Editorial

THE WIND OF CHANGE

The Clayton Memorial Lecture was founded by LEPRA in 1974 to honour the memory of the Rev. T. B. Clayton, founder of Toc H, who in the 1930's committed that self-sacrificing organization to the fight against leprosy in Africa, and in co-operation with BELRA was responsible for sending a succession of dedicated laymen to engage in field work, usually in pioneering conditions. The 1976 lecture was given recently by Dr T. W. Meade, an epidemiologist of international reputation, who has also personally been engaged in a major leprosy control project in India, and so knows our problems from the inside as it were. The material of his lecture on the question, "How effective is the treatment of leprosy?" appears by invitation in this issue of *Leprosy Review,* and some readers may well liken it to a gust of cold air shattering their illusions and challenging their complacency.

For over 20 years now it has been the accepted doctrine that in dapsone we have the means to bring leprosy under control, and applying it on a sufficiently large scale we can look forward to the eradication of the disease. Though doubts and questions have arisen in recent years this doctrine is still being put forward in the official publications of some leading anti-leprosy organizations. Dr Meade draws attention to the great fallacy in it, namely the "application gap" between, on the one side, what the planners hope will happen, and on the other side, the actual response of the patients and potential patients who are the expected recipients of their ministrations.

It has been assumed in far too facile a way that, offered dapsone, patients would want to take it and go on taking it for long periods. We now know that many of them do not, sometimes because dapsone is not offered to them in an appropriate way, but more fundamentally because we have not taken the measure of the social, religious and economic factors which are of unique importance in relation to leprosy, a point that has repeatedly been made in this Journal in recent years.

The writer was one of those optimists who lived through the heady exciting years of the first application of dapsone on a large scale, and witnessed the transformation it effected in Nigeria not only on patients but also on public opinion. More recent experience of trying to apply the same methods in central India proved a powerful corrective to optimism. Here, although many patients knew that dapsone was the best medicine available, and that they needed to take it, they were so much the victims of the circumstances which prevailed where they lived, that the kind of co-operation necessary was always difficult for them and sometimes impossible. It is now clear that similar factors operate in many places, and added to the intrinsic depressing effect of leprosy itself, have a direct

bearing on the frequency and severity of reactions, disappointing physiotherapeutic progress and the development of drug resistance.

An understanding of the force of these circumstances is only given to those who come close to the people, and who then appreciate that our patients have to be seen as *people to whom the environment has become hostile.* There can be no question of removing them from that environment. It is the hostility that needs to be removed. Unless leprosy control policy is related to the study of inhibiting environmental factors, and is adapted to overcome them, we are at worst simply beating the air, and at best condemning ourselves to the frustrations of a very long haul indeed.

We now face the ominous situation where, with the appearance of sulphone resistance in many places, the transmission of sulphone-resistant *M. leprae* is inevitable. This prospect must invite a very careful reappraisal of the standard approach to leprosy control.

Leprosy workers everywhere look to the World Health Organisation for guidance and leadership. We welcome the realistic and humane approach now being made by WHO, and in particular the creation of IMMLEP and THELEP. At the same time it is extremely unlikely that the replacement of one form of long term therapy by another will, on its own, materially influence the course of leprosy in the world. Highly effective short term therapy would be another matter, but therapy in itself does not strike at the root of the anxieties and prejudice which bedevil our hopes. From this angle the objectives of IMMLEP are more promising. Provided that any vaccine produced is administered in conjunction with others, and not on its own, leprosy hostility could effectively be bypassed.

One thing becomes clear, namely that leprosy control policy cannot be left to a committee of leprologists working in isolation. Future policy needs to be synthesized by a co-ordinating committee where clinicians, bacteriologists and epidemiologists sit together with social scientists and experts in health education who have made a special study of leprosy and its problems, and the group as a whole consider the control programme suitable for any given country. Only in this manner will adequate respect be paid to the non-medical factors which are so important.

It was concern for children at risk that prompted leprologists of the writer's generation to initiate domiciliary control programmes well before the days of sulphone therapy. That concern must always be before our eyes, but with it must go the degree of emancipation from rigid professional attitudes which will enable us to see the patient in his wholeness and the breaking down of hostility to him as a paramount concern.

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How Effective is the Treatment of Leprosy?

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This transcript of the 1976 Clayton Memorial Lecture sets the problem of eradicating leprosy against a similar situation affecting several other major diseases. We already have sufficient knowledge either to eradicate or radically influence the prevalence of such diseases, but they nevertheless continue with little prospect of any rapid decline. The reasons for this unbridged gap between knowledge and its effective application vary to some extent. The various factors in the "application gap" which are of relevance to leprosy are discussed and the importance of prevention as a primary objective is emphasized.

This paper aims not only to highlight some of the problems associated with the effective treatment of leprosy, but also the similarity of the difficulties experienced by health workers in more as well as less affluent countries, at a time when nearly all of them have less and less with which they are expected to do more and more. In health terms, Western society is confronted mainly by the burden of the non-communicable diseases that have largely replaced the communicable—ischaemic heart disease, stroke, lung cancer, dental caries, for example. All these conditions have one feature in common; we have the knowledge either to prevent or treat them—if not entirely, then certainly to a very substantial extent. Yet each continues and, with minor exceptions, there is no reason to believe that the situation will improve. Why is this? We can provide some reasons, mostly rather superficial—to do with the difficulties of giving up smoking and overeating, taboos about what we will or will not put in our drinking water, and so on—but basically, we do not know how to apply information already to hand. We have assumed that simply having the knowledge which would make treatment or prevention possible would be enough. People would, for example, follow the scientific argument linking cigarette smoking with lung cancer, they would accept it, stop smoking and live to see the disease disappear. After all, much of the knowledge in question was acquired soon after some of the most spectacular advances ever made in medicine; why should progress not go on being as straightforward, relatively speaking at least, as applying the knowledge that led to penicillin and its use, or to immunization against diphtheria? With hindsight, some of the reasons are obvious. Stopping smoking is no once-off affair, like having a course of penicillin or a smallpox vaccination; it involves a sustained long-term effort of will. What we are faced with at present is a largely unbridged gap between knowledge and its effective application. No-one has put this better than the late Lord Rosenheim (1968):

"If, for the next 20 years no further research were to be carried out, if there were a moratorium on research, the application of what is already known, of what has already been discovered, would result in wide-spread improvement in world health."

This paper is based on the Third Clayton Memorial Lecture, given in Liverpool on 1 December, 1976.

That is not all he said on that occasion; the relevance of another extract is considered later. What this paper is mainly concerned with however, is the "application gap" (*Lancet*, 1976) in the treatment of leprosy.

For hundreds if not thousands of years, the management of leprosy was based on a mixture of fear, magic, social ostracism and a few compounds for which there were some indications, however tenuous, that they might be useful, e.g. the painful injection of chaulmoogra oil. The tendency towards self-healing in the less serious forms of the disease may have been a factor which sometimes lent support to the apparent effectiveness of some of these older remedies, and, correspondingly, hampered the pursuit of other remedies.

In the early 1940s, however, the search for anti-tuberculosis agents led to the identification of certain sulphone derivatives which were actually ineffective against tuberculosis, but were shown by Faget *et al.* in 1943 to be effective in leprosy. By 1952, dapsone, or DDS, had become standard treatment for leprosy, and has continued as the sheet-anchor ever since; it is cheap and relatively free from adverse effects. After years of standing more or less helplessly by, it must have been an exhilarating experience to be working in the leprosy field during the late 1940s and early 1950s, and, indeed, one can tell from the early literature of the sulphone era that it was. For not only was it believed that DDS at last provided effective treatment for patients with leprosy—it was assumed that this treatment would reduce the pool of infectivity in the world's endemic areas, prevent the transmission of *Mycobacterium leprae* to others, and thus virtually eradicate the disease. As one follows the DDS story through, the 1950s and early 1960s were still times of high hopes for both treatment and prevention; with such a long incubation period and protracted clinical course, it was hardly to be expected that things would change overnight. One of the most striking developments at this time, and partly attributable to the increasing availability of DDS, was the gradual replacement of institutional care in isolation by domiciliary management based on case-finding and DDS treatment in the community. This movement has been carried even further in some areas through attempts to discourage the view that leprosy and its treatment are special problems that differ from other health problems, and to integrate leprosy services into the local system for providing health care as a whole.

Towards the end of the 1960s, however, serious doubts about the early assumptions of the DDS era had begun to emerge. With hindsight, some of these could perhaps have been anticipated. First of all, DDS is bacteristatic—not bactericidal—and viable *M. leprae* have been demonstrated in the tissues of lepromatous patients who have been treated with DDS for many years. Secondly, the reversal reaction may lead to the very distressing situation that treatment has in fact accelerated or even caused just those deformities it is intended to prevent; this reaction is not, of course, associated only with DDS, but to the extent that DDS is the most widely used anti-leprosy agent, it is likely to be the commonest initiator of the reversal reaction. Thirdly, the parallel tuberculosis story had shown that prolonged monotherapy was an almost certain prescription for the emergence of drug resistance. On any scale, this would be a blow of the most serious kind to leprosy treatment. There are now other preparations that are effective against *M. leprae*; rifampicin, for example, is bactericidal. But none combines the qualities of widespread availability, low cost and relative non-toxicity of DDS. Resistance to DDS was initially thought to be rare, but with the passage of time it is becoming clear that this is not so. In one study (Pearson

et al., 1975) about 2% of lepromatous patients have developed DDS resistance; as time passes, the cumulative total will almost certainly exceed this figure. Finally, the global picture today of leprosy and its consequences does not, after all, seem very different from the picture in 1952, at least to many experts. There are still millions of patients, many with serious deformities; early hopes that leprosy would now be well on its way to being a disease of the past have not been fulfilled. Yet we probably do have the means for at least some of these objectives. What then is the nature of the "application gap" in leprosy and how can we bridge it? What do we need to be able to do, between having DDS readily available on the one hand, and making sure that the right people take it in the right quantities, on the other?

First of all we have to be clear about what precisely we are trying to achieve. There is obviously no doubt that DDS is usually strikingly effective under stringently supervised clinical conditions; but only a tiny proportion of the world's leprosy patients can be treated under these rather exceptional circumstances. They live in, or, where they are rejected, alongside their own communities, and it is under these unsupervised and unsupervisable conditions that treatment will succeed or fail. Secondly, how should we measure success or failure? To the leprosy patient, what chiefly matters is whether he can live a normal and productive life within his accustomed family and community setting. In the world's endemic areas, this largely depends on the absence of significant deformity and disability, which ought increasingly to be one of our main measures of outcome. Other measures may be easier and quicker to make, and in certain circumstances are the appropriate ones—for example, the activity of skin lesions, or the number of viable bacilli. But at the end of the day, the leprosy patient's main worry is whether he has fingers or not, and whether he can use his hands and arms to earn his living; he himself is not primarily concerned with how many bacilli he is carrying, or even, usually, with the exact appearance and activity of his skin lesions. (There is very little systematic work validating the use of shorter-term microbiological and clinical endpoints as indicators of the long-term social outcome, and it would be of the greatest value to have this gap filled.) The use of new notifications, or of incidence, as an endpoint in domiciliary treatment programmes is relevant to the hypothesis that treating established cases will prevent new cases by interrupting transmission. Quite apart from the fact that figures of this kind may be difficult to interpret (Meade, 1974), it is arguable that prevention through treatment of established cases is unlikely to be achieved except under very exceptional circumstances; thus, judging community treatment by the yardstick of new notifications may be to attempt the confirmation of a hypothesis that is unjustifiably optimistic at the outset. There is, however, an even more basic reservation about the use of new notifications for assessing the impact of large-scale treatment programmes; since, by definition, these programmes aim to treat patients with established and manifest disease, they should therefore be evaluated by criteria relevant to this *therapeutic* objective, and not by those applicable to the objective of primary prevention. A realization that many large-scale programmes are using inappropriate measures of their success or failure, followed by a switch to more suitable indices, could be one of the most significant changes in modern approaches to leprosy.

It is interesting how closely these considerations mirror those encountered in other situations. In the case of ischaemic heart disease, for example, we have

exactly the same problem of having to try to introduce measures which to some extent work under close supervision—for example, dietary changes—into a largely unsupervised setting, where their acceptability and efficacy are very much more doubtful. And, secondly, there is the question of the appropriate measure of outcome; what the middle-aged man in Western society is likely to worry about is whether he is going to have a "coronary", or drop dead—not what the inside of his coronary arteries, or even his electrocardiogram, looks like. The "application gap" really does have common features across the world.

Let us take it, therefore, that while the "showcase" treatment scheme undoubtedly has its place in the study of leprosy, since this is where new ideas are tested and developed, what we must ultimately be concerned with is, first, the delivery of treatment in the much less favourable circumstances in which most leprosy patients find themselves; and secondly, with long-term social outcome.

Obviously, sheer inaccessibility, whether this is due to mountains, deserts, or the transformation of the landscape that rains may cause, has to be borne in mind. How often is it even practicable to reach patients? This is a local problem requiring local answers and a great deal of ingenuity. At the other end of the spectrum, is there a point of diminishing returns beyond which, in our anxiety to get patients to take the treatment we think they need, we actually put them off by expecting too much in the way of attendance and compliance?

LEPRA's scheme in Southern Malawi (Molesworth, 1969) has provided the opportunity to start looking at some of the questions. The data eventually available will enable outcome, measured in terms of the development of avoidance of deformities, to be assessed by various indices of regularity of DDS taking. Analyses are still in progress, but they show that many patients attend irregularly, and also suggest that regular attendance results, at best, in only marginally better outcome than irregular attendance. The precise interpretation of these results is still uncertain, but one possibility, obviously, is that DDS treatment under field conditions is not effective in terms of the onset or otherwise of deformity. Results of this kind (if confirmed) are based on the assumption that regularity of attendance, which is easy to record, is some indication of regularity of taking DDS. Unfortunately, this is very much an oversimplification. Ellard *et al.* (1974) developed a method for determining the regularity of DDS self-administration by out-patients, which was then applied in the setting of LEPRA's Malawi project (against a background of knowledge gained from work on tuberculosis that drug regimens that are successful in clinical trials may fail in the large-scale applied context because patients do not adhere to them). The results of this work strongly suggested that only about half of the total prescribed DDS doses had actually been taken within the day or so preceding the test. Low and Pearson (1974), reporting on a study in 89 out-patients in Ethiopia, found that only 42% of prescribed dosage had been taken in the previous 24 to 48 h. All this applies to patients who reach an out-patients clinic in the first place, so it is only too clear that the proportion of *all* those with leprosy who take DDS regularly must be very low. In addition, these considerations beg the still larger unanswered question as to what is the most effective DDS regimen anyway—in terms of dosage, frequency of attendance, etc. The "application gap" is all too evident. It must, however, be re-emphasized that leprosy is not by any means the only disease with a treatment compliance problem; on the positive side, in fact, it is one of a relatively small number of conditions where serious efforts have been made to study the matter.

There are obviously reservations and qualifications to be made about this kind of approach to evaluating leprosy treatment. The presence or absence of deformities is not the only yardstick by which we should judge the success of community treatment programmes, even though there is a strong case for regarding it as a very important one. It may be, for example, that lepromatous patients who attend regularly for treatment have less trouble from ENL and other complications than those who do not, and there are data (Quagliato *et al.*, 1970) which strongly suggest that bacteriological and clinical relapse are largely determined by irregularity of treatment. But we ought to be prepared to accept the possibility that within the framework and constraints of large-scale community schemes, outcome is not materially affected by regularity of treatment. It could be that there is a threshold level of total DDS dosage, which would obviously largely depend on regularity of attendance, below which treatment is ineffective; that domiciliary and community programmes simply cannot achieve this level; and that it was unreasonable at the outset to expect them to do so. Apart from its possible effects on clinical outcome, the combination of low dosage and irregular treatment is almost a guarantee for the promotion of resistance to DDS, and thus another pressing reason for being concerned with the problem. If rifampicin were widely used, an additional anxiety would be that irregular treatment is a potent cause of jaundice and other adverse reactions.

In view of what we know, or suspect, about the efficacy of leprosy treatment in the community, the assumption that the DDS treatment of established cases of leprosy is also the answer to the prevention of leprosy, by interrupting the chain of transmission, is to carry optimism to unrealistic lengths. If all patients took all their treatment, if they and their potential contacts could be confined to one area, and had no contact with anyone outside it, if there were no resistance problem, and so on, then the idea could bear further thought. But all the signs are that banking on this approach to prevention in the world's high incidence, mainland endemic areas is unjustified—and indeed it could be worse than simply this, since it could delay attempts to approach the problem in other ways.

So, 25 years into the DDS era, we have to take stock over a course of events which have, unfortunately, apparently left many of the early hopes unfulfilled. Some of the questions we now need to ask are difficult and perhaps painful. We still do not really know what the right clinical DDS regimen is, in terms of dose and duration; the main purpose of this paper has been to indicate that we know even less about the effective application of the optimal regime, whatever that turns out to be. What is the right balance between re-calling patients too infrequently and too often, and to what extent may this balance vary from one area or culture to another? What are the right yardsticks for success or failure? What is the role of other anti-mycobacterial agents such as rifampicin? For, vastly expensive as rifampicin is, by comparison with DDS, it could be that an increase in clinical effectiveness, together with a decrease in the length of time rifampicin is required, might prove that it is cost-effective. Should we devote increasing attention to studying the advantages and disadvantages of depot preparations? Is large-scale domiciliary treatment really the best use of resources, or would a return to the very close supervision of a smaller number of patients be preferable? Is the integration of leprosy treatment into the health services as a whole really likely to be effective, as well as merely well-intentioned? These are the largely unanswered questions which constitute the "application gap" in leprosy,

separating what is theoretically effective from its practical implementation, and which exemplify so many of the problems of modern medicine throughout the countries of the world, affluent or poor. Trying to answer them will be challenging and stimulating; in the case of leprosy, increasing attention should be given to the judicious use of the randomized controlled trial in planning the delivery of care (Fox, 1971; Cochrane, 1972), as well as in the more familiar field of assessing antibacterial agents.

The problem of treating leprosy effectively should not, however, distract us from what is in many ways an even more pressing question. Lord Rosenheim's words, quoted earlier in this paper, really identified the "application gap" and the benefits to be derived from bridging it, quite apart from those of acquiring new knowledge. The extract has, however, often been quoted out of the wider context of the passage as a whole, which also pointed out that: "It must increasingly be the purpose of the medical profession, and of all who work with them, to aim at prevention rather than cure", and this, of course, means the acquisition of new knowledge. There is undoubtedly new knowledge of the greatest relevance still to be gathered about leprosy, whether this is to do with the development of a vaccine, with the other factors, besides *M. leprae* itself, which determine clinical onset in those exposed, or with the social and economic changes which have been associated with eradication in previously endemic areas. The preventive approach is, after all, the one we need to pursue as hard as we can in order eventually to bypass the extremely difficult treatment problems with which this paper has been mainly concerned. (An almost identical argument could be developed around several other diseases.) Leprosy has always been a disease of uncertainties, paradoxes and the unexpected. It may be that in the not too distant future, leprologists thinking about more fundamental issues at the same time as they grapple with the problem of delivering effective care, will come up with new knowledge of the kind required to make the prevention rather than the treatment of leprosy the more realistic objective.

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On the Mode of Transmission of *Mycobacterium leprae*

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The finding that in patients with lepromatous leprosy much larger numbers of bacilli are released from the nasal mucosa and from the milk ducts of lactating mothers as compared with those present on the surface of the skin, suggests the possibility of transmission by droplet infection and by breast feeding and the consequent possibility that the primary lesions are located in the respiratory and gastro-intestinal tract and that the skin lesions are secondary lesions. Clinical and epidemiological evidence against this hypothesis is presented, and it is concluded that droplet infection via the respiratory tract is not a common mode of transmission, and the present trend of abandoning segregation and other restrictive measures against leprosy patients should not be reversed.

Introduction

The concept that leprosy is a feebly contagious disease, mainly spread by prolonged, intimate direct skin contact between highly bacilliferous patients and susceptible healthy subjects, can no longer be held to be valid. It has been difficult for some time to maintain the concept of feeble contagiousness in view of the epidemics of leprosy recorded from various countries (Wade and Ledowsky, 1952; Davey, 1957; Leiker, 1971) with 10–30% of the population developing symptoms of leprosy within a few decades of the introduction of the disease into the community. Recently, Godal *et al.* (1974) produced immunological evidence that sub-clinical infections are common. In people who had lived for some years in a country with endemic leprosy, a significantly higher percentage of positive lymphocyte transformation tests, after incubation with *Mycobacterium leprae,* was found as compared with recent immigrants from non-endemic areas. Apparently the rate of transmission of *M. leprae* is significantly higher than is indicated by prevalence surveys.

The concept of prolonged, intimate contact is also seriously challenged by the actual findings in epidemics of leprosy. Frequently, in whole-population surveys of villages with a very high leprosy prevalence, only a single one, or at most very few highly bacilliferous patients are found, and not rarely none are encountered, even though cases of leprosy are to be found in nearly all families in the community. It is inconceivable that so many patients in unrelated families can have had prolonged, intimate contact with the few highly bacilliferous patients

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present, because the intensity of contact in such communities is largely governed by family relationships. It is much more likely that in a high proportion of the patients leprosy was transmitted after short, superficial, direct contact with the few highly bacilliferous patients or with other, only moderately strong bacteriologically positive patients, or that indirect contact plays a major role, e.g. transmission by flies (Geater, 1975).

In the Netherlands, more than 50% of the 1000 recorded patients–immigrants from endemic countries were unable to recall any prolonged, intimate contact with highly bacilliferous patients, and in the great majority there is no reason to doubt their statements. Some Dutch patients have contracted leprosy after a brief sojourn in an endemic country, without being able to recall any contact at all with leprosy patients. One Dutchman, who had never left the country and who had no known contact with leprosy patients, developed lepromatous leprosy (Beek, 1961).

Recently, the concept of skin contact as the main mode of transmission has been challenged as well. Pedley (1970) has shown that the number of bacilli present on the surface of the skin of highly bacilliferous patients is relatively low as compared with the large numbers of bacilli released by the nasal mucosa. Large numbers of bacilli are also present in the secretory cells of the milk glands of lactating lepromatous mothers (Pedley, 1968). The theoretical possibility of spreading *M. leprae* by droplet infection is supported by experiments in mice with aerosols containing *M. leprae* (Rees *et al.*, 1976). These findings suggest that *M. leprae* might be spread by droplet infection and by breast feeding, and that the primary lesion of leprosy is located in the respiratory or in the gastro-intestinal tract and not in the skin. Rees and Meade (1974) have stated that the attack rate of leprosy and of tuberculosis are similar and that this finding, though not proof of identical modes of spread, is consistent with this possibility.

First, the possibility of transmission via the skin will be discussed.

Transmission via the Skin

It has been assumed that *M. leprae* is unable to pass through unbroken skin. It should, however, be emphasized that the skin is seldom unbroken, minor scratches and wounds usually being present.

In lepromatous leprosy large numbers of bacilli are usually present in the upper part of the corium. Though separated by a subepidermal zone which is usually free of bacilli, a minor wound or scratch may bring bacilli to the surface of the skin. Large numbers of bacilli may also be present in superficial lesions in reactive lepromatous patients, especially if the reaction is vesicular, bullous or ulcerating. Such lesions are most vulnerable and rupture of the bullae results in the temporary presence of large numbers of bacilli on the surface of the skin. But also in the average non-reactive lepromatous patient small numbers of bacilli may constantly reach the surface of the skin.

In skin sections, bacilli are not infrequently found in the epidermis. Occasionally they have also been seen in the subcorneal layer and even in the corneal layer of the epidermis. Bacilli have also been found in the lumen of the sweat ducts and in the orifices of sweat ducts.

