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Leprosy Review

A journal contributing to the better understanding of leprosy and its control

British Leprosy Relief Association
LEPRA

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Leprosy Review is published by the British Leprosy Relief Association (LEPRA) with the main objective of contributing towards the better understanding of leprosy and its control. Original papers on all aspects of leprosy, including research, are welcomed. In addition, *Leprosy Review* seeks to publish information of educational value which is of direct benefit to the control of leprosy under field conditions, and hence to the individual patient. The Journal aims to interpret what is being done in other disciplines, particularly for field workers.

From time to time the Editorial Board invites special articles or editorials from experts in various parts of the world, and gives consideration to the production of a supplement or special number devoted to a particular subject or theme of major importance.

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Editorial

DERMATOLOGY—GLOBAL PLANNING IN RELATION TO LEPROSY MANAGEMENT

It was in the eighteenth century that a new emphasis on the classification of biological systems, based on their appearance, stimulated in Europe the recognition, naming and classification of physical signs in the skin. The word 'lepra' was applied to a number of diseases; later it was thought better to name these in other ways to avoid confusion with leprosy. Dermatologists who further developed such classifications in the ninteenth century continued to include leprosy in their textbooks and to take an interest in its diagnosis and management.

Leprosy has many components besides its early recognition and classification. Not least of these are stigma and disability. It is these components that attracted the attention of the Church. The later discovery of bacteria as its underlying cause led to the link of leprosy with tuberculosis, with which, in many countries, it is paired for administrative purposes.

Today, the management of leprosy requires a profession interested and expert not only in early recognition but also in contact tracing, disability, as well as bacteria. Dermatology is a profession offering to play a bigger role in the management of leprosy because it can now demonstrate an interest in all of these aspects; and in some parts of the world, such as China, major eradication programmes and the management of disability, have been organized through dermatology institutes. In recent years, budding dermatologists have been expected to explore the basic mechanisms underlying disease processes, and most training programmes have a big component of basic science and especially immunology. More recently, the consequences of disease have received more attention and disability is attracting more interest on conference programmes. Dermatologists are now encouraged to measure aspects of disability that have economic value, such as the distance people with sore feet can walk, manual dexterity, and above all, what it means to be unwelcome because of disfigurement. The literature on stigma now is as likely to refer to psoriasis or vitiligo as it is to leprosy.

Skin diseases have long been paired with sexually transmitted diseases because so many early manifestations of syphilis could be seen in the skin, and in most countries this link has been retained. Consequently, dermatologists are familiar with the language of infectious disease control, social hygiene, contact tracing and the appropriate use of drugs, or terms such as 'prevalence', 'incidence' and 'distribution'. What has been lacking until recently, has been any programme formulated by dermatologists showing that they are interested in the global control of disease. An important contribution has been made

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by the International Society of Dermatology; Tropical, Geographic and Ecologic,[1] which has a journal and a regional teaching programme much concerned with this topic.

Dermatology on an international scale is organized on the basis of International Congresses, held every 5 years. The Committee which organizes these is elected by delegates from national societies. It has existed for 100 years and has always included within its remit the need for encouraging better practice worldwide. An English dermatologist, Dr Darrell Wilkinson of High Wycombe, encouraged the International Committee of Dermatology to take more seriously the problems of skin disease in the developing world. In 1987, at the International Congress of Dermatology in Berlin, the Assembly of Delegates unanimously approved the formation of the International Foundation for Dermatology, and this Foundation has a number of missions listed as follows:

THE PRIMARY AIM:

The International Foundation for Dermatology, which serves under the aegis of the International Committee of Dermatology of the International League of Dermatological Societies, has as its primary aim to: 'Aid patients afflicted with diseases of the skin, through the promotion of dermatologic service, training and science, in the developing countries.' These aims are to be carried out under the guiding principles of resource allocation to manage those preventable, curable, and common diseases of the skin which affect so many in developing countries.

The following are the principal missions of the International Foundation for Dermatology:

Mission 1 Promote dermatologic education and training in developing countries at all health-care levels.

Mission 2 Establish regional dermatological training centres in developing countries.

Mission 3 Improve delivery of dermatologic care in developing countries.

Mission 4 Promulgate collaborative programmes between institutions from developed and developing countries of the world.

Mission 5 Document the current status of dermatologic manpower, technical resources, and the burden of dermatologic disease worldwide.

Mission 6 Develop a cadre of experienced dermato-venerologists willing to serve on short- or long-term basis as visiting teachers, lecturers, advisers, or practitioners of dermatology.

Mission 7 Support the establishment of fully-fledged departments of dermatology in at least one medical school in each country.

Mission 8 Promote dermatologic education and communication in developing countries at national and international meetings.

Mission 9 Develop a model list of essential dermatological therapeutic agents for all health care levels.

Mission 10 Promote research oriented to the dermatologic priority needs in developing countries.

The Board of Directors of the Foundation include: Dr Alfred W Kopf, New York, USA (Chairman); Dr Henning Grossman, West Germany; Dr Stuart Maddin, Vancouver, BC Canada; Dr Hans R Rorsman, Sweden; Dr Stephen I Katz, Bethesda MD, USA; Dr Francisco Kerdel-Vegas, Venezuela; Dr Atsushi Kukita, Japan; Dr Ramon Ruiz-Maldonado, Mexico; Dr Terence J Ryan, Oxford, UK; Dr Jean Thivolet, France; and Dr Klaus Wolff, Vienna Austria.

At its first meeting, the Board decided that some of the most urgent problems were to be found in Africa and that its first major plan should be to set up a Regional Training Centre for Africa. A number of governments were contacted and Tanzania provided a firm indication of support in the form of promises of land and administration; so a site visit was made in May 1989. During this visit, the curriculum was discussed and leprosy was placed firmly on the list of topics to be taught. An important concept, somewhat new to dermatologists, was that the profession should concentrate on primary health care and that therefore the Training Centre should be aimed at the future organizers and teachers of programmes in rural areas. This was one reason why a rurally-based site, Kilimanjaro in Moshi, was chosen for the development of the Teaching Centre. It was made plain from the outset that the Training Centre would be run by Africans, assisted by ex-patriots, and that the curriculum should be approved by the governments and dermatologists of all 12 African members of the East African Community. Initial discussions were held with the Vice-Chancellor of Dar-es-Salam University, who emphasized that only the highest academic standards were acceptable. To ascertain what Africans require for such a curriculum, Professor A M Nhonoli, Regional Secretary of the Commonwealth Regional Health Secretariat, is arranging a workshop on Training in Dermatology at all levels, to be held in Nairobi, 27–31 August 1990. Provisionally, it is expected to include dermatology, sexually-transmitted diseases, leprosy and AIDS, a grouping that would not be unfamiliar to a number of countries with a social hygiene programme. In addition, it will include instructions on the collection and retrieval of data and will provide a component on teacher training. The Course will be aimed at medical assistants, clinical officers or leprosy officers, to whom much of the work of dermatologists will be delegated. The initial course should be thought of as a pilot scheme, taking up to 30 trainees, and it will be reduplicated elsewhere only if it is proved to be a success. For this reason the Foundation is seeking funds for an evaluation programme aimed at surveying some 20 communities before and after placing within their midst, persons who have been trained at the Centre. It is hoped that the communities will consequently have less scabies, pyoderma and fungi, and a much greater understanding of how sexually-transmitted diseases, such as AIDS, are transmitted. Great emphasis will be placed on the early detection of leprosy, its appropriate treatment and the managment of disability. It is important that early recognition should include a willingness and capability to treat nonleprosy patients. Pityriasis alba, pityriasis versicolor, vitiligo, sarcoid or localized scleroderma, for example, are not adequately managed by dismissing them as nonleprosy. Early cases of leprosy are more likely to be detected if all persons with skin lesions are encouraged to attend skin clinics, and such early recognition is easier in skin free of common infections.

The changing perception of dermatology as a discipline needed by populations with

skin disease so that they may achieve their full potential at work and play, has not yet resulted in resources being made available. Perhaps we should return to the eighteenth century and embrace more skin diseases by the term 'lepra' because they might receive more charitable funding and incite greater missionary zeal for their elimination.

The training provided by current leprosy control programmes includes the use of a disability index.[2] This is essential for assessing the economic consequences of disease and it is needed by dermatologists who, up to now, have not estimated how much disability is caused by skin disease in countries such as rural Africa.

It may be relevant that the esteem with which dermatologists are held is thought to be low because high scoring phenomena, such as mortality or high technology management, are not characteristic of skin disease. However, governments are mostly willing to support low technology and professions active in the management of chronic disabling disease, provided appropriate and cost-effective solutions are well presented to them.

In the first three years of its existence, the International Foundation for Dermatology has sought funds chiefly from within the profession, and the response of individuals and of societies has been encouraging. It has also appealed to charities concerned with leprosy, because there are many costs incurred even in the early stages of seeking to include leprosy in its curriculum. The help of many experts who have spent their lives in programmes for the eradication of leprosy or in the management of disability is needed, and indeed it is sought, in order to facilitate teaching programmes. Conversely, where leprosy is well managed and has adequate staffing, it is hoped that dermatologists will be invited to expand the programme so that other diseases affecting the skin are equally well controlled.

In the first year of its existence, the International Foundation for Dermatology took note of the work in China of an ex-patriot, Ma Haide,[3] who epitomizes what a dermatologist can achieve in the control of sexually-transmitted diseases, fungus infection and leprosy. The three eradication programmes aimed at these diseases, succeeded in his lifetime as a consequence of his policy of advising governments, setting up regional training centres, and creating armies of primary health care workers. They are examples of what can be achieved for huge populations by one man interested in creating a programme that combines dermatology, sexually-transmitted diseases and leprosy.

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References

[1] Ryan TJ. A fresh look at the management of skin diseases in the tropics. *Int J Dermatol*, 1990; **29:** in press.
[2] WHO. *International classification of impairment, disabilities and handicaps.* Geneva, 1980.
[3] Ryan TJ. Ma Haide (1910–1988). A dermatologist to emulate. *Int J Dermatol*, 1989; **28:** 413.

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Editorial

ARMAUER HANSEN RESEARCH INSTITUTE 1970–1990

The Armauer Hansen Research Institute (AHRI) is 20 years old. Thus what was clearly a bold experiment in 1970 has reached maturity and goes from strength to strength.

Its conception was extremely farsighted. There had always been a strong tradition of a link with leprosy in Scandinavia, particularly in Norway because of Hansen's work in Bergen. The Scandinavians were strong in immunology at a stage when it was less well recognized as a major research subject, and an interest in leprosy would broaden their experience. They therefore searched for a venue for the Institute, and came to the conclusion that Addis Ababa was ideal because of the development of ALERT (All Africa Rehabilitation and Training Centre) as the leprosy teaching hospital for Africa. More farsightedness was demonstrated when they offered positions for up and coming immunologists at AHRI for 2–3 years. The first Director was Professor Morten Harboe, already a well recognized figure in the immunology world.

With medical research funds becoming less available around the world, the relevance of particular research projects to actual important diseases is increasingly being questioned as grant funding bodies seek optimal value for money. This means that the resources tend to be channelled to specific goal-oriented projects in countries where the infrastructure is well established beforehand and very little left for research in countries where the disease in question is prevalent. This is certainly true for leprosy and though research workers in their ivory towers in the USA and Europe are of course performing excellent work, the relevance of this is not always immediately clear: this is where the Armauer Hansen Research Institute (AHRI) comes into its own. With a sophisticated immunological laboratory in a leprosy hospital in the centre of a country where the disease is an exceedingly important problem, this provides the ideal formula for close collaborative work at the interface of clinical and basic research. Basic funding to secure the infrastructure of the institute comes from the governmental development aid organizations of Sweden and Norway: the Institute can thus more easily attract goal-oriented funding for specific projects.

We believe that much of the success of AHRI has been the fact that it has been based at a teaching hospital for leprosy (ALERT) which has had a constant flow of distinguished leprologists and other specialists (dermatologists, ophthalmologists, plastic and orthopaedic surgeons, neurologists, epidemiologists, and histopathologists) who have provided the expertise required to collaborate in good research. Thus, for example, when there has been a need to perform research on leprosy reactions, nerve damage and anergy

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in leprosy, there has been a plethora of well prepared cases in the hospital. Fundamental to this effort has been the high quality of histopathological classification of patients being researched: this function has been ensured by collaboration between ALERT and AHRI. One of the most pleasing aspects of this collaborative research has been the readiness of patients to take part: it is always striking how exceedingly grateful they are that anyone is interested in their disease and their future.

A number of single observations from the work at AHRI stand out in the world of basic immunology. Probably more important in the long run is the slow process of initiating changes in attitudes in the field of practical leprosy work. The latter would not have been possible without the intimate interplay between the clinicians of an active hospital and leprosy control programme on one side and a sophisticated laboratory on the other. Early work on dapsone resistance was performed by ALERT clinicians on AHRI premises and formed the foundations for multidrug therapy (MDT). Collaborative work on reversal reactions, nerve damage, and on leprosy during pregnancy and lactation led to a world-wide alertness to the dangers of leprosy neuritis and thus to improved management. Studies of anergy in lepromatous leprosy formed a scientific basis for an active 'care after cure' in these patients. Many more examples could be listed.

During the development of AHRI, the research space has become much enlarged, with new buildings and increased staff. The research interests have also increased beyond leprosy to related diseases such as tuberculosis and cutaneous leishmaniasis (where there are a number of parallels with leprosy). During this time an increasing number of Ethiopians have been co-authors on the papers emanating from AHRI, and this expertise gained has been very much part of the spin off from having such a laboratory in Addis Ababa. It is also encouraging that there has been one Ethiopian Director (Dr Ayele Belehu), and more and more key positions being filled by Ethiopians.

Has this formula worked? We believe that it has, and that it has been a great success. To date 160 publications have been produced by the Institute, the majority of them in international journals of high repute. These have included two publications in *Nature* and two in the *Journal of Experimental Medicine*. The Institute has expanded vastly and now employs approximately 50 workers with some Ethiopians who have been there since its inception. This says a lot when one remembers that the last 20 years have been turbulent and difficult times in Ethiopia, particularly in the late 1970s, immediately post-revolution.

What about the future? Since 1984 applied computer technology and gene technology has been developed at the Institute. Both are prerequisites for front line research in the years to come. While most leprosy-endemic countries struggle hard to implement MDT, the Institute is now eager to face the challenge of 'the post-MDT-era'. Countering the anergy in lepromatous leprosy, identification of incompletely treated patients, and mass screening techniques for preclinical diagnosis of leprosy are growth areas of considerable importance, and which AHRI hopes to address successfully within the next few years.

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The evolution of antibody response in armadillos inoculated with *Mycobacterium leprae*

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Summary Plasma from 30 armadillos (*Dasypus novemcinctus*) was collected prior to inoculation and at approximately 3-month intervals for a period of 1–3 years. These animals were inoculated intravenously with $6{\cdot}1 \times 10^8 \pm 2 \times 10^8$ ($x \pm SD$) armadillo-derived *Mycobacterium leprae*. These samples were analysed for antibodies of IgM and IgG class to phenolic glycolipid-I (PGL-I) and to sonicated *M. leprae* components using ELISA and immunoblotting techniques, respectively. We had previously observed among a group of 11 armadillos, that some animals produced and maintained a high IgG antibody response to PGL-I. In this study, an animal's ability to produce and maintain an elevated IgG anti-PGL-I response was significantly correlated with their ability to delay dissemination of the infection and their ability to survive longer. When the animals were moribund, a significant decrease in the IgG anti-PGL-I absorbance value was observed. The detection of PGL-I in the plasma samples collected from moribund armadillos suggested that high concentrations of PGL-I in the plasma may have contributed to a drop in absorbance values by the formation of non-lattice-type immune complexes *in vivo*.

As detected by immunoblotting, the IgM and IgG response to antigens derived from sonically disrupted *M. leprae* was directed towards molecules with broad bands of immunoreactivity ranging from 21- to 45-kDa. There were no distinguishing features of these antibody responses among armadillos as was evident with the IgG anti-PGL-I responses.

Introduction

Leprosy in man has a broad clinical manifestation determined by the host parasite relationship. The spectrum of variation in resistance to infection with *Mycobacterium leprae* ranges from highly resistant (tuberculoid leprosy) to highly susceptible (lepromatous leprosy).[1] Nine-banded armadillos (*Dasypus novemcinctus*) are highly susceptible to infection with *M. leprae*[2] and when inoculated, they develop primarily lepromatous-type disease.[3] Therefore, armadillos are considered by many investigators to be a good

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experimental model for studying lepromatous leprosy. One characteristic of human lepromatous leprosy, as well as that of infected armadillos, is the production of large amounts of antibodies against mycobacterial antigens.[4,5] These antibodies have played a significant role in describing the immunogenic structure of *M. leprae*. Components such as antigen 7,[6] cell-wall polysaccharides,[4] proteins[4,7] and phenolic glycolipid-I (PGL-I)[8–10] are recognized as antibody evoking immunogens in both humans and armadillos.

Due to difficulties in detection of subclinical leprosy in man, a description of the evolution of antibodies to components of *M. leprae* among patients in the presence or absence of chemotherapy has not been reported. Armadillos experimentally inoculated with *M. leprae* offer an opportunity to describe the evolution of antibodies to *M. leprae* following exposure to known quantities of *M. leprae* and in the absence of chemotherapy.

This study describes the evolution of armadillo IgM and IgG antibodies to PGL-I and sonicated *M. leprae* using ELISA and immunoblotting.

Methods

ARMADILLO PLASMA

Plasma from 30 nine-banded armadillos was collected prior to inoculation (day 0) and at approximately 3-month intervals for a period of 1–3 years. The conditions for adopting the animals into the colony and their maintenance have been described previously.[5] These animals were inoculated intravenously with $6{\cdot}1 \times 10^8 \pm 2 \times 10^8$ ($x \pm SD$) armadillo-derived *M. leprae*.

ENZYME-LINKED IMMUNOSORBENT ASSAY (ELISA)

One hundred and ninety-two plasma samples were analysed by means of ELISA. The ELISA, for detection of armadillo IgM and IgG antibodies to PGL-I, was carried out as described previously.[10] Armadillo-derived PGL-I was provided by Dr Brennan (NIH Contract AI-52582, Colorado State University).

PREPARATION OF *M. LEPRAE* EXTRACTS

M. leprae were provided by Dr P Brennan as irradiated, lyophilized bacilli purified from the lymph nodes of infected armadillos. *M. leprae* (10 mg dry weight) was suspended in 3 ml of 0·01 M phosphate buffered saline (PBS) pH 7·0. The organisms were disrupted by sonication on ice for 30 min at 150 W on a sonifier cell disrupter with a temperature control probe (Model W1851, Heat System, Ultrasonics, Inc., North Tonawanda, New York, USA) adjusted for 8°C. The sonicated material was aliquoted and stored at −20°C until used.

IMMUNOBLOT

M. leprae components (3·33 mg/ml) were separated by SDS-PAGE and electrophoretically transferred at constant voltage (10 V) for 18 hr to BA 85 nitrocellulose paper (NCP) (Schleicher and Schuell, Inc., Keene, New Hampshire, USA) in a tris-glycine-methanol buffer, pH 8·0.[11] After transfer, the NCP was incubated at room temperature (RT) for 45

min in 0·01 M PBS containing 3% bovine serum albumin (BSA). The NCP was then incubated with armadillo plasma at 1:50 dilution for 1 hr at RT. The NCP was washed five times for 5 min each in 0·01 M PBS containing 0·05% Tween 20. It was then reacted with rabbit antiarmadillo gamma-chain at 1:1000 dilution or with rabbit antihuman u-chain at 1:50 dilution. The NCP strips were washed and treated with peroxidase conjugated goat antirabbit immunoglobulins (IgM + IgG + IgA) (Cappel Laboratories, Downington, Pennsylvania, USA) at 1:1000 dilution. Next, the NCP was washed and developed with H_2O_2/horseradish peroxidase (HRP) colour development reagent for 10 min at RT as described by the manufacturer (Bio-Rad, Richmond, California, USA). The reaction was stopped by transfer of the NCP to 5% acetic acid in deionized H_2O.

EXTRACTION OF PGL-I FROM ARMADILLO PLASMA

Plasma samples (0·3–0·5 ml) were added dropwise to 5 ml of 95% ethanol, resulting in the formation of a whitish precipitate. The samples were centrifuged at 1380 × *G* for 10 min and the supernatants were decanted. The excess ethanol was removed by inverting the tubes and allowed to drain for 10 min. Lipids were extracted from the residue with 5 ml chloroform:methanol (2:1 V/V) at 50°C overnight. The extracts were centrifuged at 1380 × *G* for 10 min. The supernatants were removed and residues were washed with 5 ml of chloroform:methanol (2:1) and re-centrifuged. The two supernatants from each sample were combined and taken to dryness at 50°C under nitrogen. The procedure for extracting the PGL-I from the total lipid extract was based on that of Hunter *et al.*[12] Briefly, dried lipids were dissolved in chloroform and applied to a silicic acid:celite column (2:1 V/V). The column was successively eluted with two bed volumes each chloroform, 2% methanol in chloroform and 5% methanol in chloroform. The 2% and 5% eluates were combined and taken to dryness under nitrogen at 50°C and analysed for PGL-I by thin-layer chromatography (TLC) and ELISA.

For TLC, samples were applied to high performance silicel gel plate (Sigma, St Louis, MO) and run in a solvent system composed of ether:acetone (8:2, V/V). The plates were air dried and PGL-I was located by spraying the plates with orcinol:sulphuric acid reagent and heating in a drying oven at 110°–115°C for 3–5 min. PGL-I at 5–10 μg served as the standard marker.

For ELISA, the samples were suspended in 100 μl of 0·05 M carbonate-bicarbonate buffer pH 9·2. The samples were further diluted 1:4 in the carbonate-bicarbonate buffer and were used for coating the microtiter plate (50 μl/well). The plate was incubated at 4°C overnight. The wells were washed 3 × with 200 μl of 0·01 M PBS pH 7·2, containing 1% BSA, and blocked by incubation with 100 μl of 0·01 M PBS containing 5% BSA at RT for 1 hr. The contents were aspirated and 50 μl of monoclonal antibody F8b4 (kindly provided by Thomas Buchanan) diluted 1:500 in 1% BSA/PBS was added to all wells. The plate was incubated at RT for 1 hr. After washing, 50 μl of peroxidase-conjugated rabbit anti-mouse IgM (μ-chain-specific (Cappel Laboratories, Downington, Pennsylvania, USA) at 1:500 dilution was added per well and incubated for 1 hr at RT. After washing the plate, 50 μl of 0·04 mg/ml solution of orthophenylene diamine (Sigma Chemical Co., St Louis, MO, USA) containing 0·02% H_2O_2 in 0·02 M sodium acetate buffer, pH 5·5, was added to each well. The plate was incubated at RT for 10 min, and the reaction was stopped by adding 5 M HCl (50 μl/well). Absorbance at 492 nm was read with a spectrophotometer (Titertek Multiscan, Flow Laboratories, Richmond, Virginia, USA). Wells not coated

with antigen served as negative control. For positive controls, 50 μl of known concentrations of PGL-I ranging from 0·025 to 80 μg/ml were used for coating the wells.

STATISTICAL ANALYSIS

Results were analysed for statistical significance on a Hewlett–Packard 9845T computer using the one tailed paired t-test and t-test. Values of $P < 0{\cdot}05$ were considered to be statistically significant.

Results

ARMADILLO ANTIBODIES TO PGL-I

The evolution of IgM and IgG anti-PGL-I response among a group of 30 armadillos is shown in Figure 1. Compared to the baseline (0 day), the anti-PGL-I response increased significantly up to approximately 450 days postinoculation (PI) for IgM and up to approximately 630 days PI for IgG. When line drawing graphs of the thirty individual armadillos IgM and IgG anti-PGL-I responsiveness *vs* days postinoculation with *M. leprae* was plotted, a homogenous clustered IgM response emerged; whereas a scattered IgG anti-PGL-I response was observed (data not shown). Although the IgG anti-PGL-I responsiveness was heterogenous, some animals clearly had higher absorbance values for IgG antibodies to PGL-I as compared to others. Animals with high absorbance values for IgG anti-PGL-I antibodies, despite the progression of their disease, maintained their high responsiveness. To summarize these data, animals were grouped into high and low IgG anti-PGL-I responders. The criteria for grouping these animals was based on absorbance

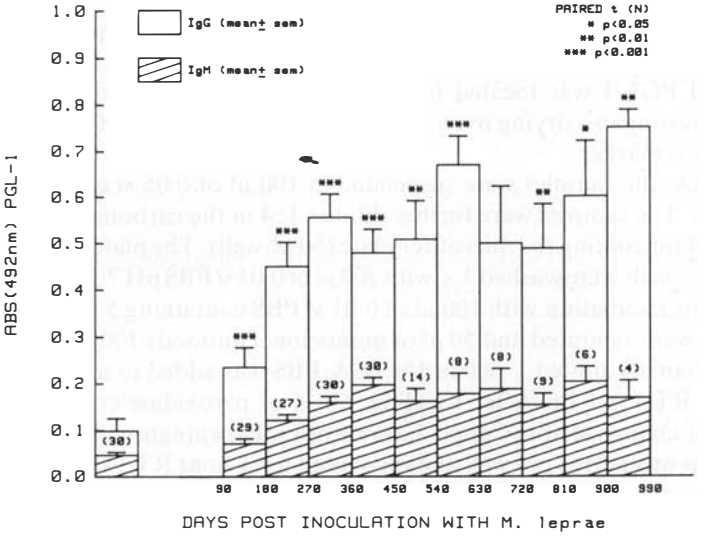

Figure 1. IgM and IgG anti-PGL-I response of 30 armadillos during course of experimental infection. Asterisks indicate IgG anti-PGL-I absorbance values significantly different from preceding absorbance values (paired t-test).

values observed at 360 days postinoculation. Eleven high IgG anti-PGL-I responders (Figure 2, Group A) had absorbance values within a mean ± 2, SEM of $0{\cdot}745 \pm 0{\cdot}136$; whereas, nineteen low IgG anti-PGL-I responders had absorbance values within a mean ± 2, SEM of $0{\cdot}212 \pm 0{\cdot}056$ (Figure 2, Group B).

When animals in Group A were compared to those in Group B in relation to their longevity after inoculation with *M. leprae*, it was shown that animals in Group A survived for a longer period (1051 days *vs* 563 days) (Table 1). The armadillos used for this study were also regularly examined histologically for the presence of acid-fast bacilli (AFB) in

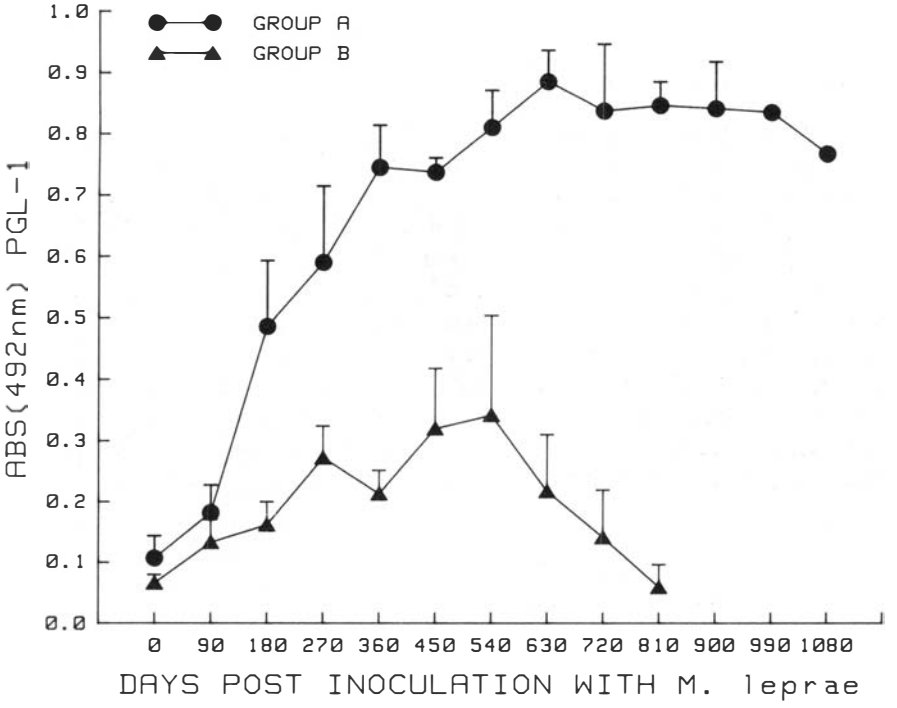

Figure 2. Kinetics of IgG anti-PGL-I mean $\pm$SEM. Animals in Group A ($n = 11$); animals in Group B ($n = 19$).

Table 1. Comparison of IgG absorbance values to PGL-I with longevity and time until the appearance of AFB in ear biopsies among 30 armadillos inoculated with *M. leprae*

Armadillo group	IgG ELISA at 360 days post inoculation (OD at 492 nm)	Longevity (days)	Time to AFB appearance in ear biopsy (days)
High IgG anti-PGL-I responder (N = 11)	$0{\cdot}745 \pm 0{\cdot}068$*	1051 ± 65	717 ± 139
Low IgG anti-PGL-I responder (N = 19)	$0{\cdot}212 \pm 0{\cdot}038$	563 ± 41 $P < 0{\cdot}0$	417 ± 39 $P < 0{\cdot}01$†

* Values expressed as mean $\pm$SEM.
† *t*-test, one tailed.

ear biopsies as a means of detecting dissemination of the disease. By this criterion, Group A animals delayed the dissemination of the disease as compared to those in Group B (717 days *vs* 417 days). These differences as represented in Table 1 were statistically significant ($P < 0{\cdot}01$).

The animals from both groups were sacrificed when they exhibited a heavy dissemination of *M. leprae* infection as determined by histological examination of their ear biopsies. Interestingly, the bacterial load in organs like the spleen, liver and lymph nodes in both populations was quite similar. However, one animal from Group A is still alive and information regarding its bacterial load is not available.

ARMADILLO ANTIBODIES TO *M. LEPRAE* COMPONENTS

Plasma samples collected during the first year postinoculation with *M. leprae* from a total of 9 animals, 4 from Group A and 5 from Group B (Figure 2), were selected and used in immunoblot analysis. The results obtained from both groups indicated a predominant IgM and IgG antibody response to be directed towards *M. leprae* components with molecular weights ranging from 21- to 45-kDa. These components were also reactive with antibody of the IgM and IgG class in normal plasma (0 day) in 8/9 and 2/9 armadillos, respectively. Representative data as derived by selection of a given animal from each group is presented in Figure 3. One unique armadillo from Group B produced antibodies of IgM and IgG class to multiple components of *M. leprae* with time postinoculation (Figure 4). Multiple bands of immunoreactivity ranging from approximately 5-kDa to 92-kDa were observed when blots were developed for IgG response using a plasma sample collected at 363 days PI. IgM response appeared as broad diffuse bands of immunoreactivity. IgM response to the 65-kDa protein was observed among most animals throughout the course of infection. IgG response to the 65-kDa protein was mostly observed during the later phase of infection. The animal with antibody activity to multiple components of *M. leprae* showed a very strong IgG response to the 65-kDa protein (Figure 4).

ANALYSIS OF COMPONENTS EXTRACTED FROM ARMADILLO PLASMA BY TLC AND ELISA

Eight armadillos, 3 from Group A and 5 from Group B were selected for this phase of the study. Plasma samples of each animal were selected at 4 periods and analysed for presence of PGL-I. These included the plasma collected prior to inoculation with *M. leprae* (normal) and 3 which were collected during the early, mid and late phase of infection. Seven out of the 8 plasma samples which were collected during the latter phase of infection contained components which had migration patterns similar to that of standard PGL-I using TLC. These included 2 animals from Group A (animals 1 and 2) and 5 animals from Group B (animals 4–8) (Table 2). Furthermore, plasma samples of 2 animals in Group B (animals 5 and 6) which were collected during the mid-phase of infection also had components with migration patterns similar to that of PGL-I (Table 2). A representative migration pattern of samples collected during the latter phase of infection from animals in Group A and B using TLC is shown in Figure 5. A broad staining band was observed at the region characteristic to that of standard PGL-I. It is clear that the RF value of tested samples are slightly smaller than that of standard PGL-I. However, it is believed that this

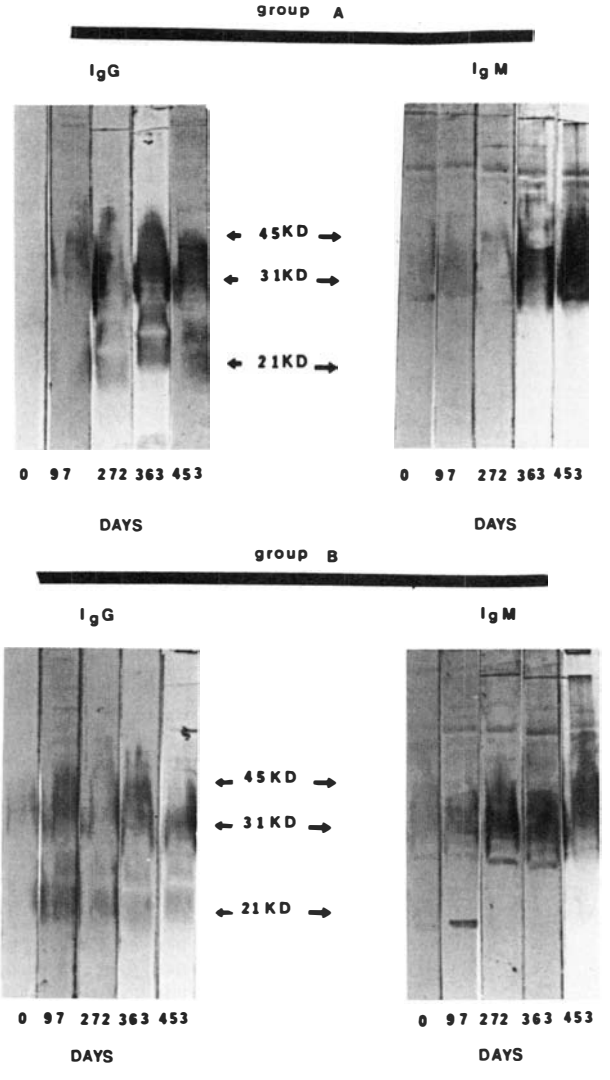

Figure 3. Demonstration of antigenic components of *M. leprae* eliciting IgM and IgG antibody response. A representative immunoblot characteristic common to animals in Group A and Group B are shown here. Sonicated *M. leprae* components were separated by SDS-PAGE and electrophoretically blotted onto NCP. NCP was incubated with armadillo serum (1:50 dilution), washed, and treated with class-specific antisera (rabbit antiarmadillo gamma-chain at 1:1000 dilution, rabbit antihuman μ-chain at 1:50 dilution). The NCP strips were washed and treated with peroxidase-conjugated goat antirabbit immunoglobulin (IgM + IgG + IgA) at 1:1000 dilution.

discrepancy may be due to the association of other components with PGL-I. The TLC results for each plasma sample were visually scored and were presented in Table 2.

To confirm that the components extracted from the plasma were PGL-I, we analysed their immunoreactivity in ELISA by using a specific monoclonal antibody F8b4 to PGL-I. The samples having migration patterns similar to that of PGL-I were shown to be

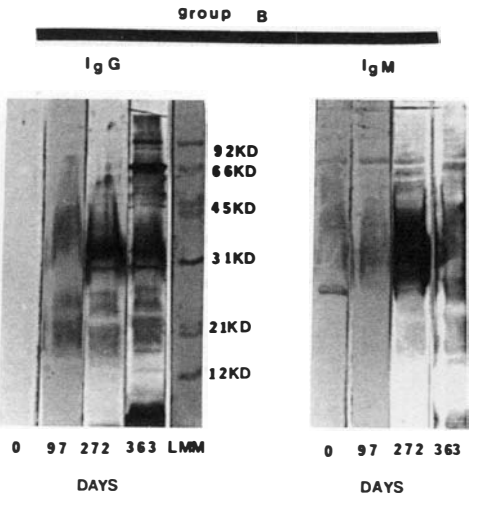

Figure 4. Demonstration of antigenic components of *M. leprae* eliciting IgM and IgG antibody response. Technical detail is similar to that of Figure 3.

