LEPROSY REVIEW

Volume 46, Number 1, March 1975

Published Quarterly for the
British Leprosy Relief Association
by Academic Press

Leprosy Review

The Scientific and Research Quarterly of the British Leprosy Association LEPRA

International Standard Series Number 0305–7518

Volume 46: 4 issues, March–December 1975; Inland, £6.50 including postage. Abroad; £8.00 including postage.

Subscription orders should be addressed to Academic Press Inc. (London) Limited, 24/28 Oval Road, London NW1 7DX, except those originating in Canada, the U.S.A. and Central and South America, which should be sent to Academic Press Inc., 111 Fifth Avenue, New York 10003. $18.00 + $1.25 postage abroad.

British Leprosy Relief Association
Registered Offices: Fairfax House, Causton Road, Colchester CO1 1PU

Obituary

Dr Ernest Muir, the doyen of British leprologists, died on 1 November, 1974 after a long period of increasing weakness and failing sight. He was 94.

Ernest Muir was born in Banffshire on 17 June, 1880, a son of the manse. He was educated at Watson's College, Edinburgh, and at the Edinburgh Medical School, qualifying in 1903. Within a few months, he was working as a medical missionary in Tiberias, Syria, under the auspices of the Edinburgh Medical Missionary Association. He passed the clinical part of the Edinburgh M.D. while on leave in 1905, and completed his doctorate 5 years later with a thesis on Kala-azar, prepared while he was a missionary in Bengal. In addition to other duties, he assumed responsibility for the care of leprosy sufferers, little imagining at the time that this would be the introduction to his life's work.

On leave in 1914, he passed the examinations for the Edinburgh F.R.C.S., no mean feat for a busy physician. Back in India, he showed himself a most competent doctor, with broad interests and a humane, kindly approach to all sorts and conditions of man. When, in 1920, Sir Leonard Rogers invited him to become Head of the Leprosy Section of the newly-opened School of Tropical Medicine in Calcutta, Muir responded to the challenge, and began a career that was to make a lasting impression on the leprosy problem in India and indeed the world. Modestly, and with quiet determination, Muir initiated research into the preparation of derivatives of chaulmoogra oil, and into more productive fields of animal experimentation and histopathology. His department attracted many outstanding Indian doctors who later contributed much to leprosy research.

He was examiner in Tropical Medicine in Calcutta for many years, and from 1933 to 1935 was Professor of Tropical Medicine. For his services to India, he was awarded the K.I.H. gold medal and bar, and was appointed C.I.E.

His connection with the British Leprosy Relief Association dates from 1924, when he interested the Viceroy, Lord Reading, in the problem of leprosy in India, and advised the Indian Council of BELRA on the policy it should adopt in the disposition of the funds becoming available. On his retirement from active clinical work in 1935, he became Secretary, and subsequently Medical Secretary of BELRA with Editorial responsibility for *Leprosy Review*. In this capacity, he travelled to West Africa and then to the Caribbean, where he was for a time Medical Superintendent of the Chacachacare Leprosy Institution in Trinidad. Further journeys followed, during which he lectured and advised governments of many countries. One of his most notable initiatives during this period was the founding of the BELRA Research Unit at Uzuakoli, Nigeria, with the first objective of investigating the practicability of oral dapsone in leprosy treatment. On his return from the Caribbean, Muir was appointed C.M.G.

A founder-member of the International Leprosy Association in Manilla, 1931, he was for many years its Secretary-Treasurer, and was Secretary-General of the International Congresses in Cairo (1938) and Havana (1948), and an Honorary

Vice-President. A careful investigator and writer, Muir will be remembered particularly for his work on diasone and dapsone. He strove to keep abreast of research in leprosy, and contributed a thoughtful paper on "Lepra reaction and the general adaptation syndrome" to *Leprosy Review* when he was 82 years old.

He was Vice-President of The Leprosy Mission. Between 1949 and 1951, and again in 1961 he worked on special assignments for the Mission at Purulia, West Bengal. The Mission honoured him at a party organized to celebrate his 90th birthday.

Throughout his long life, Ernest Muir was actuated and animated by his deep Christian convictions. His kindly smile and genuine friendliness broke through the barriers of race and culture. Wherever he went, and whatever he did, he was a gracious and sympathetic doctor, combining a keen intellect with deep compassion for the leprosy sufferer.

S. G. BROWNE

Dr Ernest Muir, the doyen of leprologists and a saint among men, has passed away in London at the venerable age of 94. His long life was a saga of service and sacrifice and "incessant toil unsevered from tranquillity". To infinite compassion he united boundless scientific curiosity and advanced knowledge in leprosy as well as promoting kindness and fellow-feeling towards leprosy patients. He had the unique privilege of working in the dark night of leprosy for the coming of the dawn, and also to work in the bright days of better drugs, better knowledge and improved outlook. Indeed, he was one of the great early pioneers who saw fruits of their work.

After working as a medical missionary in the Purulia Leprosy Home, he worked in collaboration with Sir Leonard Rogers in leprosy research at the Calcutta School of Tropical Medicine. As Medical Adviser of the Leprosy Mission and the British Leprosy Relief Association, he shaped enlightened policies. He was the Secretary of the International Leprosy Association, though he never aspired to be its President.

We in India owe him an immense debt, especially for his outlining forward policies of leprosy control through his well-known method of P.T.S. (Propaganda, Treatment and Survey), which he propounded in the dismal days of asylums when no one thought of controlling leprosy by planned work in villages.

In 1950 Dr Muir presided over the Third All India Leprosy Workers' Conference in Madras and his moving words still ring in my ears: "There is no section of the community which deserves by right more thoughtful care and consideration than those afflicted with leprosy; and, now that we have knowledge, if this care and consideration are withheld, judgement will surely fall upon those responsible".

T. N. Jagadisan,
Honorary Secretary,
Hind Kusht Nivaran Sangh,
Madras

Editorial

COMMON FEATURES IN RAPIDLY DECLINING LEPROSY EPIDEMICS

Many leprosy workers devote years of their lives to their chosen profession without seeing any marked change in the amount of leprosy around them. To the fortunate few is given the privilege of witnessing a progressive decline in the prevalence of active leprosy, which, beginning almost tentatively, gains in momentum year by year, and in a comparatively short time becomes unmistakable and even massive. In this Number of the *Review*, Dr J. N. Rodriguez, doyen of Philippine leprologists, describes such an experience in the island of Cebu.

The Philippines Republic was particularly blessed in the earlier years of this century in having a government prepared to spend considerable sums on leprosy control, and a succession of distinguished leprologists notable for their careful field work. The findings they report are in the highest degree trustworthy, and are briefly as follows. During the period 1905 to 1955 a very substantial decline occurred in the prevalence of leprosy in Cebu. Between 1920 and 1940, in an area under intensive observation, the incidence of lepromatous leprosy declined by 60%. Although at first the incidence of non-lepromatous leprosy increased, later it also declined, and between the years 1930 and 1955 the total recorded number of people with active leprosy fell from 5290 to 2882, a fall of 46% in 25 years. Sulphone treatment became routine in 1955.

This is of course not an isolated phenomenon. Other examples from the pre-sulphone era include Norway (Lie, 1929), Nauru (Bray 1930; Wade and Ledowsky, 1952) and E. Nigeria (Davey *et al.*, 1956; Davey, 1957). Thailand, Khon Kaen Province, is a more recent example. The first stage in the process, namely the decline in incidence of lepromatous leprosy, is now a feature of several modern leprosy control programmes. A comparison between the situations prevailing in the various areas where this phenomenon has occurred immediately reveals that while there is no single pattern common to them all, there are important common features.

The most important question posed by such events is how far they can be attributed to the natural course of leprosy in the situations concerned, and how far human intervention played some part. Epidemics rise and fall, sometimes rapidly, sometimes slowly, as the result of the complex interplay of many factors in a dynamic constantly changing situation. The disappearance or attenuation of the infecting agent, the development of resistance to it, whether attained through genetic influences or acquired by repeated contact with it, all these are part of the picture.

Some attenuation of the bacillus has been suggested as a possible explanation for the burning out of leprosy infection after many years even in patients with lepromatous type leprosy. Even if true, this could not account for rapid change in the course of the disease in the community. Of greater relevance is the possibility of differences in pathogenicity between one strain of *Myco. leprae* and another, with short lived epidemics caused by a mild strain. In this issue, Job *et al.* offer

evidence of a difference in pathogenicity in the mouse between one strain of the bacillus and others in India. Hitherto, strains of *Myco. leprae* from different parts of the world have produced similar pathogenic effects in mice. While not ignoring the possibility, it does not seem likely that attenuated strains of the bacillus can account for rapidly declining epidemics in places as far apart as Northern Europe, West Africa, S.E. Asia and Oceania.

Natural resistance involves genetic factors. Molesworth (1933) in a detailed study of natural selection in leprosy considers this an important influence, but only operative through succeeding generations. It could not account for major changes within the span of 25 years.

When considering the development of acquired resistance, and in particular the influence of tuberculosis, we are on much more solid ground. The prevalence of leprosy in all the areas quoted was well above the threshold at which exposure to *Myco. leprae* by the whole population is possible. While initial exposure could account for the high susceptibility of all age groups, the relative frequency of indeterminate and maculo-anaesthetic types of leprosy, and the infrequency of polar forms, repeated exposure would tend to encourage self-healing and a shift towards the tuberculoid end of the spectrum. The clinical leprosy seen in Nauru, Cebu and E. Nigeria would all suggest an early phase in the epidemic rather than a late stage, with increasing polarisation and fewer clinical cases as the epidemic declined, the whole process of rise and fall condensed into a relatively short period.

During the period under review, the Philippines was experiencing a massive epidemic of tuberculosis. Canzares (1948) gives the death rate from tuberculosis before the 1941–45 war as 230 per 100,000 population, and estimated that in 1948 no fewer than 500,000 out of a population of 18 millions had active tuberculosis. It must be presumed that a very high proportion of the population of Cebu was exposed to *Myco. tuberculosis*, that those unable to develop resistance to it died of it, and among the remainder it is at least probable that tuberculin sensitivity gave enhanced protection against *Myco. leprae*, thus providing an important element in the decline of the disease. Where Norway is concerned it is inconceivable that a disease so prevalent in N.W. Europe had passed Norway by, especially with Bergen being one of the cities of the Hanseatic League. The influence of tuberculosis could also have been considerable there. I have not been able to find data relating to tuberculosis in Nauru, but the pattern of leprosy there does not favour heavy involvement with tuberculosis (Leiker, 1960). In Nigeria however, a tuberculin and lepromin survey of an area where leprosy had been under close observation for 15 years gave in 1955 an adult plateau level for 10TU tuberculin of 65%, a figure not consistent with any long experience of tuberculosis, and indeed clinical tuberculosis was still a rare disease at that time (Davey *et al.*, 1958). Where the interplay of tuberculosis and leprosy is concerned, we need to remember that whereas both diseases spread along trade routes, it is possible to have very heavy involvement of tuberculosis along such routes with negligible involvement in static rural communities quite nearby. If tuberculosis is a factor in the decline of leprosy in such communities, its introduction there and a consequent high incidence must first have taken place. Tuberculosis is an important but inconstant factor in this story.

Reference is appropriate at this point to malnutrition and debility. Lie relates apparent periodic increases in the prevalence of leprosy in Norway to periods of economic hardship. Rodriguez on the other hand quotes the example of a locality

under close observation where serious economic hardship had no observable effect on the prevalence of leprosy. When it is recalled that the period with which we are concerned included both the economic stringency of the 1930's and the disastrous war years, it would appear that in the Philippines as in many other places there was no direct link between leprosy and economic deprivation.

Turning to human intervention in the leprosy epidemic, in the year 1907 legislation came into force in the Philippines providing for the compulsory isolation of people with multibacillate types of leprosy in the island of Culion. At one time 7000 patients were isolated there. Throughout the period under consideration we have to envisage the steady removal from the island of Cebu of people who were a source of leprosy infection to others, and this is one obvious explanation for the decline in leprosy observed. In Nauru, although 90% of patients were classified as suffering from leprosy of maculo-anaesthetic type, no less than 189 out of 368 patients were classified as infective and isolated. Isolation was thus intensive, and included all patients liable to degenerate towards the lepromatous end of the spectrum. Compulsory isolation is by general consent an inefficient method of leprosy control, not only because compulsion encourages concealment, but because early lepromatous cases are liable to be discharging large numbers of viable *Myco. leprae* from their noses into the environment long before the disease is sufficiently obvious to bring them within the legal net. A unique element nevertheless arises in the areas of leprosy decline which concern us. In the Philippines, patients obviously liked living at Culion. The small size of Nauru made the oversight of isolation there a simple problem. In Nigeria, a much more liberal system made the isolation of the same types of patient a matter of public opinion and personal choice, but there these methods worked, and almost all open cases voluntarily isolated themselves. In Norway, although only 10% of patients were isolated in hospitals, the principles of home isolation were effectively applied, according to Lie (1929). We have here the first thread binding all these examples together.

Was treatment a factor? In Norway it certainly was not, but in Cebu, Nauru and E. Nigeria a high proportion of all patients received treatment with chaulmoogra or hydnocarpus oil or their derivatives. In my experience in Nigeria, hydnocarpus oil had little effect in established lepromatous leprosy, but it was the general consensus of opinion among leprologists in those days that hydnocarpus oil did have some effect in encouraging resolution, and so preventing some indeterminate and early borderline cases from degenerating into the lepromatous type. This was certainly the opinion of Rodriguez and of leprologists in Nauru.

In my judgement, the chief virtue of hydnocarpus oil lay in a different direction. At a time when Western medicine was being appreciated for the first time, in particular forms of treatment by injection, hydnocarpus oil popularized leprosy treatment, and encouraged patients to come forward in large numbers in the early stages of their disease.

This leads us immediately to what I believe is the second thread linking these events, and one rarely given the significance it merits. In every example quoted we have a situation where ignorance and prejudice were replaced by reason, and in the atmosphere of cooperation so generated, patients felt able to come forward without fear and cooperate on a large scale in the measures provided. Lie regards this factor as of great importance in Norway, though there it was the understanding of the infectivity of leprosy which replaced the concept that leprosy was non-infectious. In Nauru the entire population was examined at

monthly intervals. Excellent cooperation was given in Nigeria and in areas under close observation in the Philippines.

Nowhere did an informed leprosy consciousness come by accident. It had to be won by sustained intensive effort, as Rodriguez indicates.

The lesson for us is obvious. While acknowledging fully the importance of immunological factors which operate quite apart from leprosy control measures, there are two common threads linking together the examples quoted of a rapid decline in leprosy in pre-sulphone days, both derived from human intervention. The first is the isolation of infective and potentially infective cases, the second a successful campaign of public education. Both have their modern counterparts. Sulphone therapy, by its speedy action on infection of the nose and throat has largely replaced isolation as an effective means of removing from public circulation large numbers of viable *Myco. leprae.* The other determining factor, the large scale cooperation of public and patients alike is as relevant as ever it was, and as in the past, it still has to be won. The maximal extension of sulphone treatment, and a skilled sustained campaign of leprosy education are priorities for us all.

References

Bray, G. (1930), *Proc. R. Soc. Med. Section Trop. Dis.* **23**, 1370.
Canzares, M. (1948). *Amer. Rev. Tubercul.* **57**, 149.
Davey, T. F., Ross, C. M. and Nicholson, B. (1956). *Brit. Med. J.* **2**, 65.
Davey, T. F. (1957). *Int. J. Lepr.* **25**, 329.
Davey, T. F., Drewett, S. E, and Cynthia Stone (1958). *Lepr. Rev.* **29**, 81.
Leiker, D. L. (1960). *Lepr. Rev.* **31**, 241.
Molesworth, E. H. (1933). *Int. J. Lepr.* **1**, 265.
Lie, H. P. (1929). *Trans. R. Soc. Trop. Med. Hyg.* **22**, 357.
Wade, H. W. and Ledowsky, V. (1952). *Int. J. Lepr.* **20**, 1.

T. F. Davey

Lepr. Rev. (1975) **46**, 9-13

The Trend of Leprosy in Cebu Province, Philippines

JOSE N. RODRIGUEZ*

Philippine Division, American Leprosy Foundation (Leonard Wood Memorial)

(1) Although covering different periods of time and different sections of the population, four studies are presented which establish the fact that there had been a downward trend of leprosy, at least of the lepromatous type, in the Province of Cebu, Philippines. (2) This decline occurred during a period when the administrative procedures for the control of leprosy consisted of compulsory segregation of bacteriologically positive cases and the out-patient treatment of pausibacillary cases at skin clinics. Moreover, the downward slope occurred during the pre-sulphone era. (3) Possible causes of the decline of leprosy in this Province are discussed.

From the time of the Spanish regime, it was common knowledge in the Philippines that the Province and Island of Cebu had the largest number of leprosy cases in the country. In fact there is historical reference to a large hospital for sufferers from leprosy built in 1854 by Bishop Romualdo Jimeno at the Carreta District, Cebu City, with the object of saving leprosy sufferers from begging in the streets. In a rapid survey made in 1896, the Medico-titular of the Province, Dr Rogel Lebres reported finding 426 cases in the city itself and estimated that there must have been more than 2000 leprosy sufferers in the Province at the time his survey was made.

The first attempt to determine the trend line of leprosy in Cebu was made by Rodriguez in 1936, using the method of least squares and based on the number of cases discovered annually from 1904 to 1934. The yearly number of discovered cases showed an insignificant downward trend ($a = 222 : 8$; $b = 1.40$).

In 1947, Doull *et al.* published an article in which they made use of historical inquiry as a method of estimating the trend of leprosy. The data which they used were collected from intensive surveys done in the towns of Cordova and Talisay, Province of Cebu, and which had served as the basis of a number of previous epidemiological studies. A detailed history was obtained for every household studied, in some cases going back to the last few years of the preceeding century. Diligent efforts were made to include all births and deaths and all entrances into and departures from the household. At the same time, intensive inquiries were made as to the existence of leprosy in every individual in these two towns. Records on 3024 families were available, which included those of 21,791 individuals, varying in age from newly born infants to people more than 80 years of age. At the same time, all the living persons with leprosy were questioned, their

* Formerly Director of Disease Control, Department of Health, Republic of the Philippines.
Received for publication 22 August, 1974.

records in the leprosaria or skin clinics were analysed, and details about the history of the disease were obtained directly from members of the household and other observing persons in the n
bacteriologically negative cases were secured and sent to Dr H. W. Wade at Culion, for confirmation of the diagnosis.

During the period covered by this study, 402 cases of leprosy had occurred in these families. The data thus obtained permitted the use for the first time of a modified life-table method of analysis to determine the attack rate of the disease.

The authors arbitrarily divided the period of observation before and after 1 January, 1915, care being taken to select two groups of individuals in such a manner that the experience of the groups was mutually exclusive and limited to the same number of years. It was found that when the two periods, each covering a life-experience of 25 years, were compared, there was evidence of a downward trend as far as the incidence of the lepromatous type was concerned, the ratio of incidence rate for the earlier period to that of the latter being 2.0 : 1 for males and 2.4 : 1 for females.

The downward trend of the lepromatous type thus revealed by historical or retrospective method was subsequently confirmed on the basis of an actual study of cases undertaken in 1954 by Guinto *et al.* This study compared the prevalence and incidence rates of leprosy in the population of both towns and the attack rates in the household associates observed during the period between the initial and final surveys.

The combined prevalence for the lepromatous type at the preliminary survey averaged 11.6 per thousand of the enumerated population, while the prevalence rate as revealed by the final survey was 5.4 per thousand. On the other hand, the corresponding prevalence rate of the non-lepromatous types were 7.7 in the initial survey and 13.1 in the final survey. There was therefore a marked downward trend of the lepromatous type accompanied, by however, almost as marked an increase in the prevalence rates for the non-lepromatous type. This latter finding was viewed with concern by some leprologists who believed that a rise in the prevalence of the tuberculoid type may be the precursor to a serious increase later in the lepromatous type. Subsequent observations have established the fact that such fears were unfounded. As a matter of fact, there followed a decrease in the prevalence of the non-lepromatous cases.

Based on their data, the authors estimated also that during the two decades, between 1920 to 1940, the attack rate among the lepromatous type cases declined at an average of approximately 3% annually, representing a decrease of the lepromatous type of 60% during the 20 year period.

In order to obtain data for the entire Province of Cebu, Rodriguez (1962) investigated the number of admissions (excluding re-admissions) of lepromatous cases from Cebu Province to all the leprosaria in the Philippines between 1907 and 1955, together with registered unsegregated cases found in Cebu from 1904 to 1906, and utilising the information already gained by Guinto *et al.* for Cordova and Talisay as a control.

During the first 26 year period, from 1904 to 1929, inclusive, there were 5290 recorded cases, compared to a total of 2882 recorded during the following 26 years (from 1930 to 1955) representing a reduction of about 46% during the latter 26 years, or a little less than 2% decrease per year. This is quite compatible with the 3% yearly reduction reported by Guinto *et al.* for Cordova and Talisay from 1920 to 1940.

Discussion

The four separate studies (Doull *et al.*, 1947; Guinto *et al.*, 1954; Rodriguez, 1936, 1962) which investigated the trend of leprosy in the Province of Cebu covered a period of half a century, from 1904 to 1955.

Starting from 1907, the administrative policy of the government regarding leprosy control consisted of "the apprehension, detention and segregation of bacteriologically positive lepers in the Culion Leper Colony". A modification of this Draconian measure was introduced in 1930 with the establishment of 8 regional leprosaria, officially called sanitaria, nearer to the homes of the patients, so that they could be visited frequently by their relatives and friends. The first local sanitarium was the Eastern Visayas Treatment Station, which later became the Eversley Childs Sanitarium built near Cebu City.

In 1952, following favourable results of trials with sulphone drugs in the leprosaria and skin clinics, Republic Act 753 was passed by Congress liberalizing the compulsory segregation law, to the extent of permitting home isolation of bacteriologically positive cases and consenting to their treatment by private physicians under certain conditions prescribed by the health authorities. The result of this step was rather unexpected. Very few patients already in the leprosaria applied for home isolation, perhaps foreseeing the socio-economic problems they would have to face in the outside world, and therefore preferring the security, assurance of medical care and food provided for them in the leprosaria. Moreover, there were only a few new cases who preferred isolation in their own homes to hospitalization in the leprosaria. Compulsory segregation was not abolished in the Philippines until 1964 with the enactment of Republic Act 4073 by Congress.

Thus during the entire period when leprosy was observed to show a decline in Cebu Province, the method of control employed by the government was that of the *compulsory segregation* of bacteriological positive cases either in leprosaria or in their homes, together with treatment of paucibacillary cases in stationary and mobile skin clinics.

Coincident with all these efforts to liberalize the segregation laws and to ameliorate the condition of the patients, an *intensive educational campaign was undertaken* using all media of communication, so as to inform the public about the true nature of the disease including its early manifestations and the necessity for early treatment. This led to voluntary presentation of many cases, including heavily bacillated ones, thus lessening to some extent the danger of public exposure to infective cases. Judging from this experience, it is felt that no leprosy control attempt can succeed without a well-planned enthusiastic and persistent educational programme to enlist public support.

As regards the treatment of leprosy employed in the Philippines during the period covered by these studies, the so-called Mercado mixture which contained chaulmoogra oil was injected to those who asked for it. During a period of 20 years (1922–1942) the standard anti-leprosy treatment consisted of systematic intramuscular and/or intradermal injections of improved chaulmoogra formulas, particularly the Iodized ethyl esters of *H. wightiana* oil (WEI).

Some authorities may view the results of chaulmoogra preparation with scepticism, but there can be no question as to the accuracy of the clinical and bacteriological examinations which were undertaken by a local "Negative Committee" in each leprosarium whose findings were reviewed in turn by a

mobile National Disposal Committee. No negative case was released unless it remained continuously negative for 2 years. However, re-examination of small sample groups of such released negatives showed a high relapse rate of about 40% in 5 years.

No explanation can be given regarding this apparent result of chaulmoogra treatment in the Philippines during the period studied. It may be suspected that a considerable number of "open" cases admitted to the leprosaria at that time were probably Borderline and reacting Tuberculoid cases which according to the experience of many leprologists could either subside spontaneously or respond favourably to chaulmoogra treatment. The proportion of such cases was probably not high, especially during the second half of the period under review, because Filipino leprologists became familiar with the diagnosis of such cases through the investigations in Cebu of Rodriguez and Wade, whose results were published in a series of articles in the *International Journal of Leprosy* between 1935 and 1940.

After the termination of World War II in the Pacific in 1945, WEI continued to be the standard leprosy treatment in Cebu, as the new sulphone drugs were not available in sufficient amounts in the country, although they did gradually supplant the chaulmoogra preparation in all the sanitaria and clinics. Mass treatment with dapsone did not become routine until the establishment of the Cebu Skin Clinic in 1955. Thus, the downward trend of leprosy took place before sulphone treatment was fully introduced.

In view of all the above considerations it is reasonable to surmise that the administrative measures and the technical procedures employed were at least partly responsible for the downward trend of leprosy in the Province of Cebu, although it was realized earlier, in the implementation of the Pilot Leprosy Programme in this Province that the roles of other factors, such as the socio-economic status, diet, health and educational standard of the general population are also important. For this reason, in conducting the continuous epidemiological surveys in Cordova (Doull *et al.*, 1936), Talisay (Guinto *et al.*, 1941) and Santander (Guinto and Rodriguez, 1941) diligent efforts were made to obtain data on which could be based some approximation as to the possible effects of environmental factors on the spread of leprosy. A fourth town, Opon (Rodriguez and Plantilla, 1934) was also specially surveyed for this purpose.

As shown in the articles referred to under condition obtaining in the towns surveyed, it was next to impossible to obtain even approximate figures for this purpose. For instance, in order to obtain data on the income of each family, the first step taken was to determine the occupation of the head of the family, but it was found out that most of them were part fishermen and part farmers in varying degrees. It was necessary to resort to the expediency of giving arbitrary estimates of income derived from fishing by hand, net or trap. On the other hand, the farming income was estimated by counting banana plants, and estimating heads of corn harvested from the small stony lots. Furthermore, the yield was consumed by the family and little of it, if any, was ever sold, so there was no cash income to record.

It is true however, that in many countries, it had been established that such extrinsic factors as socio-economic advancement, diet and proper health habits are important determining factors among others in the spread of tuberculosis, and it is generally accepted that these factors should have a similar effect in the case of leprosy.

However, relative to this question, a unique experience was brought to light by

the epidemiological studies in Cebu. This concerns the small town of Cordova. In this town, the economic condition of the population has steadily retrogressed compared to their original status in 1933. At that time, the community received a modest income derived from planting of maguey, from which was derived a fibre used for rope making which had a ready market; but the commercial demand for this fibre collapsed in the early 1940s. Fishing, which used to be another source of income as well as of food supply, had been greatly depleted, due to the use of dynamite fishing, chiefly done by people from other towns. Problems of living in this town were made more acute by a population explosion which propelled the number of its inhabitants from 6063 in 1933 to 10,904 in 1966.

All these factors naturally had their impact on the health of the people. They continued to be as malnourished as they were 36 years previously, judging from poor nutrition, low body weights, and the prevalence of such conditions as Pellagra, nicteralopia, and other concomitants of avitaminosis and malnutrition. Nevertheless the *downward trend of leprosy continued* in this town in spite of these unfavourable extrinsic factors which affected the entire community. This totally unexpected finding is difficult to explain. However, this experience is based on a single small area and does not necessarily apply to other towns in the Province and the rest of the country. In my opinion, it is one more indication that perhaps there are other factors surrounding the contagiousness of leprosy that are not known to us at the present time. An intensive survey of the town of Santander in Cebu Province undertaken by Guinto and Rodriguez (1941) in 1938, confirmed the fact that leprosy had been introduced in this town, but the disease had not spread in spite of the fact that it is inhabited by the same people as the other towns surveyed who were enjoying the same socio-economic status, were eating the same food and had the same health habits. The investigators were not able to explain why leprosy had not been able to obtain a foothold in Santander as it had in Cordova, Talisay and Opon.

References

Doull, J. A., Rodriguez, J. N., Guinto, R. and Plantilla, C. (1936). A field of study of leprosy in Cebu, *Int. J. Lepr.* **4**, 141-169.

Doull, J. A., Guinto R. S. Bancroft, H. and Rodriguez, J. N. (1947). Historical inquiry as a method of estimating the trend of leprosy. *Int. J. Lepr.* **15**, 369-375.

Guinto, R. S. and Rodriguez, J. N. (1941). A field of study of leprosy in Talisay, Cebu, Philippines. *Int. J. Lepr.* **9**, 149-196.

Guinto, R. S. and Rodriguez. J. N. (1941). A leprosy survey of a control area in Santander, Cebu, Philippines **9**, 315-325.

Guinto, R. S., Rodriguez J. N., Doull, J. A. and de Guia, L. (1954). The trend of leprosy in Cordova and Talisay, Cebu Province, Philippines. *Int. J. Lepr.* **22**, 409-430.

Rodriguez, J. N. and Plantilla, F. C. (1934). Leprosy in Cebu II. Philippines. *J. Sci.* **58**, 1-46.

Rodriguez, J. N. (1936). Our leprosy problem in the Philippines. *Monthly Bulletin of the Bureau of Health* **16**, 161-179.

Rodriguez, J. N. (1962). Evaluation of the leprosy control program of the Philippines. *Int. J. Lepr.* **30**, 111-124.

Lepr. Rev. (1975) **46**, 15-20

Treatment of Mitsuda-Negative Leprosy Patients with Transfusions of Whole Blood from Mitsuda-Positive Donors

J. C. ALMEIDA GONÇALVES AND J. CUSTÓDIO

Instituto de Assistência aos Leprosos, Lisbon, Portugal

Two lepromatous and one borderline patient improved following transfusions of whole blood from selected donors whose Mitsuda reactions were positive. Two of the patients had received no previous antileprosy therapy and remained untreated during the study. The third patient was probably drug resistant. Improvement was preceded by febrile episodes, "benign reactions", which are described.

Introduction

Present chemotherapy of leprosy is not completely satisfactory. Improvement is slow, lepromatous reactions are frequent and there is no established therapy for enhancing the immunological capacity of the patient against *Mycobacterium leprae*. However, it has been suggested by Rotberg and others that patients with lepromatous leprosy lack a genetically determined resistance factor. To test this hypothesis we postulated that patients with lepromatous leprosy, who lacked this factor, might benefit from passively transfused "resistant" cells, present in whole blood transfusions, from Mitsuda-positive blood donors. The present paper summarises preliminary results from studies designed to test this hypothesis.

Materials and Methods

The studies were undertaken on three male patients, all with active disease, two of whom were previously untreated (one with lepromatous and the other with borderline type leprosy) and the third with relapsed lepromatous type leprosy. almost certainly due to the emergence of drug resistance. A panel of blood donors who were strongly Mitsuda-positive (>5 mm) were selected and cross matched with the respective leprosy recipients. Each leprosy patient received a series of blood transfusions from a selected donor and the blood transfusions were carried out immediately after collection from the respective donors.

Case Reports

Case 1. F.A.O.P.

A 21 year old Caucasian, born in Goa; untreated lepromatous leprosy. Two months before the present study the patient suddenly deteriorated with new skin

lesions affecting the face and trunk and his vision, which had previously been normal, became blurred with excessive lacrymation. He did not notice any changes in cutaneous sensitivity or nasal obstruction. On examination his face was erythematous and infiltrated with numerous wax coloured small nodules. On the trunk there were symmetrical faint reddish copper coloured macules with indefinite edges. There was nodular infiltration of the nasal mucosa.

