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Editorials

CHANGE IN EDITORSHIP OF LEPROSY REVIEW

With the publication of this issue Dr Frank Davey retires as Editor of *Leprosy Review*. He was invited to undertake this responsibility after a lifetime of service as a leprologist, for many years in Nigeria and more recently in India, with particular experience in leprosy control, and clinical aspects of leprosy research. In Nigeria he became Senior Specialist and Adviser to the Federal Government. In an interlude in London as Medical Adviser to the Methodist Missionary Society, he was able to respond to Dr Robert Cochrane's invitation to become Joint Editor with him of the Second Edition of *Leprosy in Theory and Practice.*

During his five years as Editor, *Leprosy Review* has prospered and its circulation has reached record figures. An emphasis on the field worker and the speedy publication of original articles have been features of these years. Above all else by his enthusiasm and dedication Dr Davey sustained *Leprosy Review* as a leading Journal for the most rapid publication of practical and basic aspects of leprosy.

At his last Editorial Board as Chairman, Dr Davey paid tribute to the distinguished service members of the Board and other consultants had rendered as specialist referees, especially to Dr R. J. W. Rees, Vice-Chairman, for his encouragement and advice, and to Mr G. F. Harris, Director of LEPRA, for the constant support of *Leprosy Review* which had made possible an increase in size of the Journal and facilitated both wider circulation and Special Issues.

In recognition of Dr Davey's services, the Executive Committee of LEPRA have invited him to become Editor Emeritus.

Dr Davey is succeeded as Editor and Chairman of the Board by Dr Colin McDougall, LEPRA'S Medical Consultant, who combines particular experience of clinical leprosy and leprosy control in Africa, with most distinguished service in the sphere of histopathology. His laboratory at Oxford is well known.

The preparation of material for Vol. 50 No. 1 is already far advanced. From now on, the address of the Editorial Office is: Dr A. C. McDougall, The Slade Hospital, Headington, Oxford OX3 7JH

R. J. W. REES
(Vice-Chairman, Editorial Board)

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THE NASAL EXCRETION OF LEPROSY BACILLI

On the following pages, Dr T. F. Davey describes the nasal excretion of leprosy bacilli from one untreated lepromatous patient, during the course of one day. As he ruefully remarks in the opening paragraphs, it is a matter of continuing concern that so little *practical* notice has been taken of the enormous numbers of bacilli now proven to issue from the nose and upper respiratory tract of patients with this type of leprosy. Bearing in mind the many millions of leprosy patients currently estimated by WHO to be still undiagnosed, and that in some countries 50% or more of these may be lepromatous, one wonders if future generations will look back on this era of leprosy control as one in which a tap was running full tilt in an upstairs bathroom, causing water to pour down the stairs, perpetually flooding the lower floors, while the occupants moved from one room to another with rather small mops. Dr Davey has graphically described the dissemination of leprosy bacilli from only one patient, emphasizing the paramount importance of finding and treating the maximum number of lepromatous patients in all control schemes. Whilst admitting that most patients are not lepromatous, and that there have been some interesting observations on the apparent infectivity of non-lepromatous patients in maintaining endemics in some areas, there is surely no longer any doubt about the overwhelming importance of the nose in the pathogenesis and spread of this disease, and it may here be worth considering some of the implications of this for the patient, the community, and for the survival of the leprosy bacillus itself.

A high percentage of all untreated lepromatous patients have nasal symptoms, sometimes for many years before diagnosis, and these may include blockage, chronic discharge and epistaxis. Destruction of the nose and cartilaginous septum are of course common events and they may be difficult to correct surgically, even if the facilities are available. From a personal point of view, the nose is a central point in an area which may already be affected by skin nodulation, loss of eyebrows, eye disease, defective teeth and impairment of the voice. The additional stigma of permanent nasal deformity may have an almost irreversible effect in undermining the patient's confidence and return to normal life.

As regards the community and the health risks to susceptible people of nasal shedding, it is relevant to consider what happens during sneezing from virus infections such as the common cold, particularly as leprosy is being

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increasingly recognized as a disease of crowded, urban communities. The facts (Mims, 1977) are as follows—

"In a sneeze, up to 20,000 droplets are produced.... the largest droplets (1 mm in diameter) fall to the ground after travelling 15 feet or so, and the smaller ones evaporate rapidly, depending on their velocity, water content, and on the relative humidity. Many have disappeared within a few feet and the rest, including those containing microorganisms, then settle according to size. The smallest... in fact stay suspended indefinitely, because air is never quite still. Particles of this size are likely to pass the turbinate baffles and reach the lower respiratory tract.... shedding from the nasal cavity is much more effective when fluid is produced, and among the viruses that are shed from this site, evolution has favoured those that induce a good nasal discharge." And again "(In a sneeze), most of the droplets in fact originate from the mouth, but larger masses of material ("streamers"), as well as droplets, are expelled from the nose when there is excess of nasal secretion....." Much of this, though in lesser detail, was well appreciated many years ago by those carrying out work on the transmission of tuberculosis, in which the importance of inhalation is beyond doubt, and the pros and cons of an analogy between the mode of spread in thse two diseases have been discussed by Dungals (1961), Rees and Meade (1974) and more recently (1977) by Leiker. Dr Davey draws attention to experimental work in the mouse which indicates that inhalation may also be a mode of entry of the leprosy bacillus, but in this context it should be kept in mind that in most forms of leprosy, nasal lesions are not described and that the lung is not a target organ in any form of the disease. What matters in comparing leprosy and tuberculosis in the present context is that there is in both instances a well-established "open" positive case; an excretor of bacilli on a massive scale. The danger of this type of patient in tuberculosis has been recognized for a very long time; in leprosy, it is difficult to escape the comment that measures for dealing with the open lepromatous case, which are at the same time humanitarian and medically effective, are as yet poorly conceived.

Finally, in looking at the thing which is of most interest to the bacillus itself, namely survival, the nose, as opposed to the intact skin or the peripheral nerves, may have peculiar advantages. The induction of a good nasal discharge may clearly be of benefit, but an even more important and subtle advantage has been suggested by Shepard (1965): "the low optimum temperature of *M. leprae* might have come about through natural selection, because it is mainly those bacilli living in the cool nasal passages that cause contagion." Coupled with this, it may be relevant to recall that there is a continuous bacteraemia in lepromatous leprosy which is associated in a high percentage of cases with the finding of bacilli, many of them solid-staining and presumably viable, in the endothelial lining cells of blood vessels. These include a wide range of vessels in the nasal mucous membrane, a tissue which is delicate, easily shed, and subject to secondary infection. Having presented such a wealth of data on the nasal route of excretion in the transmission of leprosy, Dr Davey does not elaborate on the possible role of biting insects, wisely commenting that its importance has yet to be more fully established.

Some important data from this area of research have already been published in *Leprosy Review,* and it is certainly one that is worth pursuing. In view of the known importance of the vascular endothelium as a site of replication and shedding of viruses and rickettsiae that are transmitted by blood-sucking arthropods (Mims, 1977), we await with interest further research which might point to yet one more subtle device by the leprosy bacillus—a link between a continuous (and totally asymptomatic) bacteraemia, loading of endothelial lining cells by bacilli, and biting arthropods.

Taking an objective look at the "increasing complexity of leprosy control" (Lechat, 1978), particularly in the treatment of new lepromatous patients, dapsone-resistant patients, and of adverse reactions, together with the unavoidably slow pace of developments in research which are likely to have a fundamental effect on the prospects for leprosy control in the foreseeable future, it may be that we should try, yet again, and even harder, to find as many lepromatous patients as possible, and to stop their nasal excretion of bacilli, as a matter of priority. The interesting question which then arises is: Where should such an activity come in the list of priorities? Should it be at the top?

A. C. McDOUGALL

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A Day in the Life of Yeeranna — A Cautionary Tale

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Considering the clinical and bacteriological data of a known untreated patient with early lepromatous leprosy in the setting of personal habits, social behaviour, insect transmission and modern transport, it becomes possible to envisage an ordinary day in the life of this patient in which he becomes the source from which 100 people are infected with *Mycobacterium leprae* up to a distance of 50 miles from his home. In 1 month this total could become 3000, and if only 1% of these developed clinical leprosy, 30 cases of leprosy would result, of whom possibly 3 could be potentially lepromatous in type.

Background

It seems to be a common characteristic of our human condition that whereas new truth may be accepted in the abstract, its application in practical planning and behaviour is a different matter and may involve a long time-lag, especially where long established tradition or cherished religious ideas are concerned.

Leprosy is no exception to this. During recent years various strands of evidence have been accumulating regarding the mechanism of transmission in leprosy which taken together expose the inadequacy of traditional ideas and procedures, but are not as yet being given the importance they merit in current leprosy control programmes. It is worth summarizing them here.

Pedley (1970, 1973*a*, 1973*b*) demonstrated the unimportance of the unbroken skin surface in lepromatous leprosy in contrast with the nasal discharge as a source of acid-fast bacilli (AFB). Davey and Rees (1973, 1974), in a substantial series, showed (a) that a nasal discharge laden with AFB was consistent with *very early* clinical lepromatous leprosy; (b) that the AFB were undoubtedly *Mycobacterium leprae;* (c) that huge numbers of viable *M. leprae* could be involved (mean 18.59 millions in 17 early morning specimens, 30.72 millions in 14 24-h specimens); (d) that *M. leprae* could remain viable outside the body for 2, and in 1 case for 7, days. Desikan (1977) showed that this period could be extended to 9 days. Pedley (1973*b*), and Davey and Rees (1974) agree in emphasizing the association of a bacilliferous nasal discharge

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with the lepromatous form of the disease. Davey (1974) mentioned the frequency with which patients need to clear their noses as related to atmospheric humidity. In fact, while 5 or 6 times daily may be needed in humid conditions, once or twice may suffice in dry weather.