Table 2. Results obtained from thin layer chromatography (TLC) and ELISA analysis of the components extracted from armadillo plasma

	TLC*				ELISA† (ABS 492 nm)			
		Infection				Infection		
Animal number	Normal (pre-infection)	Early	Mid	Late	Normal (pre-infection)	Early	Mid	Late
1	–	–	–	+	0·0	0·04	0·09	0·10
2	–	–	–	+	0·0	0·05	0·20	0·14
3	–	–	–	–	0·0	0·00	0·00	0·00
4	–	ND‡	–	+	0·0	0·00	0·07	0·19
5	–	–	+	+	0·0	0·12	0·17	0·14
6	–	–	+	+	0·0	0·02	0·06	0·14
7	–	ND	–	+	0·0	ND	0·01	0·08
8	–	–	–	+	0·0	0·00	0·00	0·10

* TLC values were scored subjectively based on intensity of the stained band.

†ELISA absorbance values for normal plasma were considered as base line, and is presented here as zero. Subsequent values were derived by their subtraction from the preceding normal plasma value.

‡ ND = not done.

reactive with MAB F8b4 and, therefore, identified as PGL-I (Table 2). A sample collected during the early phase of infection from animal 5 was positive for PGL-I in ELISA, but not TLC.

Discussion

In the present study, the evolution of IgG and IgM antibodies of armadillos to PGL-I and to sonicated *M. leprae* were analysed using ELISA and immunoblotting.

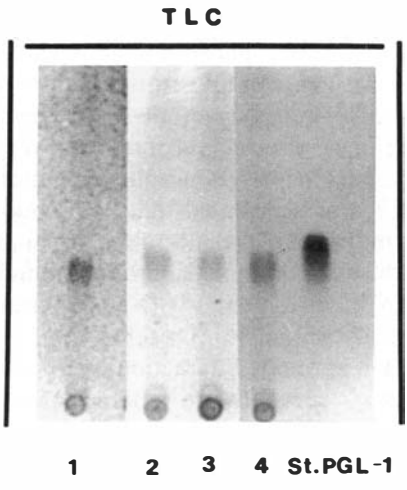

Figure 5. Comparison of the migration pattern of the component extracted from armadillo plasma with that of a standard PGL-I, using TLC. Samples were applied to high performance silicel gel plate and run in a solvent system composed of ether:acetone (8:2, V/V). Samples were located using orcinol:sulphuric acid reagent. Lanes 1–4, components extracted from plasma of 4 armadillos during the latter phase of infection.

Longitudinal IgM and IgG responses of a larger group of armadillos to PGL-I were performed in order to confirm our previous findings[10] and to distinguish the high and low IgG anti-PGL-I responders for their further characterization regarding their antibody response to other *M. leprae* components.

The results of the present study substantiate our previous findings,[10] in that IgM anti-PGL-I absorbance values increase with time postinoculation. This response was quite homogeneous and it persists throughout the course of infection, probably due to the availability of a continuous source of antigen. In comparison to the IgM response, the absorbance values for IgG anti-PGL-I were considerably higher and the response was heterogeneous. As reported previously,[10] and also in this study, due to the heterogeneity in absorbance values for IgG anti-PGL-I, we were able to separate armadillos into two groups. Group A represents those with high absorbance values for IgG anti-PGL-I response, whereas Group B represents the armadillos with low absorbance values for IgG anti-PGL-I. The animals in Group A, in relation to those in Group B, were capable of delaying the dissemination of *M. leprae* infection as measured by time to appearance of AFB in ear biopsies. These animals also had a longer life span. These differences existing among the two groups were statistically significant when a larger group of animals was analysed.

In human studies, Levis *et al.*[13] have reported high IgG anti-PGL-I in some patients with tuberculoid (BT) leprosy, a form of leprosy that is associated with controlling the infection. When Gormus, *et al.*[14] analysed longitudinal serum samples of *M. leprae*-infected sooty mangabey monkeys for antibodies of IgG and IgM class to PGL-I, they reported that high IgG and low IgM anti-PGL-I levels are associated with less severe disease. Therefore, there may be an association between elevated IgG anti-PGL-I responses and upgrading of immunological responsiveness to *M. leprae*.

We had previously observed a sharp drop in absorbance values for IgG anti-PGL-I among 4 of 11 animals during the latter phase of infection and at a time when the animals were moribund.[10] Significant decrease in IgG anti-PGL-I levels have also been described in *M. leprae*-inoculated sooty mangabey monkeys.[14] These usually preceded and/or corresponded to periods of clinical progression of the leprosy symptoms. Since the drop in absorbance values was in parallel to the systemic dissemination of infection as manifested by bacteria in buffy coats, it was speculated that high concentrations of antigens like PGL-I in the plasma could influence the results of the antibody detection assay by *in vivo* complexing of antigens with some or all of the serum antibodies. Previous investigators have demonstrated that the 3,6-di-o-methyl-B-D-glucopyranose is the hapten determinant of the species-specific glycolipid.[15–17] Therefore, due to the possible monovalent nature of PGL-I upon antigen antibody interaction one would not expect the formation of a lattice as commonly seen in precipitating immune complexes. This may explain our difficulty in demonstrating immune complexes using polyethylene glycol (data not shown). Consequently, we analysed the plasma samples for the presence of PGL-I. Analysis of selected plasma samples of 8 representative animals, 3 from Group A and 5 from Group B, indicated the presence of PGL-I in the plasma of 6 out of 8 animals. This was based on the migration pattern of the extracted component on TLC as compared with that of standard PGL-I and confirmed by its immunoreactivity with MAB F8b4 using ELISA. The presence of PGL-I in plasma was observed primarily in samples collected during the terminal phase of disease and correspondingly at a time in which a drop in IgG anti-PGL-I absorbance value was observed. Therefore, it is believed that this drop in absorbance value may be due to formation of complexes between high affinity IgG molecules and PGL-I in the plasma. This may be viewed as *in vivo* antigen excess in which the degree of drop in absorbance value may vary based on the amount of antigen bound to antibody prior to the application of plasma to the antibody detection assay. A significant drop in absorbance values for IgM anti-PGL-I antibodies was not readily observed among animals in Group A and B. A possible explanation could be that there is a higher concentration of high affinity IgG anti-PGL-I molecules than the low affinity IgM anti-PGL-I molecules.

Finally, the ability to detect *M. leprae* antigens like PGL-I in biological samples such as plasma may provide a potentially useful tool for the diagnosis of lepromatous leprosy, but such antigens do not appear promissory for early detection of disease in armadillos because they are usually abundant at a time in which clinical signs and symptoms are about to take place. Presence of PGL-I in plasma of human patients was also reported[18,19] and its significance in detection of subclinical leprosy has yet to be determined.

The plasma of selected animals in Group A and B were further analysed for antibodies of IgM and IgG class to sonicated *M. leprae* components by means of immunoblotting. The predominant IgM and IgG responses were directed toward the *M. leprae* components with molecular weights ranging from 21- to 45-kDa. Similar observations, particularly with respect to the material with migration pattern at the region of 33-kDa, was also reported in lepromatous patients.[4] The sera from armadillos having systemic infection with *M. leprae* were also shown to react significantly with 33-kDa component.[4,5] We have previously shown that the components with broad diffuse staining bands are glycoprotein in nature.[5] Others have also shown, upon electrophoresis and immunoblotting, that soluble fractions of disrupted *M. leprae* produced a major antigen with an apparent molecular mass of 30- to 50-kDa.[7,20,21] This product has now been identified as LAM.[22]

Based on our observations and those of others, it appears that the major armadillo antibody activities are directed against LAM. This could reflect the relative immunodominance and/or accessibility of LAM in intact bacilli. Furthermore, the detection of antibodies to LAM in the plasma of armadillos prior to their inoculation with *M. leprae* is suggestive of the ubiquitous nature of the antigen.

It is usually difficult to verify whether the 33-kDa glycoprotein is a single substance or a mixture of 2 or 3 substances with similar molecular weights. Based on the IgG immunoblot results seen in Figure 4, it appears that beneath this common broad diffuse band of immunoreactivity at the region of 33-kDa, there are as many as 3 distinct bands of immunoreactivity. As usually seen in IgM-type response (Figure 4), these components were not readily observed. A typical example of one such molecule is the 28-kDa protein. Recently, the gene for a 28-kDa protein of *M. leprae* has been cloned and was shown to be an important target of the humoral response in lepromatous leprosy.[23] Further analysis of these components may prove important in the immunology of leprosy.

The 65-kDa protein was also recognized as antibody evoking immunogen in armadillos. Although in our previous study,[5] we have shown the ability of this molecule in inducing antibody of IgG class, most animals analysed here had antibody of IgM class to this molecule. However, the one animal with antibody activity to multiple components of *M. leprae* also had a very intense band of IgG immunoreactivity to the 65-kDa protein. These observations suggest the individual animal variation in antibody response to the 65-kDa molecule. Also, antibody responses of armadillos to the IIIE9 epitope of the 65-kDa protein of *M. leprae* have been analysed using a competition binding assay. This assay incorporated crude cell wall extract of *M. leprae* or purified recombinant 65-kDa as antigen source. This epitope did not appear to be immunogenic.[24] Finally, attempts were made to define lymphocyte blast transformation differences in high and low IgG PGL-I responders. However, the results were highly variable within and between groups (data not shown). In conclusion, as shown here, armadillo antibody activity increased significantly with time postinoculation and this was directed primarily toward LAM as well as PGL-I. Furthermore, all animals, regardless of their ability in mounting an elevated level of IgG anti-PGL-I response, showed a similar longitudinal pattern of IgG and IgM response to sonicated *M. leprae* components.

Acknowledgments

This work was supported in part by grants from the American Leprosy Missions and the Hansen's Disease Foundation. The authors wish to express their appreciation to personnel of the Microbiology Research Department for making available the armadillo plasma samples. We are also grateful to Mr Melvyn Morales for the computer analysis, Mr Sterling Christy for processing and storing the plasma samples, and to Ms Rosemary Hauge for secretarial assistance.

References

[1] Ridley DS, Jopling WH. A classification of leprosy for research purposes. *Lepr Rev*, 1962; **33:** 119–28.
[2] Kirchheimer WF, Storrs, EE. Attempts to establish the armadillo (*Dasypus novemcinctus*) as a model for the study of leprosy. *Int J Lepr*, 1971; **39:** 693–702.

[3] Job CK, Sanchez RM, Hastings RC. Manifestations of experimental leprosy in the armadillos. *Am J Trop Med Hyg* 1985; **34:** 151–61.
[4] Chakrabarty AK, Maire MA, Lambert PH. SDS-PAGE analysis of *M. leprae* protein antigens reacting with antibodies from sera from lepromatous patients and infected armadillos. *Clin exp Imm*, 1982; **49:** 523–31.
[5] Vadiee AR, Shannon EJ, Gillis TP, Hastings RC. Partial characterization of antigens from *M. leprae* evoking IgG and IgM antibodies in armadillos. *Int J Lepr*, 1988; **56**(2): 274–82.
[6] Harboe M, Closs O, Rees RJW, Walsh GP. Formation of antibody against *Mycobacterium leprae* antigen 7 in armadillos. *J Med Microbiol*, 1978; **11:** 525–35.
[7] Praputpitlaya K, Ivanyi J. Detection of an antigen (Ny4) common to *M. tuberculosis* and *M. leprae* by 'Tandem' immunoassay. *J Immunol Methods*, 1985; **79:** 149–57.
[8] Cho SN, Yanagihara DL, Hunter SW, Gelber RH, Brennan PJ. Serological specificity of phenolic glycolipid-I from *Mycobacterium leprae* and use in serodiagnosis of leprosy. *Infect Immun*, 1983; **41:** 1077–83.
[9] Truman RW, Shannon EJ, Hagsted HV, Hugh-Jones ME, Wolff A, Hastings RC. Evaluation of the origin of *Mycobacterium leprae* infections in the wild armadillos, *Dasypus novemcinctus*. *Am J Trop Hyg*, 1986; **35:** 588–93.
[10] Vadiee AR, Shannon EJ, Gillis TP, Mshana RN, Hastings RC. Armadillo IgG and IgM antibody responses to phenolic glycolipid-1 during experimental infection with *M. leprae*. *Int J Lepr*, 1988; **56**(3): 422–7.
[11] Laemmli UK. Cleavage of structural proteins during the assembly of the head of the bacteriophage T_4. *Nature*, 1970; **227:** 680–9.
[12] Hunter Shirley W, Fujiwara Tsuyoski, Brennan PJ. Structure and antigenicity of the major specific glycolipid antigen of *Mycobacterium leprae*. *J Biol Chem*, 1982; **257:** 15072–8.
[13] Levis WR, Meeker HC, Schuller-Levis G, Sessen E, Schwarer B. IgM and IgG antibodies to phenolic glycolipid-I from *Mycobacterium leprae* in leprosy: Insight into patient monitoring, erythema nodosum leprosum, and bacillary persistence. *J Invest Dermatol*, 1986; **86**(5):529–34.
[14] Gormus BJ, Ohaski DK, Ohkawa S, Walsh GP, Meyers WM, Brennan PJ, Trygg C. Serological responses to *Mycobacterium leprae*-specific phenolic glycolipid-I antigen in sooty Mangabey monkeys with experimental leprosy. *Int J Lepr* 1988; **56**(4): 537–45.
[15] Cho SN, Fujiwara T, Hunter SW, Rea TH, Gelber RH, Brennan PJ. Use of an artificial antigen containing the 3,6-di-o-methyl-B-D-glycopyranosyl epitope for the serodiagnosis of leprosy. *J Infect Dis*, 1984; **150**(3): 311–22.
[16] Fujiwara T, Hunter SW, Cho SN, Aprinall GO, Brennan PJ. Chemical synthesis and serology of the disaccharides and trisaccharides of phenolic glycolipid antigens from the leprosy bacillus and preparation of a disaccharide protein conjugate for serodiagnosis of leprosy. *Infect Immun*, 1984; **43:** 245–52.
[17] Hunter SW, Brennan PJ. Further specific extracellular phenolic glycolipid antigens and a related diacylphthiocerol from *Mycobacterium leprae*. *J Biol Chem*, 1983; **258:** 7556–62.
[18] Cho SN, Hunter SW, Gelber RH, Rea TH, Brennan PJ. Quantitation of the phenolic glycolipid of *Mycobacterium leprae* and relevance to glycolipid antigenemia in leprosy. *J Infect Dis*, 1986; **153(3):** 560–9.
[19] Young DB, Harnisch JP, Knight J, Buchanan TM. Detection of phenolic glycolipid-I in sera from patients with lepromatous leprosy. *J Infect Dis*, 1985; **152(5):** 1078–81.
[20] Britton WJ, Hellquist L, Besten A, Raison RL. *Mycobacterium leprae* antigens involved in human immune response. *J Immunol*, 1985; **135:** 4171–7.
[21] Ivanyi J, Sinha S, Aston R, Cussell D, Keen M, *et al.* Definition of species-specific and cross-reactive antigenic determinants of *Mycobacterial leprae* using monoclonal antibodies. *Clin exp Imm*, 1983; **52:** 528–36.
[22] Hunter SW, Gaylord H, Brennan PJ. Structure and antigenicity of the phosphorylated lipopolysaccharide antigens from the leprosy and tubercule bacilli. *J Biol Chem*, 1986; **261:** 12345–51.
[23] Cherayil BJ, Young RA. A 28-kDa protein from *Mycobacterium leprae* is a target of the human antibody response in lepromatous leprosy. *J Immunol* 1988; **141**(12): 4370–5.
[24] Vadiee AR, Gillis TP, Shannon EJ. Confirmation of a false positive result associated with a competition inhibition assay used for detecting antibodies to a protein epitope of *Mycobacterium leprae*. *Clin exp Imm*, 1990; **79:** 397–402.

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Low-magnification electron micrography of leproma in human skin based on semithin and ultrathin sectioning

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Summary Low-magnification electron micrography of leprosy lesions is described. The various cell types in the lesions, the relationships to leprosy bacilli and the distribution of bacilli in the lesions of lepromatous leprosy, are neatly demonstrated in the low-magnified pictures.

Introduction

It is well known that electron microscopy (EM) combined with ultrathin sectioning has helped enormously in understanding the interrelationships between leprosy bacilli and various kinds of host tissue cells in leprosy lesions. The late Dr Nishiura[1] said very appropriately: 'We are now faced with the problems of reestablishing the pathology of leprosy based on the new morphology of lesions, with this technologic advancement of morphologic research.' Since then many papers on EM in leprosy have been published. However, there is no paper to show the microcytopathological analysis of leprosy lesions by low-magnification electron micrography of ×500–1000. The present paper is concerned with a rigorous study of how to take such low-magnified micrographs of human skin leproma. Considerable success has been achieved in obtaining satisfactory results.

Materials and methods

HUMAN LEPROMAS

Tissue specimens from lepromatous leprosy patients with fresh lepromas were examined by skin biopsy. The biopsies were collected at the National Leprosarium of Oku Kohmyo-en, Okayama and Tama Zensho-en, Tokyo.

PREPARATIONS OF TISSUES FOR ELECTRON MICROSCOPY

Prefixation

The biopsies were prefixed by immersion in 2–8% glutaraldehyde aqueous solution for one week at room temperature.

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Washing and rinsing

The prefixed materials were washed in running water for a few hours, then rinsed in distilled and/or double distilled water a few times.

Immersing in agar solution

The washed and rinsed materials were cut into 0·5–1·0 mm cubes. The cubes were placed in 2% agar sol at 45°C. After cooling and gelation, the agar was cut into small blocks. (This method greatly facilitated transfer of specimens from one solution to another.)

Fixation

The small blocks were fixed by immersion in osmium tetroxide buffered to pH 6·8–7·0 according to the technique of Millonig.[2] Fixation time was 48 hours at 4°C.

Dehydration

The specimens were dehydrated by serial passage (15–30 min. each) into 50, 70, 80, 90, 95 and 100% ethanol. Following this, the specimens were washed 2–3 additional times with fresh absolute ethanol.

Treatment with methacrylate resins

Methacrylate resins, methyl methacrylate and *n*-butyl methacrylate, as supplied by the manufacturer, contain a hydroquinone inhibitor. The inhibitor was removed by preliminary treatment with 2% sodium hydroxide solution at room temperature. After two or three treatments, the solution should be colourless. The resins were washed several times with distilled and/or double distilled water to remove the alkali, dehydrated by anhydrous calcium chloride, and stored in a refrigerator. Any particles of the agent must be removed by filtration before the resins are used for embedding.

The dehydrated specimens were transferred to a 50% solution of the methacrylate resins in absolute alcohol and left 1–2 hours. The use of resins containing 1·5% benzoyl-peroxide as catalyst was tested in place of the usual 3 to 7 mixtures of methyl and *n*-butyl methacrylate. The specimens were then passed two or three times (1 hour each) through undiluted resins.

Polymerization

Polymerization was carried out by placing the specimens in gelatin capsules and filling them with the unpolymerized resins. The temperatures employed were room temperature (4–5 hr), 35–37°C (1–2 days), 45°C (1–2 days) and 60°C (2–4 days). After 1–1·5 days at 35–37°C, the capsules filled with the partially polymerized resins were slowly swayed for 1–2 min. Upon completion of polymerization, the capsules were kept in the vacuum desiccator (EM-DSC 10E, JEOL).

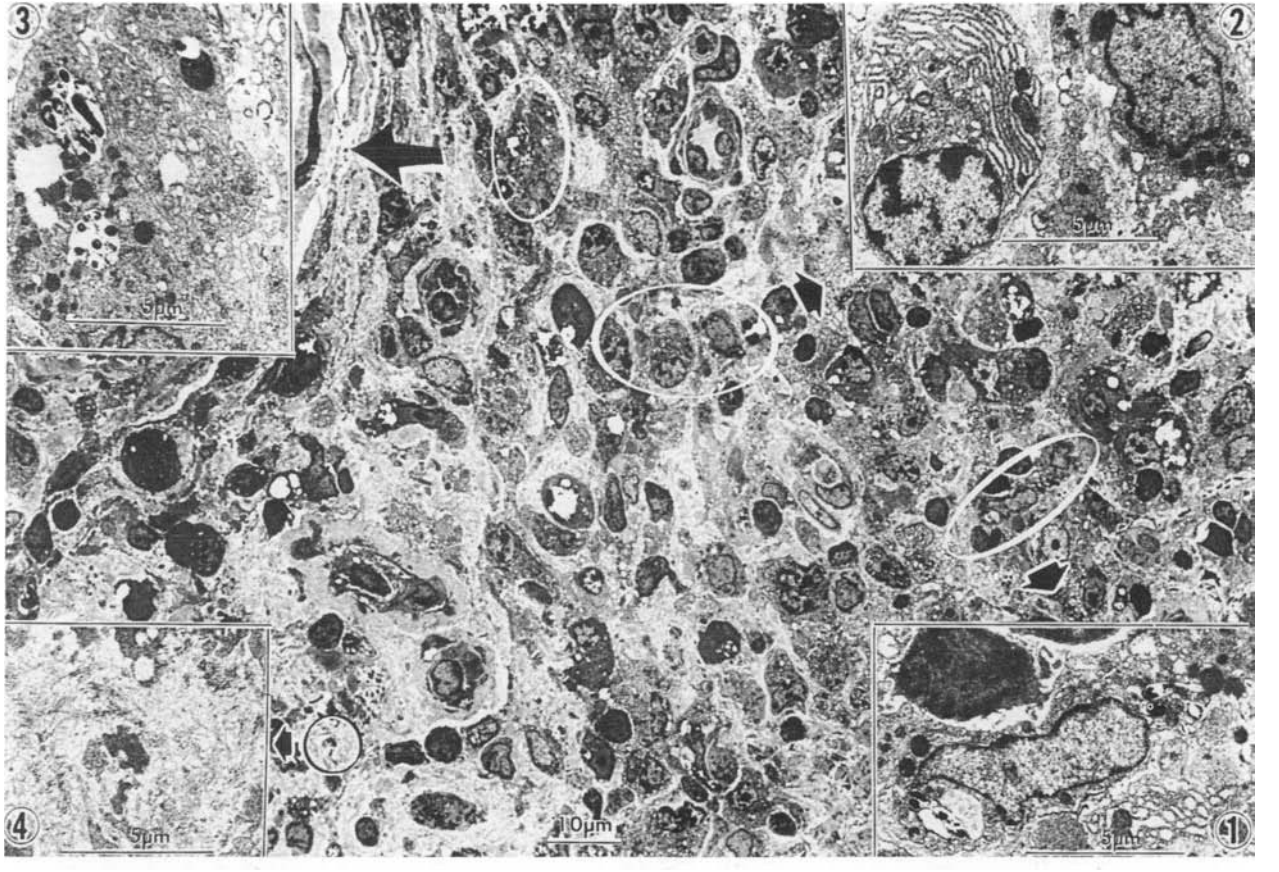

Figure 1. Low-magnified electron micrograph (original × 500). Several parts (insets 1–4) are trimmed, greatly magnified, along with the original. Photo 1 is the nucleus in macrophage and the bacilli in the cell; Photo 2, the plasma cell and the macrophage; Photo 3, the macrophage and the bacilli in the cell; Photo 4, the collagen fibres.

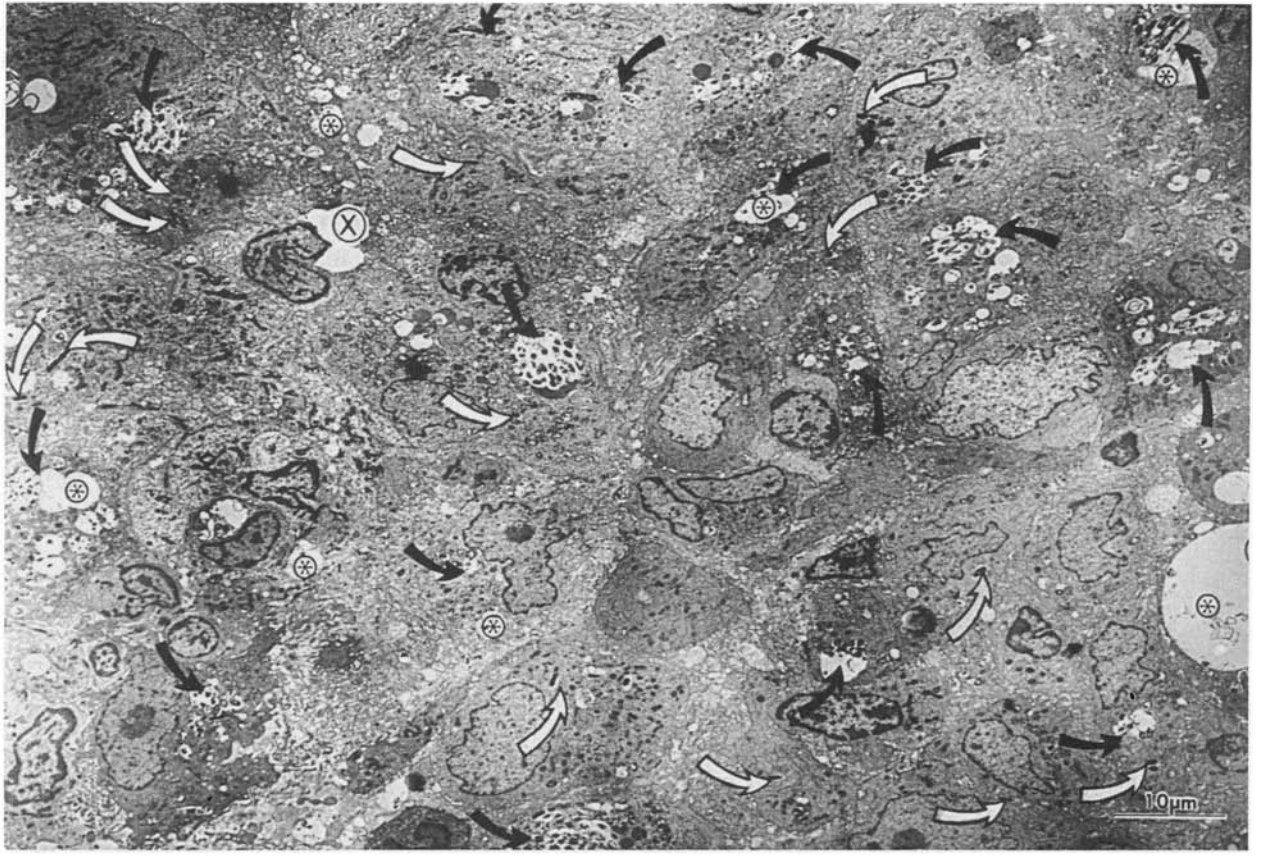

Figure 2. Low-magnified electron micrograph (original × 500). The various cell types in the lesions, the relationships to leprosy bacilli and the distribution of bacilli in the lesions of lepromatous leprosy are observed. ➡, clump of bacilli; ⇨, a single bacillus; ⊗, artifact-like gaps or openings as small lacuna-like structure; ⊛, electron less dense parts in which the cell debris-like substances are detected.

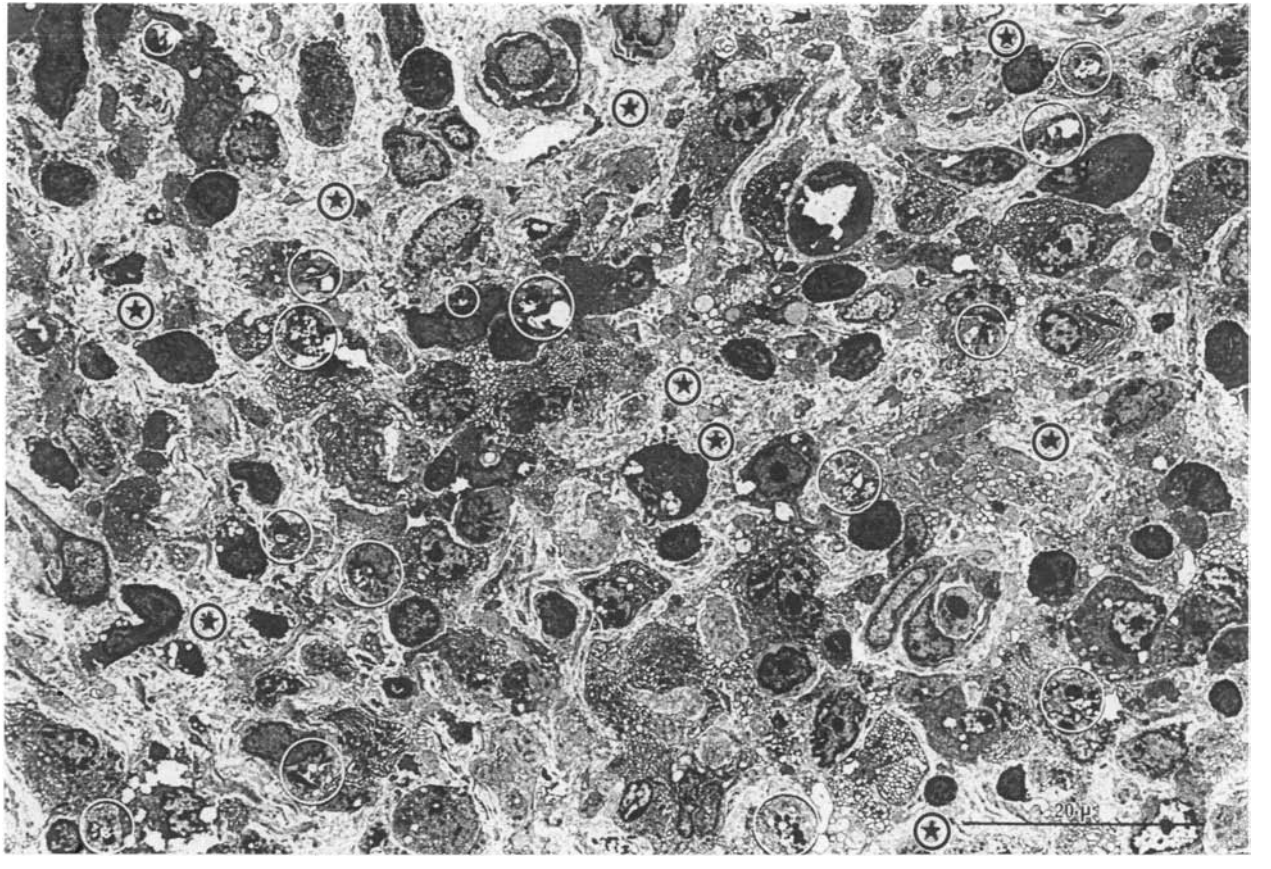

Figure 3. Low-magnified electron micrograph (original × 500). Fine fibrillar structures (⊛) are observed. It may be assumed that they are collagen fibres. In the circle-marks are shown the bacilli and the relative tissue cells.

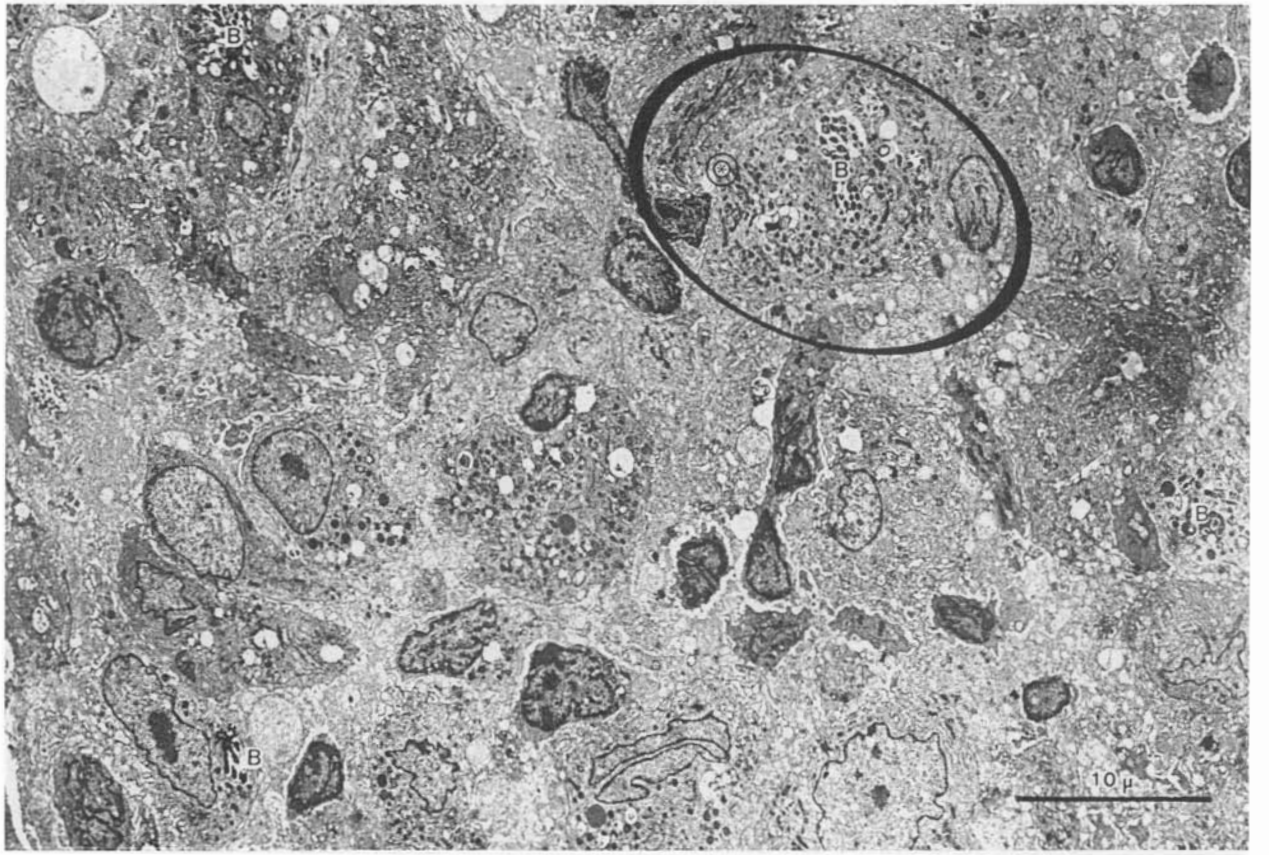

Figure 4. Low-magnified electron micrograph (original ×900). The so-called macrophages are pictured sporadically. B = leprosy bacilli.

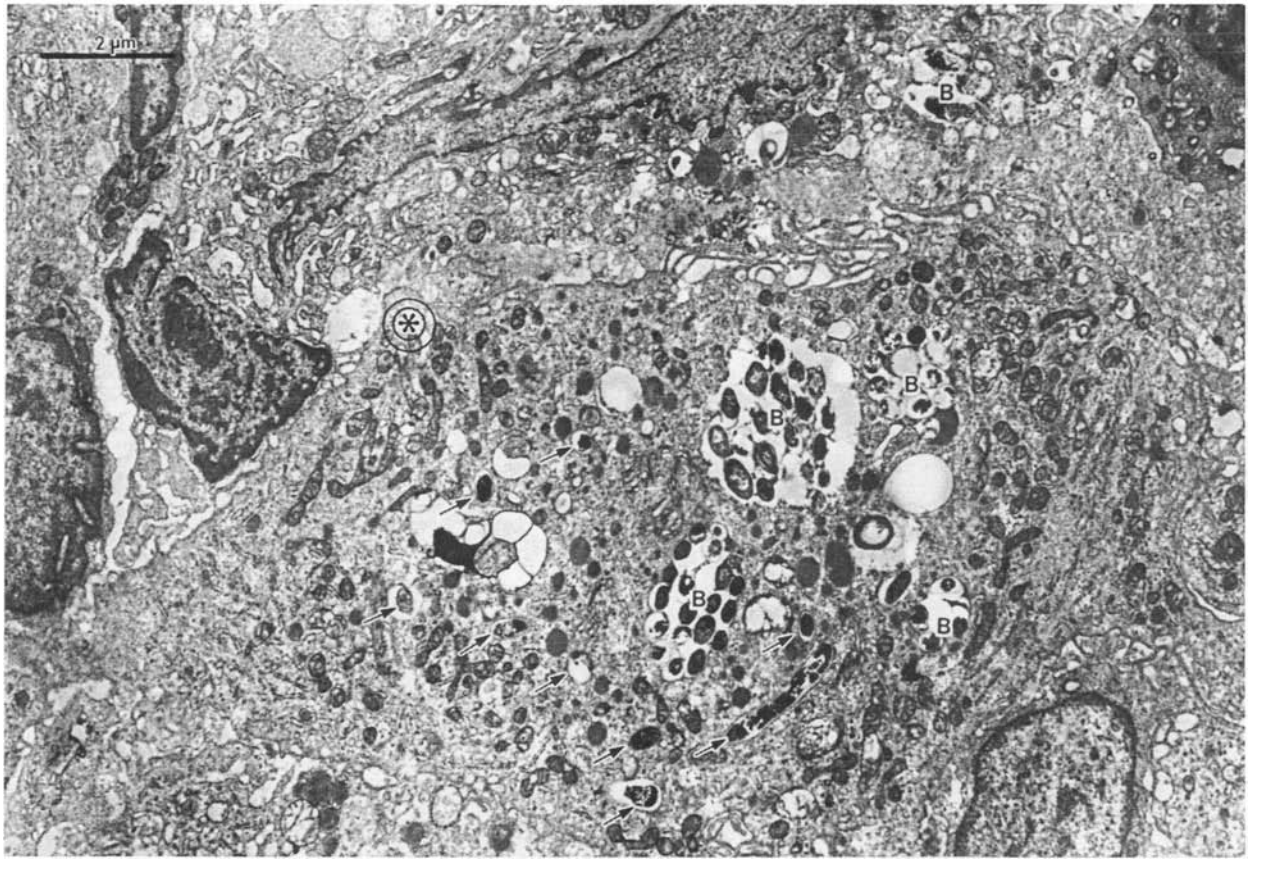

Figure 5. High-magnified electron micrograph of the circle (⊛) in Figure 4 (original × 3000). The whole aspect of one macrophage is depicted. Arrows show the single bacillus. B = leprosy bacilli in the clump or group called globi.