Bacteriological examination of skin smears and nasal mucus showed large numbers of bacilli and globi, with small numbers of bacilli in the tears. Histological examination of a biopsy from the forehead showed lepromatous leprosy, with a high BI and the majority of bacilli stained solidly. Blood examinations revealed a moderate normochromic anaemia, positive Wassermann and Kahn tests and normal serum proteins and E.S.R. Urinalysis was within normal limits. The blood group was O, Rh positive.

Treatment with transfusions of 200 ml of whole blood at 10-15 day intervals were initiated. Increased nasal obstruction was the only manifestation noticed by the patient during the first six transfusions. However, on the 9th day after the 7th transfusion the patient suddenly presented a plethora of unusual manifestations. He felt repulsed by food, vomited, and the faeces were soft and black (negative for occult blood). Nasal obstruction suddenly disappeared after the expulsion of a yellowish and gelatinous discharge from the nose. Normal vision was recovered and he felt a sensation of well-being in spite of pyrexia. On examination the redness and swelling of the face had almost completely subsided. However, he presented polyadenopathy, splenomegaly and swelling of the left testis. Because the pyrexia (38.2–40.0° C) persisted for the next four days, associated with profound asthenia and deterioration in the patient's condition, a course of prednisone (30 mg, daily) was initiated. The temperature returned to normal within two days and then the dose of prednisone was reduced and finally discontinued. In the next 20 days although the patient was emaciated and weak his original symptoms of leprosy were considerably diminished. However, there was no diminution in the number of bacilli in his nasal discharges or skin scrapes. A biopsy from the forehead, near to the first biopsy, showed a granuloma of the same type but occupying less skin area although the density of bacilli per microscope field was unchanged.

During these episodes and over the next two months a series of laboratory investigations were undertaken. All blood cultures proved negative, as did the Widal reaction, although the Wassermann and Kahn tests remained positive. The E.R.S. ranged between 23-35 mm, before returning to normal two months later. The Takata-Ara and thymol tests were positive but the Van den Berg reaction remained negative and the serum bilirubin was 0.2 mg %. The L.E. test was negative. The blood examinations revealed a normochromic anaemia with 3,750,000 erythrocytes, 75% haemoglobin and colour index 1; 18,600 leucocytes–50% neutrophils, 48% lymphocytes, 2% monocytes and 0% eosinophils and basophils. The electrophoretic serum protein pattern was as follows: total proteins 7.4 g %; albumin 45%, α-1 globulin 0.5%, α-2 globulin 10%, β 7.5% and γ globulin 37%.

Because of these unexpected manifestations no further blood transfusions were given after the 7th, and except for the short course of prednisone no specific therapy was administered. Although the patient's general condition rapidly improved, his leprosy condition seemed to slowly deteriorate after one month and was obviously worse after two months, with the reappearance of skin infiltration,

although his vision remained normal and there was no return of nasal obstruction. Therefore the series of whole blood transfusions were recommenced for a second time at a volume of 200 ml at two weekly intervals. Since after two such transfusions no recurrence of reactions had occurred the dose was increased to 400 ml for the next two transfusions. With no further reactional episodes the dose was again reduced to 200 ml. However, eight days after the 7th transfusion of the second series a "benign reaction" occurred, similar to the former but less intense. The temperature rose to only 38.4° C, there were no black stools, and there was no general deterioration in the patient's condition. Therefore this time corticosteroid therapy was not administered and he was given an 8th transfusion. This was followed immediately by swelling and pain of the left testis but no pyrexia. As previously, there was a sudden diminution in his leprosy symptoms and this time a significant fall in the BI from his nasal discharge with a high proportion of granular organisms. Specific antileprosy therapy was then initiated with Madribon and at the same time blood transfusions of whole blood were continued every two weeks for a further five months. The patient's condition has continued to improve and his Wassermann and Kahn tests have become negative without receiving any antisyphilis treatment. His Mitsuda reaction remains negative.

Case 2. F.P.M.

A 27 year old Caucasian, born in Portugal; untreated borderline leprosy. One year before this study began the patient had an indolent witlow of the left hand. At the time of our study the patient presented with lesions of the forehead, trunk and limbs. The face was infiltrated and red. There were mixed type of lesions on the trunk and limbs, some being macules with an ill-defined edge and others erythematous with very well defined edges. The nasal mucus contained a few bacilli and single globi whereas a smear from the forehead revealed a large number of bacilli and globi. The Mitsuda reaction was negative. Histology was typical of borderline (BL) leprosy (Ridley and Jopling, 1966). All other investigations were within normal limits.

Whole blood transfusions were commenced at intervals of 15 days, the first dose was 200 ml, the next four 400 ml and the following nine 200 ml.

After the 8th transfusion he had a slight reaction, without fever, characterized by repugnance against food, but without vomiting and by the appearance of enlarged axillary and inguinal lymph nodes. The symptoms lasted for seven days. Afterwards the lymph nodes diminished but the erythema and the infiltration of the face increased. He then began to improve slowly. After the 12th transfusion and six months after the first transfusion, he was much better. The infiltration of the lesions had disappeared and so had the erythema and swelling of the face. The lesions on the trunk were still present but they had a very unusual appearance. Each lesion consisted of a very clearly defined yellow oval-shaped centre surrounded by a rose coloured area, the outer edge of which was irregular and ill-defined. We were surprised at the contrast shown by the inner and outer areas of the lesion. After 14 transfusions and eight months the transfusions treatment was discontinued and the administration of 100 mg DDS a day was started. This high dose did not provoke any adverse reactions.

At the end of the transfusions treatment the smears revealed the same quantity of bacilli but half of them were granular. Histological examination showed the same structure as before but with moderate fibrosis of the superficial dermis and

many acid-fast bacilli, with a proportion granular. Routine laboratory examination remained normal. The Mitsuda reaction continued negative.

Case 3. S.N.C.

A 45 year old Caucasian born in Portugal; drug resistant lepromatous leprosy. When we first saw the patient in 1961 he had advanced lepromatous leprosy with a 25 years history, in spite of many years of irregular treatment with DDS. His skin smears were highly positive, skin histology was typical of lepromatous leprosy and his Mitsuda reaction was negative. The patient was then treated with thiambutosine and improved for one year. ENL then developed and his condition deteriorated. Treatment was changed to Madribon, he improved for two years and then deteriorated again. Throughout these three years he had continuous ENL in spite of corticosteroid therapy (5-10 mg prednisone, daily). Because we had then exhausted all the known antileprosy drugs available in this country we decided to submit him to whole blood transfusion treatment.

Whole blood transfusions of 200 ml were given at intervals of 10-30 days and Madribon therapy was continued in spite of our opinion that the drug was without effect. Some days after the 8th transfusion he noted black stools and by the 8th day he developed pyrexia (39.0° C), jaundice and hepato-splenomegaly. The patient refused hospitalization although we had diagnosed infectious hepatitis—this later proved to be incorrect. Black faeces remained for four days, pyrexia for 30 days and jaundice for four days. Transfusions were discontinued. However, in spite of the pyrexia it was possible to discontinue prednisone, *for the first time in 3 years*, without the reappearance of ENL manifestations. In the next 30-day period his general condition improved dramatically. Pyrexia was only present in the afternoons, erythema and infiltration of the face disappeared completely. The macules on the body were scarcely detectable and most of the infiltrations disappeared and the few that remained were very diminished and of a faint colour. Since then there have been no more episodes of ENL and corticosteroid therapy has never been re-instated. Blood transfusions were stopped after a period of two months, although Madribon therapy was continued. However, the patient's condition gradually deteriorated. We then started a second series of blood transfusions, but this time without Madribon. The second series consisted of 10 transfusions of 200 ml at 15-day intervals. The patient improved immediately and continued to do so throughout this period. Clofazimine therapy was then started and the patient has continued to improve.

Because this patient lived outside Lisbon only limited laboratory investigations were possible, and were confined to the period of pyrexia following the first series of transfusions. At that time blood examination showed 3.2 million erythrocytes/mm^3; haemoglobin 10.6 g %; 8300 leucocytes/mm^3 – 54% neutrophils, 32% lymphocytes, 14% monocytes and 0% eosinophils and basophils. The E.S.R was 80 mm. Urinalysis was normal and the Takata-Ara, Hanger and cadmium tests were positive. The Mitsuda reaction remained negative throughout.

Discussion

We present these three cases because the results suggest that the patients did benefit from transfusions of whole blood from Mitsuda positive donors. However, we readily admit that three cases are too few, only two were lepromatous (borderline patients can spontaneously become more tuberculoid) and complete

laboratory investigations were lacking. In spite of these limitations the results are of interest. Thus, the first case undoubtedly had untreated and progressive lepromatous leprosy which never undergoes spontaneous improvement. Yet, there was undoubtedly improvement following each series of transfusions and deterioration during the intervals when transfusions were stopped. In this case as in the other two cases improvement was associated with febrile reactions. The first and important point to exclude here is that these febrile reactions were transfusion reactions. They clearly were not because: (a) they began eight days after the transfusion, transfusion reactions begin immediately after transfusion; (b) transfusion reactions are short-lived, our reactions lasted for a month; (c) the prolonged pyrexia reactions resulting from the 7th transfusion in the first series, failed to elicit any reaction when blood from this same donor was used to initiate the first transfusion in the second series of transfusions.

The so-called "benign reactions" that resulted following a series of transfusions are not of the ENL type since they did not result in the appearance of crops of new lesions as are seen in ENL or the development of oedema of the legs and hands. On the contrary, the pyrexial episodes were associated with diminution in existing lesions, including disappearance of blurred vision and, moreover, after the first series of transfusions the patient's symptoms all returned other than blurred vision. Finally, after the second series of transfusions there was an increase in degenerate bacilli and diminution of lepromatous granuloma in the skin in a patient with lepromatous leprosy who without chemotherapy would inevitably be progressive.

Although the second patient had borderline leprosy and therefore might show spontaneous improvement, significant improvement was registered by a series of blood transfusions without any chemotherapy.

Our third case was again lepromatous, was fully active in spite of prolonged chemotherapy and therefore must have been drug resistant. Therefore, we consider that the improvement shown with the first series of transfusions in spite of continuing chemotherapy resulted from the transfusions and undoubtedly the improvement which resulted from the second series of transfusions, where no chemotherapy was given, must have been due to the effect of the transfusions. We therefore consider that the third case was as significant as the first. In addition, the third case was altered sufficiently by blood transfusions to no longer require corticosteroids, which he had previously required regularly over many years.

We consider that even this small series provides strong evidence that blood transfusions from Mitsuda-positive donors had increased the immunological capacity of all these patients and for the third case had also diminished his ENL. These beneficial effects of whole blood transfusions, particularly for the treatment of lepromatous reactions (ENL) have been repeatedly claimed by the Spanish investigators of Fontilles (Aguas, 1962, 1966; Contreras *et al.*, 1953). We claim that our very preliminary data may well be the first evidence to show that whole blood transfusions from Mitsuda-positive donors are "therapeutically" beneficial in the absence of chemotherapy.

Conclusions

(1) That the immunological capacity of a lepromatous patient can be increased by transfusions of whole blood from Mitsuda-positive donors.

(2) That this increased resistance may be due to the transfusion of immunologically competent lymphocytes.

(3) The presence of these immunologically competent lymphocytes, while sufficient to benefit the patient's bacterial infection, fail to establish a permanent Mitsuda-positive status.

(4) These preliminary and favourable results provide a possible new "imunological" basis for the treatment of patients with lepromatous leprosy.

References

Aguas, J. T. de Las (1962). Tratamiento de las Leprorreacciones. *Fontilles* **5**, 513.

Aguas, J. T. de Las (1966). Leprorreacciones. Su Tratamiento. *Fontilles* **6**, 431.

Contreras, F., Guillen, J., Ponziani, J. and Terencio, J. (1953). Hemoterapia en las Leprorreacciones. *Int. J. Lepr.* **21**, 441.

Ridley, D. S. and Jopling, W. H. (1966). Classification of leprosy according to immunity. A five-group system. *Int. J. Lepr.* **34**, 255.

Lepr. Rev. (1975) **46**, 21-27

Mycobacterium ulcerans Infections in Leprosy Patients

WAYNE M. MEYERS*

Kivuvu Leprosarium, Institut Médical Evangélique, Kimpese, Republic of Zaïre

and

DANIEL H. CONNOR†

Department of Infectious and Parasitic Disease Pathology, Armed Forces Institute of Pathology, Washington D.C., 20306, U.S.A.

In a population of 1061 patients with leprosy and 180 patients with *Myco. ulcerans* infections, we recorded a history of both diseases in 6 individuals. There was no evidence that either infection altered the tissue response or clinical course of the other.

Introduction

Cross-sensitization and cross-resistance in man to more than one species of mycobacteria has long been a lively topic for discussion among "myco-bacteriologists" and their ilk. Opposite and extreme opinions have been recorded. Mitsuda and Ogawa (1937) reported, for instance, that tuberculosis is the most common cause of death in leprosy patients, while Chaussinand (1950) proposed that by the "phénomènes de para-allergies bactériennes" the increase of tuberculosis in Europe in the Middle Ages caused the well-known decline of leprosy. Leiker (1971), while espousing the concept of Chaussinand in citing inverse relationships between the prevalence of leprosy and tuberculosis, points out the complexities of this relationship. Discussions in this vein today often revolve around the usefulness of BCG as an anti-leprosy vaccine. We shall not debate this controversy, but we do record new data on two mycobacterial diseases occurring in the same patient.

In this communication, we present six patients with both *Mycobacterium ulcerans* infection and leprosy, treated at the Institut Médical Evangélique, Kimpese, Bas-Zaïre, Republic of Zaïre. We know of no published reports of patients with both of these diseases. Verhagen (personal communication) states that in Uganda he saw three leprosy patients among 70 patients with *Myco. ulcerans* infections.

* Present address: ALM Leprosy Atelier, University of Hawaii School of Medicine, Department of Pathology, Leahi Hospital, 3675 Kilauea Avenue, Honolulu, Hawaii 96816.
† Requests for reprints should be sent to Dr Connor.

Received for publication 1 August, 1974.

Brief Discussion of *Myco. ulcerans* Infection

Infection by *Myco. ulcerans* has a focal geographic distribution, therefore some readers may be unfamiliar with its clinical and pathological features. The disease prevails in large foci in Uganda (Barker, 1972) and Zaïre (Meyers *et al.*, 1974) but has also been reported from Australia, Bolivia, Cameroon, Congo (Brazzaville), Gabon, Indonesia, Malaysia, Mexico, New Guinea, Nigeria and Peru. The aetiologic agent, first isolated by MacCallum *et al.* (1948), is a mycobacterium which grows slowly at 32° C. on Löwenstein-Jensen medium but is usually inhibited at 37° C. Feldman *et al.* (1957) suggested that the tail of the mouse was particularly susceptible to experimental lesions of *Myco. ulcerans* because of its low temperature (about 25° C). This temperature growth requirement may also be an important factor in determining the nature of human infection by *Myco. ulcerans*. In man the skin and subcutaneous tissues, with temperatures below 37° C, are nearly always the sites involved; rarely other sites, notably bone, are affected. Perhaps in those instances where bone is infected, strains growing at 37° C are responsible; however, *Myco. ulcerans* has not yet been cultured from bone lesions.

Natural reservoirs and modes of transmission are not known but the disease tends to occur only in warm climates in swampy and riverine savannah. Barker *et al.* (1972) postulate that the organism is present on grasses but have not recovered

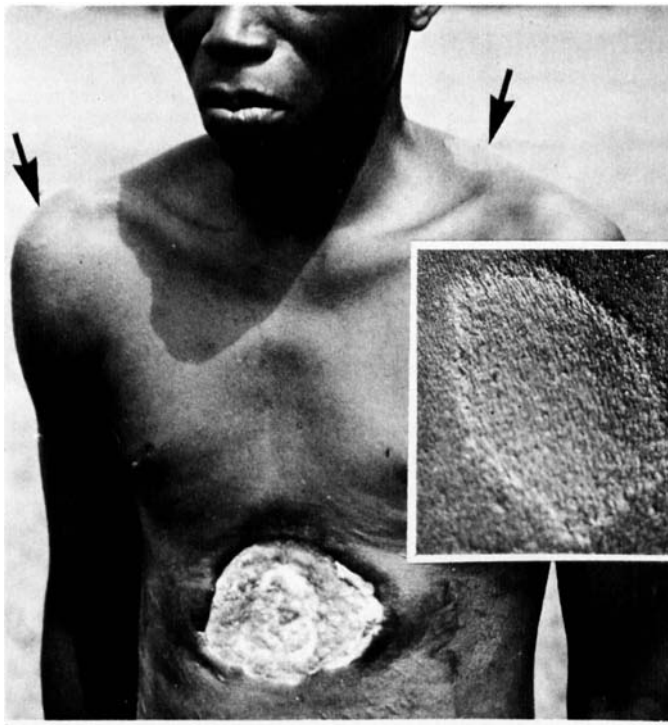

Fig. 1. Patient No. 6, showing abdominal lesion of *Mycobacterium ulcerans* and two borderline (dimorphous) (BT) lesions of leprosy (arrows). Inset is a closeup of leprosy lesion on the back of this patient.

it from this hypothetical source. Meyers *et al.* (1974*b*) observed patients who developed lesions at sites of trauma, including hypodermic injections, suggesting that the infection results from direct inoculation.

Dodge and Lunn (1962) proposed the name "Buruli ulcer" for this infection, after the geographic area where the first cluster of Ugandan patients lived. In lower-Zaïre, one indigenous term for the disease is "mputa matadi". This Kikongo expression, meaning "rock-hard sore," may refer to the nature of the early lesion which is a hard subcutaneous nodule. This expression may, alternatively, refer to the firm oedema frequently seen early in the disease. The nodule, often accompanied by itching, gradually enlarges, ulcerates, and discharges necrotic sloughs and an oily liquid. The ulcer is widely undermined, has a necrotic base, and may be surrounded by edematous skin. Ulcers are most common on the extremities, especially over major articulations, but also develop on the trunk (Fig. 1). Microscopically, the characteristic feature is a contiguous, spreading coagulation necrosis of the subcutaneous and deep dermal tissues. All tissues and structures including vessels and appendages are destroyed and this spreading necrosis is responsible for the undermining of the overlying skin, producing the distinctive contour of the ulcer margin. The necrotizing process (Fig. 2) may be caused by the toxin which Read *et al.* (1974) demonstrated in cell-free *Myco. ulcerans* culture filtrates.

Mycobacterium ulcerans infections are usually self-limiting but patients may die from complications of advanced lesions. Even self-limiting lesions often cause severe deformities from contractures, and loss of important structures (e.g. eyes and limbs). Wide surgical excision and skin grafting is the usual treatment, but locally applied heat may be a helpful adjunct (Glynn, 1972) or effective by itself (Meyers *et al.*, 1974*a*).

Description of Patients

During the period April 1960 to June 1973, 971 patients with active leprosy were registered at Kivuvu. Of this number, 770 were registered after September 1965 when diagnosis and classification became routinely based on clinical, histopathologic and bacteriologic findings and the lepromin reaction. Ninety individuals with an established history of leprosy but without currently active disease where also registered, making a total of 1061 leprosy patients in the study group. During this same interval, 180 patients with *Myco. ulcerans* infection were registered. The *Myco. ulcerans* patients all came from Songololo Territory and adjacent areas, described by Andersen (1965), Smith (1970) and Meyers *et al.* (1974). The leprosy patients came from a much larger geographic area but included the *Myco. ulcerans* endemic areas of lower-Zaïre, with about 20% of the leprosy patients coming from Songololo Territory. All patients were Bantu and approximately 95% of them were of the Bakongo tribe, with origins in either Zaïre, Angola or Congo (Brazzaville).

In the above two groups, there were six individuals with a history of both leprosy and *Myco. ulcerans* infection. Each of these patients will be described briefly:

Patient No. 1, MA (Hosp. No. 63/3501), 55 yr female, was admitted to hospital in September 1968 for a large undermined ulcer on the left knee. The lesion was excised and a biopsy specimen from the edge was typical of *Myco. ulcerans* infection. She gave a history of leprosy, treated at a nearby hospital and

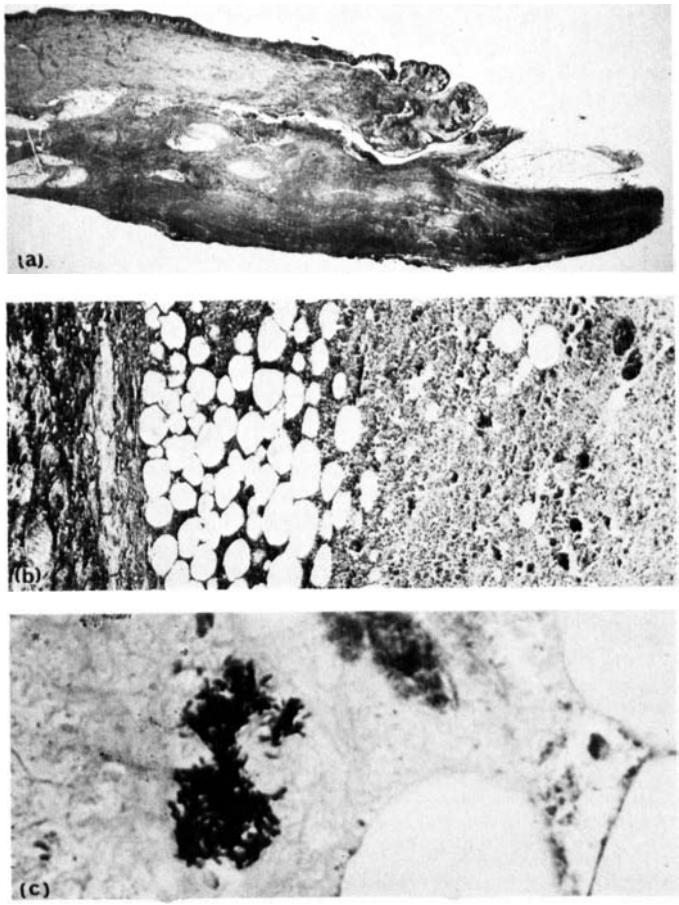

Fig. 2. Histopathologic features of *Myco. ulcerans* lesion in patient No. 6. (a) Low magnification of edge of *Myco. ulcerans* lesion. The undermining of the epidermis (top surface) and dermis, and the destruction of the subcutaneous fat are clearly demonstrated. (AFIP Neg. 74-803, Movat stain, x3.3.) (b) Higher magnification of the same lesion showing necrosis and fat cell ghosts. (AFIP Neg. 74-800, Movat stain, x90.) (c) High magnification revealing a microcolony of *Myco. ulcerans* organisms in the area of necrosis. Portions of fat cell ghosts are seen on the right. (AFIP Neg. 74-802, Ziehl-Neelsen stain, x750.)

considered inactive in 1950. We verified this history from records obtained at the hospital and our impression was that she had had borderline leprosy. There was no evidence of active leprosy on this admission. No skin tests were done. The patient died of unknown causes in December 1968.

Patient No. 2, BD (Hosp. No. 67/1398), 32 yr male, was admitted to hospital in February 1967 with a chronic undermined ulcer on the right leg. The lesion was excised and skin-grafted. A biopsy specimen was compatible with *Myco. ulcerans* infection. The patient said he had been treated for leprosy at another hospital and the records examined there confirmed a clinical diagnosis of tuberculoid leprosy. No skin tests were done. The *Myco. ulcerans* lesion healed

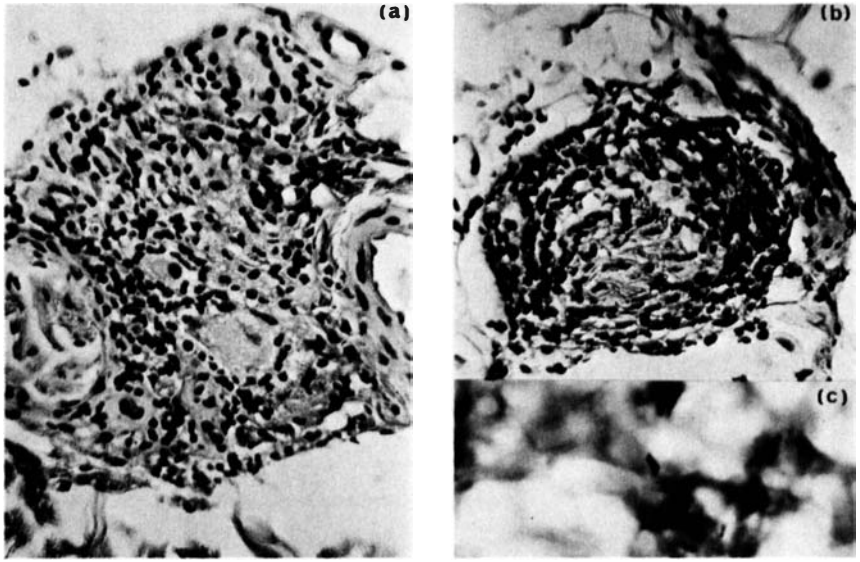

Fig. 3. Histopathologic features of leprosy lesion in patient No. 6. Biopsy specimen was from the edge of lesion on the right shoulder, shown in Fig. 1. (a) Cellular infiltration about a nerve and blood vessel in the lower dermis. Infiltration composed primarily of epithelioid cells, giant cells and lymphocytes. (Saffron trichrome stain, ×400.) (b) Infiltration and partial destruction of a small dermal nerve. (Saffron trichrome stain, ×400.) (c) Two juxtaposed acid-fast bacilli in dermal nerve shown above. (Fite-Faraco stain, ×1000.)

and he returned home in June 1967. When last seen in May 1973 he had no evidence of active leprosy or of active *Myco. ulcerans* infection.

Patient No. 3, DS (Hosp. No. 68/1223), 60 yr male, was admitted for leprosy in January 1968. His lesions began in June 1967 and a biopsy specimen revealed characteristic features of borderline (BB) leprosy. The Mitsuda reaction was 7 mm. He gave a history of *Myco. ulcerans* infection treated in 1953 at another institution. A histopathologic diagnosis was not made, but the clinical history and the appearance of the scar on the right knee were characteristic of a healed *Myco. ulcerans* infection. When last seen in May 1973 his leprosy was inactive and the *Myco. ulcerans* infection had not recurred.

Patient No. 4, MM (Hosp. No. 71/2395), 60 yr female, was admitted to hospital in March 1971 with a large undermined ulcer about the right eye and a hypopigmented, slightly infiltrated, anaesthetic skin lesion over the left elbow. Biopsy specimens confirmed *Myco. ulcerans* infection and borderline leprosy (BT) respectively, and the Mitsuda reaction was 20 mm. The *Myco. ulcerans* lesion appeared in December 1970 but the date of onset of leprosy was not known. The ulcer was successfully treated by wide excision, including enucleation of the eye, and oral rifampicin. She remains on sulphone therapy for leprosy.

Patient No. 5, ED (Hosp. No. 71/3707), 57 yr male, was admitted to hospital in June 1971 with a large widely undermined ulcer of the left leg and a second smaller ulcer on the right foot. In addition, there were numerous widely scattered, hypopigmented, slightly infiltrated, anaesthetic skin lesions, and enlarged tender ulnar nerves. The right foot was deformed. Biopsy specimens from these lesions confirmed the diagnoses of both *Myco. ulcerans* infection and borderline leprosy

(BT). Lesions of leprosy were first noted in 1969 and those of *Myco. ulcerans* in May 1971. The *Myco. ulcerans* lesions healed under rifampicin therapy and excision and grafting, and the leprosy has become inactive. The patient remains on sulphone therapy.

Patient No. 6, JA (Hosp. No. 73/2277), 20 yr male, was admitted to hospital in March 1973 with an undermined ulcer 10 x 14 cm over the upper abdomen. He also had eight widely scattered, infiltrated, hypopigmented, anaesthetic skin lesions with well defined edges (Fig. 1). The ulcer began in November 1972 and the lesions of leprosy sometime between July 1972 and February 1973. Histopathologic findings of the *Myco. ulcerans* lesion are shown in Fig. 2, and those of leprosy in Fig. 3. The latter specimen was interpreted as borderline-tuberculoid (BT) leprosy. *Mycobacterium ulcerans* was cultured from the lesion on the abdomen on Löwenstein-Jensen medium incubated at 32°C. Fernandez reaction was negative and the Mitsuda reaction was 9 mm. The ulcer was excised and grafted with a good result. He remains on sulphone therapy for leprosy.

Discussion

A direct detailed comparison of the antigenic structures of *Myco. leprae* and *Myco. ulcerans* has not been published. Stanford (1973), by immunodiffusion studies on 35 strains of *Myco. ulcerans* from various parts of the world, including 11 strains from Zaïre, found that all strains were antigenically similar. Furthermore, while possessing distinct antigenic components, *Myco. ulcerans* cross-reacted with other mycobacteria. For example, there were seven precipitins in common with *Myco. kansasii* and five with *Myco. smegmatis* and *Myco. fortuitum.* Goihman-Yahr *et al.* (1968) cited cross-reactions to lepromin in guinea pigs sensitized to *Myco. kansasii* and *Myco. smegmatis.* This indirect evidence suggests that *Myco. ulcerans* and *Myco. leprae* could possess common antigens.*

Clinically and histologically we could discern no interaction between leprosy and *Myco. ulcerans* infections. We note that all six of our patients, as well as Verhagen's three patients, had higher resistant forms of leprosy, but we are not able to attach any special significance to this fact. There is the remote theoretical possibility that the anti-mycobacterial antibodies commonly present in the serum of lepromatous patients could protect against the extracellular parasite *Myco. ulcerans* or its toxic products.

In addition, we are uncertain whether or not, in the population studied, six patients is an unusually high number with both diseases. Based on a population of 156,000 for the major area of endemicity for *Myco. ulcerans* (official Zaïre census for Songololo Territory for 1970), we estimate that 0–1 patient would have been anticipated. Extensive epidemiologic surveys for both leprosy and for *Myco. ulcerans* infection would be necessary to determine if this difference is representative of the entire population.

The low temperature growth requirement *in vitro* for *Myco. ulcerans* is well established, and there is a widely accepted belief that the clinical picture of leprosy is largely a result of the selective growth of *Myco. leprae* in the cooler parts of the human body. Thus, these six patients are especially interesting in that

* Stanford (personal communication, 1974) reports that *Myco. leprae* and *Myco. ulcerans* do share at least 5 antigens and that these are the same antigens which *Myco. ulcerans* shares with most other mycobacterial species.

they demonstrate in the same individual two mycobacterial skin diseases which are probably temperature-related, and which provoke distinctly different tissue responses.

Acknowledgements

We acknowledge with appreciation the cooperation of Drs Walter Shelly and Stuart Barber of the Institut Médical Evangélique who performed the surgical procedures on some of these patients. We thank Mr Mbongi Kiletu Mandiangu, General Director, IME, for his interest and administrative support, and Miss Rut Lindahl, R.N. and Miss Edna M. Staple, S.R.N. for their assistance in the care of patients.

This study was supported in part by the American Leprosy Missions, Inc., New York, and Grant No. DADA-17-70-G-9318 from the Medical Research and Development Command, U.S. Army, Washington D.C.

References

Andersen, F. O. (1965). Mycobacterial skin ulcers—clinical experience. *Central Afr. J. Med.* **11**, 131-135.

Barker, D. J. P. (1972). Epidemiology of *Mycobacterium ulcerans* infection. *Trans. R. Soc. Trop. Med. Hyg.* **67**, 43-50.

Barker, D. J. P., Clancey, J. K. and Rao, S. K. (1972). Mycobacteria on vegetation in Uganda. *E. Afr. Med. J.* **49**, 667-671.

Chaussinand, R. (1950). *La Lèpre.* Expansion Scientifique Française. pp. 19, 217-222.

Dodge, O. G. and Lunn, H. F. (1962). Buruli ulcer: A mycobacterial skin ulcer in a Uganda child. *J. Trop. Med. Hyg.* **65**, 139-142.