Though, admittedly, the number of bacilli thus reaching the surface of the skin is low as compared with the surface of nasal mucosa, the number is sufficiently

high for the transmission of *M. leprae*. In experiments with mice it has been shown that multiplication of *M. leprae* can be obtained after inoculation of very small numbers of bacilli only (Shepard and McRae, 1965). Therefore, the transmission of *M. leprae* via the skin remains a definite possibility.

In the following section evidence is presented against transmission via the respiratory or gastro-intestinal tract.

Clinical Course of Leprosy

In a very high proportion of patients, probably in the great majority, the first clinical manifestation of the disease is a single skin lesion or, less frequently, a few skin lesions. In epidemics of leprosy and in children the first and only symptom of the disease is a single tuberculoid patch in a high proportion of the patients.

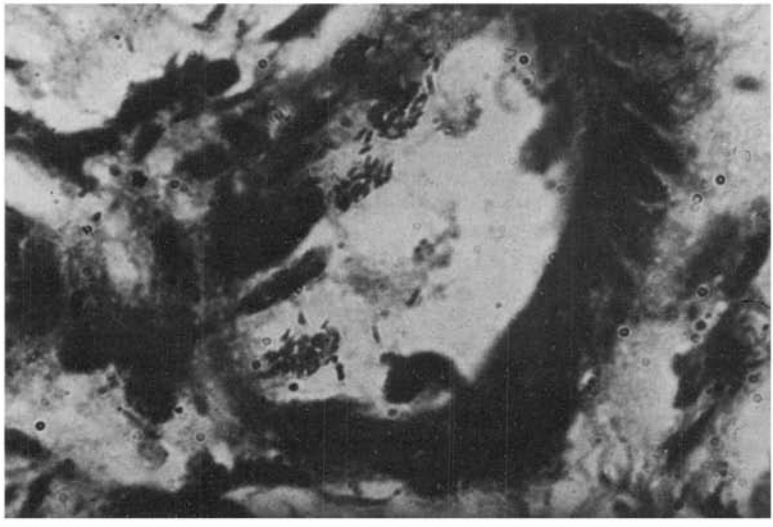

Fig. 1. Histopathological section showing *M. leprae* being released into a blood vessel. FFW. x 100.

In a small proportion of the patients the disease is progressive. However, the single patch is usually not followed by a second single lesion, but by a crop of multiple new lesions, or by successive crops of new lesions. Such a course is compatible with the hypothesis that the first skin lesion is a primary lesion, indicating the site of inoculation, and with the new lesions being the result of haematogenous spread of several bacilli at a time from the primary lesion.

Histopathologically bacilli are frequently found in endothelial cells of blood vessels. It is likely that they are usually released only after the number has grown to the extent that the cell has been damaged, or after aging of the cell. Occasionally the release can be seen in histopathological sections (Fig. 1). Apparently it is the rule, rather than the exception that not one bacillus, but several bacilli are released at a time, producing multiple new lesions at different

sites. The course of the disease is difficult to explain by the hypothesis that the primary lesion is located in the respiratory tract or in the gastro-intestinal tract and that the first skin lesions are in fact secondary lesions. It is inconceivable that so frequently only a single bacillus would escape from a lesion in these tracts, causing a single skin lesion, whereas so frequently many bacilli escape at a time from a first skin lesion causing multiple new skin lesions. The course of the disease is compatible with the hypothesis that the first skin lesion, as a rule, is a primary lesion.

The Sites of the Skin Lesions

The site of primary lesions is governed by the chance of inoculation. The site of secondary lesions, resulting from haematogenous spread, is influenced by the preference of *M. leprae* for the peripheral parts of the body. Consequently, a different distribution between the primary and secondary lesions in the individual patient, and a regional *variation* in the distribution of primary lesions is to be expected, the latter being influenced by various sociological factors such as customs influencing contact between people, the use of protective clothes, the mode of carrying and handling children, etc. The course of lower resistant (sub-polar) tuberculoid leprosy (Leiker, 1964) and of borderline tuberculoid leprosy, is illustrative.

Sub-polar tuberculoid leprosy usually starts with a single, or less frequently, with a few small indeterminate or tuberculoid lesions.

This first lesion may be located anywhere on the body. There is no obvious preference for the periphery of the body. Lesions on the trunk are about as common as those on the extremities or on the head. There is considerable regional variation in distribution. Single lesions on nose, ear, elbow, knee, hand or foot are not very common. In a high proportion of the patients the first lesion is followed by one or more successive crops of new lesions. The new lesions, however, are not distributed at random. A definite preference for the periphery of the body is seen. After a single crop of new lesions in lower resistant tuberculoid leprosy, some lesions may be seen on the trunk, more often on the buttocks than elsewhere on the trunk and the distribution of the lesions remains asymmetrical. However, many more lesions are seen on the extremities, often with a marked tendency towards symmetry. Lesions are common on the hands, feet, elbows, knees, ears and the central part of the face, indeed "the peripheries of the peripheries" are predilection sites.

This distribution strongly suggests that the first skin lesion is a primary lesion and that the new lesions are secondary lesions resulting from haematogenous spread of bacilli from the first skin lesion. If the first lesions were the result of dissemination from a primary lesion in the respiratory tract or the gastro-intestinal tract one would expect no difference in distribution between the first skin lesion and successive skin lesions and that both would show the same preference for the most peripheral parts of the body.

Epidemiology

In the last 30 years, in the Netherlands more than 200 immigrant patients with "open" leprosy, many of them not on treatment immediately after immigration and some on sulphone treatment but resistant to sulphones, have moved freely in

the community. In the crowded streets, while using public transport, during daily labour in factories, at school, etc. the conditions for the spreading of an airborne causative agent undoubtedly are favourable. If leprosy is an airborne disease, many thousands of people must have been exposed to infection. However, only once has leprosy been diagnosed in a Dutchman who has never been in an endemic country. Only very few new patients have been found outside the families of known patients. Lack of susceptibility cannot be the explanation, judging from the prevalence rates in the different ethnic groups of immigrants (Indo-Europeans 1‰, Ambonese 1.5‰, West Indians 5‰). The degree of susceptibility to *M. leprae* of the Dutch population is not known but the fact that at least 80 Dutch people contracted leprosy in endemic countries indicates that their susceptibility is far from negligible.

In the light of these observations, it appears most unlikely that in general the modes of spread of tuberculosis and leprosy are similar.

The history and the epidemiology of leprosy in parts of West New Guinea (Irian Yaja) were studied by Leiker (1960, 1971). It was possible to reconstruct in detail the course of the disease since its introduction into the community and to define with reasonable accuracy when each patient developed the first symptoms of the disease, what his family relationships were and in which house he had lived. In the Wandamen Bay area the disease was obviously largely focalized in certain families and in certain houses.

No correlation was found between the prevalence in one house and the unrelated neighbouring houses, but a correlation was present between one house and other, more distant, related houses. Family relationship, which primarily governs the degree of contact between people, was obviously more important than the distance between homes. Frequently a high prevalence was found in one clan and a low prevalence in another clan sharing the same village.

Difference in susceptibility is not a likely explanation of these findings, because once leprosy was introduced into a hitherto unaffected family, it usually spread within the family.

The population of Wandamen Bay lives in a row of a dozen villages along the beach. The administrative centre, shops, market and medical centre are in the 2 most northern villages. The third in the row is the leprosarium. Year after year, many people, who were living in the south, have made weekly visits to the northern villages, frequently taking the short cut through the leprosarium for visiting relatives or for reasons of convenience. If leprosy is an airborne infection one would expect a much more even distribution of the disease in the southern villages. The epidemiological evidence is not in favour of an airborne route of transmission.

Gastro-intestinal Infection

It is also not likely that leprosy is frequently transmitted from lepromatous mothers to their infants via the breast milk. Because of the large numbers of bacilli present in the milk glands one would expect transmission of *M. leprae* to occur soon after birth, and consequently a high incidence of leprosy in children around the age of 4-5 years. In practice, however, the incidence of leprosy in children below school age is relatively low. There is also no evidence of a particularly high incidence of leprosy in common feeding groups, or evidence that food, water or beer sellers suffering from leprosy are a high risk for their customers.

Although it is likely that *M. leprae* is frequently inhaled or digested, the environmental conditions in the respiratory and gastro-intestinal tract are probably not favourable for survival of the bacilli.

The foregoing arguments do not challenge the importance of the nasal mucosa as a very important, if not the most important source of *M. leprae.*

If hygiene is deficient the skin may easily become contaminated with nasal discharge or saliva, whether directly or indirectly, e.g. by flies feeding on nasal discharge (Geater, 1975), and the number of bacilli thus reaching the skin may be higher than those reaching the surface by other routes.

Recapitulation

The importance of the nasal mucosa and the milk ducts of lactating mothers as sources of *M. leprae* is not challenged, neither the likelihood that *M. leprae* found on the skin may frequently have originated from the nasal mucosa. It does not however necessarily follow that as *a general rule* the primary lesion of leprosy is located in the respiratory or gastro-intestinal tracts and that skin lesions are secondary. On the contrary there is considerable evidence against this hypothesis.

EPIDEMIOLOGICAL EVIDENCE

(a) The course of leprosy in a closely observed area of Irian Yaja, Indonesia, over a period of 30 years does not appear to be consistent with transmission by droplet infection.

(b) In The Netherlands more than 200 patients with "open" leprosy have moved freely in a crowded community during the past 30 years but only one definite autochthonous case of leprosy has been found. This does not suggest that droplet infection is an important mode of transmission of leprosy.

(c) The average age at onset of the disease in children of lepromatous mothers does not correspond with the average incubation period of the disease. If the disease was transmitted by the breast milk during the early months of life one would expect more cases to arise at around 4–5 years of age, whereas in practice its onset is usually later than this.

CLINICAL EVIDENCE

(a) In a very high proportion of patients with tuberculoid leprosy, in particular in children, the first and only symptom of the disease is a single skin patch. In sub-polar and borderline tuberculoid leprosy the single first lesion is followed usually not by a single second lesion but by a crop of new skin lesions indicative of haematogenous spread of bacilli. Apparently several bacilli are usually released at a time from the primary lesion, wherever this is located. Such a course is compatible with the hypothesis that the first skin lesion is a primary lesion, because if the primary lesion was located in the respiratory or gastro-intestinal tract one would expect more frequently an onset of the disease with multiple skin lesions.

(b) The distribution of single lesions varies from area to area, but the peripheral parts of the body are not sites of predilection (Bechelli *et al.,* 1973; Ganapati, 1976). The distribution of secondary skin lesions however shows a definite preference for the extremities and head. If the primary lesion was located in the internal tracts, and skin lesions are secondary, one would expect to find the first and single lesions predominantly at the periphery of the body.

BACTERIOLOGICAL EVIDENCE

It has been shown from experiments with mice that inocula containing as few as 10–100 solid bacilli produced "takes" consistently and that the minimum infectious dose of solid bacilli was 3.4 to 34 (Shepard and McRae, 1965). The number of bacilli reaching the surface of the skin from ulcerating or ruptured vesicular lesions in reactive patients or those with histoid leproma, in addition to those present as a result of minor injury or contamination with nasal discharge or saliva, is sufficiently high to provide an adequate inoculum. Transmission via the skin therefore remains a definite possibility.

The Need for Caution

So far there is no conclusive evidence that leprosy is transmitted by droplet infection from one human being to another. Until such evidence exists the utmost discretion is needed in publicizing this possibility.

The present trends towards abandoning segregation and other restrictive practices on the part of health authorities have been hardly won, but have been of immense importance in the fight against leprosy. They must not be jeopardized except for the most compelling reasons. The suggestion that leprosy can be spread by droplet infection will have far-reaching effects. Implicit in it is the threat that restrictive measures should be re-introduced. This must profoundly affect the existing basis for leprosy control programmes which relies on the co-operation of patients in the early stages of their infection. With fear once again an important factor in their lives the motivation for co-operation disappears. The effect on the general public is equally profound. The admission of children with early leprosy to general schools, the employment of leprosy patients, the admission of leprosy patients to public places and public transport, even the willingness of nurses to care for leprosy patients in general hospitals; these are all facets of the situation which have to be reckoned with. Until such time, therefore, that conclusive evidence is found that leprosy can be spread by droplet infection from one person to another and the conditions in which this can occur are determined, great caution is needed in publicizing this hypothesis.

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Phagocytosis in Leprosy I. The Levels of "Diaphorase", β-Glucuronidase, Acid Phosphatase, Alkaline Phosphatase and Lipase in Circulating Leucocytes

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Peripheral blood leucoytes were obtained from 18 patients with active lepromatous leprosy and 18 healthy volunteers. These cells were disrupted and served as the source of β-glucuronidase, β-galactosidase, acid phosphatase, alkaline phosphatase and lipase activities. A quantitative NBT test was performed with freshly prepared intact cell suspensions. Although most of the studied activities were slightly increased in the leprosy group, the differences resulted in non-statistical significance. Other enzymatic and metabolic activities have to be studied to corroborate that leucocytes from leprosy patients behave in an essentially normal manner.

Introduction

Phagocytosis of pathogenic bacteria is a first line mechanism for the host defense. Endocytosis itself, however, is not enough for the control of disease unless it is followed by the normal metabolic and bactericidal changes induced within the phagocytic cell. Some pathological situations have been explained on the basis of metabolic defects which impair the phagocytes' function even when endocytosis seems to be normal (Stossel *et al.*, 1972; Kaplan *et al.*, 1968; Holmes *et al.*, 1967; Cooper *et al.*, 1972, among others). However, most of these situations seem to have an intrinsic defect rather than being the result of an induced impairment due to some external aetiological agent of disease.

Lepromatous leprosy is an interesting disease because, among other things, some reports have appeared suggesting that the difficulty in controlling the disease could be explained on the basis of a defect in the function of the host's macrophages (Beiguelman, 1967; Barbieri and Correa, 1967; Hanks, 1947; Convit

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et al., 1972, 1974). This defect could be a primary one, induced by interference of the phagocytic cell metabolism by the mycobacterial metabolism, or it could be the result of a lack of T-lymphocyte-dependent macrophage stimulation (Godal *et al.*, 1971*a*, 1971*b*), as it has been shown that patients with lepromatous leprosy have a depressed cell-mediated immunity: low numbers of direct rosettes (circulating T-lymphocytes) (Dwyer *et al.*, 1973; Lim *et al.*, 1974*a*), depressed ability to reject allogeneic skin grafts (Job and Karat *in* Hart and Rees, 1967), anergy to *M. leprae* antigens (Mitsuda, 1953), and other aberrations in the cellular immunity (Turk, 1969; Turk and Waters, 1969).

When an impairment in phagocytic function is suspected to play a role in a given pathological state, it could be normative to survey the activity of the whole phagocytic population before attempting to analyze the function of a particular type of cell. As this is the case in lepromatous leprosy it was decided to study some metabolic and enzymatic activities in blood leucocyte populations (in which about 80% are phagocytic cells) prepared from a number of patients with the disease and compare such activities with those found in cell preparations from healthy individuals. The study of leucocytes was also decided because viable blood-borne *M. leprae* have been found in circulating phagocytes from patients with lepromatous leprosy who have received no chemotherapy. Intracellular parasites whose viability has not been definitively ruled out have also been observed in leucocytes from patients treated with dapsone or rifampin (Drutz *et al.*, 1974).

As polymorphonuclear (PMN) leucocytes are the predominant cell type in peripheral blood, the results will be largely indicative of the activity of these cells, but the possibility remains that some defect (if any) in another cell type (i.e. the monocyte) may reflect in the overall activity of the complete leucocyte population.

Materials and Methods

SUBJECTS

Eighteen patients with polar lepromatous leprosy (both diffuse and nodular types of leprosy included) were studied. This group has been under medical control at the Centro Dermatológico Pascua of Mexico City, and represented an heterogeneous group in relation to age, sex, duration of disease and clinical status at the moment of the study. Most of the patients, however, were under conventional treatment (DDS, 25–50 mg daily) and all of them presented a still active form of the disease. A very few cases were complicated with some form of leprosy reaction (mainly erythema nodosum leprosum).

Eighteen healthy volunteers (personnel and undergraduate students) with no familial antecedents of mycobacterial disease (leprosy or tuberculosis) of both sexes, and with an average age of 24 years, served as controls.

CELL PREPARATIONS

About 200 ml of blood was collected in blood collection units with citrate as the anticoagulant (Bolsang, Fenwal System, CPD, Travenol Laboratories, Costa Mesa, California, U.S.A.). The citrate-treated blood was transferred to siliconized glass cylinders and left undisturbed to sediment at 37° C for 120 min. The leucocyte-rich plasma was aspirated, poured into siliconized glass centrifuge bottles, treated with 2 vols of 0.87% ammonium chloride to disrupt erythrocytes, washed twice with citrate-saline solution (CSS, 0.4% sodium citrate in 0.85% sodium chloride), resuspended in about 10 ml of CSS, counted in a haemocytometer (differential counts were done in smears stained with Wright's dye), quick frozen and stored at −70° C until used.

Just before their use, the cell suspensions were thawed, diluted as required, briefly sonicated to disperse aggregates (30 s, 7 mA, d.c.) in a S-125 Sonifier (Branson Sonic Power, Denbury, Conn., U.S.A.) and the finely dispersed suspension was kept in an ice bath while in use. This sonicated cell suspension was employed for the assay of the following enzymatic activities: alkaline phosphatase (Enzyme Commission, EC, number 3.1.3.1), acid phosphatase (EC 3.1.3.2), β-galactosidase (EC 3.2.1.23), β-glucuronidase (EC 3.2.1.31) and lipase (a β-naphthyl laurate hydrolase, see Results). For the NBT test the cell samples were freshly prepared and received a somewhat different treatment as indicated below.

QUANTITATIVE NITROBLUE TETRAZOLIUM (NBT) TEST (Baehner and Nathan, 1968)

A 20-ml sample of peripheral blood was collected in plastic disposable syringes containing 20 iu per ml of heparin. The syringe was inverted, and the red cells were sedimented for the next 2 h at 37° C. The supernatant plasma was decanted through an 18-gauge needle bent to an angle of 90° into siliconized 50-ml glass centrifuge tubes. After 2 vols of 0.87% ammonium chloride were added to the plasma, the tubes were inverted 5 times and centrifuged immediately thereafter for 5 min at 1400 rev/min (radius = 16 cm) at 4° C. The supernatant plasma was aspirated and the cell pellet was washed twice with Krebs-Henseleit bicarbonate buffer, pH 7.4 (Dawson, 1969), containing 0.2% of glucose. The number of leucocytes per ml was calculated and diluted to 2.0×10^6 per ml. To duplicate siliconized 15-ml conical centrifuge tubes the following were added: 0.4 ml (0.35 ml in tubes containing latex particles) of the buffer, 0.1 ml of 0.01 M potassium cyanide, 0.4 ml of 0.85% sodium chloride containing 0.1% NBT (Sigma N 6876), and 0.05 ml of washed 0.8 μm latex spherules in the tubes designated for phagocytosis. The duplicate tubes labelled "resting" did not contain latex particles. This mixture was incubated in a water bath at 37° C for 15 min, then, 0.1 ml of the previously prepared cell suspension was added to each tube. The reaction was allowed to proceed for 15 min, then it was stopped by the addition of 2.0 ml of 2.5 N HCl. The tubes were then centrifuged at 2000 rev/min for 15 min. The supernatant was poured off and the sediment was extracted for 20 min with 4.0 ml of pyridine in a boiling-water bath under an exhaust hood. The tubes were centrifuged again at 2000 rev/min for 15 min, and the optical density (*D*) of the purple colour of the reduced NBT was determined in a spectrophotometer at 515 nm, against a pyridine blank. Resting and phagocyting values were obtained and the difference (increment in *D* per 15 min per million leucocytes) was calculated.

LIPASE (adapted from Nachlas and Seligman, 1949)

In 16 x 150 mm test tubes, 2.0 million leucocytes in 0.5 ml of physiological saline solution (PSS) were incubated at 37° C for 60 min with 3.0 ml of β-naphthyl laurate substrate (10 mg of β-naphthyl laurate, Sigma N 9375, were dissolved in 10 ml of acetone, added through a submerged pipette into 50 ml of an agitated solution consisting of 0.06 M veronal buffer, pH 7.4, and finally diluted to 100 ml with water). At the end of the incubation period, 0.5 ml of a freshly prepared solution containing 2.0 mg of Naphthanil Diazo Blue B (NDBB, Sigma D 3502) were added and the tubes were shaken. After 3 min the diazoreaction was stopped by adding 0.5 ml of 40% trichloroacetic acid (TCA), and the colour was extracted with 5.0 ml of ethyl acetate. The latter was cleared by a brief centrifugation and its *D* was read immediately thereafter at 540 nm against a blank without enzyme.

ALKALINE PHOSPHATASE (adapted from Manning *et al.*, 1966)

In 16 x 150 mm test tubes, 6.0 million leucocytes in 0.1 ml of PSS and 1.0 ml of the stock buffered substrate [see (a)] were incubated for 60 min at 37° C. At the end of the incubation time, 4.0 ml of glycine buffer, pH 11.2 [see (b)], were added to develop colour (the final pH of the reaction mixture was around 10.7). After thorough mixing, the tubes were centrifuged at 2000 rev/min for 10 min and the *D* was read at 550 nm using the control without enzyme as the blank. (a) The stock buffered substrate contained 1.968 g of Tris (hydroxymethyl) aminomethane (Sigma T 1503), 30 mg of sodium phenolphthalein diphosphate (Sigma P 9875), 100 mg of magnesium sulphate, and 700 mg of gelatin (Difco B 143). The pH was adjusted to

9.6 and the volume brought to 100 ml. (b) The glycine buffer, pH 11.2, was prepared by dissolving 9.9 g of glycine, 7.19 g of NaCl and 40 g of sodium pyrophosphate (Sigma T 6379) in 900 ml of distilled water. While stirring, sufficient 30% NaOH (approximately 17 ml) was added to adjust the pH to 11.2 and the volume brought to 1000 ml.

ACID PHOSPHATASE (adapted from Seligman *et al.*, 1951)

In 16 x 150 mm test tubes, the following were incubated for 30 min at 38°C: 2.8 ml of 0.1 M acetate buffer (pH 5.1) containing 1.0 million leucocytes, 0.1 ml (0.15 mg) of β-naphthyl phosphate (Sigma N 7375) and 0.1 ml (1.0 mg) of $MnCl_2$. After 1.0 ml was removed to check the pH, the reaction was stopped by adding 2.5 ml of 0.05 M veronal buffer (pH 8.5) which brought the pH of the reaction mixture to about 7.4. Diazocoupling was performed by adding 0.5 ml of NDBB reagent (80 mg in 20 ml of cold water) prepared just before use. After 3 min the reaction was stopped with 0.5 ml of 40% TCA and the colour was extracted with 6.0 ml of ethyl acetate. This was cleared by centrifugation (2000 rev/min, 15 min) and its *D* was read immediately thereafter at 540 nm against a blank without enzyme.

β-GALACTOSIDASE (adapted from Yarborough *et al.*, 1967)

Test tubes containing the following were incubated for 1 h at 38°C: 1.0 ml of PSS containing 8.0 million leucocytes, 1.5 ml of 0.1 M phosphate citrate buffer (pH 4.1) and 0.5 ml of *o*-nitrophenyl-β-D-galactoside (4.5 mg per ml, Sigma N 1127). At zero and 1 h, 1.0-ml samples were removed, mixed with 1.0 ml of 5% TCA, and centrifuged (2000 rev/min, 15 min). One and a half ml of sodium hydroxide-glycine reagent were added to 1.5 ml of the supernatant fluid. The reagent contained 0.4 M glycine and 0.8 M NaOH in amounts required to have a pH of 11.4. The resulting yellow colour was read at 420 nm against a blank without enzyme.