Geater (1975) in well controlled experiments demonstrated that some of the commonest varieties of domestic flies, *Musca, Stomoxys* and *Calliphora* could transfer AFB including globi (powerful evidence that the AFB were *M. leprae),* from infected nasal discharge to uninfected surfaces via their gut, mouthparts, abdomen and legs, and some were still capable of doing this 24 h after feeding on the infected material. (These flies are positively attracted to any defect of skin surface, and have a range in the case of *Musca* of 2 miles, in the case of *Calliphora* of 5 miles.) Rees (1975) commented on the importance of these findings.

The uncleanly nocturnal habits of cockroaches (*Blatta orientalis*) are well known and are exploited in the story which follows. These and several other biting insects are implicated in the carriage via their gut of viable *M. leprae* from the blood of lepromatous patients to other surfaces. Narayanan, Shankara Manja *et al.* (1972) obtained multiplication in mice typical of *M. leprae* from material obtained from 2 Culex mosquito pools. Sengupta, Worms and Rees (1976) showed that viable *M. lepraemurium* could be carried by *Aedes aegypti.*

Finally, Rees and McDougall (1977) found experimental evidence for the development of *M. leprae* infection in mice following the inhalation of aerosols containing the bacillus. This important finding opens up the possibility that infected house dust may be a potential source of leprosy infection.

None of these findings has been disputed. Their implications can be fully appreciated only when they are brought together and related to the actual mode of life of large numbers of people in areas of the world where leprosy is endemic today. It is easy for the scientist to be isolated by his own social background from the detailed facts of daily living experienced by the poor. The truth is that in a setting of poverty, people who are naturally clean in themselves cannot afford the standards of housing, sanitary and washing facilities, handkerchiefs and tissues taken for granted in affluent societies. When to this is added the assault on personal dignity which leprosy creates, a picture is produced of the potential for transmission of the disease by the lepromatous patient which merits much food for thought. Let us consider a typical example.

The Patient

Yeeranna is a real person, though that is not his actual name. Aged 20, he presented himself one January morning at the out-patient department of a leprosy referral hospital in a large Asian country. He gave a history of a pale patch on the right thigh which had been there for $1\frac{1}{2}$ years. Three months before coming to hospital he had experienced what was thought to be influenza, following which very numerous erythematous new patches had appeared and were still multiplying, combined with abnormalities of sensation in his legs. At the same time he had become aware of slight but definite

changes in his facial appearance, not obvious as yet to the casual observer, but plain enough when he looked at himself in a mirror, and especially involving his ears, forehead and nose. For the past month his nose had become increasingly blocked by catarrh, which he needed to clear 5 or 6 times a day when the weather was damp, but which caused hard crusting under dry conditions. He did not volunteer this information about his nose, but responded to direct questioning. He had taken no treatment, as up to this point he could not face the possibility that this was leprosy, and had indeed come secretly to hospital without the knowledge of his family.

Clinically he was suffering from very early lepromatous leprosy, a degeneration from an earlier borderline type. The diagnosis was confirmed histologically and routine smears for *M. leprae* were strongly positive (BI 5.5, MI 5). The nasal discharge was typical, showing both globi in all stages of development and individual AFB, many of them elongate with active ingestion by macrophages. Internally his nose showed severe lepromatous changes, with nodulation and erosion of both inferior turbinates and a lepromatous plaque on the left septum. Smears from these areas were very strongly positive, BI 6 plus, MI 5–10. The patient was willing to stay in hospital for a while and willingly participated in a 24 h study of the nasal discharge. A 24 h specimen flown to Dr Rees's laboratory in London gave 24 h later a total count of 1.5×10^9 *M. leprae,* with 5% viable.

Thus, on the day he provided the specimen at least 75 million viable *M. leprae* had left the body of this patient by the nasal route alone. Although the clinical condition of the patient was typical of many others, this happened to be the highest count among the 31 in the series examined in London, so for the purposes of the story which follows it has been reduced to the mean for the whole series of 24-h nose blows, namely 30 millions of viable *M. leprae* in the 24 h.

It is intriguing to consider what was happening to the bacilli discharged from the nose of this and other similar patients during the days prior to their coming to hospital. Knowing the conditions in which many of them live, it requires no great flight of the imagination to project the findings enumerated above into the life of this patient, and picture what could easily have taken place on the day before he left his home for the hospital. This is attempted in the story which follows.

One Day in the Life of Yeeranna

At 5 a.m. Yeeranna awoke as usual. This was not his first awaking since going to bed. Restless with anxiety and the discomfort of a blocked nose, he had felt at 2 a.m. that he simply must clear his nose. Not wishing to disturb other members of his family by going outside, he had in fact in his half sleepy condition cleared his nose by his bedside in a corner of the room.

The discharge contained 3 million viable *M. leprae,* and during the night was visited by 10 cockroaches, the feet, abdomens and mouth-parts of which became grossly contaminated. After feeding the insects walked about the room depositing bacilli as they did so. One crossed the legs of Yeeranna's little son

and deposited 10,000 *M. leprae* on a small scabetic lesion on his leg. Six of the insects had come from adjacent lodgings to right and left of Yeeranna's own, and deposited their quota of bacilli there. This pattern of events had been going on for 2 weeks, and with bacilli remaining viable for several days, the dust in all 3 lodgings was by now liberally impregnated with living *M. leprae,* contact with which was inevitable for all the occupants.

Round about 5 a.m. Yeeranna went outside for his morning ablutions. He needed to clear his nose and did this on the ground nearby. During the morning, before the heat of the day dried it up, the discharge was visited by 20 domestic flies of the genus *Musca,* all of which became contaminated by large numbers of AFB from the 5 million contained in the discharge. These flies scattered in all directions, and within 1 h had deposited significant numbers of *M. leprae* on cuts, abrasions and ulcers on the skin of 25 persons.

At 10 a.m. Yeeranna walked through the town. It was market day and by 11 a.m. the market was crowded. Once again he felt the need to clear his nose, and another 3 million viable *M. leprae* were deposited on the ground. This time the flies attracted included the powerful and far ranging *Calliphora,* and within 1 h the skins of 30 people were contaminated by *M. leprae,* including 10 from parts of the town over 1 mile away and 5 from adjacent villages. A new factor on this occasion promoted even wider dispersal of bacilli when 3 people one after another trod in the discharge and carried substantial numbers of bacilli away on the side of their sandals. Two of these had come from villages 3 and 6 miles away. In both cases there were still 100,000 viable bacilli still adherent to their sandals when they arrived home by ox cart some hours later, and the local flies were able to disseminate them in a fresh locality.

At 3 p.m. Yeeranna went to the local bus station to meet his brother and family who were returning home on a visit to their parents. Once again Yeeranna felt the need to clear his nose and did this outside the gentlemen's convenience, discharging another 5 million bacilli. Once again flies, both *Musca* and *Calliphora* were attracted, and this time transported viable *M. leprae* to a nearby school so that 20 children received more than sufficient to initiate infection. Once again passers by trod in the discharge, and all 5 who did this happened to be travelling by bus to villages 10, 20 30, 40 and 50 miles away, carrying substantial numbers of *M. leprae* with them.

The final nose clearance of the day took place at around 7 p.m. outside Yeeranna's house. Although flies were by now not very active, many people were still passing by, and 5 persons who trod in the discharge transported a total of 500,000 viable bacilli on the sides of their feet to their homes in various parts of the town, where a fresh series of contacts became possible.

Thus at the end of the day, Yeeranna had been responsible for providing more than sufficient viable *M. leprae* to infect at least 100 people up to a distance of 50 miles from his home.

Discussion

This is a story with a moral, not a record of scientific experiment. The sequence of events described is incapable of investigation in detail and

confirmation by a microbiologist. What can be said is that not a single element in the story is out of line with observed facts whether in the spheres of microbiology, entomology or sociology. *These events could have taken place.* Repeated daily for 1 month they could mean that this 1 patient with untreated early lepromatous leprosy could have been responsible for the transmission of significant numbers of viable *M. leprae* to 3000 people within a radius of 50 miles from his home. Very few of these would be likely to develop overt clinical leprosy, but even if the number who did was 1% of the total, there would be here 30 cases of clinical leprosy, of whom possibly 2 or 3 would be lepromatous.

Once we have accepted that vectors such as flies may transport viable *M. leprae* and that nowadays public transport facilities are widely used, 2 obvious conclusions follow. One is the inadequacy of traditional concepts which try to trace fresh infections to some existing leprosy patient *who lives in the close vicinity,* and if this person happens for example to have Indeterminate, BT or BB leprosy, conclude that non-lepromatous leprosy is a significant source of new infections.

The second point is the uniqueness of the untreated lepromatous patient as a source of infection to other people by virtue of the bacilliferous nasal discharge which is limited to this type of leprosy, may coincide with very early clinical disease, and indeed may be present at the point when a borderline type of the disease is degenerating into the lepromatous type even before the change is clinically obvious. Quite clearly, high priority needs to be given in all leprosy control programmes to the search for and treatment of every person with overt or potential lepromatous leprosy.

Nothing was said in the story regarding bacillaemia and the carriage of *M. leprae* by biting insects, the reason being that although evidence is mounting that here is another route of transmission, obviously applicable to Yeeranna's case, its importance is not yet determined. Nevertheless, here is another pointer to the unique importance of the untreated person with lepromatous leprosy in spreading the disease.

Finally we can no longer think of leprosy eradication in isolation from the wider issues of personal hygiene and insect control. Our colleagues in tuberculosis control learned this lesson a long time ago.

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Evaluation of the Activity of Streptomycin on *Mycobacterium leprae* in Mice

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The effect of streptomycin on *Mycobacterium leprae* was studied in the conventional mouse model. The drug has a relatively high bactericidal activity that places it between dapsone and ethionamide or prothionamide. Its effect is more pronounced when administered immediately after the experimental infection than when treatment is started at a later time. This is probably the result of the higher activity of streptomycin on leprosy bacilli located outside cells. It is concluded that streptomycin could be a valuable companion drug during the initial treatment of dapsone resistant leprosy in countries with limited resources. Streptomycin as monotherapy is not suited for the short course treatment of paucibacillary leprosy.