Feldman, W. H., Karlson, A. G. and Herrick, J. F. (1957). *Mycobacterium ulcerans.* Pathogenesis of infection in mice, including determinations of dermal temperatures. *Am. J. Pathol.* **33**, 1163-1179.

Glynn, R. J. (1972). The use of surgery and local temperature elevation in *Mycobacterium ulcerans* infection. *Aust. N. Z. J. Surg.* **41**, 312-317.

Goihman-Yahr, M., Raffel, S and Ferraresi, R. (1968). Cross-reactivity of lepromin with other mycobacterial antigens. *Int. J. Lepr.* **36**, 129-143.

Leiker, D. L. (1971). Some aspects of the epidemiology of leprosy. On the relationship of leprosy and other mycobacterial diseases. *Int. J. Lepr.* **39**, 610-615.

MacCallum, P., Tolhurst, J. C., Buckle, G. and Sissons, H. A. (1948). A new mycobacterial infection in man. *J. Path. Bact.* **60**, 93-122.

Meyers, W. M., Connor, D. H., McCullough, B., Bourland, J., Moris, R. and Proos, L. (1974). Distribution of *Mycobacterium ulcerans* infections in Zaïre, Including the report of new foci. *Ann. Soc. belge Méd. Trop.* **54**, 147-157.

Meyers, W. M., Shelly, W. M. and Connor, D. H. (1974*a*). Local heat treatment of *Mycobacterium ulcerans* infections without surgical excision. *Am. J. Trop. Med. Hyg.* **23**, 924-929.

Meyers, W. M., Shelly, W. M., Connor, D. H. and Meyers, E. K. (1974*b*). Human *Mycobacterium ulcerans* infections developing at sites of trauma to skin. *Am. J. Trop. Med. Hyg.* **23**, 919-923.

Mitsuda, K. and Ogawa, M. (1937). A study of one-hundred and fifty autopsies on cases of leprosy. *Int J. Lepr.* **5**, 53-60.

Read, J. K., Heggie, C. M., Meyers, W. M. and Connor, D. H. (1974). Cytotoxic activity of *Mycobacterium ulcerans. Infect. Immun.* **9**, 1114-1122.

Smith, J. H. (1970). Epidemiologic observations on cases of buruli ulcer seen in a hospital in the Lower Congo. *Am. J. Trop. Med. Hyg.* **19**, 657-663.

Stanford, J. L. (1973). An immunodiffusion analysis of strains of *Mycobacterium ulcerans* isolated in Australia, Malaya, Mexico, Uganda and Zaïre. *J. Med. Microbiol.* **6**, 405-408.

Lepr. Rev. (1975) **46**, 29-37

Glomerulonephritis in Leprosy— A Percutaneous Renal Biopsy Study

K. V. JOHNY,* A. B. A. KARAT, P. S. S. RAO
and
A. DATE

Schieffelin Leprosy Research Sanatorium, Karigiri
and
Christian Medical College Hospital, Vellore, South India

Thirty-five patients with lepromatous or borderline leprosy selected at random were investigated for evidence of renal disease. Renal functional impairment was detected in nearly two-thirds of the patients and histological lesions were present in 46%. Twenty-three per cent of the cases showed a proliferative type of glomerulonephritis, mesangial sclerosis without significant hypercellularity was seen in 11%, amyloidosis was present in 6%. One patient had interstitial nephritis.

Introduction

Renal involvement in leprosy has been recognized by Japanese workers since the beginning of the century. Mitsuda and Ogawa published their observations in English in 1937 and described "nephritis of all kinds" in leprosy in an autopsy analysis of 150 cases. Similar observations were also made by Kean and Childress (1942) from the Isthmus of Panama. Acute oedema of the hands and feet occasionally associated with proteinuria were later reported to complicate all clinical types of leprosy during reactive episodes and progressive reaction (Davison, 1961; Wheate, 1962; Cochrane, 1964). Impaired renal function and abnormal urinary sediment have also been observed in patients with leprosy in varying reactional states (Gokhale and Kurkure, 1958; Thomas *et al.*, 1970; Gutman, Lu and Durtz, 1973).

Amyloidosis of the kidney was the commonest histological abnormality observed by North American workers, occurring in nearly one-half of the patients with lepromatous leprosy (Powell and Swan, 1955; Shuttleworth and Ross, 1956; Williams, Cathcart and Calkins, 1965). Amyloidosis complicated leprosy in as many as 80% of cases in Spain (Granels, 1968). In contrast, renal amyloidosis was seen in only 6% of leprosy patients studied in Mexico (Williams, Cathcart and Calkins, 1965) and a similar low incidence was reported from Japan (Mitsuda and Ogawa, 1937) and India (Junnarkar, 1957; Desikan and Job, 1968; Sachdev, Puri and Bansal, 1969). Though amyloidosis complicated reactional leprosy much

* Reprint requests should be addressed to Dr K. J. Johny, Associate Professor and Head, Department of Nephrology, Christian Medical College Hospital, Vellore–632004, Tamil Nadu, South India.

Received for publication, 22 July, 1974.

more frequently, it was seen in non-reactional types as well (Brusco and Masanti, 1963).

Renal failure secondary to amyloidosis was the leading cause of death in U.S. Sanatoria (Powell and Swan, 1955; Shuttleworth and Ross, 1956; Williams, Cathcart and Calkins, 1965) and even more so in Spain (Granels, 1968). In contrast, in only 4 out of 37 cases of leprosy (10.8%) studied at post mortem in South India was death attributable to renal failure (Desikan and Job, 1968). Junnarkar failed to demonstrate any remarkable renal lesion in 20 cases of lepromatous and tuberculoid leprosy at post mortem except for one instance of amyloidosis (Junnarkar, 1957).

There have been only a few renal biopsy studies in patients with leprosy. Durtz and Gutman reported 2 cases of proliferative glomerulonephritis in 8 biopsied cases of lepromatous leprosy with *erythema nodosum leprosum* from Taiwan (Durtz and Gutman, 1972, 1973). Another case with proliferative glomerulonephritis has been reported by Shwe (1972). The wide discrepancy in the nature of renal lesions seen in different countries prompted this enquiry into the nature of renal disease in leprosy in India.

Materials and Methods

Patients admitted to the Schieffelin Leprosy Research Sanatorium with different clinical types of leprosy with or without *erythema nodosum leprosum* and in varying stages of therapy were selected at random. The cases were divided into lepromatous and borderline groups according to the system of Ridley and Jopling, using clinical, histological and immunological criteria (Ridley and Jopling, 1966). The bacterial load was estimated after standard skin smears from 8 sites and was expressed as the bacterial index (BI) according to Ridley's scale (Ridley, 1964). Only patients with *erythema nodosum leprosum* were classified as having reaction. A 24 h urine sample was examined for acid fast bacilli.

Immunological studies included estimation of antistreptolysin O (ASO) titre (Rantz and Randall, 1945), antinuclear factor, rheumatoid factor and examination of lupus erythematosus (LE) phenomenon by the method of Magath and Winkle (1952).

RENAL HISTOLOGY

Percutaneous renal biopsy was performed with a Franklin modified Vim-Silvermann needle following the method of Kark and Muechrcke (1954). Sections from all specimens were stained with hematoxylin eosin, periodic acid Schiff (PAS), congo red and Ziehl-Neelsen stains and examined with the light microscope. Sections were independently interpreted by two of us (KVJ and AD). The histological lesions were graded as follows:

(1) *Proliferative.* (PGN) Diffuse proliferative: showing diffuse hypercellularity of endothelial and mesangial cells with or without polymorphonuclear exudation in the glomerular tuft.

Mesangial proliferative: Hypercellularity of varying degree confined to the axial region.

(II) *Chronic sclerosing.* Showing glomerular hyalinization, focal tuft adhesions and interstitial scarring.

(III) *Mesangial sclerosis.* Glomeruli showing increase in PAS positive material in the axial region without significant hypercellularity.

(IV) *Amyloidosis.* Was confirmed by the presence of congo red positive material in the renal tissue.

(V) *Interstitial nephritis.* With predominant involvement of interstitium and tubules consisting of diffuse interstitial mononuclear cell infiltration, interstitial fibrosis and tubular atrophy.

RENAL FUNCTIONAL ASSESSMENT

Investigations included routine urine analysis for albumin and sediments, 24 h urine protein excretion (Thomas *et al.*, 1970), endogenous creatinine clearance (Bonsnes and Taussky, 1945) and blood urea estimation (Varley, 1967). Additional biochemical tests measured serum sodium, phosphorus, potassium, calcium, sugar, alkaline phosphatase and congo red retention (Varley, 1967). Serum protein was determined using cellulose acetate strips and Shandon universal electrophoretic apparatus (Kingsley, 1942; Smith, 1960).

Results

Adequate renal biopsies were obtained in the 35 patients analysed for this report. Thirty-four were males. The mean age of the group was 31.7 years and ranged from 18 to 57 years. Twenty-nine patients had lepromatous leprosy, 2 borderline lepromatous, 1 borderline borderline and 3 borderline tuberculoid. Mean duration of disease at the time of study based on the history was 9.8 years and ranged from 3 months to 25 years.

Those with lepromatous leprosy had a more prolonged illness (mean 10.3 years) than those with borderline leprosy (7.1 years). Twenty-four patients had past history of *erythema nodosum leprosum* of which 4 had ENL at the time of study. In the remaining 20 the last reaction had occurred within one week to 13 months prior to the study (mean 5 months). Five patients had received no form of anti-leprosy therapy at the time of study. Twenty-eight patients had been on therapy with single or multiple drugs for varying periods, the commonest drug employed being dapsone. The duration of treatment varied from a few months to over 10 years. The BI in the group ranged from 0 to 4.25 with a mean of 2.53. Acid fast bacilli were not present in the urine of any of the patients.

No definite statistical correlation could be established between any of the factors mentioned above and the presence of abnormal renal histology.

RENAL HISTOLOGY

Table 1 summarizes the histological findings in the 35 patients studied. Abnormal histology was seen in 16 cases (45%). Hypercellularity of the endothelial and mesangial cells was the most frequent histological abnormality.

In the most severe form seen in one case there was marked hypercellularity of the endothelial and mesangial cells and considerable polymorphonuclear exudation (15–25 per glomerulus) obliterating glomerular capillary lumena (Fig. 1). Diffuse endothelial hypercellularity without significant exudation was present in one case.

In the mesangial proliferative group, the hypercellularity was mainly confined to the axial region of the lobules (Fig. 2). The degree of hypercellularity varied.

In 1 patient, the glomeruli showed varying degrees of hyalinization, focal tuft adhesion, tubular atrophy, interstitial mononuclear cell infiltration and moderate arteriolar hyalinization. A few surviving glomeruli showed hypercellularity.

TABLE 1

Summary of renal histology in 35 cases

	Histology	Number of patients			Percentage incidence
		Lepromatous	Borderline	Total	
(I)	Proliferative	7	1	8	22.8
	Diffuse	2	—	2	5.7
	Mesangial	5	1	6	17.1
(II)	Chronic sclerosing	1	—	1	2.9
(III)	Mesangial sclerosis	3	1	4	11.4
(IV)	Amyloidosis	2	—	2	5.7
(V)	Interstitial nephritis	1		1	2.9
	Normal	15	4	19	54.3
	Total	29	6	35	

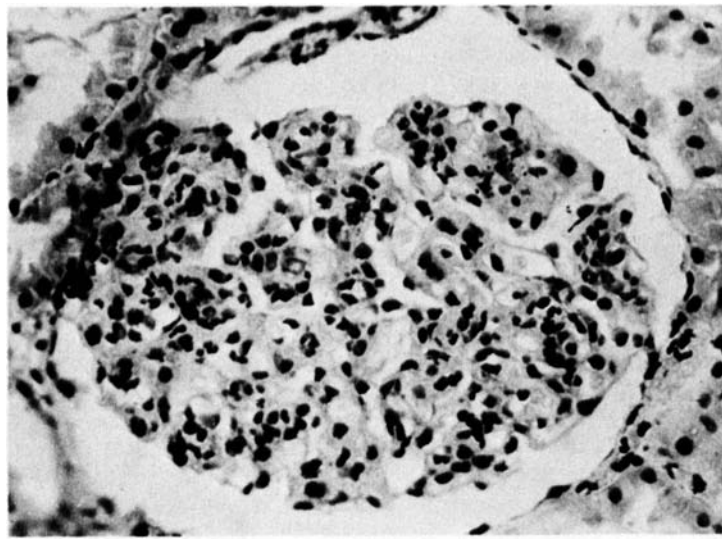

Fig. 1. Shows marked hypercellularity of endothelial and mesangial cells and polymorphonuclear exudation in the glomerulus—case from Group I (HE x 400).

Increase in PAS positive material in the axial region with no increase in cells was the only abnormality in 4 patients grouped under mesangial sclerosis (Fig. 3).

Amyloid deposition in the kidney was present in 2 cases, both of whom presented the features of nephrotic syndrome. One of these had extensive involvement of the glomeruli and vessels with associated renal failure. In the other the involvement was less extensive.

Interstitial fibrosis, mononuclear cell infiltration and tubular atrophy were the histological abnormalities in 1 case. The glomeruli appeared relatively unaffected. Two other patients showed occasional small collections of mononuclear cells along with proliferative glomerular disease. Granulomata and acid fast bacilli were not seen in any of the sections examined. Nineteen patients (54.3%) showed normal renal histology.

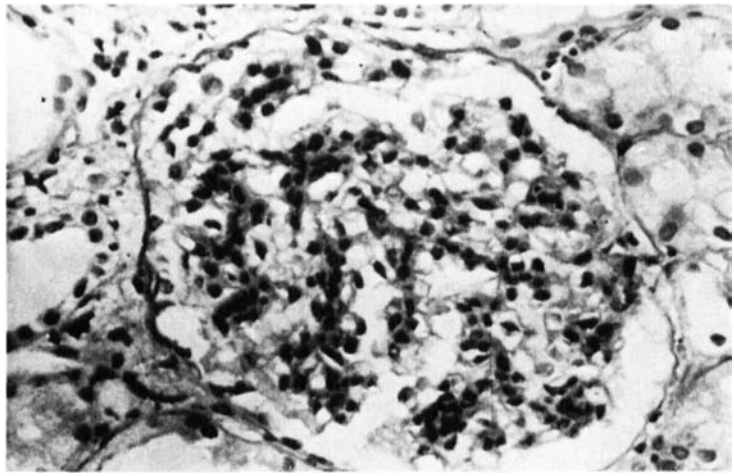

Fig. 2. Shows marked, mesangial hypercellularity grouped under "mesangial proliferative"–case from Group I (PAS x 400).

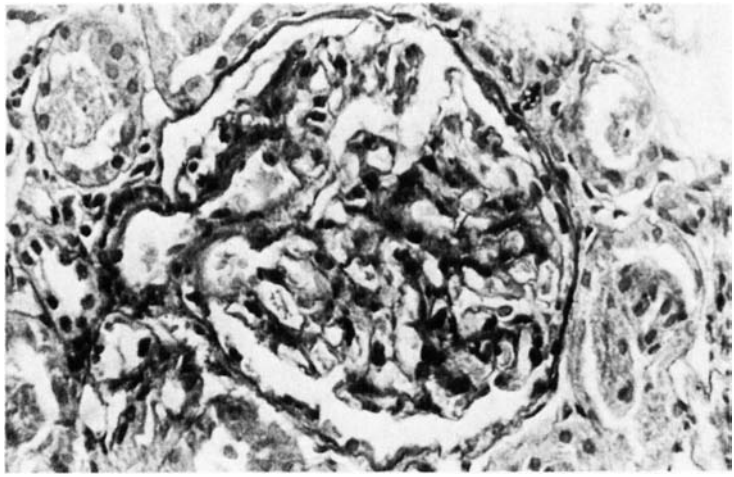

Fig. 3. Increase in PAS +ve material in the mesangium with no hypercellularity, grouped under mesangial sclerosis–case from Group III (PAS x 400).

CLINICAL FINDINGS AND INVESTIGATIONS

Table 2 summarizes the clinical features and investigations in the cases with abnormal renal histology.

The 2 patients with amyloidosis presented with nephrotic syndrome. Another patient who presented with nephrotic syndrome had no significant lesion on light microscopy. Marked mesangial proliferation was the histological appearance of the 1 patient with an acute nephritic picture with oedema, oliguria, haematuria and hypertension of sudden onset (Cameron, 1970). Massive proteinuria (>4 g/24 h) was seen in 3 patients. Eight other patients had minimal proteinuria

TABLE 2

Summary of findings in 16 patients with abnormal renal histology

No.	Histology	Leprosy			Symptom	B.P.	Proteinuria	Sediments		Creatinine clearance	ASO Titre
		Clinical	Reactional status	B.I.				RBC/HPF	WBC/HPF		
1.	Diffuse proliferative	LL	PR	1	Oedema	Normal	320 mg	8–10	–	83	166
2.	Diffuse proliferative	LL	PR	3.75	Nil	Normal			–	71	250
3.	Mesangial proliferative	LL	Nil		Acute nephritic	150/120	190 mg	35–40	–	71	–
4.	Mesangial proliferative	LL	PR	3	Oedema	Normal			–	–	125
5.	Mesangial proliferative	LL	PR	3.25		Normal			–	90	333
6.	Mesangial proliferative	LL	PR	2.62		Normal			–	80	100
7.	Mesangial proliferative	BT	Nil	0		Normal			–	58	333
8.	Mesangial proliferative	LL	PR	3.12	Oedema	Normal	380 mg	8–10	–	52	625
9.	Chronic sclerosing	LL	PR	1.12		Normal			6–10	74	333
10.	Mesangial sclerosis	LL	PR	2.62		Normal	420 mg		–	80	–
11.	Mesangial sclerosis	LL	PR	3.0	Oedema	Normal			–	62	333
12.	Mesangial sclerosis	LL	Nil	4.25		Normal			–	73	125
13.	Mesangial sclerosis	BT	Nil	0		Normal			–	71	166
14.	Amyloidosis	LL	PR	3.25	Nephrotic	Normal	6.6 g		–	104	50
15.	Amyloidosis	LL	Nil		Nephrotic	Normal	10.4 g		–	18	250
16.	Interstitial nephritis	LL	PR	3.62	Oedema	Normal	360 mg		8–12	38	125

LL – Lepromatous Leprosy. BI – Bacterial Index. BT – Borderline tuberculoid. PR – Past reactions.

(<0.5 g in 24 h), of which 5 patients had abnormal renal histology. Five patients had microscopic hematuria of which 3 had a proliferative glomerular lesion. Blood urea was within the normal range in all except 2 patients, 1 with nephrotic syndrome and amyloidosis and the one with acute nephritic disease (130 and 54 mg% respectively). The endogenous creatinine clearance was less than 75 ml/min in 21 out of 33 patients (63.6%) of which 10 had abnormal histology.

The tissue retention of congo red was 64 and 44% in 2 patients who had renal amyloidosis. In all the other patients the retention was less than 20%. The L.E. phenomenon could not be demonstrated in any of the 31 patients, each tested on 3 occasions. Antinuclear and rheumatoid factors were also negative in all 28 patients examined. ASO titre was raised above 333 Todd units in 35.5% of patients studied (Koshi, *et al.*, 1967). To examine the influence of a possible coincidental streptococcal infection in PGN of leprosy, those with normal ASO, raised ASO and the whole group were compared. No difference was found in the frequency of PGN in the various groups.

Discussion

Renal amyloidosis is the commonest renal complication and the major cause of death in lepromatous leprosy in U.S. and Spain (Powell and Swan, 1955; Shuttleworth and Ross, 1956; Granels, 1968; Brusco and Masanti, 1963). In India, renal failure is a rare cause of death in leprosy (Desikan and Job, 1968), possibly due to the low incidence of amyloidosis. However, both ante mortem and post mortem studies in India have revealed non-amyloid renal disease in more than 50% of patients (Desikan and Job, 1968; Mittal *et al.*, 1972). Renal functional impairment during reactive episodes followed by improvement in the quiescent phase has also been observed (Gokhale and Kurkure, 1958; Thomas *et al.*, 1970). These observations and also the present study suggest that renal disease in leprosy, though common in India, is resolving and self limiting and does not contribute significantly to the mortality.

The present study has revealed a high incidence of proliferative glomerulonephritis in leprosy. The presence of cases in this series showing diffuse proliferation and exudation, varying degrees of mesangial proliferation and pure mesangial sclerosis without proliferation could be interpreted as showing stages of resolution of an originally diffuse proliferative glomerulonephritis. If this is true the time taken for this process of resolution is not clear from the available data. It would seem, however, that the exudative reaction and diffuse hypercellularity resolve faster than the later stages of mesangial proliferation and sclerosis as evidenced by the larger number of cases seen with histological changes suggesting resolution in a cross-section study of this type. The one case showing changes of chronic glomerular disease may suggest that occasionally proliferative glomerulonephritis of leprosy does not resolve completely but progresses to irreversible damage.

The pathogenesis of the proliferative lesion is not clear, but the alterations in serum complement suggestive of complement consumption reported by Durtz and Gutman (1972, 1973) as well as the demonstration of immunoglobulins and BIC in the glomeruli in 3 cases of lepromatous leprosy by Shwe (1972) suggest that an immune complex mechanism is involved.

In this study, no definite relationship could be observed between the occurence

of PGN and the duration of illness, bacterial load, presence of ENL, or the ASO titre. None of these patients had a positive L.E. cell test.

The other renal lesions in leprosy such as interstitial nephritis and pyelonephritis are mostly seen at autopsy (Desikan and Job, 1968). Interstitial nephritis appears to be more often associated with advanced stages of the disease of very long standing. The one patient in the present series who showed diffuse interstitial disease had lepromatous leprosy for over 25 years, the longest duration of illness in the whole group, but only one episode of reaction. The prolonged disease state itself unrelated to reactive episodes has been held responsible for the lesion (Brusco and Masanti, 1963). Possibly, prolonged chemotherapy may also be contributory to the development of interstitial nephritis.

Acknowledgements

Presented at the Vth International Congress in Nephrology, Mexico City, October 1972. We wish to thank Drs A. Jeevaratnam and C. Chakravarthy for their valuable assistance in this work and Mr P. K. Chandran for secretarial assistance. We are also grateful to the Superintendent, S.L.R.S., Karigiri, for permitting us to investigate these patients and also extending to us all necessary help.

References

Bonsnes, R. W. and Taussky, H. H. (1945). On the calorimetric determination of creatinine by Jaffee reaction. *J. Biol. Chem.* **158**, 581-591.

Brusco, C. M. and Masanti, J. G. (1963). Causes of death of leprosy patients, influence of lepra reactions and renal disease. *Int. J. Lepr.* **31**, 14-25.

Cameron, J. S. (1970) Glomerulonephritis. *Brit. Med. J.* **4**, 285-289.

Cochrane, R. G. (1964). Complicating conditions due to leprosy. In *Leprosy in Theory and Practice*, 2nd ed. (Eds R. G. Cochrane and T. F. Davey). p. 331. Bristol: John Wright and Sons Ltd.

Davison, A. R. (1961). Acute edema of hands and feet in leprosy. *Int. J. Lepr.* **29**, 29-33.

Desikan, K. V. and Job, C. K. (1968). A review of postmortem findings in 37 cases of leprosy. *Int. J. Lepr.* **36**, 32-44.

Durtz, D. J. and Gutman, R. A. (1972). The kidney in leprosy: An Immunologic target organ. *Int. J. Lepr.* **40**, 217-218.

Durtz, D. J. and Gutman, R. A. (1973). Renal manifestations of leprosy: glomerulonephritis a complication off ENL. *Amer. J. Trop. Med. Hyg.* **22**, 496-502.

Gokhale, B. B. and Kurkure, N. B. (1958). Phenol red excretion test of kidney function in leprosy patients. *Indian J. Med. Sci.* **12**, 331-333.

Granels, M. (1968). Renal lesions in leprosy. *Int. J. Lepr.* **36**, 645-650.

Gutman, R. A., Lu, W. H. and Durtz, D. J. (1973). Renal manifestations of leprosy: Impaired acidification and concentration of urine in patients with leprosy. *Amer. J. Trop. Med. Hyg.* **22**, 223-228.

Junnarkar, R. V. (1957). Late lesions in leprosy. *Leprosy in India* **29**, 148-154.

Kark, R. M. and Muechrcke, R. C. (1954). Biopsy of kidney in pronse position. *Lancet* **1**, 1047-1049.

Kean, B. H. and Childress, M. E. (1942). Summary of 103 autopsies on leprosy patients on Isthmus of Panama. *Int. J. Lepr.* **10**, 51-59.

Kingsley, G. R. (1942). The direct Biuret method for the determination of serum proteins as applied to photoelectric and visual calorimetry. *J. Lab. Clin. Med.* **27**, 840-845.

Koshi, G., Mammen, A., Feldman, D. B., Bhakthaviziam, C. and Myers, R. M. (1967). A preliminary report on beta-haemolytic streptococci and anti-streptolysin O titers in pyogenic skin infections in children, with a case report of acute glomerulonephritis following repeated skin infections. *Indian J. Med. Res.* **55**, 920-929.

Magath, T. B. and Winkle, V. (1952). Technique of demonstrating LE cells in blood. *Amer. J. Clin. Path.* **22**, 586-587.

Mitsuda, K. and Ogawa, M. (1937). Study of 150 autopsies on cases of leprosy. *Int. J. Lepr.* 5, 53-60.

Mittal, M, M., Agarwal, S. C., Maheswari, H. B. and Kumar, S. (1972). Renal lesions in leprosy. *Arch. Path.* **93**, 8-12.

Powell, C. S. and Swan, L. L. (1955). Leprosy: Pathologic changes observed in 50 consecutive necropsies. *Amer. J. Path* **31**, 1131-1147.

Rantz, L. A. and Randall, E. (1945). A modification of the technique for determination of the antistreptolysin titer. *Proc. Soc. Exp. Biol. Med.* **59**, 22-25.

Ridley, D. S. (1964). Bacterial indices. In *Leprosy in Theory and Clinical Practice*, 2nd ed. (Eds R. G. Cochrane and T. F. Davey), p. 620 Bristol: John Wright and Sons Ltd.

Ridley, D. S. and Jopling, W. H. (1966). Classification of leprosy according to immunity—a five group system. *Int. J. Lepr.* **34**, 255-273.

Sachdev, J. C., Puri, D. and Bansal, S. (1969). Secondary amyloidosis in leprosy. *Lperosy in India* **41**, 73-76.

Shuttleworth, J. H. and Ross, S. H. (1956). Secondary amyloidosis in leprosy. *Ann. Int. Med.* **45**, 23-38.

Shwe, T. (1972). Immune complexes in glomeruli of patients with leprosy. *Lepr. Rev.* **42**, 282-289.

Smith, E. D. I. (1960). *Chromatographic and Electrophoretic Technique*, Vol. 2, p. 57. Zone Electrophoresis. London: Heinemann.

Thomas, G., Karat, A. B. A., Rao, P. S. S. and Kumar, C. P. (1970). Changes in renal function during reactive phases of lepromatous leprosy. *Int. J. Lepr.* **38**, 170-176.

Varley, H. (1967). *Practical Clinical Biochemistry* (4th ed). London: Heinemann Medical Books.

Wheate, H. W. (1962). Acute oedema in leprosy. *Int. J. Lepr.* **30**, 387-394.

Williams, R. C., Cathcart, E. C. and Calkins, E. (1965). Secondary amyloidosis in lepromatous leprosy. Possible relationships of diet and environment. *Ann. Int. Med.* **62**, 1000-1007.

Lepr. Rev. (1975) **46**, 39-49

Leproma of the Mouse Foot

C. K. JOB

Schieffelin Leprosy Research Sanatorium – 632106, Karigiri, Via. Katpadi, Tamil Nadu, S. India.
and
Department of Pathology, Christian Medical College and Hospital, Vellore 632004, Tamil Nadu, S. India.

C. J. G. CHACKO

and

R. VERGHESE

Schieffelin Leprosy Research Sanatorium – 632106, Karigiri, Via. Katpadi, Tamil Nadu, S. India.

and

S. PADAM SINGH

Department of Radio-Therapy, Christian Medical College and Hospital, Vellore – 632004, Tamil Nadu, S. India.

Leproma of the foot in six T 900r CBA mice produced by local injection with *Myco. leprae* is reported in this paper. Organisms numbering 10^4 multiplied to the order of 10^9 in 10 to 12 months. The original inoculum of *Myco. leprae* was obtained from a lepromatous patient and the bacilli were first passaged through a group of T 900r Swiss albino mice and later were subcultured three times successively in T 900r CBA mice. One or more of the animals used in each of the subcultures developed erythematous swelling of both inoculated hind feet which on microscopic examination showed typical lepromatous nodules. None of the other 23 strains of bacilli studied from different lepromatous patients showed this reaction. It is possible that this particular strain of *Myco. leprae* had undergone certain variations producing lesions characteristic of lepromatous leprosy.

Introduction

A limited multiplication of *Myco. leprae* in the footpads of mice was first reported by Shepard in 1960 (Shepard, 1960). Since then it has been shown by several workers that if 5000 to 10,000 lepra bacilli are injected into the footpads of mice, they will multiply 50 to 100 times in about 6 to 8 months. (Rees, 1964; Job, 1970; Levy *et al.*, 1970). It was also found that larger inoculum failed to give enhanced yields (Rees, 1964). If the same number of organisms are injected into immunologically suppressed mice, a marked enhancement of the growth with a yield ranging from 10,000 to 100,000 times the original number occurred (Rees, 1966; 1967; Shepard and Congdon, 1968; Gaugas, 1967; Job *et al.*, 1974). Histopathological lesions characteristic of lepromatous leprosy has also been described by Rees and his associates in thymectomized irradiated (T 900r) mice

Received for publication 9 August, 1974.

(Rees *et al.*, 1967; Rees and Weddell, 1968; Rees and Weddell, 1970). Rees has also reported swelling of the hind footpads resembling lepromatous nodules in 5% of all T 900r mice at risk (Rees, 1971). However no other worker has confirmed the finding of nodular swelling in similarly experimented animals. In this paper we record our finding of nodular leproma of the feet in 6 T 900r CBA mice.

Material and Methods

Experiments using T 900r mice belonging to both CBA and Swiss albino strains for culturing *Myco. leprae* have been going on in our laboratory for over 5 years and the finding of enhanced growth of *Myco. leprae* in these animals in 7 experiments have been reported elsewhere (Job *et al.*, 1974). In this experiment *Myco. leprae* obtained from a lepromatous patient with a morphological index (M.I.) of 2% were injected into both the hind footpads of T 900r Swiss albino mice. The organisms isolated from these Swiss albino mice were subcultured in the footpads of T 900r CBA mice successively 3 times. The results of our experience with this strain of *Myco. leprae* carried through 3 successive generations of T 900r CBA mice is being reported in this paper.

The method used for preparing the inoculum from the tissue of the lepromatous patient, for harvesting the footpads of mice, and for counting the organisms, closely followed that described by Rees in 1964. Both the hind footpads of all the mice were injected with an inoculum containing 10^4 organisms. They were kept in an airconditioned laboratory with a constant environmental temperature of 20–22°C. At the end of 6, 8, 10 and 12 months, one or two of the mice were sacrificed and the tissue from one foot was processed for counting the number of organisms present, and the other foot was amputated, fixed in formalin for 72 h, cut transversely into 3 pieces, decalcified and processed for paraffin sections. Haematoxylin and eosin stain, and acid fast stain were done on 5 μm thick sections obtained from all the blocks for histopathological study.

Four of the 6 mice which developed leproma of the feet were autopsied and the internal organs such as lung, liver, kidney, spleen, lymph nodes and heart were examined both grossly and microscopically, using the same histopathological techniques as described above.