β-GLUCURONIDASE (Yarborough *et al.*, 1967)

Test tubes containing 3.0 million leucocytes in 1.2 ml of PSS, 1.5 ml of 0.1 M acetate buffer (pH 4.5) and 0.3 ml of 0.01 M phenolphthalein-β-glucuronic acid (Sigma 105-4, pH 7.0), were incubated for 2 h at 38°C. After 1.0 ml was removed to check the pH, 2.0 ml of 5% TCA were added and the tubes were centrifuged (2000 rev/min, 15 min). Two millilitres of alkaline reagent were added to 1.0 ml of the supernatant. The reagent contained 1.0 M glycine and 0.4 M NaOH, approximately 1 : 4, so that the pH was 10.4. The resulting purple colour was read at 540 nm in a photocolorimeter against a blank without enzyme. Zero hour samples were consistently colourless as reported by Yarborough *et al.* (1967).

ENZYMATIC ACTIVITIES

One unit was arbitrarily defined as the amount of enzyme (number of disrupted leucocytes) that should cause an absorbance increase of 1.00 under the conditions of the assays. All determinations were performed in the 0.1–0.4 range where linearity was held. The specific activity was defined as the total units of activity per mg of protein. Protein was determined by the Lowry procedure (1951), using bovine serum albumin as a reference solution.

STATISTICAL ANALYSIS

The Student *t*-test for small samples was used to calculate the level of significance (*P*) of every determination done between normal and leprosy populations. Because of the natural internal variation within groups a correction was introduced: the control group was randomly divided into 2 subgroups and, for each assay performed, the Student *t*-test was used to calculate the level of significance between subgroups. This value served to correct the *P*-values between control and leprosy groups. In this paper, the reported *P*-values are the corrected ones.

Results

NITROBLUE TETRAZOLIUM TEST

Eighteen patients with lepromatous leprosy and 18 healthy (control) individuals were included in the test. Both control (*N*) and leprosy (*L*) populations were able to reduce the oxidized NBT dye (Fig. 1). Although a certain difference between *L* and *N* groups could be observed, this difference resulted in non-statistical significance. Table 1 shows the activity found in each

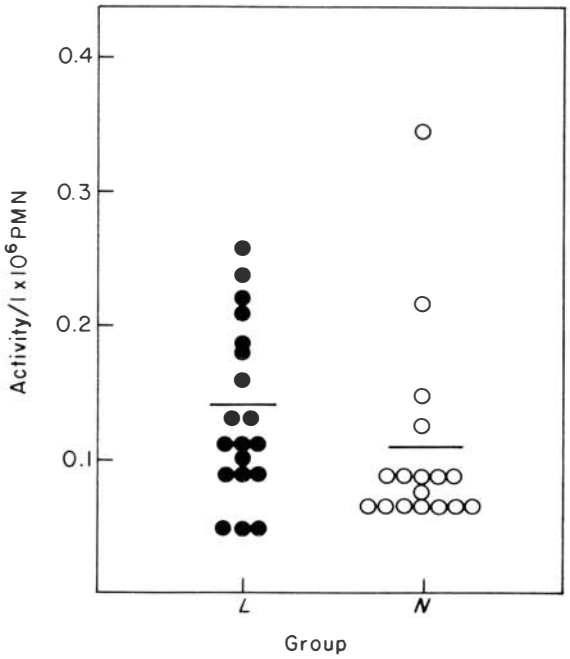

Fig. 1. NBT reduction by leucocytes from patients with lepromatous leprosy (*L*) and by leucocytes from normal individuals (*N*). The activity is given as the increment in *D* (phagocytosis minus resting) per one million leucocytes, per 15 min incubation at 37°C. Horizontal lines are the mean value.

group (range, mean value ± the standard error, and the *P*-value). The activity is given as the increment in D_{515} nm (phagocytosis minus resting) per one million leucocytes, per 15-min incubation at 37°C. It can be deduced that, as a group, lepromatous patients are not defective in their circulating phagocytic cells' ability to endocytose latex spherules, nor in their ability to undergo the oxidative changes that accompany the phagocytic process and which permit, among other things, the reduction of the oxidized NBT dye.

TABLE 1

Reduction of the Nitroblue Tetrazolium dye by leucocytes from healthy and lepromatous individuals

Group	No. of individuals	Activity * Range	Mean ± S.E.	*P*
Leprosy (*L*)	18	0.051–0.262	0.141 0.015	0.5
Normal (*N*)	18	0.042–0.351	0.110 0.017	

* Increment in *D* (phagocytosis minus resting) per one million leucocytes, per 15 min incubation at 37°C. Other conditions were as described under Materials and Methods.

LEUCOCYTE HYDROLASES

Figure 2 shows the results when the alkaline phosphatase (AlPh), the acid phosphatase (AcPh), the β-glucuronidase (β-Glu), the β-galactosidase (β-Gal) and the lipase (Lip) activities were assayed. It can be observed that, for every enzyme, the cell population derived from the leprosy group (*L*) showed a somewhat higher activity than that found in the normal group (*N*). However, when these differences were analyzed they resulted in non-statistical significance. The mean specific activity (total units of activity per mg of protein), the standard error, the number of samples assayed and the *P*-value, are given in Table 2. Each assay was performed at least twice and the reported results are those obtained with an optimal number of cells as determined by preliminary experiments. It is clear that there is not a significant difference between groups *L* and *N* for most of the assayed enzymatic activities although, in the case of the lipase, a certain difference was observed as judged from the *P*-values: 0.05 (uncorrected) and 0.1

TABLE 2

Some enzymatic activities present in leucocytes from patients with lepromatous leprosy in comparison with those found in healthy individuals

Enzyme	Specific activity in * Leprosy	Normals	*P*
Alkaline phosphatase	1.540 ± 0.619 (11)	0.738 ± 0.220 (13)	0.5
Acid phosphatase	3.290 ± 0.897 (12)	2.449 ± 0.322 (12)	0.9
β-Glucuronidase	0.410 ± 0.053 (12)	0.365 ± 0.028 (11)	0.6
Lipase	1.472 ± 0.272 (10)	0.800 ± 0.095 (11)	0.1
β-Galactosidase †	0.088 (5)	0.095 (14)	

* The specific activity is given as the total units of activity per mg of protein. The mean value and the standard error are shown and the number of samples analyzed is given in parenthesis.

† Because of the small number of samples included (see text) neither the standard error nor the *P*-value were calculated.

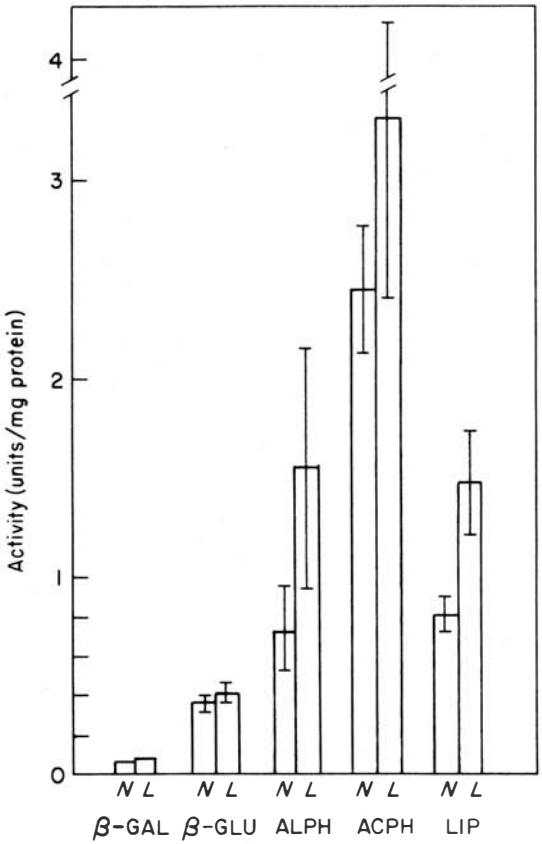

Fig. 2. Levels of β-galactosidase, β-glucuronidase, alkaline phosphatase, acid phosphatase and lipase in leucocytes from patients with lepromatous leprosy (*L*) and normal individuals (*N*). The activities are given as the total units per mg of protein (see Materials and Methods). The mean value and the standard error are shown.

(corrected). Because several authors consider that the technique used in this study (β-naphthyl laurate as the substrate; Nachlas and Seligman, 1949) is related with an esterase more than with a lipase, we are now using a natural complex substrate (coconut oil) and the results will be presented in a further communication. The assay for β-Gal required a large amount of cells. As described under Materials and Methods, 8.0 million leucocytes had to be used in the test and even with this number, *D* readings lower than 0.10 were obtained. Although the mean specific activity in *L* and *N* groups showed no apparent difference, because of the small number of samples a statistical analysis was not possible.

Discussion

Some reports have previously appeared regarding the ability of PMN from leprosy patients to reduce the NBT dye (Lim *et al.*, 1974*b*; Goihman-Yahr *et al.*, 1975). This test has been used to measure the overall oxidative changes that

follow the phagocytic process and which are related to the normal function of phagocytes. These changes include an increase in oxygen and glucose consumption, an increase in the production of hydrogen peroxide and other bactericidal peroxides, the activation of the "hexose monophosphate shunt", and other related changes (see DeChatelet, 1975, for a recent review). Under these conditions, reduced NAD and NADP co-factors reach high levels and they can be used, among other things, to reduce the oxidized NBT dye, providing adequate levels of "diaphorase" (the total of all enzymes that can catalyze a reaction between NBT dye and reduced pyridine nucleotides to give the insoluble blue formazan) are present. Compared with controls, leucocytes from lepromatous patients have normal levels of both reduced co-factors (NADH and NADPH) and "diaphorase" activity as can be deduced from their ability to efficiently reduce the oxidized NBT dye (Lim *et al.*, 1974*b*; Goihman-Yahr, 1975; this paper, Fig. 1).

Peripheral leucocytes of leprosy patients are not depressed in their ability to produce normal levels of lysosomal hydrolytic enzymes. This seems to be a logical finding because (a) the leprosy bacillus does not primarily parasitize polymorphonuclear leucocytes but monocytic leucocytes and tissue macrophages, and (b) the PMN is the predominant phagocytic cell in peripheral blood. On the other hand, it has been demonstrated that only a small proportion (0.1–0.3%) of the blood PMN leucocytes of lepromatous patients contain bacilli, but the number of bacilli per cell is usually 1 and rarely 2 or 3, while up to 3% of the blood monocytes contained a number of bacilli which was between 1 and more than 10, per cell.

Probably the short half-life of PMN leucocytes (about 6 h in circulation and 1–2 days in tissues) and their tendency to "commit suicide" while engaged in phagocytic processes, could be a simplistic explanation for the fact that this type of cell is usually not shown to be more broadly parasitized by the long-lived mycobacteria. An alternate explanation could be based on the fact that although PMN leucocytes possess immunoglobulin-receptors (Wardley *et al.*, 1976; Zighelbaim *et al.*, 1976), they do not seem to have both immunoglobulin (IgG_1 and IgG_3) and complement (C_{3b}) receptors which make the mononuclear phagocytes, highly phagocytic cells.

The mean value for each enzymatic activity was slightly higher within the patients' group although this difference, for most of the cases, was not statistically significant. Therefore, from our results it was concluded that the leucocyte population from lepromatous patients, is not deficient in the activity of the studied lysosomal enzymes, at least under our conditions of assay. Even when parasitized leucocytes could have impaired metabolic or enzymatic activities, the defect might not reflect in the overall activity of the leucocyte population due to dilution, as only about 0.3% of the total leucocyte population in untreated patients has been found to be parasitized by acid-fast bacilli (Drutz *et al.*, 1972, 1974).

In relation to the lipase activity, although a complex lipid substrate was not used, we believe that because of the waxy components of the wall structure of *M. leprae* and other mycobacteria, it is an enzyme that must be studied in more detail and with a more appropriate methodology. Other enzymatic activities and oxidative metabolic changes have to be studied to definitively state that circulating leucocytes of lepromatous patients behave in an essentially normal manner as compared with leucocytes from healthy individuals.

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Failure of *Mycobacterium leprae* to Incorporate Tritiated Thymidine Administered *In vivo*

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Tritiated thymidine ([^{3}H]TdR) was administered to mice infected with *Mycobacterium leprae* in attempts to label the *M. leprae in vivo*; injections were made either intraperitoneally or locally into the infected foot-pads. Although labelling of the tissue cells was heavy, indicating that [^{3}H]TdR was available to *M. leprae*, no labelled *M. leprae* were observed in either of the 2 studies conducted.

Introduction

Labelling of *Mycobacterium leprae in vitro* with a radioisotope has been accomplished in 4 laboratories. Drutz reported (Drutz and Cline, 1972) the incorporation of tritiated thymidine ([^{3}H] TdR) by *M. leprae* already resident in cultured macrophages derived from blood monocytes of bacteraemic patients with lepromatous leprosy. Talwar and his co-workers (Talwar *et al.*, 1974) subsequently reported incorporation of [^{3}H] TdR by *M. leprae* that had been inoculated into human macrophage cultures. Ambrose *et al.* (1974) described radiolabelling of *M. leprae* in cultures of human macrophages following the addition of [^{3}H] TdR or of [^{3}H] dihydroxyphenylalanine ([^{3}H] DOPA) to the culture. Finally, Prabhakaran (Harris and Prabhakaran, 1975) reported binding of [^{3}H] DOPA by *M. leprae in vitro.* No workers have reported success in attempts to label *M. leprae in vivo.*

In our first experiment, we were unable to demonstrate radiolabelling of *M. leprae,* which had multiplied in the mouse foot-pad, by [^{3}H] TdR administered intraperitoneally. Therefore, we carried out a second experiment in which

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[^{3}H]TdR of high specific activity was administered repeatedly into the infected foot-pad tissues during the period of logarithmic multiplication of *M. leprae*.

Materials and Methods

Methyl-labelled [^{3}H]TdR was purchased from New England Nuclear Corp., Boston, Massachusetts. Locally-bred BALB/c mice and thymectomized, irradiated, and bone-marrow reconstituted B6C3F ([C57Bl/6♀ x C3H/AnF♂] F_1) hybrid mice (supplied by C. C. Congdon, Oak Ridge Laboratory, Oak Ridge, Tennessee) were inoculated in the hind foot-pads with *M. leprae* of the strain used in most experiments in these laboratories.

In the first experiment, 2 BALB/c mice inoculated 112 days earlier with $10^{3\cdot7}$ *M. leprae* and 2 thymectomized, irradiated B6C3F_1 mice inoculated 356 days earlier with $10^{3\cdot7}$ organisms were given an intraperitoneal injection of 0.1 mCi of [^{3}H]TdR (specific activity, 6.7 Ci/mmol) every hour for 10 h; a third animal from each group served as a control. One hour after the last injection, the mice were killed; both hind foot-pads were removed, fixed in 2% glutaraldehyde, postfixed in OsO_4, and embedded in Araldite (Evans *et al.*, 1973*b*). One-micron sections were cut for light microscopic autoradiography and coated with Ilford L-4 nuclear emulsion. After the sections were exposed for up to 10 weeks, the autoradiographs were developed and stained with toluidine blue. For electron microscopic autoradiography, gold sections were placed on a grid and covered with Ilford L-4 nuclear emulsion. After exposure times of up to 8 months, these sections were developed and viewed under a Philips 200 electron microscope (Evans *et al.*, 1973*a*).

In the second experiment, 60 BALB/c mice inoculated in both hind foot-pads with $10^{3\cdot7}$ *M. leprae* were divided into 4 groups. One group served as a control. Approximately 0.05 mCi [^{3}H]TdR [0.05 ml of a solution containing 1 mCi ^{3}H (specific activity, 50.8 Ci/mmol) per ml] was administered daily, 5 days per week, into each infected foot-pad of the mice of the 3 experimental groups (Groups A, B and C). The mice of Group A were injected daily for 10 days between day 77 and day 93 after inoculation, those of Group B were injected with [^{3}H]TdR daily for 10 days between day 93 and day 108 after inoculation, and the mice of Group C were injected daily for 20 days between day 77 and day 108 after inoculation with *M. leprae*. For control mice, *M. leprae* were harvested from the pooled tissues of 4–8 foot-pads at intervals by published methods (Shepard, 1960; Shepard and McRae, 1968). For [^{3}H]TdR-treated mice, *M. leprae* were harvested from the foot-pads at intervals of 121, 156 and 197 days after inoculation. At the 2 earlier intervals, the organisms were recovered by differential centrifugation from each tissue homogenate and washed 3 times with Hanks' balanced salt solution. An 0.8-ml aliquot of each suspension of washed *M. leprae* was placed in a liquid scintillation vial, 14.2 ml of NCS solubilizer (Nuclear Chicago, Chicago, Illinois) was added, and the radioactivity of the organisms together with tissue debris was measured in a Nuclear Chicago Series 720 liquid scintillation spectrometer. In addition, portions of the bacterial suspensions resulting from the harvests and the foot-pad soft tissues of additional mice were processed for autoradiography; the methods used were the same as those described for the first experiment.

Results

INTRAPERITONEAL ADMINISTRATION OF [^{3}H]TdR

Organisms were found in small infiltrates of mononuclear cells in the foot-pads of the mice inoculated 112 days earlier with *M. leprae*. Light microscopic autoradiography revealed heavy nuclear labelling in cells of the infiltrate and epidermis. Very little background labelling was present. Although numerous *M. leprae* were observed, none were labelled. Electron microscopic autoradiography also showed no labelled *M. leprae*. In the group of thymectomized, irradiated

mice inoculated 356 days earlier, organisms were found mainly in mononuclear cells; however, *M. leprae* were occasionally seen in other connective tissue and muscle cells. As in the study of immunologically normal mice, nuclear labelling of various cell types was observed, but no labelled *M. leprae* were observed with either light or electron microscopic autoradiography. Interestingly, no mononuclear cells containing *M. leprae* showed nuclear labelling.

ADMINISTRATION OF [^{3}H]TdR INTO THE FOOT-PAD TISSUES

The results of harvests of *M. leprae* from the control and [^{3}H]TdR-treated mice are shown in Fig. 1, in which the common logarithm of the number of acid-fast bacilli (AFB) per foot-pad is plotted as a function of time after inoculation. The least-squares line fitted to the results of harvests performed from control mice between days 77 and 156 after inoculation represents the growth curve of *M. leprae* in untreated mice. Multiplication of *M. leprae* appears to have been inhibited by [^{3}H]TdR administration, as shown by the results of harvests performed 121 days after inoculation. However, between days 156 and 197, the organisms multiplied in the foot-pads of mice of Groups A and B at the same rate as that in control mice.

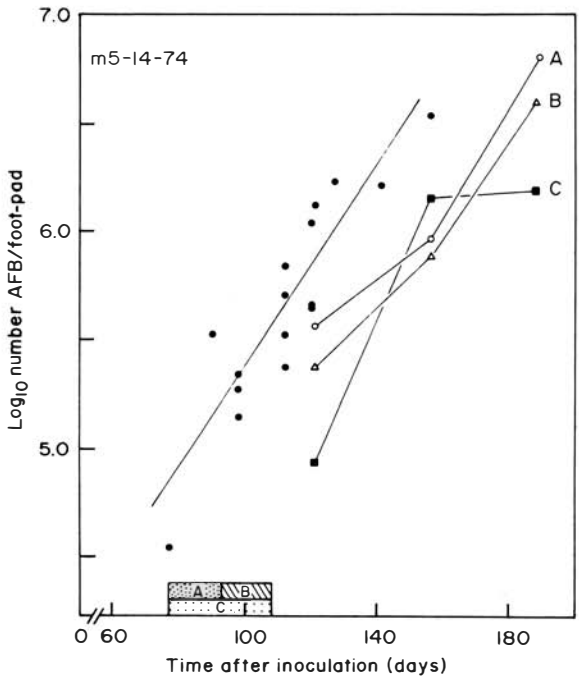

Fig. 1. Log_{10} number of AFB per foot-pad as a function of the time after mice had been inoculated with *M. leprae*. The closed circles represent harvests from untreated control mice; the straight line drawn through these points is the regression line representing the logarithmic phase of multiplication of *M. leprae* in control mice. The horizontal bars on the abscissa represent the periods of administration of [^{3}H]TdR; the letters within the bars identify the corresponding bacterial growth curves.

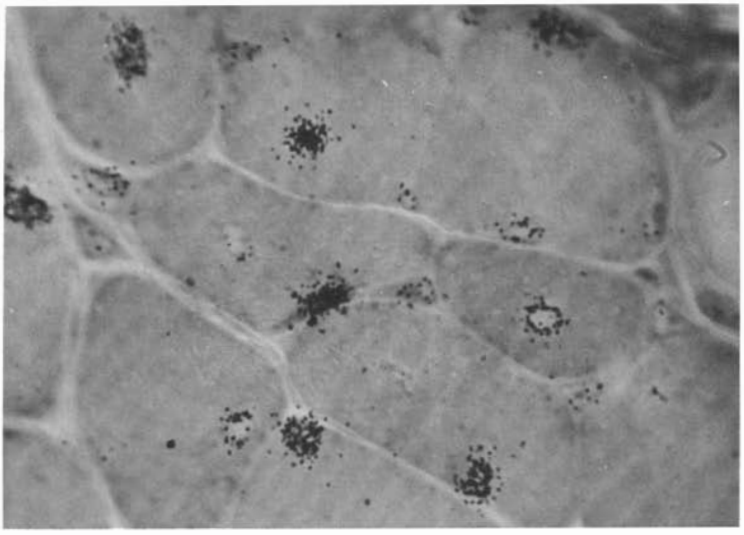

Fig. 2. Labelled nuclei in muscle from mouse foot-pad; Group A at 121 days. x 1250.

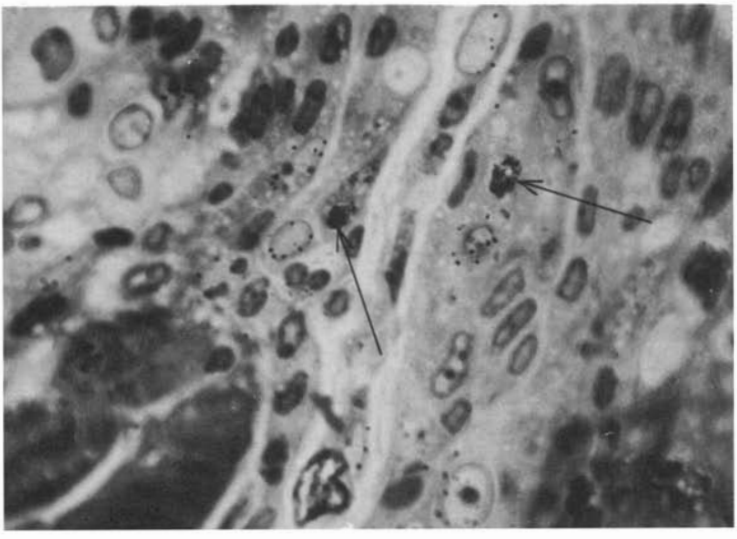

Fig. 3. Labelled nuclei and unlabelled globi (arrow) in mouse foot-pad; Group C at 197 days. x 1250.

In the autoradiograph prepared from the tissues of mice killed 121 days after inoculation, we observed moderate cellular infiltrates but few organisms. Almost all nucleated cells in the tissues from Groups A, B and C were labelled (Fig. 2). Very little background labelling was present, and although most nuclei were labelled, diffuse cytoplasmic labelling was not observed. At no time were labelled *M. leprae* observed.

In the preparations made from the tissues of mice killed 156 days after inoculation, cellular infiltrates were present together with many organisms. Again, almost all of the nucleated cells in the tissues of Groups A, B and C mice were labelled. Diffuse cytoplasmic labelling was observed in the tissues of mice from Group C. Organisms were observed both in globi and singly within cells, but none were labelled. Again, no cells containing *M. leprae* organisms were labelled.