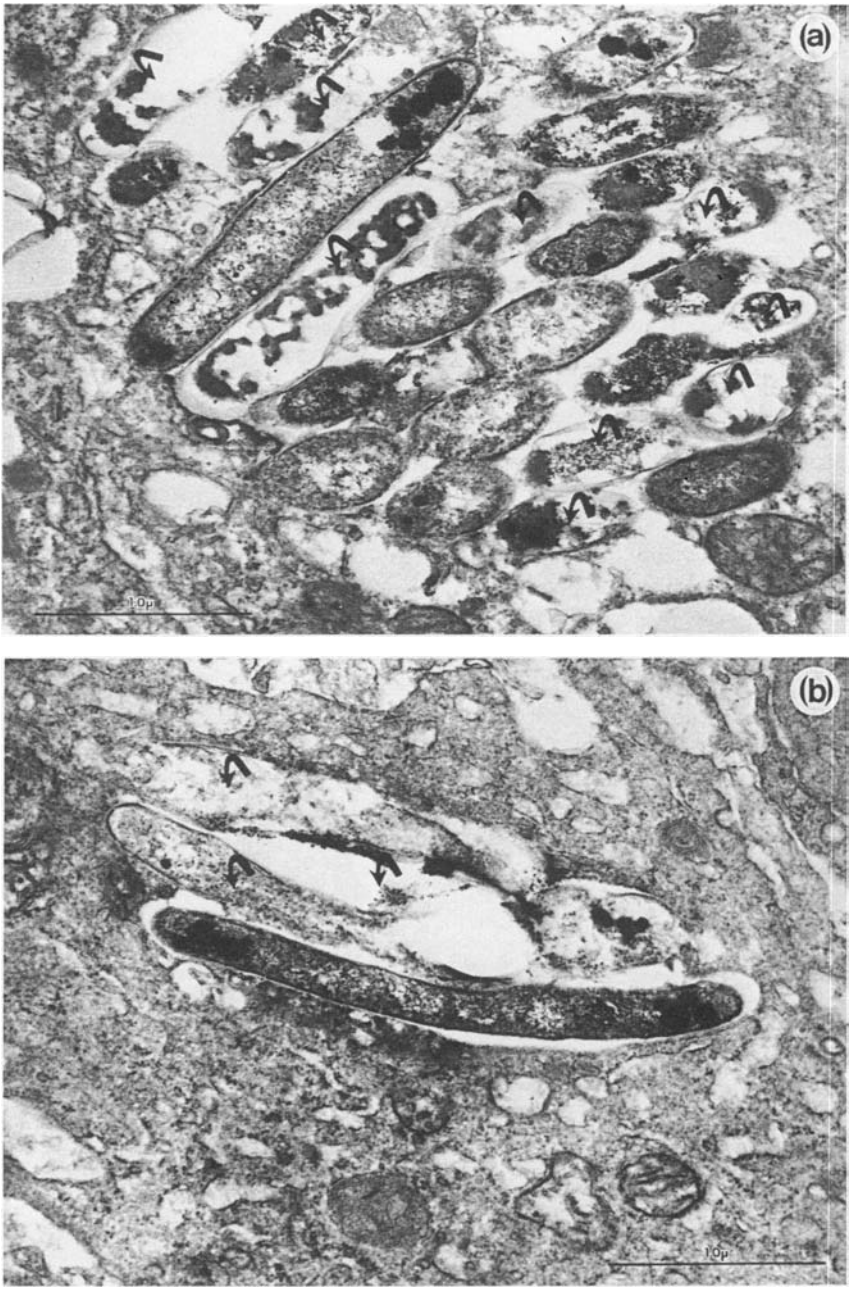

Figure 6. Thin sections of a group of bacilli. ↰ = degenerated bacilli: (a) Longitudinal and oblique sections of the bacilli. There are several intracytoplasmic inclusions in the bacilli (original × 10,000); (b) Longitudinal sections of the bacilli, intact and degenerated and arranged in parallel. Several intracytoplasmic inclusions are observed in an intact bacillus (original × 10,000).

Sectioning and electron microscopy

The semithin and ultrathin sections were processed on an LKB Ultratome and picked up on Formvar-covered grids. The sections were smoothed over by chloroform vapour. More than 500 sections of the specimens were made, and they were observed on a JEM 1200EX electron microscope operated at 40 kV, without electron staining as a general rule. If necessary, the sections were contrasted with the lead electron staining solution (Katayama Chemical Industries, Co. Ltd, Osaka, Japan). They were rinsed rapidly in distilled water, after contrasting. Pictures of the whole specimens were made at low magnifications; 500, 800, 1000, 1200, 1500 and 3000 diameters. The important and significant parts were filmed at high power magnification of $\times 5000$ to $\times 10{,}000$.

Results

The electron micrographs demonstrated in Figures 1–6 show that the processing of specimens for electron microscopic examination used here produced good results. The so-called polymerization damage, which results from conventional procedures of methacrylate embedding, seemed to be avoided.

The microcellular structures are in a fine state of preservation, both in host tissue and bacterial cells in the leproma. Consequently, it was possible to enlarge directly parts of the original negative film at high magnification (Figure 1). On scrutinizing the electron micrographs narrowly, however, two forms of artefact-like gaps were observed (Figure 2): electron less dense parts in which cell debris-like matter was detected, and small lacuna-like structures in which the cellular components were deemed non-existent. They did not seem to be the so-called lumen or lumen-like structures of the tissue.

Besides several kinds of tissue cells, the cell components of well-developed lepra cells were seen, as described in former papers:[1,5,6] foamy structures, opaque droplets, electro-transparent zones, onion-like structures and other organelles. Macrographs with such cytoplasm were predominant in the specimens. And also fine fibrillar structures were observed as shown in Figure 3.

Bacilli in the leproma were distributed as globi and single bacillary cells (Figures 2–5). As shown in Figure 6(a) and (b), it was possible to elucidate the fine structures of such bacilli at higher magnification. The various intracellular structures of the intact bacillary cell were well preserved.

Discussion

Because of the polymerization damage which results from conventional procedures, methacrylate embedding has fallen into disuse lately, though impregnation is good and the specimens cut readily. The damage is said to be an explosion phenomenon that becomes evident during polymerization, not during fixation or dehydration. It is characterized by a degree of shrinkage and/or disruption of the tissue cells in biomaterials, with concomitant internal distortion. Under these conditions, electron microscopists have been forced, more or less unwillingly, to search for more suitable methods.[5–11] Yet these kinds of damage were not detected in the present study, and the procedures used seemed good from this point of view, though the methods are not new. It may be safely said that good results depend upon the following points: (a) prolonged pre-fixing in

glutaraldehyde aqueous solution; (b) preliminary immersing and embedding of the materials in agar; (c) fixing of the small agar blocks in osmium tetroxide; (d) removing and/or discarding hydroquinone inhibitor from methacrylate resin; and (e) swaying the capsules filled with partially polymerized resins. (Some of these points have been reported previously.[7]) Moreover, a matter of great import is to carry out the preparatory procedures without haste.

The cells of the lesions show a characteristic morphologic pattern in their response to the parasites. To study their relationships, it is imperative to examine a wide area at low magnifications of $\times 500$–1000, and after that to examine selected areas at high magnifications of $\times 5000$–10,000. Only then are the intimate interrelationships between host and parasite clearly seen.

The electron microscopic features of various aspects of leprosy lesions have been described.[1,3,4,7] However, low-magnification electron micrography has been rarely employed though it is fundamental to a true comprehension of the lesions. It is primarily a research tool, but it provides a general view of the lesion that is helpful for patient evaluation, and provides data that otherwise is available only through histopathology. It acts as a bridge between light and electron microscopy. The results shown in this paper justify further studies of microcytopathology in leprosy.

Acknowledgments

I wish to express my thanks to all the staffs at the National Leprosarium of Oku Kohmyo-en, Okayama and Tama Zensho-en, Tokyo, who helped in this study.

References

[1] Nishiura M. The electron microscopic basis of the pathology of leprosy. *Int J Lepr*, 1960; **28:** 357–400.
[2] Millonig G. *Further observations on a phosphate buffer for osmium solutions.* The 5th International Congress for Electron Microscopy, Philadelphia, 1962 (S.S. Bress, Jr., editor). New York: Academic Press, Inc., 1962, **2,** 8.
[3] Imaeda T. Electron microscopic analysis of the components of lepra cells. *Int J Lepr*, 1960; **28:** 22–37.
[4] Imaeda T, Convit J. Electron microscope study of *Mycobacterium leprae* and its environment in a vesicular leprous lesion. *J Bacteriol*, 1962; **83:** 43–52.
[5] Condie RM, Howell AE, Good RA. Studies on the problem of preservation of myelin sheath ultrastructure: evaluation of fixation, dehydration, and embedding. *J Biophysic Biochem Cytol*, 1961; **9:** 429–43.
[6] Hashimoto T, Naylor HB. Studies of the fine structure of microorganisms. 1. A study of factors influencing the "Explosion Phenomenon" in ultrathin sections of bacteria. *J Bacteriol*, 1958; **75:** 640–6.
[7] Hirata T. Electron microscopic observations of cell wall and cytoplasmic membrane in murine and human leprosy bacilli. *Int J Lepr*, 1985; **53:** 433–40.
[8] Holt SJ, Hicks RM. Studies of formalin fixation for electron microscopy and cytochemical staining purposes. *J Biophysic Biochem Cytol*, 1961; **11:** 31–45.
[9] Koike M, Takeya K. Fine structures of intracytoplasmic organelles of mycobacteria. *J Biophysic Biochem Cytol*, 1961; **9:** 597–608.
[10] Low FN, Clevenger MR. Polyester-methacrylate embedments for electron microscopy. *J Cell Biol*, 1962; **12:** 615–21.
[11] Pease DC. *Histological techniques for electron microscopy.* Academic Press: New York and London, 1960.
[12] Ryter A, Kellenberger E. L'inclusion au polyester pour l'ultramicrotomie. *J Ultrastruct Research*, 1958; **2:** 200–14.
[13] Ward RT. Prevention of polymerization damage in methyacrylate embedding media. *J Histochem Cytochem*, 1958; **6:** 398.
[14] Watson ML. Reduction of heating artifacts in thin sections examined in the electron microscope. *J Biophysic Biochem Cytol*, 1957; **3:** 1017–31.

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Histoid lesion in nerve of a lepromatous patient

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Summary This report pertains to a patient who had untreated diffuse lepromatous disease of 8- to 10-years' duration. Two peripheral nerves were beaded, which on biopsy showed histoid features. Because of its rarity, the case is reported.

Introduction

Beaded thickening of nerves in lepromatous leprosy is not uncommon. However, histoid morphology in the nerve is a rarity, there being only few such recorded cases in the literature.[1,2] Such a case is presented here.

Case report

RC, a 30-year-old male labourer from the western part of Rajasthan attended the outpatient department complaining of swelling all over the body of 8- to 10-years' duration. The condition started with paraesthesia in the distal parts of limbs, and thereafter insidiously progressed with diffuse infiltration all over the body. The patient was not aware of any patch or skin lesion at any time. He gave a history of frequent blood-stained nasal discharge. Apart from this he had no other problem and denied having taken any treatment whatsoever for his complaints.

On examination, he was found to have diffuse infiltration of the skin all over the body. It was more marked on the face, back, abdominal folds, buttocks, scrotum and the extensor aspects of the limbs. On the infiltrated skin of the left buttock, one pea-sized papule was present; otherwise there was no overt nodulation of the skin. He had thickening of the ears. In addition, there was loss of eyebrows on both sides. The tongue was infiltrated, the nasal mucosa ulcerated, and his hard palate showed nodulation. There was no evidence of ENL or of shrivelling of the skin anywhere. Both ulnars, superficial radials, and lateral popliteal nerves were moderately thickened, soft, smooth and

* Corresponding author.

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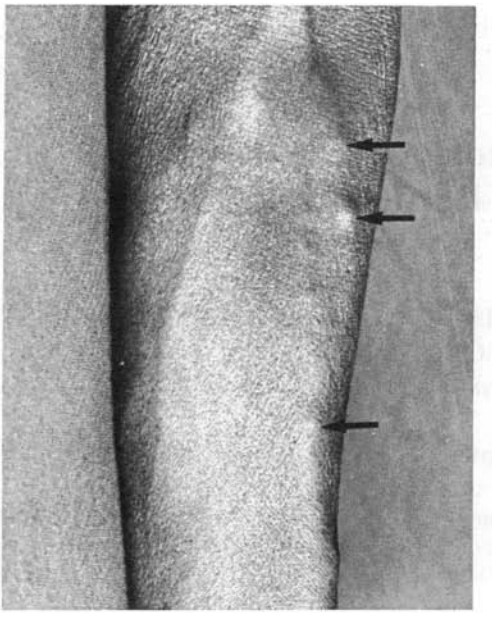

Figure 1. Nodules in the medial cutaneous nerve of the forearm.

nontender. The left medial cutaneous nerve of the forearm and the right superficial peroneal nerve were found to be grossly thickened, firm and beaded (Figure 1). There was glove and stocking distribution of pinprick analgesia on the limbs extending up to the middle of the legs but no paralytic or nonparalytic deformities. Systemic examination revealed no abnormality.

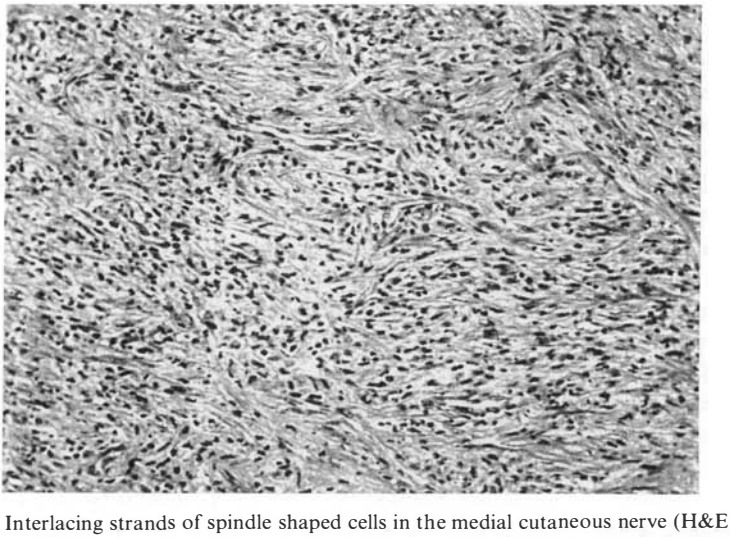

Figure 2. Interlacing strands of spindle shaped cells in the medial cutaneous nerve (H&E × 10).

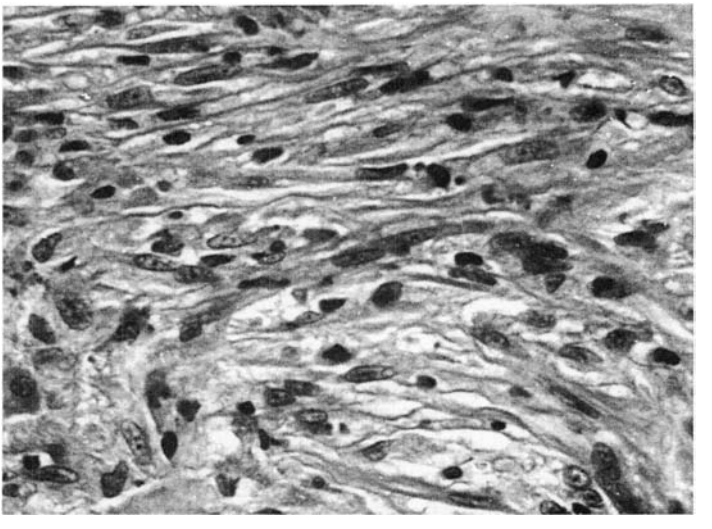

Figure 3. High power view of Figure 2 showing spindle shaped cells (H&E × 40).

A clinical diagnosis of untreated lepromatous leprosy was made. A spot urine check for DDS was negative. Skin-smear examination showed that all sites were positive for acid-fast bacilli (AFB), the BI ranging from 4+ to 5+, mean 4·5+. A nasal smear and the sputum too, were positive for AFB, the organisms being present in globi. Sputum culture for AFB was negative. A chest X-ray was normal. Liver function tests, blood urea and serum creatinine were found to be within normal limits.

Biopsy sections were processed, and stained with haematoxylin and eosin and Fite Faraco's stain for AFB. The Gless and Marsland technique was used for identifying nerve

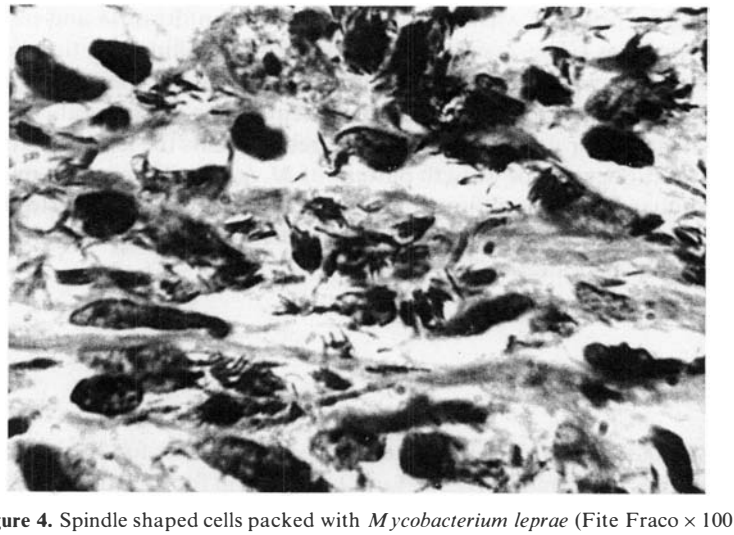

Figure 4. Spindle shaped cells packed with *Mycobacterium leprae* (Fite Fraco × 100).

fibres. Skin from right flank showed a typically lepromatous picture with foamy macrophages loaded with AFB (6+). The left medial cutaneous nerve of the forearm, which was beaded, showed nerve fibres and connective tissue infiltrated by spindle-shaped cells (Figure 2). In some areas there were interlacing strands of these spindle-shaped cells. Foamy macrophages were seen in other areas. Plasma cells and lymphocytes were seen scattered among the foamy macrophages (Figure 3). Solid-staining AFB were packed in the spindle-shaped cells (Figure 4)—a picture consistent with histoid leprosy in nerve.

Discussion

Since the original description of histoid leprosy by Wade[3] the cutaneous and subcutaneous manifestations of histoid leproma have been well documented by several workers.[4–8] While describing the histoid lesions in the skin of relapsed lepromatous patients, Wade[3] suggested that the histoid lesions could occur in other situations as well. Indeed, soon afterwards it was found that several of the untreated lepromatous patients had histoid lesions on skin and possibly on palatal mucosa.[5] In all the above studies, the histoid nodules were confined to the skin and/or mucous membrane and not elsewhere. More recently a few reports have appeared of histoid lesions occurring in nerves. Roy Chaudhari & Srinivasan[9] reported a 'histoid habitus' in a nerve abscess affecting the superficial radial nerve in an untreated nodular patient. Gaulier[10] also reported a histoid morphology in the nerve of an untreated leprosy patient in whom large subcutaneous nodules were attached to the nerve trunk, or developing from it or its smaller branches. Ramanujam *et al.*[1] and Rajan & Palande[2] have each reported typical histoid lesions in the nerves of relapsed leprosy cases.

Considering the frequency and extent of involvement of neural tissue in lepromatous patients, very few reports of neural histoids are available in literature. Further, all the previously reported cases of histoid leprosy were either relapsed patients with possibly resistant organisms, or if untreated they had nodular lepromatous disease. In contrast, the present lepromatous case was untreated, had diffuse infiltration and no cutaneous or subcutaneous nodules. The lesion was a fusiform swelling of the nerve. Histoid morphology was seen within the nerve bundles, the overlying sheath was normal.

The origin of histoid lesions in untreated patients, as in the present case and those of others[9,10] remains unclear. It is likely that in all these patients the lesions in the nerves were due to altered multiplication or growth pattern of *M. leprae*. This in turn might result in a morphological change in the infiltrating cells. The possibility that histoid lesions may result from a localized and unchecked multiplication of *M. leprae* due to focal loss of immunity has been suggested by Job *et al.*[11]

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References

[1] Ramanujam K, Arunthathi S, Chacko CJG, Jacob M. Nerve histoid leproma in peripheral nerve; a case report. *Lepr Rev*, 1984; **55:** 63–8.

[2] Rajan MA, Palande DD. Histoid leprosy with histoid leproma in peripheral nerve—a case report. *Lepr India*, 1985; **57:** 389–92.

[3] Wade HW. The histoid variety of lepromatous leprosy. *Int J Lepr*, 1963; **31:** 129–42.

[4] Price EW, Fitzherbert H. Histoid lepromatous leprosy. *Int J Lepr*, 1966; **34:** 367–74.

[5] Ramanujam K, Ramu, G. Wade's histoid lepromatous leprosy. *Lepr India*, 1969; **49:** 293–7.

[6] Rodriguez JN. The histoid leproma—its characteristics and significance. *Int J Lepr*, 1969; **37:** 1–21.

[7] Desikan KV, Iyer CGS. Histoid variety of lepromatous leprosy. *Int J Lepr*, 1972; **40:** 149–56.

[8] Bhutani LK, Bedi TR, Malhotra YK, Kandhari KC, Deo MG. Histoid leprosy in North India. *Int J Lepr*, 1974; **42:** 174–81.

[9] Roy Chaudhari SB, Srinivasan H. Nerve abscess in lepromatous leprosy. A case report and discussion of pathogenesis. *Lepr India*, 1977; **49:** 330–8.

[10] Gaulier A. Spindle shaped leproma cells arising from perineurium. A link with Wade's histoid leprosy, one case. *Arch Anat Cytol Path*, 1980; **28:** 277–82 (In French) *Abs Int J lepr*, 1981; **49:** 476.

[11] Job CK, Chacko CJG, Taylor PM. Electronmicroscopic study of histoid leprosy with special reference to its histogenesis. *Lepr India*, 1977; **49:** 467–70.

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The anatomical distribution of single leprosy lesions in an African population, and its implications for the pathogenesis of leprosy

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Summary Data on the anatomical sites of single leprosy lesions found in 635 newly diagnosed and biopsy-confirmed leprosy patients are presented. These patients were found during total population surveys carried out by the Lepra Evaluation Project, a prospective longitudinal study of the epidemiology of leprosy in Karonga District, Northern Malawi. There was a striking excess of single lesions on the face and the back of the arms, compared to the distribution of skin surface area, and a deficit on the legs, regardless of age. There is some evidence for a sex difference in lesion distribution among adults, with facial and arm lesions being relatively more common in females and back lesions being more common in males. The excess of lesions on the face compared to the lower limbs is similar to data from Uganda, but very unlike data from Burma and elsewhere in Asia. Overall, the distribution of lesions does not suggest a pattern reflecting entry of *Mycobacterium leprae*, nor does it suggest an association with anatomical distribution of the nervous or vascular system. It is argued that the distribution reflects the influence of some 'local' environmental or behavioural factors.

Introduction

Continued uncertainty over the natural history of leprosy has encouraged several workers to investigate the possible relevance of the anatomical distribution of leprosy lesions for the transmission of *Mycobacterium leprae* or the pathogenesis of subsequent clinical disease. The predilection of *M. leprae* for the skin was once taken as evidence for skin-to-skin transmission of the infection.[1] This view has been challenged in recent decades by investigations demonstrating that skin is an unlikely portal of exit for bacilli compared to the respiratory tract.[2]

The most thorough studies of the distribution of leprosy skin lesions and their implications were carried out by Doull *et al.*[3] in the context of population studies in the Philippines. They found an excess of lesions on the extremities, and commented cautiously that, although the lesion distribution might be an indicator of skin entry, 'It

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should be borne in mind that such a distribution of lesions could be satisfactorily explained by assuming a portal of entry other than the skin, with a tendency to localization of the infection wherever the resistance of tissues is lowered by inflammation or injury'. Similar findings and opinions were later published by Guinto & Rodrigues,[4] also based on studies in the Philippines. Newell reviewed data published up to 1965 on lesion distributions in different age and sex groups, and concluded that there was no evidence favouring the skin, rather than the respiratory tract, as the major portal of entry of *M. leprae*.[5] More recently, Machin[6] has argued that in children the distribution of single leprosy lesions is essentially random, suggesting a systemic distribution of the infection.

A major problem in evaluating lesion distribution data is the fact that observed distributions of lesions are affected strongly by the methods of skin examination. Skin examinations may be incomplete, and social taboos or staff habits are such that certain parts of the body are liable to be examined less frequently and less thoroughly than others. This is particularly true for female suspects or patients in Asia. Published data from South India indicating lesions to be more common on legs and buttocks of males than of females are consistent with such a bias.[2] Such distributions are impossible to interpret without detailed information on the methods and relative thoroughness of the examinations of the two sexes.

In this paper we present and analyse a unique data set derived from complete examination of more than 97% of people living in a leprosy endemic area in Northern Malawi. The work was carried out as a part of the LEPRA Evaluation Project.

Methods

The LEPRA Evaluation Project (LEP) is a prospective longitudinal study of the epidemiology of leprosy in Karonga District (population approximately 150,000 in 1990), Northern Malawi.[7] The first total population survey was carried out between 1980 and 1984, and the second between 1985 and 1989. Individuals are examined at their homes by trained paramedical workers (leprosy control assistants, LCAs) who complete a 2-page 'General Examination Form' for every individual seen. In addition to entering any findings which might be signs of leprosy LCAs indicate whether they consider the examination to have been 'complete' or 'incomplete'. For all incomplete examinations the part of the body which was inadequately examined is indicated on the form. 'Incomplete' usually means that the buttocks were not seen. Only the lower abdomen (below the umbilicus) is omitted from the routine examination of adults, and is not generally examined unless an individual self-presents with a lesion on that part of the body. Regular supervision by medical officers (JMP, PJKG) and a senior LCA ensure adherence to protocol. Ninety-seven per cent of examinations have been recorded as complete.

All individuals suspected of having clinical leprosy (and who have no history of previous antileprosy treatment) are referred to an LEP Medical Officer (JMP or PJKG) for review examination. All lesions are then drawn onto an outline of the human body superimposed upon a grid.[8] During these review examinations a numerical grade indicating the clinical certainty of the diagnosis of leprosy is given by the medical officer,[9] and one or more 4 mm punch biopsy specimens are taken for histopathological examination.[10] The clinical certainty grade, slit-skin smear results and histopathology

results are coded, entered onto computer, and then combined in an algorithm to provide an overall measure of diagnostic certainty.[9] For the purpose of this analysis only patients with a high overall certainty of diagnosis, (N and M cases, see ref. 9) were considered.

The clinical records of all new (previously untreated) leprosy cases ascertained between 1980 and 1987 (inclusive) were reviewed. The large majority of these cases had been found by active case detection during the first total population survey (1980–84) or the first half of the second survey (1985–87). Patients with only a single lesion (including up to 2 small satellites), when first diagnosed, were selected for this study. Grid location codes for the initial lesion were entered into a computer, and combined with other demographic and clinical information for analysis. Anatomical distributions of lesions were compared with standard statistics on the distribution of skin surface area.[11]

Because adult females were slightly less likely than adult males to be completely examined in the general survey,[7] we have excluded patients with single buttock lesions (6 females and 12 males) from the analysis comparing male and female adults.

Results

Table 1 shows the anatomical distribution of lesions by mode of detection. The difference between the self-reporting and actively found patients is not statistically significant and thus they are combined for all subsequent analyses. On the other hand it is of interest that only 9% of self-reporting patients had lesions on the back, whereas single back lesions were found on 22% of those ascertained by active case detection.

Table 2 shows the distribution of lesion sites by age for males and females together. There is no significant difference in the overall anatomical distribution of single leprosy lesions by age ($\chi^2 = 11{\cdot}98$, $p = 0{\cdot}75$). For all age groups there is a preponderance of single lesions on the face, back and on the back of the arms. Together these sites account for 74% of single lesions found in new patients in Karonga District.

Figures 1 and 2 compare the distributions of lesions with the distribution of surface area of the skin in each anatomical location.[11] The differences between lesion and skin distribution are striking, and are strongly statistically significant ($p < 0{\cdot}001$ by comparing

Table 1. Numbers (and percentages) of newly diagnosed leprosy patients with single lesions in Karonga District, Northern Malawi, by mode of ascertainment and site of lesion

	Anatomical site									
Mode of detection	Face	Chest (ant. trunk)	Back (post. trunk)	Buttocks	Arms (front)	Arms (back)	Hands	Legs (front)	Legs (back)	Total
Actively detected	152 (27%)	18 (3%)	125 (22%)	25 (4%)	43 (8%)	133 (24%)	5 (0·1%)	34 (6%)	22 (4%)	557
Self-reporting	26 (33%)	0 (0%)	7 (9%)	1 (1%)	7 (9%)	27 (35%)	1 (1%)	5 (6%)	4 (5%)	78
Total	178 (28%)	18 (3%)	132 (21%)	26 (4%)	50 (8%)	160 (25%)	6 (1%)	39 (6%)	26 (4%)	635

Table 2. The anatomical distribution of single leprosy lesions by age for males and females among newly diagnosed leprosy patients in Karonga District, Northern Malawi

	Anatomical site									
Age (years)	Face	Chest (ant. trunk)	Back (post. trunk)	Buttocks	Arms (front)	Arms (back)	Hands	Legs (front)	Back (front)	Total
0–10	16 (35%)	3 (7%)	8 (17%)	2 (4%)	3 (7%)	9 (20%)	0 (0%)	1 (2%)	4 (9%)	46
11–20	36 (26%)	4 (3%)	27 (20%)	6 (4%)	10 (7%)	33 (24%)	1 (1%)	11 (8%)	8 (6%)	136
>20	126 (28%)	11 (2%)	97 (21%)	18 (4%)	37 (8%)	118 (26%)	5 (1%)	27 (6%)	14 (3%)	453
Total	178 (28%)	18 (3%)	132 (21%)	26 (4%)	50 (8%)	160 (25%)	6 (1%)	39 (6%)	26 (4%)	635

likelihoods based on multinomial distributions) for both sexes. There is an excess of lesions relative to surface area on the face and the upper arms and to a lesser extent on the back of the trunk. The relative deficit of lesions is mostly on the legs. The deficit on the anterior trunk is an exaggeration in so far as the lower abdomen is not examined in adults.

Table 3 presents lesion distributions by sex, for individuals up to and older than 20 years at time of diagnosis. Buttock lesions are omitted from the adult analysis because of the slight difference between the sexes in completeness of examinations.[7] Table 3 reveals

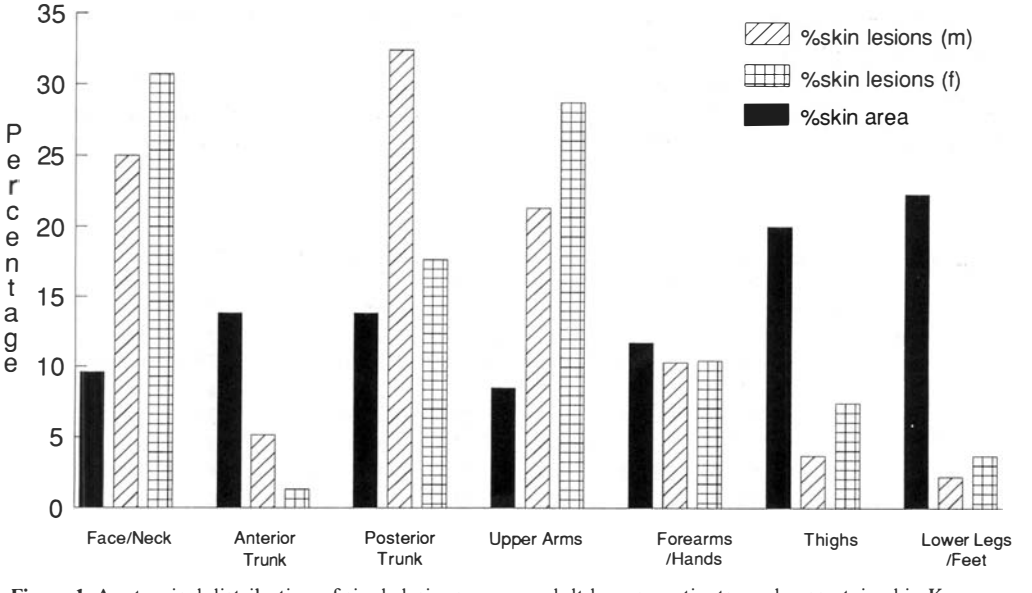

Figure 1. Anatomical distribution of single lesions among adult leprosy patients newly ascertained in Karonga District, Northern Malawi, by sex, compared with skin surface area distribution (buttocks and genital areas omitted).

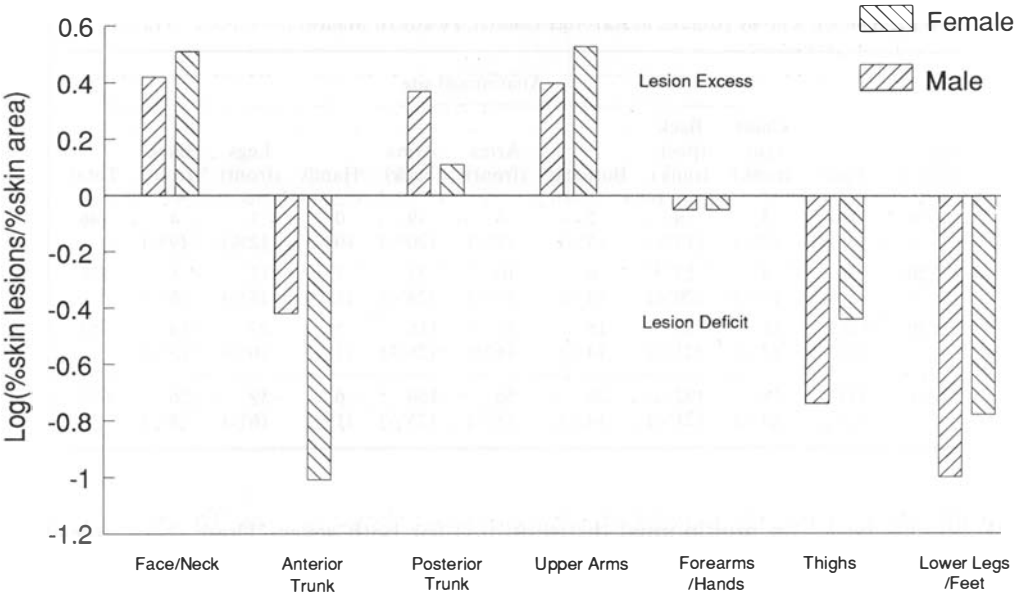

Figure 2. Relative excess and deficit of skin lesions in different anatomical sites, among adult leprosy patients newly ascertained in Karonga District, Northern Malawi, by sex. Vertical axis is the logarithm of the ratio of observed to expected relative frequencies, assuming that the lesions were randomly distributed on the body. Primary data identical to those presented in Figure 1.