Results

Of the 13, T 900r CBA mice infected with *Myco. leprae* obtained from T 900r Swiss albino mice, 6 died before 6 months, and only 7 were available for study. Of these, 3 developed erythematous and nodular swelling of both the hind feet resembling human lepromatous nodules (Fig. 1). There was no evidence of external ulceration and the nodules were not warmer than the normal skin of the mice. Smears obtained from them showed numerous macrophages filled with acid fast organisms. The swelling of the feet developed gradually and was noticeable as early as the eighth month. One animal was sacrificed and studied at the tenth month and the other two by the twelfth month. The bacillary counts from one footpad of each of these animals were 5×10^9; 1×10^9 and 3×10^9.

The strain of *Myco. leprae* obtained from one of these mouse lepromas was subcultured into 10 T 900r CBA mice. Of these, 5 died within 6 months, and 5 were available for study. One among them developed swelling and nodularity of

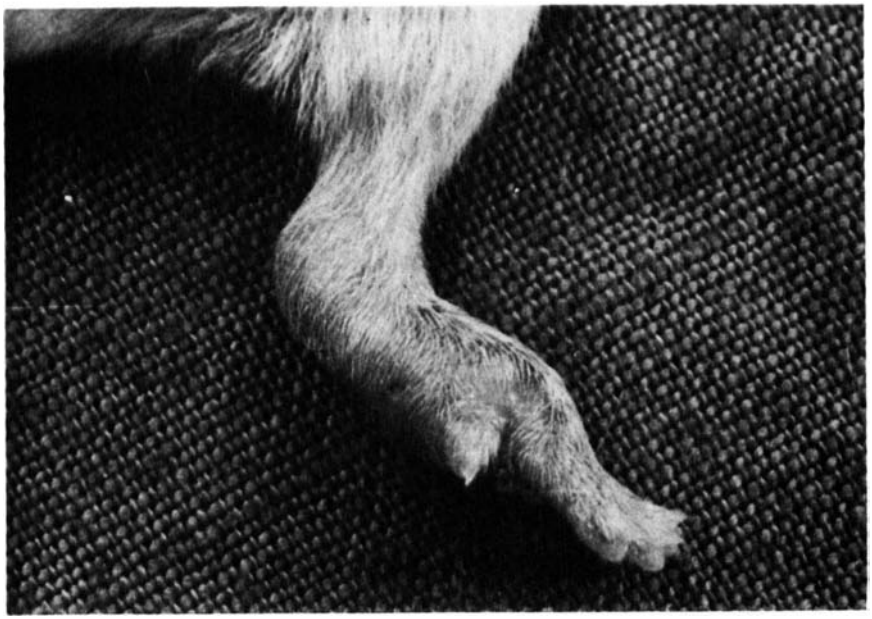

Fig. 1. Photograph of the hind footpad of T 900r CBA mice 10 months after injection with 10^4 *Myco. leprae.*

the hind feet at the eighth month and was sacrificed at the end of the tenth month giving a yield of 1.4×10^9.

The *Myco leprae* obtained from one of the mice from the previous group were further subcultured for the third time into 15 T 900r CBA mice. Ten of them died within 6 months, and of the remaining 5, two developed swelling and nodularity of both hind feet beginning from the tenth month and were harvested at the end of the twelfth month giving a yield of 1×10^9 and 3×10^9 organisms. The organisms isolated from this experiment were also subcultured for the fourth time into a group of T 900r CBA mice and the results of this study are awaited.

Microscopic examination of the feet was most interesting. The appearances were almost identical in all the specimens examined from 6 different animals. The lepromatous granuloma involved all the tissues of the foot, namely. the skin, its appendages, subcutaneous fat, tendon, muscle and bone (Fig. 2). The epidermis was atrophic and flattened. The subcutaneous tissue was packed with large macrophages, most of which had a foamy cytoplasm, but some had a granular pink cytoplasm. These macrophage collections were separated from the epidermis by a clear area (Fig. 3), but in focal areas the inflammatory cells reached up to the epidermis (Fig. 4). There were also a few scattered plasma cells and lymphocytes. No polymorphonuclear leucocytes were seen. The striated muscle bundles and tendon tissues were infiltrated and destroyed by the macrophage granuloma (Fig. 5). In some areas the striated muscle fibres were completely replaced by macrophages. The nerves and their perineurium looked normal although surrounded by macrophages (Fig. 6). However, in one instance the nerve was infiltrated by foamy macrophages (Fig. 7). The bones of the foot and bone marrow also showed infiltration by macrophages (Fig. 8). Acid fast stain showed

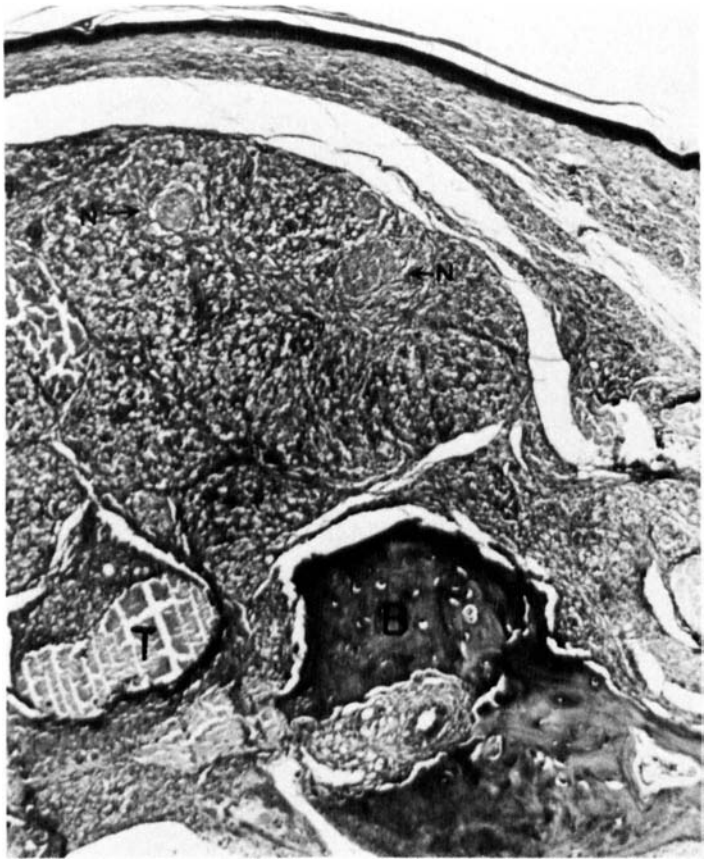

Fig. 2. Low power photomicrograph to show the "leproma" beneath the flat epidermis infiltrating muscle, tendon (T) and bone (B). Note the small cutaneous nerve bundles (N) surrounded by macrophages. (H & E x 50.)

macrophages packed with *Myco. leprae* (Fig. 9) in the subcutaneous tissue, tendon, bone and bone marrow. Bacilli were also present in large numbers inside striated muscle cells, but only very rarely inside nerve bundles. The nerve bundle infiltrated with foamy macrophages contained a large number of acid fast bacilli (Fig. 10).

In one animal the macrophage granuloma was, in focal areas, densely infiltrated by lymphocytes (Fig. 11) and *Myco. leprae* were considerably reduced in number at these sites.

Four of the 6 animals which developed leproma, 2 at the tenth month and 2 at the twelfth month were autopsied, and lung, liver, spleen, kidney, heart and lymph nodes were examined both grossly and microscopically. Gross examination did not reveal any abnormality in any of the organs. On microscopic examination acid fast bacilli were seen in Kupffer cells of the liver and in reticulo-endothelial cells lining the sinusoids of spleen. No granuloma was present in any of the organs in all the animals examined.

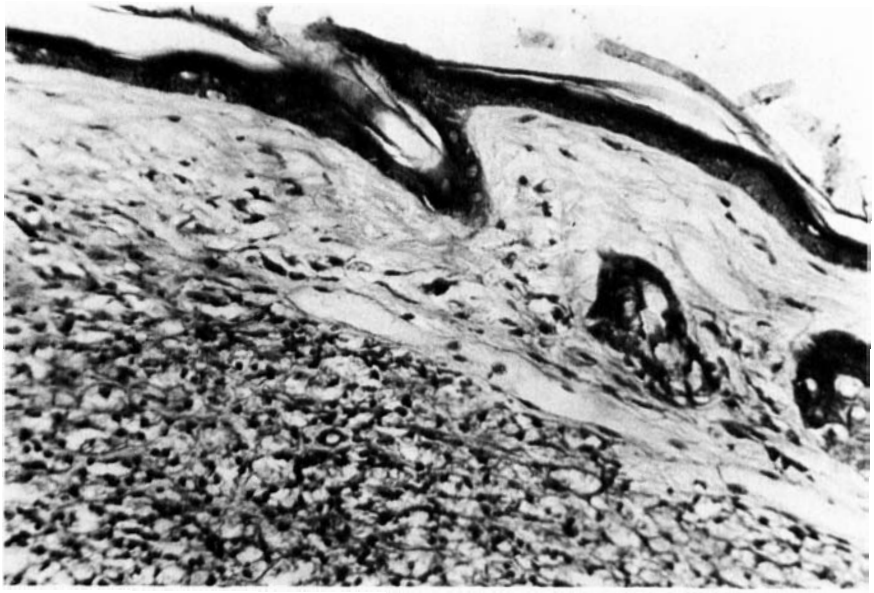

Fig. 3. Microscopic picture of the leproma of the mouse footpad. Note the flattened epidermis, beneath which was seen a clear area separating large collection of foamy macrophages. (H & E x 130.)

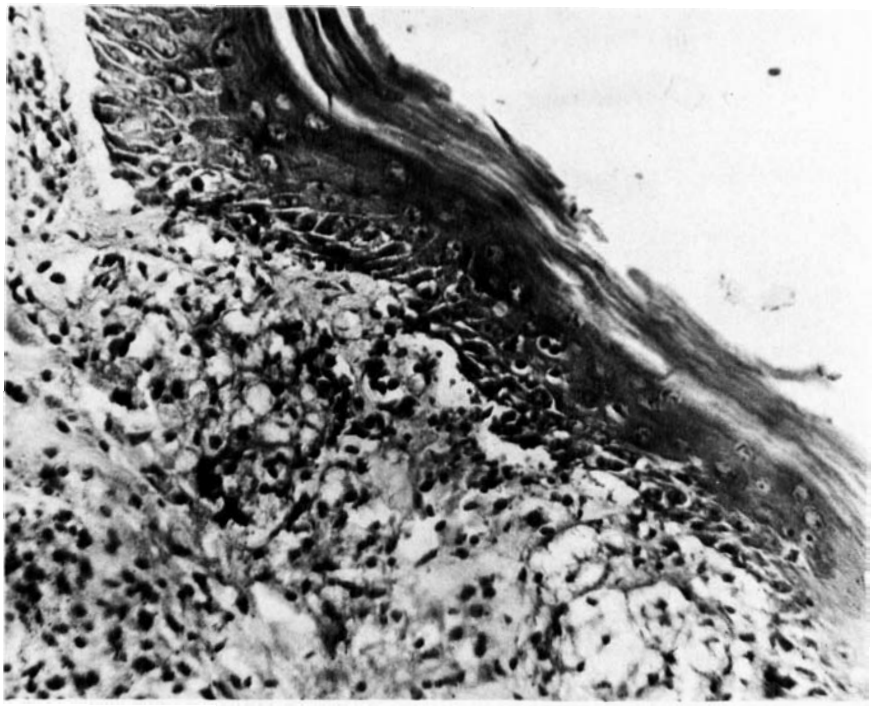

Fig. 4. In focal areas of the lepromatous lesion, the macrophage collections reach up to the epidermis. (H & E x 500.)

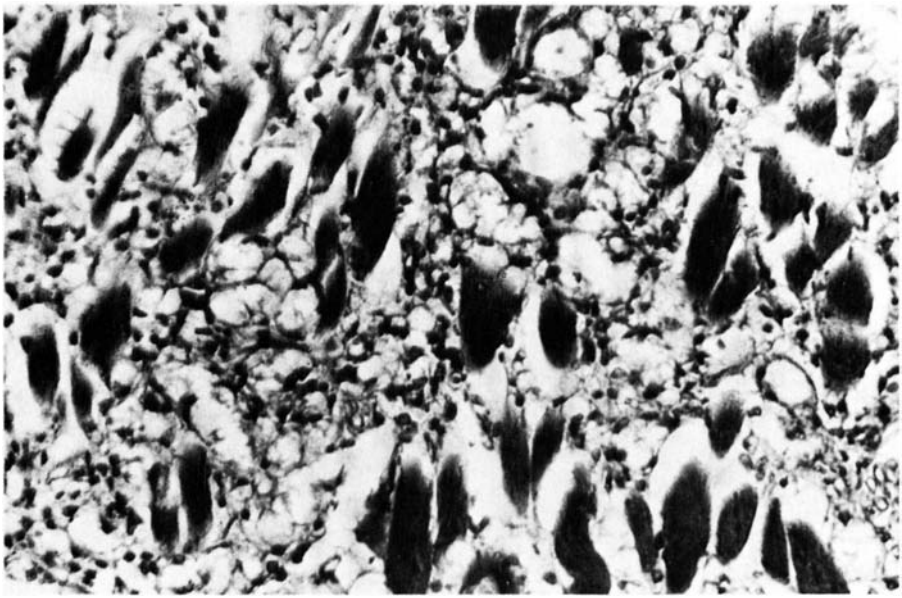

Fig. 5. Foamy macrophages infiltrate the striated muscle cells some of which also underwent foamy change due to the presence of intracellular bacilli (H & E x 500.)

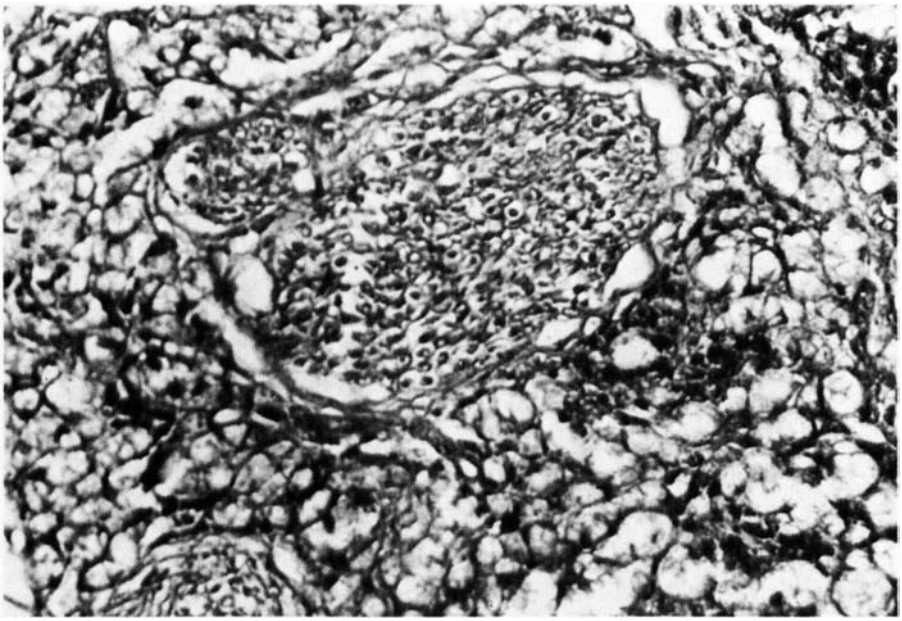

Fig. 6. Apparently normal cutaneous nerve bundles were surrounded by foamy macrophages. (H & E x 500.)

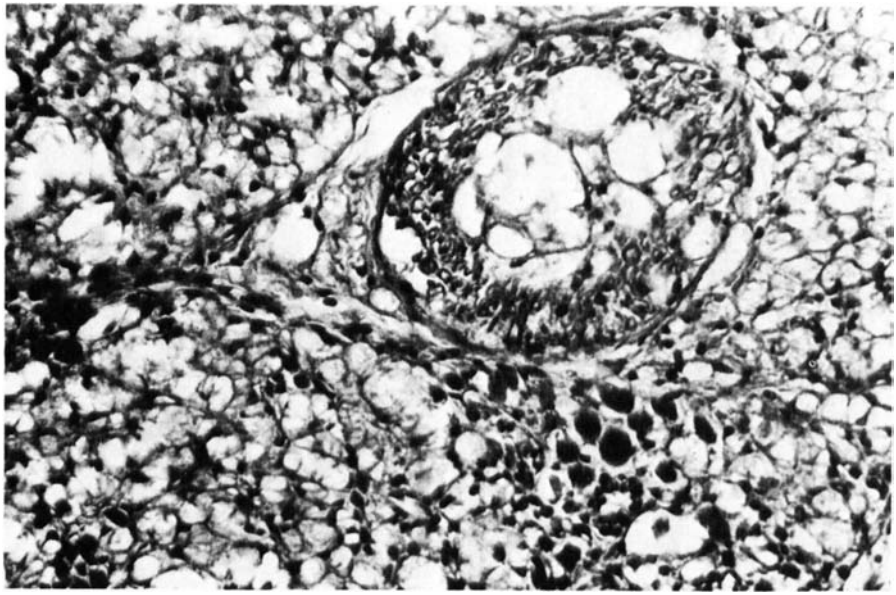

Fig. 7. One nerve bundle was infiltrated with macrophages. Atrophic muscle cells were also seen in the photomicrograph. (H & E x 500.)

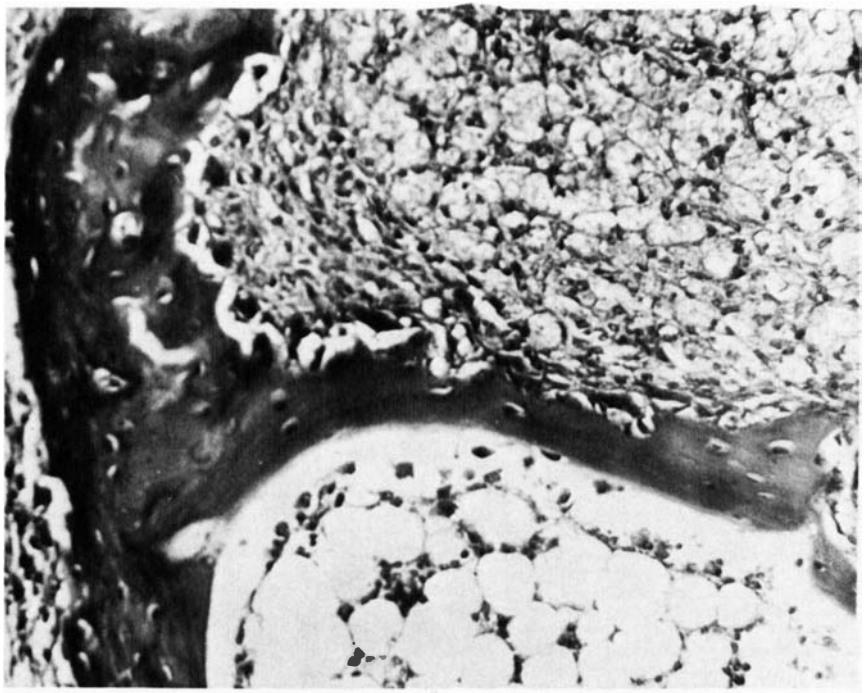

Fig. 8. Bones in the mouse foot were infiltrated with collections of foamy macrophages. Note the normal marrow in the lower part of the photomicrograph. (H & E.x 500.)

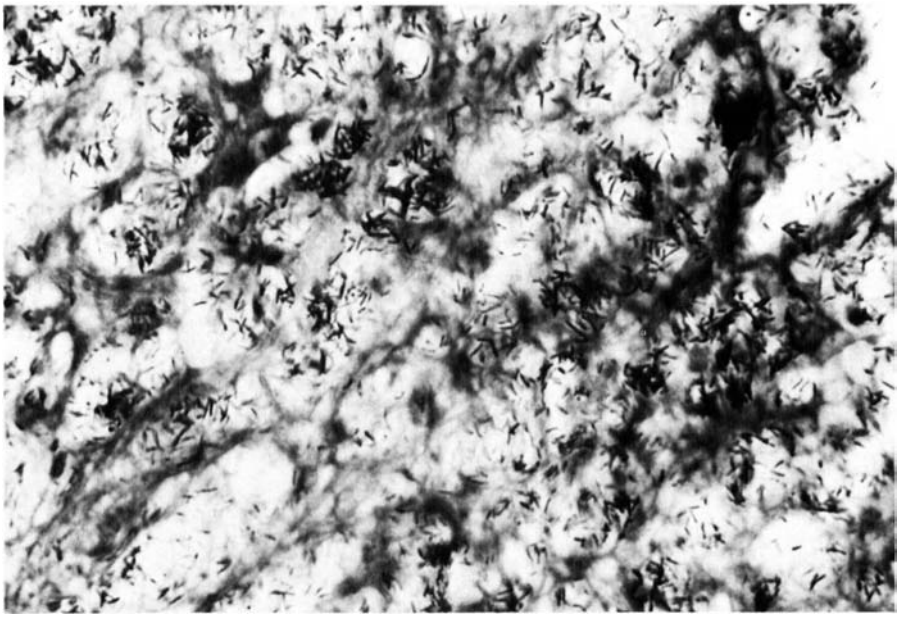

Fig. 9. Foamy macrophages were packed with acid-fast bacilli. (A. F. x 1300.)

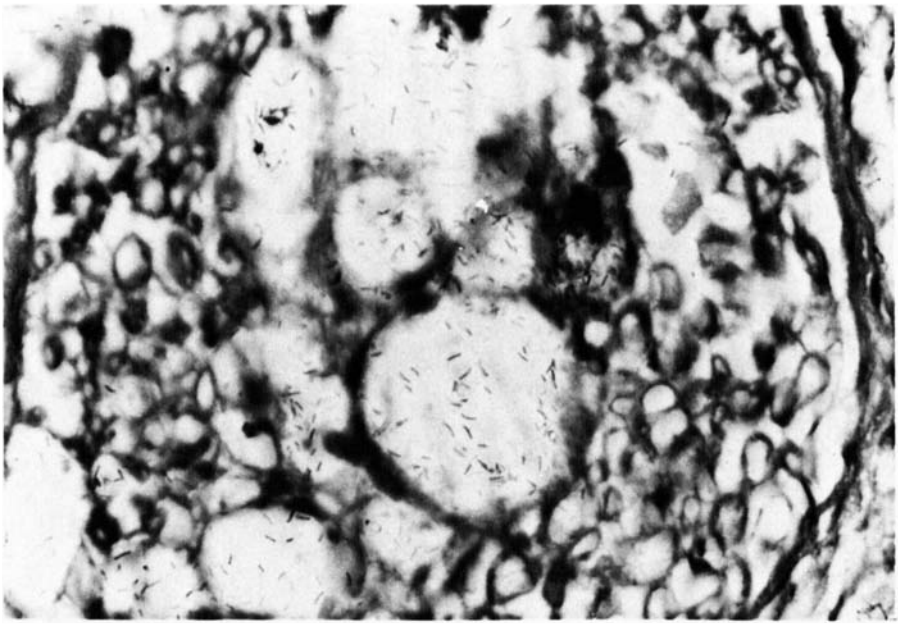

Fig. 10. The intraneural foam cells also contained numerous bacilli. Note the numerous normal axons around the foam cells. (A. F. x 1300.)

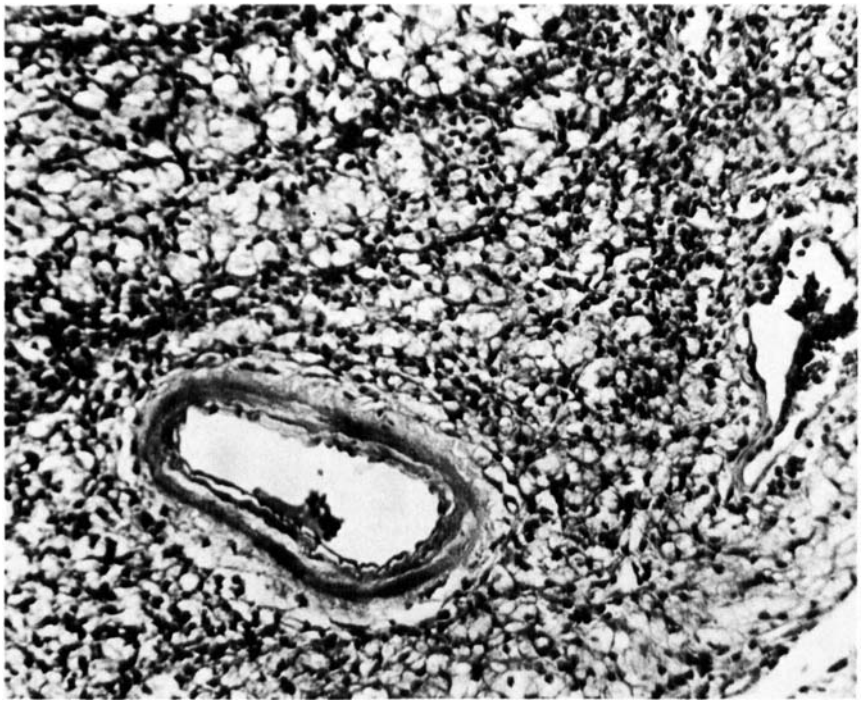

Fig. 11. In one mouse in focal areas of the leproma there were collections of lymphocytes infiltrating the foamy macrophages. (H & E x 330.)

Discussion

The development of swelling and nodularity of the footpads of T 900r mice resembling human lepromatous leprosy seems to be an exception rather than the rule. Rees *et al.* (1968) refer in their paper to some animals among the many T 900r CBA mice they studied, which developed swelling of the footpads, and also describe in detail the histopathological picture in one. In most of the animals there was no obvious change at all in the infected foot. In our experiments conducted with T 900r mice using organisms obtained from 23 different patients with lepromatous leprosy this is the only strain of *Myco. leprae* in which nodularity of the feet of the animals was noticed. Six of the 17 animals available for study showed leproma of the feet. The procedure of thymectomy, irradiation and bone marrow replacement was exactly the same in all experimental animals, was done by one well trained technician, using the same equipment, and therefore less likely to have any appreciable variation. The CBA mice are being inbred in our own laboratory. Variability in their immunological status, though possible, is also not very likely. Further we have found this strain of *Myco. leprae* consistently giving rise to nodular swellings in 3 successive subcultures in T 900r CBA mice. Therefore one might suggest that this particular strain of organisms proliferated more rapidly than the others. If that be the case, should it not produce nodular granulomatous swelling in all the 17 mice inoculated with this organism? Instead, only 6/17 mice injected with this strain of the bacilli

developed the swelling. Whether the swelling and nodularity of the feet and proliferation of the 10^4 organisms to 10^9 in a period of 10 to 12 months are due to a change in the immunological status of the experimented animals, or whether they are due to a variation in the nature of the organism used in the infection, is not clear, although judging from our experience in this study the latter is more likely.

The animals could not be followed up for a period longer than 12 months because most of them developed a tapeworm infestation and died soon after 12 months. *Myco. leprae* in small numbers were seen in Kupffer cells in liver and reticulo-endothelial cells of the spleen in animals sacrificed at the end of 10 and 12 months showing that dissemination of the bacilli through the blood stream of various internal organs occurred within 10 months after a local infection in a T 900r CBA mouse. However, granuloma formation in the internal organs was not observed. Therefore it is reasonable to infer that the dissemination of the organism in the blood stream could not have taken place much earlier.

The organisms were found in abundance in macrophages, and equally so in the muscle cells. We may state that this strain of *Myco. leprae* would grow freely not only in macrophages but in striated muscle cells also. The bacillary invasion and proliferation of striated muscles of the feet of T 900r mice was far more than what was seen in our previous study using normal mice (Job, 1970). This finding is in agreement with the observation of Rees and Weddell in 1968. Many of the striated muscle cells in the feet of these animals were colonized by bacilli and were destroyed. It is very likely that if these animals survived for a longer period, paralysis of the foot due to destruction of muscle tissue could be observed.

Most of the cutaneous nerves examined did not show invasion by inflammatory cells in haematoxylin eosin section. The granuloma only surrounded the nerve bundles (Fig. 6). Intraneural bacilli were very scanty. Shepard (1968) did not find nerve invasion in the early months of *Myco. leprae* infection in T 900r mice. However, in one cutaneous nerve of a mouse foot there was infiltration of the nerve bundle by foamy macrophages (Fig. 7). Bacilli were present in large numbers in intraneural macrophages (Fig. 10) as seen in nerves of lepromatous leprosy patients. It is interesting to point out that the nerve invasion was seen as early as 10 months after inoculation of *Myco. leprae*.

The lepromatous tissue in all animals had infiltrated bone and bone marrow (Fig. 8). Bone trabeculae also had been destroyed. These lesions are well known in small bones of the fingers in lepromatous leprosy patients (Job, 1963). Further, the lesion in the mouse skin showed flattened epithelium and a band of foamy macrophages containing *Myco. leprae* separated by a clear area from epithelium (Fig. 3). Cutaneous nerves were surrounded by bacilliferous macrophages (Fig. 6). All these resembled exactly the skin lesions of human lepromatous leprosy.

If lepromatous granuloma such as described here could be produced consistently in most of the T 900r mice in all experiments within 8 to 10 months, we would have here a good animal model to study lepromatous leprosy. But since it is a rare phenomenon its use is limited. However, we intend to study this particular strain of *Myco. leprae* further and will report later on any further developments in its pattern of behaviour.

Acknowledgements

I am deeply grateful to Mr Samuel Joseph for the devoted and careful technical work and to Mr J. Ramamurthy for secretarial assistance. The funds for this study were provided by The Leprosy Mission, London, and American Leprosy Mission Inc., New York.

References

Gaugas, J. M. (1967). Effect of X-irradiation and thymectomy on development of *M. leprae* infection in mice. *Br. J. exp. Path.* **48**, 417-422.

Job, C. K. (1963). Pathology of leprous osteomyelitis. *Int. J. Lepr.* **31**, 26-33.

Job, C. K. (1970). Bacteriology and pathological study of leprous lesions in the foot pads of mice. *Ind. J. Path. Bact.* **13**, 109-111.

Job, C. K., Chacko, C. J. G., Verghese, R. and Padam Singh, S. (1974). Enhanced growth of *M. leprae* in the foot pads of thymectomized irradiated mice. *Lepr. India.* Accepted for publication.

Levy, L., Murray, L. P. and Shepard, C. C. (1970). A comparative study of mouse foot pad inoculation of skin biopsy specimens from patients with lepromatous leprosy in San Francisco and Atlanta. *Int. J. Lepr.* **38**, 54-59.

Rees, R. J. W. (1964). Limited multiplication of acid fast bacilli in the foot pads of mice inoculated with *Mycobacterium leprae*. *Br. J. exp. Path.* **45**, 207-218.

Rees, R. J. W. (1966). Enhanced susceptibility of thymectomized and irradiated mice to infection with *M. leprae*. *Nature, Lond.* **211**, 657-658.

Rees, R. J. W., Waters, M. F. R., Weddell, A. G. M. and Palmer, E. (1967). Experimental lepromatous leprosy. *Nature, Lond.* **215**, 599-602.

Rees, R. J. W. and Weddell, A. G. M. (1968). Experimental models for studying leprosy. *Ann. N.Y. Acad. Sci.* **154**, 214-236.

Rees, R. J. W. and Weddell, A. G. M. (1970). Transmission of human leprosy to the mouse and its clinical implications. *Trans. Roy. Soc. Med. Hyg.* **64**, 31-47.

Rees, R. J. W. (1971). The impact of experimental human leprosy in the mouse on leprosy research. *Int. J. Lepr.* **39**, 201-215.