Fig. 4. Labelled tissue fragment in suspension of mouse foot-pad; Group B at 156 days. x 1250.

In the tissues of mice killed 197 days after inoculation, large cellular infiltrators and many *M. leprae* organisms were present. Many cells were labelled but not as many as in the tissues obtained at earlier intervals. Many mononuclear cells contained *M. leprae* in globi. No labelled *M. leprae* were observed (Fig. 3).

The results of liquid scintillation spectrometry of the suspensions of *M. leprae* resulting from harvests performed on day 121 and day 156 after inoculation are summarized in Table 1. These results suggest that there had been some incorporation of ^{3}H into the particulate material of the suspensions. The very small quantity of ^{3}H detected in the filtrates of these suspensions after filtration through an 0.22 μm pore-size membrane filter indicates that washing was complete. The quantity of the radioisotope incorporated appears to be the same for all harvests, although it is perhaps a little greater in the material harvested from Group B mice. Certainly, there does not appear to have been a decrease in the quantity of isotope incorporated between the day-121 and day-156 harvests.

TABLE 1

Incorporation of [^{3}H]TdR into foot-pad tissue homogenates

Mouse group	Counts per min* Day of harvest 121	156
Control†	< 1	< 1
A	855 ± 9‡	934 ± 9
B	1333 ± 13	1404 ± 14
C	950 ± 10	934 ± 10
Filtrates	12	4

* Corrected for background.

† Control mice were mice that had been inoculated with *M. leprae* but received no [^{3}H]TdR; *M. leprae* were harvested from control animals and experimental animals at the same time.

‡ Mean ± standard deviation.

Autoradiographs of these suspensions revealed no labelled *M. leprae* but numerous labelled tissue fragments (Fig. 4).

Discussion

The purpose of these studies was to label *M. leprae in vivo* with [^{3}H] TdR. Our first attempt was designed to expose the organisms to [^{3}H] TdR almost continually for 10 h by multiple intraperitoneal injections of the material. The numerous labelled tissue cells in the mouse foot-pad verified that [^{3}H]TdR had been available for incorporation by the organisms. However, no *M. leprae* were labelled in this experiment, whether the organisms were single or in globi. In the second experiment, multiple injections of [^{3}H] TdR were given directly into the infected foot-pads of mice over a period of days. The organisms were in logarithmic multiplication at the start of injections. Again, no labelled *M. leprae* were observed, either singly or in globi, although most tissue cells were labelled. Suspensions of washed *M. leprae* from treated mice showed more counts by liquid scintillation spectrometry than did organisms harvested from untreated controls, suggesting that [^{3}H] TdR had been incorporated. However, autoradiography of these suspensions failed to show labelled *M. leprae*, although it did show considerable labelling of tissue fragments. Unfortunately, uninfected mice had not been injected with [^{3}H] TdR; thus, no suitable control was available.

Other investigators have reported labelling *in vivo* of *M. leprae* with [^{3}H] TdR. Only Talwar and his co-workers (1974) presented data not entirely based on autoradiographs. By means of liquid scintillation spectrometry, these workers observed a large increase in [^{3}H]TdR incorporation, and they found autoradiographic evidence to suggest that the counts were coming from labelled *M. leprae*. Drutz and Cline (1972) observed an increased grain count over globi compared to cells without globi. Ambrose *et al.* (1974) reported successful labelling of *M. leprae* with [^{3}H]TdR. Unfortunately, all these reports presented insufficient information about controls. For example, it is important to exclude *Mycoplasma* contamination of macrophage cultures, which can produce spurious incorporation

of [^{3}H]TdR (Paul, 1975). The above studies would have been more convincing if they had included autoradiographs of uninfected cultures exposed to the isotope.

The problems encountered in attempting to label *M. leprae* were recently reviewed by Drutz (1975). Our own failure to show labelling of *M. leprae in vivo* may have been caused by several factors. First, it may be that *in vivo M. leprae* do not utilize thymidine in the form injected, as has been suggested by Wayne (L. G. Wayne, personal communication). If *M. leprae* utilize exogenous thymidine for DNA synthesis, it is possible that, in our experiment, not enough [^{3}H]TdR was incorporated by the organisms to be apparent by autoradiography. This could have resulted from dilution of [^{3}H]TdR in the body of the animal or from a slow rate of DNA synthesis. Another possibility is that only a few *M. leprae* synthesize DNA at any one time. In the studies by Drutz and Cline (1972), only 1–2% of the globi were labelled. If that were the case *in vivo,* it is conceivable that the few labelled *M. leprae* could have been missed during examination of the slides.

In our second experiment, failure to obtain labelled organisms could have resulted from several additional factors. First, the growth curves of Fig. 1 suggest that multiplication ceased during the period of multiple [^{3}H]TdR injections, so that the *M. leprae* were not synthesizing DNA at the time [^{3}H]TdR was available. The reason for cessation of multiplication is not clear; however, it was recently demonstrated that repeated administration of saline into the foot-pad tissues of mice produces an inflammatory reaction that is associated with cessation of multiplication of the *M. leprae* (L. Levy and T. C. Merigan, unpublished data). Second, if the organisms did incorporate [^{3}H]TdR, subsequent multiplication may have diluted the label to an undetectable level. Re-utilization of the radiolabelled compound would have been beneficial in this study, because it would have increased the opportunity for labelling of *M. leprae.* Because of the large numbers of labelled tissue cells present and the time course of this study, re-utilization must have been occurring; nevertheless, *M. leprae* were not labelled.

An interesting result of this study was that, despite the many labelled tissue cells present, the vast majority of those containing *M. leprae* were not labelled. This is in agreement with previous observations (Evans, 1974) and raises the question of how mononuclear cells increase in number to accommodate multiplication of *M. leprae* in the mouse foot-pad.

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Surgical Management of Gross Mid-foot Damage

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A technique is presented for radical surgical management of gross mid-foot damage with preserved, useful plantar skin in the heel area. It is essentially a combination of pretalar amputation and calcaneo-tibial fusion with the calcaneum in 45 degrees rotation. This ensures a sound weightbearing surface and a trouble-free take-off area. This technique does not depend on sophisticated orthoses or prostheses.

Introduction

Severe damage to the mid-foot is fairly common in leprosy patients. Basically this is dependent on plantar anaesthesia. It may be a late feature of neuropathy of the foot with mid-foot collapse, ending with a boat-shaped foot with marked equinus of the calcaneum and the fore-foot in dorsiflexion. This alters the mechanics of plantar ulceration, which now predominantly takes place at the presenting plantar surface, i.e. the mid-foot. The end result is chronic ulceration with mid-foot osteomyelitis. It may also be a late result of longstanding ulceration of the fore-foot with chronic, ascending osteomyelitis of one or more metatarsal bones, usually that of the little toe, again leading to mid-foot ulceration and osteomyelitis. Valgus and varus deformities, fixed or mobile, also throw additional strain on the mid-foot with the same end result. Occasionally direct damage to the mid-foot may trigger off this unhappy sequence.

Fortunately useful sensation of the heel area is preserved in many of these feet. This, combined with the frequently found boat-shaped foot, gives rise to the rather bizarre picture of a foot with well preserved heel, occasionally in varus or valgus position, almost inevitably in equinus, a fore-foot that usually presents scars and absorptions from previous ulcerative damage, but now appears to be remarkably well preserved, and finally extensive damage to the mid-foot. In many cases this disastrous situation is not at all apparent from the dorsum, certainly not to the uneducated patient. This has been a source of some difficulties to us. It has proved comparatively easy to persuade a patient to accept an operation where "the dead and useless bones are taken out", in other words a formal fore-foot amputation or one of the modifications of transverse metatarsal head resection. It is quite another story to convince a patient that he had to have the whole, apparently normal fore-foot removed, just because of a mid-foot ulcer. I have

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even had patients suggesting that I should cut out the bad mid-foot, and then put the "good" forefoot on to the hind-foot.

Feet with gross mid-foot damage are notoriously difficult to treat. Although the basic, conservative treatment—absolute non-weightbearing, elevation of the affected limb, daily soaks in soap water, bland dressing, and judicious removal of obvious sequestra—certainly will cure the majority of these feet, it is a time consuming procedure, that effectively blocks a large number of beds. For that reason it is not a particularly cheap therapy, either. Of greater importance is the virtual certainty that these feet will re-ulcerate within a short span of time. Much effort and serious thinking have been spent on the production of orthoses that could obviate this regular re-ulceration. They are expensive, require sophisticated workshops with highly trained personnel. Even if we could persuade our patients to wear such orthoses, they simply are not available to the vast majority of them. Chances are slender that this situation will improve in the foreseeable future. Neither are there hopes that we shall see fewer people with such disabilities, when we contemplate the depressing situation of world-wide leprosy control.

In this situation it is reasonable to look for more radical therapy. One is entirely justified in abandoning the time honoured precept, "the damage to anaesthetic feet is progressive, so let us preserve whatever can be preserved". It appears logical to look for a solution that deliberately sacrifices what cannot be preserved in the long run, and to aim at serving a useful foot with a good chance of retaining it.

One very radical solution is to perform a below-knee amputation. There are 2 major drawbacks to this. First of all we condemn the patient to a definite prosthesis for life. Secondly it is hardly acceptable to most of our patients. In my view this solution is only acceptable if we are dealing with a foot where even the heel is destroyed beyond salvage.

Syme's amputation appears to offer a solution. It is comparatively easy to perform. It does not require sophisticated equipment, and can be performed adequately by doctors with less than a full orthopaedic training. However, even such modifications that prevent the classical dorsal migration of the stump pad, have serious draw-backs. The major one is that it requires a sophisticated prosthesis, which is even more difficult to make and service than a below-knee prosthesis. I entirely fail to see any advantage of this technique over a below-knee amputation.

Pirogoff's amputation is more rational. It depends on a servicable heel-pad. Its advantage is that with the frequently preserved heel sensation, we need not absolutely depend on a non-end-weightbearing prosthesis. A serious disadvantage is that the stump is too long for a comfortable prosthesis, and the leg is too short for a simple orthosis, such as an elephant boot. A valid objection to this technique is that we often find fairly extensive fibrosis round the ankle joint in these patients. This may well make impossible the required 90 degrees rotation of the posterior, osteotomized part of the calcaneum into the ankle mortice. Altogether it appears to be more difficult and less satisfactory than the technique offered in this paper.

Boyd has proposed an interesting solution. He describes a calcaneo-tibial fusion, which may be combined with a pretalar amputation. After talectomy the shaped calcaneum is fitted snugly into the denuded ankle mortice. Achillis tenotomy is essential to prevent the calcaneum from wandering. However, in the particular situation in which we are interested here, there are certain deficiencies

in this technique. There is an inevitable shortening of the leg, though this can probably be handled with a moderate raising of the shoe. Of more importance is the fact that since the articular surfaces of the calcaneum are removed at right angles to the long axis of the leg, there is an unfortunate chance that the ulcerated/scarred part of the sole will remain within the take-off area of the foot. It is my contention that this technique as it stands is unsuitable for the particular problem with which we are dealing.

Suggested Technique

INDICATIONS

Any foot with severe damage to the mid-foot so that ulcer-free ambulation cannot be achieved.

CONTRAINDICATIONS

The only absolute contraindication that is recognized is damage to the heel to the extent that a sound weightbearing surface cannot be obtained. It should be realized that local infections and osteomyelitis do not constitute any contra-indication, though they may cause the technique to be modified. Neither does the state of leprosy as such constitute any contraindication. It is well known that lepra reactions and progressive lepra as well as failure to respond properly to anti-leprosy treatment may be precipitated by such infective and necrotic conditions. General poor health with low haemoglobin readings, low plasma protein level, etc., may also be precipitated by such conditions. A radical clearance may have a very beneficial effect, indeed. On the other hand a general sepsis constitutes a relative contraindication. This must be brought under control before any surgery is attempted.

TECHNIQUE

The operation is always carried out in a bloodless field. The first incision is carried from just anterior to the tip of the medial malleolus across the ankle joint to just distal to the tip of the lateral malleolus. The second incision is carried in a long sweep across the plantar surface, outlining the longest possible plantar flap. The talo-navicular joint is opened, and the ligaments between these bones divided. Next the bones of the fore- and mid-foot are dissected off the thickest possible plantar flap until the calcaneo-cuboid joint is reached. The pre-talar bone block is removed. The ligaments on either side and the plantar surface of the talus are divided, and by putting strong equinus force on the talus it is delivered from the ankle mortice. Occasionally it is possible to remove the talus *in toto*. More commonly it is necessary to remove it piecemeal. This makes no difference. All joint cartilage from the ankle mortice is removed down to fresh cancellous bone. The anterior margin of the tibia is carefully removed, so that the distal surface of the tibia is flat and at right angles to the long axis of the leg. The next step is osteotomy of the calcaneum. This is a critical step. The division runs obliquely, approximately at an angle of 45 degrees with the axis of the foot. The sustentaculum tali is removed and soft tissue from the sides of the calcaneum is cleared off. After Achillis tenotomy it is now possible to rotate the osteotomized calcaneum into a snug fit in the ankle mortice. The anterior end of the calcaneum is cut down to avoid unnecessary projections beyond the anterior margin of the

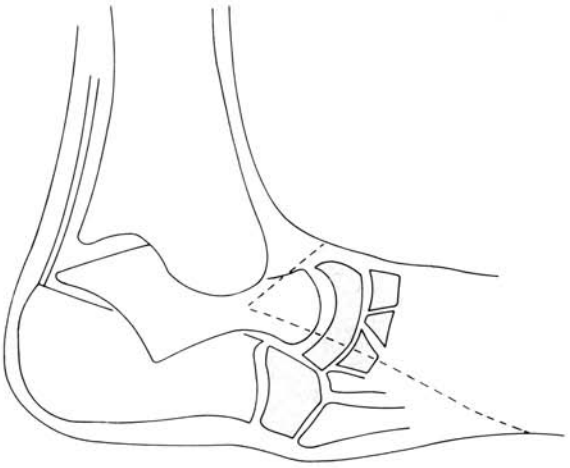

Fig. 1. The foot is shown from the tibial side. The line of incision is indicated, running from the tip of the tibial malleolus across the ankle joint to the tip of the fibular malleolus.

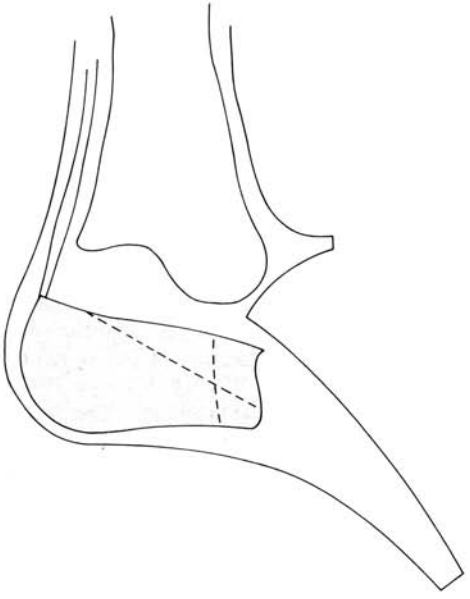

Fig. 2. After pretalar amputation and talectomy all joint cartilage from the ankle mortice is removed, and the calcaneum is osteotomized as indicated.

tibia. The plantar flap is now trimmed to secure a snug, but not tight fit. If the flap is too loose, there a real danger of the formation of haematomata. If it is too tight, there is an equally obvious danger of edge necrosis. Before skin suture the tourniquet is completely removed and careful haemostasis is effected. Since we have to suture thin skin to thick skin, vertical mattress sutures are recommended. No attempts are made to correct the inevitable dog's ears, which might jeopardize the blood supply. Anyway, they disappear within a short time. Remaining blood and oedema is expressed, and the calcaneum is firmly pressed into the ankle mortice. A fairly voluminous dressing is applied. The whole leg up to the knee is enclosed in a thin, well-fitting plaster of Paris cast. We avoid compression clamps and rely on the compression from early ambulation. One reason is that it has been a firm objective to develop a technique that did not require excessive equipment. Another reason is that since we are operating on actually or potentially infected extremities, we consider it unwise to introduce foreign bodies with added risk of post-operative infection. The high prevalence of osteomyelitis in Africans has made us extremely careful.

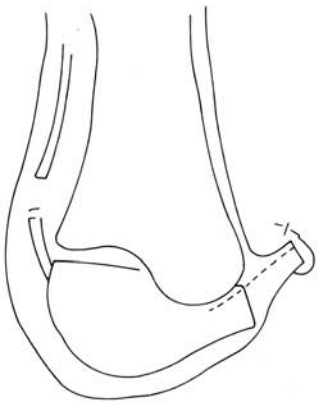

Fig. 3. After trimming of the calcaneum and Achillis tenotomy the calcaneum is rotated up and anteriorly to fit snugly into the ankle mortice. Notice that tuber calcanei is now the presenting, weightbearing surface. After trimming of the plantar flap, skin suture is carried out well away from the weightbearing and take-off surface.

POST-OPERATIVE MANAGEMENT

Elevation of the operated extremity is absolutely essential in order to avoid the formation of haematomata. This must be strictly enforced, right from the operating table, through the transport to the ward, and for at least 48 h after surgery. Two weeks after surgery the plaster cast is removed. If no evidence of post-operative infection or necrosis of skin edges are found, a well-fitting plaster of Paris cast, incorporating a walking device is applied, and ambulation is encouraged. At the same time the position of the heel is verified, and if necessary corrected. The walking cast is changed as required. Solid bony union might be expected from the twelfth week, although this is extremely variable. If possible, this should be confirmed radiologically.

ORTHOTICS

After confirmation of bony union, the patient is fitted with an "elephant boot". Since there is little if any shortening of the extremity, there is no need for more raising of the foot than can be incorporated in a simple boot. There is no need for ankle braces. Since we are dealing with patients with plantar anaesthesia, that at any time might extend to the heel area, the usual precautions for such feet should be taken.

COMPLICATIONS

There are 5: healing of the suture line by secondary intention, ischaemic necrosis of the plantar flap, haematoma formation with secondary infection, continued infection from remnants of pre-existing plantar ulcers, and finally non-union.

We are dealing with at least potentially infected feet. It is therefore little wonder that a proportion of these feet do not heal by primary intention. So long as the plantar flap and the osteotomized calcaneum are secured in their proper position, this has little influence on the course, except for an unpredictable delay. It is essential in case of this complication that the foot is maintained in the proper position in a plaster of Paris cast, while weekly changes of dressing and plaster cast may be needed. Usually the whole situation quickly resolves itself, and the regime will then return to that for the uncomplicated operation.

Ischaemic necrosis of the plantar flap is, of course, a serious complication, that practically always necessitates a formal below-knee amputation. It is almost invariably caused by damage to the posterior tibial vessels during the operation. This is a technical error, and should carefully be guarded against.

Haematoma formation and secondary infection can invariably be traced to one of 2 errors, careless haemostasis or failure to secure proper post-operative elevation. Strict theatre and nursing discipline must be insisted on.

Ideally the scarred/ulcerated area of the mid-foot should be excised during the trimming of the plantar flap. This is not always possible. There is therefore at least a potential risk of continued infection. We have not found any advantage in a regime with post-operative antibiotics. If there is the slightest risk of this complication arising, it is wise to suture the 2 flaps loosely to each other. Even if such infection does develop, it rarely has any influence on the post-operative regime, other than a delay in the introduction of weightbearing.

Non-union is naturally a late complication. So far we have not experienced it. General experience would indicate that in most cases it is not a true non-union, but rather delayed union. In any case a generous trial with continued weightbearing in a walking cast should be given, before resort is taken to the drastic procedures of secondary bone grafting, etc. It is essential to maintain the calcaneum in correct position the whole time.

We have avoided introducing bone chips between the calcaneum and the ankle mortice. The reasons are the potentially infected foot on which we operate, and the high risk of haematogenous osteomyelitis in African patients.

TWO-STAGE OPERATION

Unfortunately a high number of patients present themselves with feet that are not suitable for this technique. In many cases the ideal situation is obtainable—no active ulceration, no osteomyelitis, no sequestra—if one is prepared to institute a

time consuming regime of conservative ulcer therapy. In many cases this is not practical. The patients may be impatient for definite treatment; and we always have the problem of bed occupancy.

Whenever it is decided to operate in spite of the ideal conditions not being met, it is wise to perform the operation in 2 stages.

The first stage is a pre-talar amputation. Since this is active osteomyelitis surgery, the incision should be left open. This, however, cannot be done, since it would jeopardize the position of the plantar flap. The compromise is to cut the plantar flap more generously and to fix it loosely with one or a few widely spaced sutures to the dorsal flap. Instead of plaster of Paris coverage, the foot is secured in a mild compression bandage over a generous padding. This is changed weekly until signs of infection have subsided. The foot is then protected in a thin plaster of Paris shell as for the definite operation. When healing is either complete or well under way, the second stage operation is embarked on. This is a calcaneo-tibial fusion after talectomy as described.

The final results of the 2-stage operation are fully comparable to those of the one-stage procedure. Naturally longer time is required before the final result is achieved.

NOTES ON CHANGING OF DRESSING OR PLASTER CASTS

In many cases a less experienced surgeon will be under considerable pressure to change plaster casts or dressing frequently, even daily. It seems to be firmly rooted in the training of nurses that any dressing should be changed soon after surgery. Many patients have an identical conviction that dressings should be changed, and wounds inspected frequently.

In the case of the one-stage procedure we are dealing with a foot with no overt pre-operative infection. There should therefore be no reason for such changes before the second week. The few indications for earlier and more frequent changes are related to the following complications:

1. Swelling of the operated extremity to the extent where there is danger of plaster constriction could indicate a haematoma. In such a case it is wise to open the plaster cast, drain a possible haematoma, and re-apply the plaster cast.
2. Post-operative infection, either from a haematoma or from inherent infection of the foot rarely emerges before the end of the first week. There will probably be some swelling of the extremity, but the picture will be dominated by a fairly copious discharge, which may seep through the plaster cast or even spill over the edge of the cast. There is usually a distinct smell, sweetish and nauseating. In these cases it is important to remove the plaster cast, ensure free drainage of the infected cavity, and maintain the foot in a well-padded compression bandage, which is then changed weekly until the situation has settled down, and a plaster cast can once more be applied. Care must be taken to maintain the osteotomized calcaneum in the correct position.
3. Ischaemic necrosis may present as a post-operative infection. More commonly it is seen as copious discharge with relatively little swelling of the extremity. One notices the characteristic sweetish nauseating smell. When this is found on opening the plaster cast, active preparations for a definite below-knee amputation must be started immediately. Obvious necrotic tissue is removed, and the extremity is treated with daily soap soaks, followed by eusol dressing.

Eventually the raw area should be covered with a split skin graft. It is unwise to attempt a definite below-knee amputation while there still are signs of active infection in the extremity.

These conditions must be clearly distinguished from the peaceful extremity in a soaked plaster cast with a pungent, cheesy smell. This is never an indication for early change of plaster casts. It is inevitably an indication of delayed healing with some discharge, usually mixed with sloughed-off cuticle from the sole of the foot. At normal changing time a surprising amount of such "pus" can be seen. However, after simple cleaning the wound is seen to be clean and peaceful. In many cases this "pus" will be sterile.

It is notoriously difficult to rely on statements of pain from the patients. In many cases they are unable or unwilling to make the important distinction between pain and discomfort. It is also important to rely on such clinical features as raised temperature, unless of course one should have the misfortune of meeting a real, generalized sepsis, increasing WBC count or left shift of the differential count. These difficulties would appear to be connected with the fact that we are dealing with anaesthetic limbs. ESR of course is unreliable, since it may be raised anyway in many of these patients.

Changes of dressing for the first stage operation follow much the same rules, only it should be realized that here we know that we are dealing with frank infections. Still it is wise to limit the dressings to once weekly.