Table 3. Distribution of new leprosy lesions by anatomical site, sex and age (up to and older than 20 years). Data from Karonga District, Northern Malawi. Buttock lesions of lesions of adults in square brackets

		Anatomical site									
Age (years)	Sex	Face	Chest (ant. trunk)	Back (post. trunk)	Buttocks	Arms (front)	Arms (back)	Hands	Legs (front)	Legs (back)	Total
0–20	M	25 (30%)	5 (6%)	17 (20%)	4 (5%)	7 (8%)	15 (18%)	1 (1%)	6 (7%)	4 (5%)	84
	F	27 (28%)	2 (2%)	18 (18%)	4 (4%)	6 (6%)	27 (28%)	0 (0%)	6 (6%)	8 (8%)	98
	Both	52 (29%)	7 (4%)	35 (19%)	8 (4%)	13 (7%)	42 (23%)	1 (1%)	12 (7%)	12 (7%)	182
> 20	M	34 (25%)	7 (5%)	44 (32%)	[+12]*	12 (9%)	29 (21%)	2 (1%)	4 (3%)	4 (3%)	136
	F	92 (31%)	4 (1%)	53 (18%)	[+6]*	25 (8%)	89 (30%)	3 (1%)	23 (8%)	10 (3%)	299
	Both	126 (30%)	11 (3%)	97 (2%)	[+18] [4%]	37 (9%)	118 (27%)	5 (1%)	27 (6%)	14 (3%)	435 [+18]
Total		178	18	132	26	50	160	6	39	26	635

* Buttock lesions of adults not included in percentage calculations.

Table 4. The anatomical distribution of single leprosy lesions in children and young individuals in Malawi, Uganda and Burma. Malawi data from this study. Uganda[14] and Burma[15] data from BCG trial populations

	Anatomical site								
Population	Face	Chest	Back	Buttocks	Upper Arms	Forearms + hands	Thighs	Lower legs + feet	Total
Karonga District, Malawi	52 (29%)	7 (4%)	35 (19%)	8 (4%)	32 (18%)	24 (13%)	15 (8%)	9 (5%)	182
Uganda	79 (44%)	7 (4%)	17 (9%)	13 (7%)	32 (18%)	24 (13%)	15 (8%)	9 (5%)	181
Burma	12 (3%)	13 (3%)	47 (10%)	86 (18%)	80 (17%)	75 (16%)	89 (19%)	65 (14%)	469

no difference between the sexes for individuals less than 20 years of age. On the other hand there appears to be a sex difference in lesion distribution among adults (heterogeneity $\chi^2 = 21{\cdot}51$, $p = 0{\cdot}003$), with an excess of lesions on the trunk of males and on the face and back of arms of females.

Further analyses by occupation associated with different clothing requirements did not reveal any significant differences between the generally well-dressed teachers and office workers and the generally less well-dressed farmers and fishermen.

Table 4 and Figure 3 present data on the distribution of single leprosy lesions in

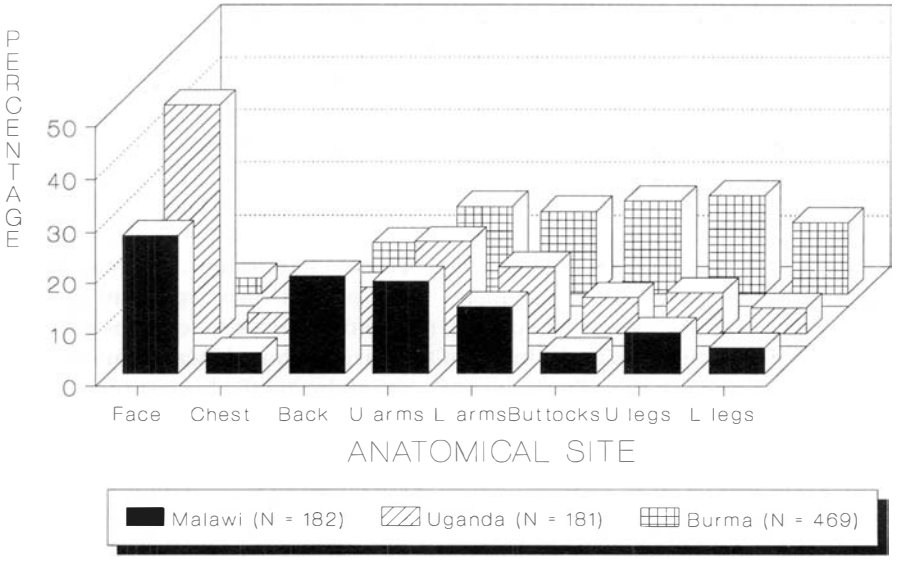

Figure 3. Anatomical distribution of single lesions in young leprosy patients in Malawi (this study), Uganda[12] and Burma.[13] Data from Table 4.

Malawi (this study), Uganda[12] and Burma.[13] All data refer to individuals less than 20 years of age and are unlikely to be influenced greatly by ascertainment bias. It appears that single lesions are far more common on the face than the buttocks or lower limbs of young African patients, and vice versa for the Burmese.

Discussion

The anatomical distribution of single leprosy lesions presented here is unlikely to have been distorted to an appreciable extent by incompleteness of examination. More than 96% of the general population, and all leprosy suspects, were examined completely, with the exception of the lower abdomen. Some parts of the body are more difficult to examine than others, in particular the feet and lower legs, which may be covered with dirt or dust. However, because the feet are closely inspected during the routine palpation of superficial peroneal nerves, it is unlikely that many lesions on the feet and lower legs escaped attention. Frequently LCAs ask people to wash their feet or lower legs if they believe that the examination may be hampered by dirt or dust. We therefore think that our main findings, a marked preponderance of lesions on the face in both sexes and all ages, an excess of lesions on the back of adult males and on the back of the arms of adult females, and a deficit of lesions on the legs in both sexes, at all ages, are genuine, and not artefacts due to incomplete examinations. It is of interest that single lesions on the back were more common among actively than passively detected patients, perhaps reflecting greater awareness of lesions which can be more easily observed. The fact that sex differences in lesion distribution are more apparent in adults than in children is reminiscent of the fact that sex differences in prevalence rates are also observed in adults but not in children.[2,14]

The distribution of single lesions found among leprosy patients in Karonga District is not consistent with the simple hypothesis that sites of single leprosy lesions reflect sites of entry of *M. leprae* through the skin via wounds or skin abrasions. The relative paucity of lesions on the legs speaks against that hypothesis. This deficit is in conspicuous contrast with the anatomical distribution of Buruli ulcer lesions, a mycobacterial disease believed to be transmitted through broken skin. Approximately 68% of Buruli ulcer lesions in adult males and 29% of the lesions in adult females have been reported to occur on the legs.[15]

On the other hand, it might be argued that the observed distribution of leprosy lesions in Karonga District does not contradict the hypothesis that *M. leprae* enter the skin via bites of flying insects, with subsequent local development of lesions.[2,16] Men in Karonga District usually wear long trousers, which should protect their legs from insect bites. Women always cover the chest and back but frequently wear sleeveless tops which would allow flying insects easy access to the backs of their arms. Though Malawians in Karonga District usually sleep with their faces covered, except during the hottest time of the year (October and November), their faces are probably more exposed to flying-biting insects than are other parts of the body.

If the distribution of leprosy lesions does not reflect the sites of entry of *M. leprae*, then it must reflect either differential seeding or proliferation of *M. leprae*, or else differential pathological responses to infection, in different parts of the body. Such mechanisms might in turn reflect differential vascular or nervous supply to various parts of the body, or differential immune responses (perhaps based on density of Langerhans or other cell

types), or else other factors such as body temperature.[17] If the determining factors are physiological, we might expect the anatomical distribution of leprosy lesions to be similar in different populations. To test this hypothesis, we compared lesion distributions in three data sets which we believe to have been relatively little affected by selection or examination biases (Table 4, Figure 3). These data pertain to children (and thus avoid possible incompleteness of examination associated with taboos in adults) in this Malawian study and in the actively followed-up populations of the BCG trials in Uganda[12] and Burma.[13] The two African data sets are roughly similar, with strong predilections for lesions on the face and a paucity of lesions on the buttocks, legs and feet. These distributions are in striking contrast to the Burmese data which show more than 50% of lesions on the buttocks and lower limbs, but only 3% of lesions on the face. Other published data sets from Indian and Philippine populations resemble those from Burma more than they do those from Malawi and Uganda, in that they show a higher predilection for lesions on the lower limbs than on the face.[2,3,18,19]

We believe these differences between African and Asian populations to be real, and not merely a reflection of biased data. The considerable difference between the anatomical distribution of single leprosy lesions in Burma and in Malawi makes it unlikely that 'universal' anatomical or physiological factors, such as skin surface temperature distribution, blood vessel distribution, peripheral nerve distribution or turnover rates of Schwann cells[20] determine the distribution of leprosy lesions, as such factors are unlikely to differ greatly between people in different parts of the world. The differences suggest rather that there are strictly 'local', presumably environmental or behavioural, factors which determine where single leprosy lesions arise. An important factor could be clothing and sleeping habits, if biting insects were involved in the transmission of *M. leprae* or if sun exposure were associated with response to infection. We could find no evidence in our data that clothing habits related to occupation were associated with the anatomical distribution of lesions, but such an indirect test of the hypothesis is obviously open to confounding by many extraneous occupation-related factors. The puzzle remains to be solved.

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References

[1] Badger LF. In *Leprosy in theory and practice*. Cochrane & Davey (eds), 1964, Ch. 6, pp 69–97.
[2] Fine PEM. Leprosy: The epidemiology of a slow bacterium. *Epidemiologic Reviews*, 1982; **4:** 161–88.
[3] Doull JA, Rodriguez JN, Guinto R, Plantilla F. Field study of leprosy in Cebu. *Int J Lepr*, 1936; **4:** 141–70.

[4] Guinto RS, Rodriguez JN. A field study of leprosy in Talisay, Cebu, Philippines. *Int J Lepr*, 1941; **9:** 149–66.
[5] Newell KW. An epidemiologist's view of leprosy. *Bull Wld Hlth Org*, 1966; **34:** 827–57.
[6] Machin M. In *Essays on leprosy*. Ryan & McDougall (eds). 1988, Ch. 1, pp 1–29.
[7] Ponnighaus JM, Fine PEM, Bliss L, Sliney IJ, Bradley DJ, Rees RJW. The Lepra Evaluation Project (LEP) an epidemiological study of leprosy in Northern Malaŵi. I: Methods. *Lepr Rev*, 1987; **58:** 359–75.
[8] Boerrigter G. Grid system and body diagram for leprosy. *Lepr Rev*, 1983; **54:** 115–18.
[9] Ponnighaus JM, Fine PEM, Bliss L. Certainty levels in the diagnosis of leprosy. *Int J Lepr*, 1987; **55:** 454–62.
[10] McDougall CA, Ponnighaus JM, Fine PEM. Histopathological examination of skin biopsies from an epidemiological study of leprosy in Northern Malaŵi. *Int J Lepr*, 1987; **55:** 88–98.
[11] Lund CC, Browder NC. The estimation of areas of burns. *Surg Gynec and Obst*, 1944; **79:** 352–8.
[12] Sutherland I. Personal communication.
[13] Bechelli LM, Gallego-Garbajosa P, Gyi MM, *et al*. Site of early skin lesions in children with leprosy. *Bull WHO*, 1973; **48:** 107–11.
[14] Ponnighaus JM, Fine PEM, Maine N, Bliss L, Kalambo M, Ponnighaus I. The Lepra Evaluation Project (LEP), an epidemiological study of leprosy in Northern Malaŵi. II. Prevalence rates. *Lepr Rev*, 1988; **59:** 97–112.
[15] The Uganda Buruli Group. Epidemiology of mycobacterium ulcerans infection (Buruli ulcer) at Kinyara, Uganda. *Trans Roy Soc Trop Med Hyg*, 1971; **65:** 763–75.
[16] Kirchheimer WF. The role of anthropods in the transmission of leprosy. *Int J Lepr*, 1976; **44:** 104–7.
[17] Hastings RC, Brand PW, Mansfield RE, Ebner JD. Bacterial density in the skin in lepromatous leprosy as related to temperature. *Lepr Rev*, 1968; **39:** 71–4.
[18] Bedi BMS, Narayan E, Doss AG, Kirchheimer WF, Balasubrahmanyan M. Distribution of single lesions of tuberculoid leprosy. *Lepr India*, 1975; **57:** 15–22.
[19] Horton RJ, Povey S. The distribution of first lesions in leprosy. *Lepr Rev*, 1966; **37:** 113–14.
[20] Weddell AGM, Palmer E. The pathogenesis of leprosy. *Lepr Rev*, 1963; **34:** 57–61.

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Effect of treatment on immune responsiveness in lepromatous leprosy patients

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Summary This study was performed in order to analyse whether the immune unresponsiveness to *Mycobacterium leprae*, largely seen in lepromatous patients, persisted after discharge from treatment. Lymphoproliferation and skin tests were performed using two mycobacterial antigens (*M. leprae* and BCG) in three groups of lepromatous patients grouped by treatment status. Forty-seven per cent of the lepromatous patients tested acquired reactivity to *M. leprae* after long-term treatment.

Introduction

Lepromatous leprosy patients (LL or BL forms) display a selective immunological unresponsiveness to *Mycobacterium leprae* antigen with the absence of delayed-type-hypersensitivity,[1] T-cell proliferation,[2] and deficiency in the production of growth factors such as IL-2.[3] These patients also fail to produce interferon-gamma (IFN-γ) in response to *M. leprae*.[4] Active suppression by macrophages and/or T cells may explain their inability to respond to leprosy bacilli.[5,6] Lepromatous patients carry a high load of bacilli which may play a role *in vivo* in the induction of immune tolerance.[7] Cellular anergy observed in lepromatous patients appears to be *M. leprae* specific since the immune response against other antigens is largely normal.[8]

The effect of treatment on the recovery from the immunological anergy in lepromatous patients is a controversial subject. Findings from a number of studies suggest that an unresponsiveness to *M. leprae* seen in lepromatous patients is long-lasting and unrelated to the bacterial load.[9,10] However, some studies have revealed different immunological reactivity to mitogens and mycobacterial antigens when cellular immune responses of short-term treated patients were compared with untreated patients.[11–15]

To determine the effect of long-term treatment on the immune status of patients, we

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have assessed the cellular immune responses of 64 lepromatous patients to *M. leprae* and to BCG.

Materials and methods

PATIENTS

Sixty-four multibacillary leprosy patients who attended the Outpatient Unit of the Oswaldo Cruz Foundation, Rio de Janeiro, Brazil, were included in this study. Forty-one patients were diagnosed as borderline lepromatous (BL) and twenty-three were classified as polar lepromatous (LL) according to Ridley–Jopling classification.[16] The patients were grouped by length of treatment. Twenty-four patients were recently diagnosed and had received no treatment (NT) at the time of the study. Twenty-five patients were on multidrug therapy, ranging from 2 to 15 months (on treatment, OT). Fifteen patients had received monotherapy with dapsone from between 10 to 30 years (mean 16·6 years) and had terminated therapy from 1 to 6 years prior to participation in this study. Patients in this group, designated AT (after treatment) were without lesions and had negative lymph smears for acid-fast bacilli (AFB). None of the patients included in this study presented episodes of reaction during the study.

LEPROMIN SKIN TEST

Armadillo-derived lepromin (NHDC, Carville, USA, $3–4 \times 10^7$ bacilli/ml) was injected intradermally in the forearm and the reaction was measured 3 to 4 weeks after the injection (late lepromin reaction). Induration ≥ 3 mm was considered positive.

LYMPHOPROLIFERATION ASSAY

Heparinized blood was collected under sterile conditions from the patients and mononuclear leukocytes (PBL) were isolated by Ficoll–Hypaque gradient centrifugation. The cells were resuspended in RPMI 1640 (Gibco Lab.) supplemented with 10% human AB serum, 100 U/ml penicillin and 100 μg/ml streptomycin and 2 mM L-glutamine (complete medium). All proliferation assays were performed in microtitre wells in a final volume of 0·2 ml complete medium. Stimulation with antigen was carried out for 6 days at 37°C in a 5% CO_2 atmosphere. For these experiments, 2×10^5 PBL were incubated with 20 μg/ml *M. leprae*, or 25 μg/ml BCG in triplicate. One μCi per well of [^{3}H]thymidine (Amersham Co., specific activity 6·7 Ci/mM) was added 18 h before harvesting cells for measurement of radiolabelled thymidine incorporated into newly synthesized DNA. The results are expressed as stimulation index (SI) derived as the ratio of mean cpm cultures with antigen to the cpm of cultures without antigen. Proliferation to the antigen was considered positive for SI $\geq 3·0$.

ANTIGENS

M. leprae was kindly provided by Dr R. J. W. Rees (IMMLEP Bank, Mill Hill, England) and BCG was obtained from the Ataulfo de Paiva Foundation, Rio de Janeiro, Brazil.

STATISTICAL ANALYSIS

For comparison of the cellular immune response to *M. leprae* and BCG among the groups, Student's *t*-test and the Mann–Whitney test were used.

Results

LEPROMIN TEST

As expected, all the patients in NT and OT groups showed a negative lepromin skin test. In AT group, four patients developed a skin-test reaction; however, no correlation with the duration of treatment was noted (Table 1). Before the onset of treatment all patients in the AT group had negative skin tests (data not shown).

LYMPHOPROLIFERATION ASSAY

The number of *M. leprae* nonresponders was significantly lower in the AT group in comparison to that of the NT and OT patients ($p < 0{\cdot}05$). Of the AT patients 53·4% were unresponsive to *M. leprae* (SI < 3·0) (Figure 1). In contrast, 95·8% and 92% of the NT and OT patients, respectively, failed to respond to leprosy bacilli. There was no difference between the response of LL and BL patients in any of the groups studied. However, a significant difference was found between the mean SI of AT group as compared to the NT

Table 1. Particulars of the individuals of the after treatment lepromatous patients group

Name	Histopathology classification	Lepromin test†	In vitro test to *M. leprae* antigen	Time of treatment until became negative to bacilloscopy (years)	Time of total treatment (years)
RCN	BL	NEG.	POS.*	04	16
TSS	BL	2 mm	POS.*	20	25
PCP	BL	NEG.	POS.*	05	18
NAN	BL	NEG.	POS.*	08	13
AM	BL	NEG.	POS.	06	11
SBC	LL	NEG.	POS.*‡	10	16
CN	BL	NEG.	POS.*	08	14
MLB	BL	2 mm	NEG.	05	10
JLL	LL	NEG.	NEG.*	08	17
SSM	BL	NEG.	NEG.	10	17
SDR	BL	4 mm	NEG.	08	16
CA	BL	3 mm	NEG.	03	12
YST	LL	NEG.	NEG.	08	16
ASM	BL	NEG.	NEG.‡	05	18
SML	BL	NEG.	NEG.	20	30

* Presence of frequent episodes of erythema nodosum leprosum (ENL) during the time of treatment.

† All patients had a negative lepromin skin test at the beginning of treatment.

‡ Relapse of the disease with leprosy lesion compatible to the indeterminate form with AFB^+ in the skin biopsy.

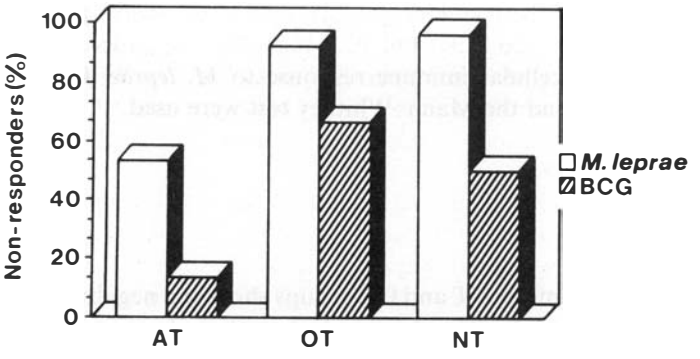

Figure 1. Relationship between treatment and response to *Mycobacterium leprae*. PBL from patients after treatment (AT) ($n=15$), on treatment (OT) ($n=25$), and untreated (NT) ($n=25$) were stimulated with *M. leprae* or BCG. Proliferation to antigen was considered negative for SI $<3{\cdot}0$.

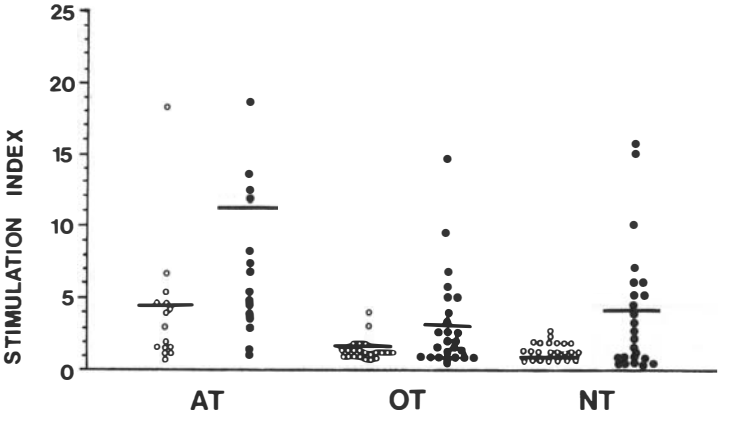

Figure 2. Proliferative responses of PBL from patients with lepromatous leprosy. Each point represents the SI of PBL from each patient and the bars represent the mean SI in each group, as described in the legend of Figure 1. A SI ≥ 3 was considered a positive response. There was a significant difference between the response to *Mycobacterium leprae* ($P<0{\cdot}05$) and BCG ($P<0{\cdot}02$), when the AT group was compared to NT and OT groups (Student's *t*-test).

and OT patients ($p<0{\cdot}05$). The AT group mean SI was 4·2 (ranging from 0·9 to 18·8) in comparison to mean SI of 1·5 (ranging from 0·5 to 3·0) in the NT group and 1·04 (ranging from 0·2 to 4·0) among the OT group (Figure 2). To determine whether the duration of treatment was correlated to the *M. leprae* response in the AT patients, we divided this group into responders and nonresponders. Among the 8 (53·3%) responder patients, the mean treatment time was $16{\cdot}2 \pm 4{\cdot}5$ years, while in the group that remained unresponsive, the mean duration of treatment was $17{\cdot}0 \pm 5{\cdot}0$ years. No statistical difference was observed between the nonresponder and responder patients with regard to the duration of treatment before their lymph smear became AFB negative ($8{\cdot}7 \pm 5{\cdot}3$ years for the responder patients *vs.* $8{\cdot}3 \pm 5{\cdot}2$ years for the nonresponders).

During the course of these studies, two *M. leprae* responsive patients from the AT group developed lesions clinically and histologically compatible with indeterminate leprosy, and rare AFB was seen in the skin biopsies (Table 1). With regard to reactional states, it is important to note that 7 patients (46·6%) of the AT group had erythema nodosum leprosum during their course of treatment. All but one showed a positive response to *M. leprae* in this study.

Stimulation with BCG, similarly, evoked a higher response in PBL from patients in the AT group as compared to the OT and NT groups ($p < 0{\cdot}02$). As shown in Figure 2, the mean SI for AT patients was 7·52 compared to 3·44 and 4·20 in the OT and NT patients. All patients showing a positive response to *M. leprae* (1 patient in the NT group, 2 patients in the OT group, and 7 patients in the AT group) were also responsive to BCG.

Discussion

The present study supports previous findings concerning the lack of cellular immune response to *M. leprae* in LL and BL patients. While the majority (80·7%) of the patients included in this study did not respond to *M. leprae* (SI < 3·0%), only 30% were unresponsive to BCG. However, when patients from the whole spectrum of leprosy were compared to household contacts, a good correlation was found between the response to *M. leprae* and BCG.[17]

When lepromatous patients were grouped by their treatment status, the percentage of *M. leprae* nonresponders was significantly lower among the long-term treated patients (AT) compared to untreated, newly diagnosed patients (NT) and the short-term treated (OT) patients. Likewise, the number of BCG responsive patients also increased after treatment. The number of responder patients was higher, and an intensified response was observed to both *M. leprae* and BCG as evaluated by the mean SI. This is another indication that the continuous presence of mycobacteria could contribute to the depression of the host's cellular immunity.

The improved immune response to BCG demonstrated that the unresponsiveness in lepromatous patients is not restricted to *M. leprae*. Reitan *et al.*[18] have, similarly, observed that PPD evokes a stronger reaction in PBL from treated patients as compared to the untreated leprosy patients. An improved response to mitogens in treated patients has also been reported.[19] The long-lasting unresponsiveness seen in almost half of the long-term treated patients might support the hypothesis which attributes the absence of responsiveness in LL patients to genetic factors,[20] absence of *M. leprae*-reactive T cells from the circulation[1] or the presence of suppressor mechanisms.[5,6] However, reversion of the unresponsiveness of lepromatous patients has been documented in many reports under different clinical and experimental conditions.[4,7,9,14,21]

The immune reactivity observed after chemotherapy suggests that the unresponsiveness in lepromatous patients might not be long lasting and unchangeable in all cases. The inability to kill and clear bacteria during the early phase of infection could result in a high antigenic load which may in turn induce a tolerant state. Recent studies have demonstrated that immune tolerance may develop in the presence of a high concentration of antigens[22] and this state may be reversed after decreasing the antigenic load.[23]

The fact that many of the *M. leprae* patients in the AT group had previously presented episodes of ENL during the course of treatment raises the hypothesis that *M. leprae*-

reactive T cells had emerged during the reactional stages.[24] Waldorf *et al.*[25] have reported similar findings using skin tests to assess immune responses in leprosy patients. Lepromatous patients with ENL showed higher positivity to DNCB sensitization as compared to patients without ENL.

Taken together, findings from the present investigation support the hypothesis that reduction in *M. leprae* post-therapy may contribute to the reversal of unresponsiveness in some lepromatous patients.

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References

[1] Godal T, Myklestad B, Samuel DR, Myrvang B. Characterization of the cellular immune defect in lepromatous leprosy: a specific lack of circulating *M. leprae* reactive lymphocytes. *Clin exp Imm*, 1971; **9:** 821–31.

[2] Haregewoin A, Godal T, Mustafa AS, Belehu A, Yemaneberhan Y. T-cell conditioned media reverse T-cell unresponsiveness in lepromatous leprosy. *Nature (Lond)*, 1983; **303:** 342–4.

[3] Haregewoin A, Longley J, Bjune G, Mustafa AS, Godal T. The role of interleukin-2 (IL-2) in the specific unresponsiveness of lepromatous leprosy to *Mycobacterium leprae* studies *in vitro* and *in vivo*. *Immunol Letters*, 1985; **11:** 249–52.

[4] Nogueira N, Kaplan G, Levy E, Sarno EN, Kushner P, Granelli-Piperno A, Vieira LMM, Gould VC, Lewis W, Steinman R, Yip YK, Cohn ZA. Defective interferon-gamma production in leprosy. Reversal with antigen and interleukin-2. *J exp Med*, 1983; **158:** 165–70.

[5] Sathish M, Bhutani LK, Sharma AK, Nath I. Monocyte-derived soluble suppressor factor(s) in patients with lepromatous leprosy. *Infect Immunol*, 1983; **42:** 890–9.

[6] Mehra V, Convit J, Rubinstein A, Bloom B. Activated suppressor T-cell in leprosy. *J Immunol*, 1982; **129:** 1946–51.

[7] Mohagheghpour N, Gelber RR, Engleman EG. T-cell defect in lepromatous leprosy is reversible *in vitro* in the absence of exogenous growth factors. *J Immunol*, 1987; **138:** 570–4.

[8] Myrvang B, Godal T, Ridley DS, Froland S, Song YK. Immune responsiveness to *Mycobacterium leprae* and other mycobacterial antigens throughout the clinical and histopathological spectrum of leprosy. *Clin exp Imm*, 1963; **14:** 541–53.

[9] Kaplan G, Weistein D, Steinman RM, Levis WR, Elvers U, Patarroyo ME, Cohn Z. An analysis of *in vitro* T-cell responsiveness in lepromatous leprosy. *J exp Med*, 1985; **162:** 917–29.

[10] Nath I, Curtis J, Sharma AK, Talwar GP. Circulating T-cell numbers and their mitogenic potential in leprosy-correlation with mycobacterial load. *Clin exp Imm*, 1977; **29:** 393–400.

[11] Mehra VL, Talwar GP, Balakrishnam K, Bhutani LK. Influence of chemotherapy and serum factors on the mitogenic response of peripheral leukocytes of leprosy patients to phytohaemagglutinin. *Clin exp Imm*, 1972; **12:** 205–13.

[12] Closs O, Reitan LJ, Negassi K, Harboe M, Belehu A. *In vitro* stimulation of lymphocytes in leprosy patients, healthy contacts of leprosy patients and subjects not exposed to leprosy. *Scand J Immunol*, 1982; **16:** 103–15.

[13] Tan Trao V, Huong PLT, Thuan AT, Long HT, Trach DD, Wrigth EP. Responses to *Mycobacterium leprae* by lymphocytes from new and old leprosy patients: role of exogenous lymphokines. *Ann Inst Pasteur Immunol*, 1988; **139:** 121–33.

[14] Cree IA, Smith WCS, Rees RJW, Swanson Beck J. The influence of antimycobacterial chemotherapy on delayed hypersensitivity skin-test reactions in leprosy patients. *Lepr Rev*, 1988; **59:** 145–51.

[15] Rao SSL, Stanley JNA, Kiran KU, Dharma Rao T, Rao PR, Pearson JMH. The effect of dapsone in high and normal dosage on the clinical and cell-mediated immune status of patients with borderline (BT–BL) leprosy. *Lepr Rev*, 1986; **57:** 19–26.

[16] Ridley DS, Jopling WH. Classification of leprosy according to immunity: a five group system. *Int J Lepr*, 1966; **34:** 255–73.

[17] Sarno EN, Espinosa M, Sampaio EP, Vieira LMM, Figueiredo AA, Miranda CF, Esquenazi D, Salgado JLF, Nogueira N. Immunological responsiveness to *M. leprae* and BCG antigen in 98 leprosy patients and their household contacts. *Braz J Med Biol Res*, 1988; **21:** 461–70.

[18] Reitan LJ, Closs O, Belehu A. *In vitro* lymphocyte stimulation in patients with lepromatous and borderline tuberculoid leprosy. The effect of dapsone treatment on the response to *Mycobacterium leprae* antigens. Tuberculin purified derivative and non-mycobacterial stimulants. *Int J Lepr*, 1982; **50:** 455–66.

[19] Prasad HK, Mishra RS, Nath I. Phenolic glycolipid-I of *Mycobacterium leprae* induces general suppression of *in vitro* concanavalin-A responses unrelated to leprosy type. *J exp Med*, 1987; **165:** 239–44.

[20] Prasad KVN, Mohamed All P. Some aspects in the epidemiology of leprosy. *Lepr Rev*, 1966; **38:** 49–56.

[21] Convit J, Aranzazu N, Ulrich M, Pinardi ME, Reyes O, Alvarado J. Immunotherapy with a mixture of *Mycobacterium leprae* and BCG in different forms of leprosy and in Mitsuda-negative contacts. *Int J Lepr*, 1982; **50:** 415–24.

[22] Feldmann M, Zanders ED, Lamb JR. Tolerance in T-cell clones. *Immunol Today*, 1985; **6**(2): 58–62.

[23] Morahan G, Allison J, Miller JFAP. Tolerance of Class I histocompatibility antigens expressed extrathymically. *Nature (Lond)*, 1989; **339:** 622–5.

[24] Laal S, Bhutani LK, Nath I. Natural emergence of antigen-reactive T-cells in lepromatous leprosy patients during erythema nodosum leprosum. *Infect Immunol*, 1985; **50:** 887–92.

[25] Waldorf D, Sheagren J, Trautman J, Block J. Impaired delayed hypersensitivity in patients with lepromatous leprosy. *Lancet*, 1966; **8:** 773–6.

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Epidemiological pattern of leprosy in Ethiopia: a review of the control programmes

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Summary Leprosy control started in a limited area of Ethiopia in 1956. Extended coverage of the country was achieved in the early seventies. Review of the data from the control projects since 1976 revealed that leprosy is a disease of the Ethiopian highlands where prevalence rates as high as 7 per thousand have been recorded in some provinces, while the cumulative national average for the last 13 years was 2·6 per thousand. The paucibacillary form was predominant. However, unlike other African countries, a relatively high proportion of multibacillary leprosy was found in Ethiopia. The male-to-female ratio was 2:1 with the highest prevalence in the 15–44 years age bracket. Detection rates for new cases have shown a gradual decline since 1982, a year before multiple drug therapy (MDT) was introduced into the country. For the last 5 years the number of new cases has stabilized at 4700/year. These trends probably reflect a general reduction in the prevalence of leprosy in the country, while the conspicuous decline in 1982 is most likely related to discharge of cases during screening before MDT. The new villagization policy of Ethiopia with its effective reorganization of the populations is believed to make control programmes and supervision of MDT easier and presumably more effective. Similarly, more reliable prevalence and incidence studies could be undertaken with success.

Introduction

Over 10 million people in the world are estimated to have leprosy. Only 50% are registered cases and of these, 12% are found in Africa. Ethiopia belongs to the endemic regions of the continent, with prevalence rates of 1·0–1·9.[1] Situated in the north-eastern part of the continent, Ethiopia covers an area of 1·25 million sq.km, and has a population of 46 million.[2] The topography of the country is dominated by the high central plateau (2000–

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3000 metres), which is split diagonally by the Rift Valley. In 1977 Cap & Banjaw[3] estimated that less than 50% of the leprosy patients in the endemic highland regions were registered for treatment. Thus, in Ethiopia, leprosy poses a major national public health problem with serious medicosocial consequences.

The data available on the prevalence of the disease are far from complete. Many rural parts of the country are not easily accessible, and lack basic medical services. In addition, because of social stigma and ostracism, those affected by the disease may fail to seek medical attention. However, in Ethiopia, compared with other infectious diseases leprosy has received significant attention from government and international agencies. Thus, there has been reliable registration of cases by leprosy control programmes that have been operational in the country since 1969.

This study was designed to review the epidemiology of the disease in Ethiopia, based on accumulated data from the control programmes. It is also intended to give some predictive forecast on the general trends in the prevalence of the disease as related to the leprosy control activities in the country.

Materials and methods

HISTORICAL BACKGROUND AND ORGANIZATION OF LEPROSY CONTROL PROGRAMMES

Organized leprosy treatment was started in 1934 at the Princess Zenebe Work Hospital, which was built on the outskirts of Addis Ababa by the Sudan Interior Mission (SIM), under the auspices of the Ethiopian Ministry of Health. This modest nucleus of leprosy care expanded over the years into a leprosy hospital with facilities for diagnosis and treatment, as well as a base for leprosy control activities. In the 1960s other smaller leprosaria were established in the northern, central and southern parts of the country, with emphasis on treatment and agricultural rehabilitation of the leprosy patients and their families.

A leprosy control programme was effectively started in 1956 with the policy of 'bringing leprosy treatment as near to the patient's home as possible'.[4] Accordingly, in estimated low and moderate prevalence areas (1–4 and 5–9 per thousand respectively), the treatment and follow-up of patients was carried out by the existing basic health services, supervised by the provincial medical officer with guidance and coordination from the National Leprosy Control Programme. In areas with high prevalence rates (10 per thousand), the basic medical service staff was supplemented by a specially trained leprosy health worker. In addition to his duties in the basic medical services, whenever possible the leprosy health worker is made responsible for three to five leprosy treatment centres situated in a market-place, not far from his post. The overall supervision and coordination of the control activities are under the provincial leprosy officer, who is attached to the Provincial Health Department.

In 1965, with international supporting agencies, the leprosy hospital in Addis Ababa was turned into the All Africa Leprosy and Rehabilitation Training Centre (ALERT), with the aim, 'to train men and women in all aspects of leprosy, with special emphasis on control, treatment and rehabilitation for work in Africa'.[5] As part of a national antileprosy campaign, and with the need for a model for training purposes, ALERT took up the leprosy control programme in Ethiopia's central administrative region of Shoa and Addis Ababa town.