Introduction

There are at least two reasons why there is a need for additional antileprosy drugs. The first is that it is now evident that at least some forms of the disease will require combined treatment (Pattyn, 1972; Ellard, 1974; Pattyn, 1977; Colston *et al.,* 1978). The second is the necessity for reserve drugs for the treatment of dapsone resistant cases. To be useful these drugs should fulfil a number of criteria: easy administration, well tolerated, low price and possibility of supervised administration with convenient intermittent dosage.

The widely available streptomycin (SM) undoubtedly has an antibacterial activity against *Mycobacterium leprae* as shown by Shepard and Chang (1964) and Gaugas (1967) in mice, who found SM active in dosages of 80 and 100 mg/kg body weight respectively. Later Shepard (1967) found SM at

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80 mg/kg in the mouse to be bacteriostatic. No further work appears to have been done on the experimental chemotherapy of leprosy with SM.

Observations in man have shown that SM is active in leprosy (Faget and Erickson, 1947; Driesbach and Cochrane, 1958; Doull, 1954; Doull and Wolcott, 1956; Floch, 1966; Schultz *et al.,* 1966; Edwards *et al.,* 1972, Waters, 1974). However, Hastings *et al.* (1969) and Jacobson and Hastings (1976) presented evidence for the development of resistance after 23–21 months of monotherapy. Unfortunately SM resistance was not proven by mouse inoculation in these cases.

We therefore decided to investigate in more detail the value of SM against *M. leprae* in the mouse model.

There are at present four techniques to evaluate the antibacterial activity of a drug in the experimentally infected mouse:

(1) The continuous method (Shepard and Chang, 1964). Drug is administered during the whole observation period, until the multiplication of *M. leprae* in the control mice has reached the plateau level. This technique demonstrates whether a drug has any antileprosy activity and enables the minimal effective dose (MED) to be measured. If corresponding drug levels in mouse plasma are known or measured, the minimal inhibitory concentration (MIC) can be estimated.

(2) The kinetic method (Shepard, 1967). Drug is administered during the first 90 days after inoculation of the mice. The growth curve in treated mice is compared with that in the controls. This technique enables the drug's activity to be characterized as being bacteriostatic or of a bactericidal type.

(3) The proportional bactericidal test (Colston *et al.,* 1978). In this test drug is administered for a limited period to groups of mice inoculated with logarithmic dilutions of *M. leprae*. This test measures the proportion of bacilli killed by the drug.

(4) The total minimal inhibitory test (Pattyn and Saerens, 1975). Drug is administered during different periods of time to different groups of mice. The suppression of the bacterial multiplication of *M. leprae* is monitored. This technique gives information concerning the minimal period of time paucibacillary *M. leprae* infections have to be treated.

The antileprosy effect of SM was studied in the continuous method, in the proportional bactericidal (PBT) and the total minimal inhibitory (TMIT) tests.

Material and Methods

Mice of strain OF1 (Lyon, France) were inoculated with *M. leprae* strain 17547, previously described (Pattyn, 1972). All experiments were performed in duplicate, starting treatment respectively on days 1 and 22, after inoculation of the mice.

Except for the PBT all inocula were calculated to contain between 1 and 5×10^3 *M. leprae* per foot pad. Bacterial multiplication was monitored by the counting method as described by Shepard (1960).

Results

A. MINIMAL EFFECTIVE DOSE

In Experiment 1 (Table 1) the minimal effective dose was 50 mg/kg. In Experiment 2 all mice given 100 mg/kg body weight (b.w.) 3 times weekly (3x/w) died from an unidentified toxic effect after about 2 months, a few animals in the groups treated 2x/w and 1x/w with this dosage survived. There were also some irregular results in this experiment, but the minimal effective dose ranged between 50 and 100 mg/kg. The different frequencies of administration did not profoundly influence the results.

TABLE 1

Determination of the minimal effective dose (MED) of streptomycin (SM) against M. leprae

SM dose	Experiment 1 Treatment started day 1 Twice weekly	Experiment 2 Treatment started day 22 Thrice weekly	Twice weekly	Once weekly
100 mg/kg b.w.†	N.T.‡	—	0/3*	0/4
50 mg/kg b.w.	0/8	4/17	1/7	1/7
25 mg/kg b.w.	2/9	1/8	2/9	4/8
12.5 mg/kg b.w.	6/8	2/9	5/10	2/8
6.25 mg/kg b.w.	4/8	8/9	1/9	3/9
MED 50	50 mg	50 mg	100 mg	100 mg

* Number of mice showing multiplication/number of mice inoculated.
†b.w. = body weight
‡N.T. = Not tested.

B. THE PROPORTIONAL BACTERICIDAL TEST (PBT)

In this test 100 mg/kg b.w. of streptomycin was administered 2 times a week for 60 days.

Treatment for 60 days starting 24 h after infection killed 93% of the inoculum, when the same treatment was started 3 weeks after infection the killing rate was 81%.

C. TOTAL MINIMAL INHIBITORY TEST (TMIT)

Table 3 shows the results of the total minimal inhibitory test. Treatment three times a week during 3 or 6 weeks was unable to prevent the multiplication of *M. leprae*. Treatment for 8 weeks gave a growth delay of *M. leprae*.

In all groups of mice treated twice a week for periods from 8 to 24 weeks *M. leprae* multiplied in some of the animals.

D. EFFECT OF TREATMENT DURING DIFFERENT PHASES OF THE GROWTH CURVE

To illustrate the effect of treatment during different phases of the growth curve, the following experiment was performed: mice were inoculated with *M.*

TABLE 2
Activity of streptomycin (SM) on M. leprae *in the proportional bactericidal test (PBT)*

Dry regimen (twice weekly	Inoculum size (*M. leprae* per footpad) 10^4	10^3	10^2	10	1	MPN* of viable *M. leprae*	Survival (%)	Killing (%)
Control	4/4†	4/4	4/4	5/7	4/9	1750		
SM 100 mg/kg b.w.‡ Starting day 2	5/5	3/3	4/5	0/5	0/5	130	0.07	93
SM 100 mg/kg b.w. Starting day 22	5/5	5/5	5/5	1/5	0/5	340	0.19	81

* Most probable number of bacteria in the highest inoculum.
† Number of mice showing multiplication/number of mice inoculated.
‡ b.w. = Body weight.

TABLE 3
Total minimal inhibitory test (TMIT) of streptomycin (SM) on M. leprae

Dose SM 100 mg/kg b.w.	Duration (weeks)	Number of mice showing growth of *M. leprae*/number inoculated at plateau*	+ 4 weeks
Thrice weekly	3	5/10	8/10
	6	2/10	10/10
	8	0/9	4/5
Twice weekly	8	15/18	—
	18	7/9	—
	24	2/6	—

* Mice examined when the number of bacilli reached $10^{5.5}$ in the controls.

leprae and divided into one control and three treatment groups, the latter receiving SM 100 mg/kg b.w. for 10 weeks, but treatment starting on days 2, 29 and 57 respectively. As can be seen from Fig. 1, all treatment regimens caused growth delay but the administration of SM from the start of the experiment had a greater effect than the treatments started on days 29 or 57.

Discussion

It is almost impossible to extrapolate the MED of SM as determined in the mouse to drug levels obtained in man, because the rate of elimination of SM in both species is so different. The mouse excretes SM much more rapidly than man. In mice the half-life for the elimination of SM is about 0.4 hr (J. M. Dickinson, personal communication) while in man it is of the order of 3 to 4 hr. In experimental tuberculosis in mice SM has to be administered in doses of 100–200 mg/kg body weight in order to be effective, whereas tuberculosis patients are routinely treated with a daily dose equivalent to about 20 mg/kg.

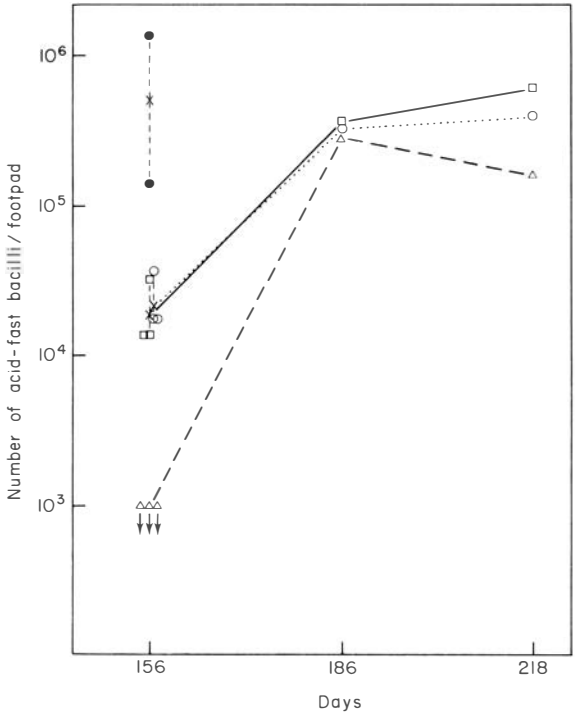

Fig. 1. Growth curves of *M. leprae* in mouse pads of untreated animals and animals treated with streptomycin (SM). ●, untreated; △, SM once weekly for days 2–72; ○, SM once weekly for days 29–99; □, SM once weekly for days 57–127.

The cause of death for the mice receiving 100 mg/kg in Experiment 2 of Table 1 has not been determined and later on this dosage was administered without any harm.