Experience has shown that this procedure is suitable not only for a reconstructive surgery centre, but that peripheral centres with less sophisticated experience can handle these cases competently. It has been possible to teach doctors with less than a full surgical training to perform this operation confidently, and also to select patients for it.

We have seen more than 18 months trouble-free follow-up outside the hospital.

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Leprosy and the Community

LIBERIAN NATIONAL LEPROSY CONTROL PROGRAMME

The campaign against leprosy in Liberia has been greatly strengthened by the appointment in November 1975 of Sr Dr Chambers, a leprologist of wide experience. In a penetrating first report Dr Chambers reveals a fluid situation with 991 patients registered in the 6 months of January–June 1976 in a leprosy control programme staffed by 4 full-time area supervisors and 21 junior leprosy workers. In the past the programme operated in isolation from the general medical services, but reorganization is in progress with partial integration one of its objectives. Courses of lectures in leprosy have been given to medical students and final year Physician Assistants. The position as at 30 June 1976 was as shown in Table 1.

TABLE 1

County hospitals, health centres and health posts, indicating number at which leprosy patients are treated (June 1976)

County	Population	Hospitals		Health centres		Health posts	
		Total	Integrated	Total	Integrated	Total	Integrated
Montserrado	439,997	10	3	3	1	50	11
Cape Mount	56,605	2	1	1	1	10	10
Bassa	150,926	3	2	1	1	9	9
Sinoe	67,599	2	1	1	1	25	14
Maryland	91,619	2	1	1	1	15	15
Bong	194,191	2	1	5	5	32	25
Loffa	180,737	3	2	3	3	36	29
Nimba	249,702	3	2	3	2	21	17
Grand Gedeh	71,825	1	1	2	2	9	9
Total	1,503,201	28	14	20	17	207	139

Registered patients under treatment on 30 June 1976, 2303 (T 631, B 1078, L 502, I 92).

HIND KUSHT NIVARAN SANGH (INDIAN LEPROSY ASSOCIATION) ANNUAL REPORT FOR 1975

The Hind Kusht Nivaran Sangh, almost certainly the first association of its kind in the world, continues to flourish and expand its concerns, as is apparent from its Annual Report for 1975. With the President of India as its President, supported by many distinguished leprologists and men in public life, and with branches in most Indian states, the Sangh is well equipped to exercise an important role in a

country with over 3 million sufferers from leprosy. Its responsibilities are exercised particularly in 5 directions.

1. *The encouragement of research and technical excellence and the bringing together of leprologists and other leprosy workers*

The Sangh has been responsible for convening an All India Leprosy Workers Conference once every 2 years since 1947. The latest of these was at Baroda in April 1976, immediately following the Conference of the Indian Association of Leprologists. In the field of research the Sangh rendered its good offices in the clinical trial of rifampicin in leprosy therapy. It instituted the Dr K. C. Sahu Memorial Gold Medal for the promotion of research in leprosy, and this was awarded to Dr A. J. Salvapandian at the Baroda Conference. Another of its projects is the proposed award of prizes to leprosy institutions for outstanding work.

2. *Training*

The training of physiotherapists in leprosy has been an important function of the Sangh, carried out mainly at the Christian Medical College and Hospital, Vellore, but also at the Purulia Hospital of the Leprosy Mission. Eighteen students were trained in 1975 and 54 attended refresher courses. Orientation courses in leprosy for Medical Officers were also sponsored. A Training Scholarship for one year's special training in leprosy was awarded to Dr S. B. Mahaptra to be undertaken at the Central Leprosy Teaching and Research Institute, Chingleput. A Travelling Fellowship was awarded to 2 paramedical workers.

3. *Publicity and health education*

This traditional activity of the Sangh is assuming great and increasing importance. Posters and pamphlets have been revised and multiplied. A new book, *Leprosy, Diagnosis and Management,* by Drs Job, Salvapandian and Kurian was published under the auspices of the Sangh. A manual for public health nurses is under preparation. A major health education scheme, prepared jointly by the Sangh and the Gandhi Memorial Leprosy Foundation, was submitted to the Government during the year.

4. *Co-ordinating the work of Government and voluntary agencies*

This is a highly important function. During the year the Sangh shared in the promotion of an important workshop on "The Promotion of Leprosy Work in India", in which all the important anti-leprosy agencies participated, and which promises to lead to much closer working together in the future.

5. *Relief and rehabilitation*

During the year the Sangh became directly responsible for sponsoring 10 children under a leprosy child adoption scheme worked out with the Government of India and the American-Korean Foundation. A pilot project was also sanctioned for training patients in typewriting.

Under the Fifth Five-Year Plan the Government of India has made a comparatively larger allocation to the leprosy programme, and contemplates the establishment of rehabilitation cum treatment centres in a programme in which it is hoped that voluntary agencies will actively participate. This involves the State Branches of the Sangh in a very active way. It is indeed the State Branches which

"constitute the base and the strength of the Sangh". We wish our colleagues in India every success.

REPORTS RECEIVED

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ELEP Leprosy Control Project, Dharmapuri. Annual Report for 1975.
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News and Notes

WHO EXPERT COMMITTEE ON LEPROSY

The Fifth Expert Committee was called by the World Health Organization from 19–25 October, 1976. Position papers and reviews had been circulated for study well in advance, and the views of many eminent leprologists, tuberculosis specialists and public health authorities had been previously sought. The 9 members came from: Belgium, Brazil, India, Iran, Malaysia, Mexico, Norway, United Kingdom and USSR.

The main theme of the meeting was the control of leprosy in the world, and the members were conscious of the constraints apparent in the future prospects for control occasioned by the twin spectres of drug resistance and persister organisms. The somewhat depressing atmosphere was partly illuminated by a review of the present advances in immunological research and the mycobacterial activity of rifampicin. The encouraging initiative taken by the WHO in the IMMLEP and THELEP projects, and in the inclusion of leprosy among the major tropical diseases calling for special research effort, was noted with satisfaction.

Dr S. G. Browne acted as Chairman of the meeting, with Dr P. M. Kaul as Vice-Chairman. Dr M. F. R. Waters was Rapporteur.

The publication of the Report of this Expert Committee is awaited with great interest, both in countries where leprosy is a major health problem, and by voluntary organizations that are making an important contribution to its solution.

HISTOPATHOLOGY OF LEPROSY: A TRIBUTE TO KENSUKE MITSUDA

The July 1976 issue of *Cutis* contains a delightful tribute to Kensuke Mitsuda in the shape of reproductions of 17 photographs from Mitsuda's *Atlas of Leprosy*, selected by Paul Fasal. The tribute was stimulated by the discovery by Dr Fasal of numerous *M. leprae* in the pulp of a tooth extracted from a patient with active lepromatous leprosy, and though standard textbooks were silent on this subject, he found it not neglected by the great Japanese master of pathology in leprosy. For those not fortunate enough to possess Mitsuda's Atlas these reproductions will be appreciated, and a copy of Fasal's paper may be obtained from Dr Paul Fasal, U.S. Public Health Service Hospital, 35th Avenue and Lake Street, San Francisco, California 94118, U.S.A.

LEPROSY SEMINAR IN EAST AFRICA

A postgraduate seminar on leprosy was held at the Kilimanjaro Christian Medical Centre, Moshi, Tanzania, from 27 to 29 October, 1976. This was the ninth seminar to be organized, and the first dealing with leprosy. To judge from the

attendance—over 200 participants, mainly doctors—from Tanzania itself and also from Kenya and Uganda, it met a real need. Some important topics in tropical dermatology were discussed, as well as aspects of reconstructive surgery, but the chief emphasis was on treatment and control of leprosy. Discussion groups for senior field workers, and also doctors concerned with the making and implementation of policy, proved to be most fruitful.

A rather sombre background to the whole seminar was provided by the reports of the emergence of a disturbing level of sulphone-resistant leprosy bacilli in many countries, and the presence of viable but non-metabolizing bacilli not amenable to standard doses of leprostatic drugs as long as they remain dormant. Concern was expressed by many doctors that the recommended high doses of dapsone, in Bantu patients suffering from borderline leprosy and inclined to unexpectedly severe reversal reactions, might pose a real hazard both to themselves and to the image of mass leprosy control programmes.

The guest lecturer was Dr S. G. Browne, and Dr John Pearson from the ALERT Centre, Addis Ababa, shared with the participants some of his latest findings. The National Leprosy advisory and Co-ordinating Committee of Tanzania, and the governments of the other East African countries, will be studying the Report of the Fifth Expert Committee on Leprosy of the World Health Organization when it is published.

SCHIEFFELIN LEPROSY RESEARCH AND TRAINING CENTRE, KARIGIRI, S. INDIA, TRAINING COURSES IN 1977

Once again we are glad to bring to the notice of our readers the following training courses at Karigiri which may be of international interest.

	Courses	Duration	Date
I.	FOR DOCTORS		
(a)	Condensed course for doctors in full-time leprosy work	1 week	June 13–18 Sept. 26–Oct. 1 Nov. 14–19
(b)	Medical students' course	1 week	Sept. 12–17
(c)	Medical officers' training course	6 weeks	July 18–Aug. 27
(d)	Ophthalmic aspects for doctors only	1 week	Annually in Feb.
(e)	Inservice training—in medical, surgical, ophthalmic, pathology and control	By arrangement	
II.	FOR OTHERS ENGAGED IN FULL-TIME LEPROSY WORK		
(a)	Supervisory paramedical workers (5 years' experience)	4 months	From June 6
(b)	Orientation course for nurses, administrators, etc.	1 month	Sept. 26
(c)	Paramedical workers	6 months	Apr. 4; Oct. 3
(d)	Medical record-keepers	2 months	April 4; Oct. 3
(e)	Physiotherapy technicians	9 months	June 15
(f)	Social workers' course	1 week	Sept. 26
III.	Inservice training is also available for technicians of all types engaged in leprosy work		

For prescribed forms and other details, please contact the Training Officer, SLR and Training Centre (B.O.), Karifiri, via Katpadi 632, 106 North Arcot Dt., S. India.

ESTABLISHMENT OF THELEP

WHO have followed up the IMMLEP programme by the establishment of the THELEP task force, the first meeting of which was held recently. The new task force has as its objective the development of more effective chemotherapy for leprosy.

The plan of attack of THELEP is two-pronged. First, laboratory and clinical investigations are proposed to find more effective ways of using existing drugs so as to hinder the emergence of drug resistant *M. leprae* and also shorten the duration of treatment. Secondly a programme for designing and testing new drugs is proposed involving simultaneous studies in several areas.

We wholeheartedly welcome this development and wish all involved every success in their efforts.

JUNE 1977 ISSUE OF *LEPROSY REVIEW*

The next Number of *Leprosy Review* will largely be devoted to a Symposium on the theme of sulphone resistance and its implications. Several distinguished leprologists with special experience in this field have agreed to participate, and will make this an Issue of particular interest and importance.

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Letters to the Editor

Confirmation of the Spot Test for the Identification of *Mycobacterium leprae* and Occurrence of Tissue Inhibitors of DOPA Oxidation

We reported previously a spot test using D-dopa for the identification of *Myobacterium leprae* (Prabhakaran, 1973, 1974). In these reports, no controls using heat-inactivated *M. leprae* were given. Results obtained with both heated and unheated bacilli are presented in this communication. Some recent observations on the occurrence inhibitors in armadillo tissues which interfere with oxidation of dopa by the bacilli are also discussed.

SPOT TEST

Suspensions of *M. leprae* were prepared from the liver of an experimentally infected armadillo. The preparation contained $2.0 \pm 0.12 \times 10^{10}$ bacilli/ml. Part of the bacterial suspension was heated at 100° C for 30 min. $Na_2HPO_4 - KH_2PO_4$ buffer (0.5 M, pH 6.8) and D-dopa solution (0.01 M) were used in the reaction. The dopa solution may be also made up in the buffer.

In Fig. 1, spot 1 contained a drop (approximately 0.05 ml) of bacterial suspension and a drop each of buffer and dopa solution; spot 2 contained a drop of the bacilli and 2 drops of buffer; and spot 3 a drop of dopa and 2 drops of buffer. In the upper spots unheated bacilli were used and in the lower spots the heated bacilli. The reaction was started at 4 p.m. and left overnight at room temperature (25° C). The photographs were made the following day at about 8 a.m.

It is evident that the bacilli oxidized D-dopa giving rise to melanin pigment. Under identical experimental conditions, the heated bacilli with dopa and dopa by itself show little colour development. The results clearly distinguish between the enzymatic and the non-enzymatic conversion of dopa to pigment. Similar tests were done with a cultivable mycobacterium, *M. phlei* (grown on Proskauer-Beck medium, Youman's modification) and 2 unidentified strains of mycobacteria separated from the skin and liver tissues of 2 species of mammals. (The tissues were received from elsewhere.) *M. phlei* and the organisms separated from the infected tissues showed no reaction with dopa.

TISSUE INHIBITORS

Recently, it was observed that suspensions of *M. leprae* separated from the liver tissues of some armadillos (especially those that were infected intravenously with heavy inocula of the bacteria) contained inhibitors which interfered with dopa oxidation by the bacilli. At the same time, organisms separated from other tissues like the spleen of the animals oxidized dopa. Some bacterial preparations from fresh liver (not kept frozen) which failed to oxidize dopa had a greenish tinge, probably indicating the presence of bile pigments. It is important that tissue

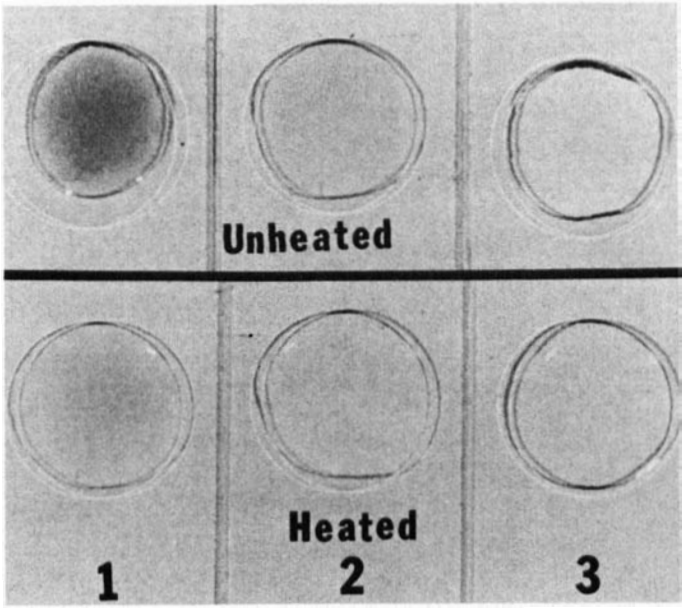

Fig. 1. Upper spots: unheated bacilli; lower spots: heated bacilli. 1, bacilli + D-dopa; 2, bacilli; 3, D-dopa.

inhibitors be excluded from *M. leprae* preparations before testing them for dopa oxidation. We obtain concentrates of *M. leprae* from infected organs by differential and density-gradient centrifugation in solutions of sucrose and KCl; further purification is achieved by treatment with trypsin, acetone and ether or dilute alkali.

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Note added in proof When the dopa oxidase reaction is used for the indentification of presumed *M. leprae* cultures, false positive results may be obtained, if the organisms are not thoroughly washed to remove the components of the culture media. This is best done by growing the bacilli, whenever possible, in liquid media.

Primary Sulphone Resistance

Several thousand leprosy patients live at the Agua de Dios Sanatorium, Columbia, in close contact with an even greater number of healthy people. Sulphone resistance, ascribed to irregular treatment, is believed to occur quite frequently among these patients, and is considered as such on clinical and histological grounds (secondary histoid leprosy); evolutionary grounds (lepromatous reactivation in spite of sulphone treatment); and bacilloscopic grounds (the reappearance of solid staining bacilli in patients under sulphone treatment). A case of what is believed to be primary sulphone resistance is reported here.

CLINICAL HISTORY

The patient P. B. (female), was born in this environment 33 years ago and lived here for 14 years. In August 1968 she came for consultation as a result of the appearance in the elbow area of an anaesthetic, erythematous and infiltrative plaque. Smears were made from the lesion, the nasal septum, the right elbow, ear lobe and knee. With the exception of the nasal septum all the samples were positive for AFB, with globi and solid staining bacilli. The lepromin reaction (Mitsuda) was negative.

Treatment was started with dapsone at a dose of 300 mg/week. In January 1969 the original lesion remained unchanged and a similar lesion 6 cm in diameter had appeared on the right leg. The same treatment was continued, and in June 1970 erythematous spots appeared on both thighs, with smears continuing positive both in skin and in nasal mucosa. Sulphone treatment was however persisted with until July 1971 (35 months), when severe clinical deterioration was apparent, characterized by extensive lepromatous infiltration of the face and right ear lobe, perforation of the nasal septum, and numerous large areas of iron hard purplish infiltration on the torso and limbs. Sulphone resistance was suspected and the treatment was changed to Ciba 1906 (1.5 g/day). The patient in fact took only 500 mg daily, notwithstanding which clinical improvement was noticeable 2 months later, and in 6 months had become marked, with bacilloscopy of the nose negative, and though skin smears remained positive, only granular bacilli were seen. In October 1972, i.e. 15 months after treatment with Ciba 1906 was started, only a small iron-like spot persisted at the site of the original lesion, the nasal mucus continued negative and only occasional granular bacilli were found in the skin. At that time she was mistakenly put back again on dapsone treatment on a dose of 300 mg/week and this was continued until May 1973, at which time the patient again presented extensive lepromatous infiltration of the face, infiltrated plaques in the lumbar areas, arms and legs, and the reappearance of solid bacilli in skin smears.

The patient had been continuously regular in taking treatment, and these facts strongly support the suggestion that she was suffering from lepromatous leprosy caused by a sulphone-resistance mutant strain of *Mycobacterium leprae,* acquired at the Agua de Dios Sanatorium, where there is strong evidence of many cases of sulphone resistance.

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Acid-fast Bacilli in the Fingers of Long-treated Lepromatous Patients

May I be permitted to offer some comments on the conclusion reached by the authors in the final paragraph of their paper entitled "Acid-fast bacilli in the fingers of long-treated lepromatous patients" (*Lepr. Rev.* (1976) **47**, 93). This paragraph reads as follows:

> "The fingers are yet another possible site of the persister bacilli that may be responsible for relapse after prolonged therapy. The public health importance of bacilli in the fingers is difficult to evaluate, but the facts that solid forms are so often present there after they have disappeared from all other skin sites and the nose, and that fingers are one of the most likely sites for skin to skin contact, are hazards that cannot be overlooked."

In my view the presence of "persister bacilli" in the fingers of such patients cannot possibly constitute a public health hazard. The concept of skin to skin transmission has been scientifically challenged and strong evidence adduced that leprosy bacilli seldom emerge, if ever, from intact lepromatous skin (Pedley, 1970*a*,*b*). In view of this, can anyone seriously believe that bacilli lurking in the finger (perhaps in Pacinian corpuscles—mentioned by the authors) would be able to work their way to the surface of the skin of the finger pulp—there to emerge in viable form, and thus constitute a public health hazard? To my mind this highly speculative suggestion is fanciful in the extreme, and, because of the stigma which attaches to the disease (Pedley, 1972), is an unfortunate conclusion to an otherwise interesting paper.

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J. C. PEDLEY

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Pedley, J. C. (1972). The stigma of leprosy—in four countries. *Lepr. Rev.* **43**, 94.

Lepr. Rev. (1977) **48**, 53–56

Book Reviews

Pathology in the Tropics, by G. M. Edington and H. M. Gilles. Published by Edward Arnold. Price £25.

A new edition of this useful book deserves a warm welcome. New material on malignant tumours and viruses, and the bringing up to date of the original text, some chapters more so than others, has added 200 pages to the volume. The original aim has been maintained: to describe the pathology of diseases that are exclusive to the tropics, and also the peculiarities special to the tropics of some more cosmopolitan diseases. The approach is mainly systematic, and the first-hand autopsy experience of the authors will be particularly valuable to the many people to whom autopsy material of tropical diseases is not freely available. As would be expected the book is particularly good on African diseases, with excellent chapters on malaria, schistosomiasis, diseases of the liver and heart and the haemoglobinopathies. If some other chapters are not up to the same standard (the one on leprosy is not outstanding), they all contain much succinct information and the selected references number nearly 3000. The influence of epidemiology on disease patterns is very well done and there is adequate background information on clinical correlations and on parasitology. Immuno-pathology is not a strong feature as regards either the tissue or serological responses. The sort of evaluation of immuno-diagnosis that is given for amoebiasis ought to be extended to other parasitic diseases. The book is well produced, though the illustrations are no more than adequate, and nothing has been done about the rather chaotic headings.

Despite a certain unevenness this book is a commendable achievement. Usage of the first edition has shown that its strength far outweighs its weakness, and this second edition is a worthy successor. It is a valuable source of information for pathologists both in the tropics and elsewhere which deserves a place on the shelves of most pathology departments. The book published by Arnold which the reviewer has seen costs £25, but it is understood that a cheap paperback edition is available at £8.50 through the English Language Book Society in most areas of the tropics.

D. S. RIDLEY

The Memories and Reflections of Dr Gerhard Armauer Hansen, translated by G. A. Hansen and with a foreword by Frederick B. Watt. Published by German Leprosy Relief Association, Würzburg, 1976.

For this English edition of "Memories and Reflections", written in Norwegian by Dr Hansen in 1912 shortly before his 70th birthday, we have to thank Mr Frederick B. Watt, a Canadian writer, and Mr Gerhard Armauer Hansen, a business executive and grandson of his famous namesake. They first met as naval officers during the Second World War and continued their friendship during the years that followed. It was in 1972 that the idea took shape that the two of them should combine to translate Dr Hansen's book, and the result of their labours appeared in print 4 years later.

The reader is greatly indebted to Mr Watt for his foreword to the book (consisting of 23 pages) in which he describes some important personalities and events which are omitted from Dr Hansen's story: his two marriages (his first wife, who was the daughter of the celebrated Dr Daniel Cornelius Danielssen, dying of T.B. 6 months after the marriage); his son Daniel, who

became a doctor and took up leprosy work in Bergen; the famous trial in 1880 when Dr Hansen admitted having inoculated a patient with leprous material without having obtained permission to do so; and it is from Mr Watt's pen that we learn that Dr Hansen participated in Nansen's Polar Expedition of 1876-78, and that he wrote a book on Darwin in 1886.

Dr Hansen begins his story with his childhood in Bergen, and goes on to describe his life as a University student in Oslo where he had to combine his studies and athletic pursuits—of which gymnastics was a favourite—with work as a tutor to enable him to meet his expenses. As he puts it, "With my father having ten sons to bring up and no money to spare, I naturally had to earn my own way as a student". He particularly enjoyed teaching in the Anatomy Department and, later, coaching in Medicine. He took his duties seriously, and describes how his regular routine would be to get up at 5.30 each morning in order to complete 2 hours of work before proceeding to University, and his working day would continue to 8 p.m. However, he enlivens his account of student days with perceptive descriptions of teachers and fellow students.