All patients received monotherapy with dapsone until 1970, when the first cases of resistance were reported.[6] Subsequently, multiple drugs were used in the management of selected resistant cases. Multiple drug therapy (MDT), as recommended by WHO,[7] was officially adopted by the Ethiopian leprosy control programmes in 1983. In this study, the 13 years' records, since 1976, of the National and ALERT leprosy control programmes are reviewed. The Ethiopian Central Statistics Office provided the national census figures.

Results

The age and sex distribution of the leprosy patients, as shown in Table 1, is based on the records of the ALERT Leprosy Control Programme (1984–88). Ten per cent were under 15 years of age. The age group 15–44 was predominantly affected (70%). The male-to-female ratio was 2:1. This distribution is similar to that reported by Adamu & Naafs.[8]

Analysis of the diagnostic classification of leprosy over the last 5 years, using a modification of the Ridley–Jopling classification,[9] revealed borderline–tuberculoid leprosy to be the commonest (38·3%), followed by borderline–lepromatous leprosy (27·6%) (Table 1). In the classification of leprosy used by the leprosy control programmes in Ethiopia, the indeterminate (I) and borderline (BB) groups were not used. The age distribution of newly registered cases has remained relatively constant while the proportion of lepromatous patients has shown an increase over successive years since 1986 (Table 2).

Figures 1 and 2 show the detection rate of leprosy from the Shoa Administrative Region and the whole country respectively over the last 13 years. One sees a definite decline of detection rates starting in 1982. The decline forms a plateau over the last 5 years (Figure 2), at an average of 4700 new cases per year,[10] The number of new cases will

Table 1. Distribution of new leprosy cases by age, sex and classification in the Shoa Administrative Region (1984–88)

Age group (years)	TT		BT		BL		LL		Total					
	M	F	M	F	M	F	M	F	M	%	F	%	M+F	%
0–14	79	46	128	100	71	56	27	22	305	5·9	224	4·4	529	10·3
15–24	139	76	300	188	201	120	110	70	750	14·6	454	8·9	1204	23·5
25–34	129	87	264	169	256	132	144	85	793	15·5	473	9·2	1266	24·7
35–44	119	47	288	154	208	74	154	70	769	15·0	345	6·7	1114	21·7
45–54	73	32	155	62	128	51	73	39	429	8·4	184	3·6	613	11·9
55+	47	27	106	49	90	29	42	15	285	5·5	120	2·3	405	7·9
Total	586	315	1241	722	954	462	550	301	3331	64·9	1800	35·1	5131	100·0
%	11·4	6·1	24·2	14·1	18·6	9·0	10·7	5·9						
Total	901		1963		1416		851							
%	17·6		38·2		27·6		16·6							

Table 2. Yearly distribution of new leprosy cases by age and classification in Shoa Administrative Region (1984–88)

Age group (years)	1984						1985					
					Total						Total	
	TT	BT	BL	LL	No.	%	TT	BT	BL	LL	No.	%
0–14	35	35	25	17	112	9·3	23	30	22	9	84	9·5
15–24	91	68	57	47	263	21·9	39	98	40	30	207	23·5
25–34	82	57	83	49	271	22·6	43	82	75	51	251	28·4
35–44	80	75	63	65	283	23·6	29	65	48	43	185	21·0
45–54	50	32	38	31	151	12·6	22	27	28	17	94	10·7
55+	37	31	29	23	120	10·0	19	18	14	10	61	6·9
Total	375	298	295	232	1200	100·0	175	320	227	160	882	100·0
%	31·3	24·8	24·6	19·3	100	—	19·9	36·3	25·7	18·1	100·0	—

Age group (years)	1986						1987					
					Total						Total	
	TT	BT	BL	LL	No.	%	TT	BT	BL	LL	No.	%
0–14	26	61	21	11	119	11·8	19	48	23	6	96	9·5
15–24	35	101	57	28	221	22·0	27	110	80	36	253	25·0
25–34	37	85	62	38	222	22·1	32	117	78	45	272	26·9
35–44	36	93	50	36	215	21·4	12	98	58	36	204	20·2
45–54	14	58	39	17	128	12·7	8	57	37	22	124	12·2
55+	5	50	36	10	101	10·0	3	33	18	9	63	6·2
Total	153	448	265	140	1006	100·0	101	463	294	154	1012	100·0
%	15·2	44·5	26·3	13·9	99·9	—	10·0	45·8	29·0	15·2	100·0	

Age group (years)	1988					
					Total	
	TT	BT	BL	LL	No.	%
0–14	22	54	36	6	118	11·4
15–24	23	111	87	39	260	25·2
25–34	22	92	90	46	250	24·3
35–44	9	111	63	44	227	22·0
45–54	11	43	37	25	116	11·3
55+	10	23	22	5	60	5·8
Total	97	434	335	165	1031	100·0
%	9·4	42·1	32·5	16·0	100·0	

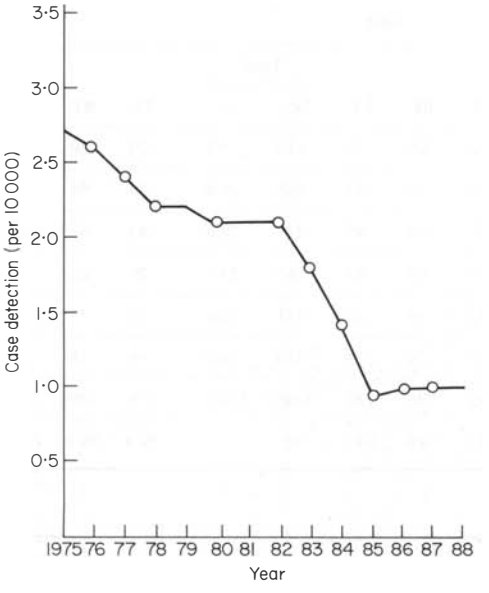

Figure 1. Leprosy case detection rate in Shoa Administrative Region, 1975–88. (*Source*: Annual Reports, ALERT Leprosy Control.)

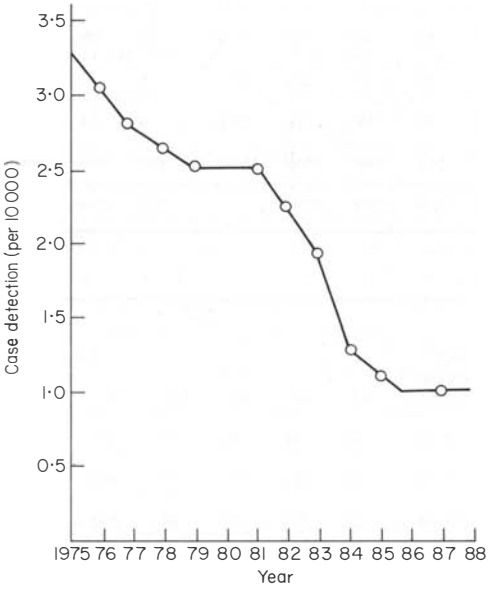

Figure 2. Leprosy case detection rate in Ethiopia, 1975–88. (*Source*: Annual Reports, National Leprosy Control Project.)

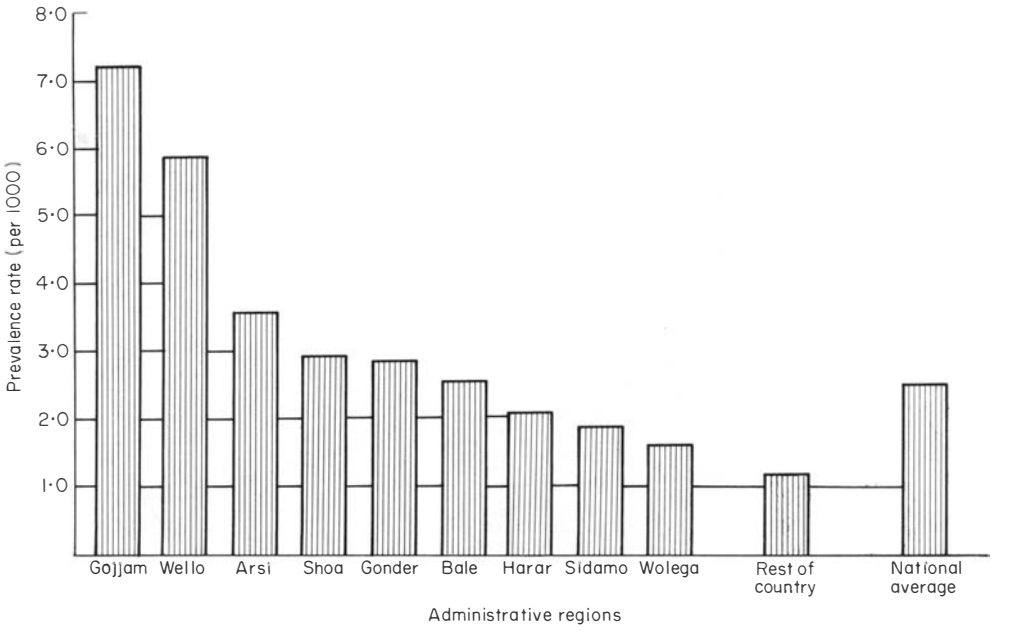

Figure 3. Prevalence rate of leprosy in the different administrative regions of Ethiopia. (*Source*: Annual Reports (1975–81), National Leprosy Control Project.)

probably remain at the same level for some years to come, until the real effect of multiple drug therapy is expected to halt the transmission of the disease.

Figure 3 represents the prevalence pattern in the different administrative regions, as compared to the national average of 2·6 per thousand over 6 years (1976–81) two years prior to the start of MDT. The prevalence of leprosy is highest in Gojjam and Wello (north-west and north-east of the country, respectively) while moderate rates are observed in Arsi, Shoa, Gonder and Bale (respectively of south, central, north and south-east Ethiopia). As shown in Figure 4, these hyperendemic and endemic areas occupy the highland regions of Ethiopia. The prevalence rates in the lowlands of the Rift Valley are very low, except in some densely populated areas (the districts of Yifat and Timuga, and Haikoch and Butajira) within the Shoa Administrative Region, where hyperendemicity (prevalence rates 1·5–7·8 per thousand) has been documented by the ALERT Leprosy Control programme in the years 1981 to 1986.[11]

Discussion

Epidemiological studies of leprosy have been very difficult to make for many reasons, particularly because leprosy patients are self-selected groups, not representative of the population as a whole.[12] Previous prevalence and incidence studies have used both physical examination and verbal recall in data collection and analysis. These methods have been criticized for bias and variability. Population-based studies to determine

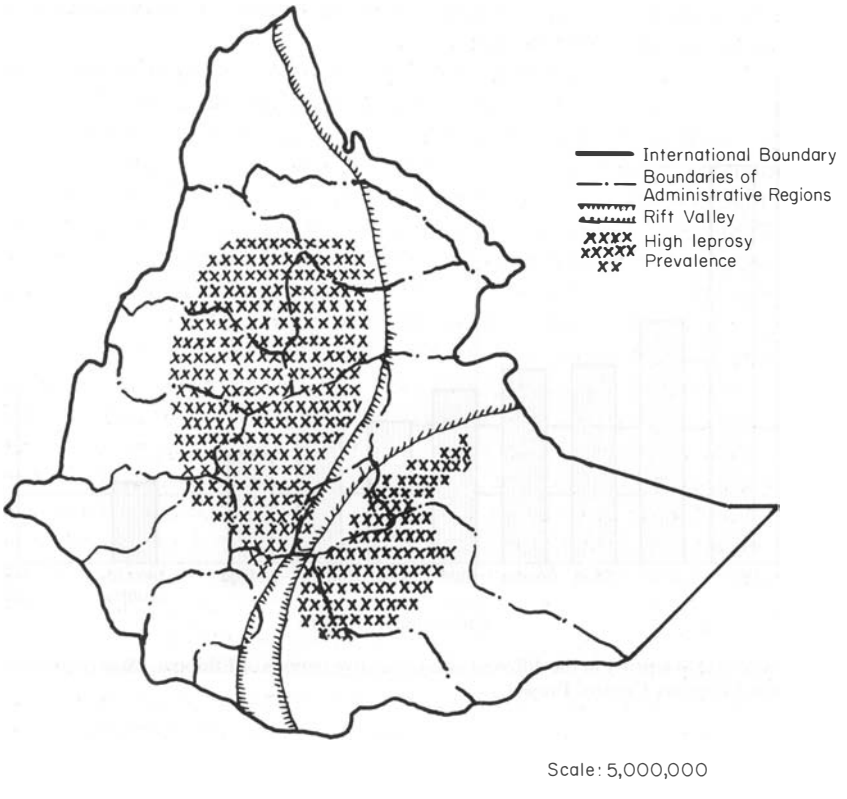

Figure 4. Ethiopia—showing areas of high leprosy prevalence corresponding to the highland regions of the country.

prevalence are very few and certainly not yet available for Ethiopia. We are therefore forced to rely on the information gathered by Control Projects.

Leprosy in Africa is characterized by a low proportion of lepromatous cases.[13] However, as shown in this study, there is a significantly high prevalence of the multibacillary form of leprosy in Ethiopia, sufficient to make the distribution different from the rest of Africa.

As observed by Schaller,[14] and later Cap & Banjaw,[3] this study clearly demonstrates that leprosy is endemic over the highland regions of the country, but also affects a few of the districts of the Shoa Administrative Region (central Ethiopia) which lie either bordering or within the Rift Valley.

One study[15] found a high prevalence of leprosy in the lowland Mendi district within the Blue Nile Valley of western Ethiopia. It suggested that the previous endemic leprosy situation in the highlands had been overshadowed by tuberculosis prevalence; nevertheless, there was an ongoing leprosy epidemic in the lowlands.

Except for these isolated endemic areas, for Ethiopia at large, leprosy is a disease of the highland regions. However, it is interesting that this geographical distribution is contrary to the findings of one study[16] in Malawi, which found a five-fold increase in the

prevalence rates of the Rift Valley compared with the Central African plateau. We have been unable to explain this obvious difference.

The gradual decline of the prevalence of leprosy as observed in this study, may be a welcome result of the effort of the well-organized control projects, mainly with dapsone monotherapy. However, among others, Meade[17] has argued that secondary prevention of leprosy, as practiced in the Ethiopian or Malawian Control Programmes, is unlikely to contribute much towards the ultimate eradication of leprosy. Nevertheless, we see a definite decline of leprosy prevalence in Ethiopia, as registered both by the National and ALERT Leprosy Control Programmes. Similar trends expressed in a significant reduction of prevalence rates have been observed in Thailand,[18] and Burma,[19] Ponnighaus & Boerrigter, who have also registered declines in detection rates in Malawi, believe that the trend may actually reflect a genuine decline in the incidence rates.[16] Although analysis of the 5 years data from the Shoa Administrative Region did not show an obvious shift towards older age groups, the increase in lepromatous rates over the last 3 years (1986–88) may reflect a decline in the incidence of leprosy in Ethiopia as suggested by Irgens.[20]

The conspicuous start of the decline in registered and new cases as well as in the prevalence of the disease in 1982 has attracted attention because it coincided with the launching of multiple drug therapy in the country. This was not definitely a direct effect of MDT, however, because MDT was effectively started only in 1983. However, as part of the preparations for the start of the MDT programme, there was a general reorganization and up-grading of the leprosy clinics in terms of diagnosis and treatment. The leprosy workers were re-educated and motivated. This, coupled with new awareness created in patients, resulted in release from treatment of many patients, particularly the paucibacillary patients who were found to have been adequately treated, provided the following criteria were met:

(a) the disease was clinically inactive and bacteriologically negative; and
(b) there was a cumulative attendance of 75% of 5 year's treatment of paucibacillary patients, and of 10 year's treatment of multibacillary patients.

One study[21] using a hypothetical mode, shows that there will be significant falls in prevalence rates in the first 5 years of the introduction of MDT into leprosy endemic districts, mainly as a result of discharge of cases during screening and due to shortening of duration of treatment. In his extensive editorial review of the common features in the decline of leprosy epidemics, Davey[22] pointed to the voluntary isolation of infective and potentially infective leprosy cases on dapsone treatment, and the creation of an atmosphere of mutual trust and cooperation between patients and those engaged in control programmes, with strong public health education, as the most essential elements of a successful policy of leprosy control. In this context, in present-day Ethiopia, much is to be gained from the recent introduction and active implementation of villagization programmes, in which previously scattered populations have been brought together in order to establish centralized services. This will certainly be most useful in the early detection of leprosy cases. With their well-organized and regimented administrative structures, these villages should make the diagnosis, treatment and follow-up of leprosy cases more efficient. Health education should also be easily propagated and much more effective.

It is therefore suggested that those in leprosy control work might exploit the good organization of the Peasant' Associations. An additional advantage of these organized

villages is the possibility of conducting prevalence and incidence studies with limited resources. Such studies should be both accurate and reliable, because they will be based on a stable and controlled population whose social and economical characteristics are well defined.

In spite of Ethiopia's other priorities for dealing with communicable diseases of higher prevalences, leprosy has gained recognition and an advantageous position, with relatively good financial resources for it's control activities. Working closely with the basic medical services and the Peasant Associations, an operationally efficient control programme, with active case detection and MDT, can achieve a further and more significant reduction in the prevalence of leprosy in the country.

References

WHO. *A Guide to leprosy control*. WHO; Geneva, 1988.

Ethiopia, Central Statistical Office. People's Democratic Republic of Ethiopia: Facts and figures. 1986.

[3] Cap JA, Banjaw M. *Leprosy in Ethiopia*. German Leprosy Relief Association (DAHW), Wurzburg II/West Germany, 1977.

[4] Price EW. *Leprosy control in Ethiopia—policy documents*. Addis Ababa, Ethiopia, 1977.

[5] Widad KM. Historical outline of ALERT. *Ethiop Med J*, 1986; **24:** Suppl. 1, 19–25.

[6] Pearson JMH, Haile GS, Barnetson R StC, Rees RJW. Dapsone-resistant leprosy in Ethiopia. *Lepr Rev*, 1979; **50:** 183–99.

WHO. *Chemotherapy of leprosy for control programmes*. WHO Technical Report Series No. 675, 1982.

Adamu A, Naafs B. The age at onset of overt leprosy among patients presenting at the Addis Ababa Leprosy Hospital. *Ethiop Med J*, 1982; **20:** 117–24.

[9] Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five-group system. *Int J Lepr*, 1966; **34:** 255–73.

[10] National Leprosy Control Project. Ministry of Health, Addis Ababa, Ethiopia. *Annual Report*, 1988.

[11] All Africa Leprosy and Rehabilitation Training Centre (ALERT). Leprosy Control Project, Addis Ababa, Ethiopia. *Annual Report*, 1987.

[12] Bryceson A, Pfaltzgraff RE. *Leprosy*. London: Churchill Livingstone, 1979, p 126.

[13] Cap JA. The epidemiological situation in Africa. *Lepr Rev*, 1981; **52:** Suppl 1, 53–60.

[14] Schaller KF, Kuls W. *Ethiopia. A Geomedical Monograph*. Springer Verlag: Berlin, Heidelberg and New York, 1972.

[15] Gundersen SG. Leprosy and tuberculosis in the Blue Nile valley of Western Ethiopia. *Lepr Rev*, 1987; **58,** 1–140.

[16] Ponnighaus JM, Boerrigter G. Ten years' leprosy work in Malawi (central Africa)—II. Patterns of endemicity since 1973. *Lepr Rev*, 1986; **57:** 221–36.

[17] Meade TW. Epidemiology and leprosy control. *Lepr Rev*, 1971; **42:** 14–25.

[18] Pakdi AC, Sanyolorn CK, Seal KS. Some results from sixteen years of leprosy control work in the Kohn Kaeh province of N.E. Thailand. *Lepr Rev*, 1974; **45:** 205–10.

[19] Kyaw L, Zuiderhoek B. Case detection rates for central Burma (1962–1972). *Int J Lepr*, **43:** 125–8.

[20] Irgens LM. Leprosy in Norway. *Lepr Rev*, 1980; **51:** Suppl 1, 1–130.

[21] Jesudasan K, Vijayakumaran P, Pannikar VK, Christian M. Impact of MDT on leprosy as measured by selective indicators. *Lepr Rev*, 1988; **59:** 215–23.

[22] Davey TF. Editorial: Common features in rapidly declining leprosy epidemics. *Lepr Rev*, 1975; **46:** 5–8.

Lepr Rev (1990) **61,** 267–272

Carvable silicone rubber prosthetic implant for atrophy of the first web in the hand

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Summary Muscular atrophy of the first web space in the hand is a common finding following ulnar nerve palsy and this deformity is very stigmatizing among leprosy patients in some countries and cultures.

We present our experience with the carvable soft-silicone rubber block implant to correct this deformity. We discuss the procedure, results and advantages over other techniques.

Fifteen operations were performed at the 'Lauro de Souza Lima' Research Institute, Bauru, Brazil during a period of six years. One complication was encountered due to an implant that was too large. The results were considered good in twelve instances and fair in three.

Introduction

Muscular atrophy of the first web space in leprosy is common following ulnar nerve palsy. The shallow aspect of this space is due to atrophy of the first dorsal interosseous and the adductor pollicis muscles (Figure 1).

From the social point of view and with some cultural differences, this deformity is one of the most stigmatizing signs among leprosy patients. In Brazil, we have seen that this deformity is considered by the public and the patients as one of the most stigmatizing deformities together with madarosis and megalobule.

Different surgical techniques have been described in order to restore fullness of the first web space and solve this aesthetic problem. We intend to discuss some of these surgical techniques and present our experience with a carvable silicone implant.

Materials and method

We operated on thirteen patients with leprosy and one with longstanding ulnar nerve damage secondary to trauma. The ages ranged from 21 to 67 years. Eleven patients were male and three female. Six were classified as lepromatous, seven as borderline and one as

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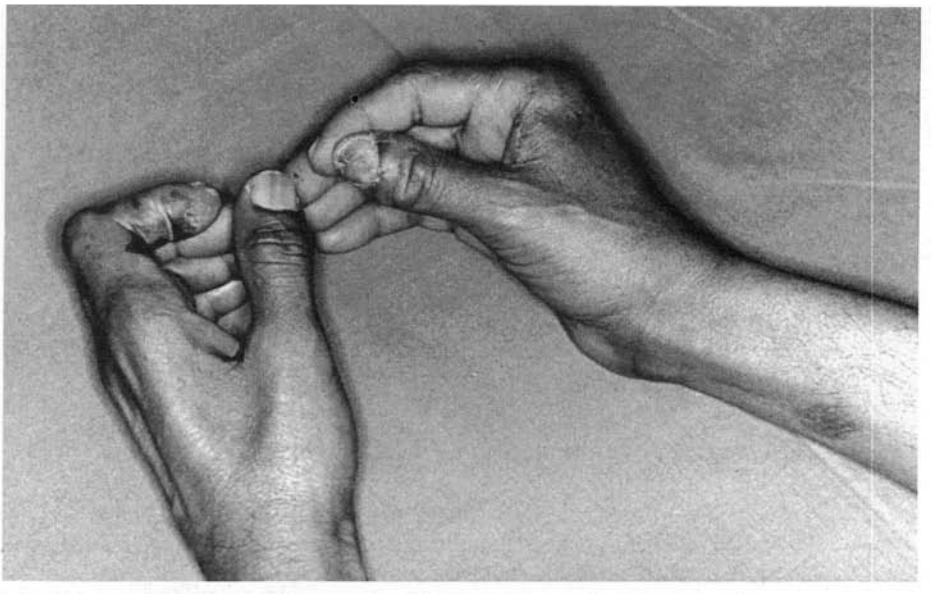

Figure 1. Marked atrophy of the first web space in the left hand. The right hand has been operated on with silicone implant.

tuberculoid. All leprosy patients were under regular treatment of dapsone or MDT for at least one year prior to the operation and any tendon transfer either for claw hand or lack of opposition were performed prior to the silicone implant. The total number of hands operated on was 15.

SURGICAL PROCEDURE

Local anesthesia was used in all cases. A 2-cm incision was made along the first web following the interdigital line and close to the index finger. A pocket was created through this incision by blunt dissection between the paralysed fibres of the adductor pollicis and the first dorsal interosseous preserving both fasciae. Having estimated the pocket size, a silicone piece was cut from a soft silicone block (Silastic Dow Corning) and was carefully carved with fine and sharp scissors. We used two basic designs—fusiform and elliptical (Figure 2). After thoroughly rinsing the carved piece and the pocket with saline solution, the prothesis was introduced (Figure 3). Two or three fine nylon sutures were used to close the deep fascia, closing securely the pocket. The skin was then closed with interrupted 6/0 nylon stitches. A plaster cast was applied and two weeks later all dressings and sutures were removed.

Results

We used two parameters to evaluate the results: preoperative and postoperative abduction angle and preoperative and postoperative cosmetic appearance. A goniometer

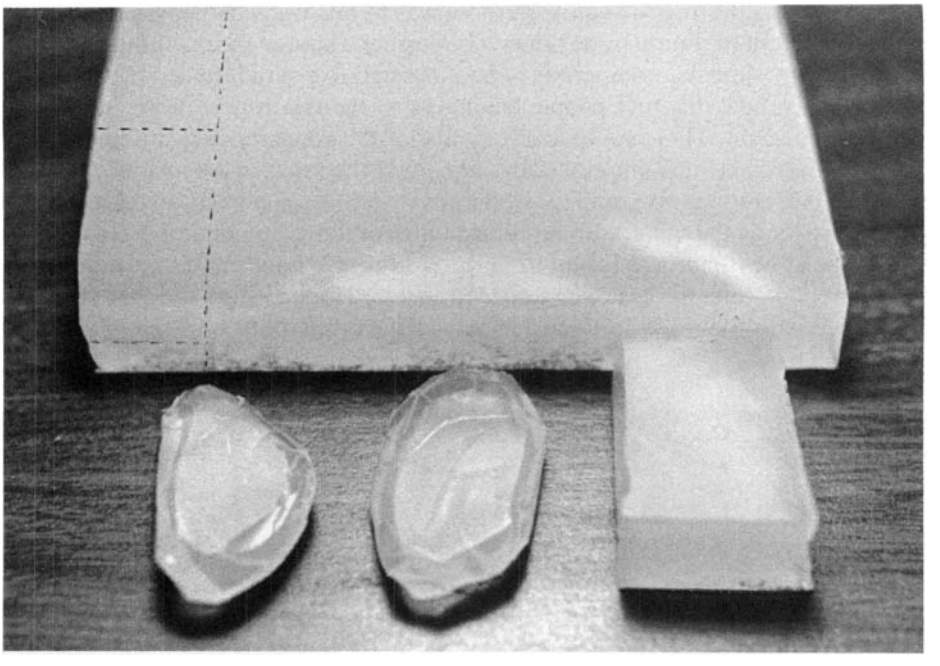

Figure 2. Soft silicone-rubber block, the dotted lines indicate primary cuts. For small hands each piece can be divided into two halves. Two basic designs are used: fusiform and elliptical, seen on the left-hand side).

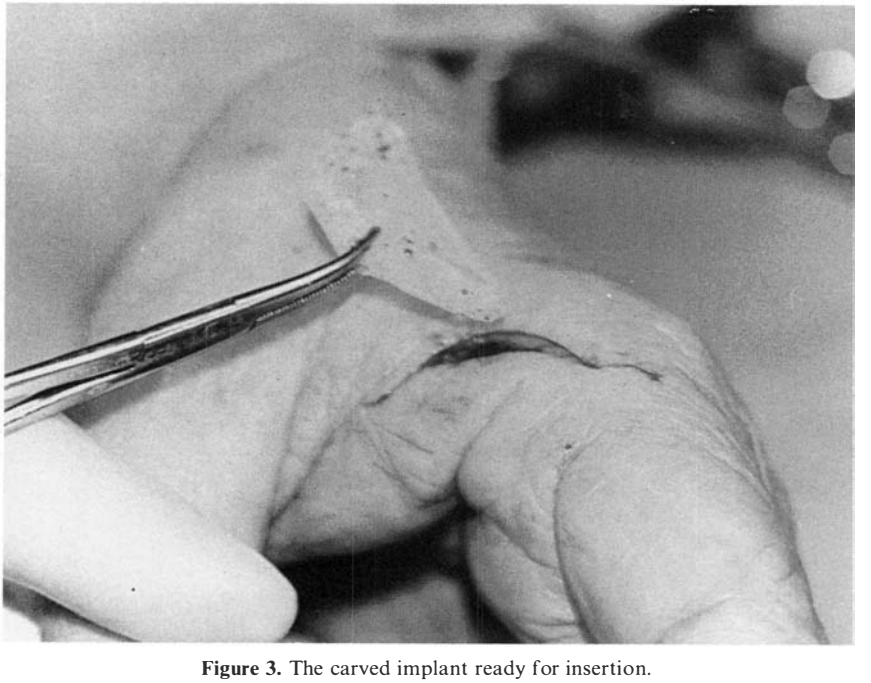

Figure 3. The carved implant ready for insertion.

was used to obtain the angles and the purpose was to find out whether the implant could create any problem to thumb opposition. The cosmetic appearance, although subjective, was evaluated by showing preoperative and postoperative standardized black and white photographs to three different people belonging to the Institute staff but not from the Surgical Department. They had to answer whether the appearance had improved (good result), not improved substantially (fair), remained the same or was worse (poor). The analysis of the preoperative and postoperative abduction angles revealed that they remained essentially the same, with no contractures or limitation of motion to the thumb. The cosmetic appearance was found to be good in twelve hands and fair in three by the independent observers. No case was recorded as poor (Figures 4(a) and (b)). All patients were satisfied with the result in their own subjective evaluation.

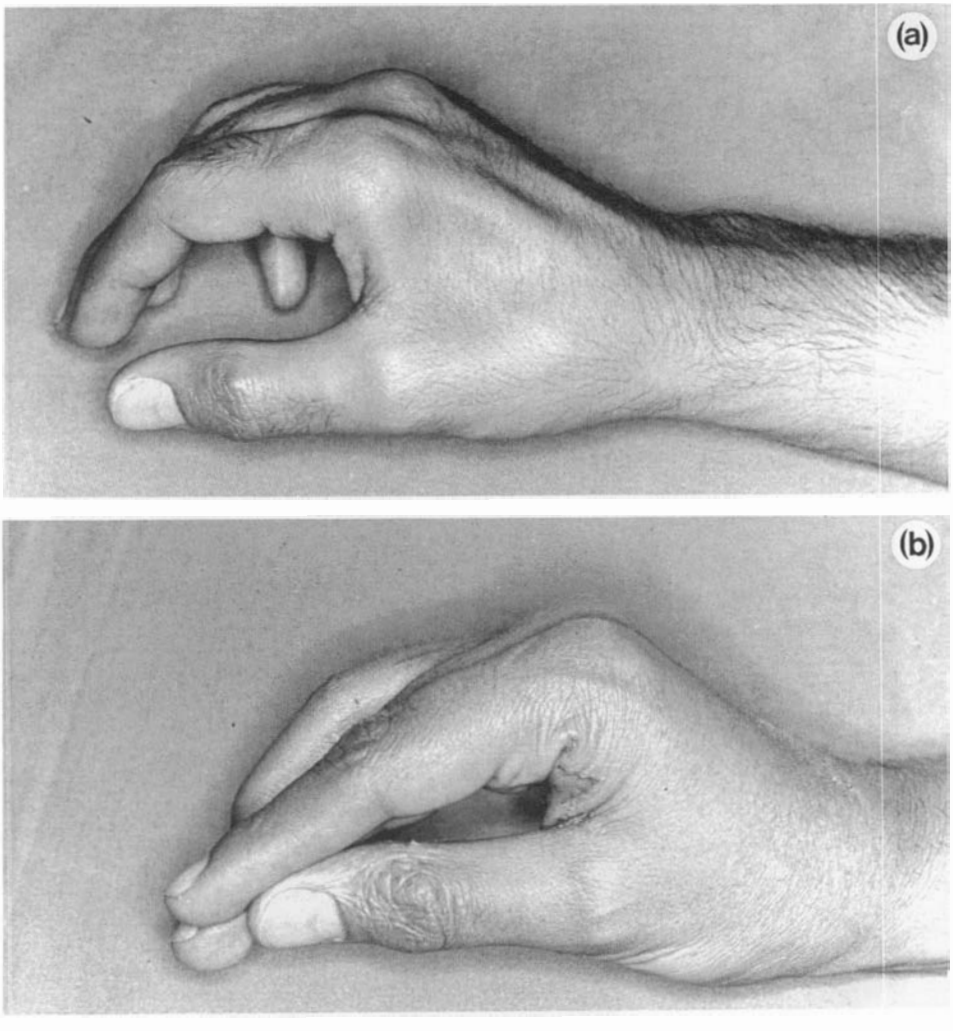

Figure 4. Preoperative and postoperative views.

Discussion

The most evident wasting or atrophy in the hand is the atrophy of the first web secondary to ulnar nerve palsy and in endemic countries there is a close association of this deformity with leprosy.

A variety of techniques have been described to correct this atrophy both with autogenous and alloplastic materials. In the autogenous tissue group, fat grafts have been used but they are likely to loose up to one half of their original bulk. Dermal or dermal-fat grafts are probably the most useful autogenous grafts[1,3] although they present similar problems. Fascia lata grafts have been used[3] but these also scar down, retract and lose their bulk.

Concerning alloplastic materials the most suitable is medical silicone. The use of silicone gel injection is definitely not recommended due to many serious complications that have been described.[5,6] The use of silicone gel contained in a bag, like the testicular implant,[4] would seem to be the most feasible because it mimics exactly the tissue consistency of the first web, although the three sizes available for these implants are too large for most hands and also the cost of each one is very high. We have used custom made gel bag implants but the cost is also too high for leprosy patients, usually living in developing countries.

The soft carvable silicone block (Silastic Dow Corning) has a consistency slightly

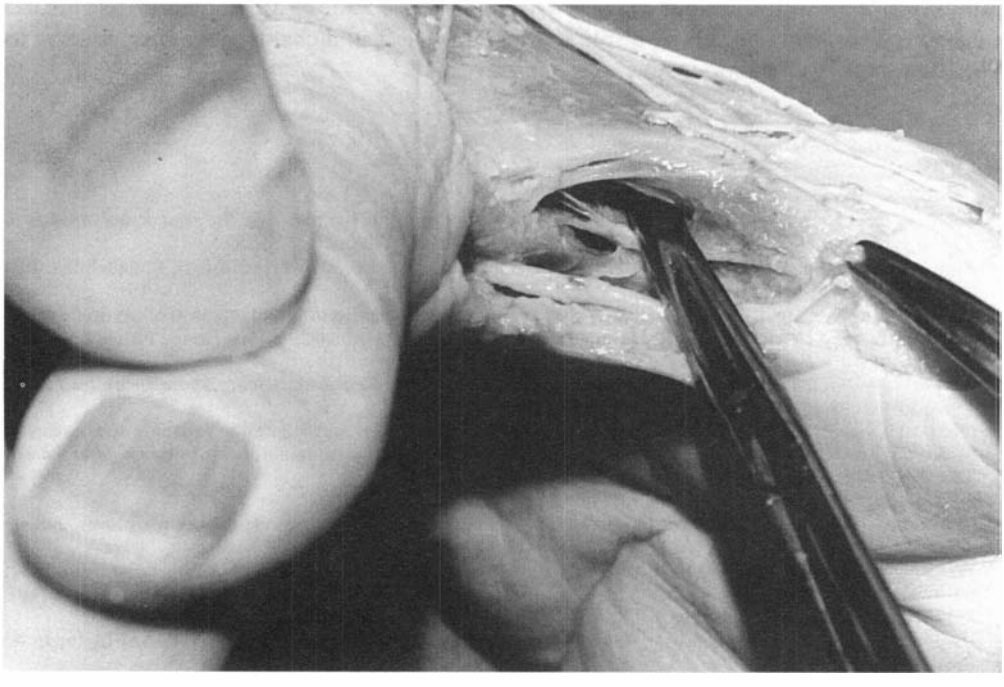

Figure 5. Anatomical dissection demonstrating the pocket between first dorsal interosseous and adductor pollicis.

harder than the normal muscle tissues in the first web but it is easy to carve and economic since we can produce an implant with a cost of less than US$ 10.00 each.