It is generally accepted that SM in experimental tuberculosis in mice is less effective than in man because, in an established murine infection, in contrast with man almost all tubercle bacilli are located intracellularly, and the drug is known to be less active intracellularly (Suter, 1952; MacKaness and Smith, 1953; Grumbach, 1965).

M. leprae has an exceptionally long lag phase (Shepard, 1960). During the latter part of this phase the bacilli are situated intracellularly, and although the site of the bacilli during the early phase after inoculation is uncertain (Levy *et al.*, 1974; Desikan, 1975) it could well be partly extracellular. In the PBT administration of doses of 100 mg/kg b.w. of SM twice a week starting on day 1 had a high killing effect (93%). When treatment started after 3 weeks the killing effect was only 81%.

The higher antileprosy activity of SM when administered from day 2, as compared with treatment started on day 22, could be the result of its greater

activity on at least part of the inoculum situated extracellularly during the early phase of the infection. The effect of a delayed start of treatment was also apparent in the experiment depicted in Fig. 1, when treatment started on day 29, although starting treatment even later was no worse.

In terms of bactericidal activity SM falls between the activities of dapsone and ethionamide or prothionamide (Colston *et al.*, 1978) when treatment is started early during the experimental infection and near to the activity of dapsone when started later. However, it is the latter situation that more closely resembles the condition in man where treatment is started when the infection is well established and almost all *M. leprae* bacilli are in an intracellular situation.

Due to its side effects and the inconvenience of long periods of intramuscular injections of streptomycin, it would be difficult to use SM in monotherapy for long periods of time in the treatment of human leprosy. It could be a companion drug during the initial phase of treatment of multibacillary leprosy to prevent the emergence of resistance, and a component of regimens used in the treatment of dapsone resistant leprosy in countries with limited resources.

Finally the results of the TMIT indicate that SM in monotherapy would not be suited for short course treatment of paucibacillary leprosy in man, since SM did not sterilize the paucibacillary infection in the mouse within 24 weeks, when administrated twice a week.

Acknowledgements

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Reliability of Dapsone Self-administration by Leprosy Patients in the Rangoon Area

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The application of urine tests to assess the reliability of dapsone self-administration by leprosy patients in the Rangoon area is described. Dapsone/creatinine ratios were determined on urine samples collected from the patients and the results compared with those from supervised controls. The results obtained demonstrated that the taking of dapsone by patients attending the out-patient dispensaries of the Rangoon General Hospital Skin Department and both the out-patients and in-patients served by the Htauk Kyant Hospital was good. However patients from Hlegu, Hwawbi, Htauk Kyant and Taik Kyi villages appeared to take dapsone rather irregularly. Possible reasons for their poor compliance are discussed and suggestions are made as to how they might be encouraged to take their dapsone more regularly.

Introduction

Dapsone has been used for the country-wide treatment of leprosy since the institution of antileprosy campaigns in Burma. It still remains the drug of choice for the world-wide treatment of leprosy (Ellard, 1974). Most patients receive their treatment from out-patient clinics or through a system of drug distribution by leprosy health workers. The successful mass treatment of leprosy is therefore largely dependent on the regularity with which patients take the drugs they are given and also upon the effectiveness of the drug distribution system.

Dapsone is almost completely absorbed from the gastrointestinal tract and up to 90% of the dose is excreted in the urine as unchanged drug together with its metabolites (Israeli *et al.*, 1973). Estimation of dapsone in the urine should therefore indicate whether a patient is regularly taking the prescribed treatment. There, can, however be a wide range of dapsone concentrations in

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urine samples from patients taking the same dosage of the drug. This variability is largely due to the effects of diuresis and can be greatly reduced by estimating the creatinine concentration of the urine and expressing the results as the ratio of the concentration of dapsone (μg/ml) to that of creatinine (mg/ml) D/C ratio) (Ellard *et al.*, 1974*a*,*b*; Low and Pearson, 1974). This paper describes the results of such analyses on samples obtained from out-patients and in-patients in the Rangoon area.

Patients and Methods

The study was composed of 3 parts. In the first part dapsone/creatinine (D/C) ratios were determined on urine specimens collected from patients in the Htauk Kyant leprosy hospital 24 h after they had received the 4th consecutive supervised daily dose of 50 mg dapsone. Ratios were also determined on control urine samples obtained from patients and staff not receiving dapsone. In the second part of the study D/C ratios were determined on surprise urine samples collected from out-patients attending the dispensaries of the Htauk Kyant and Rangoon General Hospitals, from patients from Hlegu, Hwabi, Htauk Kyant and Taik Kyi villages, and from in-patients of the Htauk Kyant leprosy hospital. All these patients should have been taking 50 mg dapsone 6 days a week. Finally, D/C ratios were determined on urine samples collected every day for 15 days from 10 normal volunteers who took 50 mg dapsone daily for the first 4 days.

Dapsone, plus its diazotizable metobolites, was estimated by the method of Bratton and Marshall (1939) as modified by Ellard *et al.* (1974*b*). Creatinine was determined by the alkaline picrate method. Urine samples were preserved by the addition of half volume of 2N HCl and dapsone and creatinine estimations completed within 1 month of urine collection. The proportion of prescribed doses taken by the patients was calculated according to the procedure of Ellard *et al.* (1974*a*).

Results

The results summarized in Table 1 show that the self-administration of dapsone by patients attending the out-patient dispensary of the Rangoon General Hospital was excellent, and that the compliance by both the in-patient and out-patient at the Htauk Kyant leprosy hospital was also good. However it was estimated that less than half of the prescribed dapsone doses were being taken by patients from the 4 villages studied. Figure 1 illustrates the progressive increase in the D/C ratios of urine samples obtained from the 10 normal volunteers after daily administration of 50 mg dapsone, peak ratios being obtained on the 5th day 24 h after giving the final dose. Thereafter the D/C ratios declined steadily and reached pretreatment values by the 11th day.

Discussion

In order to minimize the chances of patients relapsing with dapsone-resistant leprosy, it is essential that they should take their prescribed treatment

TABLE 1

Ratios of dapsone/creatinine in urine samples from different groups of patients in the Rangoon area

Origin of samples	Number of subjects	Dapsone/creatinine ratios Range	Mean*	Estimated % doses taken†
Controls not on dapsone	20	1.0– 7.1	3.7 ± 0.4	0
Supervised controls on dapsone	20	6.0–135.2	34.9 ± 7.5	100
In-patients				
Htauk Kyant hospital	56	4.0– 89.5	29.4 ± 2.9	82
Out-patients				
Htauk Kyant hospital	45	0.7–134.9	25.6 ± 2.9	70
Rangoon General Hospital	45	2.7–132.5	e4.2 ± 4.8	98
Hlegu village	35	1.7– 60.6	17.7 ± 3.0	44
Hmawbi village	46	1.0– 56.8	13.3 ± 1.7	31
Htauk Kyant village	33	2.1– 59.7	17.0 ± 2.4	43
Taik Kyi village	45	0.5–120.5	19.0 ± 3.8	49

*Mean ± standard error of mean (μg/mg).

† $\frac{\text{Mean test ratio} - \text{Mean blank ratio}}{\text{Mean control ratio} - \text{mean blank ratio}} \times 100.$

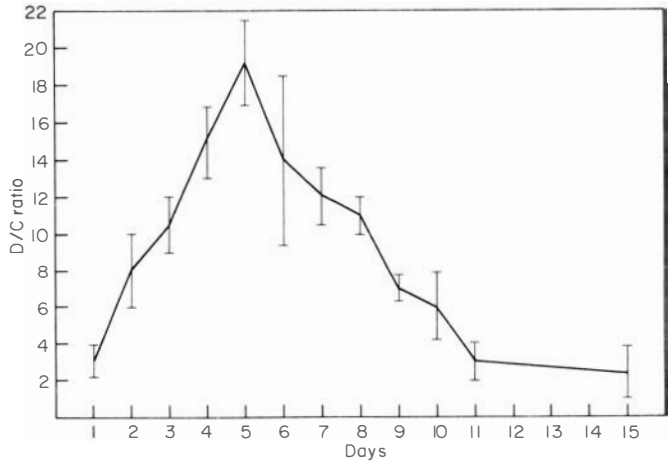

Fig. 1. Ratios of dapsone/creatinine in controls after taking 50 mg dapsone daily from day 1 to day 4.

regularly. Many field workers consider that leprosy patients are generally unreliable in this respect and that as a consequence their treatment should be given under the closest supervision possible. This study supports such a view since out of the 305 patients studied (including 56 hospital in-patients), over half (159) were estimated to be taking less than 50% of their prescribed

dapsone. This finding is in agreement with the results obtained among African patients by Ellard *et al.* (1974*a*) and Low and Pearson (1974).

In this study the most compliant patients were those attending as hospital out-patients. These patients are very keen to obtain treatment and attend the dispensaries of their own volition. Clearly their motivation has also ensured that they take their dapsone treatment regularly. The results obtained among the in-patients of the Htauk Kyant leprosy hospital also indicate that the supervision of their treatment in the hospital is generally satisfactory. However the patients from the 4 villages studied do not appear to self-administer their dapsone regularly.

Three possible reasons are suggested for their poor compliance; namely inadequate supervision of their treatment, inadequate motivation on the patients' part, and lack of proper selection of patients for release from more strictly controlled treatment to the leprosy villages.

The treatment of patients in the 4 leprosy villages clearly needs to be more effectively supervised. When their supplies of dapsone are distributed, a full explanation needs to be given concerning the importance of regular drug taking and it is essential that they be instructed by someone in whom the patients have faith and trust. The person giving them their medication needs to be available whenever the patients need help or advice during the course of their treatment since the quality of the patient/physician relationship is probably the most important determinant of patient compliance. Medical officers, lady health visitors, nursing staffs posted in that area or country health workers, in order of preference, probably suit the role better than the present junior leprosy workers.