On qualifying in 1867 he spent a year as an intern before taking up an appointment in the Lofoten Islands, and he makes many pertinent observations on the problems besetting a Norwegian fisherman's life. It was on his return to Bergen that he was appointed to the leprosy hospital and his career in leprosy began. Within a year he published his first paper on the disease, the result of which was a stipend to travel abroad to further his studies. His travels first took him to Germany, where he studied microscopy in Bonn, and he writes of his impressions of the country and its people. He would spend convivial evenings with male companions, and he and his friends would spend Sundays tramping through the countryside and exploring lakes and forests. These were often very light-hearted trips, thanks to the local wine, for he describes one occasion when the good food and wine "left us sufficiently exuberant that we leapfrogged nearly 7 miles on the return trip to our steamer". He was in Bonn when the Franco-Prussian war broke out, and, joining the Red Cross, he arrived in Saarbrucken in time to witness the scene of carnage that resulted from the previous day's battle; he saw further evidence of the tragic consequences of war in a military hospital in Heidelberg before leaving Germany for Austria. While in Vienna one of the most important events in his life occurred, and this is how he describes it:

> "It began in ordinary enough fashion with my walking into a bookstore but when I came upon a copy of 'Natural Evolution', fate was at my elbow. The title itself challenged everything I had been taught about creation. I went home fascinated by my purchase and for 2 days read it to the complete neglect of my laboratory. Never had I read anything like it. The whole world stood out in an entirely different light than that which I had known. All I had been taught as a child collapsed as something unreal. The track on which my thought had formerly moved suddenly terminated and everything beyond was out of focus. There was, however, one compensation; my scientific searching had prepared me spiritually to absorb the mental shock of those days. . . . Later, after I had returned to Norway, I studied the works of Darwin in depth. They became the foundation of my outlook on life."

His stay in Vienna was followed by a visit to Venice before he returned to Bergen and leprosy work. At the same time he made a careful study of Darwin's writings:

> "I now commenced to study his books thoroughly and from them reached the heart of scientific research and reasoning: to set aside every preconceived opinion and to diagnose from every approach that might have a bearing on an ultimate solution. Nothing I had previously encountered had so fertilized my thought and my work. My goal had become that of researching as open mindedly and honestly as Darwin had, to be as thorough and, at the same time, as cautious as he in arriving at my conclusions. My previous scientific experience had left me well prepared to accept his teaching."

During the next 2 years, in which he spent each summer in the country districts seeking new sufferers from the disease, he was increasingly drawn towards the concept of leprosy as a communicable disease, and the fact that this was a view generally held by the country folk in Norway probably encouraged him in his search for an infective agent such as a bacterium. The

remarkable thing (and Dr Hansen makes no mention of this in his book) is that at that time the concept of bacteria causing disease in humans was in its infancy, and pathogenic organisms such as the gonococcus and the bacilli causing tuberculosis, tetanus, diphtheria, anthrax, etc., were all discovered *after* 1873. Later in the book he mentions the profound impact that Pasteur's researches had on him, and it is very likely that Darwin and Pasteur, each in his own way, influenced him in his search for the cause of leprosy. He says nothing about the stains he used, nor does he tell us what we would like to know about the actual finding of an organism under his microscope, but says:

> 'At that time I had a remarkable work endurance. I could sit tirelessly for hours on end, focussing through the microscope with great enlargement. Soon I found sufficient cells that appeared suspiciously like bacteria. Then began a time of seemingly interminable testing. One day I was positive I had discovered the bacteria, the next day the magnificent certainty had collapsed and I would be back where I had started. It was always again and again and again. Finally, though, I wrote the first record of my research. I could say no more than that I had found bacteria in the knots of leprosy and that I thought they were the poison causing the disease. . . . The suspense through those years of searching was great but personal success was not the overriding issue. It was whether I could solve the twisted and unanswered questions surrounding the heart of the illness. Success would leave us more certain of the precautions to take against the scourge. It was obvious to me that we could do nothing, or next to nothing, against it if it were hereditary but that there was every promise of achieving eventual results if it were caused by bacteria and infectious."

Characteristically he makes light of the episode of Neisser's visit to Bergen and subsequent publication in which he claimed to be the discoverer of the leprosy bacillus, except to record that his chief, Danielssen, was "absolutely furious".

In 1888 Dr Hansen went to the U.S.A. to observe the leprosy situation in the descendants of Norwegians who had emigrated from Norway:

> "Approximately 200 Norwegian lepers had immigrated there and I had the conviction that further concrete evidence towards confirmation of my claim could be found in that setting. Since the disease, if inherited, would not disappear simply because of a move to a far country, there would be obvious value in making a study of those leprous immigrants and their relatives and descendants, especially as so many of the leper emigrants had numerous offspring and other relatives."

He met many Norwegians on his travels in the U.S.A. and noted how well they had prospered in the new land as a result of hard work, but he has not given us any information on the one thing we want to know–did he find any leprosy? Here we have to turn to other authors who have studied Dr Hansen's life, and they tell us two things; firstly, that Dr Hansen found no leprosy in those Norwegian families, and, secondly, that he gave it as his opinion that this was largely due to good housing and living conditions.

In the pages of this book we learn a great deal about the author's character and philosophy of life– his disillusionment with the Christian faith in general and with the Lutheran Church in particular, his pacifism and opposition to any form of racialism (natural corollaries to his abiding faith in the brotherhood of man), his love of truth and detestation of cant and hypocrisy, and his faith in the future development of scientific thought and research:

> "This is a great comfort to me in my old age–that future generations will solve many–yes, all of the riddles that the present one has struggled with in vain."

W. H. JOPLING

Adams and Maegraith's Clinical Tropical Diseases, 6th edit. Edited by Brian Maegraith. Published by Blackwell. Price £10.50.

The Sixth Edition of this standard textbook of tropical medicine is distinguished in many aspects, but none more so than the chapter on leprosy written by Dr Stanley Browne. It is a pleasure to encounter in a textbook of general medicine a section on leprosy which is commensurate with the importance of leprosy in the world, and is entirely authoritative and up to date. Strongly recommended.

T. F. DAVEY

Lepr. Rev. (1977) **48**, 57–76

Abstracts

1. PAUL, R. C., STANFORD, I. J. L. & CARSWELL, J. W. **Multiple skin testing in leprosy**. *J. Hyg. (Lond),* 1975, v. 75, 57-68.

Ten reagents prepared by ultrasonic disintegration from *M. tuberculosis, M. duvalii, M. chelonei* and 7 other species of mycobacteria were skin tested in groups of patients and hospital staff from 6 leprosaria in E. Africa together with non-contact groups. It was found that the specific defect to *M. leprae* of lepromatous patients also applied to a variable extent to 6 other species tested, but most noticeably to *M. nonchromogenicum* and *M. vaccae,* suggesting that these species are more closely related to *M. leprae* than others tested.

T. F. Davey

2. BARTON, R. P. E. **Clinical manifestations of leprous rhinitis.** *Ann. Otol. Rhinol. & Laryngol.,* 1976, v. 85, 74-82.

This detailed study of the clinical appearances in the nose especially in early lepromatous leprosy is of great value and should be essential reading for all concerned with the diagnosis and care of those with early leprosy, coming as it does from an author with unique experience in this field.

T. F. Davey

3. BARTON, R. P. E. **Importance of nasal lesions in early lepromatous leprosy.** *Ann. Roy. Coll. Surg. Engl.,* 1975, v. 57, 309-312.

The pathological changes which occur in the nose of early lepromatous leprosy are outlined and attention drawn to the heavily bacillated nasal discharge as the most important source of viable leprosy bacilli discharged from the body. The necessity for early diagnosis and treatment is emphasized.

T. F. Davey

4. JAMANS, A. G. **A dermatological survey of the Ghurka Brigade.** *J. roy. Army med. Cps.,* 1976, v. 122, 135-142.

A thorough dermatological survey of 4500 serving officers and soldiers of the Brigade of Ghurkas revealed a prevalence of 11.3 cases of leprosy per thousand in this highly selected group, and almost doubled the previously known prevalence, suggesting that indeterminate lesions overlooked on recruitment later underwent development. Only 1 of the 25 new cases discovered had lepromatous leprosy. Some previous estimates of the prevalence of leprosy in the general population of the Himalayan foothills may have underestimated the problem.

T. F. Davey

The following Abstracts from the August, September, October and November 1976 Issues of *Tropical Diseases Bulletin* are reproduced here by courtesy of the Director, Bureau of Hygiene and Tropical Diseases. They are listed according to subject.

1. MICROBIOLOGY

5. SAXENA, H., AJWANI, K. D., PRADHAN, S., CHANDRA, J. & KUMAR, A. **A preliminary study on bacteremia in leprosy**. *Lepr. India,* 1975, v. 47, No. 2, 79-84.

Leprosy bacilli were found in the peripheral blood in 2 cases of lepromatous leprosy (classified on clinical and histopathological grounds) but not in 29 cases of tuberculoid leprosy. One to 5 bacilli were present, mainly within mononuclear cells, 1 cell in about 500 being affected. The authors conclude that patients suffering from tuberculoid leprosy are completely non-infective and need not be segregated, whereas those suffering from lepromatous leprosy—"a very infective disease"—should be segregated.

S. G. Browne

6. PRABHAKARAN, K. **Specificity of *o*-diphenoloxidase in *Mycobacterium leprae*: An identification test**. *Lepr. India,* 1976, v. 48, No. 1, 19-23.

Mycobacterium leprae from human skin, spleen, and testes, from mouse foot-pad, and from armadillo skin, spleen, and liver gave positive reactions in the dopa spot test [*Trop. Dis. Bull.,* 1974, v. 71, abstr. 513] but all other *Mycobacterium* spp. tested, including *M. lepraemurium* and *M. tuberculosis,* gave negative reactions. In a modification of the test, filter paper discs, dipped in the dopa solution and dried, gave the same colour change as the solution. Bacilli from biopsy specimens gave the best results. The specimens may be stored at -20°C for up to 4 weeks without appreciable loss of enzyme activity in the bacilli. The author stresses the importance of using a sufficient quantity of bacilli, at least 5×10^7.

F. I. C. Apted

7. DESIKAN, K. V. & VENKATARAMANIAH, H. N. **A modified method of harvesting *M. leprae* from foot-pads of mice**. *Lepr. India,* 1976, v. 48, No. 2, 157-162.

"A modified technique of harvesting *M. leprae* from the foot-pads of mice is described. The method is simple and takes less time for its performance than the conventional techniques. The yield of bacilli is also better. No difficulties have been encountered in its application in these laboratories."

8. LEVY, L. **Bactericidal action of dapsone against *Mycobacterium leprae* in mice**. *Antimicrob. Agents Chemother.,* 1976, v. 9, No. 4, 614-617.

"Dapsone (4,4′-diaminodiphenylsulfone), incorporated into the mouse chow in a concentration of 0.1 g/100 g of diet, was administered for 1 week to mice in which *Mycobacterium leprae* had multiplied to the level of 10^6 organisms/foot-pad. *M. leprae* were harvested from these and also from control mice, diluted serially, and inoculated into additional mice. The organisms recovered from untreated mice multiplied in passage with a mean doubling time of 12.2 days, and 35% or more of the inoculated organisms were viable, i.e. capable of infecting mice. Growth curves of *M. leprae* recovered from dapsone-treated animals lagged behind those of organisms from control animals by an average of 78 days, equivalent to 98.8% killing. Foot-by-foot harvests showed that only 0.2% of the *M. leprae* recovered from treated mice were

viable, suggesting that treatment of mice with dapsone had been accompanied by killing of 99.4% of the viable *M. leprae*."

9. ULRICH, M., CONVIT, J., CENTENO, M. & RAPETTI, M. **Immunological characteristics of the armadillo. *Dasypus sabanicola*.** *Clin. Exp. Immunol.,* 1976, v. 25, No. 1, 170-176.

"The immunological responses of the armadillo are of interest because of its susceptibility to generalized lepromatoid infection with *Mycobacterium leprae*. In this study, specimens of *Dasypus sabanicola* were found to have a typical mammalian distribution of lymphoid cells in thymus, spleen, lymph nodes and blood. Their complement was active in bactericidal, protozoan immobilization and haemolytic systems. Blood lymphocytes responded to phytohaemagglutinin and to pokeweed mitogen. Sensitization with ovalbumin in CFA resulted in the production of circulating precipitins; strong Arthus reactions were detectable in the sensitized animals. Responses of cell-mediated immunity to DNCB and to *M. tuberculosis* were very discrete. Heat-killed *M. leprae* elicited granulomatous reactions characterized by microscopic necrosis, but without abundant lymphocytic infiltration; skin tests and lymphocytic transformation were generally negative in the animals injected with *M. leprae*."

10. HOLMES, I. B., BANERJEE, D. K. & HILSON, G. R. F. **Effect of rifampin, clofazimine, and B1912 on the viability of *Mycobacterium leprae* in established mouse foot-pad infection.** *Proc. Soc. Exp. Biol. Med.,* 1976, v. 151, No. 4, 637-641.

Rifampicin (Rifampin) and clofazimine (B663) were administered continually or intermittently (1 day in 30, over 5 months). Doses were: rifampicin, 0.03% in the diet (75 mg/kg/day); clofazimine and B1912, 0.01% continually (25 mg/kg/day) or 0.03% intermittently. The strains of *M. leprae* were sensitive to dapsone (DDS) and would not grow in mice receiving 0.0001% dapsone in the diet. The effect of rifampicin in the absence of host immune response was also studied in mice inoculated with 10^6 *M. leprae* and immediately immunosuppressed with anti-mouse-thymocyte globulin (0.2 ml, subcutaneously, twice weekly) and hydrocortisone acetate (4.0 mg/kg/day). In infected mice treated continuously with rifampicin the bacillary solid ratio was reduced with a survival half-life of 5-6 days, this being 12-13 days in rifampicin-treated immunosuppressed animals in the absence of host immunity. Both clofazimine and B1912 produced a significant effect only after a lag period of 100 days, the rate of action being considerably slower than rifampicin. Intermittent or continuous administration of both clofazimine and B1912 produced comparable results.

W. Houston

11. SKINSNES, O. K., CHANG, P. H. C. & MATSUO, E. **Acid-fast properties and pyridine extraction of *M. leprae*.** *Int. J. Lepr.,* 1975, v. 43, No. 4, 339-347.

"The reportedly unique pyridine extractability of acid-fastness as an identifying characteristic for *M. leprae* was examined in the leprosy bacilli and in eight other strains of mycobacteria. The initial findings were, in general, in accord with previous reports except that *M. smegmatis* and *M. phlei* likewise demonstrated 2 h pyridine extractability of acid-fastness. Perhaps, more significantly, it was found that this characteristic in *M. leprae* is related to aged, probably nonviable bacilli. Some other strains of mycobacteria when tested in aged cultures showed the same phenomenon while *M. leprae* cultivated *in vitro* in a recently developed medium resisted pyridine extraction up to 3 weeks of growth, but thereafter as the culture aged pyridine extractability became characteristic. It is concluded that this pyridine extractability of acid-fastness is a characteristic of ageing or nonviable bacilli. As such it is not definitive in the determination of whether or not *in vitro* cultivation of *M. leprae* has been achieved."

12. COLSTON, M. J. & HILSON, G. R. F. **Growth of *Mycobacterium leprae* and *M. marinum* in congenitally athymic (nude) mice.** [Correspondence.] *Nature.* London, 1976, July 29, v. 262, 399-401.

Congenitally athymic (nude) mice were tested for susceptibility to infection with *Mycobacterium leprae* in the hope that they would provide a more convenient model for experimental infections of the lepromatous type. A previous attempt to infect nude mice (Prabhakaran *et al., Experientia,* 1975, v. 31, 784) had only been maintained for 6 months, which was regarded as insufficient. Thirty homozygous nude mice were inoculated in the foot-pads with *M. leprae,* together with a group of heterozygous phenotypically normal littermates which were used as controls.

Survival of the nude mice was poor, but enhancement of growth in the two longest surviving mice at 266 and 322 days, by comparison with controls, was highly significant. In addition to the foot-pad, significant numbers of bacilli were found in the liver ($10^{5.3}$) and spleen ($10^{5.3}$) and scanty bacilli were found in testes, nose, tail and forepaw. In another experiment, enhancement of growth of *M. marinum,* which does not curtail survival of nude mice, was even more convincing.

If the problem of survival could be overcome, nude mice might provide a very useful model for leprosy.

D. S. Ridley

13. KAWAGUCHI, Y., MATSUOKA, M., KAWATSU, K. HOMMA, J. Y. & ABE, C. **Susceptibility to murine leprosy bacilli of nude mice.** *Jap. J. Exp. Med.,* 1976, v. 46, No. 3, 167-180.

"Comparative observations were made on the development of experimental murine leprosy in various inbred strains of mice, including nude mice of congenital thymic aplasia. The susceptibility of these strains of mice to murine leprosy bacilli was evaluated by the development of leproma at the subcutaneous infection site and also by the involvement of visceral organs.

"Nude mice developed a much more severe disease than C3H mice which is the representative of the malignant type. Their high sensitivity was also demonstrated in the case of intraperitoneal infection.

"The observations in nude mice and other mouse strains confirmed our concept that experimental mouse leprosy can be classified into 3 clinical types, benign, intermediate and malignant, and suggested that such mouse strain differences are related with their cell-mediated immunity."

2. IMMUNOLOGY, PATHOLOGY

14. SAINT-ANDRE, P. La stimulation de l'immunité à médiation cellulaire dans la lèpre lépromateuse: état actuel du problème. [**A survey of the stimulation of cell-mediated immunity in lepromatous leprosy**.] *Méd. Trop.,* 1976, v. 36, No. 1, 80-85.

The English summary appended to the paper is as follows:

"Lepromatous leprosy is caused by a deficiency in cell-mediated immunity (C.M.I.) and recent advances about C.M.I. are reviewed by the author. He, then, considers the test tactical approach for anti-leprosy action and he favours the stimulation of C.M.I. associated with chemotherapy: injections of leucocytes, the use of transfer factor, unspecific stimulations by B.C.G., various bacterial lysates and Levamisole (original experiments).

"The author emphasizes a new anti-leprosy procedure beginning with Rifampicin (900 mg a week for the first 2 months) then C.M.I. stimulation associated with chemotherapy."

15. HARDAS, U. D. & SAOJI, R. G. **17-Ketosteroids in leprosy**. *Int. J. Lepr.,* 1975, v. 43, No. 3, 249-251.

"Urinary 17-ketosteroids were estimated in 29 lepromatous leprosy cases. Correlation between 17-ketosteroid values, histopathologic findings, and serum S.G.P.T. values is discussed. Low values of 17-ketosteroids were associated with definite leproma in liver indicating the value of liver damage to 17-ketosteroids. This was more marked in males than in females."

16. MEYERS, W. M., KVERNES, S. & BINFORD, C. H. **Comparison of reactions to human and armadillo lepromins in leprosy**. *Int. J. Lepr.,* 1975, v. 43, No. 3, 218-225.

Skin reactions to lepromins prepared from human and armadillo sources were compared in 115 leprosy patients. Lepromin derived from the armadillo provoked a pattern of response identical with that derived from human lepromatous tissue, and gave consistently more intense reactions. The armadillo is thus a promising source for a standardized lepromin.

T. F. Davey

17. MILLAR, J. W., GANNON, C. & CHAN, C. S. P. **Comparison in leprosy patients of Fernandez and Mitsuda reactions using human and armadillo antigens. A double-blind study.** *Int. J. Lepr.,* 1975, v. 43, No. 3, 226-233.

A careful study of Mitsuda and Fernandez reactions to lepromins derived from armadillo and human sources led to the conclusion that lepromin prepared from *Mycobacterium leprae* obtained from infected armadillos is as effective as that prepared from bacilli obtained from human lepromatous tissue.

T. F. Davey

18. BARNETSON, R. ST C., BJUNE, G. & DUNCAN, M. E. **Evidence for a soluble lymphocyte factor in the transplacental transmission of T-lymphocyte responses to *Mycobacterium leprae*.** [Correspondence.] *Nature.* London, 1976, Mar. 11, v. 260, 150-151.

The *in vitro* lymphocytic blastogenic response to whole washed *Mycobacterium leprae* was used to demonstrate specific cell mediated hypersensitivity in normal mothers and their babies at birth. Cord blood lymphocytes from babies of 5 sensitive mothers were consistently shown to be sensitized; those from babies of insensitive mothers were shown not to be sensitized. This condition was statistically highly significant. There was correlation in BCG responsiveness between the 2 maternal groups and between the 2 neonatal groups. Mothers unresponsive to *M. leprae* were also unresponsive to PPD, but this correlation was not found between the 2 neonatal groups.

It was concluded that the strict correlation between maternal and neonatal lymphocyte responsiveness to *M. leprae* implied the transplacental passage of either antigen, lymphocytes or a soluble factor released from lymphocytes. Antigen seemed unlikely as no mother showed signs of leprosy or other mycobacterial disease. The question of transplacental passage of maternal lymphocytes is still debated, but recruitment of foetal lymphocytes would seem necessary to produce the demonstrated response. A soluble lymphocyte product, such as the small molecular weight molecule known as transfer factor, might cross the placenta relatively easily and could be expected to sensitize foetal lymphocytes.

A. D. M. Bryceson

19. BJUNE, G., BARNETSON, R. ST C., RIDLEY, D. S. & KRONVALL, G. **Lymphocyte transformation test in leprosy; correlation of the response with inflammation of lesions.** *Clin. Exp. Immunol.,* 1976, v. 25, No. 1, 85-94.

"Lymphocyte transformation tests (LTT) using 'whole washed' and 'sonicated' preparations of *Mycobacterium leprae (M. leprae)* as antigen were studied in 81 patients with borderline leprosy. The results were correlated with the histological and the clinical pictures.

"There was a good correlation with the histological spectrum, LTT responses generally being higher in the borderline tuberculoid leprosy patients and lower in the borderline lepromatous. However, considerable variation was noted in each group of the borderline leprosy spectrum, and it was found that this was due in part to the degree of inflammation in the skin. Thus those with 'inflamed' skin lesions had higher responses than those with 'silent' lesions, and even those with borderline lepromatous leprosy with inflamed lesions had higher responses than those with borderline tuberculoid leprosy whose lesions were silent. Those who had reversal reactions, where inflammation is very marked, had very high LTT responses which fell with treatment of the reaction with steroids.

"It thus appears that the LTT in leprosy is influenced by the occurrence of hypersensitivity reactions as well as by the patient's ability to resist bacillary multiplication."

20. SCHEVING, L. E., ENNA, C. D., HALBERG, F., JACOBSON, R. R., MATHER, A. & PAULY, J. E. **Mean circadian cosinors of viral signs, performance of blood and urinary constituents in patients with leprosy.** *Int. J. Lepr.,* 1975, v. 43, No. 4, 364-377.

"We have herewith examined the characteristics of circadian rhythms in patients with lepromatous leprosy, active or inactive, allowing a comparison with corresponding properties of rhythms in healthy subjects mapped earlier. Group results were illustrated by cosinor plots, produced directly on microfilm by computer. Eventually such reference standards in the form of cosinors, among other displays, notably of waveform, may be individualized and carried on a person's health record. Such a quantitative assessment of an individual's rhythms in health may serve for rigorous comparison with any changes accompanying increased susceptibility or occult or overt disease."

21. CARAYON, A., LANGUILLON, J., GIRAUDEAU, P., CAMAIN, R. & MAYDAT, L. Névrites micro-angiopathiques d'origine auto-immune probable après migrations inverses dans la zone borderline du spectre de la lèpre. [**Micro-angiopathic neuritides, probably of auto-immune origin and following immunological changes in the borderline zone of the leprosy spectrum.**] *Méd. Trop.,* 1976, v. 36, No. 1, 16-33. English summary.

The authors break important new ground in these studies of the multifactorial aetiology of nerve damage in leprosy. Clinical observations, histopathological examination of tissue removed at biopsy, direct inspection of nerves exposed at operation, and evaluation of medical and surgical decompression of constricted nerves lead them to suggest that an important factor in nerve damage in leprosy lies in the occurrence of multiple minute vascular lesions. These are attributed essentially to changes in the immunological status of the patient and, particularly, to a down-grading following a reversal reaction. The resulting vaso-constriction leads to localized oedema in the nerve. The breakdown of the myelin in the nerve sheaths releases products that provoke auto-immune reactions on the one hand and a Guillain-Barré type of allergic neuritis on the other.

Anti-inflammatory treatment by systemic corticosteroids associated with specific leprostatics (like clofazimine) is advocated, with surgical decompression where indicated.

[It is to be hoped that the authors will supplement these studies with the demonstration of the immune complexes, antigens and antibodies that their elegant suggestions require.]