Most complications related to medical silicone are related to the use of injectable gel[5,6] or to silicone implants in joints where they are subjected to extreme wear and tear, causing particles to be freed which can get into limphatic or venous circulation.[7–9] The incidence of complications is really very small considering the thousands of implants that have been used over the years. However, we plan to keep a close follow-up study of our patients over the next years.

The use of silicone rubber carved implants in leprosy patients was described in 1967 by Reginato[10] but we believe that the newer soft silicone blocks give a more natural feel and that the exact place of implantation must be the space between the first dorsal interosseous and the adductor pollicis. This gives a good tissue cushion on both sides to protect the implant from trauma and avoid extrusion (Figure 5).

COMPLICATIONS

In our series we had one complication. A patient had a partial extrusion from the pocket because the implant was too large. This was solved by reshaping it to a smaller size and adequate closure of the pocket. The final result was good.

Conclusions

Analysing the results obtained and the aspects discussed above, we conclude that the use of a carved soft silicone rubber implant is a simple, safe and cheap procedure, leading to very satisfactory cosmetic results.

References

[1] Johnson HA. Dermal grafts for post-leprosy muscular wasting in the hand. In *Surgical Rehabilitation in Leprosy*. McDowell F, Enna GD (eds) Baltimore: Williams & Wilkins, p 273, 1974.

[2] Peer LA. *Transplantation of fat in Reconstructive and Plastic Surgery*. Converse JM (ed), Philadelphia: WB Saunders & Company, p 109, 1969.

[3] Reginato LE, Homem de Mello P, Belda W. Ensaio da Correcao das deformidades amiotroficas do dorso da mao por un novo metodo: Enxertos Dermicos e Retalhos Dermogordurosos e Enxertos de Fascia Lata. *Rev Lat Amer Cirurg Plast*, 1966; **10:** 78.

[4] Zacharia AG, Gelber RN. Silastic implant of the first dorsal interosseous space (correspondence). *Int J Lepr*, 1985; **53**(4): 643.

[5] Okano Y, Nishikai M, Sato A. Scleroderma, primary biliary cirrhosis and Sjogren's syndrome after cosmetic breast augmentation with silicone injection: a case report of possible human adjuvant disease. *Ann Rheum Diseases*, 1984; **43:** 520.

[6] Silicone pneumonitis (editorial). *Lancet* Oct. 1983: 833.

[7] Gordon M, Bullough PG. Synovial and osseous inflammation in failed silicone-rubber prosthesis. *J Bone Joint Surg*, 1982; **64-A,** No. 4: 574.

[8] Worsing RA, Engber WD, Lange TA. Reactive synovitis from particulate silastic. *J Bone Joint Surg*, 1982; **64-A,** No. 4: 581.

[9] Smith RJ, Atkinson MD, Jupiter JB. Silicone synovitis of the wrist. *J Hand Surg*, 1985; **10A:** 47.

[10] Reginato LE, Belda W. Correcao das Deformidades Amiotroficas do Dorso da Mao pelo Uso de Inclusoes de Silicone Liquido e Solido. *Rev Brasil de Leprologia*, 1967; **35:** Dec.

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New cases of leprosy in the Cross River Region, Nigeria

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Summary Rates of leprosy cases newly reporting during 1986 are examined for a region of south-eastern Nigeria. Figures reveal that in the part of the region which was designated in 1987 as a new state, half of the administrative units had new case reporting rates higher than in adjacent areas, while the other half had very few cases reporting in 1986. Possible explanations are offered and the implications of the pattern for leprosy control in the new state are examined.

The Region

The Cross River Region was one of the nineteen states of the Federation of Nigeria until 1987, and was known as Cross River State. In September 1987 it was carved into two states, the larger northern and eastern portion retained the name of Cross River State, and the smaller but much more populous southern and western portion (locally known as the 'Mainland') became Akwa Ibom State, (Figure 1). Until the Civil (Biafran) War in 1967, it was part of the Eastern Region of Nigeria which had been important in the world of leprosy research and control for forty years. The leprosy hospitals at Itu and Uzuakoli were known beyond Nigeria for the pioneering work conducted there by leprologists of international repute.

The region lies between latitudes 4°N and 7°N. The southern one third, which includes the whole of the new state, lies below 100 metres in altitude. Akampka Local Government Area (LGA) in the east includes the Oban Hills which rise to 1070 metres, and in the extreme north-east the Obudu Plateau rises to 1841 metres. All areas of the region are cultivable and habitable. Annual rainfall in the south is 3500 millimetres; it decreases northwards but there are no water shortage problems. Population densities vary greatly, with the highest densities in the south throughout the new state, but with areas of scattered and sparse population in the north, which is thought to have suffered disruption and depopulation during the period of the Atlantic slave trade.

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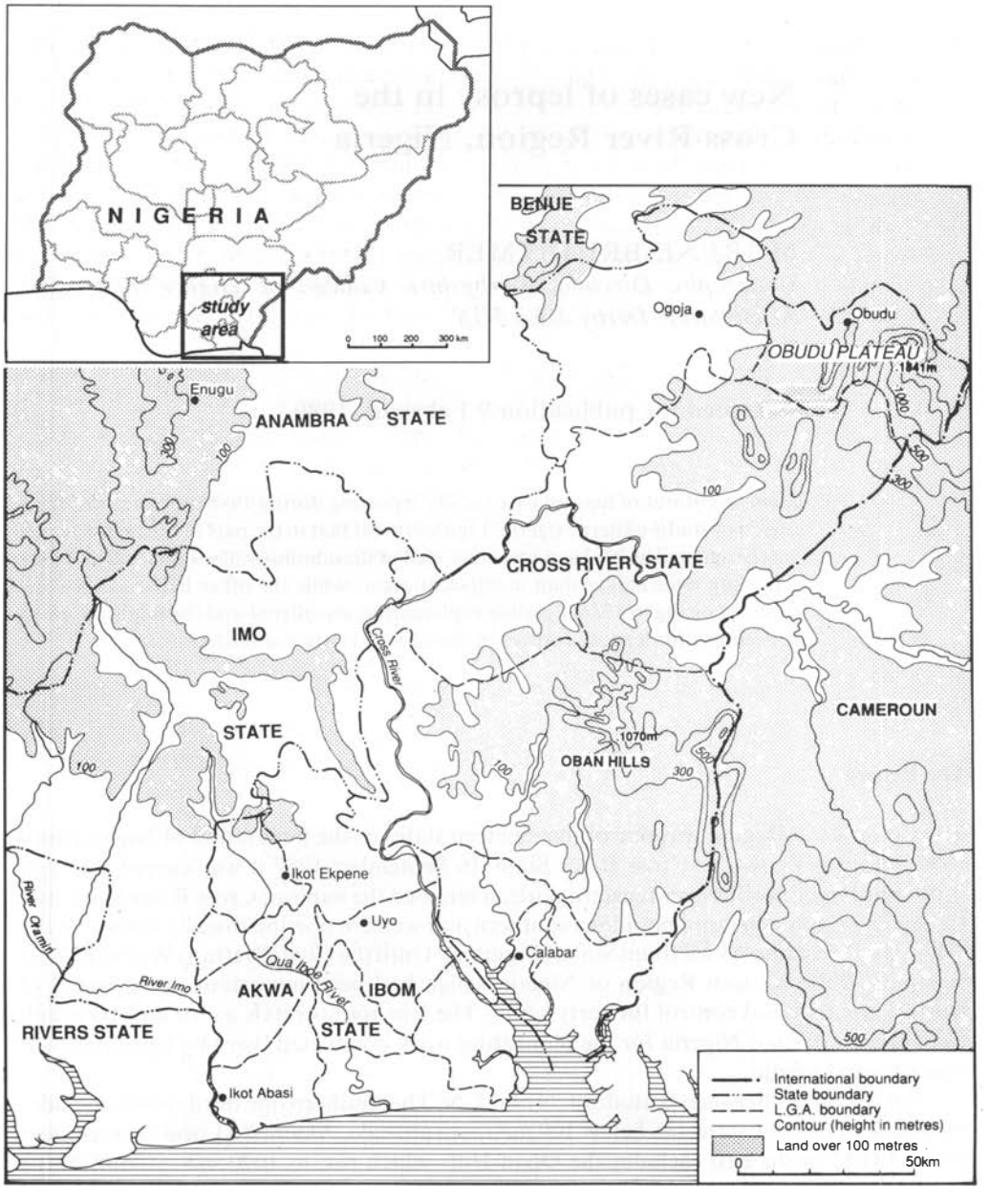

Figure 1. South-eastern Nigeria.

Leprosy control

Two specialist leprosy hospitals are located in the Cross River Region at Etinan and Ogoja. (Uzuakoli lies outside the region in the neighbouring state of Imo, and the leprosy hospital at Itu lies in ruins since the Civil War.) They provide surgery and treatment of complications for inpatients, as well as diagnosis and chemotherapy for outpatients. Outpatient diagnosis and chemotherapy is also provided at 223 leprosy clinics throughout the region, usually held monthly, and from where complications are referred to the hospitals. Periodic visits are made to some of the clinics by the hospital doctors. By 1986 the WHO (1982) recommended multidrug therapy (MDT) was in limited use in the region. It had been used selectively at the leprosy hospital in Etinan in the south since 1984, and in 1986 implementation began in the north of the state in Ikom, Obudu and Ogoja LGAs.

Leprosy rates in the Cross River Region in 1986, i.e. the original Cross River State), are examined here using the local clinic and hospital registers. 'Registered cases' refers to cases which had already been diagnosed with active leprosy prior to 1986, were still receiving chemotherapy and recorded on treatment registers. (In 1959, 3000 untreated cases of leprosy were found when 536,256 people were examined in this and the adjacent region during routine yaws surveys.[2]) It has been estimated that registered cases in this part of Nigeria represent only one half the true number,[1] as the stigmatization of leprosy

Table 1. Cross River Region. Leprosy by local government area 1986. Population density and rates of registered active leprosy cases on chemotherapy

LGA	Pop. (1000s)	Pop. dens. km^2	Dens. rank	Reg. lep. patients	Lep. rate per 1000	Lep. rank
Abak	325	630	5	120	0·37	10
Akamkpa	190	28	17	266	1·4	4
Calabar Mun.	188	563	6	126	0·67	7
Eket	580	781	2	53	0·09	17
Etinan	473	901	1	495*	1·05	5
Ikom	200	37	16	1285	6·43	2
Ikono	324	463	10	82	0·25	14
Ikot Abasi	419	530	8	128	0·31	12
Ikot Ekpene	438	679	3	128	0·29	13
Itu	273	458	11	99	0·36	11
Obubra	420	201	12	417	0·99	6
Obudu	130	82	15	764	5·88	3
Odukpani	224	132	13	91	0·41	9
Ogoja	313	89	14	2674	8·54	1
Oron	551	540	7	120	0·22	15
Ukanafun	390	491	9	163	0·42	8
Uyo	607	664	4	119	0·20	16
Total	6045	211 (mean)		7130	1·18 (mean)	

* Figures for Etinan are inflated by cases reported to the Etinan Leprosy Hospital from other LGAs and from outside the region.

patients especially in the south of Cross River, discourages reporting of cases. 'New cases' refers to cases newly diagnosed in 1986 and never treated before. Almost all leprosy cases in the region were self-reporting. There were no mass surveys nowadays as previously, nor even systematic contact-tracing. It is unlikely that there are variations between LGAs in the degree of reliability in the clinical diagnosis of leprosy.

RATES OF REGISTERED CASES

I have previously examined the pattern of registered leprosy cases for the region using the 1984 figures and compared the rates with the population distribution.[3] The pattern corresponded with that of other observers who have remarked on the apparent association in tropical Africa of areas of higher leprosy rates coinciding with areas of sparser population density.[4] The same pattern of an apparent association occurs in 1986 using the figures of already registered cases (Table 1). However, an association noted elsewhere between low leprosy rates and higher altitude does not occur in the region. The highest leprosy rates per thousand people in Cross River are in Obudu which is the area of highest land.

DISTRIBUTION PATTERN OF CASES NEWLY REPORTING IN 1986

However, a more complex pattern emerges when new cases reporting in 1986 are examined (Table 2 and Figure 2). The mean new case rate for the whole region in 1986 is 0·79 per 10,000, ranging from a low of 0·07 in Oron in the extreme south, to a high of 6·23

Table 2. Cross River Region. Leprosy by local government area 1986. New case rates

LGA	New cases	New cases per 10,000	Rank
Abak	23	0·71	6
Akamkpa	5	0·26	11
Calabar	12	0·64	7=
Eket	6	0·10	15
Etinan	4	0·08	16
Ikom	78	3·90	2
Ikono	18	0·56	9
Ikot Abasi	9	0·21	12=
Ikot Ekpene	28	0·64	7=
Itu	14	0·51	10
Obubra	35	0·83	5
Obudu	81	6·23	1
Odukpani	3	0·13	14
Ogoja	104	3·32	3
Oron	4	0·07	17
Ukanafun	38	0·97	4
Uyo	13	0·21	12=
Total	475	0·79 (mean)	

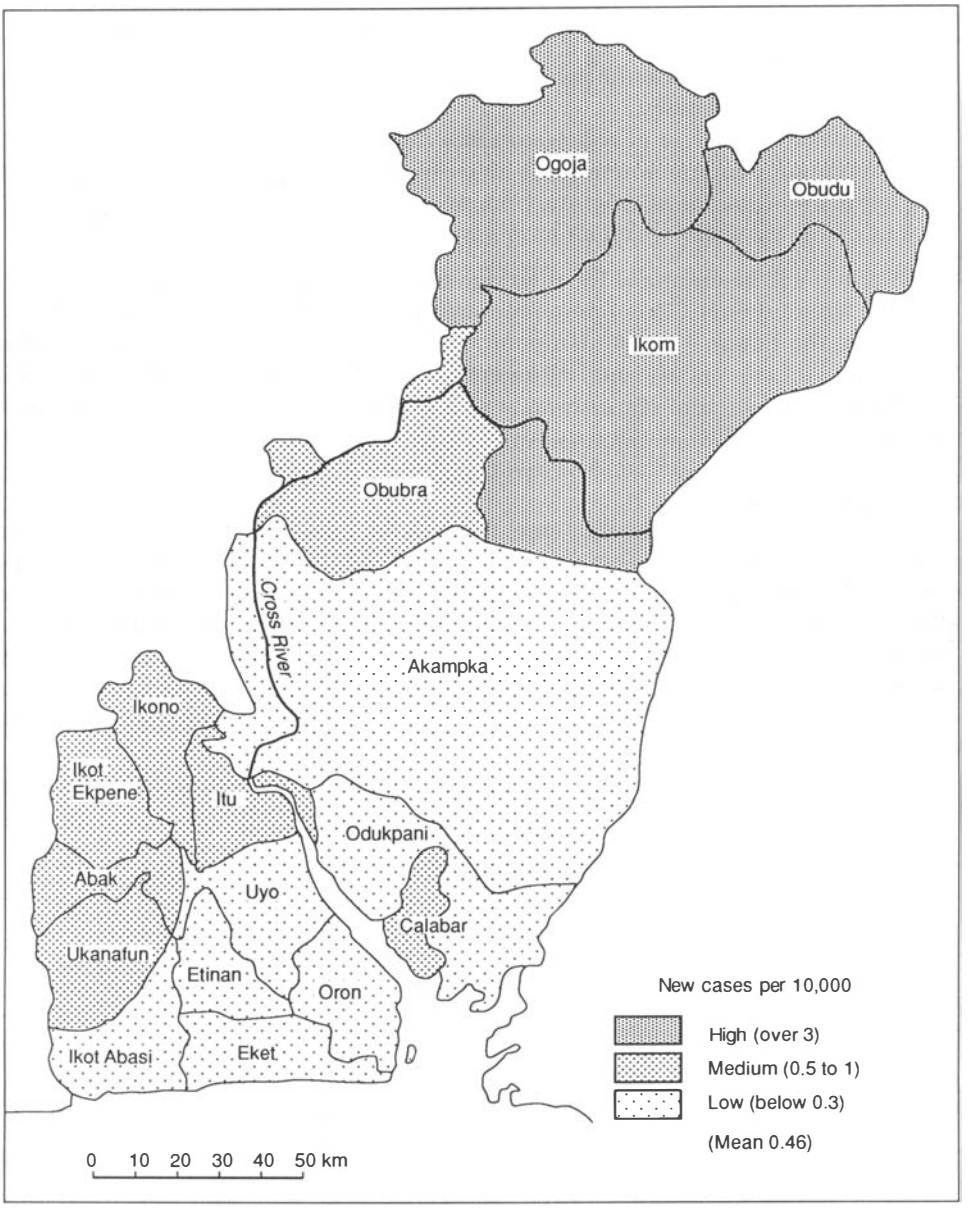

Figure 2. Cross River Region, Nigeria. Leprosy cases newly reported in 1986.

in Obudu in the extreme north. Another two LGAs are well above the mean, seven are around the mean and the rest are well below the mean.

The ten LGAs with a new case rate above and around the mean fall into four categories:

Ogoja, Obudu and Ikom in the north, which also have much higher than average rates of already registered cases;
2 Obubra which has a rate of registered cases close to the mean;
3 Calabar the state capital, where numbers are higher because cases report from outside the locality wishing for anonymity, because of the fear of ostracism; and
4 five LGAs in the south which all have very low rates of registered cases.

The last group will be examined for their significance for leprosy control.

For the ten southern LGAs of the whole region, in the 'Mainland', i.e. the new state of Akwa Ibom, the Etinan Leprosy Hospital registers and local clinic returns have been examined, and the cases newly reported and registered in 1986 are identified by their LGA of *residence* (rather than of registration, which is how Ministry statistics are recorded, thus inflating figures where the leprosy hospitals are located, as noted in Table 1). The new case rates are tabulated (Table 3) and mapped (Figure 3) separately from the rest of the Cross River Region.

The number of confirmed leprosy cases from the Mainland reporting for the first time in 1986 either to local clinics or the leprosy hospital was 157, a mean rate of 0·358 per 10,000, about half that for the whole of the Cross River Region, whereas the rate of registered cases for the Mainland was less than one third of the rate for the whole region, i.e. 0·34 compared with 1·18 per 1000. New case rates per 10,000 for individual LGAs varied from 0·08 in Etinan to 0·97 in Ukanafun. The five LGAs with highest rates have only 40% of the population of the new state but have 77% of the cases newly reporting in 1986.

Forty-five of the new cases in the Mainland reported to the leprosy hospital, where

Table 3. Cross River Region Mainland Area. Leprosy 1986 by local government area. Population and new cases, actual and expected

LGA	Pop (1000s)	% Total pop.	Actual new cases	Expected* new cases	Ratio actual to expected
Abak	325	7·44	23	11·60	1·98
Eket	580	13·24	6	20·65	0·29
Etinan	473	10·80	4	16·85	0·24
Ikono	324	7·40	18	11·54	1·56
Ikot Abasi	419	9·57	9	14·93	0·60
Ikot Ekpene	438	10·00	28	15·60	1·79
Itu	273	6·23	14	9·72	1·44
Oron	551	12·58	4	19·62	0·20
Ukanafun	390	8·90	38	13·88	2·74
Uyo	607	13·86	13	21·62	0·60
Total	4380	157			

* Number of cases expected if all the local government areas had the same new case rate per 1000 population.

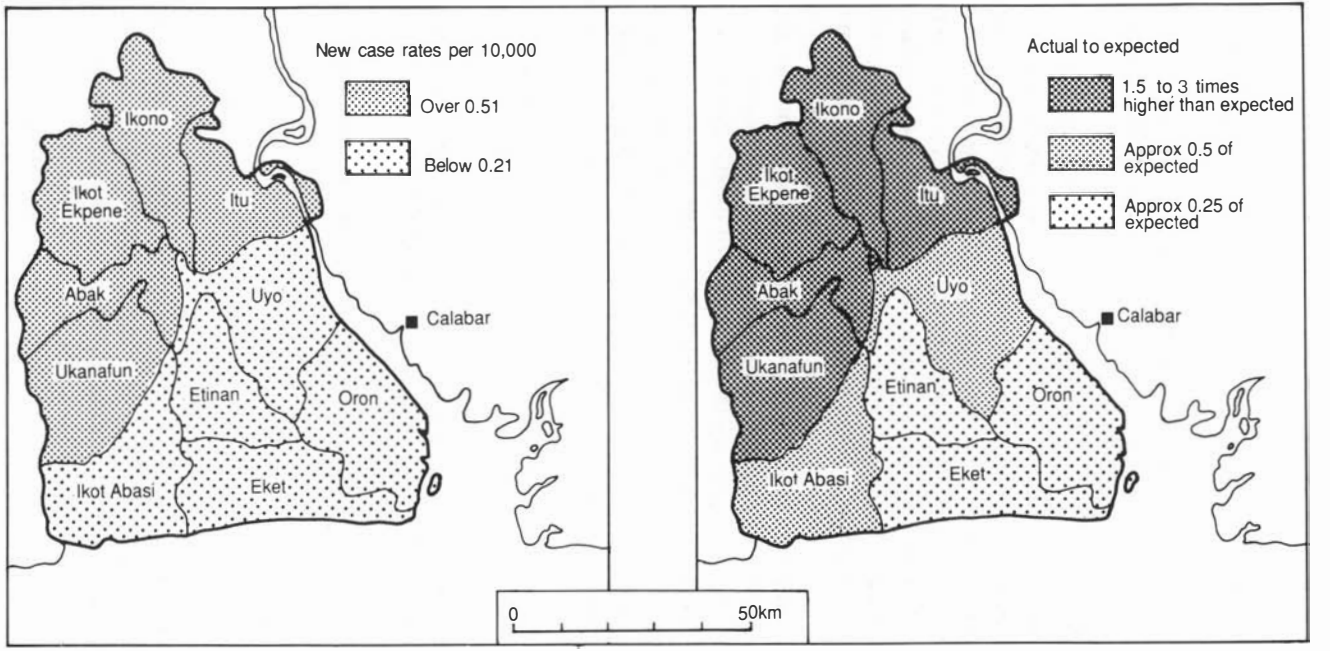

Figure 3. Cross River Region, Mainland Area. New leprosy cases in 1986.

classification records show that approximately one third (16 cases) were multibacillary, one of whom was under fifteen years of age. Two thirds (29 cases) were paucibacillary and eight of these were under fifteen years of age.

Discussion

Although leprosy rates overall were fairly low in the Cross River Region in 1986, there was a pattern of locally high rates of leprosy, with contrasts between rates of registered cases and rates of new cases.

The higher new case rates in the north and west of the new state area where existing registered rates are low, require special comment. The stigmatization of the disease especially by the Annang people who occupy most of the area may be one contributing factor; fieldwork has shown there is less stigmatization among the other main ethnic group of the Mainland. The effect of the disruption of leprosy control services during the Civil War (1967–70) should not be underestimated. These LGAs (excluding Itu) bordered the Ibo heartland of Biafra, and the formerly well-organized clinic system collapsed here in the early months of the conflict. There were also large-scale and frequent movements of refugees into and out of the area throughout the war, under conditions favourable for the transmission of disease. The famous leprosy hospital at Itu was bombed and thousands of patients dispersed, many never re-appearing anywhere for treatment.

Fieldworkers are believed to be reliable in respect of diagnosis and it is reasonable to assume that the figures represent true differences between leprosy rates within the new state area rather than variations in the certainty of the clinical diagnosis. The forty-five new cases which reported directly to the leprosy hospital were diagnosed by the experienced leprologist. That same leprologist made several visits during the year to clinics in Abak, Ikot Ekpene, Itu and Ukanafun, because of the frequency of cases from here reporting to the hospital, and confirmed the clinic diagnoses. The much higher than expected number of new cases in Ukanafun reflects a revival of leprosy control work there during 1985 and 1986; the newly reported cases in 1986 represent a backlog of untreated cases. This revival was initiated by the leprologist as a response to the number of leprosy cases from that LGA taking the trouble and expense to report to the Etinan Leprosy Hospital. There is every reason to believe that a similar backlog may exist in Ikono where leprosy control has lapsed in recent years and from where new patients also travel to the Etinan Leprosy Hospital.

Recommendations

The pattern revealed suggests that for effective leprosy control in the new state priority needs to be given to the five northern and western LGAs, where a greater number of previously untreated cases were reporting in 1986, and where more than one third were diagnosed as multibacillary. Although a few cases report each year from the other 5 LGAs, the low numbers of the previous years support the 1986 figures in suggesting that leprosy has almost disappeared, at least from Eket, Etinan and Oron.

Any new action against leprosy which the Akwa Ibom Ministry of Health might wish to take should begin in the north and west, and include the following priorities:

1 contract tracing, especially of all registered multibacillary cases;
2 the appointment and training of additional field staff for rural clinics, especially in the five northern and western LGAs;
3 the widespread implementation of MDT, based upon a guaranteed regular supply of drugs; and
4 a programme of health education, especially in the schools and communities of the LGAs with the highest rates of leprosy. This should emphasize the curability of leprosy and the availability of free treatment, and attempt to reduce the stigma of the disease.

The creation of the new state with its additional resources, reorganization and raised morale gives a good reason for optimism that with appropriate policies and serious commitment leprosy can be eradicated from this part of Nigeria in the not too distant future.

Acknowledgments

I am grateful to LEPRA for financial support and to the University of Cross River State which provided me with opportunities for fieldwork during 1987. The cooperation and encouragement of staff and patients of the leprosy hospitals and of the Leprosy Control Service of the Cross River State are also gratefully acknowledged.

References

[1] WHO Medical Officer, Visit to Cross River State, February 1983. Unpublished report.
[2] *Government of Nigeria Ministry of Health Annual Report* 1959, Enugu. p. 16.
[3] Brightmer I. Leprosy in Cross River State, Nigeria. *Lepr Rev*, 1987; **58:** 69–78.
[4] Hunter JM, Thomas MO. *Soc Sci Med*, 1984; **19:** 1, 22–57.

Lepr Rev (1990) **61,** 282–288

Obituaries

ALEXANDER GRAHAM MCDONNELL WEDDELL MD, DSc 1908–1990

Graham Weddell, who died on 21 March 1990 at the age of 83 was Emeritus Professor of Human Anatomy at Oxford. After qualifying in medicine at St Bartholomew's Hospital in 1933 he set out immediately on an academic career in anatomy as demonstrator in anatomy under Professor Woollard at St Bartholomew's and University College with, in between, a Commonwealth Fund Fellowship in neuroanatomy at Washington University. In 1939 he served with the RAMC, including a period in the neurosurgical unit at Oxford under Sir Hugh Cairns, which may well have stimulated him to join in 1945 the Department of Human Anatomy at Oxford as demonstrator, then reader and finally professor. Weddell's main research was concerned with neuropathies and particularly the processes of degeneration and regeneration of peripheral nerves, using the best currently available light and electron microscope techniques. He was one of the first working in this field to use electron microscopy.

It was the appreciation by Robert Cochrane in the early 1950s of the potential relevance of Weddell's studies on peripheral nerves to nerve damage in leprosy and Weddell's initial willingness to investigate, that resulted in him giving, over the next 25 years, a major proportion of his team's research time and his own life to leprosy.

Weddell's expertise as a neuroanatomist, wide knowledge of neural structural changes, including the application of light and electron microscopy and most recently ultra structural studies on leprosy lesions in experimental leprosy infections in animals and in man, have added significantly to our understanding of the mechanism of nerve damage and host response to infection.

During the late 1960s, by which time the Department of Anatomy's studies on leprosy neuritis was beginning to receive international recognition, Dr Cochrane proposed the establishment of a small clinical facility for leprosy patients, to boost still further Oxford's contribution to the field of leprosy research. With the powerful support of the then Director of Dermatology, Dr Vickers, and financial backing from the Nuffield Foundation, this centre, known as the 'Cochrane Annex', was opened in August 1970 in the grounds of the Slade Hospital. The centre was in fact a partial recognition of Weddell's present achievements and a base from which he and others in Oxford could develop and extend their leprosy research facilities. Undoubtedly, with the assistance of Dr McDougall from the Department of Anatomy, and Drs Vickers and Ryan from the Department of Dermatology, Weddell's researches benefited from the direct clinical materials.

While Weddell's important scientific work, based always on technical skills of the highest order, are of no mean achievement, they represented, however, only a part of his makeup which contributed to his achievements. He had an inborn belief in being responsible for teaching and sharing *all* his relevant knowledge with others. This he provided in Oxford to all visiting workers, or

provided to those abroad during his many visits to leprosy endemic countries. This was of greatest benefit for centres wishing to set up electron microscopy facilities.

Weddell was also endowed with an engaging and infectious sense of humour, as well as being an untiring raconteur. These gifts combined with generous entertaining at Oriel College, or by his wife Barbara at their home or in the garden of their delightful 14th century house in Oxford. It was always his delight to show the small, similarly aged chapel in the grounds of their garden where the floor was sloped away from the alter to allow it to be washed down after 'lepers' had attended the service.

R J W REES

Following an introduction from Dick Rees in the National Institute for Medical Research, I was fortunate enough to meet Graham Weddell in Oxford and to have the opportunity to work with him from 1970 onwards. Though well into middle-age and clinically orientated, I was attempting to make a change to some form of leprosy research based in the UK and Graham offered me the chance to work in his unit on the histopathology of leprosy. It was he who taught me how to use a research microscope, revitalized my knowledge of histology and then gradually introduced me to the complexities of the histopathological response to *Mycobacterium leprae*, first in animal tissues and later in human tissues. Through the 1970s and even into his retirement from the Department of Dermatology at the Slade Hospital, we worked together on a wide range of material from the NIMR in Mill Hill and MRC Unit in Malaysia. Research workers joined his unit from Europe, the USA and India and often completed D.Phil. projects on subjects related to leprosy, making full use of both light and electron microscopy, under his expert guidance.

Graham combined enthusiasm, imagination, energy, scientific ability and kindness in a way which endeared him to medical students, postgraduates and visiting research workers over a period of many years. Although he remained cautious about advances and 'breakthroughs' in what he recognized to be a difficult subject, his own contribution was both formidable and sustained. Following a few visits from Bob Cochrane, he not only established high quality research in the science area of a prestigious university, but he also personally carried out a great deal of work over a period of about 20 years, whilst at the same time stimulating and teaching many others. I was privileged to be one of them.

A COLIN McDOUGALL

I first met Dr Graham Weddell in 1963 in Oxford, England, where he was Professor of Anatomy and had already made a name for himself as an international authority in neuroanatomy. His contributions to the understanding of sensory nerve endings in human skin is monumental.

In 1963 I was getting interested in neuropathology of leprosy and was planning to do some electronmicroscopic work. However, I was reluctant to embark on a project using a complex instrument of which I had very little knowledge. On hearing of my interest Dr Weddell gladly showed me how to use the instrument quickly dispelling my misconceptions and fears. His willingness to spend so much of his time with a novice, the generous way he shared his expertise and his genuine friendliness touched me deeply. It was the beginning of a friendship which lasted for many years. There are many beside me who were inspired by Dr Weddell, trained by him and benefited from his ready willingness to share his knowledge.

At a period when leprosy was a neglected field and had little to do with academic medicine, Dr Weddell took an interest in leprosy research. His work on the Schwann cell as a host cell of *Mycobacterium leprae* opened up a wide field for investigative studies. His original contributions to the understanding of the transmission of leprosy were significant. He helped to stimulate many

scientists to do leprosy research and make their own contributions to further the knowledge of leprosy.

In Dr Graham Weddell we have lost a brilliant scientist, a great teacher, and a kind and generous friend. We are thankful to see his work continuing in the lives of so many of his students and coworkers who are engaged in leprosy research throughout the world.

C K JOB

It has been my privilege to have known Dr Graham Weddell when he was Reader in Anatomy at Oxford University in the early 1950s. I was struggling with the interpretation of my findings on intravitally stained intradermal nerves in over 200 skin biopsy specimens from normal sites or hypesthetic or anaesthetic skin lesions from patients with leprosy in Bombay. Professor Khanolkar introduced me to Dr Weddell and for the first two years our communications were solely postal. In 1953 he visited Bombay after I had sent him my thesis on the above subject. We established closer professional and personal contact; he looked at my preparations under a microscope and chatted with me about the neurohistological substrate of cutaneous sensibilities.

It was most reassuring to me that based on his own observations and mine, he was in agreement with my 'thesis' that the normal hairy skin of man did not have and did not need any organized nerve endings to subserve the modalities of touch, pain, heat and cold. In 1958 I had a chance to visit him in Oxford and again in 1964 when I lectured on Nerves in Leprosy.

In 1967 we had the pleasure of a visit from Dr Weddell in Bombay; his personal friendliness as well as professional astuteness were again in evidence. In continuation of his interest in the neuritis of leprosy, he also visited with us the Acworth Leprosy Hospital. His remarks at the CIBA Foundation Symposium at about the same time that the Schwann cell was the target organ in leprosy, was among the earliest of such observations. Along with Dr Dick Rees, he was instrumental in developing in England the experimental mouse model of leprosy.

In 1974, after he had been Professor of Anatomy for some time, my wife and I visited him at his department in Oxford and his charming informality was again a delightful experience. During one of my visits to Oxford, I had the privilege of meeting Mrs Weddell at a luncheon there. Her wit and graciousness matched Graham's.

Because Graham was ill on my last visit to Oxford I was greatly disappointed not to be able to meet one who had been my great friend and mentor.

D K DASTUR

The progress in the scientific knowledge on leprosy has passed through several phases in the past five decades. While today there is a focus on immunology, there was a time when all attention was focused on the understanding of the pathology of the disease. Dr Graham Weddell was one of the founder fathers in building up the knowledge on pathology of leprosy, particularly the pathology of nerve damage. His insight into the subject was so deep and his commitment so firm that he inspired several other scientists in different disciplines and stimulated research on various aspects of leprosy. No wonder Oxford became an important centre for learning about leprosy, attracting several scientists from different parts of the world. I had the privilege of working for a brief period at Oxford and derived benefit from the tutorage of Dr Weddell. He was an excellent teacher. His unique quality was that even the most junior of students would feel absolutely comfortable with him and could discuss and argue without fear or prejudice. This made him a person who was greatly loved and respected by his students. Also it was evident that he was the most popular professor with the students in the medical school. Dr Graham Weddell was a unique person, with a deep knowledge of his subject, an inimitable style of teaching, an inexhaustible store of energy for work

and above all an infinite love and concern for his juniors and students. Men of his qualities are rare to find.

K V DESIKAN

In the early 1950s Dr Robert Cochrane, who had recently established in London what was then known as the Leprosy Research Fund, visited Dr Graham Weddell at the Department of Human Anatomy in Oxford. Dr Weddell had been investigating experimental damage to cutaneous nerves and the resultant level of sensory loss, and Dr Cochrane asked him if he would bring his new and detailed findings to bear upon the problem of peripheral nerve damage in leprosy. Fortunately Dr Weddell immediately became interested in this new line of investigation, and facilities were made available for him to study some leprosy patients in India and also much biopsy material. From that time on he and his staff in the Department were ever increasingly engaged in studying the disease in many of its aspects.

I started working with Dr Cochrane in 1961 in the renamed Leprosy Study Centre and I thus had the opportunity of contact with Dr Weddell and his colleagues for many years. I should like to record my deep gratitude to him for his friendship and for his constant readiness to help with any histopathological problems which came to us in the biopsy service work of the Centre. It was always a privilege to discuss and to share with him any interesting material we received and I personally was greatly indebted to him for the light which his knowledge of the tissues, the spread of infection and the defence mechanisms of the body shed on many an obscure problem. He was also very generous in making available the special facilities of his laboratory, and the resultant work, be it stained section, photomicrograph or report, was always of an enviably high standard and most helpful.

Dr Weddell's death is very sad news for those of us who knew and admired him, but at the same time we rejoice in his brilliant and very productive life's work and in the important contributions which he made to leprosy research.

D J HARMAN

Graham Weddell was an academic visionary motivated to apply his wide knowledge of human anatomy to the specific problem of nerve damage in leprosy patients.

At the request of Dick Rees, Graham made available not only his expertise, but also provided essential space and facilities in his laboratory for Lepra's Research Unit at a time when leprosy research was vital. Graham not only made this possible, but was an original member of the newly formed Lepra Medical Advisory Board which had, and still has a major influence on the way Lepra develops its work.

Graham was also a humanist and enjoyed entertaining friends and colleagues in the Senior Common Room at Oriel College as much as sitting waiting for his flight at an African airport observing his fellow travellers.

