male) presenting signs of peripheral neuropathy and, in 1 case, myositis. Multiple subcutaneous granulomas were seen in 2 patients, commonly surrounding blood vessels, nerves, hair follicles and sweat glands. Acid-fast bacilli were demonstrated. Extensive granulomatous change, with fragmentation of axons and myelin sheaths, and visible acid-fast bacilli, was noted in peripheral and intramuscular nerves. Inflammation seen in muscles was restricted to perivascular, perineural and intraneural foci and muscle spindles. Segmental atrophy affecting groups of fibres was a consistent change. Sarcoplasmic structural changes included phagocytosis, vacuolar change and

basophilia, chiefly in areas remote from inflammation and associated with regions of segmental atrophy. The evidence supports the view that a concurrent myopathic process need not be invoked to explain the sarcoplasmic changes. It was concluded most of these changes were secondary to leprous neuropathy and consequent denervation.

E. R. Long

17. **Leprosy in twins**, by Y. A. KETKAR, P. N. KULKARNI and P. N. PATIL. *Leprosy in India*, 1969, 41, 85-88.

A report is made of tuberculoid leprosy in a pair of identical twins, aged 15 years. There was no family history of leprosy, nor was any specific contact recognized. The pair shared the same environment. Blood groups, iris colour and other characteristics were identical. *M. leprae* were not found in either patient. The duration and course of the disease were similar. In each case there was a severe initial response to DDS treatment followed by good response. The observations support views, many times expressed, on the role of genetics in leprosy.

E. R. Long

18. **Preservation of sensation in a cutaneous vascular malformation in lepromatous leprosy**, by T. D. SABIN. *New Engl. J. Med.*, 1970, 282, 1084-1085.

A case of leprosy is reported in which a palmar congenital vascular malformation was spared neurologic involvement, although sensation to pinprick was lost over much of the body surface. The temperature in this area as measured by thermography was 7°C warmer than in adjacent parts. The author suggests that the increased vascularity with the increased skin warmth created a relatively unfavourable site for growth of bacilli.

G. L. Fite

19. **Ethambutol en el tratamiento de la lepra. Resultados del tratamiento de 20 pacientes durante 12 meses (Ethambutol in the treatment of leprosy. A twelve-month trial in 20 patients)**, by A. SAUL and R. BARCELATA. *Dermatología (Mexico)*, 1969, 13, 152-159.

This preliminary trial of ethambutol involved the treatment of 20 leprosy patients: 16 lepromatous, 3 tuberculoid and 1 borderline. A single daily dose of 800 mg was given to all patients for 6 months in tuberculoid cases and for 12 months in the lepromatous. Complete regression of tuberculoid lesions was observed after 6 months of treatment. In lepromatous cases improvement began after the first 15 days followed by flattening and atrophy of nodules, and healings of ulcers. At 12 months clinical cure was evident in 4 cases, improvement in 3 and relapse in 5. Although bacteriologic changes were observed in all patients, smears remained positive in 9 cases after 12 months. Histologic modifications were also noted. Neither lepra reaction nor side-effects were observed. Ethambutol seems to work more quickly than other drugs, but the evidence of bacillary resistance suggests need for further trials.

A. Saúl

20. **Experimental and clinical studies on Rifampicin in treatment of leprosy**, by R. J. W. REES, J. M. H. PEARSON and M. F. R. WATERS. *Br. Med. J.*, 1970, 1, 89-92.

Rifampicin showed high activity against experimental leprosy, inhibiting the multiplication of dapsone-sensitive and dapsone-resistant strains, of *M. leprae* in mice fed 5 mg/kg body weight. In a formal pilot-type trial on 6 previously untreated patients with active lepromatous leprosy, Rifampicin (600 mg daily by mouth) was as effective as standard treatment with dapsone. *M.*

leprae, however, appeared to be killed more rapidly by Rifampicin than by dapsone or other antileprosy drugs so far studied. This was confirmed on another 10 patients, including 2 with dapsone resistance, and from the infectivity in mice of bacilli recovered from patients during treatment with Rifampicin or dapsone. These results are consistent with the bactericidal activity of Rifampicin against other microorganisms, which could be important to the chemotherapy of leprosy, since all antileprosy drugs in current use are bacteriostatic. The final place of Rifampicin alone or in combination with other antileprosy drugs must await more knowledge gained from larger and long-term studies.

Authors' Summary

21. **The elusive diagnosis of leprosy**, by J. G. SINKOVICS and M. L. IBANEZ. *Postgrad. Med.*, 1970, **47**, 109-115.

As the incidence of tuberculosis decreased the last 10 years, new cases of leprosy increased. The highest incidence of new cases in the United States was reported in Texas. It may be said that with the decline of tuberculosis, the natural ecology of mycobacteria is reversed, and if measures are not taken, the leprosy/tuberculosis ratio may again favour leprosy. In a patient with a lesion of the nasopharynx, the first histologic diagnosis was compatible with rhinoscleroma. Acid-fast stains showed that the lesion was a leprous infectious granuloma. In a patient with lipofibrosarcoma of the leg, lepromatous leprosy was not apparent until injury of the amputation stump and probable septicaemia with *E. coli* occurred. During treatment with antibiotics, metaraminol and hydrocortisone, livid haemorrhagic skin eruptions appeared and later sloughed off. Acid-fast staining of nasal scrapings and tissue biopsy specimens established the diagnosis of lepromatous leprosy.

Authors' Summary

22. **El bacilo de Hansen en algunas formas de neuritis de lepra tuberculoide (Bacilli in certain types of neuritis in tuberculoid leprosy)**, by M. M. GIMÉNEZ, H. I. RISSO, C. A. MOGLIA, J. J. RIBICHINI and R. WAISMAN. *Leprologia*, 1969, **14**, 11-16.