There should be effective health education and a reward system for reliable and improving patients. Regular urine tests should be carried out to assess the reliability of patients in taking their prescribed treatment. Those cases who are well controlled clinically and bacteriologically should be released from control. If these measures cannot be carried out there should be a system for regular administration of drug to the patients.

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Alveolar Bone Loss in Leprosy— A Clinical and Radiological Study*

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Alveolar bone loss in 47 patients with lepromatous, borderline or tuberculoid leprosy was studied clinically and radiographically. Alveolar bone loss was greater in the maxillary anterior region than in other areas. Alveolar bone loss around maxillary central incisors, measured on periapical radiographs, was significantly greater in patients with lepromatous leprosy. No changes in alveolar bone loss could be detected over 6 months. These results were compared with measurements of alveolar bone loss from 56 patients without leprosy who sought dental treatment. These data are interpreted to mean that bone loss between maxillary anteriors is a characteristic manifestation of leprosy, particularly of the lepromatous type.

Introduction

Oral manifestations of leprosy have been well documented. Lighterman *et al.* (1962) have described nerve and soft tissue involvement in patients with lepromatous and tuberculoid leprosy. While oral lesions usually develop late in the disease, they can be present soon after onset or without systemic involvement (Sala, 1957).

Skeletal manifestations of leprosy are characteristically resorptive in nature and their incidence and treatment in the upper and lower extremities have been studied (Paterson, 1961). Resorption of the anterior nasal spine and maxillary alveolar process were first noted by Møller-Christensen (1952, 1953) in skeletons from a leper cemetery from medieval Denmark. Michman and Sagher (1957), studying these changes in a group of patients with leprosy in Jerusalem, noted that resorption of the anterior nasal spine and maxillary alveolar process tended to occur together, varied directly with the duration of the disease, and correlated with other skeletal changes in the nose, hands and feet.

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The objectives of the present report were to measure alveolar bone loss in patients with different types of leprosy and to determine if alveolar bone loss is different among the types. Furthermore, we assessed the periodontal condition of these patients to determine if alveolar bone loss could be attributable to advanced periodontal disease or to leprosy. We have found that alveolar bone loss is greatest in the maxillary incisor region and that patients with lepromatous leprosy have a significantly greater loss of alveolar bone in this location than do patients with borderline or tuberculoid leprosy.

Materials and Methods

Forty-seven patients with anterior teeth were selected from the patient population at the National Leprosy Control Centre, Sungei Buloh, Malaysia. The type of leprosy was determined by smears and clinical examination (Jopling, 1971). All patients were under treatment. The oral condition of each patient was evaluated clinically by noting the gingival condition, by measuring periodontal pocket depth at 3 buccal and 3 lingual positions on each tooth, and by periapical and occlusal radiographs.

The gingival condition of each patient was classified as good (stippling present without inflammation), fair (inflammation limited to marginal gingiva) or poor (inflammation extending beyond marginal gingiva to include other parts of the periodontium). Pocket depths were measured with a periodontal probe and recorded to the nearest millimetre (Glavind and Löe, 1967).

Radiographs were taken with a Siemens Heliosphere machine (60 kV, 10 mA) using the paralleling long-cone technique where possible (Lang and Hill, 1977). For occlusal radiographs, the angle between the film and X-ray beam was individually adjusted between 50°–60° for each patient. In 10 patients representing each type of disease, intra-oral periapical radiographs were taken of the entire mouth. In the other patients, radiographic studies were confined to the maxillary anterior region. Alveolar bone support was measured on radiographs by a modification of the method of Schei *et al.* (1959). The modified method expresses the height of alveolar bone, from root apex to alveolar crest, as a percentage of the distance between the root apex and the cemento-enamel junction on that side of the tooth (see Fig. 5). Measurements of these distances on periapical radiographs were made to the nearest 0.1 mm using an adjustable fine-point compass and an engineer's calipers (micrometer). Measurements were expressed as the mean of determinations made on the mesial and distal of each tooth. In several patients we were unable to make these measurements because of overlapping teeth, or difficulties in locating landmarks. Measurements were not affected by our inability to standardize X-ray beam angles because most measurements were made in the maxillary anterior region where variations of up to 10 degrees have little effect on the calculation of alveolar bone support using this method (Schei *et al.*, 1959). Data were converted to percentage alveolar bone loss by subtracting these values from 100. Statistical evaluation of results was by the Student's *t*-test.

After the initial evaluation, some patients received a thorough scaling and polishing. All patients were instructed in oral hygiene and given toothbrushes and toothpastes for maintenance. Thirty patients who received scaling and polishing and 17 who did not were followed on a monthly basis for up to 6 months. Each month, radiographs and clinical examinations were repeated and scaling and polishing were continued on those patients in whom they had been done initially.

Results

Characteristics of our patient population are summarized in Table 1. The proportion of patients with lepromatous leprosy in our study is the same as that in the leprosy population in Malaysia. We increased the proportion of patients with borderline leprosy in our study primarily for statistical reasons and did this at the expense of patients with the tuberculoid type of the disease. The distribution of patients by ethnic group is similar to that in the leprosy population in Malaysia. The known duration of leprosy in these patients by disease type is shown in Fig. 1. These data underestimate the duration of the disease in many cases. The range of duration of disease is similar among the 3

TABLE 1
Characteristics of patient population

(a) *By Disease Type*

	Lepromatous	Borderline	Tuberculoid
Number of patients	20	14	13
Percentage of patient population	43	30	27
Percentage of diagnosed leprosy population in Malaysia*	44	15	38

(b) *By Ethnic Group*

	Indian	Malay	Chinese
Number of patients and age range	6 26–76 yr	10 15–54 yr	31 15–80 yr
Percentage of patient population	13	21	66
Percentage of diagnosed leprosy population in Malaysia*	14	35	50
Percentage of general population in Malaysia*	9	56	34

*Data taken from the 1976 Annual Report of the National Leprosy Control Centre, Sungei Buloh, Malaysia.

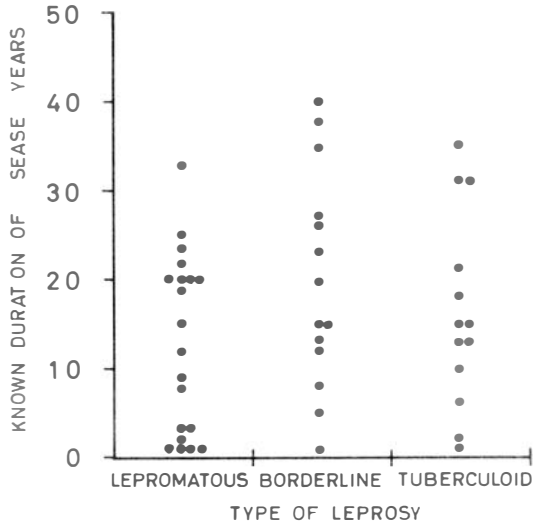

Fig. 1. Distribution of patient population by type and known duration of leprosy.

types. The duration of untreated leprosy in each patient was unknown and not obtainable from the data to which we had access. Notice that 7 patients with lepromatous leprosy and 2 patients in each of the other 2 groups had the disease for 5 years or less. The mean age of patients with lepromatous, borderline and tuberculoid leprosy was 40, 48 and 47 years respectively.

The periodontal condition in the majority of these patients was healthy. Of the 18 patients with lepromatous leprosy, 15 had either good or fair gingival condition and pocket depths of less than 3 mm. In the remaining 3 patients, the gingival condition was poor, and one or more periodontal pockets greater than 3 mm were present. In 14 of 16 patients with borderline leprosy, the gingival condition was good or fair. All 16 had pocket depths less than 3 mm. In 10 of 13 patients with tuberculoid leprosy the gingival condition was fair or better and only 1 of the 3 remaining patients with poor gingival condition had any periodontal pockets greater than 3 mm.

Alveolar bone loss was evaluated clinically and radiographically in 10 patients representing each of the 3 types of leprosy. In all of these patients, bone loss, measured radiographically and by clinical examination, was greater around anterior teeth than posterior teeth. In 9 of them, bone loss was greater around maxillary anteriors and in 1 around mandibular anteriors. As a consequence of these observations, we focused the rest of our investigations on the maxillary anterior region.

Clinical intra-oral photographs of representative patients with lepromatous, borderline and tuberculoid leprosy are shown in Figs 2, 3 and 4 respectively. Notice that gingival recession around maxillary incisors is greater in the patient with lepromatous leprosy (Fig. 2) than in those with borderline (Fig. 3)

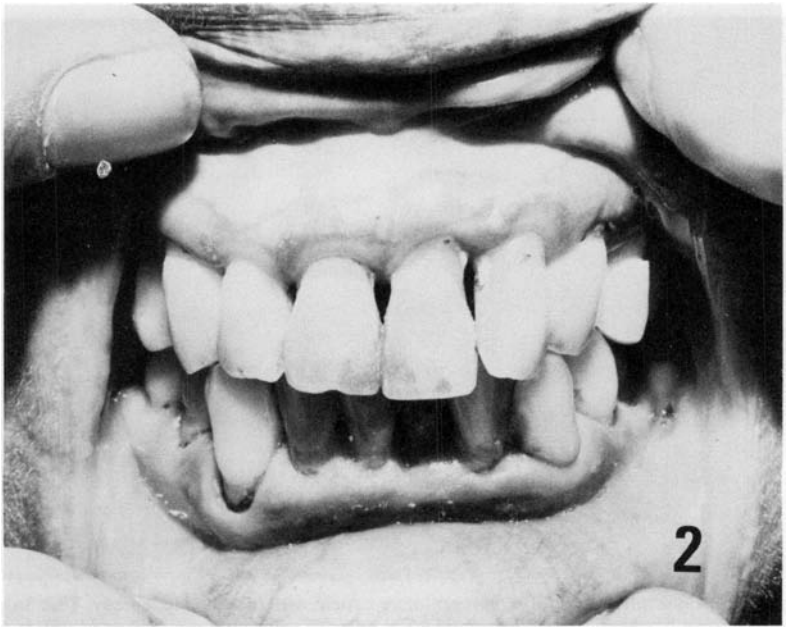

Fig. 2. Intra-oral photograph of the dentition and gingiva of a representative patient with lepromatous leprosy. This 53-year-old Malay male has been treated for leprosy for over 32 years.