I was very fortunate to be the Director of Lepra during this time, and not only enjoyed Graham's Oxford hospitality, but also his generous and constructive advice and support on very many occasions.

G F HARRIS

CHAPMAN H BINFORD, AB, MD, DSc(Hon) 1900–1990

Dr Binford had a long and distinguished career in medical science. His career began in 1930 when he was assigned, as a Public Health Service Officer, to Harvard Medical School for training in preventive medicine. Then followed research in a leprosy laboratory in Hawaii, training in histopathology at NIH, and pathology service at several Marine hospitals. He was assigned to the Armed Forces Institute of Pathology in 1951. He retired from the Public Health Service in 1960, but continued to work at the AFIP until he retired for a second time, in the autumn of 1988. Dr Binford was a pioneer in leprosy research and had a special interest and dedication to research on the understanding of the spread of leprosy within the body. His knowledge and astuteness became known nationally and internationally and his opinions on leprosy and other infectious diseases were sought from all over the world. Even in his 89th year he continued to consult on cases of special merit and these included cases of leprosy, fungal diseases and some exotic tropical diseases.

At the AFIP, Dr Binford served as Chief of the Infectious Diseases branch (1951–60), as Registrar of the Leprosy Registry (1951–76) and in 1960 he established the Geographic Pathology Division, and served as its first chief (1960–63). His approach to 'international medicine', and in particular his approach to 'geographic pathology' is illustrated by the contacts and interactions he developed in the Third World. For instance, while chief of the Geographic Pathology Division, he established research units in Uganda, South Africa, the Philippines and Thailand, and he developed liaisons with mission hospitals in many developing countries. In 1963 he stepped aside as Chief of the Geographic Pathology Division to become Medical Director of the Leonard Wood Memorial (American Leprosy Foundation). He continued however to serve at the AFIP as chief of the Special Mycobacterial Diseases Branch (1963–76), and since then has worked closely with succeeding chiefs of the Geographic Pathology Division—which in 1970 became the Department of Infectious and Parasitic Diseases Pathology.

Until the mid-1970s, the American Registry of Pathology (ARP), although unchartered, was the AFIP's link with civilian medicine. In 1975 a strong move surfaced in the Pentagon to eliminate the ARP, and to reform the mission of the AFIP along narrow military lines. At the time of this threat, Dr Binford worked tirelessly as a private citizen, serving as liaison between the AFIP's professional staff and a representative of the Senate Health Subcommittee, in an attempt to save the traditional missions of the ARP and the AFIP. As a consequence the ARP received a Congressional Charter (1976), which made legal and protected the valuable liaison between the AFIP and civilian medicine. Dr Binford acted as Executive Officer of the ARP (1977–80), until a permanent Executive Officer was appointed. The mission of the ARP has grown steadily since 1976, and at present the ARP not only links private and military medicine but serves also as a resource for research and teaching in national and international medical science. As the scope and impact of the ARP grow, Dr Binford's foresight is increasingly appreciated.

Dr Binford's interest in the clinical and pathological aspects of leprosy began in the days before sulphone when he was assigned for three years to the Public Health Service Laboratory adjoining Kalihi Hospital in Honolulu (1933–36). There, on a daily basis, he observed and studied the clinical and pathological progression of the various types of leprosy. Since the mid-1950s Dr Binford has been a pioneer in the search for animal models for leprosy–first in an experimental laboratory at the Centers for Disease Control, in Georgia (1956–60), and subsequently at the Leonard Wood Memorial (American Leprosy Foundation) research laboratory at the AFIP (1960–72). It was Dr Binford's long experience with the clinical and pathological aspects of leprosy that led him to hypothesize in 1956 (as recorded by Dr George L Fite) that '...the leprosy bacillus has a natural preference for sites of lower body temperature...'. This observation led to the discovery of the first animal model for leprosy—the mouse footpad (Shepard), now used to detect the viability of *Mycobacterium leprae*; and to the inoculation of *Mycobacterium leprae* into the armadillo (Storrs), an animal with a body temperature of 32–35°C. Dr Binford's persistence in seeking animal models

for leprosy and his support and contributions to others seeking animal models was the sustaining force in an era that has witnessed a revolution in leprosy research—from a time when no models were available, to the present when armadillos and a variety of primates have led to rapidly expanding fields of leprosy research—an expansion which depends completely on experimental models.

Today armadillo tissues provide the only abundant source of *Mycobacterium leprae* for clinical and laboratory studies, and this abundance has advanced our knowledge of the immunology and pathogenesis of leprosy and of the physiology of *Mycobacterium leprae*. *Mycobacterium leprae* from armadillos led also to the Immunology of Leprosy Programme (IMLEP), begun in 1974 and sponsored by the World Health Organization. The goals of the programme were the development of a vaccine, and a method for identifying patients with subclinical infections. Studies with vaccines are now underway and significant advances have already been made in our understanding of the immunopathology of leprosy.

Dr Binford was also an expert on the histopathology of fungal diseases. He was coauthor of *Medical Mycology*, which is now in its third edition (1963, 1970 and 1977); and he also authored or coauthored articles on cryptococcosis, chromomycosis, cladosporiosis and histoplasmosis. Dr Binford contributed chapters to and co-edited *The Pathology of Tropical and Extraordinary Diseases* (1976) the definitive work in this field.

One of Dr Binford's great contributions was the formulation, over many years of teaching and consultation, or the criteria that enable pathologists to identify the microbial cause of infections in tissue sections. Perhaps only those who have worked with Dr Binford are aware of this contribution. Although simple in concept these criteria are profound in application for they enable the pathologist to identify by light microscopy, the organisms that cause infection. 'Binford's criteria' are especially valuable when the organism remains uncultured, thus precluding the more traditional evaluation using Koch's postulates. Binford's criteria state in general that infectious agents have a symmetrical distribution in the area of reaction, that they increase in number as the lesion expands, and vanish as the lesion resolves. These criteria enable the pathologist, who takes pains to apply them, to exclude spurious organisms as a cause of infection—such as contaminants and early growth of putrefactive organisms. The application of these criteria has led in recent years to the identification of many microbial agents as causes of human disease—including most recently the gram-negative bacillus that causes cat scratch disease.

In closing I must add a more personal appreciation of Dr Binford as a person, as a friend and colleague, and as a scientist. From his record it is clear that he was astute, but it is not clear that he was selfless in his promotion of his colleagues and that he was also very generous. He was tireless in promoting others, their projects and their welfare. His style was to train others then gracefully step aside when they were ready for increasing responsibility. When approached with ideas for research or diagnosis he was always supportive and strove to garner the best from the suggestions of his colleagues. He seemed always to be able to bring ideas into being and studies to fruition. He was always willing, and in fact frequently insisted on remaining anonymous, when collaborating on projects. Dr Binford's long and distinguished career as a consultant, researcher, educator, administrator, advisor and friend will continue to be a source of inspiration for all who had the good fortune to know him and to work with him.

DAMEL H CONNOR

ERNEST W PRICE, OBE, MD, FRCSE, DTM & H 1907–90

Dr Ernest Price joined the leprosy service in the then eastern province of Nigeria in 1957, after serving for 21 years in Baptist Missionary Society Hospitals in Zaire, the last 10 years of those spent as a specialist in orthopaedic surgery. In Nigeria, he served first at Uzuakoli under the late Dr T F Davey, and later was transferred to Oji river where it was intended to establish a leprosy surgical unit.

Based on his experience in orthopaedics and with leprosy work in Zaire, Dr Price very quickly concluded that ulcers of the foot constituted a major unsolved problem in leprosy, and immediately began to make significant contributions to the understanding of the problem. Publications flowed from his pen following his extensive studies of patients, as did a variety of simple footwear designed to prevent the recurrence of ulcers. This work, together with the work concurrently being undertaken by Dr Paul W Brand and his colleagues in India, had a revolutionary impact on ideas concerning the aetiology and treatment of ulcers occurring in neuropathic feet.

The end of Dr Price's first tour in Nigeria was marred by involvement in a head-on collision which almost cost him his life. A few months later he was again seriously ill, following a gastrointestinal haemorrhage that occurred while he was attending a conference in Zaire, at which he presented his work on foot ulceration. Following these episodes he was unable to return to Nigeria, but after being in England for a little over three years, he went back to Africa. This time his post was in Ethiopia, at the Princess Zenabework Hospital in Addis Ababa. There he held the position of Leprosy Advisor to the Ministry of Health.

Dr Price quickly came to the conclusion that the major problem to be solved in leprosy in Ethiopia was not ulceration of the foot or even disability generally, but the fact that patients were not able to obtain access to chemotherapy early enough in the disease for there to be reasonable possibilities for the prevention of disability altogether. This understanding led him to organize and find funds for the support of simple clinics in rural areas, often in rented huts in market places from which the majority of patients began their journeys to Addis. In the course of time the existence of these clinics resulted in a drastic reduction in the numbers of patients migrating to the metropolis. This work became the foundation of the present national leprosy control programme.

Concurrent with the establishing of rural clinics, Dr Price reversed the former policy of more-or-less open admission of patients and their families to the hospital in Addis Ababa, and helped to institute a programme of settlement of displaced and homeless patients in agricultural settlements far from the city.

In 1965, Dr Price welcomed the establishment of ALERT in Addis Ababa. He made many important contributions to the development of ALERT and was an influential member of its Board of Directors until he left Ethiopia.

During his time in Ethiopia, Dr Price became interested in nonfilarial elephantiasis, a widespread problem in Ethiopia as well as elsewhere in Africa, and the cause of significant disability. In this field also he made important contributions, pioneering methods for the alleviation of swelling and prevention of its occurrence. His efforts to elucidate the cause of this problem continued after he retired from Ethiopia in 1974, and shortly before he died his extensive monograph on this topic was accepted for publication.

Ernest Price was a man of many talents—a first-rate pianist, who also became an accomplished cellist later in life. During his first 10 years in Africa he became fluent in Lingala and in the local Ngombe language, and wrote a grammar in Ngombe which is still in use. He was an excellent teacher. His deep concern for leprosy patients and those with elephantiasis grew out of his Christian convictions, 'which sustained and motivated him throughout his life'.

He is survived by his wife Marjorie and by his son, Michael, and daughter, Gilian.

W FELTON ROSS

Lepr Rev (1990) **61,** 289–296

Letters to the Editor

CLOFAZIMINE-INDUCED LYMPHOEDEMA

Sir,

I would like to report my observations of six patients who were being treated with multidrug therapy (MDT) for multibacillary leprosy in a leprosy centre in Karnataka, India, where I was working as a medical officer from 1984 to 1986.

These six patients developed significant and symptomatic pedaloedema, two of them also complained of subjective oedema of the hands. The patients belonged to the 30–50 year age group, and included one woman. The oedema of the feet was first seen about 3 months after starting the MDT. The oedema was characteristically bilateral, symmetrical, pitting, non-tender and progressive, with postural variations.

Baseline investigations done on these patients before starting the therapy ruled out cardiac, renal, or hepatic diseases, filariasis or nutritional deficiencies. The development of the pedaloedema was observed only in the multibacillary patients who were on three drugs, rifampicin, dapsone and clofazimine, and not in the paucibacillary patients who were only on two drugs, rifampicin and dapsone. It appears that this oedema is due to clofazimine.

Clofazimine has been shown to be deposited in lymph nodes by various histopathologists,[1–3] and such deposition was considered responsible for abdominal pain.[4] One report also mentions the development of persistent and generalized oedema in a patient who was given clofazimine 100 mg daily, with prednisolone 10 mg.[5]

The fact that pedaloedema occurs in patients with lepromatous or borderline lepromatous leprosy is appreciated. But since the oedema became significant to the patients only after the therapy was started, I would like to suggest that the pedaloedema referred to above could be due to the lymphatic stasis produced by the depostion of clofazimine in the lymphatic channels, ultimately causing lymphoedema.

I would be interested to know if any similar report or observation has been made in any other leprosy centre, since this could perhaps have further implications on the role of clofazimine in the management of leprosy.

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References

[1] *Lepr Rev*, 1976; **47:** 1.
[2] *Lepr Rev*, 1975; **46:** 105.
[3] *Ann Dermatol Venerol*, 1982; (F) **109** (6/7); 585–7.
[4] *Lepr Rev*, 1979; **50:** 258–9.
[5] *Lepr India*, **53;** 285–7.

PROTECTIVE FOOTWEAR FOR LEPROSY PATIENTS: A RAPID METHOD FOR THE CUTTING OUT OF SANDAL COMPONENTS

Sir,

Egypt has a very considerable number of leprosy patients with loss of sensation on the sole of one or both feet, and we have attempted, both at the Abu Zaabel Centre outside Cairo and at the Citadel Clinic in the city, to provide suitable protective footwear. The large number of patients with severe anatomical distortion of the foot and/or ankle has, however, taken up much of our working time in recent years because of the need for individual constructed shoes or boots, but we are now increasingly interested in the provision of protective footwear for patients with loss of sensation, sometimes with small or healed ulcers, but with anatomically normal shaped feet.

Stimulated mainly by the need to save working time with our limited staff, we have devised, with the help of the Bailey Machinery Co., Louisville, Kentucky, USA, a metal 'cut-out' device for this purpose, as shown in Figure 1. It consists of a strip of high quality spring steel, 2·5 cm wide and 1 mm thick, one long edge of which is sharpened and positioned in a 'sandwich' of wood–metal–wood as a base or holding platform. The dimensions of the wood are not critical, but there should be a margin at the sides and ends of the base of about 4 cm from the metal strip. Plywood approximately 16 mm thick is preferable, if available. From the piece of wood which is to form the upper layer, a sole shape is cut out accurately from its central region and put to one side. Working with the cutting edge downwards on a wooden bench, the steel strip is then forced into the perimeter of the space, the ends being very accurately cut at right angles, so that they oppose exactly; welding is not necessary. The cut wooden centre is then forced back into its original position, thus holding the metal strip tightly. This assembly is placed over sheet metal 0·5 mm thick and these two layers are in turn fixed to a third of wood; all three are then screwed together. The material to be cut is placed over the cutting edge of the metal strip and struck with a heavy rubber hammer until the entire sole shape is cut through. This device is suitable for cutting out soles of various sizes from stiff soling material, 8-mm microcellular rubber for the upper, or 16-mm resilient microcellular rubber for the central layer of a sandal. For stiff soling material, the cutting edge of the steel strip should be set 8 mm above the wood surface, but for other materials it can be set to project up to twice this

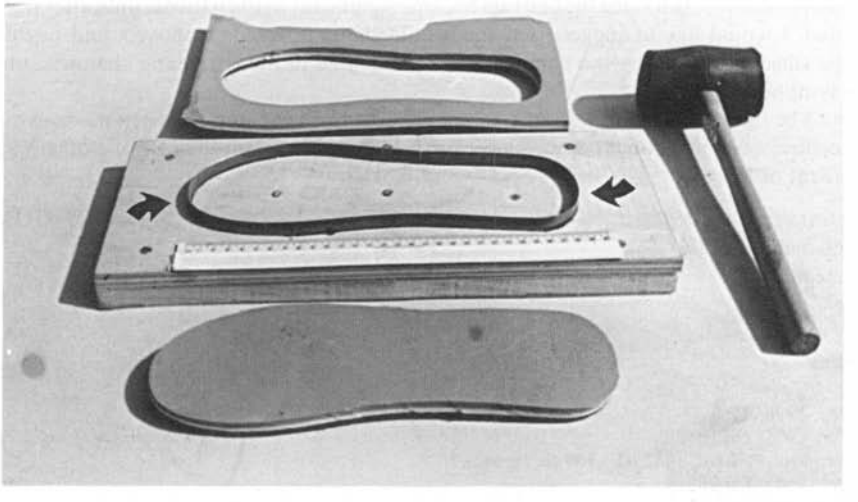

Figure 1. The wooden platform or base is shown at the centre, with the sharpened steel strip *in situ* (arrowed). A typical microcellular cut-out is shown on either side of the wooden base and on the right is the heavy rubber hammer used to strike the material until the sole shape is cut through. The ruler is 30 cm in length.

height. If the material which has to be cut has a different pattern on the top and bottom side, it is first cut on one side, then turned and rotated 180 degrees for the second cut, thus producing a similar right and left sole shape from the same cutter.

The construction and assembly of this device is best carried out by a workshop supervisor, or by a patient with no sensory or motor defects in the hands, but the actual production of soles, using a heavy rubber mallet or hammer to 'bang out' the required shapes, can safely be entrusted to patients under supervision, following careful initial instruction. Everyone in the workshop should be aware that the upper edge of the strip is extremely sharp, but in the almost daily use of this device during the past year we have no problems, and it is undoubtedly safer (and much faster) than cutting out shapes with a knife.

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PROTECTIVE FOOTWEAR FOR LEPROSY PATIENTS WITH LOSS OF SOLE SENSATION: LOCALLY MADE CANVAS SHOES, DEEPENED FOR A 10-MM RUBBER INSERT

Sir,

During the past 4 years, in close cooperation with a local shoe company in KwaZulu, South Africa, we have used modified canvas shoes, similar to the 'trainer' shoes produced by BATA and many other companies, for patients with loss or diminution of sole sensation.

The essential modification centres on the production of a deepened internal space to accommodate a 10-mm rubber insert (Figure 1). We are greatly indebted to the managing director of our local shoe company for the following information:

'The method by which we deepen the metal moulds is relatively simple. An insole pattern that fits the bottom of the mould (last) is used to produce a "10-mm rubber insert". This is cut from a calendared sheet of 10-mm thickness and is stuck on by means of a "hot melt" adhesive to the bottom of the mould (last). The insole on to which the upper is lasted (generally 2·5-mm insole board) is now placed on this rubber insert and the canvas upper is lasted over the mould by means of a lasting machine. Subsequently all standard procedures pertaining to the production of built-up canvas footwear are followed. After the shoes are vulcanized or "cured" they are removed or "off-lasted" from the mould (last) and thereafter a 10-mm EVA (ethyl vinyl acetate) invert of appropriate size is added. (Note: When the shoes are "off-lasted" the rubber insert still adheres to the bottom of the mould.) Two further points must be noted: 1, all upper patterns have to be modified according to the new mould (i.e. with the 10-mm rubber insert) stuck on the bottom of the mould; and 2, the 10-mm rubber insert has to be vulcanized before being stuck to the bottom of the last.'

These shoes have been produced in different colours and in all the usual sizes for both male and female leprosy patients with diminution or loss of sensation in the feet, some of whom have one or more ulcers. Essentially, however, the shoes are suitable for patients with anatomically normal feet. They are unsuitable for patients with a significant deformity of the foot and/or ankle and for these we continue to try to provide specially made orthopaedic shoes or boots. The straps are of Velcro and easily handled by patients with deformed hands or loss of fingers. The canvas seems to allow good ventilation and we have not encountered any problems with 'sogginess' and fungal or other infections, such as are common in leprosy patients using tight-fitting plastic shoes that are bought from shops. The cost per pair in South Africa is in the region of R8 (currently 2,30 SA Rand = US $1). On average a pair of these shoes will last 6 months (sometimes a year) and they stand up well to use by patients walking on uneven ground or engaged in agriculture.

Currently we supply 827 pairs of shoes to 549 patients in four of our field areas. This means that some patients require a new pair twice a year while others will use a pair for a year. A major task is to educate rural people to wear protective footwear at all times. The tendency is to 'look after them' by not wearing them except for 'best' or special occasions. We recently discovered a patient who walked to the clinic carrying his sandshoes and then sat at the entrance to the clinic to put them on!

Figure 1. Canvas shoe, deepened to take the 10-mm rubber insert shown below. The two fastening straps are of Velcro and the insert is made of ethyl vinyl acetate. The ruler is 30 cm in length.

Current research into the effectiveness of this programme in Swaziland indicates the following: 90 patients received sandshoes; and 36 arrived with open ulcers. After 6 months' use of the special shoes: 15 were completely healed; 13 much improved; 5 were the same; 3 were worse; and 6 developed new ulcers. After 12 months: a further 25 were completely healed; 6 much improved; 1 was worse; and 3 developed new ulcers.

The deterioration appeared in those cases who did not wear the shoes. We do not subscribe to the view that it should be possible to develop some kind of internationally acceptable form of footwear for leprosy patients and the shoe described here may not be acceptable in some other countries. However they are successful in Southern Africa and have been used in Swaziland, Lesotho and Malawi. Their production is not technically demanding and their cost, although by no means insignificant, is very small in comparison with the costs in terms of disability and human suffering which result if protective footwear is not provided for all leprosy patients with loss or diminution of sole sensation.

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L A WISEMAN

COMMENT: THE USE OF HISTOPATHOLOGY IN LEPROSY DIAGNOSIS AND RESEARCH

Sir,

'The use of histopathology in leprosy diagnosis and research' by Lucas and Ridley, published as an editorial (*Lepr Rev*, 1989; **60:** 257–62), in which some immunopathological techniques have also been reviewed is highly informative. While sharing their concern about the interobserver discrepancy in the reporting of early/indeterminate leprosy I would like to make a few comments based on the limited experience I have.

In developing countries like India leprosy histopathology is confined to a few institutions. Why talk of histopathology and other newer tests when an acceptable standard of smear techniques has not been maintained in field programmes. Histopathology should only be considered as the next medium for diagnosis and classification of leprosy after a good smear technique has been established.

Diagnosis of early leprosy is the concern of many, both clinicians and patients, and it is natural that the histopathologist's help is expected. Biopsy has two clear advantages over other tests. First, a thorough search is possible by studying multiple sections, and second, the host agent interaction shows earlier in histology than in clinical features. So far as the criteria for diagnosing the early or preganulomatous stage of leprosy is concerned, it is to be noted that with present-day knowledge, *Mycobacterium leprae* is the only bacterium having affinity for or capable of invading peripheral nerves.[1-3,6] Inflammation of peripheral nerves (as evidenced by perineural infiltration, Schwann cell proliferation and loss of Schwann cell polarity etc.) and the presence of acid-fast bacilli (AFB) may be taken individually as a diagnosis for indeterminate leprosy. Similar views have also been expressed in several other studies.[1-6] The scanty histopathology services available in developing countries must concentrate on these features. Many studies indicate that examination of several sections definitely show either foci of neuritis or AFB.[3,5,6] Periappendageal and perivascular infiltrate only mean study of more sections or that a repeat biopsy must be done and is not a clear diagnosis. Noncommital statements like 'non specific dermatitis', 'suggestive of leprosy' etc. need to be avoided as much as possible in the diagnosis of leprosy. Leprosy is basically a disease of the peripheral nerves and its agent is *M. leprae*. These two aspects must decide the diagnosis of leprosy not only in early but also in advanced (determinate) cases. Even in less well-equipped laboratories disease can be diagnosed histopathologically with considerable certainty if one is particular about the following prerequisites. In early or pregranuloma stage the infiltrate needs to be supported by nerve involvement or the presence of AFB and in advanced/granuloma stage the granuloma needs to be qualified again by nerve damage (anaesthesia clinically) or the presence of AFB. If the pathologists insist on these criteria leprosy will be differentiated from all other conditions (referred to in the article) producing epithelioid cell or macrophage granulomas, and the interobserver variation will be minimized. In countries with verticle programmes, histopathology services must be organized to meet the minimum requirement for diagnosis and classification thus enabling the laboratories in developed countries to concentrate more on research.

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References

[1] Dharmendra, Kirchheimer WF. Mycobacterium leprae. *In Leprosy* Vol 2, Dharmendra (ed), Bombay: Kothari Medical Publishing House, 1985, p. 766.
[2] Pearson JMH, Ross WF. Nerve involvement in leprosy—pathology, differential diagnosis and principle of management. *Lepr Rev*, 1975; **46:** 199–212.
[3] Nayar A, Narayanan JS, Job K Charles. Histopathological study of early skin lesions in leprosy. *Archives of Pathol*, 1972; **94:** 199–204.

[4] Ridley DS, Jopling WH. Classification of leprosy according to immunity. *Int J Lepr*, 1966; **34:** 255–73.
[5] Ridley DS. Indeterminate leprosy. Editorial. *Lepr Rev*, 1974; **45:** 95–7.
[6] Binford CH. The histologic recognition of early lesions in leprosy. *Int J Lepr*, 1971; **39:** 225–30.

REPLY: THE USE OF HISTOPATHOLOGY IN LEPROSY DIAGNOSIS AND RESEARCH

Sir,

The intention of our editorial (*Lepr Rev*, 1989; **60:** 257–62) was to reassess the role of histology in leprosy in relation to recent developments, which are mainly technological. Early diagnosis, with which Dr Porichha's letter is concerned, is an outstanding problem for which, we had to conclude, newer methods have not produced a solution. A patient must not be diagnosed without near proof, yet early treatment is needed if the risk of irreparable nerve damage is to be avoided. We suggest that new thinking is needed.

The primary lesion of leprosy becomes clinically apparent at a very early stage, partly due to depigmentation. Histology reflects well the immunological response, but at this stage there is no response at the site: the scanty bacilli are in immunologically protected positions, mainly nerves. Not surprisingly, such inflammation as is present is non-specific. Unless bacilli happen to be detected, an uncommon event in lesions of less than 6 months' duration, a biopsy is likely to be inconclusive. Later, especially after one year, the finding of bacilli is more probable and the histology perhaps more specific. Many studies of early leprosy, and most 'comparability studies' between histologists, have been on lesions under one year, which of course is when a diagnosis is wanted; but it is difficult to see how at this stage histology alone is ever going to be decisive. Reliance on finding bacilli is hampered by the time needed to search serial sections, and the possibility that those found could be contaminants.

It has to be remembered that all skin inflammation is perivascular *ab initio*, and nerves accompany vessels. Identification of the point at which inflammation constitutes specific involvement of the nerve component of a neurovascular bundle is one of the main points of contention between histologists, not all of whom have regular experience of skin diseases other than leprosy. It would be of great educational benefit if a reference biopsy collection of early skin diseases could be compiled, and an atlas published. But it is to be feared that the outcome of greater familiarity with other diseases might be even more noncommital reports on early leprosy. A reference collection of early cases that proved on follow-up to be leprosy, if it were feasible, would be similarly useful. Without these two reference points comparability studies highlight the problem without contributing to its solution. We fully support Dr Porichha's plea for an improvement of laboratory services and standards in endemic countries. In our experience, outside leprosy centres, dermatopathology is the least well served of the histological subspecialties. But this is not the whole answer.

It is interesting that cell mediated and antibody responses to leprosy are already detectable at the contact stage. Presumably the bacilli (at non-protected sites) that induce these responses are destroyed in the process. It would seem logical therefore to use immunological tests as the basis for diagnosis, but the results are disappointing. Either the antigens are insufficiently specific or they fail to differentiate healthy contacts from early infections. Diagnostic immunocytochemistry tends to fail in complex diseases.[1]

There is an admirable tradition that a histological report stands on its own evidence and is complete in itself. It should, and for the classification of leprosy it can be so. For diagnosis, more progress might be made, we suggest, if it were the rule to take histological reports in conjunction with other available evidence. A tuberculoid granuloma in skin points to leprosy if it is associated with loss of sensation; but is against it if the lepromin test is negative. Lymphocytes in a nerve are stronger evidence of leprosy if supported by independent immunological evidence. Yet any one of these criteria alone may be insufficient.

More studies are needed, with full evaluation and follow-up of cases, both for early diagnosis and prediction of the outcome. A probability scale that incorporated data from diverse sources ought to be compiled, on the lines of the histopathology scale already in use.[2] One wonders if a comprehensive prospective study carried out by a multidisciplinary working group might not offer the best, perhaps the only, way forward.

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References

[1] Gatter K C. Diagnostic immunocytochemistry: achievements and challenges. *J Pathol*, 1989; **159:** 183–90.
[2] Fine PEM, Job CK, McDougall AC, Meyers WM, Ponnighaus JM. Comparability among histopathologists in the diagnosis and classification of lesions suspected of leprosy in Malawi. *Int J Lepr*, 1986; **54:** 614–25.

COMMENT: VALUE OF THERMAL SENSIBILITY TESTING IN LEPROSY DIAGNOSIS IN THE FIELD—FIELD TRIAL OF A POCKET DEVICE

Sir,

We have the following comments to make on the above paper by H Srinivasan & B Stumpe (*Lepr Rev*, 1989; **60:** 317–26). Since no 'blind' was included in the study the results obtained do not have as great a credance as they might otherwise.

The trial was carried out as a multicentric one which implies, for example, that a common protocol, standardized definitions and procedures for examination were used. It is therefore surprising that the article does not explain why data from one of the six participating centres with 59 subjects could not be used.

Out of the original 319 persons included for analysis only 204 (63·9%) were examined for all sensory modalities and analysis. This means that data on more than one-third was left out, perhaps resulting in selection bias and therefore effecting the validity of the outcome. Even the original number of 319 persons proposed for the study appears to be too small to draw firm conclusions.

Because results from the individual centres are not presented in the same way it is difficult to make comparisons.

Under field conditions the groups who are difficult to diagnose are the suspect cases and those with indeterminate leprosy. Analysis of various sensory modalities individually and in combination with reference to these groups would have given more useful information of the practical application of the device and its extent.

It is a well known fact that interobserver and intraobserver variations do occur in eliciting sensory deficit in the skin on the same lesions and in the same patient. No mention is made whether these variations have been tested for and if so, the extent of variation.

We feel it to be desirable for further trials to be carried out with the proposed thermal sensibility testor in support of the conclusions drawn. We would welcome a response on the above comments from the authors.

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COMMENT: RIFAMPICIN PHARMACOLOGY

Sir,

The above item appeared in 'News and Notes' (*Lepr Rev*, 1989; **60:** 334) and I would like to make the following comments:

The list omits one important action of rifampicin. Rifampicin is one of the important causes of drug induced pemphigus.[1] It can trigger off the disease or modify the course of pemphigus. It may also have effect on steroid requirement as mentioned in the article.

I would like to record our experience. One of our pemphigus patients on a maintenance dose of corticosteroid needed anti-tubercular treatment for pulmonary tuberculosis. During a subsequent relapse, she did not respond satisfactorily to 80 mg. per day of prednisolone as was the case in previous relapses. We were able to get a good response to treatment after substituting streptomycin for rifampicin.

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Reference

[1] Pisani M, Ruocio. Drug-induced pemphigus. *Clin Dermatol*, 1986; **4:** 118–28.

Lepr Rev (1990) **61,** 297–298

Book Review

***Practical dermatology in pigmented skins.* M. D. Preciado**

This manual is a pocket book intended for the primary health worker, nurse and paramedic. It is written by a nurse who has worked for many years in East Africa. Taking into account the dearth of dermatology specialists in Africa and the fact that most dermatology is in the rural areas, this book makes a thoroughly worthwhile attempt at solving an enormous problem. It deserves to be successful.

Dermatology has developed from the recognition of minute physical signs which are then named. This has resulted in about 2000 or so entries which are used for communication between dermatologists. Whether in rural areas of Africa it is necessary to know all these names remains debatable. Dermatologists practise by pattern recognition. They learn by seeing skin lesions and noting their distribution. One can compare dermatologists to radiologists and pathologists and say that their practice is impossible without pictures. This creates a problem for textbooks for the developing world because pictures are expensive.

This manual is illustrated by only 64 photographs, about 50 of which are very good, and the remainder are either not good pictures or probably irrelevant to practice (plate 31 cylindroma; plate 26 adamantinoma).

How then does this book attempt to teach dermatology. It uses a classification based on physical signs using terms like 'swollen', 'large' and 'generalized'. The leprologist might begin with 'lesions flat' and then pass on to the section on macular lesions, alighting on the 'hypopigmented section and would eventually find leprosy under the further heading of non-scarring. One is then given various numerals—sometimes in brackets and sometimes not, which indicate the page numbers of major texts, like Rook's *Textbook of Dermatology*. Unfortunately, this is based on the second edition and the editors are already preparing the fourth. The system works quite well, nevertheless. The reader proceeds on the simplest recognizable pathological condition to the more complicated and the author emphasizes characteristic and pathognomonic signs. However, anyone who has had a period of training with a dermatologist in a dermatology department and has had the chance to look at a few skin lesions, might move beyond this book and require a more typically organized dermatology manual.

The same may be said about management. In the developing world, it is difficult to know exactly what perspective should be propagated, at least in terms of cost effectiveness. When some clinics cannot even purchase benzyl benzoate, perhaps it is right to say that 'any oil can be used effectively against scabies: paraffin oil, petroleum, engine oil, palm oil, peanut oil, etc'. However, I can imagine that some reviewers will read these management sections with thoroughly western eyes. For instance, in the UK, there is currently a campaign by some of the nursing profession against Gentian violet and Eusol. The former can produce cancer in mice and the latter is not too popular with cells grown in tissue culture. The reviewer has got into trouble for saying that he regards these agents as excellent for practical use and hopes that western views will not result in such excellent agents becoming unavailable in the developing world.

Overall, Miss Preciado has done extremely well but dermatology is a very difficult subject.

There are a lot of minor criticisms that I have listed as I have gone through this book but no two

readers would probably agree on any one, and overall, I would wish to recommend this book and say it is a splendid effort and it deserves to be widely distributed.

Inn Publishing Co Ltd, 11 Eastcheap, London EC3M 1BN, UK.

WHO Expert Committee on Leprosy, *Sixth Report*. Technical Report Series No. 768

This important report (52 pp) covers so many aspects of leprosy, such as epidemiology, chemotherapy, control, bacteriology, immunology and research, that the reviewer proposes to concentrate on certain aspects of particular importance to those concerned with the treatment and control of the disease:

Definition of a case of leprosy. A 'case of leprosy' is a person showing clinical signs of leprosy with or without bacteriological confirmation of the diagnosis, and requiring chemotherapy.

Prevalence of leprosy. This should be computed on the basis of patients requiring or receiving chemotherapy. Separate lists should be maintained for (a) those who have completed chemotherapy and are under surveillance, and (b) those released from surveillance but need care and assistance because of disabilities.

Classification for control programmes. The classification of patients into multibacillary (MB) and paucibacillary (PB) leprosy is not an attempt to formulate another system of classification but only a method of grouping patients together for the purpose of multidrug therapy (MDT). Whereas it was previously considered acceptable that PB patients could have positive skin smears so long as the BI was less than 2, it is now advised that such patients be classified as MB for purposes of MDT.

Bacteriological examination. It is considered essential to train control programme personnel in taking smears of good quality and to organize an efficient service for collecting and processing them. Although clinical improvement is accelerated by MDT, the attainment of smear negativity is not.

MDT for leprosy control. The original standard regimens are approved. Annual follow-up examinations should be carried out for a minimum of two years in PBL and of five years in MBL. Relapses in PBL are about 1 per thousand, and in MBL are about 0·2 per thousand.

W H Jopling

Published by WHO, 1211 Geneva 27, Switzerland, 1988, 52 pp, £3.25.

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Teaching Materials and Services

WHO Regional Training Centre, University of New South Wales, Australia

The World Health Organization Regional Training Centre within the School of Medical Education, Faculty of Medicine is concerned with the development of human resources in health. The staff of the Centre have extensive experience as consultants and trainers in both developing as well as industrialized countries. This experience has enabled staff to become familiar with conditions in many countries, and to develop relationships with a wide network of educators and administrators in the health professions. Collaboration with governments, international agencies, professional associations and educational institutions has been established to:

1 collaborate in the design and implementation of training and educational programmes for health personnel geared to regional and national health priorities; 2 conduct research in the planning, education, training and management of human resources as integral components of health systems; and 3 provide technical services for the implementation of country and intercountry activities in the broad area of health development with emphasis on human resources.

The activities of the Centre, directed to these purposes, include postgraduate academic programmes at masters and doctoral level, special courses tailored to specific needs of short-term fellows, workshops and seminars conducted both in the School and on-site, research and development projects in planning and evaluation, consultations and facilitation of in-country programmes.

Apply: PO Box 1, Kensington, New South Wales, Australia 2033.

Training Materials Catalogue, World Neighbors

After identifying three basic problems which inhibited communication and education in development programmes World Neighbors, in 1970, started to develop materials to overcome these problems, which are: inadequate supply of relevant materials which could be understood by local groups; insufficient training of extension workers in communication and non-formal education methods; and, lack of inexpensive, reliable and readily available teaching materials. World Neighbors committed resources, staff and time to the production of teaching materials for use in their assisted programmes. Communications staff work directly with programme personnel in developing ideas, writing scripts and producing photographs and drawings. Each teaching material is prepared in the country and locality for which it is designed, and is based on actual programme experience. Before being produced in a final form, it is field-tested with people representing the audience. Materials are provided as filmstrips, printed materials—books, posters, newsletters—flipcharts, photoseries and projector equipment. Many of these items are also available in French, Spanish, Portuguese and Hindi. An extensive number of materials are now available, eg over 100 filmstrips (most are in colour and cost US$10). Catalogues are available from: World Neighbors, 5116 North Portland Avenue, Oklahoma City, Oklahoma 73112, USA.