Shepard, C. C. (1960). The experimental disease that follows the injection of human leprosy bacilli into foot pads of mice. *J. Exp. Med.* **112**, 445-454.

Shepard, C. C. and Congdon, C. C. (1968). Increased growth of *M. leprae* in thymectomized irradiated mice after foot pad inoculation. *Int. J. Lepr.* **36**, 224-227.

Lepr. Rev. (1975) **46**, 51-67

Perineurial Changes in Untreated Leprosy

J. M. H. PEARSON* AND A. G. M. WEDDELL†

Leprosy Research Unit, National Leprosy Control Centre, Sungei Buloh, Malaysia
and
Department of Human Anatomy, South Parks Road, Oxford, England

Perineurial changes were studied by light microscopy in biopsies of skin and nerve from 64 patients covering the full range of the leprosy spectrum. In all types of leprosy a multilayered appearance of the perineurium could be observed: in lepromatous cases the layers tended to consist of swollen cells which contained more leprosy bacilli than the Schwann cells; in borderline and tuberculoid biopsies they took on a thinner, more fibrotic appearance, and bacilli were scanty or absent. Epithelioid changes were seldom observed in this site. The possible effects of perineurial damage in the endoneurium, and of endoneurial damage on the perineurium, are discussed.

Introduction

The "scientific era" of leprology may be considered as starting in 1847, when Danielssen and Boeck published their treatise on leprosy. They divided patients into two groups, "nodular" and "anaesthetic," according to their dominant clinical features. Clearly therefore nerve damage was already well recognized as commonly present in the disease.

Virchow (1864) examined nerves from leprosy patients, and considered that there was an interstitial neuritis, in which an important role was played by "brownish cells" in the endoneurium. He also however commented on the presence of a perineuritis i.e. proliferation of the outer layers of the nerve. This appearance has been consistently noted by workers since that time, and it has been considered to play a part in causing nerve dysfunction by exerting a strangling action on the nerve bundles.

With the advent of electron microscopy it became possible to study the ultrastructure of perineurium, and to show that it is not a simple membrane but a compact multilayered structure, composed of up to ten laminae, each covered by a basal lamina. It is anatomically well suited to act as a semi-permeable barrier to isolate the interior of nerve from some of the contents of the fluid outside the nerve, and has, indeed, been shown to have that function (Waggener, Bunn and Beggs, 1965). The sequence of events following experimental perineurial injury

* Present address: MRC Leprosy Project, P.O. Box 1005, Addis Ababa, Ethiopia.
† Requests for reprints should be addressed to AGMW.
Received for publication 10 October, 1974.

has been analysed by Morris, Hudson and Weddell (1972); this study also indicated its importance as a barrier.

There have been a number of studies of nerves in leprosy in recent years, both by light and electron microscopy (Iyer and Desikan, 1968; Job, 1971; Dastur, Ramamohan and Shah, 1973): but the perineurial changes receive only incidental mention. Pearson (1972) discusses the perineurium, but only in relation to lepromatous leprosy. The purpose of this paper is to describe the changes seen by light microscopy in the perineurium in untreated leprosy of all types. Possible mechanisms causing these changes, and the interrelationship of perineurium and endoneurium are also discussed.

Patients and Methods

Sixty four patients were studied, covering the whole range of leprosy, from tuberculoid to lepromatous. Men, women and children over 12 years were included, their nationalities being Malay, Chinese, Indian, or Gurkha. Patients with both early and advanced lesions were selected.

All patients appeared to be suffering from active untreated disease, and all denied receiving previous treatment. No patient was suffering from other significant disease, and in no case was dapsone found in the urine. Classification was according to the system of Ridley and Jopling (1966) and there was good agreement between clinical and histological diagnoses.

All patients were subjected to biopsy of an active skin lesion and of an enlarged nerve. The nerve usually chosen was the superficial radial at the level of the styloid process of the radius (Pearson and Weddell, 1971), but in some cases enlarged subcutaneous nerves in the immediate vicinity of tuberculoid skin lesions were biopsied. Two separate skin lesions were biopsied in two cases. Not all the nerve biopsies however, were processed for light microscopy—figures are given in Table 1.

TABLE 1

Classification of patients and number of biopsies examined

Classification		Number of patients	Number of skin biopsies	Number of nerve biopsies
Tuberculoid	TT	3	3	2
	BT	24	24	14
Borderline	BT/BB	3	3	1
	BB	6	6	4
	BB/BL	2	2	1
Lepromatous	BL	8	8	4
	LI	16	17	8
	LL	2	3	1

The skin biopsies were divided into two, one part being examined for independent histological classification by Dr D. S. Ridley, the other fixed by immersion in 10% buffered formaldehyde and examined in the Department of Human Anatomy, Oxford. Nerve biopsies were intended primarily for electron microscopy, and in most cases were fixed by immersion in 3% glutaraldehyde for

2 h; larger specimens were sometimes subdivided for light as well as electron microscopy. Some nerve biopsies, however, to be used primarily for light microscopy, were fixed in 10% buffered formaldehyde.

The specimens for light microscopy were subjected to routine processing, embedded in wax, and cut into 6 μm sections. They were always stained with haematoxylin and eosin, and haematoxylin and cold carbol fuchsin. Additional stains used in some cases included methods for elastic fibres, PAS stains, and silver techniques for axons. In a few cases silver stains of 25 μm sections were combined with staining for acid-fast bacilli. Additionally in a few cases thin (1 μm) sections of araldite embedded material stained with toluidine blue were available.

Findings and Comments

The appearance of normal perineurium is shown in Fig. 1.

TUBERCULOID LEPROSY

Twenty seven patients were included in this category. Eight biopsies (all BT) were taken from lesions which appeared clinically to be rather early in their evolution; and a further two (both BT) were biopsies taken across the edge of the lesion and extending into apparently normal skin outside it. In such biopsies the earliest stage of the evolution of the disease could be seen outside the active edge, and its development followed across the edge and into the lesion.

The remaining biopsies were from the active areas of mature lesions; three were classified TT and the remainder BT.

(1) *Early Lesions (10 cases, all BT).* The dermal nerves in these cases were usually normal in size or only slightly enlarged. Most of them however had a rather fibrotic appearance, and a few showed marked swelling and hypercellularity of the endoneurium, though there was never a mature epithelioid granuloma. In general, the more normal a nerve looked, the more likely were bacilli to be found within it.

Even in these early cases the perineurium was usually markedly abnormal. Instead of being a very compact structure, the layers appeared to be separated into thin fibrotic looking strands, and there were a large number of inflammatory cells, chiefly lymphocytes, lying among the strands and apparently invading the perineurium from outside (Fig. 2). It was not uncommon for there to be the appearance of a dense cellular cuff occupying the perineurial zone, with a somewhat fibrotic looking but relatively normal and preserved endoneurium. Only in one instance was the perineurium normal in appearance, and even in this case (where the only abnormality of the nerve itself was the presence of very scanty bacilli lying within Schwann cells) there were a number of lymphocytes clustering round the outside of the nerve. Acid-fast bacilli were never seen in the perineurial zone.

(2) *Mature Lesions (17 cases; TT-3, BT-14).* Dermal nerves of fairly well preserved morphology could be identified in eight cases (TT-1, BT-7), and structures recognizable as formerly neural in another 7 (TT-1, BT-6). Only in 2 biopsies could no nerves be found. The destroyed nerves were grossly swollen, chiefly due to expansion of the endoneurium, in which there were seldom recognizable Schwann cells, the whole zone being replaced by epithelioid cells.

In the more normal looking nerves the perineurium looked much the same as in the early cases; there was a multilayered fibrotic appearance with some cellular

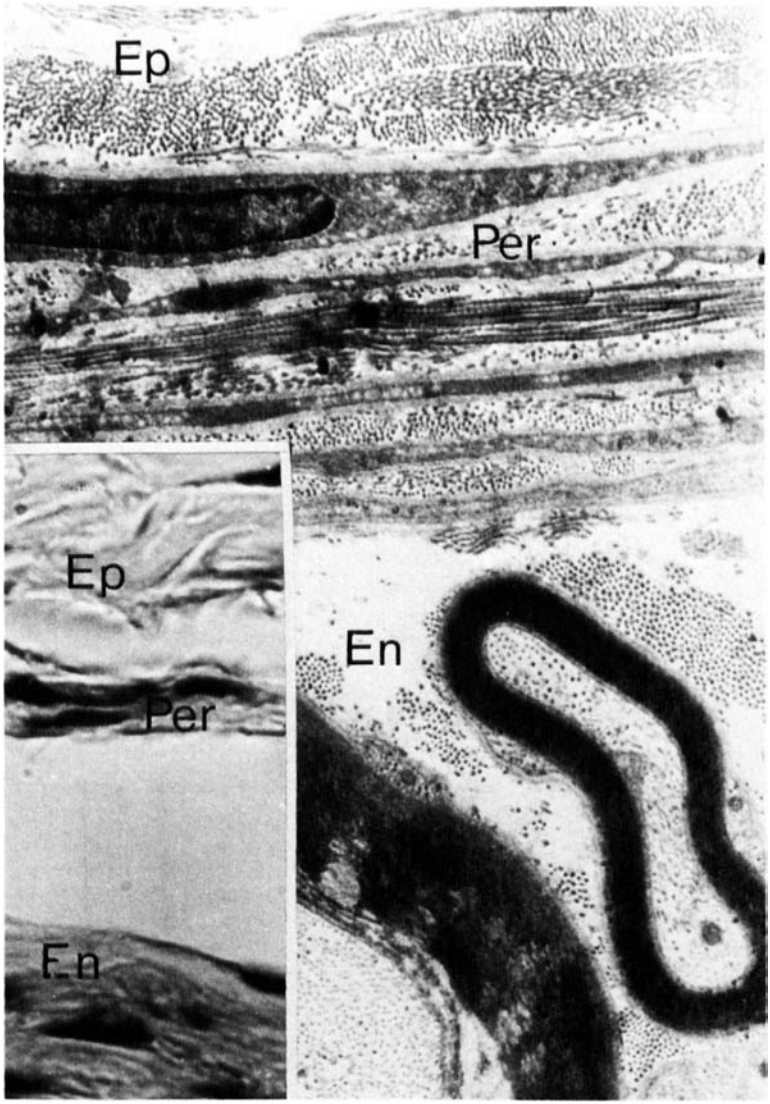

Fig. 1. Electron-micrograph of mouse sciatic nerve (×16,000). Inset: light photomicrograph of fascicle of normal human radial cutaneous nerve (×1500). Note the multilayered structure of the perineurium which is hardly to be seen by light microscopy. The separation of perineurium from the other nerve layers in the light micrograph is a shrinkage artefact. Ep = epineurium; Per = perineurium; En = endoneurium.

infiltration. In addition there sometimes appeared to be fine septa of perineurium extending into the endoneurium, forming multiple compartments in the normally monofascicular nerve bundles.

In the grossly swollen nerves the perineurium was less abnormal than the endoneurium, but it never remained intact, and sometimes appeared to be hanging

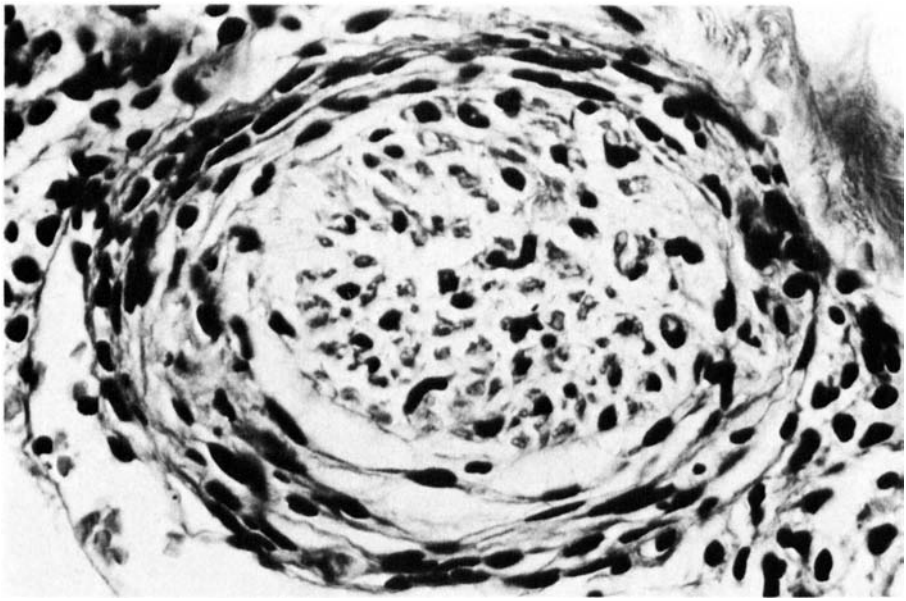

Fig. 2. Early tuberculoid (BT) leprosy. This dermal nerve shows a multilayered perineurial zone with infiltrating lymphocytes. The endoneurium is almost normal. (×800.)

in thickened shreds outside the nerve. More commonly, however, it formed a widened perineurial zone with lymphocytes within the fibrotic perineurial strands (Fig. 3). These lymphocytes tended to form rather dense foci at the point where blood vessels penetrated the perineurium and were about to pass into the endoneurium. At these points it appeared that inflammatory cells could readily emerge from the blood vessels. In two biopsies the perineurium appeared, in some places, to be replaced by epithelioid cells which were usually in continuity with endoneurial granuloma.

(3) *Nerve Trunks (16 cases; TT-2, BT-14).* There was no significant difference between the TT and BT cases: nor between the radial nerve biopsies (8 cases) and the subcutaneous nerves close to skin lesions (8 cases). Two radial nerves were normal, and a third normal apart from the presence of very scanty bacilli in the Schwann cells.

The changes in these biopsies were much the same as those seen in the severely damaged dermal nerves; and though the inflammatory response chiefly affected the endoneurium, the perineurium did not escape unscathed. It was usually fused with the epineurium into a thick fibrotic cellular collar; the whole structure was highly vascular, and many inflammatory cells, predominantly lymphocytes, appeared to be passing out of the blood vessels into the perineurial zone. Moreover, the boundary between peri and endoneurium was often indistinct; all the components of the nerve tended to coalesce, and lymphocytes appeared to be entering the endoneurium via the perineurium as well as through the endoneurial blood vessels. In two biopsies epithelioid granulomata could be seen in the perineurial zone.

The endoneurium was usually wholly replaced by an epithelioid granuloma, but

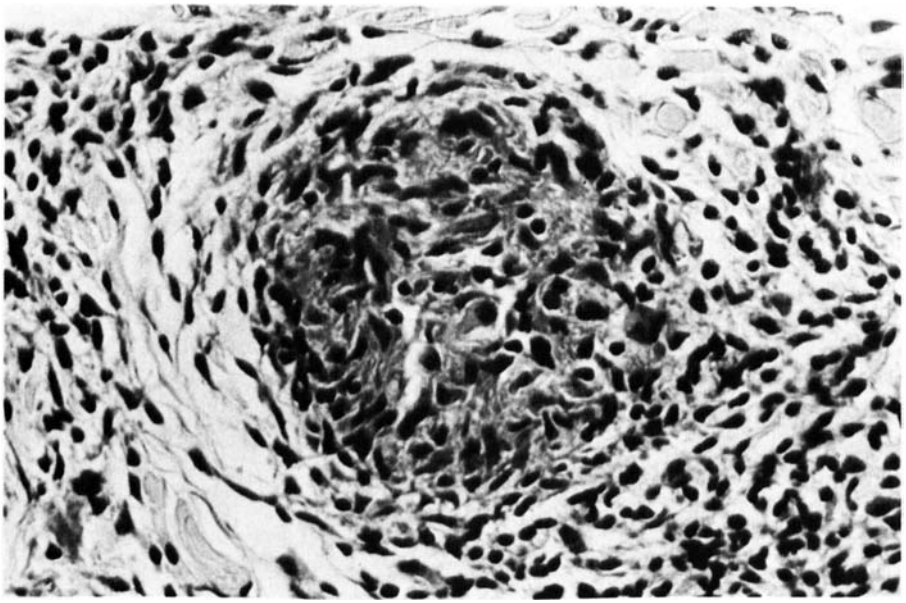

Fig. 3. Tuberculoid (BT) leprosy. The endoneurium of this dermal nerve is replaced by epithelioid granuloma, and there is a loose focus of lymphocytes occupying a sector of the perineurial zone at the site of entry of a blood vessel. (x500.)

the inflammation sometimes showed a focal quality. Occasionally surviving strands of Schwann cells could be identified, and in one instance a radial nerve biopsy included two fascicles, one grossly swollen with epithelioid cell change, the other normal.

LEPROMATOUS LEPROSY

(1) *LL Cases.* Three biopsies (from 2 patients) were in this category, but dermal nerves were only recognizable in two of them. The perineurium had lost its compact appearance and formed a perineurial zone, a multilayered structure many times wider than normal (Fig. 4). This zone was not clearly demarcated from either epi- or endoneurium; the three layers merged into one another with no definite lines of transition. The perineurial layers were thick, and appeared to be cytoplasmic rather than fibrotic; their nuclei resembled those of the Schwann cells of the endoneurium, and were quite unlike those of normal perineurium. Histiocytes and plasma cells were seen both among the perineurial layers and in the endoneurium, but lymphocytes were scanty or absent.

Bacilli, including globi, were present in very large numbers in the perineurial layers and in the histiocytes among them. The bacillary concentration in the perineurial zone was markedly higher than in the endoneurium, which, though hypercellular in one biopsy and rather fibrotic looking in the other, was relatively much more normal in appearance.

(2) *BL Cases; Early Lesions.* Three biopsies were included in this group. The general appearance of the nerves was rather similar to that of the early BT lesions,

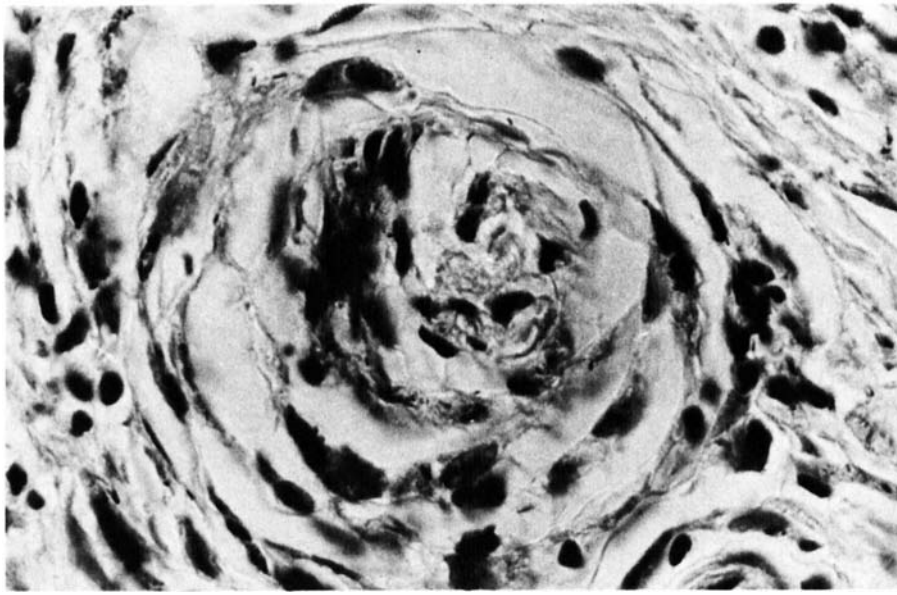

Fig. 4. Lepromatous (LL) leprosy. This dermal nerve shows thickened perineurial strands, containing large numbers of leprosy bacilli, encircling a few surviving Schwann cells. (×1500.)

though there were far more bacilli in the Schwann cells. However, the perineurial zone was less cellular and bacilli could be found in probable histiocytes among its rather scanty layers. The bacilli often lay in cells, including small foci of macrophages, which appeared to be related to blood vessels, rather than nerves, in the neurovascular bundles.

(3) *BL Cases; Mature Lesions (5 biopsies).* The general appearance of the dermal nerves, which could be identified in all 5 biopsies, was similar to that of the LL cases, but the strands which formed the perineurial zone (in 3 cases) were thinner and appeared somewhat more fibrotic and less cytoplasmic (Fig. 5), and lymphocytes were seen in considerable numbers among the layers in 2 biopsies. In the remaining 2 biopsies the perineurium appeared normal.

Bacilli were seen in all 5 cases, but the preference for perineurium seen in LL cases was not evident, being present in 1 case only. In another case the concentration was less in the perineurium, and in the remainder it was much the same as in the endoneurium.

(4) *LI Cases (17 biopsies. (For definition of LI see Ridley and Waters 1969.)* Dermal nerves could be identified in all but 3 biopsies, including 2 cases where the skin was anaesthetic at the biopsy site. The perineurial changes were most advanced in these 2 cases, with a higher bacillary concentration in the perineurial zone than in the endoneurium.

The other 12 biopsies showed a wide range of appearances. The earliest lesion (and the only one with normal sensory acuity) showed no perineurial "layering," but there were clumps of bacilli in the Schwann cells (whose nuclei appeared increased in number) and rather fewer in the perineurial cells. The rest of the

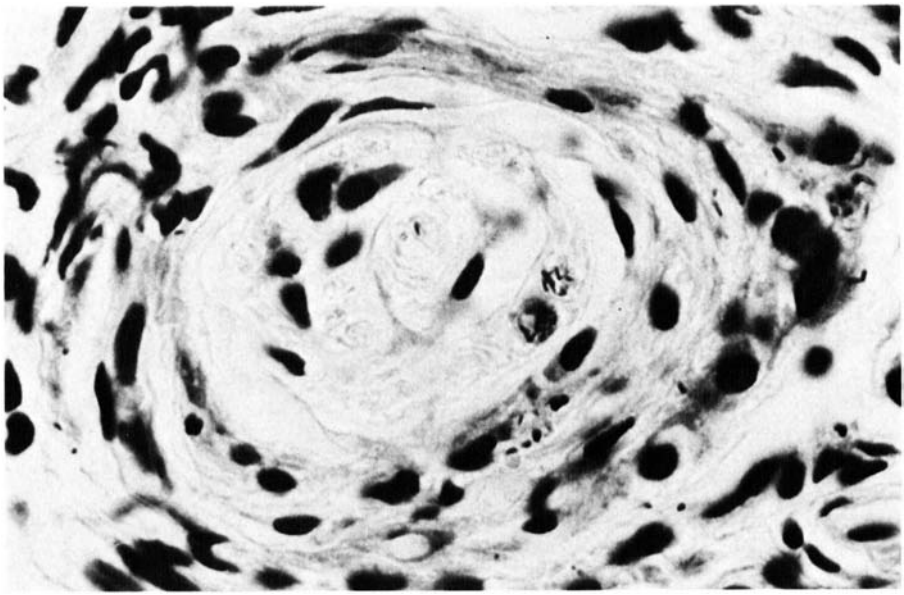

Fig. 5. Lepromatous (BL) leprosy. The perineurial layers of this dermal nerve are somewhat less thick than those seen in LL. The perineurial zone contains some infiltrating inflammatory cells, and its bacillary concentration is much the same as that of the endoneurium. (×1500.)

biopsies showed varying degrees of layering which was imprecisely related to the degree of sensory loss (Fig. 6) and could not be related to the probable duration of the disease. The appearance of the perineurial layers usually fell between the rather fibrotic strands of the BL cases and the thicker fleshier form of the LL cases. There were always some macrophages among the layers and, commonly, also a small number of lymphocytes and plasma cells. Acid-fast bacilli were always present in greater (5 biopsies) or similar (6 biopsies) concentration in the perineurial layers compared to the endoneurium.

(5) *Nerve Trunk Lesions.* Thirteen biopsies of nerve trunks were available, and though they included LL (1 case), LI (8 cases) and BL (4 cases) there were no major differences that could be associated with the classification. They are therefore considered together as a group and demonstrate the evolution of the infection; 4 biopsies were early, 2 advanced, and the remaining 7 lay somewhere between.

In the early biopsies (BL, 2; LI, 2) the bacilli lay singly and in clumps in the Schwann cells of the endoneurium. They tended to be linearly arranged, so that long thin segments of nerve were affected and larger zones between them contained no bacilli. It was often possible to see small endoneurial blood vessels close to these foci of infection. In the areas where the bacilli were more dense and where small globi might be present, the number of nuclei was increased. This appeared to be due chiefly to Schwann cell proliferation, but the nuclei were less elongated than normal, and some could have been inflammatory cells entering via the blood vessels. In all these cases there were already considerable numbers of bacilli, but there was minimal cell response to their presence. Most of the

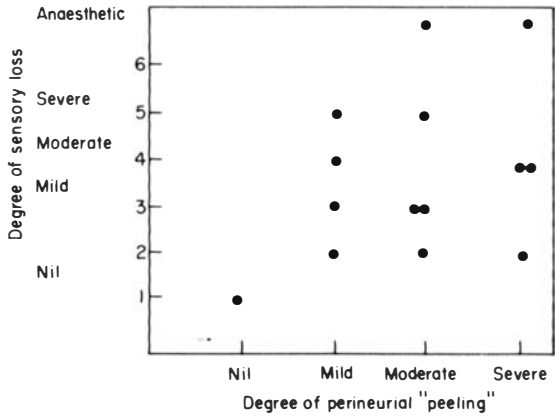

Fig. 6. The relationship between the degree of perineurial "peeling" and the sensory acuity of the biopsied area in fourteen biopsies from patients with lepromatous (LI) leprosy. Sensory testing was performed using graded nylon bristles (Pearson and Weddell, 1971); the figures in the vertical axis represent the finest bristle the patient could feel ranging from 1 (very fine) to 6 (coarse).

Schwann cells appeared intact, even though bacillated, and and the sensory acuity in the area supplied by the radial nerve was normal in the 3 cases in which it was tested.

Even at this early stage the perineurium was also affected. The two earliest cases (both BL) showed bacilli present in perineurium in about the same concentration as endoneurium. In the two more heavily infected cases (both LI) the concentration was greater in the perineurial zone, which showed the same multilayered appearance as was seen in the dermal nerves. Moreover, bacilli were seen in large numbers in the endothelial cells of the endoneurial blood vessels in these two biopsies.

As the infection progressed the endoneurium became more cellular, till in moderately advanced cases no Schwann cells of normal configuration survived. Before this stage, however, they formed strands between zones of more abnormal looking endoneurium. These zones were centred on blood vessels, and were more cellular than the remainder. The cells could not always be identified but there appeared to be monocytes and, in the more subpolar cases, lymphocytes, which clearly delineated the blood vessels, forming a cuff around them. Plasma cells were often seen, and in one case small foci of polymorphs. In addition to the cellular infiltration, however, the tissues had a cloudy appearance and took up stains more readily than usual. This abnormality was also present in a zone just within the perineurium. It was as if some abnormal material was leaking into the nerves through both the perineurium and the endoneurial blood vessels. The contrast between the two zones was most clearly evident by phase contrast microscopy.

There were also abnormalities in the other parts of these nerves. Here the myelin was very markedly swollen and took up stains fairly readily, so that nodes of Ranvier and even Schmidt Lantermann clefts could be identified in haematoxylin and eosin stained sections. These abnormalities were probably reversible, as the 3 cases where such axons were present in large numbers all had

normal sensation on follow up after 6–12 months' treatment, though one of them was anaesthetic at the time of biopsy (the other two were not tested initially).

In the most advanced cases the structure of the nerve was almost completely obliterated, and only strands of foam cells, in places encircled by strands of collagen which appeared perineurial in origin, could be seen. The bulk of such "nerves" consisted of collagen bundles, with occasional inflammatory cells and bacilli among them. In slightly less advanced cases, where there was readily recognizable endoneurium, the number of blood vessels in this zone was increased. The increase was recognizable, though less marked, in the earlier stages of the infection.

The multilayered appearance of the perineurium was seen in all these biopsies, and appeared to be maximal in the more advanced cases. The perineurial zone showed infiltration (with lymphocytes mostly in BL cases, histiocytes mostly in LI and LL cases) similar to that seen in the dermal nerves. Bacilli were always present in both endo- and perineurium; in the BL cases they tended to be more concentrated in the endoneurium, whereas in LI and LL there were as many or more bacilli in the perineurial layers.

BORDERLINE LEPROSY

(1) *Skin Lesions.* Six biopsies were classified as BB, and nerves were identified in every case. They showed two characteristic features, one or both of which were present in every biopsy.

(a) In 4 cases the Schwann cells were bacillated but otherwise almost normal.
(b) In 4 cases there were strands of bacillated Schwann cells, and also zones of epithelioid cells, which tended to lie at the periphery of the nerves.

Silver stains showed that axons were only present in the relatively intact Schwann cell strands, and even there they were reduced in number.

The perineurium always showed a multilayered fibrotic appearance with many lymphocytes among the strands. In three cases macrophages were also present. Nuclei within the strands themselves were very much less elongated than normal perineurial nuclei (Fig. 7). Bacilli were usually present in the perineurial zone, but the concentration was always less than in the relatively preserved Schwann cell strands. In two cases epithelioid granulomata were present in the perineurial zone; they were usually in continuity with the endoneurial granuloma.

The nerves of the two patients classified BB/BL were very similar to each other. The Schwann cells of the endoneurium contained many acid-fast bacilli, but their concentration was almost as high in the perineurial zone. The perineurium showed moderate layering, with strands which usually looked fibrotic, but in a few places were thicker and contained bacilli. Most nuclei lay within the perineurial strands, but were more rounded than normal perineurial nuclei and much greater in number (Fig. 8). There were also occasional lymphocytes and histiocytes among the layers. In both cases the perineurial strands were not confined to the normal perineurial zone, but appeared also to have proliferated within the endoneurium, which was split into multiple small compartments, each containing at least one Schwann cell.

Three patients were classified BB/BT; scanty dermal nerves could be identified in two of them; and the Schwann cells contained very few bacilli. The perineurial zone was replaced by a wide dense band of lymphocytes, which almost

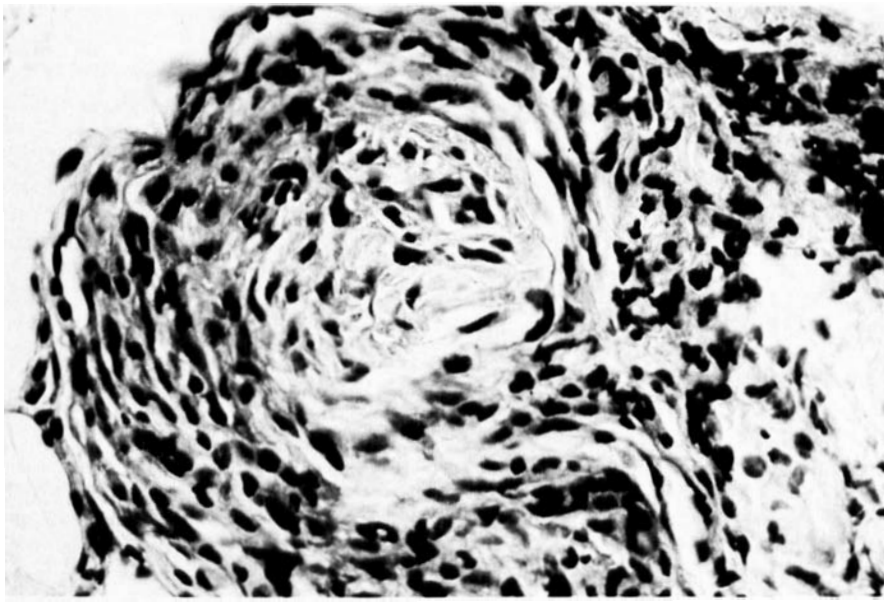

Fig. 7. Borderline (BB) leprosy. A dermal nerve showing a multilayered perineurium with rounded nuclei and some infiltrating cells. Epithelioid granuloma has formed in the outer part of the endoneurium, and in one sector appears to involve the perineurium. (x600.)