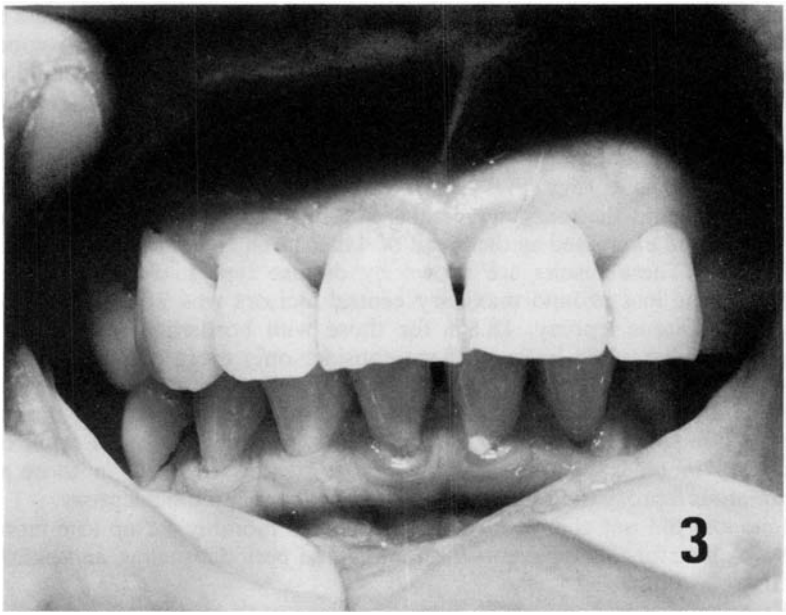

Fig. 3. Intra-oral photograph of a representative patient with borderline leprosy. This 40-year-old Chinese male has been treated for over 27 years. Gingival condition is very good.

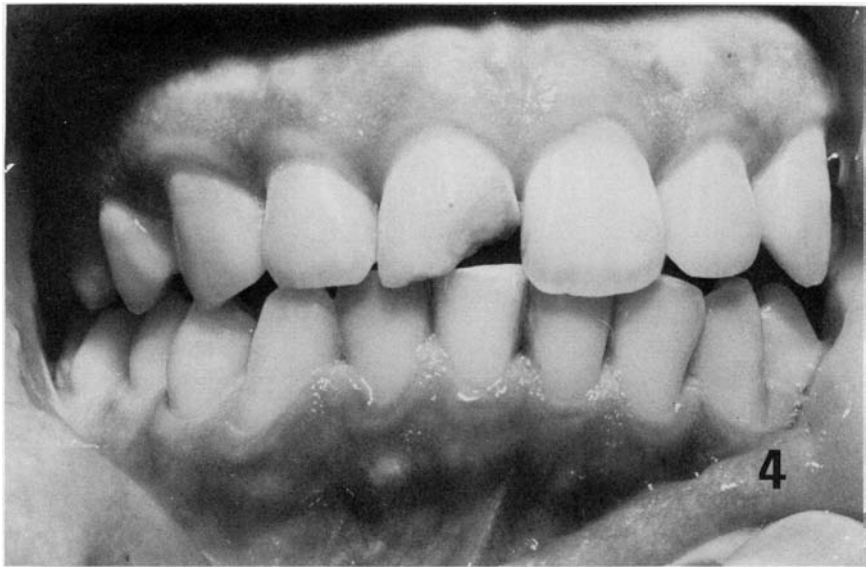

Fig. 4. Intra-oral photgraph of a representative patient with tuberculoid leprosy. This 36-year-old Malay male has been treated for leprosy for over 20 years. His gingival condition is much better than the patient shown in Fig. 2.

or tuberculoid (Fig. 4) leprosy. Pocket formation in all 3 patients was less than 2 mm. While the patient with tuberculoid leprosy (Fig. 4) is much younger than the patient with lepromatous leprosy (Fig. 2), the periodontal condition of older patients with tuberculoid leprosy was similar to that of the patient shown in Fig. 4.

A periapical radiograph of the maxillary central incisors from the patient with lepromatous leprosy (Fig. 2) is shown in Fig. 5. Measurements of alveolar bone loss around the maxillary central incisors were made from radiographs like Fig. 5 and expressed as the mean of 4 measurements, mesial and distal on each tooth. These results are shown by disease type in Fig. 6. The mean alveolar bone loss around maxillary central incisors was 26.1% for patients with lepromatous leprosy, 18.8% for those with borderline and 18.5% for those with tuberculoid leprosy. If we consider only those patients known to have leprosy for more than 5 years (shown in "O" column above lepromatous and less 2 patients each for the borderline and tuberculoid types), the mean alveolar bone loss is 31.8%, 19.4% and 19.9% respectively. In the latter case, bone loss in older patients is significantly greater ($t < 0.01$) in those with lepromatous leprosy than those with borderline or tuberculoid leprosy.

Bone loss did not change in patients followed monthly for up to 6 months. This was true for those patients with initial and periodic scaling and polishing and those without.

We attempted to compare alveolar bone loss in these patients with leprosy to that in patients without leprosy from the general population. Similar

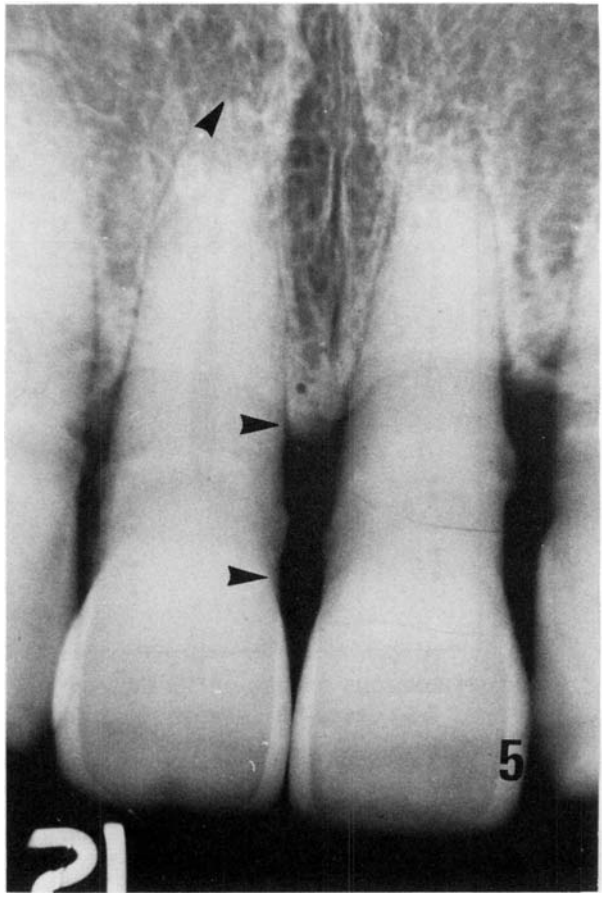

Fig. 5. Periapical radiograph of maxillary central incisors from the patient with lepromatous leprosy shown in Fig. 2. The landmarks used to measure alveolar bone loss are indicated by arrows. Alveolar bone loss in this patient was 32.5%.

measurements were made on periapical radiographs of 56 randomly selected patients who had presented at the University of Malaya Faculty of Dentistry for evaluation of maxillary incisors. Data from these patients were subdivided by age group. Mean alveolar bone loss for patients without leprosy was 18.2% in the 3rd decade, 23.2% in the 4th, 30.1% in the 5th and 32.8% in the 6th.

Discussion

The relative effectiveness of radiographs and clinical examination for evaluating periodontal condition and bone support have been recently reviewed (Lang and Hill, 1977). Because periapical radiographs and clinical

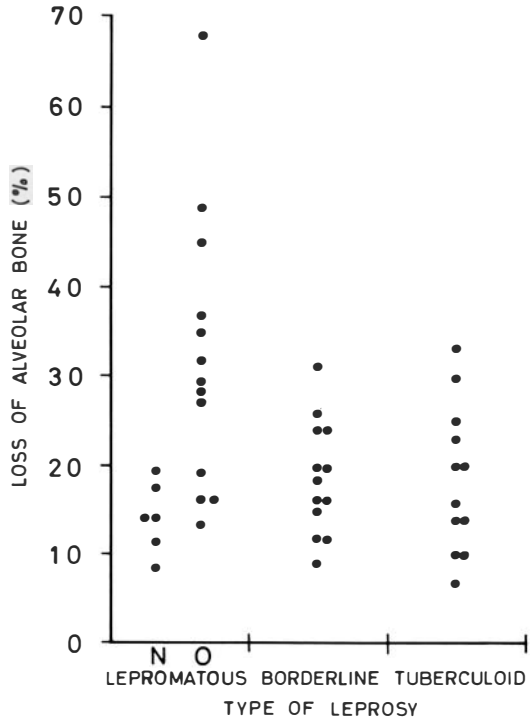

Fig. 6. Graph of alveolar bone loss around maxillary central incisors in patients with leprosy by disease type. In the lepromatous group, patients known to have the disease 5 years or less are shown above N (new); those known to have the disease longer than 5 years above O (old). Only 2 patients each in the borderline and tuberculoid groups were in the former group. We have not indicated these 4 patients separately because their alveolar bone loss was near the mean for their groups (see text).

probing underestimate alveolar bone loss, often by as much as 1–2 mm (Glavind and Löe, 1967; Soumi *et al.,* 1968), combined use of these methods is recommended (Lang and Hill, 1977). With simple standardized techniques, periapical radiographs may furnish quantitative estimates, albeit underestimates, of alveolar bone loss (Schei *et al.,* 1959).