The authors present 4 cases of tuberculoid leprosy, all Mitsuda positive, and all without bacilli in cutaneous lesions. In these cases painful ascending neural lesions developed, in which bacilli were readily demonstrated in granulomatous tissues from the nerves, some with a little caseation, and some groups of organisms as globi. Treatment with sulphones and vitamins A, B₁, B₁₂, and D proved effective. The authors suggest that the hypersensitization in these cases is somehow related to the pathogenesis of these lesions.

G. L. Fite

23. **Sarcoidosis**. *Postgrad. Med. J.*, 1970, **46**, 465-541.

At the Central Middlesex Hospital (London) a Conference on Sarcoidosis was held 29 September, 1969. The *Postgraduate Medical Journal* records the presentations, 17 of them formal, together with many less formal discussions, consuming an entire issue. Although much material would be found only of indirect interest to students of leprosy, some articles such as that of Cronin on skin changes in sarcoidosis (with its nice illustrations in colour, pp. 507-509) deserve recognition. This issue should be found in all leprologists' archives. Rees' "Kveim test in leprosy" is treated separately.

G. L. Fite

Studies toward the standardization of lepromin, by J. H. HANKS, M. ABE, T. NAKAYAMA, L. M. BECHELLI and V. MARTÍNEZ DOMINGUEZ. *Bull. WHO*, 1970, **42**, 703-709.

Because of the wide range of concentrations of *M. leprae* in existing lepromins the authors studied methods of producing a standardizable lepromin containing 160 million bacilli/ml. The effects of using different dilutions of lepromin on the incidence of false-positive reactions were also studied. Progress reported includes a convenient method for preparing large batches of nonsedimenting lepromin, which is directly suitable for microscopic counting of *M. leprae* cells; and a validation of current methods for microscopic enumeration of *M. leprae*. Skin tests with diluted lepromins have demonstrated that dilutions up to 1 : 16 increase progressively the ability to distinguish between lepromatous and tuberculoid leprosy. This work has provided further evidence that 20 million bacilli/ml (a 1 : 8 dilution of the initial lepromin) should produce adequate Mitsuda reactions in general populations, provided that 3 mm reactions are taken as the criterion for 1+ positivity. The net effect of these findings is equivalent to expanding the world supply of lepromin by 8 times. Recommendations for further research are proposed.

Authors' Summary

25. Serology in leprosy, by OLIVEIRA DE ALMEIDA. *Bull. WHO*, 1970, **42**, 673-702.

A critical survey of the literature on serology in leprosy has shown that sera taken from lepromatous patients display some striking differences in comparison with sera from tuberculoid patients. The tests most frequently employed were complement-fixation, hemagglutination, electrophoresis, precipitation and immunofluorescence, together with a variety of antigens not only from lepromas but also from *M. tuberculosis* and other actinomycetales. With the exception of the Rubino test, all these serologic tests are lacking in specificity for leprosy since leprosy sera have a broad range of reactivity with different antigens, including those employed in the serologic diagnosis of syphilis. Some features of the leprosy sera could be related to a hypersensitivity state involving circulating immune complexes, low levels of complement and the presence of antibodies similar to those found in sera from patients with autoimmune diseases.

Author's Summary

[It should be added that this is a useful detailed review of the topic, which includes an elegant bibliography of 300 or more citations.—G.L.F.]

26. Considerações sobre o real valor da sulfonoterapia nos programas de profilaxia da lepra (The value of sulfone treatment in programs of prophylaxis against leprosy), by L. de SOUZA LIMA. *Rev. brasileira Leprol.*, 1968-69, **36**, 31-36.

The author considers the real value of sulphone therapy in the programmes of control of leprosy based on the results of the sulphone treatment of cases of lepromatous, borderline and indeterminate leprosy. He points out that the regular sulphone treatment of the cases of the indeterminate group is the most efficient procedure for the control of leprosy, because of the capacity of this drug to prevent transformation of these noninfectious into infectious cases of the lepromatous type or of the borderline group. Emphasis is given to the possible development of sulphone-resistance and the author advises the use of a triple association of drugs (parent-sulphone, thiambutostine, long-acting sulphonamides) in order to avoid this occurrence.

G. L. Fite

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CONTENTS

Editorial	149
News and Notes	151
Damien-Dutton Award for 1971. Award to Dr. C. K. Job. <i>The Star</i> , Carville. Royal Society of Tropical Medicine and Hygiene. National Health Council, Brazil. Leprosy in Hong Kong. Leprosy in Iran. Lepra and the East Central State, Nigeria. Training in Ophthalmology for Leprosy Workers. Second Congress of the Association de Leprologues de Langue Française.	
Obituary Notice	156
Orthopaedic Appliances for Leprosy Patients: The Fixed Ankle Brace Walker, by LUTZ WOLLSTEIN and JOHN GIRLING	158
Treatment of Moderately Severe Erythema Nodosum Leprosum with Clofazimine—A Controlled Trial, by HELMY SYED HELMY, J. M. H. PEARSON and M. F. R. WATERS	167
Forty-four Months' Experience in the Treatment of Leprosy with Clofazimine (Lamprene (Geigy) , by E. J. SCHULZ	178
Leprosy in Bhutan: A Pilot Survey, by J. S. BERKELEY	188
Leprosy in Peru, by COLIN McDUGALL	197
Histoid Variety of Lepromatous Leprosy, by D. S. CHAUDHURY, M. CHAUDHURY and K. ARMAH	203
Nerve Enlargement in Relation to Classification of Leprosy, by M. A. FURNESS and D. A. RANNEY	208
Exacerbation of Dimorphous Leprosy Apparently Due to BCG Vaccination, by F. J. WRIGHT	219
Book Reviews	223
Abstracts	227