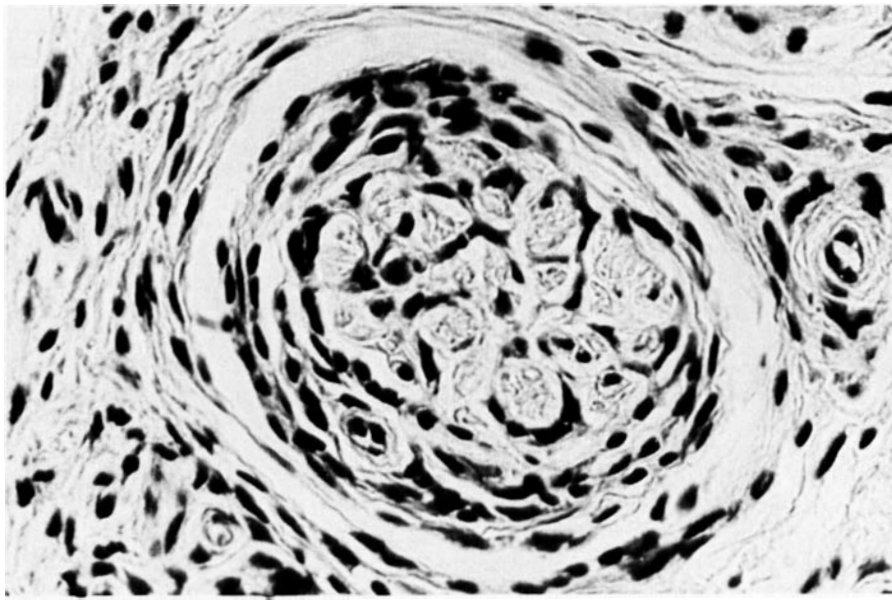

Fig. 8. Borderline(BL/BL) leprosy. The perineurial strands of this dermal nerve contain many well rounded nuclei, and the endoneurium is split into multiple compartments by similar looking strands. (x750.)

obliterated the fibrotic strands of perineurium. There were no bacilli in the perineurial zone.

(2) *Nerve Trunk Lesions.* Six biopsies were available (BB, 4; BB/BL, 1; BB/BT, 1), but were normal in two of the BB cases. The remaining four can be considered as a group.

The endoneurium was affected in a strikingly focal manner. There were strands of normal looking Schwann cells which, however, contained many acid-fast bacilli, including even some small globi. There was some increase in the number of Schwann cell nuclei in these zones. Surrounding these strands were areas where the normal neural architecture was lost and replaced by a cellular granuloma which in some places had matured to fully differentiated epithelioid cells. Lymphocytes were rather scanty except round the endoneurial blood vessels, where they sometimes formed loose foci. The number of blood vessels was markedly greater than normal.

The granulomatous zones usually lay adjacent to perineurium, which formed a widened and highly vascular perineurial zone. There was a moderate degree of layering, and the perineurial strands usually had a fibrotic appearance. In some places however, they were obliterated by dense foci of lymphocytes, which tended to be situated at positions where the larger perineurial blood vessels penetrated into the endoneurium. Acid-fast bacilli were present in the perineurium, although they were scantier than in the relatively normal sectors of endoneurium. However, in one case there was a thin, but very dense, zone of bacilli in the outer part of the perineurial zone. One biopsy showed areas of epithelioid cells in the perineurial zone.

Discussion

Previous comments on the perineurial changes seen in leprosy have been largely confined to observations on the multilayered appearance which can be observed in all types of the disease. However, even this appearance is not absolutely uniform, and the perineurial changes in leprosy form a spectrum of their own, which can be related to the classification of the disease.

(1) THE MULTILAYERED APPEARANCE

(a) The "quality" of the layering was by no means uniform: in LL and many LI cases the layers took on a thick, cytoplasmic appearance. This appearance was less marked in the BL cases, and in BB and tuberculoid lesions the layers took the form of thin fibrotic strands.

(b) In lepromatous leprosy the nuclei in the layers appeared identical to those of Schwann cells of the endoneurium. In BL/BB and BB cases there were nuclei within the layers but they were more elongated, though still much rounder and greater in number than normal perineurial nuclei. At the tuberculoid end of the spectrum there was too much cellular infiltration for perineurial nuclei to be identified or localized.

(c) The degree of "layering" was generally related to the maturity of the lesion—the earlier lesions showed it less intensely than the more advanced ones.

(d) In lepromatous cases the amount of layering was also roughly proportional to the degree of sensory loss. This may be a causal relationship, or may simply mean that both develop slowly in lepromatous leprosy.

(2) CELLULAR INFILTRATION

In most cases infiltrating cells were seen among the perineurial layers. At the tuberculoid end of the spectrum they were almost all lymphocytes: in borderline cases a few macrophages were sometimes identified, and in a few BT and BB cases frank epithelioid changes could be observed: in lepromatous leprosy histiocytes and plasma cells predominated, though there were considerable numbers of lymphocytes in BL cases, and a few in the LI group.

(3) ACID-FAST BACILLI

No bacilli were found in the perineurial zone in TT or BT cases, or in the patients classified BB/BT. They were, however, present in the remainder and could usually be seen both in the perineurial strands and in infiltrating histiocytes. (In the LL and LI cases, however, it was often impossible to be certain of their cellular location.) The bacillary concentration was higher in the endoneurium in the borderline cases, but in the two LL biopsies and six of the LI cases there were markedly more in the perineurium. The concentrations were much the same in both sites in the remaining LI and BL patients.

(4) ENDONEURIAL "INVASION" BY THE PERINEURIUM

This appearance was seen in a few BT and BB/BL cases, but it is hard to assess from this rather small series just how commonly it occurs. Fibrotic strands of tissue extended inwards from the perineurium, giving a reticular appearance to the endoneurium, and dividing it into multiple small compartments. We have seen, in two biopsies from borderline leprosy (not included in this series) what may be a more advanced stage of this change, when a small nerve that should have been monofascicular was split into many tiny fascicles, each comprising one or several Schwann cells surrounded by well organized perineurium.

(5) ENDONEURIAL CHANGES

Two findings deserve special comment:

(a) The survival of bacilli in the endoneurium in the tuberculoid and borderline cases, and particularly their presence in higher concentration than in extraneural sites, offered good evidence that the protection within peripheral nerves was immunological as well as, perhaps, histochemical.
(b) In some lepromatous cases the cloudy appearance of the endoneurium, and the swelling and altered staining quality of the myelinated axons, suggested very strongly that in such cases the perineurial and vascular barriers had been breached.

In speculating about the way in which these striking perineurial changes may be brought about, it is convenient to consider first, the effect of perineurial damage on the endoneurium, and secondly the effects of endoneurial damage on the perineurium.

The Effect of Perineurial Damage on the Endoneurium. The function of the perineurium appears to be to act as a semi-permeable barrier between the extraneural fluid and the endoneurium (Shantha and Bourne, 1968); it provides a degree of chemical isolation for the Schwann cells. Thus, it has been shown that ferritin applied around a nerve will not pass into the perineurium (Waggener *et al.*, 1965). Any failure of this barrier function is therefore liable, by allowing ingress of abnormal constituents to the endoneurium, to cause alterations of structure and function of the nerve.

Morris *et al.* (1972) have coined the colourful phrase "environmental draught" to describe this endoneurial exposure, and investigated (in the rat sciatic nerve) the sequence of events following the deprivation of endoneurium of its perineurial protection. Within a few hours an abnormal floccular substance was seen in the endoneurium. During the next few days a fine meshwork of fibres developed around the Schwann cells, which in the next 3–4 weeks became organized to form many small fascicles of Schwann cells each encircled by tissue morphologically identical with perineurium. The floccular substance was seen only outside the new fascicles. By electron microscopy they demonstrated that the new perineurium was in part at least derived from Schwann cells, which divested themselves of their axons and extended lateral processes enclosing groups of other Schwann cells. Thus, under these experimental conditions, Schwann cells could metamorphose to take the form and function of perineurial cells.

Lepromatous leprosy partly reproduces the experimental conditions of Morris *et al.*, in that the perineurial cells are always colonized by *Mycobacterium leprae,* and in experimental leprosy the perineurial layers have been shown to be abnormally permeable (Boddingius *et al.*, 1972). Thus the endoneurium is exposed to environmental draught, and it seems likely that the swollen axons seen in some biopsies from lepromatous leprosy are the result of this exposure, and that the altered staining quality of the endoneurium represents the floccular substance seen by electron microscopy. Furthermore, changes very similar to the compartmentation reported by Morris *et al.* have been observed in some patients in the borderline range (this is the type of leprosy in which sudden nerve destruction is most likely to occur, i.e. the type that might most closely reproduce their experimental conditions).

The concentric multilayered appearance of the perineurium is, however, much more commonly seen. To account for its development in terms of the processes described by Morris *et al.*, it is necessary to take into account two major differences between lepromatous leprosy and their experimental situation:

(1) Their injury was a single acute insult. In leprosy the processes occur slowly, and the final situation is the end result of months or years of bacillary multiplication.

(2) In their experiments the whole nerve was exposed to an environmental draught which could reasonably be described as gale force. In leprosy the perineurial changes are best considered as "micropunctures," chiefly affecting the immediately adjacent endoneurium, and having a directional element lacking in the experimental model.

Our hypothesis to account for the development of the multilayered appearance of the perineurium in lepromatous leprosy is that, under these circumstances, the endoneurial response to perineurial injury is for cells, including Schwann cells, to go through the same processes. However, instead of encircling other Schwann cells they respond to the directional element of the environmental draught by applying themselves as "patches" to the perineurium. The cells involved would probably themselves be bacillated, and the patches liable to break down sooner or later and need further patching. The stage is thus set for the development of the multilayered appearance characteristic of the bacillated perineurial zone in lepromatous leprosy (see Fig. 9). But whether or not this concept is correct, in lepromatous leprosy the nerve damage is, in part at least, brought about by a perineuropathy, though this does not exclude the effects of other processes, such as the direct damage to Schwann cells by contained bacilli, the possible strangling

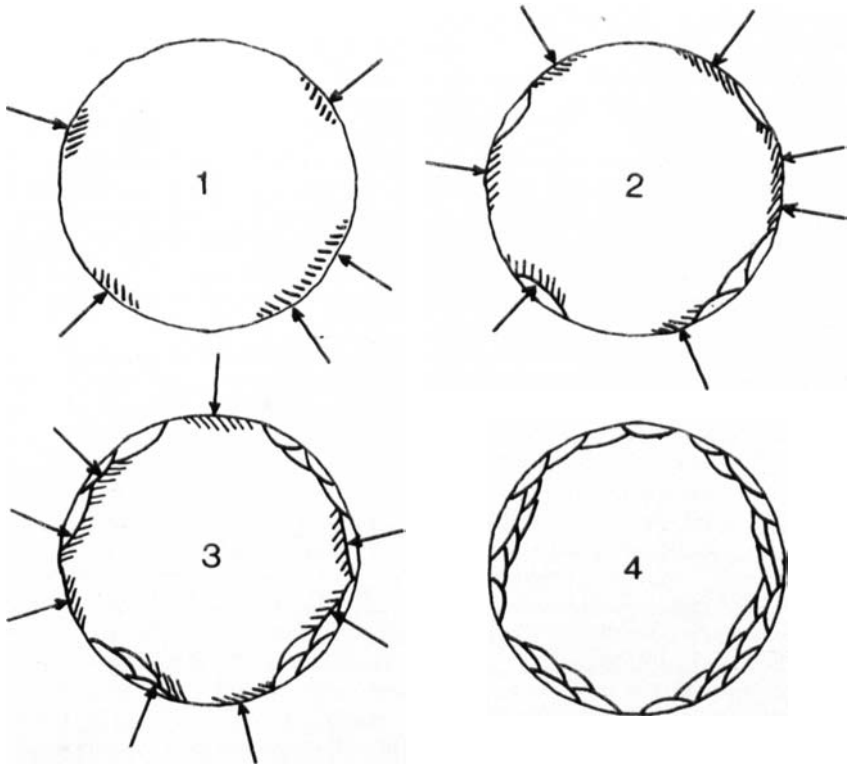

Fig. 9. Diagrammatic representation of the processes which may be involved in the development of "multilayering" of the perineurium in lepromatous leprosy. → = site of "micropuncture"; //// = zone of "endoneurial draught".

effects of intraneural and perineurial collagen formation, and limitation of blood supply.

The Effects of Endoneurial Inflammation on the Perineurium. In tuberculoid leprosy the nerve damage is primarily endoneurial in origin. Bacilli enter Schwann cells, multiply in them for a period, and then the mycobacterial antigen reaches a critical level at which, despite the protected environment, it is recognized by the tissue defences. A delayed hypersensitivity response (cell mediated immune response) ensues, in which the bacilli are attacked and largely destroyed. In the process the cells which contain them, and indeed the whole nerve, are also destroyed, and replaced by epithelioid granuloma, and the inflamed nerve becomes grossly swollen.

It is hard to assess how efficiently the perineurium functions in borderline (and tuberculoid) leprosy. In this series of patients the two classified BB/BL showed early changes of "compartmentation," indicating that the perineurial barrier was not fully effective. There were considerable numbers of bacilli in the perineurial layers of these biopsies. This was not so in those classified BB, where very few bacilli were seen in this zone; and none were present in the more tuberculoid cases. Moreover, it was in the BB and BT group of patients that bacilli could be

seen preserved in Schwann cells, despite the presence of perineurial layering and lymphocytic infiltration of the perineurial zone. In such cases, there appeared to be at least partial preservation of barrier function.

Frank epithelioid changes were probably observed in the perineurium of a few BB and BT cases, though the distorted neural architecture in these biopsies makes the site of any changes hard to define. In such zones it is most unlikely that the perineurium is functioning effectively, and not, therefore, surprising that epithelioid changes were to be found in the endoneurium adjacent to the affected perineurium. The infrequency of such findings, however, argues against this being the usual way in which the perineurium is breached and the endoneurium damaged. Certainly in the larger nerve trunks some foci of epithelioid change were centred on endoneurial blood vessels.

It seems then that in borderline and tuberculoid leprosy the perineurial layers tend to look fibrotic, have few or no bacilli, and retain some function, whereas in lepromatous cases they look more cytoplasmic, contain many bacilli, and have little or no barrier function. These are major differences, and raise the question of whether the layering of non-lepromatous leprosy has the same pathogenesis as that described for lepromatous leprosy.

It is very difficult to apply the hypothesis of Schwann cell metamorphosis to explain the multilayering seen in borderline and tuberculoid cases. The theory presupposes the presence of bacilli in the perineurium with consequent functional impairment, whereas the perineurial barrier is, to some extent, at least, intact, and bacilli are very seldom seen in the perineurial zone. Epithelioid cells (which would provide evidence of bacillation at an earlier stage, before an immune response had fully developed), are seldom seen. It seems more likely that the perineurial changes seen in borderline and tuberculoid cases represent a perineurial response to endoneurial inflammation (just as Schwann cell metamorphosis can be regarded as an endoneurial response to perineurial injury). This hypothesis also presents problems, for there can be marked perineurial layering when the endoneurium shows only slight inflammatory changes, and (less commonly) very little perineurial change despite epithelioid cell formation in the endoneurium. This inconstancy implies that the factors initiating the response have yet to be defined. An important argument in favour of such a process is that it might be expected, on the whole, to preserve the function of the perineurium. The same argument can be applied against such a process being solely responsible for the changes of lepromatous leprosy.

For the time being, therefore, it seems impossible to go beyond attributing these changes to a perineurial response to endoneurial inflammation. When there is also perineurial damage endoneurial changes ensue. The situation is a complex one, and further progress is likely to require electron microscopy, and the development of experimental models which will reproduce the inflammation of leprosy independently in endoneurium and perineurium. It is clear however, that perineurial involvement deserves more attention than it has hitherto received in studies of the pathogenesis of nerve damage in leprosy.

Acknowledgements

We are grateful to Dr D. S. Ridley for independent histological classification of these patients, and to the British Leprosy Relief Association (LEPRA) for their support to one of us

(A. G. M. W.). The electron micrograph in Fig. 1 was supplied by Dr J. Boddingius. The Leprosy Research Unit is jointly administered by the (British) Medical Research Council and the Malaysian Ministry of Health.

References

Boddingius, J., Rees, R. J. W. and Weddell, A. G. M. (1972). Defects in the "Blood-nerve barrier" in mice with leprosy neuropathy. *Nature, New Biology* **237**, 190.

Danielssen, D. C. and Boeck, C. W. (1847). *Om Spedalskhed.* Christiana.

Dastur, D. K., Ramamohan, Y. and Shah, J. S. (1973). Ultrastructure of lepromatous nerves. Neural pathogenesis in leprosy. *Int. J. Lepr.* **41**, 47.

Iyer, C. G. S. and Desikan, K. V. (1968). Nerve involvement in leprosy; Pathogenesis and significance. *Neurology (India)* **16**, 89.

Job, C. K. (1971). Pathology of peripheral nerve lesions in lepromatous leprosy—A light and electron microscopic study. *Int. J. Lepr.* **39**, 251.

Morris, J. H., Hudson, A. R. and Weddell, G. (1972). A study of degeneration and regeneration in the divided rat sciatic nerve based on electron microscopy. 4. Changes in fascicular microtopography, perineurium, and endoneurial fibroblasts. *Z. Zellforsch.* **124**, 165.

Pearson, J. M. H. (1972). Mechanisms of nerve damage in leprosy. *Annals of the Academy of Medicine, Singapore. (New series)* **1**, 156.

Pearson, J. M. H. and Weddell, A. G. M; (1971). Changes in sensory acuity following radial nerve biopsy in patients with leprosy. *Brain* **94**, 43.

Ridley, D. S. and Jopling, W. H. (1966). Classification of leprosy according to immunity. A five group system. *Int. J. Lepr.* **34**, 255.

Ridley, D. S, abd Waters, M. F. R. (1969). Significance of variations within the lepromatous group. *Lepr. Rev.* **40**, 143.

Shantha, T. R. and Bourne, G. H. (1968). *The Structure and Function of Nervous Tissue.* (Ed. G. H. Bourne). New York and London: Academic Press.

Virchow, R. (1864). *Die Krankhaften Geschwulste*, Vol. 2. Berlin: A. Hirschwald.

Waggener, J. D., Bunn, S. M. and Beggs, J. (1965). The diffusion of ferritin within the peripheral nerve sheath. An electron microscopic study. *J. Neuropath. Exp. Neurol.* **24**, 430.

Lepr. Rev. (1975) **46**, 69-71

News and Notes

LEPROSY REVIEW IN 1975

At the end of November 1974, with the transfer of LEPRA Headquarters from London to Colchester, the Editorial Office of *Leprosy Review* returned to 57A Wimpole Street, London W1M 7DF at the invitation of Dr Browne. We very much appreciate his kindness and the facilities made available at the Leprosy Study Centre.

Inflation strikes at the cost of printing as at everything else. It is regretted that an increase in subscription rate for Volume 46 has become inevitable, but subscribers should be well satisfied with what Volume 46 has to offer. First, the average number of pages per Number is being raised permanently to 80. In addition we are proud to announce an additional Special Number, available to subscribers without additional cost, and devoted to the recent Borstel Colloquium.

With this Number there opens a series of invited articles in the Field Workers Forum Section, devoted to basic leprosy teaching, with contributions from younger specialists in various aspects of leprology.

XIII WORLD REHABILITATION CONGRESS, 1976

Rehabilitation International announces that the XIII World International Congress will be held in Tel Aviv, Israel, 21–25 June, 1976. The Secretary-General is Dr E. Chigier (P.O. Box 16271, Tel Aviv, Israel), from whom all particulars may be obtained. At several of the past quadrennial Congresses, leprosy has been well represented, and special sessions of interest to leprosy workers have been organized.

TROPICAL DERMATOLOGY

The Third World Congress of the International Society of Tropical Dermatology was held in Sao Paulo (Brazil) from 1 to 5 September, 1974.

As usual, leprosy attracted considerable attention, with a symposium all to itself under the able chairmanship of Prof. R. D. Azulay, and about 25 papers on leprosy presented as "free communications". While no new material was disclosed in these papers, they engendered vigorous discussion. Other subjects of interest to leprologists included vasculitis, skin lesions of atypical mycobacterioses, pigmentation, and such conditions as cutaneous leishmaniasis. One welcome feature of the Congress was the presence, at the sessions concerned with leprosy, of dermatologists and research workers who were attracted by the growing relevance to their own subject of leprosy investigations. Another feature was the interest displayed by leprosy workers in diverse tropical dermatoses, and their contributions in these sessions.

At the General Assembly of Members, Dr Arthur Rook (of Cambridge) was elected President of the International Society of Tropical Dermatology, and Dr S. G. Browne was elected to the Board of Directors.

ARGENTINA LEPROSY SOCIETY CELEBRATES ITS 20th ANNIVERSARY

The Society celebrated the 20th Anniversary of its foundation by organizing an international symposium on 7 September, 1974, in Buenos Aires. A score of invited guests from a dozen countries presented papers on their work to an audience of upwards of a hundred interested persons. The following day, the congressists visited the B. Sommer Leprosy Sanatorium, situated some 50 km from the capital, and saw a wide range of clinical presentations of leprosy.

LEPROSY SEMINARS IN THE SOUTH PACIFIC

Thanks to the initiative of the Lepers' Trust Board of New Zealand, Dr S. G. Browne recently conducted seminars in Western Samoa, Tonga and Fiji. Doctors from distant islands were brought by air to the centres. In addition to the lectures, clinical demonstrations and visits to outlying hospitals, useful contacts were made with Health Departments and the general public through the radio and public meetings. Student and graduate nurses, community nurses and physiotherapists also profited from some of the courses given. People in New Zealand can be proud of the continuing contribution they are making, through this voluntary agency, towards the effective control of the scourge of leprosy in the islands of the South Pacific.

1974 DAMIEN-DUTTON AWARD

Dr Jose N. Rodriguez, former Director of the Bureau of Disease Control of the Philippines, and doyen of leprologists in that country, is the 21st recipient of the Damien-Dutton Award, and we add our congratulations to those of Dr Rodriguez' friends around the world. A dedicated research worker and administrator, Dr Rodriguez has devoted his life to the cause of sufferers from leprosy, and this Award is entirely fitting. We are happy to have a contribution from Dr Rodriguez in this Number of *Leprosy Review*.

IMMUNOLOGY OF LEPROSY PROJECT GROUP (IMMLEP)

WHO has decided to establish a Special Programme for Research and Training in Tropical Diseases. The programme is at present in its planning phase. A major part of it will be to establish working groups covering six major communicable diseases. The members of these groups will actively participate in co-operative research. The first of these groups (IMMLEP) met in Geneva from 4 to 8 November, 1974. The objective agreed upon was to explore the possibility of developing and applying new techniques for investigating the various immunological aspects of leprosy. The ready availability of large amounts of *Myco. leprae* from infected armadillos has made new approaches possible.

Priority will be given to work on the purification of *Myco. leprae* from armadillo tissue for the preparation of a specific soluble skin test antigen. This

test will permit for the first time direct measure of endemicity levels of leprosy in different populations throughout the world. The bacilli and fractions thereof will be used to investigate the role of cell-mediated immunity in resistance to the infection and pathogenesis of reactional phase and nerve damage. Immunoprophylaxis by vaccination is a realistic possibility and the long-term objectives of the group will be to explore various approaches to this end.

Further information can be obtained from World Health Organization, 1211 Geneva 27, Switzerland.

KARIGIRI TRAINING PROGRAMME

Schieffelin Leprosy Research Sanatorium, Karigiri, is offering the following courses for 1975–76:

1. *Introductory Courses in Leprosy – 6 days* – Intended for general medical practitioners who will be including leprosy work in their practice (35 hours teaching plus demonstrations and excursions).
   4 courses per year – 20 candidates per course.
2. *Certificate Courses in Leprosy – 6 weeks* – Intended primarily for doctors, but senior nurses training for full time responsibility in leprosy institutions, are also accepted. It teaches clinical leprosy, diagnosis and comprehensive treatment including complications etc.,
   2 courses per year – July–August and February–March. 20 candidates per course.
3. *Para Medical Workers Courses – 6 months* – Training for village level workers according to curriculum recognized by the Ministry of Health, Government of India.
   1 course per year – July to December – 10 candidates.
4. *Orthopaedic Technicians Course – 2 years* – School Leaving Certificate candidates will be given a full training in manufacture of orthopaedic, footwear, appliances, splints, braces and artificial limbs.
   6 candidates admitted every year. Course commences in April, 1975.
5. *Course in the Management of Ophthalmic Manifestations of Leprosy – one week* – Open to doctors primarily, but other senior responsible personnel may be accepted. Lectures and demonstrations in eye complications of leprosy.
   One course per year to commence in January – 6 candidates.

Accommodation available for all courses. Enquiries for further particulars to be addressed to:

The Training Officer,
Schieffelin Leprosy Research Sanatorium,
S L R Sanatorium (P.O.), Karigiri,
via Katpadi, 632 106, North Arcot,
South India.

Lepr. Rev. (1975) **46**, 73-78

Leprosy and the Community

The strength of a leprosy control project, and the best hopes for its success, lie less with the doctor at its centre than with the junior staff at its periphery, whose primary duties, concerned with case finding and case holding, involve a daily confrontation with the general public. Their work is planned to fit into a pattern of leprosy control activity, but only rarely have the planners any personal experience of the personal problems and difficulties which are the every day experience of these essential workers, whatever we designate them, Leprosy Inspectors, Non-Medical Assistants, Health Home Visitors, or just plain para-medical workers.

An independent time–work study of the duties of this grade of leprosy worker is something of a novelty. The findings of such a study of a leprosy control project in Tanzania are presented here in condensed form, because the problems exposed are common to many rural leprosy control projects in more than one continent, and are therefore of wider interest. Out of respect for all concerned, the anonymity of the project under study has been preserved.

Editorial note

AN ANALYSIS OF SOME FIELD ACTIVITIES IN A LEPROSY CONTROL SCHEME IN TANZANIA

JAN DE KEIJZER*

This study was made in order to analyse some aspects of the field work in a rural leprosy control project, in particular the activities of the Health Home Visitor, and make recommendations for a more efficient and effective performance.

The Leprosy Control Scheme Concerned

The project is a substantial one. Some geographical and demographic data are shown in Table 1. The area is divided into four districts.

The Regional scheme is supervised by one Leprosy Medical Officer, assisted by one Medical Assistant, two clerks, three shoemakers, three drivers, one nursing orderly/laboratory auxiliary, two Rural Medical Aides (concerned with routine clinic supervision) and 20 Home Health Visitors (HHV's) distributed throughout the four districts. These are polyvalent staff, whose primary duties are, health education, case finding, and case holding, in relation to leprosy and tuberculosis.

In-patient treatment is given in four general hospitals and at Rural Health Centres. Out-patient treatment is given at all Rural Health Centres and general

* c/o Dr D. L. Leiker, Royal Tropical Institute, Amsterdam, the Netherlands.

TABLE 1

District	A.	B.	C.	D.	Total region
Area in sq miles	3500	2350	1500	250	7600
Population	371,396	305,645	236,581	104,218	1,017,840
Main tribes	Sukuma Zinza	Sukuma	Sukuma	Kerewe	
Migration	yes	yes	yes	no	

dispensaries, supplemented by roadside clinics (mango tree stations). The coverage of the area is satisfactory. All patients are living within 3–4 miles of a treatment centre.

The treatment centres are visited monthly by the Medical Officer, Medical Assistant, or Rural Medical Aide, the HHV participating when the touring team is in his locality. Treatment is given at all centres by the visiting team. Patients who are absent on the date of the visit are able to collect their drugs afterwards at the nearest treatment centre. Persistent defaulters are visited at home by the HHV.

Method of Assessment of the Activities of Health Home Visitors

The author joined four HHV's in their daily work, for a period of two weeks each, a total of eight weeks. Based on this personal experience of their work and its problems, a questionnaire was devised and sent to all the HHV's in the region (20). In addition, an analysis was made of a defaulter study made in the previous year, and covering 527 cases, while the monthly reports of six HHV's were also subjected to detailed study over a period.

Results

(a) *Time spent on various activities*

On average, 23.4 days per month were actually being spent by HHV's on their duties, and time devoted to the various aspects is shown in Table 2.

TABLE 2

Time spent on various activities by HHV's as reported and as actually observed

Activity	Monthly reports		Personal observation	
	Average working days per month	%	Average working days per month	%
Treatment safari	7.9	33.9	3.5	17.2
Home visits	5.7	24.2	9.9	42.4
Administration	2.9	12.3	2.1	9.1
School examination	1.7	7.4	1.7	7.6
Health education	1.2	5.1	0	0
Miscellaneous	4.0	17.1	6.1	25.7
Total	23.4	100.0	23.4	100.0

Points of difference, and relative priorities, will be noted.

(b) *Health education*

Although undoubtedly health education is one of the most important duties of the HHV, during the eight weeks I accompanied HHV's, no specific, intentional health education activity was undertaken. This does not exclude the possibility that in other periods, and by other HHV's more attention is being paid to this activity, but it strongly suggests that there is some lack of motivation in this respect. From the questionnaire it was gathered that over the region as a whole health education was given as an integrated part of the work on 34 occasions during the month, and on 37 occasions as a special activity. Health education is time consuming, because many questions are usually asked and detailed discussions required, but the stated time of 1.2 days per month suggests that if health education is given at all, it is rather casually done. Many workers feel the need for more and better visual aid material.

(c) *Administration*

Sixteen of the HHV's are employed by Government, and official administrative requirements demand that they travel to the District centre to collect their salary on a fixed day each month. Much time is spent on this. If payment could be made through the Medical Officer on his monthly safari, one or two working days each month would be saved.

The personal administrative work required of HHV's consists of the making of notes in respect of home visits, sorting out cards of defaulters, and compiling monthly reports. Although HHV's only accounted for 5.5 working hours per day, they were of the opinion that they needed 3.5 days per month for this work. From personal observation I would consider that one day a month should suffice. The questionnaire showed that HHV's do not think that office work is important and do not like this part of their duties.

Recording system. In addition to the central District recording system, records of patients are kept at static treatment centres. The HHV has thus two alternatives. He can either collect the list of defaulters each month at the District headquarters while sharing in the treatment safari, or he can do it in more fragmentary fashion by collecting information on a day to day basis from the treatment centres he visits. The first method has the advantage that it is more easy to plan efficiently the home visits to be made in the following month. The second, more commonly practised method, often makes it necessary to visit a village more frequently than once in a month, and may miss altogether patients who prefer to attend clinics away from their area of residence. It is recommended that HHV's compile a "Home visit book" containing the names of all patients in their area, listed according to their place of residence.

(d) *Mode of transport*

Table 3 gives numbers of patients in relation to the distance between their homes and the HHV's base.

At present 15 HHV's are using a bicycle and five have a bicycle and also light motor cycle at their disposal. All desire a motor cycle. Table 4 shows the results of case finding using bicycle or motor cycle.

The differences are statistically significant (X^2 14.39 P 0.01).

A careful study of the relative usefulness of bicycle and motorcycle means of transport from the standpoint of actual results achieved, brings out the

TABLE 3

Distance from base to homes of patients

Distance	Numbers of patients. Whole region (questionnaire)	Area directly observed
less than 5 miles	257 (55.3%)	10 (20%)
5–10 miles	82 (17.6%)	13 (26%)
over 10 miles	126 (27.1%)	27 (54%)
not stated	62 (11.8%)	
Total	527 (100.0)	50 (100)

TABLE 4

Results of case finding using bicycle or motorcycle

Transport	Patients seen	Patients not seen	Case finding ratio
Bicycle	175 (68.4%)	135 (52.3%)	0.77
Motorcycle	65 (25.4%)	97 (37.6%)	1.49
By foot	16 (6.2%)	26 (10.1%)	1.63
Total	256	258	1.0

unexpected finding that the results of case finding using a motorcycle are inferior to case finding by bicycle or by foot. It is possible that the status symbol of a motor cycle creates a greater distance between the HHV and the people in rural areas. In addition, the cost per unit of a worker plus his transport where this includes a motorcycle, is nearly double what it is when transport is limited to a bicycle, and there is no evidence that the HHV with a motorcycle is significantly more inclined to visit distant homes than the HHV with a bicycle. It is concluded that preference should be given to bicycles, provided that the distance to be covered does not exceed 20 miles per day.