Our data indicate that in patients with leprosy, alveolar bone loss is greater around maxillary anterior teeth than in other areas and that maxillary alveolar bone loss is significantly greater in those patients with the lepromatous form of the disease than in those with either tuberculoid or borderline leprosy. Furthermore, mean alveolar bone loss among our patients with advanced lepromatous leprosy, mean age of 40 years, was equal to that observed in patients from the general population without leprosy in their 5th and 6th decades. Alveolar bone loss in patients with borderline and tuberculoid leprosy, on the other hand, was comparable to that found in the general populace during the 4th decade.

Schei *et al.* (1959) measured alveolar bone resorption in 737 Norwegian males and found maximal bone loss in the maxillary anterior region in all age groups. Bone loss between maxillary central incisors was less than 15% during the 3rd decade, 12–18% in the 4th and 18–33% in the 5th. The range indicated mean measurements from patients with good and poor oral hygiene respectively (Schei *et al.,* 1959). We found the same predilection for maximal bone loss in maxillary anteriors in our patients with leprosy. However, our measurements of bone loss between maxillary centrals in 56 patients without leprosy were at, or exceeded, the upper limit observed in the Norwegians.

Because radiographic evaluation of the oral cavity is not routinely done for all patients here, we had to take our measurements of alveolar bone from patients without leprosy who presented with potentially pathological conditions of the maxillary dentition that justified radiography. Thus, these patients probably do not represent the general population, in which mean maxillary bone loss might be less.

We were unable to detect any increase in alveolar bone loss over a 6 month period in leprosy patients with or without periodic scaling and polishing. Thus, alveolar bone loss even in this group is a slow process. The low incidence of periodontal disease in our patients suggests that maxillary alveolar bone loss in leprosy is not dependent upon underlying periodontal disease. We conclude that it is a characteristic manifestation of the disease, particularly of the lepromatous type, as previously suggested (Møller-Christensen, 1953; Michman and Sagher, 1957).

In this study we were not able to determine if alveolar bone loss was related to duration of treatment or if early treatment could prevent this bone loss, because we could not accurately estimate the interval between onset of disease and the initiation of effective treatment. These questions are certainly worth investigating.

Acknowledgements

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The Cellular Basis for Alveolar Bone Loss in Leprosy*

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Maxillary alveolar bone biopsies from 7 patients with lepromatous, borderline or tuberculoid leprosy and 6 patients without leprosy were examined microscopically to identify cellular sources of bone loss. Osteoclasts and osteolytic osteocytes were found in greatest numbers in 3 patients with lepromatous leprosy who also had the greatest loss of alveolar bone. These cells were scarce or absent in bone biopsies from the patients with borderline or tuberculoid leprosy and from the patients without leprosy. These data are interpreted to mean that osteoclasts and osteolytic osteocytes represent the cellular basis for alveolar bone loss in leprosy.

Introduction

The discovery of resorption of the anterior nasal spine and of maxillary alveolar bone in patients with leprosy was made by Møller-Christensen (1952, 1953) in a unique and thorough examination of skeletal remains from a medieval cemetery for lepers in Naestved, Denmark. Documentation of these changes in contemporary patients was confirmed by Michman and Sagher (1957) in a study of 44 patients with lepromatous, borderline or tuberculoid leprosy. They found that resorption of nasal spine and maxillary alveolar process were greatest in patients with long-standing disease and most common in patients with lepromatous leprosy. Loss of alveolar bone was greatest in the maxillary midline, resembling an inverted triangle on radiographs. This characteristic resorption was a constant finding in the severely affected patients, but it could not be attributed solely to leprosy because these patients also had severe periodontal disease, a process in which this type of vertical alveolar resorption is routinely found (Michman and Sagher, 1957).

We have demonstrated in patients with leprosy at Sungei Buloh, Malaysia, that alveolar bone loss was maximal in the maxillary anterior region and that

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patients with lepromatous leprosy had a significantly greater loss of maxillary alveolar bone than patients with either borderline or tuberculoid leprosy (Subramaniam and Marks, 1978). The objective of this report is to identify in a cytochemical study of alveolar bone the possible cellular basis for this accelerated alveolar bone loss in patients with leprosy. Our data indicate that osteoclasts and a subgroup of osteocytes are the causes of alveolar bone resorption in leprosy.

Materials and Methods

Patients with leprosy were under treatment at the National Leprosy Control Centre, Sungei Buloh, Malaysia. The type of leprosy was determined by smears and clinical examination (Jopling, 1971). A small piece (3×4 mm) of bone was removed from the mesiolabial alveolar bone surface in 7 patients after extraction of a maxillary central incisor. Three patients had lepromatous leprosy for 5, 20 and 25 years, 3 patients had tuberculoid leprosy for 2, 22 and 30 years and 1 patient had borderline leprosy for 14 years. Alveolar bone specimens were fixed, demineralized, reacted for the histochemical demonstration of acid phosphatase activity using β-glycerophosphate as substrate, fixed again and embedded in epoxy resin as described previously (Marks, 1978). Sections 1-μm thick were counter-stained lightly with 1% toluidine blue. Specificity of the histochemical reaction for acid phosphatase was studied using the following controls: incubation without substrate, incubation in a medium containing an enzyme inhibitor (0.1 M sodium fluoride) and incubation with heat-inactivated (90°C for 30 min) sections.

Alveolar bone samples were obtained from patients without leprosy after extraction of central incisors at the Oral Surgery Clinic of the University of Malaya Faculty of Dentistry. Bone was taken from identical sites from 6 patients who were closely matched in age and ethnic group with the leprosy patients. Treatment of bone samples after extraction was identical to that described above.

Results

At least 10 non-adjacent sections (separated by at least 10 micra) were examined for bone cells in each patient. Osteoclasts were found in large numbers in the 3 patients with lepromatous leprosy, 1 or 2 were present in the patient with borderline and 1 patient with tuberculoid leprosy and no osteoclasts were found in the remaining 2 patients with tuberculoid leprosy. Up to 30 non-adjacent sections were examined in the latter 2 patients to reduce the possibility of missing an osteoclast if present. The osteoclasts found were of normal morphological appearance and were often in groups (Fig. 1). Most were on the external surface of the alveolus (Fig. 1), but a few were found in resorbing canals within alveolar bone (Fig. 2). These cells were of normal cytochemical appearance with respect to intracellular distribution of the lysosomal enzyme acid phosphatase. The enzyme was concentrated next to the bone surface (Fig. 3) with some enzymatic activity distributed generally within

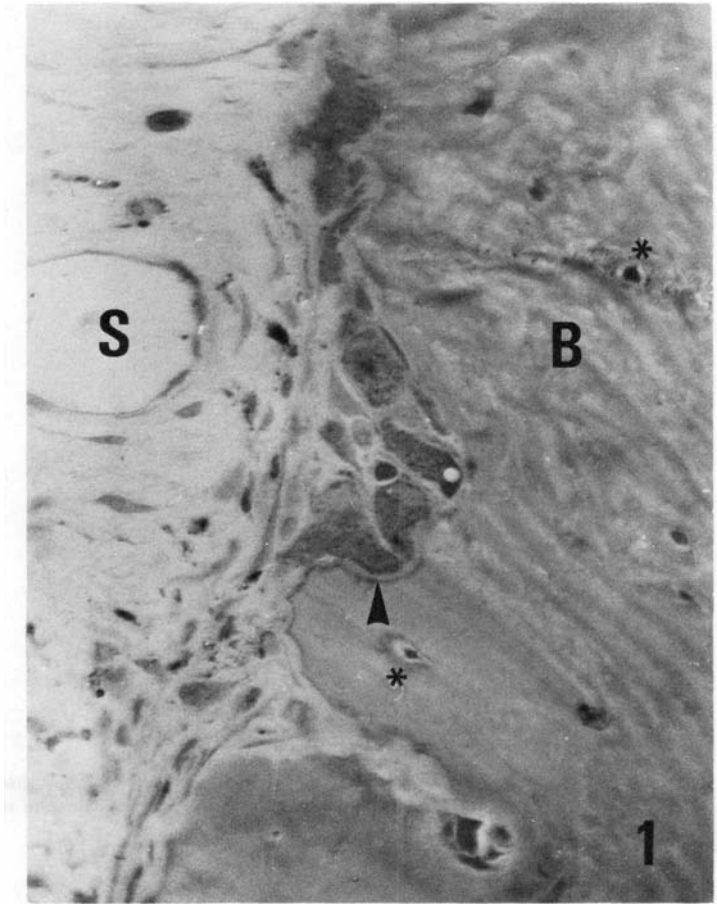

Fig. 1. Photomicrograph of the external surface of an alveolar bone biopsy. Seven osteoclasts are aligned next to the bone (B) surface above the arrow head. Black dots in the cytoplasm of these cells are lysosomes revealed by the histochemical reaction for the enzyme acid phosphatase. Enzymatic activity in the osteoclast next to the arrow is concentrated in a linear array next to the bone surface. The lacunae of adjacent osteocytes (*) are enlarged. A large venous sinus (S) is conspicuous in the loose connective tissue. All photomicrographs are from patients with lepromatous leprosy. × 300.

the cytoplasm (Figs 1–3). Osteocytes with enlarged lacunae were frequently observed in bone near osteoclasts (Figs 1 and 2). Osteocytes without enlarged lacunae were found in all bone samples. Alveolar bone support between the maxillary central incisors of these 7 patients was measured (Subramaniam and Marks, 1978) and expressed as the percentage loss of alveolar bone. Bone loss was 28, 29 and 37.5% in the 3 lepromatous patients, 19% in the borderline and 14, 16 and 20% in the 3 tuberculoid patients.