S. G. Browne

22. PRICE, M. A., ANDERS, E. M., ANDERS, R. F., RUSSELL, D. A. & DENNIS, E. S. **Cell-mediated immunologic status of healthy members of families with a history of leprosy.** *Int. J. Lepr.,* 1975, v. 43, No. 4, 307-313.

"The cell-mediated immune status of 20 apparently healthy children from families with a history of leprosy has been studied. They have been compared with 20 age- and sex-matched controls from families with no history of leprosy. Lymphocyte transformation tests using PHA, PPD and lepromin and skin tests to lepromin, PPD and candida were carried out. No evidence of a depression of cell-mediated immunity in the children from families with leprosy was obtained.

"The only 2 children giving a negative Mitsuda lepromin skin test both subsequently developed leprosy in the succeeding 16 months. One was classified histologically as indefinite lepromatous and the other as borderline lepromatous. This emphasizes the practical significance of a negative lepromin skins test in an endemic leprosy area as a prognosis of clinical lepromatous leprosy."

23. KRISHNAMURTHY, S., VERGHESE, R. & JOB, C. K. **The Kveim test in leprosy.** *Int. J. Lepr.,* 1975, v. 43, No. 4, 333-338.

"The response to lepromin and Kveim antigens was compared and studied in 15 leprosy patients who were tuberculin negative. Of the 11 lepromin positive tuberculoid patients, 4 were Kveim positive, 1 was equivocal, and the rest were negative. Of the 4 lepromin negative lepromatous patients, 1 gave a positive Kveim test while the other 3 were negative. It has been shown that false-positive Kveim reactions are found in a higher percentage of South Indian leprosy patients than in those of other backgrounds, such as Japanese and Malaysian Chinese patients. It is also suggested that no definite relationship exists between the reaction of leprosy patients to lepromin and Kveim antigens. We further suggest that the anergy exhibited by lepromatous patients to the antigen of *M. leprae* is specific, as evidenced by the positive Kveim response in one lepromatous patient."

24. REA, T. H. *et al.* **Immunologic responses in patients with lepromatous leprosy.** *Arch. Derm.,* 1976, v. 112, No. 6, 791-800.

"Immunologic responses were measured in 46 patients with lepromatous leprosy. These patients were not distinguishable from controls on the basis of responses to soluble intradermal antigens, sensitization to contactants, peripheral blood T- and B-cell percentages, *in vitro* lymphocyte responses to a mitogen, or the prevalence of autoantibodies. Generalized immunologic abnormalities in patients with lepromatous leprosy are neither predisposing causes nor necessary accompaniments of lepromatous leprosy, but are probably remote sequelae of the illness. By implication, the generalized immunologic abnormalities reported in other diseases are likely to be remote sequelae of the particular illness."

25. GUPTA, M., BHARGAVA, M., KUMAR, S. & MITTAL, M. M. **Platelet function in leprosy.** *Int. J. Lepr.,* 1975, v. 43, No. 4, 327-332.

"In a group of 50 leprosy patients, platelet function tests were found to be abnormal in 44. More than half the patients showed significant impairment in platelet adhesiveness and aggregation to collagen which correlated best with increase in serum IgM levels. ADP-induced aggregation of platelets was not a major defect and Pf-3 availability was reduced only in a fourth of the patients. *In vitro* incubation of collagen with plasma from leprosy patients significantly reduced its ability to clump normal platelets. This appears to be the first report of

defective platelet function in leprosy, and it is thought that such changes may in part be due to increased IgM globulins in the blood and/or to alterations in the collagen brought about thereby."

26. SAHA, K., DUTTA, R. N. & DASGUPTA, A. **Immunologic aspects of leprosy with special reference to the study of immunoglobulin E.** *Int. J. Lepr.,* 1975, v. 43, No. 4, 314-319.

"The serum levels of IgG, IgM, IgD and IgE have been determined in normal subjects, individuals suffering from ascariasis and filariasis, and in leprosy patients. Allergic and parasitic diseases were excluded in these normal subjects and in leprosy patients before they were taken for the study of their serum levels of IgE. The circulating IgG was significantly raised in both tuberculoid and lepromatous forms of leprosy and also in filariasis; IgM was significantly elevated in only the lepromatous form of leprosy, ascariasis as well as in filariasis; while IgA was exclusively raised in both forms of leprosy. IgD was detected in the sera of more subjects with ascariasis and filariasis than in normal individuals and leprosy patients. The mean level of serum IgE in 35 normal Indian subjects was 1025 iu per ml, 9 of them (25%) having serum IgE concentrations above 700 iu per ml. The highest mean level of serum IgE was found in ascariasis (7328 iu per ml), followed by leprosy (5180 iu per ml), and filariasis (4244 iu per ml). Furthermore, no significant difference between the mean serum IgE levels of tuberculoid and lepromatous leprosy patients was observed. Although the rise of serum IgE level in these parasitic diseases, as well as in leprosy, was spectacular, the augmented synthesis of this unique class of immunoglobulins was not invariably present in all patients. The results have been discussed on the basis of recent ideas on immunoglobulin synthesis."

27. ESTRADA-PARRA, S., PEREZ-MOSQUEIRA, N., GOMEZ-VIDAL, M. & ROJAS-ESPINOSA, O. **A serological profile in leprosy.** *Revta Lat.-am. Microbiol.,* 1975, v. 17, No. 4., 211-212.

"Serological profiles were studied in 54 patients with different types of leprosy and the data compared with those obtained from 30 healthy individuals. The results indicate that the patients' group have increased levels of total proteins, alpha 2 and gamma globulins. All, IgG, IgA and IgM immunoglobulins were elevated. The higher values for these serum components were found in the group of patients with nodular lepromatous leprosy. However, C_4 seemed to be in lower concentration within the patients group. Patients with erythema nodosum leprosum showed higher incidence of soluble immune complexes. Twenty per cent of the patients were positive for the C-reactive protein test. Most of the patients (80%) were under treatment at the moment of the study."

28. BROCHARD, C., LANGUILLON, J., SAIMOT, G., GENITEAU, M., COULAUD, J. P. & PAYET, M. Intérêt de la recherche des cryoglobulines dans la lèpre. [**Value of the detection of cryoglobulins in leprosy.**] *Méd. Trop.,* 1976, v. 36, No. 1, 69-79. English summary (7 lines).

The authors investigated the presence of cryoglobulins in a series of 274 patients in Senegal. The proportion of patients with cryoglobulins in their sera varied from 65% in those with lepromatous leprosy to 15% in those with the tuberculoid form. In 3 patients out of 7 with borderline lepromatous leprosy, cryoglobulins were present, but in none out of 7 with borderline tuberculoid leprosy. In patients with multibacillary forms of leprosy passing through an episode of erythema nodosum leprosum, the percentage of cryoglobulinaemia reached 84.

A useful indication of the potential polarity of indeterminate forms of leprosy was provided by the investigation of the presence of cryoglobulin. In the majority of patients in whom the globulin was found, the eventual evolution towards a multibacillary form of leprosy was in accord with the initial finding.

The authors also investigated the titres of complement present in the sera, utilizing macrophage receptors and ^{125}I tagged Clq: the results will be published shortly.

S. G. Browne

29. KRONVALL, G., BJUNE, G., STANFORD, J., MENZEL, S. & SAMUEL, D. **Mycobacterial antigens in antibody responses of leprosy patients.** *Int. J. Lepr.*, 1975, v. 43, No. 4, 299-306.

"A reference system for *M. smegmatis* antigens in crossed immunoelectrophoresis was used to study antibody activities in serum samples of 91 leprosy patients. All polar and borderline lepromatous patients were positive. Mean numbers out of 14 *M. smegmatis* antigens involved were 4.3 and 3.5, respectively. Precipitins against antigen no. 1 were seen in all lepromatous cases. Antibodies against this antigen were detected in 50% of tuberculoid (polar, subpolar and borderline) cases. Antibody activity against *M. avium* and *M. duvalii* antigens was also detected usina staphylococcal radioimmuno-assay. Borderline and polar lepromatous cases showed elevated levels. Antigenic comparisons were made between 4 slow growing mycobacteria, 14 fast growing mycobacteria and the leprosy bacillus using lepromatous serum pools as antibody reagents. Four of the antigens detected in *M. leprae* were also found in slow growing as well as fast growing species indicating a common occurrence among mycobacteria. Antigen no. 1 of *M. duvalii,* with an apparent molecular weight of 290,000, showed nonprotein characteristics. Further analysis of antigen no. 21, using lepromatous serum pools as antibody reagents, indicated the existence of at least 2 groups of antigenic determinants. In addition to determinants shared by all mycobacteria, there were antigenic structures apparently unique to *M. leprae*."

30. WILHELM, G. & SELLIER, J. L. **Presence of antibodies reacting with a ribonucleoprotein from *Mycobacterium tuberculosis* in sera from leprous patients.** *Zentbl. Bakt. I. Orig., Ser. A,* 1976, v. 234, No. 1, 68-71.

Ribonucleoprotein (RNP) with a molecular weight of between 12,000 and 13,000 was isolated from *Mycobacterium tuberculosis.* It was tested by an agar-gel double diffusion method against sera from 10 subjects with lepromatous leprosy, 201 subjects with tuberculosis and 114 healthy blood donors. All the sera from the leprous subjects reacted with the RNP, 4 of the sera from the tuberculous subjects gave weak reactions and none of the sera from the blood donors reacted. When tested in a radioimmuno-assay system, the sera from the leprous subjects had significantly higher titres than the sera from tuberculous subjects. It is concluded that the antigenic determinants in RNP isolated from *M. tuberculosis* must be similar to those in *M. leprae.*

RNP is capable of protecting guinea pigs and mice against infection with *M. tuberculosis.* In view of the cross-reactivity with *M. leprae* it may also protect against infection with this organism.

P. A. Jenkins

31. SAINT-ANDRE, P. LOUVET, M. & SCHLECH, B. Stimulation de l'immunité à médiation cellulaire par le B.C.G. dans la lèpre lépromateuse et intermédiaire. **[Stimulation of cell-mediated immunity by BCG in lepromatous and borderline leprosy.]** *Méd. Trop.,* 1976, v. 36, No. 2, 133-136. English summary.

This interim report continues the previous work of the authors. Their original posology is now modified, and they give progressively increasing doses of BCG, intradermally, beginning with 0.1 ml of 1 in 100 dilution. This dose is increased every fortnight, until a maximum of 0.1 ml

of a 1 in 10 dilution is attained. The injections were well tolerated, except that necrotic nodules developed at some injection sites in all the patients.

The authors concluded that acceptable degrees of stimulation of cell-mediated immunity had been demonstrated in all patients. In 7 suffering from polar lepromatous leprosy, the Mitsuda reaction became positive clinically, but histopathological examination revealed a predominantly borderline response. In 6 patients with borderline leprosy, there was rapid clinical and bacteriological improvement, even of signs of nerve damage in 4 out of 5 patients. In 2 patients with lepromatous leprosy out of a total of 10 treated with BCG, erythema nodosum of moderate severity occurred.

It is concluded that the clinical improvement noted was more rapid than that observed when dapsone alone is given, and that further investigations are indicated.

[See *Trop. Dis. Bull.*, 1976, v. 73, abstr. 1815.]

S. G. Browne

32. SAINT-ANDRE, P., LOUVET, M., GIRAUDEAU, P. & SCHLECH, B. Effets de la stimulation de l'immunité cellulaire par les lysats et extraits bactériens dans la lèpre lépromateuse. **[Results of the stimulation of cell-mediated immunity in lepromatous leprosy by bacterial lysates and extracts.]** *Méd. Trop.*, 1976, v. 36, No. 2, 137-145. English summary.

The authors attempted to stimulate cell-mediated immunity in leprosy patients by giving them a series of injections (every other day) of a glycocolic lysate of *Neisseria perflava* (Ducton), an agent that non-specifically accelerates phagocytosis of carbon particles in the experimental animal.

In 3 of the 7 patients with lepromatous leprosy, treatment was abandoned after 7 to 12 months, in the absence of improvement. In 2 others, however, rapid improvement was noted for 18 months, but relapse followed. In the 6th patient, rapid and sustained improvement occurred and the Mitsuda test became positive. The variable and unpredictable results are attributed to differences in the potential for cell-mediated immunity. In 3 patients with borderline leprosy, improvement in the clinical state and in signs of nerve damage was thought to be due to the treatment given. Moreover, the improvement was maintained for 21 months.

A mixture of bacterial lysates intended to stimulate local rhinopharyngeal defence mechanisms against infection (Stimugène) was given to 9 patients suffering from lepromatous leprosy. Sublingual and injectable preparations were used. The results as demonstrated by improvement in lesions in the nasopharynx (rhinitis and epistaxis) and the skin were "astonishing", and the authors consider that they were at least as good as those achieved by standard chemotherapy. The histopathological and bacteriological results were thought to be equally satisfactory. The injectable form of the product had a more rapid action than that administered sublingually.

[This novel form of attack deserves further critical evaluation in larger series of patients, and its long-term effects on the disease and lymphocyte activity should be more precisely determined.]

S. G. Browne

33. SAHA, K. MITTAL, M. M. & MAHESWARI, H. B. **Passive transfer of immunity in leprosy patients by transfusion of lymphocytes from lepromin positive healthy donors.** *J. Indian Med. Ass.*, 1976, v. 66, No. 5, 93-101.

Four-hundred-million viable lymphocytes from the peripheral blood of healthy tuberculin and lepromin positive individuals were transfused into 5 patients with leprosy [3 lepromatous (LL), 1 borderline lepromatous (BL) and 1 borderline tuberculoid (BT)], all in a reactive condition and all negative to lepromin and normal lymphocyte transfer tests. Three transfusions were given at monthly intervals. Reactive episodes followed each transfusion in all cases, but definite

bacteriological and histological improvement was observed in 4 of the 5 patients; clinical improvement was also witnessed, most marked in the BT and BL patients. In repeat immunological assessment in 3 patients 5 months later, the only change observed was that the BL patient developed a positive Fernandez reaction.

T. F. Davey

34. CARAYON, A. Gamme lésionnele des névrites hanséniennes. (État actuel des acquisitions récentes et des orientations thérapeutiques.) **[The pathological range of neuritis in leprosy. (A survey of recent advances and of trends in treatment.)]** *Méd. Trop.,* 1976, v. 36, No. 1, 41-61. English summary.

The author reviews the recent contributions made by clinicians, histopathologists and immunologists to the elucidations of the various patterns of nerve damage in leprosy, and attempts to correlate the different findings with the pathological features of the various types of leprosy. He asserts that biopsy specimens taken from mixed nerve trunks, especially at sites of maximal damage, would show changes in structure (and hence, in function) much more obviously related to the type of leprosy, its stage of advancement and its state of clinical activity, than a biopsy taken from a small superficial sensory nerve.

The concordance in the cases of tuberculoid and borderline leprosy is now generally accepted, but further investigation is needed in the case of multibacillary forms of leprosy, and the neuritides occurring in erythema nodosum leprosum and secondary auto-immune phenomena. He makes the point that, in the acute forms of neuritis, intrafascicular oedema and multiple small vascular lesions may predominate and these are frequently reversible with anti-inflammatory treatment or surgical decompression.

His studies emphasize the role of mechanical constriction of nerves in fibrotendinous or fibro-osseous canals and the damage that results from unrelieved constriction and traumatic elongation of the nerve trunks in this situation. In conclusion, he pleads for further unprejudiced observation of early and reversible impairment of peripheral nerve function, so that the incubus of permanent nerve damage may be relieved.

S. G. Browne

35. COUTELIER, L., FLESHMAN, K. & NOEL, H. Observations sur les remaniements osseux dans un cas de lépre. **[Observations on bone changes in a case of leprosy.]** *Ann. Soc. Belg. Méd. Trop.,* 1975, v. 55, No. 4, 359-371. English summary (8 lines).

Using the special techniques of microradiography and fluorescent microscopy developed by one of the authors, the team record their investigation of the changes observed in the 5th metatarsal of a patient who had suffered from tuberculoid leprosy, whose foot had to be amputated because of gangrene.

Illustrated with excellent photographs, the article emphasizes the different kinds of bony change that follow peripheral damage—destruction alone, new bone formation without preceding destruction, and bone destruction and new bone formation proceeding concurrently. The authors emphasize the rapidity with which the new bone is formed, and the extent of the subperiosteal erosion. They suggest a kind of compensation between peripheral bone destruction and central bone formation and deposition, and suspect that the vascular component plays a decisive role in the process.

S. G. Browne

36. GUPTA, J. C., JESUPADAM, T., GUPTA, M. C. & GUPTA, D. K. **A histopathologic study of striated muscle biopsies in leprosy.** *Int. J. Lepr.,* 1975, v. 43, No. 4, 348-355.

"Histopathologic changes in striated muscle biopsies in 50 cases of leprosy were studied; 40 being the lepromatous type and 10 the non-lepromatous type. All the biopsies were obtained

from midportions of normal looking bicep muscles and paraffin embedded. Sections cut in transverse and longitudinal planes were stained by hematoxylin and eosin, Masson's trichrome, Mallory's PTAH, Gomori's silver impregnation, and Ziehl-Neelsen's technic. Lepromas, focal or confluent, in the endomysium, perimysium, muscle fibers and perineurally, constituted the most common pathologic lesion, being observed in 34% of all cases with a higher frequency in the lepromatous type. Acid-fast bacilli could be demonstrated in some of these lepromas. These nodules were observed even in younger patients and increased in frequency as the age of patient advanced. Three cases of non-lepromatous leprosy showed granulomas. Other changes noted in varying proportions were loss of striations, hyaline change, fatty change, sarcolemmal changes, along with endomysial thickening, muscle necrosis and fibrosis. Bacillemia in leprosy and the possible route of muscle invasion resulting in subsequent production of leprous nodules with associated degenerative changes, independent of nerve involvement, have been postulated."

37. DISCAMPS, G., LANGUILLON, J. & SAINT-ANDRE, P. La biopsie ganglionnaire dans le diagnostic de la forme de lepre. **[The biopsy of lymph nodes in the diagnosis of the various types of leprosy.]** *Méd. Trop.*, 1976, v. 36, No. 1, 62-68. English summary (5 lines).

This biopsy study of supratrochlear and other lymph nodes (numbers unspecified) in relation to the immunological spectrum of leprosy follows closely the study of Turk and Waters [*Trop. Dis. Bull.*, 1971, v. 68, abstr. 2270]. The immunological spectrum is reflected in the histology of the lymph nodes, which in turn parallels to a considerable extent the histology of the skin lesions. The examination of lymph nodes is recommended as a useful adjunct for the diagnosis and classification of leprosy.

Lymph nodes from patients of the lepromatous type who had received a non-specific immunological stimulus (*Neisseria perflava* or BCG) showed hyperplasia of the follicular centres and, apparently, a dissolution of the acid-fast bacilli in some cases. In others there were signs of a tuberculoid transformation, with well differentiated epitheloid cells and an occasional Langhans giant cell. [This original observation ought to be substantiated in a more detailed and factual account.]

D. S. Ridley

38. ANTIA, N. H. & PANDYA, N. J. **Qualitative histology and quantitative bacteriology in various tissues of 50 leprosy patients.** *Lepr. Rev.*, 1976, v. 47, No. 3, 175-183.

"Fifty patients, 45 males, and 5 females, from different parts of the leprosy spectrum and at various stages of the disease and its treatment, were examined both by multiple skin smears, nasal scrapings and also by qualitative histology and quantitative bacteriology of skin, dartos, lymph node, nasal mucosa, muscle and nerve. A total of 797 tissues were studied by histology as well as homogenization.

"Our study revealed that the qualitative involvement and quantitative bacillary load in the nerves was highest of all the tissues examined. A high incidence of *M. leprae* in the nerves of tuberculoid patients (40%) as opposed to other tissues–skin (7%), dartos (8%), nasal mucosa (7%), lymph node (7%), voluntary muscle (0%) was also observed. The nerve was also found to be a major and the most important reservoir of *M. leprae.* Scrotal skin biopsy was shown to be a suitable and practical site for diagnosis of leprosy. A smear obtained from the homogenate of the scrotal skin can be a useful investigation when histological facilities are not available. The findings of histology and homogenization correlate fairly well except in the skin where homogenization (24%) was better than histology (18%) for detection of bacilli. Nasal mucosa had a similar bacillary load while the lymph node showed a higher load. The importance of voluntary or involuntary muscle (dartos) as a reservoir of *M. leprae* was not borne out in our study."

3. CLINICAL ASPECTS

39. DONGRE, V. V., GANAPATI, R. & CHULAWALA, R. G. **A study of mononeuritic lesions in a leprosy clinic.** *Lepr. India,* 1976, v. 48, No. 2, 132-137.

"An analysis of 11,581 leprosy patients registered at the Acworth Leprosy Hospital clinic showed that 494 cases (4.3%) had primary polyneuritic leprosy and 143 (1.2%) localized cutaneous anaesthetic lesions (or non-visible anaesthetic lesions), accounting for 5.5% who had no evidence of obvious skin lesions."

40. CHATTERJEE, B. R., TAYLOR, C. E., THOMAS, J. & NAIDU, G. N. **Acid-fast bacillary positivity in asymptomatic individuals in leprosy endemic villages around Jhalda in West Bengal.** *Lepr. India,* 1976, v. 48, No. 2, 119-131.

This interesting study follows up the findings of Figueredo and Desai [*Trop. Dis. Bull.,* 1949, v. 46, 1052] of high rates of acid-fast bacillary positivity in clinically normal family contacts of leprosy patients. The entire population of 9 villages in a highly endemic area of West Bengal was examined for leprosy, clinically and bacteriologically, using for bacteriological assessment a snip from one ear lobe, collected with a sclerocorneal punch. Of apparently healthy subjects 5.8% gave positive findings for acid-fast bacilli in such tests, the prevalence rising with age to early adult life and then levelling off. In this area the entire population was regarded as being at risk of contact with *Mycobacterium leprae.* Among nuclear family contacts of leprosy cases marginally higher rates of positivity (5.9%) were found than in the general population, with no striking contrasts between the contacts of lepromatous cases and the contacts of tuberculoid and indeterminate cases. All persons with positive findings were kept under constant surveillance, and the whole population was re-examined after 2 years. During this period 13.6% of asymptomatic persons with positive ear lobes developed early clinical leprosy. When at the end of 2 years the entire population was re-examined, 2.3% of those with negative ear lobes had developed overt leprosy. Among nuclear family contacts the rate was 4.8%.

[The large-scale bacteriological study of whole populations gives this paper unusual interest. Some aspects of methodology and interpretation are controversial, but the positive findings are important and should provoke similar studies elsewhere.]

T. F. Davey

41. JOSHI, P. B. **Pilocarpine test in assessment of therapeutic efficacy in maculoanaesthetic leprosy.** *Lepr. India,* 1976, v. 48, No. 1, 55-60.

The sweat response in maculoanaesthetic lesions of 132 leprosy patients was tested every 2 months over a period of 12 months. 0.2 ml of a 1 in 1000 solution of pilocarpine nitrate was injected intradermally, the injection site was painted with tincture of iodine, and starch powder was dusted over the site. Sweating caused a blue discolouration of the starch granules. The results are shown in a series of tables. 111 patients showed improvement in the sweating mechanism, improvement being maximal in most cases by the end of the trial period.

W. H. Jopling.

42. SEHGAL, V. N. **The significance of the local sweat response in assessing the progress of leprosy.** *Br. J. Derm.,* 1976, v. 94, No. 6, 615-618.

Twenty-nine patients with tuberculoid leprosy and 5 with borderline leprosy were selected for a study of sensation and sweat response in hypopigmented skin lesions while on dapsone

treatment over a trial period of 2 years. Significant improvement was recorded in both these tests, and the author stresses the importance of early diagnosis and treatment if optimal results are to be obtained.