(e) *Home visits*

Unless the HHV has considerable local knowledge, it is frequently very time consuming to locate the house of a patient. The "village" often covers a large area in which the people live scattered in family groups. The patient's home is traced through the local Ballozi (ten house chairman). The Ballozi may not be at home. After he has been traced, his confidence and cooperation has to be won by explaining in full the importance of leprosy control activities in general and the reasons for contacting the patient in particular. The whole procedure may easily take one half to one hour. If the Ballozi is away, other people in the village have to be contacted. Time spent on these preliminaries diminishes rapidly once the HHV knows his area and is known by the people, but this process takes at least one year. Frequent transfers are thus undesirable.

Out of 527 home visits only one half of the total patients sought were found. The main reasons for failure were, the patient was absent temporarily (7%); emigration of patient (71%); patient unknown (i.e. name given was incorrect) 22%. Other reasons were a failure of the HHV to gain the confidence of the

Ballozi, community, or patient; and finally the HHV giving up the search too easily.

Home visit working hours. The average numbers of working hours spent on home visit days were given by five HHV's as 6–8 h, by four HHV's as 8–10 h, and by six HHV's as 10–12 h. The time actually observed personally averaged 9 h per day. Although long working days are unavoidable, HHV's object on the whole to staying in villages overnight because of a lack of restaurants in local areas, and the custom that one does not take food for the road from home. Six HHV's made use of restaurants often, five occasionally, one rarely, and five never. Though occasionally patients do offer food, the HHV's are reluctant to accept this. Seven HHV's accepted food occasionally, five rarely, and seven never. There is here a real administrative problem, but not one totally beyond solution.

During the weeks of personal observation, it was felt that an average of 3.5 home visits could be made in a normal days work. In answers to the questionnaire, the following average figures were given; 3.2 by bicycle, 2.5 by motorcycle, 1.5 by foot. All three figures exceeded those actually observed in practice. Suggestions offered by HHV's to promote more efficient work included, uniform and raincoat to permit work on rainy days, a few simple drugs to heighten patient cooperation, a portable stretcher to encourage overnight stays in villages.

Reasons for defaulting. Once the patient has been located, the HHV has first to discover the reason for his not attending for treatment, and convince him of the need for re-adjustment. This may be a time consuming and sometimes unrewarding activity, the true reason being anxiety that the patient will be recognized as a sufferer from leprosy. Only when this is revealed can the HHV direct his health education towards problems which are relevant to the patient.

Public relations. It becomes clear that in his contacts with patients and the public, the public relations of a Health Home Visitor are of great importance, and in the selection of candidates as much emphasis should be placed on their potential in this direction as on intellectual capabilities. Social engagements of HHV's are important. Out of the 20 men in this scheme, three are TANU members, one an Area Chairman, and three are members of the Ward Development Committee. Although such activities consume 1.5 days a month on average, this is more than balanced by the gain in information on social affairs and the usefulness of this in health education, and by the raised status of the worker in the community.

Summary of Conclusions

(1) The duties of the HHV are time consuming and his life is relatively hard.

(2) Health education activities deserve more attention. There is a shortage of visual aids.

(3) Administration consumes more time than is necessary. The HHV needs his own patient register arranged according to the residence of patients.

(4) The training of HHV's should be directed towards greater polyvalent activity and not be restricted to leprosy and tuberculosis. Limited facilities for first aid and the treatment of other diseases should be made available.

(5) Local knowledge and social responsibilities enhance the efficiency and importance of the HHV.

(6) As a means of transport the bicycle is to be preferred to the motorcycle. More use could be made of public transport.

(7) The area of operation of each HHV should not exceed a diameter of 20 miles.

(8) Staying overnight in rural areas may be promoted by the supply of portable stretchers and by stimulating workers to take food from home.

(9) Both the number of home visit days and the number of actual visits per day could be increased.

Acknowledgements

The study was made as a stage in the preclinical year of the Medical Faculty, University of Leyden.

I thank Dr A. Hertroijs, M.O. Leprosy, Mwanza and his wife for their guidance and hospitality, the HHV's Mr Mlowezi, Mr Mikomanga, Mr Ferdinand and Mr Deo Gratias for their kind cooperation in the field and Dr D. L. Leiker and Dr A. van Wijnen of the Royal Tropical Institute at Amsterdam for their assistance in preparing this report.

Lepr Rev. (1975) **46**, 79-84

Field Workers' Forum

THE DIAGNOSIS OF LEPROSY: CLINICAL AND BACTERIOLOGICAL

COLIN McDOUGALL

Cochrane Annexe, The Slade Hospital
and
The Department of Human Anatomy, Oxford, England

One of the continuing basic problems of leprosy control is that the diagnosis is made in only about one third of those estimated to be suffering from the disease. In 1966 it was thought that nearly a million new cases might appear in the subsequent 5 years in endemic areas with a prevalence of 0.5 per 1000 or more, but in fact the number actually diagnosed and registered was only about half this expected total (WHO 1966, 1970). For between two and three million children estimated to need leprosy treatment in UNICEF-assisted countries, the proportion who have been diagnosed, registered and treated for any reasonable length of time may be considerably lower. Editorials in the *Leprosy Review* (1970, 1971) have drawn attention to countries where as few as '. . . 6000 out of 80,000 . . .' and again '. . . 1 in 20 of the estimated 250,000 suffering from the disease . . .' are receiving treatment. In fact, in any part of the world where leprosy is prevalent, a penetrating analysis of the registered patients by an experienced observer is likely to reveal that the situation is even worse than is suggested by the national or regional total. This total is often an accumulated figure, unrevised by the health authorities over the decades, giving little emphasis to the number of new cases per month or year. It will not infrequently be found that it is composed largely of in-patients in leprosaria (many of whom have no medical need to live in an institution), together with a high percentage of those who are advised to "trudge weary miles every week (on insensitive feet) to obtain a supply of an anti-leprosy drug that will have no effect whatever on neuropathic ulcers." (Editorial, *Leprosy Review,* 1973). Even those who have been fortunate enough to participate in a vigorous and well-supported out-patient service, and who can look back impartially on 5–10 years' of hard work, may have to admit the unspectacular effect of their control programme and to ask if the fault lies mainly on the side of the patient, or the service provided. While such factors as the defaulter rate amongst bacilliferous cases (itself a neglected subject, still calling for the most serious study), may be important, concealment of disease by the patient – whether wilful or from ignorance – may clearly block diagnosis at the outset. Yet the reasons for this have been poorly investigated; one of the few detailed studies of this aspect of leprosy control (Giel and van Luijk, 1970) failed to identify factors in Ethiopia accounting for either concealment or default, and amongst 377 papers at the recent Tenth International Leprosy Congress in Bergen (1973), the subject was barely discussed.

If one cane use the word "fault", where does it lie? Numerous publications describe extraordinary delays and confusions in diagnosis in patients seen in America and Europe, often with exotic or subtle presentations. These are salutory, yet somewhat misleading, for in the endemic areas such errors are not important factors in the overall low level of diagnosis. The clinical diagnosis may on occasion be difficult, but it is not usually so. Guide-lines to the recognition of leprosy have been so fully published over the years that it would be out of place to repeat them here. Furthermore, there is now an increasingly valuable array of teaching material in the form of short textbooks*, a memorandum, and a guide to leprosy control†, films‡, colour transparency teaching sets§, and other texts and audio-visual aids‖. Surely any doctor called upon to diagnose leprosy owes it to his professional conscience to obtain and also make freely available to his staff a number of these inexpensive sources of information. Despite the excellent range of basic knowledge which these will provide however, a few clinical and bacteriological points still merit emphasis.

---

*(a) *Handbook of Leprosy* (1971) W. H. Jopling. Publisher: William Heinemann Medical Books Ltd., 23 Bedford Square, London WC1 B 3HT. Price £1.20.

(b) *Leprosy for Students of Medicine* (1973) A. Bryceson and R. E. Pfaltzgraff. Publisher: Churchill Livingstone, Ravelston Terrace, Edinburgh, Scotland, U.K. Price £1.50.

(c) *Leprosy* (1970) S. G. Browne. Publisher: J. R. Geigy, S. A. Basle, Switzerland. Available in English, French, German and Spanish.

(d) *Leprosy, diagnosis and management* (1973) H. L. Arnold and P. Fasal. Publisher: Charles Thomas, Springfield, Illinois, U.S.A. Price $14.75.

(e) *Leprosy for practitioners* (1974) S. J. Yawalkar. Publisher: Popular Prakashan, Bombay. Price Rs 40 (£2.2).

†(a) *Memorandum on Leprosy Control* (1971) S. G. Browne. Issued jointly by OXFAM (274 Banbury Road, Oxford OX2 7DZ; U.K.), LEPRA (50 Fitzroy Street, London W1P 6AL; U.K.) and the Leprosy Mission, (50 Portland Place, London W1N 3DG, U.K.). Currently (1975) under revision.

(b) *A Guide to Leprosy Control* (1966) W.H.O. Avenue Appia, 1211 Geneva, Switzerland. New edition currently (1975) in preparation.

(c) *Guidelines for the Campaign Against Leprosy* (1970) Medical Commission of the European Federation of Anti-Leprosy Associations (ELEP)4, rue Saint-Geoffroy, F 80, Amiens, France.

‡(a) *Leprosy.* Science Service, Berlin 31, Sächsische Str., 26, Germany. 30 minutes. 16 mm Eastman-Color Kodak: price DM 2000. ½-inch magnetic tape (Philips): price DM 500.

(b) *Leprosy.* British Leprosy Relief Association (LEPRA), 50 Fitzroy Street, London W1P 6AL. 35 minutes. ½-inch magnetic tape.

§(a) Netherlands Leprosy Relief Association, c/o Royal Tropical Institute, Mauritskade 63, Amsterdam. "Leprosy: Various Aspects." 48 coated slides, daylight viewer and textbook. Price about £3. (D. L. Leiker).

(b) Medical Recording Service Foundation (Royal College of General Practitioners) Kitts Croft, Writtle, Chelmsford, CM1 3EH, England. "Leprosy in the Tropics." 48 colour transparencies and tape recording. (S. G. Browne).

(c) US Public Health Service Hospital, Carville, Louisiana, U.S.A. "Clinical Aspects of Leprosy." 60 colour transparencies and text. (John Trautman).

(d) Institute of Child Health, 30 Guilford Street, London WC1N 1EH, England. "Leprosy in Childhood." 24 colour transparencies with text: price 75p., or 50p. to those working in developing countries. Slide Tape Tutor £4–£5. (Colin McDougall).

‖(a) Ernst-Rodenwalt Institute, Viktoriastrasse 11-13, Koblenz, Germany (Professor K. F. Schaller).

(b) Fontilles Leprosarium, Alicante, Spain (Dr José Terencio de las Aguas).

(c) ALERT (All-Africa Leprosy and Rehabilitation Training Centre), P.O. Box 165, Addis Ababa, Ethiopia (Dr Felton Ross).

(d) Central Leprosy Teaching and Research Institute, Chingleput, Tamil Nadu, India (Dr C. G. S. Iyer).

Clinical

(1) The first step is to decide whether the patient has leprosy or not. Thorough examination in good light and a knowledge of the cardinal signs are essential. Yet this step is not enough; minimal information on first diagnosis must include;– classification, state of activity, bacteriological findings if available, and disability grading. These vital facts must be recorded, dated and signed; without them, subsequent assessment by others will be gravely hampered. Furthermore, in practice one recording of these facts is not enough; the patient must carry away a personal note of his diagnosis, classification, treatment and next date of attendance. He must be registered locally and centrally and there must be appropriate forms for his transfer to other parts of the country. Setting up and–even more difficult–actually maintaining such a system may seem administrative (and tedious) rather than medical practice. Yet without it, your diagnosis is hardly worth making.

(2) The key words for diagnosis are; *prepared mind–observation–fingertips–simple test for anaesthesia.* If you are not in some way mentally alerted to the possibility of the disease, you may miss it. You need to use your eyes, all over the patient's body surface, and in good illumination, and follow this by palpating the relevant superficial nerves for enlargement, asymmetry or tenderness. Testing lesions or areas of apparently normal skin for anaesthesia can be done expertly with a wisp of cotton wool or even a blade of grass; it is not the apparatus that matters, but the way you do the test, listen to replies, and draw your conclusions.

(3) In an endemic area, any unusual or persistent lesion on the skin, especially if it does not respond to "routine" treatment, should be regarded as leprosy until proved otherwise. Indeed any skin lesion which is not obviously congenital, fungal or "simple" infective should be similarly suspected. Yet take care before making a diagnosis which may consign the patient to years, possibly a life-time of drug treatment for leprosy. If you have recently arrived, you will in fact gain, not lose, respect by asking the opinion of an experienced medical assistant. Never hesitate, if your facilities or experience are in doubt, to send the patient a hundred miles for an expert opinion. Our dermatological colleagues can give invaluable guidance in puzzling cases of lupus, psoriasis, syphilis, avitaminosis and the like.

(4) With great frequency, and the more one looks for it, the initial symptom of leprosy is numbness or anaesthesia (Cochrane, 1965). Any unusual symptom which could be arising in dermal nerves, or any unusual motor or sensory finding in named peripheral nerves, is to be regarded as leprosy until proved otherwise.

(5) An unusual or persistent complaints in the eye, nose or joints should lead to a suspicion of leprosy, and call for further careful investigation.

Bacteriological

In an effort to back your diagnosis with the finding of acid-fast bacilli, slit-skin smears remain indispensible as a general routine. The techniques have been described in detail (for instance Bryceson and Pfaltzgraff, 1973) and it is here appropriate to add only a little advice and a few words of warning.

(1) If you are going to use slit-skin smears, and particularly if you expect technicians with limited educational background to produce reliable results year in, year out, you must be entirely familiar with every step of the technique, from

the rational selection of skin sites to the final interpretation of numbers and morphology or bacilli.

(2) The block selection of personnel with limited para-medical knowledge and interests, to be trained in a few weeks as "Laboratory Technicians", and then posted to remote corners of the endemic area, is likely to be disastrous. They will need constant encouragement and supervision. If you are unable to question your staff—even in the most diplomatic way possible—about the bleeding they are producing in taking skin smears*, the age of their carbol-fuchsin and the thick golden scum which floats on its surface, the strength of the decolouriser, and the reason why they have casually taken to using a weak solution of haematoxylin (in alchol!) instead of methylene blue as the counterstain—your ignorance will be apparent, and results of little value.

(3) Good smears and wonderful staining are valueless if the microscope column is floating loose on its rack-and-pinion, or the technician has not been shown how to centre the light source, or the latter is inadequate.

(4) Writing a request for "skin smears" to be taken by the patient to a laboratory in which you have not previously established your precise technical needs, is likely to be misleading. Positive smears are diagnostic of leprosy provided someone has checked the staining and interpretation on a large number of specimens over weeks or months. Negative smears need even more thought. They may be negative because the selection of lesions is wrong, staining is faulty, or the search for bacilli too short. Obvious though it may be, it bears repeating that experience reveals an excellent correlation between clinical and bacteriological findings. Any discrepancy should alert one to the need for repeating both forms of examination.

(5) Although there are occasional exceptions, particularly in Asia, leprosy in the indeterminate, tuberculoid and borderline-tuberculoid range is nearly always non-bacillary on slit-skin smears. Negative findings on smears are therefore frequently compatible with the clinical diagnosis of leprosy.

(6) Don't be misled into setting up a staining and microscope service simply because it is advised by "experts" sitting (quite comfortably in some cases) in far-off places. Some of the very real difficulties in maintaining reliable staining of *Myco. leprae* have been described in detail (Ridley and Ridley, 1971). If you are faced with a decision between doubtful laboratory results and your own clinical observations, stick to the latter; bad laboratory work is far worse than no laboratory work at all.

Before commenting on the use of biopsies in diagnosis, it is here relevant to recall that recent years have seen an expansion of research on the large number of bacilli to be found in (1) the nose, and (2) the circulating blood of lepromatous patients. Numerous studies (Pedley, 1970, 1973; Davey and Rees, 1973, 1974; McDougall *et al.*, 1974; Davey and Barton, 1973) have drawn attention to the intense pathology in septum and turbinates of the lepromatous nose, and the large numbers of apparently viable bacilli excreted into the environment from nasal mucus. A nose-blow smear or suitable scraping may now be considered important as an aid to diagnosis and the assessment of infectivity. The possible application of all this to the early detection of lepromatous leprosy has yet to be worked out,

*It is the compressing thumb and first finger which need watching; they must render the skin avascular before incision, and maintain this during the taking of the smear. On the other hand, when the skin is released, *slight bleeding* is reassuring that the correct depth has been sampled for bacilli.

but the fact that the nose is known to be heavily involved in some instances when the skin shows little or nothing clinically, could have epidemiological significance. The findings of Drutz (1971, 1972, 1974) and Shankara Manja *et al.* (1972) on the remarkable numbers of *Myco. leprae* circulating in the blood in lepromatous leprosy similarly await practical application in the field of early diagnosis, partly because they rest, as yet, on relatively complicated techniques. But early lepromatous leprosy can easily be missed clinically – at a stage when the blood and nasal mucus may contain large numbers of bacilli. Is it beyond the realms of research possibility that some form of blood test, possibly combined with those recently summarized (Godal *et al.*, 1974) for the immunological detection of sub-clinical infection, may develop as a practical aid to really early diagnosis in the field?

On the question of biopsies, those who work with full clinical and bacteriological information, particularly in various fields of research, have come to realize that they are essential not only to accurate diagnosis and classification, but also to the full understanding of reactions, and response to drugs. At various stages of the disease, slit-skin smears, however well taken and interpreted, will not reveal the full facts. The special value of biopsies has been fully described in the diagnosis of early relapse (Ridley, 1973), paucibacillary leprosy (Leiker, 1971) and lepromatous leprosy after some years of treatment (Harman, 1968). There are numerous other important applications, and it is here appropriate merely to record some thoughts on biopsies in leprosy as they affect diagnosis.

(1) There is far too much leprosy in the world, much of it clinically obvious but yet untreated, to consider biopsies as a routine.

(2) The field of diagnosis should rest firmly on your knowledge of the disease, together with observation, palpating for abnormal nerves, and simple testing for anaesthesia.

(3) If this can be backed by reliable slit-skin smears, so much the better.

(4) If your facilities are ever further developed, the service to the patient and your own level of classification and understanding of the disease (and its reactions) will rise considerable if you can add biopsies of the skin, and in selected instances, of peripheral nerve and scrotum.

(5) While scrotal biopsy is technically no more difficult than skin, it has psychological disadvantages, should be used with care and only when a biopsy of suitably chosen skin has failed to provide the information needed.

(6) Successful nerve biopsy, in which *useful* tissue is obtained without risking damage to the patient, is technically somewhat difficult, and should not be undertaken without prior instruction from an expert. It does not in any case have a "routine" application in the diagnosis or assessment of this disease.

(7) To take biopsies which show evidence of instrumental squeezing, or excessive bleeding, place them in a fixative of unknown composition and age, and submit them for examination without full clinical and bacteriological information is worse than useless. In all these procedures, meticulous attention to detail (Harman, 1973) is the least we can offer not only to achieve success under the microscope, but in consideration for a patient who may already be scarred on the skin, and short of functioning fibres in his nerves.

Despite minor disagreements, those who work at the cutting edge of the leprosy control programme in endemic areas have one undoubted thing in common—they all have too much work. Even if logical emphasis and priority are given to the lepromatous patient, must we still accept (Editorial, *Leprosy Review*,

1968) that it is "quite impossible to treat adequately and render non-contagious all patients with lepromatous leprosy in the world in the foreseeable future"? Are the "masked" and "confluent macular" forms of lepromatous leprosy (Davey, 1942; Browne, 1965) so difficult to detect, except to the experienced observer (and on a fully stripped patient) that they are likely—through nasal excretion of bacilli—to constitute a continuing pool of infection while attention is focussed on paucibacillary patients? Rapid advances in research make such questions hard to answer, but for the moment a few conclusions may be drawn.

(1) Leprosy is not being diagnosed accurately, fully and frequently enough in the endemic areas.

(2) There is an urgent need for a laboratory test, a marker or epidemiological indicator to achieve primary prevention and the detection of very early disease.

(3) There are some "faults" on the side of the patient who is, for various reasons, concealing his disease but

(4) Most of the fault is ours; we pass from one decade into another without facing the true extent of this disease in the world, and without attracting a sufficient number of the right people to help us.

Is there not a strong case—probably long overdue—for research councils, voluntary agencies and universities to set up an intensive research programme to define factors which account for the continuing non-diagnosis of leprosy?

Acknowledgements

The author wishes to thank Dr T. F. Davey for many helpful comments in the writing of this article. His work is supported by grants from the Medical Research Council and the British Leprosy Relief Association (LEPRA).

References

Browne, S. G. (1965). Confluent macular lepromatous leprosy. *Lepr. Rev.* **36**, 157.

Bryceson, A. and Pfaltzgraff, R. E. (1973). Leprosy for students of medicine. Edinburgh: Churchill Livingstone.

Cochrane, R. G. (1965). The diagnosis of leprosy with special reference to tissue defence. *Lepr. Rev.* **36**, 189.

Davey, T. F. (1942). Masked lepromatous leprosy. *Lepr. Rev.* **13**, 3.

Davey, T. F. and Barton, R. P. E. (1973). Multiple nasal smears in early lepromatous leprosy. *Leprosy in India* **XLV**, 54.

Davey, T. F. and Rees, R. J. W. (1973). *The nasal discharge in leprosy.* Abstracts of Tenth International Leprosy Congress, Bergen, p. 30.

Davey, T. F. and Rees, R. J. W. (1974). The nasal discharge in leprosy; clinical and bacteriological aspects. *Lepr. Rev.* **45**, 121.

Drutz, D. J. and Levy, L. (1971). Further studies of leprosy bacteremia. *Clin. Res.* **19**, 457.

Drutz, D. J., Chen, T. S. N and Wen-Hsiang Lu. (1972). The continuous bacteremia of lepromatous leprosy. *N. Eng. J. Med.* **287**, 159.

Drutz, D. J., O'Neill, S. M. and Levy, L. (1974). Viability of blood-borne *Mycobacterium leprae. J. Infect. Dis.* **130**, 288.

Editorial (1968). Report on the Ninth International Leprosy Congress. *Lepr. Rev.* **39**, 188.

Editorial (1970). *Lepr. Rev.* **41**, 1.

Editorial (1971). *Lepr. Rev.* **42**, 85.

Editorial (1973). *Lepr. Rev.* **44**, 1.

Giel, R and van Luijk, J. N. (1970). Leprosy in Ethiopian Society. *Int. J. Lepr.* **38**, 187.

Godal, T., Myrvang, B., Stanford, J. L. and Samuel, D. R. (1974). Recent advances in the immunology of leprosy with special reference to new aproaches in immunoprophylaxis. *Bull. Pasteur.* **72**, 273.

Harman, D. J. (1968). *Mycobacterium leprae* in muscle. *Lepr. Rev.* **39**, 197.
Harman, D. J. (1973). The microscope and leprosy. *Trop. Doc.* **3**, 11.
Leiker, D. L. (1971). Assessment of bacteriological changes in leprosy, based on serial biopsies. *Lepr. Rev.* **42**, 121.
McDougall, A. C., Rees, R. J. W., Weddell, A. G. M. and Wadji Kanan M. (1974). *J. Path.* **108**, in press.
Pedley, J. C. (1970). Composite skin contact smears; a method for demonstrating the non-emergence of *Mycobacterium leprae* from intact lepromatous skin. *Lepr. Rev.* **41**, 31.
Pedley, J. C. (1973). The nasal mucus in leprosy. *Lepr. Rev.* **44**, 33.
Ridley, D. S. (1973). A skin biopsy study of lepromatous leprosy. *Papua New Guin. Med. J.* **16**, 100.
Ridley, M. J. and Ridley, D. S. (1971). Stain techniques and the morphology of *Mycobacterium leprae*. *Lepr. Rev.* **42**, 88.
Shankara Manja, K., Bedi, B. M. S., Kasturi, G., Kirchheimer, W. F. and Balasubrahmanyan, M. (1972). Demonstration of *Mycobacterium leprae* and its viability in the peripheral blood of leprosy patients. *Lepr. Rev.* **43**, 181.
WHO (1966). *Guide to leprosy control.* Geneva, Switzerland.
WHO (1970). Techn. Rep. Ser. No. 459. Expert Committee on Leprosy Fourth Report.

Lepr. Rev. (1975), **46**, 87-88

Letters to the Editor

In Dr Warren's article: "The Bacterial Load in the Nasal Mucosa of Chinese Patients" (Warren, 1973), in which she makes some valuable observations, there is one statement which I wish to challenge. It reads: "Attempts at examination of noseblows *did not yield any useful information,* as the bacillary load (in the noseblow smears) was always much lower than in the nasal smears" (i.e. those made from nasal mucosa scrapes) [italics and brackets—J.C.P's].

In recent years, I have personally examined smears of noseblows for the presence of leprosy bacilli in more than 700 patients with all types of leprosy. A report of 322 of these patients is given in a former paper (Pedley, 1973). In my opinion the finding of a positive noseblow smear for *Myco. leprae* in a lepromatous patient undergoing early treatment, *always* yields valuable information for the following reasons:

(1) The disparity between the bacillary load in a noseblow smear and a smear made from a nasal mucosa scraping (to which Dr Warren refers) can readily be deduced from the noseblow smear. For, a positive noseblow smear yields the information that the load of bacilli in the nasal mucosa membrane is so great that the phagocytes are unable to prevent the escape of bacilli into the nasal secretion. This important observation was made by Harman, following an extensive study of nasal mucosa biopsies which I sent him from Nepal, and it is recorded in a previous paper (Pedley, 1973).

(2) Noseblow smears which are positive for *Myco. leprae* yield information on the state of a patient's infectivity which it is *essential* to know. Rees has shown that a single noseblow may contain millions of morphologically normal bacilli. This finding, coupled with another (Pedley, 1970*a, b*), serves to emphasize the importance of the information which positive noseblows yield. In a prolonged search of one million consecutive microscopic fields of lepromatous skin it had been shown that leprosy bacilli rarely (if ever) emerge from intact skin. This being so, it is the *noseblow* smears which provide the *true* information (and not the skin smears) as to whether a patient is infectious or not. If the noseblow smears do not contain morphologically normal bacilli, than the patient is *not* infectious. The noseblow smears are the true index of a patient's *infectivity,* whereas the skin smears are an index of the *activity* of the disease.

(3) Finally, such observations as: (a) whether the bacillary load in the noseblows is less than that in the nasal mucosa, or (b) whether the M.I.% of the bacilli in the nose is generally higher than that in the skin, or (c) whether the nasal mucosa is the site where the bacilli first make their appearance, and from which they disappear last, are all valuable in themselves, but in the final analysis the most important consideration of all is: *Are bacilli being shed from the nose in the mucoid discharge?* If so the patient must be regarded as contagious until he ceases (as a result of treatment) to discharge morphologically normal bacilli in the noseblows. In my experience this generally takes between 4 to 6 months.

Thus, a careful check, periodically, on the noseblows for the presence of *Myco. leprae* in a patient suffering with lepromatous leprosy, especially during the first 6 months of treatment, is highly desirable for the information it yields as to whether the patient is infectious or not.

Mongar General Hospital J. C. PEDLEY
(TLM), East Bhutan

References

Pedley, J. C. (1970*a*). Composite skin contact smears: a method of demonstrating the non-emergence of *Myco. leprae* from intact lepromatous skin. *Lepr. Rev.* **41**, 31-43.
Pedley, J. C. (1970*b*). Summary of the results of a search of the skin surface for *Myco. leprae*. *Lepr. Rev.* **41**, 167-168.
Pedley, J. C. (1973). The nasal mucus in leprosy. *Lepr. Rev.* **44**, 33-35.
Warren, A. G. (1973) The bacterial load in the nasal mucosa of Chinese patients. *Lepr. Rev.* **44**, 183-185.

Pandya, N. J. and Antia, N. H. (1974).
"The value of scrotal biopsy in leprosy"
***Lepr. Rev.* 45, 145-152.**

I was most interested in this article on the scrotum, and wonder if you will allow me to raise two points for discussion, arising out of our experience with this tissue in Oxford?

In their introduction, I see that the authors have the impression that bacilli *in* muscle have been emphasized in the article they quote. In the case of human striated muscle, however, I am sure that most authorities would agree that even where bacilli are reported *in* fibres, they are almost invariably much commoner *between* fibres, and in interfascicular macrophages. This is certainly the case in our histology.

Secondly, I wish to record disagreement with their statement that: "A stained smear obtained from scrotal skin homogenate is recommended for bacteriological diagnosis as a superior method than routine skin smears or nasal scrapings."

In a very preliminary count of the last 20 consecutive patients for whom we have had multiple biopsies, following various periods of treatment, the scrotum has in fact proved negative on no fewer than 8 occasions, when skin and/or peripheral nerve biopsies were positive.

Quite apart from this, I feel it would be extremely unfortunate if any of your readers gained the impression from this article that they should set aside the use of routine slit-skin smears (or properly carried out skin biopsies, *taken from a lesion*), in favour of incising the scrotum with a knife for the purpose of obtaining a smear. In many parts of the world this approach is unpopular and even feared by the patient. With respect I would doubt the wisdom of recommending it under any circumstances as a routine, though it may clearly be of value for research purposes.

University of Oxford, COLIN McDOUGALL
Department of Human Anatomy,
South Parks Road,
Oxford, OX1 3QX

Lepr. Rev. (1975), **46**, 89

Book Review

Surgical Rehabilitation in Leprosy, by Frank McDowell and Carl Enna. Baltimore, Williams & Wilkins Company. 438 pp.

It is good to be able to welcome another book on this subject, especially one which is so admirably produced and profusely illustrated. The co-editors are to be congratulated on the large number of authors that they have been able to recruit to write on the different topics.

The entire range of the deformities of leprosy is covered. Of the 438 pages 115 are devoted to the face and its deformities, 140 to the hand, 107 to the foot including footwear and prosthesis and the rest to other aspects of the problem including nerves, skin, breasts, testes and the social rehabilitation of the patient.

On the whole the editors have made an excellent choice of authors. A number of names completely new in the field of leprosy surgery have found their way into the pages. These names are in the main well known in their respective specialties, but some of them have, on their own admission, had only a limited experience of leprosy. Consequently, a great variety of procedures are described and there is no means for the reader to know which are the most reliable and useful. It is a reference book of possible alternatives, but what it gains in this direction it loses in the direction of authoritativeness. Some of the chapters tend to contradict each other especially in areas where there is controversy such as in the surgery of nerves. This is of course inevitable when different authors are working on different races and often aiming at different end results.

The field of surgical reconstruction in leprosy is however still wide open for new developments. Reconstruction should be done by specialists in their own field, and not by a peculiar brand of surgeon who limits himself to leprosy and tackles everything that he finds in it. This is a good principle and worthily upheld in this book. It will undoubtedly have a great impact on the world of reconstructive surgery and help to lift the repair of deformity in leprosy out of its present plight, and bring it into an area of respectability.