CBM/LEPRA Ophthalmic Course, Karigiri, India 1990

The fifth annual five-day ophthalmic teaching module was held at the Schieffelin Leprosy Research and Training Centre, Karigiri from 26 February to 3 March 1990. This course, which was again sponsored jointly by the Christoffel Blindenmission and LEPRA, was designed to give instruction

to leprologists on the detection, prevention and management of the ocular complications of leprosy by means of a series of lectures, clinical and surgical demonstrations, videos and slide-tapes.

Teaching included presentations on basic anatomy, physiology and pathology of the eye with special emphasis on leprosy: in addition there were lectures on the clinical signs and management of lagophthalmos, corneal ulcers, intra-ocular inflammation and infiltrative lesions, together with discussions on 'high risk eyes', ocular manifestations of relapsed disease and the global aspects of blindness in leprosy.

The course, which was attended by 11 participants, was run by Dr Margaret Brand of The Leprosy Mission and Mr Timothy ffytche from St Thomas's Hospital, London, together with contributions from Dr A Rajashwari and Dr Mary Jacob of Karigiri.

The Director and staff of Karigiri and The Leprosy Mission are to be congratulated on their continued support for this important and popular contribution to teaching.

Application for Research Grants, LEPRA UK

Purpose of LEPRA Research Grants

The eradication of leprosy is LEPRA's ultimate goal. Towards that end, LEPRA's main policy is to extend the WHO recommended multidrug therapy to as many leprosy patients as possible by means of domicillary control programmes and to encourage and support research which is directly relevant to the understanding, prevention and cure of leprosy.

LEPRA is therefore prepared to make grants for single projects which are designed to answer a single question or a small group of related questions in these areas. Such support will usually be limited to a maximum period of 3 years. Continuation of a grant within that period will be subject to annual review after receipt of a progress report, required at the end of each calendar year. Proposals for the support of a programme of research, rather than a finite project, will also be considered but not normally for an initial period of more than 3 years. In both cases an application for an extension of the grant beyond the normal 3-year period will be considered on its merits.

Personal direction of projects

It is expected that the grant holder will be actively engaged in his/her own project.

Applications

Applications must be submitted on the official grant application forms (which are available on request) and will be considered at the earliest possible meeting of LEPRA's Research Grants Committee, which normally meets in late January, May and early October. The deadlines for applications are 1 December, 1 April and 1 August.

For full application protocol and forms, please write to the Research Officer, LEPRA, Fairfax House, Causton Road, Colchester, Essex CO1 1PU, England and **NOT** to ILEP.

Centre for Medical Education, Dundee, Scotland

'The Centre is unique in the United Kingdom and has as one of its main functions the training of medical teachers.

The staff have qualifications and experience in both medicine and education. The Centre is actively involved in innovations in medical teaching in Dundee and has played a leading role in developing newer approaches to teaching and learning.

The city is situated centrally in Scotland and surrounded by some of the most attractive countryside in Britain. It is most conveniently reached via Dundee Airport, Edinburgh, Airport or by direct train services from London.'

Numerous courses are held throughout the year: Apply: Centre for Medical Education, Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland. Telephone: 0382 60111 Ext. 3090; Facsimile: (0)382 645748.

International Federation of Library Associations and Institutions (IFLA)

The main purposes of the International Federation of Library Associations and Institutions are: 'The Federation shall be an independent international nongovernmental association, without profit motive, whose purposes shall be to promote international understanding, cooperation, discussion, research and development in all fields of library activity, including bibliography, information services and the education of personnel, and to provide a body through which librarianship can be represented in matters of international interest.

In pursuance of these objectives, the Federation shall undertake such tasks and enterprises as may be determined appropriate and desirable, and notably:

—undertake, support and coordinate research and studies,
—collect, collate, publish and otherwise disseminate information relating to library, bibliography, information and training activity,
—organize general and specialized meetings and conferences,
—collaborate with international organizations in the field of information, documentation and archives,
—set up offices to carry out specific tasks,

and shall undertake such other activities as will promote fulfilment of theoretical and practical objectives in every field of library activity.'

There are currently members in 123 countries, of whom 67% are in the Third World. Further details can be obtained from: Royal Library, 5th Floor, POB 95312, Prins Willem Alexandrof 5, The Hague, The Netherlands.

Teaching material on leprosy: Bengali translations

Dr D S Chaudhury, Director, Greater Calcutta Leprosy Treatment and Health Education Scheme, 35/1/A Old Ballygunge First Lane, Calcutta 700 019, West Bengal, India has supplied the following useful list of books/booklets which have already been translated into Bengali:

1 *Technical Guide for Smear Examination for Leprosy by Direct Microscopy*, D L Leiker and A C McDougall.
2 *Preventive Rehabilitation of Leprosy Patients*, Dharmendra.
3 *Questions and Answers on the implementations of Multiple Drug Therapy (MDT)—(OXFAM Practical Guide No. 3)*, A C McDougall.
4 *Preventing Disability in Leprosy Patients*, by Jean M Watson.
5 *A Practical Guide to the Diagnosis and Treatment of Leprosy in the Basic Health Unit*, H W Wheate and J M H Pearson.
6 *A Simple Sandal for Insensitive Feet*, Miss P J Neville.
7 *A Footwear Manual for Leprosy Control Programmes*, Miss P J Neville.

A translation of the Ciba-Geigy booklet *Leprosy: basic information and management* is in the process of being produced.

Tropical Diseases Videodisc Project, London

The Wellcome Trust, 1 Park Square West, London NW1 4LJ, has produced a detailed descriptive brochure of a new project to catalogue and transfer all the visual parts of the Wellcome Trust Museum of Tropical Medicine onto videodisc. In addition, all the necessary information will be put into computer storage and made available for reference, teaching and learning. Interactive tutorials and interactive video programmes will be developed. Further information of this initiative may be obtained from Miss J Steward at the above address, or The Interactive Video Unit, Department of Pathology, School of Medical Sciences, University Walk, Bristol University, BS8 1TD, England.

Catalogue of Video-tapes, Schieffelin Leprosy Research and Training Centre, Karigiri

Topic	Minutes	System	Size	Author	Target Group	Cost (Rupees)*
1. Keep Blinking	22	PAL	VHS	Dr N Suryawanshi	Medical Officers, P.G. students of Ophthalmology and Medical students	175.00
2. Painless Feet	21	PAL	VHS	Dr E P Fritschi	Students, nurses and therapists	175.00
3. Healing While Walking	46	PAL	VHS	Dr E P Fritschi	Doctors, Medical students, nurses and therapists	175.00
4. The Red Eye	23	PAL	VHS	Dr N Suryawanshi	Medical officers and Medical students	175.00
5. Chemotherapy of Leprosy	38	PAL	VHS	Dr K Jesudasan	Medical students, Medical Officers, Non-Medical Supervisors and Para-Medical workers	175.00
6. Nerve in Leprosy	42	PAL	VHS	Dr E P Fritschi	Doctors and Medical students	175.00
7. Eye in Leprosy	28	PAL	VHS	Dr N Suryawanshi	Para-Medical Medical Supervisors	175.00
8. Malli Vasantham Ochinthi Health Education Programme in Telugu	36	PAL	VHS	Mr Sanjay Agrawal	Rural community in Andhra Pradesh	175.00
9. Phul Phutuk Health Education Programme in Bengali	37	PAL	VHS	Mr Sanjay Agrawal	Rural community in West Bengal	175.00
10. Tiraskaar A Health Education Programme in Hindi	28	PAL	VHS	Mr Sanjay Agrawal	Rural community	175.00
11. Skin Smears For *M. Leprae*	39	PAL	VHS	Dr C J G Chacko	Laboratory technicians, medical students and doctors	175.00
12. Looking Beyond The Bacillus Health Education Programme	27	PAL	VHS	Dr V P Macaden	Doctors, Medical students, Non-Medical Supervisors, para-medical workers and Health Educators.	175.00

Catalogue of Video-tapes (*continued*)

Topic	Minutes	System	Size	Author	Target Group	Cost (Rupees)*
13. Mice Against Leprosy	10	PAL	VHS	Dr Joel Almeida	Physicians	175.00
14. Mechanics, Not Medicine	40	PAL	VHS	Dr Paul W Brand	Medical Officers, Medical students, Orthopaedic technicians, multi purpose workers and para-medical workers.	175.00
15. Not Pills Alone	30	PAL	VHS	Dr E S Thangaraj	Para-Medical workers, Non-Medical Supervisors, Medical students and Medical Officers.	175.00
16. Apne Aap A Health Education Programme in Hindi	26	PAL	VHS	Mr Sanjay Agrawal	Leprosy patients	175.00
17. Nijer Prati Najer A Patient Education Programme in Bengali	26	PAL	VHS	Mr Sanjay Agrawal	Leprosy patients	175.00
18. Swayam Sahayam A Patient Education Programme in Telugu	26	PAL	VHS	Mr Sanjay Agrawal	Leprosy patients	175.00

* Postage and packing extra

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News and Notes

Dr Dharmendra retires as Editor of *Indian Journal of Leprosy*

The name of Dr Dharmendra has been closely linked with the *Indian Journal of Leprosy* from the time of its inception. He was the Editor of the Journal for almost 40 years with a few short breaks; and even during these breaks he maintained a close link with the Journal. Finally with the October 1989 issue of the Journal he retired at 90 years of age; only when he was physically unable 'to hold the baby' any longer. The Journal was indeed Dr Dharmendra's baby which he has carefully nurtured from 1938.

The Journal originally named *Leprosy in India* was started by the Indian Council of the then British Empire Leprosy Relief Association (now LEPRA) under the editorship of Dr Ernest Muir in 1929. It still continues to be the official organ of the Indian Council of BELRA renamed Hind Kusht Nivaran Sangh after India attained independence. In the early years the Journal only contained reports of surveys carried out on the prevalence of leprosy in different parts of India. These reports, although providing useful information, formed very monotonous narratives. After Dr Dharmendra took over as Editor, he converted the periodical into a regular scientific journal, with papers on original research, review articles, news and notes, abstracts of papers, etc. It thus fully justified being re-christened the *Indian Journal of Leprosy* in January 1984. While names of prominent scientists like Ernest Muir, John Lowe, N Mukherjee and C G S Iyer have been associated with the Journal as editors for short spells, it was Dr Dharmendra who gave the Journal its life and sustained it despite several obstacles and difficulties. In the earlier years when there were very few scientists engaged in leprosy research, Dr Dharmendra had to solicit scientific papers from those few scientists, persuade and urge many of the workers to record their findings for publication and at the same time maintain scientific standards. He wrote long editorials for most of the issues. He also had the problems of production; finding good printers and overseeing the quality of print, illustrations and layout of the Journal. While others tried to do all these and gave up, Dr Dharmendra stuck to the editorship for almost 5 decades with admirable tenacity and perseverance. It is only now, with advancing age and natural physical limitations that Dr Dharmendra had to hand over to the new Editor, Dr H Srinivasan, Director, Central JALMA Institute, Agra. The readers of the Journal the world over and scientists engaged in leprosy work greatly appreciate Dr Dharmendra's glorious contribution of editing and bringing out the Journal successfully.

K V Desikan

Report of the African Ministerial Consultation on Medical Education, Nigeria, 1989

The following report is the final one of the African Ministerial Consultation on Medical Education held in Abuja, Nigeria, 8 July 1989:

The African Ministerial Consultation on Medical Education just concluded at Abuja is a logical follow-up of the programme of the World Federation for Medical Education and World Health Organization leading up to the Edinburgh Declaration of August 1988. That Declaration was indeed a unanimous commitment to the improvement of the health of populations through strategies aimed at rethinking the pupose and reshaping the content of medical education worldwide. Responses and reactions to the Six-Themes Document of the World Federation for

Medical Education were followed by activities at the institutional, national and subregional levels in Africa over a three-year period. Then came the formulation at a Regional Conference in Brazzaville in October 1987 of a set of objectives for achieving the desired reorientation of medical education in Africa. These objectives were in keeping with the imperatives of primary health care.

The Brazzaville meeting, sponsored by WHO and WFME, was attended by an assemblage of Ministers of Health, Vice-Chancellors and Rectors of Universities, Provosts and Deans of Medical Schools, Heads of allied professional institutions and Representatives of Bodies such as the Association of Medical School of Africa (AMSA), the International Conference of Deans of French-speaking Medical Schools (ICDFMS), the Confederation of African Medical Associations and Societies (CAMAS), the NETWORK of Community, Oriented Medical Schools, the World Medical Association (WMA) and the Association of African Universities (AAU). It examined present trends in medical education on the African continent in the light of national strategies for primary health care. The Brazzaville Conference proposed to governments and health institutions in the region a plan of action for the implementation of the desired institutional changes for the training and utilization of appropriate medical manpower to meet present and future changes in health development.

The Abuja Ministerial Consultation further reviewed the earlier statements of commitment, now strengthened by the recent World Health Assembly Resolution (WHA) 42.38 on this subject by involving all *Dramatis Personae* (both Intersectoral and Multidisciplinary) so as to ensure speedy and effective implementation of agreed strategies. From the deliberations of this consultation should emerge paradigms of medical curricula relevant to the African situation, with primary health care as the foundation for their structure or at the very least existing curricula that are adapted to the health needs of the wider community.

A revised plan of action thus seems inevitable and should include the following elements:

a, a comprehensive restatement of goals; b, specific strategies for meeting such defined goals; c, definition of the modalities of resource allocation and co-ordination of the various activities in medical education; d, a realistic timescale for the implementation of the objectives; and e, a mechanism for periodic evaluation of the impact of various initiatives in health manpower development in all parts of the African region.

In order to meet these growing challenges, it is necessary to emphasize the importance of the *Political Will* as indispensable in the process of formulation, acceptance and implementation of national health policies within the overall context of national goals. All this calls for a careful appraisal of: the nature and extent of supporting resources, and skills in the organization and management of such resources, limited as they might be; admission criteria into medical schools; the increasing role of continuing medical education; and the challenges of integrating primary health care into existing medical curricula as well as the daunting task of countering traditional resistance by teaching staff of Faculties of Medicine to envisaged changes in the curriculum.

In updating the Brazzaville Plan of Action, it is necessary now to indicate what has been done since October 1987 and how best to proceed from this meeting:

a, all countries in the AFRO region have now received reports of the Brazzaville Conference; b, the World Conference on Medical Education took place in Edinburgh in August 1988 with the African region fully involved in its planning and deliberations. From the Edinburgh Meeting emerged a report which featured a twelve-point Declaration. It also went on to emphasize the need for *international collaborative programmes* for reorienting medical education. This has obvious implications for funding support; and c, the World Health Assembly at its meeting in May 1989, adopted a resolution embodying the essential components of the Edinburgh Declaration and urging member nations to widely disseminate and give serious consideration to its recommendations.

The three themes that formed the basis of the present consultations have been exhaustively treated at both plenaries and group discussions. The conclusions drawn from them are embodied in

the set of recommendations that constitute *The Abuja Plan of Action*. It is sufficient at this stage to highlight the subthemes under each major heading:

a, *Political Will and Mobilization*: implications of political will and commitment; leadership training in medical education; and mobilization in medical education.

b, *Relevance and Resources*: relevance of change for optimal impact; resource imperatives for change; and modalities of change.

c, *Overview of Existing Medical Education Systems in the African Region and their Orientation Towards Primary Health Care*: a round-table discussion featuring the experiences of Cotonou, Ife, Ilorin and Yaounde in integrating primary health care into their curricular structure *ab initio* and what lessons were to be learned from constraints in the implementation process.

Special attention was also drawn to the importance of the health team approach to manpower development and to the need to emphasize intersectoral and multidisciplinary collaboration.

The need for intra and inter country exchanges of personnel was also identified, as were integrated teaching, student-centred learning, problem-solving and community-based activities.

To put the recommendations in proper perspective and accord them the appropriate sense of urgency it was agreed that they should be structured by levels of implementation within a designated time frame.

Such levels of implementation should take the form of institutional, national, regional and global arrangements and the designated time frame would be categorized as immediate, medium and long term. On the basis of this format, a flow-chart was thought most practicable:

Activity	*Immediate 1989–90*	*Medium Term 1990–91*	*Long Term Beyond 1992*	*Level and Linkages*
Establishing of Medical Education Task Forces				National, Regional (WHO, AMSA, CAMAS)
Meeting of Deans (National Plans for Implementation)				Directors General—Health Education; Deans, & Provosts, Chief Medical Directors
Establishing of broad-based faculty curriculum committees with PHC emphasis or national curriculum committees				Institutional (University, Faculty, Student, Allied Professions) Government, Institutional, Community.
Organisation of Workshops, Reorientation & Training of Faculty and other categories of Health Manpower				Institutional, National, Regional, International
Establishment & Strengthening of Practice Areas with Intersectoral Approach				Institutional, Governmental (local, state), Community
Community Mobilisation/HFA				Community, Ministries (National, State) Medical Institutions
Staff Development with emphasis on leadership. Student exposure to Innovative Programmes				National, International

The medical school, the medical student and the control of leprosy in Africa (LEPTAC)

The above was a background paper for the Ministerial Consultation on Medical Education held in Lagos, Nigeria, 5–7 July 1989 (see previous item) for Leprosy Teaching and Training in African Countries (LEPTAC) and is reproduced here:

1 Leprosy is no longer regarded as a scourge with patients hidden away in leprosaria and none but a few benevolent workers to care for them. This disease can now be cured and has consequently been brought into the mainstream of medicine. Just as it is unthinkable that a medical student will graduate unable to diagnose, treat, manage and have the right attitude to malaria, tuberculosis or even AIDS, so too should be the case with leprosy. Leprosy is still a major problem in Africa. It is therefore paramount that urgent and serious consideration is given to the inclusion of adequate and appropriate instruction in leprosy, in the curriculum of all medical schools in Africa.

2 Doctors in Africa usually have important and varied roles not just as providers of care, but also as educators, supervisors, planners, decision-makers and implementors. All these roles are crucial for successful leprosy control. This paper aims to point out that it is important for leprosy control to ensure that all medical students in Africa reach a desired level of competence regarding leprosy patients.

3 *Leprosy in Africa*

The Continent of Africa (estimated population in 1985: 421,782,000) has a total of 886,465 registered cases of leprosy. Although there has been a considerable reduction in prevalence rates in the past 20 years, mainly due to the discharge or release from the control of cases following chemotherapy, many countries still report large numbers of registered cases, many of whom would normally be eligible for discharge or release from control if carefully assessed. Although there are some notable exceptions, most countries have shortcomings in the design and operation of their national leprosy control programmes, including the necessary training and supervision of health personnel.

4 *Multiple drug therapy: available, effective and in need of implementation*

In 1982, WHO published recommendations for the treatment of all cases of leprosy with multiple drug therapy (*'Chemotherapy of leprosy for control programmes'*; *Report of a Study Group*; *Technical Report Series 675*, *WHO*, *Geneva*, *1982*), using combinations of dapsone, clofazimine and rifampicin in regimens of relatively short duration. These have now been applied in most parts of the world and at the *13th International Leprosy Congress in the Hague* (September 1988) it was reported that over 2 million of the registered cases had been put on multiple drug therapy and that of these, over a quarter had completed their treatment and were no longer considered to have active leprosy. Despite these advances, however, the pace and extent of the implementation of multiple drug therapy worldwide calls for improvement, and in the Continent of Africa there are particularly serious grounds for concern in that only 8% of all patients with leprosy have so far received this form of treatment.

5 *The curriculum content; teaching modules; the availability of teaching–learning materials on leprosy*

The subject of leprosy is outstandingly well supported by a wide range of teaching–learning materials, in English, French, Spanish and (to a lesser extent) in Portuguese, which have been produced, printed and distributed by various agencies during the past 20 years. The International Federation of Anti-Leprosy Associations (ILEP) has a working 'sub-group' of 7 members (TALMILEP) coordinated by the German Leprosy Relief Association (P.O. Box 348, D-8700 Würzburg, West Germany) which is responsible for the origination, assessment, printing, publication, distribution, and translation of suitable items of health learning materials for various grades of leprosy worker. The 'English language book list' of all items will be available at the Ministerial Conference. In addition, videos, colour transparency text teaching sets, exhibits, atlases and other teaching aids (not necessarily included in the above book list) are also available. Finally, three points with regard to curriculum content and the teaching of leprosy in medical schools bear

emphasis: 1, the remarkable range of teaching–learning material described above is available now, much of it free or at low cost. It can be supplied, with minimal delay, to both teachers and students and there is no reason why the medical school libraries in all leprosy-endemic countries of Africa should not have on their shelves an up-to-date selection of books and other items for study and reference; 2, the construction of appropriate teaching modules would present no difficulty to professional people with experience of teaching in leprosy and, if required, they are available to help, and 3, if the education 'formula'—a sound basis of accurate information, plus all the necessary teaching–learning materials for both teacher and student, plus appropriate modules, backed by problem-based, self-instructional and distance-learning techniques—is acceptable and successful, it might well have 'spin-off' for the teaching of other subjects of major public health importance in Africa.

Global evaluation of the introduction of MDT, 4th edition, *WHO Leprosy Epidemiological Bulletin*, No. 4, 1990

This Report is mainly statistical and is divided into three sections: 1, detailed statistics of WHO regions; 2, summary of statistics by country; and 3, detailed statistics by country. The Introduction includes definitions used, sources of data and limitations of the report. It opens as follows:

Introduction of Multidrug therapy (MDT) was recommended by a WHO study group in 1981 mainly because of the ever increasing threat caused by the worldwide development of secondary and primary resistance to dapsone.

With the experience gained so far, it becomes more evident every day that if a major breakthrough is to be made in leprosy control, it is through the worldwide use of highly bactericidal multidrug regimens.

Besides the effective capacity to cure the leprosy patients harbouring dapsone resistant bacilli, the WHO MDT regimens permit:

a shortening of the duration of treatment, leading to a better compliance of the patients, and an increased rate of self-reporting;

a rapid decline of the leprosy prevalence resulting in a decreased workload for the health workers;

a reduced risk of post-therapeutic relapses.

More important, generalization of MDT in an area seems also to result in a sharper decline of the leprosy incidence than was experienced with dapsone monotherapy.

Nowadays, multidrug therapy regimens are used in most endemic countries. Effective coverage of the patients with MDT differs however widely from country to country. The 'Bulletin' presents information on MDT from 174 countries and territories worldwide. It does not intend to be just one more compilation of figures, but rather a stimulus for all those in charge of leprosy control programmes to implement MDT in the field and to collect the necessary information to monitor the process.

The *Bulletin* was prepared in consultation with Professor M F Lechat of the International Federation of Anti-Leprosy Associations (ILEP) and Département d'Epidémiologie, Université Catholique de Louvain, EPID 30/34, Ecole de Santé Publique, Clos Chapelle-aux-Champs 30, 1200 Bruxelles, Belgium.

Tropical Diseases, Progress in International Research, 1987–88, WHO

This book reviews recent progress in international efforts to combat the huge scale of suffering caused by tropical diseases. Prepared by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), the book concentrates on progress made in controlling the Programme's six target diseases: malaria, schistosomiasis, filariasis, trypanosomiasis, leishmaniasis, and leprosy. Though work supported or coordinated by TDR is emphasized, the report also considers advances in any area of academic or industry research that may contribute to the control of tropical diseases. Throughout, an effort is made to illustrate the diversity of

approaches, whether involving the tools of molecular biology or the use of simple insect traps, that are needed to match the complexity of these difficult and dangerous diseases.

The book opens with an overview of selected recent advances that are either challenging conventional research approaches, particularly concerning strategies for drug and vaccine development, or yielding new practical tools for diagnosis, prevention, patient care, treatment, and control. Examples cited range from new diagnostic tests for malaria and schistosomiasis to the use of insecticidal paints in the control of Chagas disease. Though the traditional emphasis on drug and vaccine development is readily apparent, the report records a number of new efforts to strengthen field research as a major contribution to the development and refinement of disease control strategies.

In keeping with this emphasis, the second chapter, authored by a science writer, presents a series of impressionistic 'scenes from the field'. Focused on the field use of ivermectin for the treatment of onchocerciasis, and multi-drug therapy for leprosy, these first-hand accounts offer a rare opportunity to view the terrain and personalities that compose the real challenge of bringing new technologies to the people who need them.

The third and most extensive chapter profiles international research contributing to the control of each of the six target diseases, including numerous examples of the progress made and problems encountered, the opportunities for intervention specific to each disease, and the actions being taken to exploit these opportunities. Whether concerning the effectiveness of pyramidal traps for reducing the numbers of tsetse flies or experimental work indicating that a safe and effective schistosomiasis vaccine may become a reality, the picture that emerges is one of a vastly diversified and globally coordinated effort to out-smart diseases that strike in an almost infinitely varying environment of ecological conditions. The book concludes with an over-view of several new policies and structures introduced to strengthen research capability, followed by a brief explanation of how TDR is structured, managed, and financed.

This is the Ninth Programme Report of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), WHO 1989; 136 pages; Order No. 1150327; Price Sw fr. 20, US$16.00. From WHO, Distribution and Sales; 1211 Geneva 27, Switzerland.

Research on interactions between AIDS and tropical diseases

Special funds have been made available by the World Bank to TDR and the Global Programme on AIDS (GPA) to support high quality research to investigate the nature and expected consequences of interactions of HIV infection with the major endemic diseases in developing countries.

Points of particular concern include the interactions between malaria and HIV in pregnancy and the neonatal period; HIV and visceral leishmaniasis (kala azar); technological advances for ensuring a safe blood supply (e.g. simplified diagnostic tests that simultaneously detect multiple infections such as HIV, Epstein-Barr virus, malaria, and Chagas disease); and operational issues such as effects of multiple diseases on treatment and prophylaxis.

A document titled 'Inter-relations of Tropical Diseases and HIV Infection: Report of an Informal consultation Held at the Kenya Medical Research Institute (KEMRI), Nairobi, December 1987' contains protocol outlines of high priority field research aimed at investigating such interactions and may be useful in preparing the desired research proposals.

For a copy of this document and the standard TDR research proposal forms, please write to: Dr Richard H Morrow, TDR, World Health Organization, 1211 Geneva 27, Switzerland.

The Heiser Program for Research in Leprosy

Beginning Postdoctoral Research Fellowships, Research Grants, and Visiting Research Awards available in amounts up to $25,000 per year, plus other allowances. Applicants should have an MD, PhD, or equivalent degree. Applications by 1 February 1991, for awards to be activated June to December 1991. For information, write to: The Heiser Program, 450 East 63rd Street, New York, NY 10021, USA.

Editorial and subscription address for *Leprosy Review*

Please note that submission of manuscripts and all subscription queries should be made to: LEPRA, Fairfax House, Causton Road, Colchester, Essex CO1 1PU, England.

WHO *Guide to Leprosy Control* in French, Spanish and Portuguese

It is perhaps not widely known that the *Guide to Leprosy Control* produced by WHO is also available in French, '*Guide de la lutte antilepreuse*'. Published in 1989 it has an extent of 140 pp, WHO Order No. 2152064, and costs Swiss franc 23/US $18.40. Spanish and Portuguese versions may be requested from: Pan American Sanitary Bureau, 525, 23rd Street, N.W. Washington, DC 20037, USA.

Technical guide for sputum examination in tuberculosis

This well-established Guide, originally published in 1978 as Supplement No. 2 in the *Bulletin of the International Union Against Tuberculosis*, is available from the International Union Against Tuberculosis and Lung Disease (IUATLD), 68 Boulevard Saint-Michel, 75006 Paris, France. It describes in detail: collection of specimens; storage and transport of sputum specimens; the laboratory; receptor and registration of sputum specimens, staining technique; examination by microscopy; results and recording; disposal of examined slides; despatch of results of examination; and formulation of reagents.

Because of the date of publication it does not include advice on the additional health risks to staff brought about by the HIV/AIDS epidemic.

International Community Eye Centre, Adelaide, Australia

The following is extracted from the June 1989 *Newsletter* of the School of Medical Education, The University of New South Wales, PO Box 1, Kensington, New South Wales, Australia 2033.

The human suffering caused by blindness is obvious. Less obvious are the social and economic consequences, especially in developing countries, where the majority of the world's blind live and where economic reserves are minimal. The World Health Organization estimates there are between 28 and 42 million blind in the world today.

There is an opportunity to reduce the impact of visual disability on communities, particularly rural communities in developing countries. To achieve a reduction in visual disability requires the effective application of medicine at a community level.

The International Community Eye Care Centre in the Department of Ophthalmology at Flinders Medical Centre is providing leadership in this important area.

The Flinders' Centre aims to provide the following services:

(i) Carry out basic and applied ophthalmic research on problems amenable to epidemiologic techniques, collaborating with whomever is able and available to contribute.
(ii) Serve as a resource for epidemiology and biostatistics for investigators, offering advice and consultation on study design and data analysis.
(iii) Provide training in epidemiology and public health ophthalmology for physicians from the region either in their own country or in Australia.
(iv) Provide consultation to national blindness prevention programmes either through existing agencies and foundations (WHO, Helen Keller International, Royal Commonwealth Society for the Blind and Christian Blind Mission International) or on a bilateral basis.
(v) Develop unique teaching programmes for those delivering ophthalmic care in developing countries. These programmes will be designed to fit the particular needs of the community bearing in mind racial, social, economic and political factors influencing health care delivery.

Limited funding has been provided to set up the Centre and to conduct the first blindness prevalence survey in South Australia. In addition to such specific project related funds, however, both governmental and non-governmental support is required for this unique resource.

More information about this Centre may be obtained from: Dr Henry S Newland, Senior Staff Specialist/Senior Lecturer in Ophthalmology, Flinders Medical Centre, Department of Ophthalmology, Bedford Park, South Australia 5042.

International Union Against Tuberculosis and Lung Diseases (IUATLD)

The International Union Against Tuberculosis and Lung Disease (IUATLD) is a nonprofit, nongovernmental voluntary organization founded in 1920. Its members, an international federation of organizations and individuals, are dedicated to the prevention and control of tuberculosis and lung disease (including the respiratory complications of AIDS), to disseminating information about the hazards of smoking, and to the promotion of overall community health. The IUATLD's headquarters are in Paris, France.

Main objectives:

1 To coordinate, assist, and advance the work of the IUATLD Constituent Members throughout the world.
2 To establish and maintain close relationships with the World Health Organization and other international health organizations and institutions.
3 To collect and disseminate knowledge on all aspects of tuberculosis and lung disease, and on related community health problems. This objective is pursued through conferences, research, and published materials.

Main activities:

- *Communication* with members through circular letters, the *Bulletin* (the journal of the IUATLD), conferences, and scientific activities.
- *Dissemination of scientific knowledge* through publications, world and regional conferences, seminars, lectures, and correspondence.
- *Collaboration* with other international agencies—particularly with the World Health Organization, but also with the International Union Against Cancer, the International Union for Health Education, the International Federation of Anti-Leprosy Association, the International Children's Center, and others.
- *Operational and applied research* through the Scientific Committees and through field projects such as those described below.
- *Field projects* carried out through the Mutual Assistance Program, which was created in 1961. Under this programme, the IUATLD extends technical and material support to efforts designed to control tuberculosis in developing countries. These activities are supported by special funds donated by member associations and government agencies from more affluent countries.

Address: Dr Annik Rouillon, Executive Director, IUATLD, 68 Boulevard Saint-Michel, 75006 Paris, France.

MAP International, USA

MAP International (Medical Assistance Programs) is a non-profit-making Christian global health organization. The following is extracted from information supplied by the Organization:

Medical supplies

- MAP receives and distributes more than $20 million worth of medicines and medical supplies each year.
- These FDA-regulated medicines are donated through MAP by more than 200 leading US health-care industries.
- 650 mission hospitals and clinics in nearly 80 developing countries order these otherwise scarce and unaffordable supplies.
- Cash donations from individuals, churches and other friends help make arrangements for inventory, processing, warehousing and shipping to remote areas.
- Cash contributions for the hospital supply programme provide more than 15 times their value in life-saving supplies because they are donated.

- During emergencies like floods, earthquakes, typhoons and other natural and civic disasters, relief medicines reach victims through professionals working on the scene.
- Cooperative efforts with Christian missions and organizations on location ensure that appropriate and requested supplies reach the people for whom they are intended, and reach them quickly

Community assistance

- MAP's community health assistance helps Third World rural communities work together to detect and eliminate causes of disease, such as impure water and malnutrition.
- Field staff in South America, the Caribbean and Africa assist missionaries and national church leaders in developing projects that improve health in the home and community.
- MAP's Learning Resource Center and training workshops provide current publications and practical help for medical missionaries working in developing countries.
- On-site training programmes develop the skills needed by village health workers, supervisory staff and project leaders to implement effective community health programmes.

For further details write to: MAP International, 2200 Glynco Parkway, PO Box 50, Brunswick, GA 31521-0050, USA.

Intermediate Technology

The Intermediate Technology Development Group (known as IT) works with Third World rural communities on long-term sustainable development projects. Using appropriate technologies to create jobs in some of the poorest areas of the world, IT offers hope and opportunities for people to work their way out of poverty. Founded by E F Schumacher, the author of *Small is Beautiful*, the charity has worked in over 60 countries since its formation in 1965. IT has country offices in Peru, Sri Lanka, Zimbabwe and Bangladesh and is reliant on public donations to fund over half of its work.

Small World is the Newsletter of IT at Myson House, Railway Terrace, Rugby CV21 3BR, England.

International Gandhi Award 1990 for Dr M F Lechat and Dr R V Wardekar

Dr M F Lechat, a leading epidemiologist from Belgium, and Dr R V Wardekar, a pioneer in introducing leprosy control programme on the national scale in India, have been selected to receive the International Gandhi Award for 1990.

The selection was done by the International Gandhi Award Committee: Dr Shankar Dayal Sharma, Chairman, Shri Ramvilas Paswan (Minister for Welfare), Shri P Upendra (Minister for Information and Broadcasting), Shri S K Singh (Secretary, Ministry of Foreign Affairs), Dr S D Gokhale (Convenor) and Shri S P Tare (Director, GMLF).

Dr Lechat is a leading epidemiologist who has greatly contributed to the epidemiological understanding of the leprosy problem. He was President of the International Leprosy Association and is President of the International Leprosy Union. Dr Wardekar is the father of leprosy control work in India and evolved a methodology for leprosy control work which was accepted by the Government of India in 1955–56 with the introduction of the National Leprosy Control Programme. Dr Wardekar was instrumental in the drafting of the first four 5-year plans for leprosy.

The International Gandhi Award is given bi-annually and was founded by the Gandhi Memorial Leprosy Foundation, Wardha which is a voluntary agency with a network of centres in seven Indian States. The first recipients of the Award were Dr (Mrs) Turkan Saylan (Turkey) and Dr Dharmendra (India) in 1986; the 1988 Award was given to Dr Ma Haide (China) and Professor T N Jagadisan (India).

Instructions to Authors

Papers submitted for publication in *Leprosy Review* should be sent to the Editor, Professor J. L. Turk, LEPRA, Fairfax House, Causton Road, Colchester CO1 1PU, England. The name(s) of the author(s) and the place where the work was done should be clearly indicated below the title of the paper. Degrees and diplomas are not to be included.

It is understood that the paper is offered to *Leprosy Review* alone, that it will be subject to editorial revision, and that its copyright becomes the property of the British Leprosy Relief Association. Manuscripts should be typewritten, in double spacing, on one side of A4 (297 × 210 mm) paper, with wide margins (4 cm all round). Contributors must send three complete copies of the text, tables and figures. On a separate sheet give the title, short title, name and postal address of the author, together with the name of the institution where the work was done. Abbreviations of titles of journals should follow the list of journals indexed in *Index Medicus*. References to books should include the editor(s), publisher and place of publication.

Units and Abbreviations. The Journal recognizes the adoption of the Système International d'Unitès (SI Units) proposed in *Units, Symbols and Abbreviations* (1972) published by the Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. Abbreviations should only be used for unwieldy names, and only when they occur frequently.

Proofs are submitted to authors for immediate return by air.

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