W. H. Jopling

43. SEBILLE, A., SAINT-ANDRE, P., GIRAUDEAU, P. & ROUGEMONT, A. Manifestations cliniques de la multinévrite lépreuse chez l'African de l'Ouest. A propos de 90 observations. **[Clinical manifestations of leprous polyneuritis in West Africans. Report of 90 cases.]** *Bull. Soc. Path. Exot.,* 1975, v. 68, No. 4, 335-344. English summary (5 lines).

The authors report the results of the clinical examinations of 10 main peripheral nerve trunks, together with the corresponding sensory and motor deficits, in each of 90 West African leprosy patients in the Institut Marchoux in Bamako, Mali. They emphasize the importance of enlargement of the nerve trunk at sites of predilection as the most frequent and earliest sign of nerve damage, and refer to the probable importance of compression of the trunk in fibro-muscular canals. Obvious atrophy and weakness of the muscles supplied, and sensory deficit (as demonstrated by testing with a wisp of cotton wool, and pinpoint) were less useful signs, though sensory impairment usually preceded motor weakness.

The ulnar nerve was most commonly affected, and the facial least. In the latter no enlargement was detected in the nerves of the superficial cervical plexus. [The small nerves passing over the malar bone are not mentioned.]

The authors claim that the immunological classification of the disease had no bearing on the peripheral nerve damage [a statement at variance with the findings of most authors], and that erythema nodosum leprosum had a transitory effect only on the appearance of the signs of neuropathy.

[A greater precision of the clinical findings would be welcome, together with a correlation of the enlargement and hardness of the nerve trunks with the stage of the disease and the immunological classification of the form of leprosy concerned. Other sensory modalities (such as temperature sense) might well have been included in the examination.]

S. G. Browne

44. MAHAPATRA, S. B. & RAMU, G. **Transformation from lepromatous to borderline leprosy under clofazimine therapy. A case report.** *Lepr. India,* 1976, v. 48, No. 2, 172-176.

This is a report of a patient suffering from subpolar lepromatous leprosy (lepromatous leprosy which has been preceded by a borderline phase) upgrading to borderline during combined therapy with clofazimine and dapsone as shown by the appearance of new erythematous plaques with borderline histology.

4. THERAPY

45. MARTINEZ, D. & ZAIAS, N. **Levamisole as adjunct to dapsone in leprosy.** [Correspondence.] *Lancet,* 1976, July 24, 209-210.

Patients with modular lepromatous or nodular dimorphic leprosy took part in this trial. Lesions were graded from 4 (nodule) to 0 (totally flat macule). All 12 patients who completed the trial were clinical grade 4+ at the start. All were receiving dapsone or acedapsone. Six of the 12 received, in addition, levamisole 150 mg every 2 weeks, and 6 received a placebo pill. After 6 months, the 6 patients who had been on levamisole had lesions graded 1+ or 0. Of the 6 who were taking the placebo, 4 had 3+ lesions, and 2 had 0, similar to the results to be expected

from dapsone alone. The prevalence of reactions was studied in 6 patients, all with 4+ reactions before the trial. In 3 on levamisole plus dapsone there was a gradual decrease of intensity to 0 or ± over the 6 months, whereas the 3 on placebo + dapsone continued to have reactions (3+ or 4+). When levamisole was withdrawn at the end of 6 months one patient's reactions increased again.

F. I. C. Apted

46. EKAMBARAM, V. & VENKATACHARI, S. **A trial of long-acting sulphonamide R.O. 4-4393 (Fanasil) in treatment of cases of lepromatous leprosy with repeated E.N.L.** *Lepr. India,* 1976, v. 48, No. 1, 24-30.

Long-acting sulphonamides, including the drug sulfadoxine (Fanasil), have had a limited vogue in the treatment of leprosy. A small trial is reported here of the use of this drug in relation to recurrent erythema nodosum leprosum (ENL). After 2 years on sulfadoxine in a dose of 1 g weekly, 5 out of 6 patients subject to severe recurrent ENL experienced marked relief and were able to continue on standard dapsone treatment (300 mg weekly). Two out of 3 patients given sulfadoxine before ENL became recurrent gave the same result. While clinical and bacteriological improvement during the trial was not regarded as satisfactory, the authors nevertheless consider a larger trial worth while.

T. F. Davey

47. LANGUILLON, J. La clofazimine dans la lèpre (son action sur les formes réactionnelles et les formes resistantes). **[Clofazimine in leprosy (its effect on the reactive and resistant types).]** *Méd. Trop.,* 1976, v. 36, No. 2, 127-130. English summary (7 lines).

The author summarizes his experience with clofazimine [Lamprene (Geigy), B 663] in Bamako (Mali) and Dakar (Senegal). In his first series of 15 patients suffering from lepromatous leprosy, untreated, and given clofazimine at a daily dose of 100 mg, he obtained good clinical and bacteriological results, the Morphological Index falling to zero in 24 weeks and the Bacterial Index falling by one-half in 12 months. No patient showed signs of reaction during the period of treatment.

His second trial was designed to evaluate the practicability of using clorazimine in a mass treatment scheme, and to compare the results of treatment of patients with lepromatous leprosy given either a weekly dose of 600 mg of clofazimine or a weekly dose of 600 mg of dapsone. No difference was noted in the speed of clinical or bacteriological improvement between the groups, but among the 13 patients treated (and followed up) with clofazimine, there were only 2 instances of erythema nodosum leprosum: both were considered to be of slight degree and were easily controllable; whereas there were 8 cases of severe reaction among the 13 patients treated (and followed up) with dapsone. The author quotes the experience of Menke, who gave a loading dose of 600 mg of clofazimine daily for 7 days, followed by a monthly dose of 1 g to 23 patients suffering from lepromatous leprosy in Papua New Guinea.

A group of 34 patients suffering from erythema nodosum leprosum was treated with clofazimine at doses varying from 200-600 mg a day, 19 of them being given 300 mg daily. Improvement in the systemic and skin manifestations of the reactive state was noted in about 20 days for the majority, the limits being from 15-60 days. The author stopped all other leprostatic treatment when he gave clofazimine in these cases.

Another group of 26 patients treated at Bamako for "reaction" in lepromatous leprosy was given, in addition to clofazimine, either thalidomide (for males) at a dose of 400 mg daily for 7-10 days, or aspirin or a corticosteroid (for females) at a dose of 10-15 mg daily for 10 days. Excellent results were obtained in this regimen.

To 15 patients with lepromatous leprosy, suspected on clinical grounds of harbouring sulphone-resistant bacilli, clofazimine was given as follows: 300 mg daily for 6 months, then 200 mg daily for 3 months, followed by 100 mg daily. The clinical and bacteriological results

were good, and pigmentation was no problem in the dark-hued African. [It may be that some of the patients in this group were slow responders, and did not harbour dapsone-resistant bacilli.]

The author concludes that clofazimine is the antileprotic of choice in the treatment of patients with lepromatous leprosy, especially those prone to reaction, and could with obvious advantage be used in mass treatment programmes in Africa, where the lepromatous/tuberculoid ratio is low. For patients in the throes of the severe reaction of lepromatous leprosy, and those harbouring dapsone-resistant bacilli, clofazimine is the drug of choice.

[A word of warning should be uttered regarding the toxic effects of prolonged high-dose clofazimine therapy.]

S. G. Browne

48. U.S. LEPROSY PANEL (U.S.-JAPAN COOPERATIVE MEDICAL SCIENCE PROGRAM); LEONARD WOOD MEMORIAL. **Spaced clofazimine therapy of lepromatous leprosy.** *Am. J. Trop. Med. Hyg.,* 1976, v. 25, No. 3, 437-444.

Reports of the delayed effect of clofazimine (Lamprene; B663) in killing *Mycobacterium leprae,* its slow elimination, and its capacity to accumulate in the tissues, prompted this trial comparing the effect of spaced administration of the drug with that of smaller doses given more frequently. In this trial, carried out in the Philippines, 46 patients suffering from borderline-lepromatous and lepromatous leprosy were assigned randomly to 5 treatment regimens: (1) 200 mg daily for 6 days per week; (2) 100 mg three times weekly; (3) 300 mg weekly; (4) 600 mg every other week; and (5) 600 mg on 2 consecutive days every 4 weeks. Although skin smears and biopsies were taken regularly throughout the trial, this report deals with the findings on mouse foot-pad inoculations. By the end of 24 weeks it was confirmed that all 5 regimens were effective but the best results came from regimens 1 and 2. Erythema nodosum leprosum (ENL) was of equal frequency and severity in all 5 regimens and occurred in nearly a quarter of all patients; skin pigmentation was universal and was proportional to dosage of clofazimine, and there were no toxic effects.

After 24 weeks of treatment the patients were randomly allocated to treatment either with 200 mg daily for 6 days per week or with dapsone. ENL was more frequent in the latter group. The authors conclude that, for a constant average dose, the longer the interval between doses of clofazimine the less efficacious is the regimen, and the drug which has accumulated in the tissues is not readily available to exert an antibacterial effect.

W. H. Jopling

49. CARAYON, A. Limites actuelles de la chimiothérapie antihansénienne sur la névrite et danger de ses effets secondaires immunologiques. [**Limits of the chemotherapy of leprous neuritis. Its dangers and its immunological side-effects.**] *Méd. Trop.,*1976, v. 36, No. 1, 86-96.

The English summary appended to the paper is as follows: "Anti-leprous drugs have a poor effect on leprous neuritis. In this prospect a review of all available medical treatments is made.

"The advantages and inconveniences are considered for the four major antibacterial drugs, for the anti-inflammatory ones and for those raising or lowering the immunity."

[There are 67 references.]

50. LEGRAND, A. Essai de traitement par auto-hémothérapie de la réaction lépreuse. A propos de 27 cas suivis à l'Institut Marchoux Bamako (Mali). [**An attempt to treat leprosy reaction (ENL) by autohaemotherapy.**] *Méd. Trop.,* 1974, v. 34, No. 4, 495-507. English summary.

An uncontrolled trial of whole blood as the sole treatment for erythema nodosum leprosum in 27 patients with lepromatous leprosy is reported. In 15 the reaction, as judged by the clinical

state, was considered to be severe, and in the others, moderately severe. The treatment was thought to be effective in all cases of moderately severe reaction, and in 10 out of the 15 cases of severe reaction.

The initial dose of whole blood given was 2 ml; daily doses, with a 2 ml increment, were given until a maximum dose of 10 ml was attained. Thereafter 3 fortnightly booster injections of 10 ml were given, followed by monthly injections of a similar volume.

In the case of relapse, in patients whose initial reaction was successfully controlled by autohaemotherapy, a further series of daily injections of 10 ml of whole blood, given for 2 or 3 days, sufficed to control the reaction.

S. G. Browne

51. SHUKLA, R. K., CHATURVEDI, S. N., SRIVASTAVA, R. K. & GUPTA, A. K. **Modified Zancolli's operation in claw hand in leprosy.** *Lepr. India,* 1976, v. 48, No. 1, 48-54.

The technique is briefly described. In operations on 25 hands, results were assessed as good in 15, fair in 8, and poor in 2. There were few complications.

F. I. C. Apted

52. CARAYON, A., COURBIL, J. L. & GIRAUDEAU, P. Evolution actuelle de certains procédés de chirurgie palliative de la main lépreuse paralytique. [**A study on some surgical procedures in the treatment of the paralytic leprous hand. Present trends.**] *Méd. Trop.,* 1976, v. 36, No. 2, 181-191.

The English summary appended to the paper is as follows: "A review of surgical procedures used in the treatment of the leprous paralytic hand. Four points are emphasized:

1. The proximal attachment of the activating transplant.
2. A new pattern for the passage through the carpal canal.
3. A peculiar treatment of the contracture of the interosseous muscles (resection).
4. The pattern to activate the thumb, with use of 2 transplants."

[The surgical procedures are illustrated in a series of line drawings.]

53. CARAYON, A. & GIRAUDEAU, P. Valeur de la résection de l'épitrochlée dans la décompression et le déroutement de 87 névrites cubitales hanséniennes. [**Value of the resection of the epitrochlea for decompression and diversion of a leprous cubital nerve.**] *Méd. Trop.,* 1976, v. 36, No. 2, 163-173.

The English summary appended to the paper is as follows: "The translocation of a leprous cubital nerve has good physio-pathological bases and has proved to be a reliable technic.

"The rerouting may be carried out by a limited anterolateral diversion, by an anterior one. The resection of the epitrochlea which prevents the elongation of the nerve without vascular risk is today preferred. A study of 87 cases is reported."

5. EPIDEMIOLOGY, PREVENTION, CONTROL

54. ESCOBEDO VALDES, E. Evaluación del programa de vigilancia epidemiologica de la lepra en la frontera norte de Mexico. [**Evaluation of the programme for epidemiological surveillance of leprosy along the northern border of Mexico.**] *Bol. Of. Sanit. Panam.,* 1976, v. 80, No. 1, 23-31. English summary.

Of the 273 municipalities in northern Mexico, along the border with the United States, 102 have a leprosy problem and cases have been notified in 22 of 36 municipalities on the boundary

line. In 1973 and 1974, 277 cases were discovered in these areas (whereas 1498 new cases had been found in the country as a whole). Eighty-six of these cases occurred along the border, 84 of them in subjects aged over 15 years; 47 were in men. Sixty-eight cases were lepromatous, 12 tuberculoid and 6 undetermined. In 39 cases the illness was in its first 5 years. Eight cases were discovered by examination of contacts. Twenty-one cases were in settled frontier inhabitants; the others had emigrated there from other Mexican states where leprosy was known to be prevalent. Sixty-nine lived in towns. Twenty-one cases in California were notified to Mexico as being Mexican in origin (9 were in subjects who had left more than 5 years previously). Eight appeared to have been suffering from leprosy when they had entered the United States.

Up to the end of 1974 there was a total of 14,882 cases in Mexico, of which 1224 were along the northern border. There were 541 cases in Sonora, 46 of them from the six municipalities bordering Arizona. Principal foci were in San Luis Río Colorado (23 cases) and in Nogales (16). In Baja California Noerte there were 166 cases, with principal foci in Tijuana and in Mexicali (60 cases each). There were 215 cases at Tamaulipas, bordering Texas, with principal foci at Matamoros (40) and at Reynosa (28). Another focus was at Ciudad Juárez (22).

The leprosy frontier problem exists but it is not of great magnitude. The endemic is active and the disease is diagnosed late, when patients are already infectious. Where specific control services exist, these are satisfactory. The Health and Welfare Ministry is considering the creation of mobile services devoted to the promotion, supervision and evaluation of antileprosy activities in northern Baja California, and in the states of Chihuahua and Coahuila. Systematic early and correct notification, as well as early diagnosis and hygiene education, and also the control of contacts, must be encouraged.

E. Agius

55. CAP, J. A. & MULATU, B. La lépre en Ethiopie: situation actuelle, **[Leprosy in Ethiopia.]** *Méd. Trop.,* 1976, v. 36, No. 1, 11-15. English Summary (7 lines).

The estimated number of leprosy sufferers in Ethiopia is between 128,000 and 135,000, of whom about 59,000 are registered. In a population of 24 million, the prevalence rate varies from 0.1–7.0 per thousand, or an overall rate of 2.5 per thousand. Most of the registered patients live in the central, hilly areas, but the higher prevalence rate in these districts may be a reflection of such factors as population density, activity of case-finding teams and the provision of more adequate facilities for treatment. Where the prevalence is low, treatment is given at general dispensaries (1 for 28,000 persons in some areas; 1 for 220,000 persons in others); a special leprosy service is organized in areas where the prevalence is high, each trained medical auxiliary being responsible for the treatment of leprosy patients in from 3–5 centres.

S. G. Browne

56. LOUVET, M., SAINT-ANDRE, P. & BERNARD, L. Epidémiologie de la lèpre en Afrique de l'Ouest. **[Epidemiology of leprosy in West Africa.]** *Méd. Trop.,* 1976, v. 36, No. 2, 121-125. English summary.

According to official statistics in the French-speaking countries of West Africa, there has been little reduction recently in the total numbers of leprosy patients under treatment. Either, then, the excellent and costly leprosy service (inaugurated in 1957) is not as successful as it was thought to be, or the figures are suspect. Basing their conclusions on detailed investigations in mali, and opining that a similar state of affairs would be disclosed in the Ivory Coast, Dahomey, Upper Volta, Niger, Senegal and Togo, the authors suggest that the anti-leprosy campaign has indeed been much more successful than the official figures indicate. Many patients have had treatment for up to 18 years for tuberculoid leprosy; the medical auxiliaries show a reluctance to discharge such patients from treatment, or to place them "on observation without

treatment"; they also have a lackadaisical attitude towards the compilation of reports and the furnishing of statistics; they are, in a sense, "too competent" in their assiduity in giving treatment and too conscientious in continuing treatment. Thus, the total figure of patients under treatment for leprosy in these countries, now officially 437,041 (representing a prevalence rate of 14 per 1000), should be reduced considerably. As a consequence, the medical auxiliaries attached to the leprosy control service could be redeployed and absorbed in the general medical service for the control of endemic diseases, including such activities as treatment of tuberculosis and onchocerciasis and examination of schoolchildren in their daily round, as well as continuing their important case-finding of patients suffering from early leprosy.

S. G. Browne

57. NEBOUT, M. Le traitement ambulatoire des lépreux par la méthode de l'autotraitement. Bilan d'une étude réalisée en République du Tchad de 1966 à 1973. [**The ambulatory treatment of leprosy patients by the "self-treatment" method. A study conducted in the Chad Republic from 1966 to 1973.**] *Méd. Trop.,* 1976, v. 36, No. 2, 147-152. English summary (8 lines).

This enthusiastic and reasoned report provides an excellent summary of the author's programme of "self-treatment". The accepted methods of control of leprosy in the West African countries that were formerly colonies of France consisted mainly of circuits maintained by motor vehicles and/or cyclists. Because of the small number of doctors (1 to 65,000 inhabitants), the inaccessibility of many of the villages, the lack of credits, and the relatively poor results of the leprosy programme then in operation, a district in the Republic of Chad containing about 700,000 inhabitants was selected for the "self-treatment" trial.

A total of 18,412 leprosy patients in this population was placed under treatment. Clinical examinations were performed every 6 months by a competent team of medical auxiliaries headed by a doctor; the bacteriological status was determined (skin smears being obtained from all patients suffering from infectious or potentially infectious forms of leprosy); adequate records were kept; the opportunity was taken for health education talks. The team visited the centres every 3 or 6 months to check the patients gathered by convocation and to distribute packets containing sufficient tablets for a daily dose of dapsone: the dose was 100, 50 or 25 mg, according to body weight. Each team was on the road for 20 days a month, covering an average of 500 km. About 60 leprosy patients a day were seen.

At the end of 7 years of effort along these lines, the prevalence of leprosy had fallen from 32 to 8 per 1000, and the incidence from 0.8 to 0.1 per 1000. A total of 24,418 patients have been discharged, disease arrested, and in 50% of the remainder the disease is no longer considered to be active. Useful comparative tables are included.

[These impressive results in an area of high prevalence and a high proportion of tuberculoid and spontaneously resolving forms of leprosy, may not be automatically reproducible in other situations, but the principles of "self-treatment" merit further application and evaluation.]

S. G. Browne

58. LOUVET, M., SAINT-ANDRE, P. & GIRAUDEAU, P. Place de la chimioprophylaxie dans la prévention de la lèpre. [**Role of chemoprophylaxis in the prevention of leprosy.**] *Méd. Trop.,* 1976, v. 36, No. 2, 153-156. English summary.

In view of the disturbing observation that leprosy appears to be increasing in many countries as their population increases, the possibility of prevention of the spread of the disease should be re-examined. The authors review the role of temporary and voluntary segregation, the use of rifampicin as a mycobactericidal drug in selected situations, the efficacy of dapsone in mass treatment schemes in slowly reducing the size of the reservoir of infection, the need to improve standards of environmental and personal hygiene, the value of BCG vaccination in the control

of tuberculosis and the possibility that it might concurrently and non-specifically enhance resistance to leprosy infection. In a group of 57 children studied in the Bamako Leprosy Institution (Mali Republic) for a period of from 1-10 years (average 2½ years), prophylactic dapsone was considered to be a factor in their remaining entirely free from all signs of leprosy, despite the fact that all were exposed for a long time to a person suffering from lepromatous leprosy in the household—a parent or sib. The dose of dapsone varied from 25-100 mg, weekly. Mention is made of the other factors that undoubtedly played a role in this highly satisfactory accompaniment of sulphone prophylaxis, for example, the drug treatment of the index case, health education, improvement in domestic hygiene. In this group of 57 children, the tuberculin reaction was positive in 28, and the Mitsuda positive in 34; of the remaining 23 children, some were considered to be too young to show their immunological polarity, but in the unknown number in this group who would be persistently Mitsuda-negative, prophylactic dapsone might prevent the development of clinical signs of multibacillary leprosy.

[This study illustrates the difficulty of isolating and evaluating the role of chemoprophylaxis in the prevention of leprosy in an exposed child population.]

S. G. Browne

6. REHABILITATION AND SOCIAL ASPECTS

59. DE SINCAY, B. Attitudes envers la lèpre et son traitement dans une communauté ethiopienne. [**Attitudes towards leprosy and its treatment in an Ethiopian community.**] *Ann. Soc. Belg. Méd. Trop.*, 1975, v. 55, No. 4, 313-320. English summary (5 lines).

The author analyses the responses obtained by oral interrogation (through an interpreter) of a group of 100 patients who presented themselves for diagnosis of leprosy at the Princess Zenebe Work Hospital in Addis Ababa in the months of March and April, 1974.

No fewer than 29 had been divorced by the healthy partner because of their disease, either because of inability to provide the necessities of life (10), or because of fear or shame (10), or because the sick partner wanted to leave the conjugal home in order to seek treatment in Addis Ababa. In general, leprosy entailed a lowering of economic and social standards, and rejection by relatives and friends.

Six patients had been discharged from work. The real motives of 17 patients who declared that they came to Addis to seek treatment may have been a desire to hide their sickness or to leave their homes. Apparently, 25 patients who were married when they came to Addis experienced no rejection on the part of their partners.

The author is uncertain concerning the awareness of the patients of the true nature of their disease, and cites the criteria for diagnosis popularly held, such as obvious deformity of hands and feet. A majority of those interviewed (58) had had no previous contact with Western medicine: traditional healers and Coptic priests or other religious leaders had fulfilled the role of diagnostician and therapist, the prescriptions consisting of natural "remedies", that is burning, the application of leaves, the drinking of infusions, and the like.

Other factors that caused people to postpone seeking medical advice were the demands of their job (usually farming), poverty, and fear of travelling alone.

Women (numbering 31) seemed so tied to their domestic duties that they neglected their personal health.

Town-dwellers were less reluctant than country folk to come to hospital, and those with obvious tuberculoid lesions were more ready to present themselves than those with the potentially more serious forms of leprosy.

S. G. Browne

The Pathogenesis of Infectious Disease

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Most textbooks of medical microbiology deal with the subject either microbe by microbe or disease by disease. The how and why of disease production rarely gets more than a few inadequate paragraphs. Yet this is surely the most important aspect of the subject. When we consider the entry of microorganisms into the body, their spread through the tissues, the role of immune responses, toxins and phagocytes, the general are the same for viruses, rickettsiae, bacteria, fungi and protozoa.

book adopts a novel approach, considering all microorganisms as each stage of the infectious process is dealt with and the of disease production is described. This comprehensive and readable text will give the reader a unified concept of infection and pathogenicity that is equally relevant for typhoid, gonorrhoea, yellow fever or the common cold. Most of the examples are from man, but because the principles apply to all vertebrate infections, the book will prove of value not only to the student of medicine but also to students of veterinary science and dentistry, and to the non-medical scientist interested in the immunology and microbiology of infection.

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