This book should be in the library of every plastic and orthopaedic surgeon practising in any country where leprosy is reasonably prevalent.

ERNEST P. FRITSCHI

Lepr. Rev. (1975), **46**, 91-99

Abstracts

The following Abstracts are reprinted from *Tropical Diseases Bulletin,* Volume 71, by courtesy of The Director, Bureau of Hygiene and Tropical Diseases.

1. TALWAR, G. P., KRISHNAN, A. D. & GUPTA, P. D. **Quantitative evaluation of the progress of intracellular infection in vitro: incorporation of ^{3}H=thymidine into deoxyribonucleic acid by *Mycobacterium leprae* in cultivated blood monocytes.** *Infection & Immunity,* 1974, v. 9, No. 1, 187-91.

"Growth of intracellular parasites such as *Mycobacterium leprae* in macrophages derived from human peripheral blood monocytes can be assessed by selective incorporation of [*methyl*-^{3}H] thymidine into deoxyribonucleic acid of the bacterial cells. The radioactive precursor is not taken up by the host cells, and evidence has been presented for its incorporation into bacteria. The procedure is sensitive, reproducible, and highly quantitative."

2. SUGIYAMA, K. & IZUMI, S. **Electron microscopic study of the Morphologic Index.** *Int. J. Lepr.,* 1973, v. 41, No. 1, 1-6.

"A new method of examining the Morphologic Index of leprosy bacilli by electron microscopy, using the microsuspension method, is reported. The Morphologic Index determinations of 28 lepromatous and two borderline-lepromatous cases were determined by comparative light and electron microscopy. In almost all cases the electron microscope gave higher values than the light microscope. A correlation between the two kinds of M.I. can be expressed by the formula: E.M.-M.I. (%) = (L.M.-M.I.) x 4.38–8.08. By using this equation, it is possible to estimate more reliable M.I. value from the data obtained by the light microscope and then it is possible to more precisely evaluate the early therapeutic effect of antileprosy drugs than by use of the light microscopy values alone. It was also found that M.I. negative values by light microscopy may be positive by electron microscopy."

3. LOUIE, J. S., KORANSKY, J. R. & COHEN, A. H. **Lepra cells in synovial fluid of a patient with erythema nodosum leprosum.** *New Engl. J. Med.,* 1973, v. 289, No. 26, 1410-11.

Leprosy bacilli were found free as well as in foamy macrophages and neutrophils of the synovial fluid of a patient with polyarthritis associated with erythema nodosum leprosum. The authors give reasons for thinking that the organisms were not contaminants from the skin.

D. S. Ridley

4. DRUTZ, D. J., CLINE, M. J. & LEVY, L. **Leukocyte antimicrobial function in patients with leprosy.** *J. Clin. Invest.,* 1974, v. 53. No. 2, 380-86.

"Patients with lepromatous leprosy are unresponsive to lepromin skin-test material and possess defective lymphocyte function *in vitro,* including impaired mitogenesis in response to antigens of *Mycobacterium leprae.* It has been claimed that their macrophages cannot digest *Myco.*

leprae in vitro; such a defect could explain both lepromin nonreactivity and impaired lymphocyte function on the basis of failure of the afferent limb of the immune response i.e. defective macrophage 'processing' of *Myco. leprae.*

"The present studies indicate that macrophages from patients with lepromatous and tuberculoid leprosy and from normal donors do not differ in their ability to digest heat-killed *Myco. leprae in vitro*, or in their ability to sustain the viability of *Myco. leprae* in tissue culture; that monocytes, macrophages, and polymorphonuclear leukocytes of leprosy patients and controls possess equivalent microbicidal activity against *Listeria monocytogenes, Escherichia coli, Proteus vulgaris, Staphylococcus aureus,* and *Candida albicans*; and that polymorphonuclear leukocytes from patients with lepromatous leprosy iodinate ingested bacteria normally. Whether the basic immune defect leading to the development of lepromatous leprosy resides in the lymphocyte or in the macrophage remains to be determined. However, the present study shows that phagocytic cells from patients with either principal form of leprosy function normally in a variety of sophisticated tests of antimicrobial function."

5. BULLOCK, W. E., CALLERAME, M. L. & PANNER, B. J. **Immunohistologic alteration of skin and ultrastructural changes of glomerular basement membranes in leprosy.** *Am. J. Trop. Med. Hyg.*, 1974, v. 23, No. 1, 81-6.

"Immunofluorescent 'banding' of the dermal-epidermal junction of skin was demonstrated in 3 of 7 patients with lepromatous leprosy by direct immunofluorescence microscopy. The 'banding' was caused specifically by deposition of IgM. Within the glomeruli of one patient, dense, amorphous deposits in subendothelial and intramembranous position were also demonstrated by electron microscopy. These preliminary findings suggest that lepromatous leprosy may be associated with immunologic disturbances of both skin and glomerular basement membranes."

6. GRABOSZ, J. A. J., DERBLOM, H. & GODAL, T. **IgE serum levels in leprosy.** *Acta Path. Microbiol. Scand., Sect. B,* 1973, v. 81, No. 6, 806-7.

Forty-nine adult patients with lepromatous leprosy, 52 with tuberculoid leprosy, 19 healthy household contacts of patients with leprosy and 19 healthy Ethiopian members of staff were studied. The median serum concentrations of IgE were respectively 2700 units/ml, 1690, 1830, and 668 units/ml, the last group being statistically lower than the others. The difference between the two control groups is probably due to different exposures to intestinal parasites.

C. S. Goodwin

7. MALCHOW-MØLLER, A. **A three-year leprosy control programme in Tamil Nadu (India).** *Dan. Med. Bull.*, 1973, v. 20, No. 6, 198-203.

Senior Danish medical students have co-operated in the organization of a programme of leprosy treatment/control in a circumscribed area of 746 km^2 in Tamil Nadu, India, based on the central hospital in Kumbakonam. The prevalence of leprosy in the population (estimated at about 300,000) is approximately 2.5%, giving a probable total of 7500 patients suffering from leprosy.

Following closely the principles laid down by the WHO, the team employed trained paramedical workers for the routine surveys, contact examination, absentee tracing and weekly leprosy clinics. Adequate laboratory facilities were provided for each of the 12 zones in the care of each paramedical worker.

Simple drug regimens of dapsone, given orally in a standard fashion, were applied throughout the area and for all kinds of leprosy. *Erythema nodosum leprosum,* lesion

exacerbation and neuritis, if not responding to roadside treatment, necessitated removal to the central hospital for a time.

Self-reporting on suspicion provided the greatest number of patients with leprosy (25% of those reporting), while routine whole-population surveys were the least productive (only 1%).

Health education and propaganda have gone hand in hand with determined efforts to discover all those needing treatment for leprosy; over 90% of patients were detected because of health education or through mass surveys. Preliminary findings among schoolchildren indicate an annual incidence of 5 per thousand. So far, 4501 patients have been placed on treatment, of whom 161 have been declared inactive (on WHO criteria).

Reconstructive surgery was available for patients with remediable deformity.

S. G. Browne

8. JOB, C. K. **Culture study of *Myco. leprae* in mice in tropics with and without controlled environmental air temperature.** *Indian J. Med Res.*, 1973, v. 61, No. 10, 1485-8.

"In 5 experiments, multiplication of *Myco. leprae* in the footpads of mice kept in ordinary room temperature in South India varying from 18°C to 38°C was compared with that in mice kept in air conditioned rooms with constant temperature of 22°C. Although bacillary growth was found in the footpads of mice kept in both conditions, the growth was inconsistent and the number of bacilli harvested was significantly lower in animals kept in non-air conditioned rooms. It is recommended that the mice used for the culture of *Myco. leprae* especially in tropical countries be kept in air conditioned rooms at 20–22°C to obtain consistent and maximum possible multiplication."

9. MERKLEN, F. P., PENNEC, J. & HORNER, C. Raréfaction, mais possibilité persistante, de lèpres contractées en France métropolitaine. **(The rarity of endemic leprosy in France, but its possible persistence.)** *Bull. Acad. Natn. Méd.*, 1973, v. 157, No. 6, 439-43.

The authors provide a useful summary of the numbers of cases of leprosy arising in metropolitan France for each decade since 1923. The totals were 13 and 12 for the first 2 decades, but have been 5 for each of the last three. Despite the influx during recent years of leprosy sufferers from abroad (especially the West Indies), the numbers of infections apparently contracted in France itself show a progressive decline. It is, of course, difficult to establish without doubt that patients who develop the first signs of leprosy while living in France did not actually become infected during a period of military service overseas.

In 1973, 4 new cases were reported, 3 from the neighbourhood of Lyons and one from Nice. The authors indicate that indigenous foci of leprosy in France, quite unknown and perhaps unsuspected, may exist, and utter a salutary warning that doctors should be made aware of this possibility.

S. G. Browne

10. TÉMIME, P. & PRIVAT, Y. Un cas de lèpre apparemment contractée en France. **(A case of leprosy apparently contracted in France.)** *Bull. Acad. Natn. Méd.*, 1973, v. 157, No. 6, 444-5.

A gardener aged 47 years presented with signs of severe iridocyclitis, which was associated with unsuspected advanced lepromatous leprosy with all the classical signs. The nasal discharge contained numerous leprosy bacilli, as did the skin.

The interest lies in the source of contagion. The patient had never left France, and had had no known contact with anybody from abroad. None of his family has leprosy. The question is raised whether there might be a persistent focus of leprosy in the vicinity of Nice, and the suggestion is tentatively made that he might possibly have been infected through the intermediary of one of the exotic plants, which he was in the habit of handling in the course of his work.

S. G. Browne

11. SÉRIE, C., SABOURIN, G., DUJEU, G. & MERCIER, J. Considerations sur l'encemie hansénienne en Guyane Française. **(Features of the leprosy situation in French Guiana.)** *Bull. Soc. Path. Exot.*, 1973, v. 66, No. 3, 371-80.

This intensive study of the small population of French Guiana (about 50,000 people) discloses facts that are of general epidemiological interest. All the 957 patients at present under treatment for leprosy are seen twice annually by a doctor, and regular case-finding surveys are conducted at the schools (which are attended by 95% of the children of school age).

Despite an excellent coverage of the whole population since 1952, and the vaccination of all children with BCG since 1961, very little impression appears to have been made on the situation. The numbers of new notifications year by year remain unchanged; the male : female ratio stands at 62 : 38; the age incidence is the same, and so is the distribution of the various types of leprosy.

Some 557 patients have been declared disease-free during this period, and a further 267 are still under observation, "disease arrested".

A special section of the paper is concerned with leprosy in children. Apparently, no difference in incidence was noted between children in households where a parent had leprosy, and those whose parents were free from the disease, and no differences were noted in the proportions of the forms of leprosy in the 2 groups.

According to the authors, other factors besides the presence of the infective agent in the vicinity must be at work; these may well be concerned with the "soil" rather than with the "seed".

S. G. Browne

12. NAVALKAR, R. G. **Immunologic studies on leprosy. 2. Antigenic studies of *Mycobacterium leprae*.** *Ztschr. Tropenmed. Parasit.*, 1973, v. 24, No. 1, 66-72.

"Antigenic mosaic of *Myco. leprae* was determined first by analysing sera from leprosy patients in various stages of infection by the use of antigenic preparations derived from a number of mycobacterial species. These studies led to the detection of two serologically distinct types of antibodies and the antigens reacting with these antibodies were found to be shared by a number of other mycobacterial species. Further extension of these observations was carried out by preparing antiserum against tissue separated *Myco. leprae*. The analysis of the *Myco leprae-anti-Myco. leprae* system showed the presence of 5 detectable antigens, two of which were the same as those seen in earlier studies with the sera. Chromatographic separation of the *Myco. leprae* antigens resulted in obtaining a number of fractions, some of which gave immuno-precipitates when tested against the anti-leprae serum. These fractions were tested in animals sensitized with *Myco. leprae* and other mycobacteria to determine their hypersensitivity eliciting potential. Preliminary results indicate that a few of the fractions were able to elicit hypersensitivity in the homologously sensitized animals. These studies are in progress for further confirmation of the specificity of the reactions noted."

13. WALL, J. R. & WRIGHT, D. J. M. **Antibodies against testicular germinal cells in lepromatous leprosy.** *Clin. Exp. Immunol.*, 1974, v. 17, No. 1, 51-9.

"Testicular germinal cell antibodies were found in 44 out of the 59 patients with lepromatous leprosy and in 4 out of 10 patients with tuberculoid disease. A similar pattern was found in 12 out of 262 control patients and normal subjects.

"The antibody was found to be of the IgG class and 40 out of 49 of these antibodies were shown to be complement fixing. Spermatozoal antibodies were detected in 12 patients, but no ovarian antibodies were found in any specimen. There was no close correlation between *erythema nodosum leprosum* (ENL) and testicular antibodies. It was found that the characteristic of the testicular antibody in leprosy was its ability to be absorbed by

Mycobacterium BCG suspension suggesting that this is another antibody induced by infection. A similar fluorescent pattern was seen in some patients who did not have leprosy, but in these cases it could not be abolished with BCG. It is concluded that autoimmunity may be one of the factors involved in the pathogenesis of orchitis in leprosy."

14. DUTTA, R. N. & SAHA, K. **Australia antigen and lepromatous leprosy: its incidence, persistence and relation to cell mediated immunity.** *Indian J. Med. Res.*, 1973, v. 61, No. 12, 1758-65.

Hepatitis B antigen was detected by counter-immunoelectrophoresis in the serum of 2 (2.08%) out of 96 military personnel with leprosy of all types and in 3 (5.35%) out of 56 civilian patients with leprosy. When the cases of lepromatous leprosy and borderline lepromatous cases were grouped together, the antigen was detected in 1 (3.3%) of 30 army patients and in 3 (8.1%) of 37 civilian patients. The respective prevalence of the antigen among army and civilian voluntary blood donors was 2.88% and 2.67%.

It is considered that the greater frequency of hepatitis B antigen in patients with lepromatous leprosy is due mainly to impairment of the cell-mediated immune response in this form of the disease.

It is also noted that the number of tuberculoid forms of leprosy was much higher in the army group (59 out of a total of 96 cases) and it is suggested that the better nutritional status and physical condition may be factors in resisting the development of lepromatous variety of the infection.

A. J. Zuckerman

15. PATTYN, S. R. & SAERENS, E. J. **Results of intermittent treatment with dapsone and rifampicin of mice inoculated with *Mycobacterium leprae*.** *Ann. Soc. Belg. Méd. Trop.*, 1974, v. 54, No. 1, 35-41.

"Dapsone administered continuously in the food at a 0.01% concentration during 6 months was bactericidal for *Myco. leprae* in the mouse footpad test. When the same dose was given once a week or less frequently the effect was bacteriostatic. The MID for once weekly regimens of rifampicin is situated between 0.125 mg and 0.062 mg. In a dose of 1.5 mg once a week and once every 2 weeks this drug had a bactericidal effect. A dose of 0.5 mg once a week and once every 2 and 4 weeks was bactericidal. A dose of 0.25 mg was bactericidal when given once a week and once every 4 weeks, bacteriostatic only when given once every 8 weeks.

Such experiments should provide information on the possibility to use low doses of rifampicin as an introductory treatment in lepromatous leprosy."

16. AXELSEN, N. H., HARBOE, M., CLOSS, O. & GODAL, T. **BCG antibody profiles in tuberculoid and lepromatous leprosy.** *Infection & Immunity,* 1974, v. 9, No 5, 952-8.

"In sera from 12 patients with polar tuberculoid leprosy, 12 with subpolar tuberculoid leprosy, and 16 with lepromatous leprosy were demonstrated a total number of 125 anti-BCG precipitins by means of crossed immunoelectrophoresis with intermediate gel. Up to 14 different precipitins were found in individual sera, and the complexity in antibody response was higher than previously realized. The specificity of 69% of the antibodies was defined, and these antibodies were titrated in three arbitrary titer units. A highly significant difference ($P < 0.002$) was found in antibody response between the tuberculoid and the lepromatous group. Due to simplicity, sensitivity, and high resolution, the method used is a promising tool for providing exact data to be used as guidelines for purification of important individual mycobacterial antigens. The need for reference antisera is emphasized."

17. GELBER, R. H., DRUTZ, D. J., EPSTEIN, W. V. & FASAL, P. **Clinical correlates of C1q-precipitating substances in the sera of patients with leprosy.** *Am. J. Trop. Med. Hyg.*, 1974, v. 23, No. 3, 471-5.

"*Erythema nodosum leprosum* (ENL) is often interpreted as a manifestation of immune-complex deposition in patients with lepromatous leprosy. We used a C1q precipitin assay technique to demonstrate directly the presence of immune complexes in sera from patients with leprosy. Seven of 15 patients with ENL had serum C1q precipitin activity; serial tests often showed continued C1q precipitin activity. Only 3 of 27 lepromatous patients without ENL had positive tests; multiple positive tests were not seen in these patients. Single positive tests were encountered in patients with borderline (dimorphous) leprosy, especially those with downgrading reactions. There was no relationship between C1q precipitin activity and serum levels of C3, CH_{50}, or cryoglobulins. Single positive C1q precipitin tests may occur sporadically in patients with leprosy, but repeatedly positive tests are closely associated with occurrence of ENL, supporting the concept that ENL is a complication related to the presence of circulating immune complexes."

18. PATTYN, S. R., ROLLIER, R., SAERENS, E. J. & ROLLIER, M. R. **Initial three months continuous and intermittent therapy in lepromatous leprosy. A controlled clinical trial. Preliminary data.** *Ann. Soc. Belg. Méd. Trop.*, 1974, v. 54, No. 1, 43-9.

The results of intermittent treatment with rifampicin of mice infected in the footpad with *Mycobacterium leprae* (this *Trop. Dis. Bull.*, 1974, v. 71, abstr. 1518) suggested that this was a useful initial treatment of leprosy. Fifty-four adults, previously untreated, with lepromatous or borderline lepromatous leprosy were randomly allocated to one of 4 treatment schedules: dapsone 100 mg daily (D100D), rifampicin 450 mg daily (R450D), rifampicin 900 mg weekly (R900W), and clofazimine 300 mg weekly (C300W). Treatment was given for 3 months on an in-patient basis. Following this initial period, patients were discharged and further treated with dapsone 100 mg daily. Biopsies were taken before treatment, and at 1, 2, 3, and 6 months. Bacterial and morphological indices were determined. Results of treatment on the morphological indices are shown in the table below.

	Months of Treatment				
	0	1	2	3	6
D100D	26 (11–45)	12 (0–30)	7 (0–20)	4 (0–14)	No. insufficient
R450D	36 (10–60)	1.5 (0–8)	1.6 (0–8)	1.7 (0–11)	1.8 (0–2)
R900W	31 (10–58)	3 (0–12)	2 (0–7)	2 (0–10)	0 (0–1)
C300W	28 (10–51)	22 (3–50)	15 (1–42)	7 (0–25)	No. insufficient

Morphological indices (mean and range)

G. H. Rée

19. ELLARD, G. A., GAMMON, P. T., HELMY, H. S. & REES, R. J. W. **Urine tests to monitor the self-administration of dapsone by leprosy patients.** *Am. J. Trop. Med. Hyg.*, 1974, v. 23, No. 3, 464-70.

"Three qualitative and one simple quantitative urine test methods are described for monitoring the self-administration of daily doses of dapsone (DDS) by leprosy patients. The qualitative

methods can be employed for monitoring the taking of daily doses of 50 mg DDS or more. In the quantitative method the ratio of DDS plus its diazotizable metabolites to creatinine in the urine is determined using simple colorimetric methods. This method is considerably more sensitive and efficient than the qualitative methods and is capable of monitoring the taking of daily doses of DDS of as little as 10 mg."

20. NG, H., JACOBSEN, P. L. & LEVY, L. **Analogy of *Mycobacterium marinum* disease to *Mycobacterium leprae* infection in footpads of mice.** *Infection & Immunity,* 1973, v. 8, No. 6, 860-67.

"Because it appeared likely that the disease process that follows inoculation of footpads of mice with *Mycobacterium marinum* might serve as a useful model of mouse footpad infection with *Myco. leprae* for immunological studies, an attempt was made to establish an analogy between the two processes. As a second objective, the adequacy of measurements of mouse footpad thickness as an index of the total number of *Myco. marinum* and of the number of viable *Myco. marinum* was determined. The evolution of *Myco. marinum* disease in the footpads of BALB/c mice was observed, and the influences of mouse age and sex and of inoculum size were measured. Mice were challenged with *Myco. marinum* in one footpad at several intervals after inoculation of the contralateral hind footpad with the same organism. In all of these experiments, mouse footpad thickness was noted to parallel multiplication of *Myco. marinum.* during the phase of increasing footpad swelling. Cessation of bacterial multiplication was noted to occur just before maximal swelling had been achieved, and was followed by rapid loss of viable *Myco. marinium.* The total number of organisms and mouse footpad thickness decreased only slowly and incompletely. Analogy between *Myco. marinium* disease and *Myco. leprae* infection of the mouse footpad was established by the self-limited nature of both processes, and by similar patterns of protection against homologous and heterologous challenge conferred by the two processes."

21. NAKAMURA, M. **Quantitative multiplication of *Mycobacterium lepraemurium* in a cell-free liquid medium (NC-5).** *J. Gen. Microbiol.,* 1974, v. 82, Pt 2, 385-91.

"*Mycobacterium lepraemurium* multiplies in a cell-free liquid medium, referred to as NC-5, which is enriched Kirchner medium plus goat serum, α-ketoglutaric acid, cytochrome *c,* haemin, and L-cysteine. At 30° C, the bacilli gradually elongated before multiplying 100- to 1000-fold. The maximum number of bacilli is reached after 8 weeks' incubation. The generation time of *Mycobacterium lepraemurium* is between 8 and 14 days, depending upon the size of inoculum. Bacilli grown in NC-5 medium maintain their capacity to produce leprosy in mice. Optimum growth was with the basal medium at pH 7.3 using a small number of bacilli in the inoculum."

22. WALTER, J., SEAL, K. S., SANSARRICQ, H. & ENGLER, V. **Random sample surveys in leprosy control programmes–are they a nuisance?** *Ztschr. Tropenmed. Parasit.,* 1974, v. 25, No. 1, 89-95.

Since reliable statistics of the incidence of leprosy are not available for the countries where leprosy constitutes an important public health problem (that is, where the prevalence rate of known cases is 1 in 1000 or higher), the authors describe methods of random sampling surveys specially conceived for the purposes of leprosy investigation in a population.

The leprosy prevalence rate in schoolchildren aged 5–14 years may furnish a rough indication of the total prevalence in a given area. A method more generally applicable, described by the authors, consists of determining the situation at 5- and 10-year intervals in countries in which a leprosy control programme is in operation, integrated or not (depending on the local circumstances) into the general health services.

By comparing the projected prevalence rates, as calculated from the basic data obtained at the initial random sample survey and 5 years later, with the actual findings, the value of any control measures adopted in the meantime will become obvious in the discordance noted between the projected rate and the actual rate found.

The investment of money and time into such random surveys is held to be more than justified because of the data they bring to the effectiveness of the anti-leprosy programme.

The paper is illustrated with explanatory figures.

S. G. Browne

23. PARIKH, A. C., D'SOUZA, N. G., CHAULAWALA, R. & GANAPATI, R. **Leprosy lesions in the scalp.** *Lepr. India,* 1974, v. 46, No. 1, 39-42.

"The few references on the incidence of leprosy lesions on the scalp are pointed out.

"The case histories of 2 patients, one with borderline leprosy showing raised anaesthetic lesions on the scalp and another with lepra reaction showing lesion resembling ENL on the scalp are described.

"It is concluded that though, in the vast majority of lepromatous patients, the bacilli cannot be demonstrated in the smears from the scalp there is evidence to show that the scalp is a site where *Myco. leprae* do thrive and produce lesions though rarely."

24. TEXIER, L., DAVID-CHAUSSE, J., TAMISIER, J. M., GAUTHIER, O., GAUTHIER, Y. & BORAUD, P. Enfermedad de Hansen. Reacción leprosa con intensas manifestaciones articulares. **(Leprosy. Lepromatous reaction with intense articular manifestations.)** *Medna Cutánea,* 1973, v. 7, No. 6, 69-70.

The English summary appended to the paper is as follows:
"We report the case of a patient with lepromatous leprosy, who for a certain period showed criteria of the Lucio-type leprosy. The incubation is remarkably long. Undergoing treatment with disulone, this patient now shows articular reactions similar to a rheumatoid polyarthritis in addition to the symptomatic leprotic reaction. The presence of BH [Hansen's bacillus] in the liquid of the joint cavity and in synovial cells, leads us to connect these symptoms to Hansen's disease. The facts have only recently come to light and occur in all cases of lepromatous leprosy in the reaction phase. We report the satisfactory therapeutic results obtained with rifampicine."

25. SEBILLE, A., BOISSON, M. E. & ROUGEMONT, A. Manifestations cliniques de la névrite lépreuse. **(Clinical manifestations of leprosy of the nervous system.)** *Méd. Afr. Noire,* 1974, v. 21, No. 3, 193-7.

The authors present an analysis of the gross clinical manifestations of peripheral nerve damage seen in a selected series of 90 patients suffering from various kinds of leprosy (61 lepromatous, 20 tuberculoid, 4 borderline, and 5 indeterminate). All were receiving treatment for leprosy at the Marchoux Institute, Bamako, Mali.

Their results, which disclose no novel findings, confirm the generally accepted views that the ulnar nerve trunk is more frequently affected than the median or radial, and the external popliteal more frequently than the posterior tibial. Despite modern anti-leprosy treatment, peripheral nerve lesions either appeared or became worse in about half the patients. Dissociation of sensory modalities is held to be early and transitory. The role of compression of the nerve trunk in osseous or fibrous canals is emphasized.

(The outstanding clinical sign in the nerve trunk itself, at the sites of predilection, is said to be "enlargement." No indication is given of the diameters of the trunks in relation to the pathological changes within the nerve, and in its sheath, changes that are determined by the form of leprosy and its duration.)

S. G. Browne

26. KREISLER, M., ARNAIZ, A., PEREZ, B.,CRUZ, E. F. & BOOTELLO, A. **HL-A antigens in leprosy**. *Tissue Antigens,* 1974, v. 4, No. 3, 197-201.

"HL-A phenotype frequencies were studied in 30 patients with leprosy and in 149 healthy controls. Leprosy patients had a significantly higher frequency of HL-A14. In addition, a majority of the HL-A14 patients gave a negative response to leproma antigen using the Mitsuda test."

27. PETERS, J. H. *ET AL.* **Metabolic disposition of dapsone in patients with dapsone-resistant leprosy**. *Am. J. Trop. Med. Hyg.,* 1974, v. 23, No. 2, 222-30.

"To investigate the question of whether dapsone (DDS) resistance in leprosy patients is related to the metabolic disposition of DDS, we studied a group of 22 patients who had relapsed with DDS-resistant disease after approximately 19 years of sulfone therapy. Tests for acetylator phenotype with sulfamethazine (SMZ) showed that this group of patients contained a lower percentage of slow and a higher percentage of intermediate and rapid acetylators than had been observed previously in other populations. Acetylation of SMZ and DDS were directly related. In addition, plasma clearance of DDS for the DDS-resistant group was significantly faster than that found previously in any other population. These observations suggest that the emergence of DDS resistance may be associated with the rapid or intermediate acetylator phenotype and an ability to clear DDS from the circulation at a fast rate. Combining the two parameters into a multirisk factor yielded a significantly higher mean value in DDS-resistant patients than that of any other group studied previously. The implications of these findings for the large-scale treatment of leprosy patients are discussed."

28. PATTYN, S. R. **Conservation of *Mycobacterium leprae* in liquid nitrogen**. *Ann. Soc. Belg. Méd. Trop.,* 1973, v. 53, No. 6, 645-50.

"Suspensions of *Myco. leprae* can be successfully preserved if they are slowly frozen in buffered dimethylsulfoxide 7.5% final concentration, and maintained in liquid nitrogen."

29. STORRS, E. E., WALSH, G. P., BURCHFIELD, H. P. & BINFORD, C. H. **Leprosy in the armadillo: new model for biomedical research**. *Science. Washington,* 1974, March 1, v. 183, 851-2.

About 40% of armadillos captured from the wild and inoculated by various routes with suspensions of *Mycobacterium leprae,* developed disseminated leprosy which was confirmed by histopathological examination after necropsy. These animals died of leprosy and its complications after widely differing intervals following infection, from 15 to 41 months. Noteworthy features of the disease included the enormous numbers of bacilli present, the frequent involvement of the central nervous system and the lungs, and massive invasion of the bone marrow. This latter finding may be related to the severe depression of immunological competence.

From the dead armadillos, 988 g of highly bacilliferous tissue was obtained, containing minimal amounts of stroma. This tissue contained probably 15 to 20 g of *Myco.leprae* at a concentration of about 10^{10}/g. The store of bacilli is now available for immunological and chemotherapeutic research.

S. G. Browne

Subscription Renewal/Application

LEPROSY REVIEW

Volume 47 (quarterly)

1976

U.K.: £8.10 inclusive of postage and packing

Overseas: £9.30 inclusive of postage and packing

For Volume 47

Quotations for air mail postage provided on request

Please complete the form below and return it immediately. To avoid lapse in service and subsequent delay in obtaining missed issues when renewing your subscription *it is recommended that this application reaches us NOT LATER than the end of this month.*

Should you customarily place your orders with a **subscription agency** or a **bookdealer,** please forward renewals to that agency or dealer as usual. But in that case, please do not send an advance or confirming order to us, as this may cause duplication.

ACADEMIC PRESS INC. (LONDON) LIMITED,
24-28 Oval Road, London NW1. Registered office. Registered no. 598514

Enclosed please find £.....for.... ..renewal subscription(s) to

LEPROSY REVIEW, Volume 47, 1976

@ £8.10 (U.K.) or £9.30 (Overseas) inclusive of postage & packing.

Please continue each year on standing order until countermanded ☐

Please tick

Name

Please sign

Name

Please PRINT

Institution

N.B. Institutional buyers are requested to send an official purchase order.

Full postal address

Date

Leprosy Control in Malawi...

Leprosy work in Malawi is entering a new phase with the expansion of domiciliary treatment to areas outside the original LEPRA project. A framework has been set up, which, within the next few years, will ensure coverage of the whole country.

The Ministry of Health in Malawi is looking for a Dermatologist, aged 25–50, with a medical degree obtained in the UK and post-graduate experience in dermatology and leprosy control.

You will be based at the Queen Elizabeth Hospital, Blantyre, which is an acute general and central referral hospital with teaching and training facilities.

The salary for this post is £6408 of which there is a tax-free element of £3936. The initial contract is for 2½ to 3 years, and there is a terminal gratuity of 25% of the basic salary over the contract period. There is low taxation and cost of living, subsidised housing and free medical care. Free passages, baggage allowance, education allowance and generous paid leave are included in the contract terms. Please write for an application form, and any further information you need, to:

Malawi Buying and Trade Agents, Recruitment Section (Ref 860/5B) c/o Berners Hotel, Berners Street, London W1A 3BE.

Malawi

®Lamprene Geigy

Effective in all forms and in all stages of **leprosy**

Anti-inflammatory action

clear improvement
in skin and nerve lesions [1]

no bacterial resistance[2]

prevents
lepra reactions [3]

treats
ENL and leprotic iritis [4]
often caused by other
anti-leprotic agents

References:
1. Browne, S.G., Int. J. Leprosy *34,* 289 (1966)
2. Waters, M.F.R., Leprosy Review *40,* 21 (1969)
3. Hastings et al., Leprosy Review *39,* 3 (1968)
4. Warren, H.A., Leprosy Review *39,* 61 (1968)

For further information, see the Prescriber's Guide to GEIGY Pharmaceuticals

011 LAM 7474 e