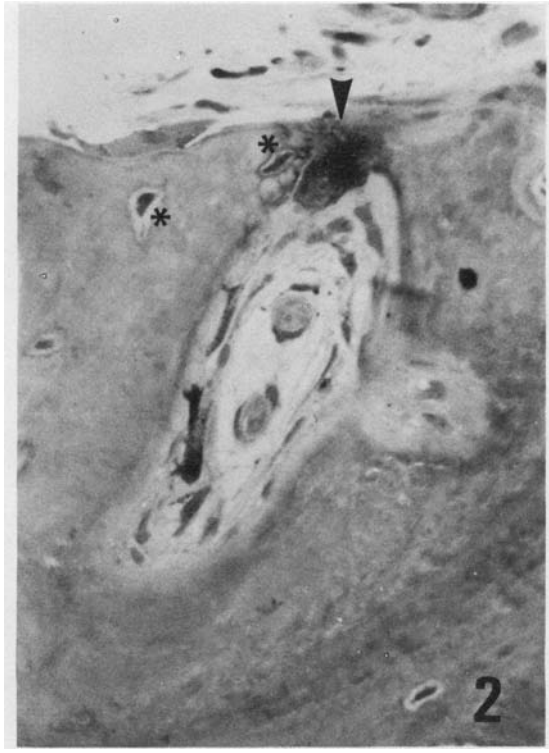

Fig. 2. An osteoclast (arrow head), very reactive for the enzyme acid phosphatase, is resorbing a thin plate of bone between a resorption canal and the surface. Lacunae of adjacent osteocytes (*) are greatly enlarged. × 300.

The frequency of osteoclasts observed in these patients was compared with that in alveolar bone from identical sites in 6 patients without leprosy, matched for age and ethnic group. We found osteoclasts in only 2 of these patients (a total of 3 osteoclasts) after microscopic examination of over 15 non-adjacent sections from each patient. These osteoclasts were indistinguishable morphologically and cytochemically from those shown in Figs 1–3. In 3 of these 6 patients over 40% of the osteocyte lacunae were empty. The lack of pre-extraction X-rays precluded measurement of alveolar bone loss in these patients. However, because most of the extracted teeth were carious and the gingival condition was good with no pockets deeper than 2 mm, we infer that these patients without leprosy did not have advanced periodontal disease. These results are summarized in Table 1. Osteoclasts were most numerous in patients with the greatest loss of alveolar bone, i.e. the patients with lepromatous leprosy. Osteoclasts were rare in alveolar bone samples from patients with borderline and tuberculoid leprosy and in patients without leprosy.

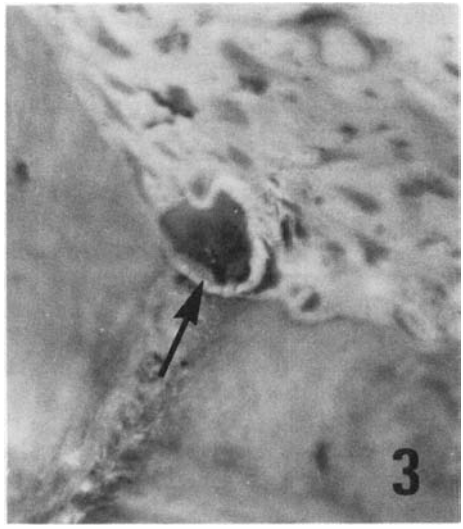

Fig. 3. A slight separation of this osteoclast from the bone surface reveals some of the thin cytoplasmic strands of the striated border that connect it to the bone surface. Note the concentration of acid phosphatase activity (above arrow head) in the cytoplasm next to bone. × 400.

TABLE 1

	Type of leprosy			Patients without leprosy
	Lepromatous	Borderline	Tuberculoid	
Number of patients	3	1	3	6
Range of number of osteoclasts	12–25	1	0–2	0–1
Percent alveolar bone loss*	28–37.5	19	16–20	Not available

* Data taken from Subramaniam and Marks, 1978.

Discussion

Recent evidence has shown that osteoclasts and a subgroup of osteocytes are the major cell types responsible for bone resorption (Marks and Walker, 1976). Electron microscopy has demonstrated that osteoclasts possess a specialization of the plasma membrane next to the bone surface which localizes its release of lysosomal enzymes during bone resorption (Lucht, 1971). Studies of osteocytes have shown that they can be divided functionally into 3 groups; osteogenic osteocytes which behave like osteoblasts, osteolytic

osteocytes which have enlarged lacunae and resorb bone, and resting osteocytes (Jande, 1971). Acid phosphatase, a lysosomal enzyme, is released from bone cells during bone resorption (Lucht, 1971; Vaes, 1968).

Our demonstration of osteoclasts and osteocytes with enlarged lacunae in alveolar bone from patients with bone loss strongly suggests that these cells are the basis for the advanced alveolar bone loss present in patients with lepromatous leprosy (Subramaniam and Marks, 1978). The method used to identify osteoclasts in this study, a combination of cytochemical staining of the lysosomal enzyme acid phosphatase and excellent preservation of cytological detail has many advantages over classical methods to identify these cells (Marks, 1978). Thus, it is likely that our failure to find many osteoclasts in alveolar bone from patients with borderline and tuberculoid leprosy and from patients without leprosy represents a reduction in numbers rather than a failure of the survey or identifying methods used.

The absence of almost half the osteocyte population in three patients without leprosy is puzzling. Less than 10% of osteocyte lacunae are usually empty in the osteocyte population (Jande, 1972). This observation coupled with the absence of osteoclasts could indicate that bone turnover in these patients is extremely low.

Osteoclastic resorption in maxillary alveolar bone in patients with lepromatous leprosy may be related to nasal spine resorption and the presence of large numbers of *M. leprae* in the adjacent nasal mucosa in these patients (Job *et al.,* 1966; Michman and Sagher, 1957; Rendall and McDougall, 1976; Southam and Venkataraman, 1973). Osteoclast function might be specifically accelerated in maxillary alveolar bone and nasal spine by release of some product from the neighbouring mycobacteria. This hypothesis might be tested by organ culture of bone with *M. leprae.*

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Lepr. Rev. (1978) **49,** 305–317

The Clayton Memorial Lecture, 1978: "Is Immunoprophylaxis in Leprosy Feasible?"

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Mr Chairman, Ladies and Gentlemen,

Before I reveal my incompetence in the subject to be discussed, I should like to thank Lepra with its Director, Francis Harris and the Chairman of the Medical Advisory Board, Dr Rees, for the invitation to give this year's Clayton Memorial Lecture.

As you all know, the World Health Organization, over the last years, has increasingly focused its attention on the health of the poorest billion in the world. By the slogans "Health by the people" and "Health for all by year 2000" the principle of "self-reliance" is promoted at all levels. This also applies to medical research.

It has been estimated that only 1% of the total global biomedical research effort is being devoted to diseases from which two-thirds of the world population are suffering.

In order to correct this very unsatisfactory situation and stimulate self-reliance, a special programme for research and training in tropical diseases has been established by the World Health Organization.

However, it has been realized that in the field of biomedical research, a considerable period of time is needed to reach self-reliance. The programme has therefore two components, one concerned with institution strengthening in developing countries, and another with research by which expertise anywhere in the world is recruited into the field of tropical diseases.

The research component, organized into scientific working groups (SWGs), is goal-orientated with the objective of developing new methods, such as drugs or vaccines, or simplified methods, for use in the control in tropical diseases. Initially six diseases have been selected: malaria, schistosomiasis, filariasis, trypanosomiasis, leishmaniasis and leprosy.

The courageous attitude of WHO, by making such an ambitious goal as a leprosy vaccine as target for a research programme, has provoked an open and continuous discussion on all aspects of the targets, including both the feasibility of reaching them and their desirability in the context of disease control.

This year's Clayton Memorial Lecture should be viewed as a part of this ongoing discussion. Thus, if any one of you can put a convincing argument against the development and use of a leprosy vaccine in the context of leprosy control, both considerable human and other resources could be saved.

The discussion may be divided into two parts:

(1) The continuous discussion of problem areas with regard to leprosy control.

(2) The achievements made so far in the Immunology of Leprosy Scientific Working Group (IMMLEP).

In so doing, I shall adopt the health administrator's approach, i.e. start with the size of the health problem and end up with technical, basic immunological questions.

(A) The Size of the Problem

Leprosy is a chronic infectious disease caused by an acid-fast bacillus *(Mycobacterium leprae)*. Among diseases caused by acid-fast bacilli (or mycobacteria), tuberculosis still represents the greatest health problem. Leprosy comes second to tuberculosis and is estimated to affect between 10 and 15 million people in the world today. The patients are found in the tropical and sub-tropical belt, especially in developing countries. Climatic factors *per se,* however, are unlikely to have a significant impact on the disease, since several thousand cases were registered in Norway in 1860, with cases as far north as the Lofoten islands beyond the polar circle.

In hyperendemic areas, the annual incidence of leprosy may reach 4–6 per thousand, and the prevalence of the disease frequently exceeds 10 per thousand in Africa and some parts of Asia. In comparison with several other infectious diseases, these figures are not high. Moreover, leprosy is rarely — directly, at least — a cause of death. On the other hand, 20–30% of the patients develop severe forms of deformity. These could amount to several hundred thousand patients per year, but certainly less than 1 million per year.

Thus, in terms of the recent trend to use economic impact as a measure of quantifying a disease problem (e.g. Card and Mooney, 1977) leprosy does not appear a major health problem in any part of the world. Nevertheless, many developing countries rank leprosy among their major health problems (Sansarricq and Walter, 1976).

Therefore, leprosy represents a challenging problem with regard to priority ranking between different diseases. How is one to weigh economic impact against social ostracism? Who should quantitate health problems — the people concerned or health economists?

These problems are heavily influenced by a society's basic view on health. In this decade, especially in relation to aid, health has been judged in an economic

context. However, evaluation of disease in monetary terms is not easy. For example, the monetary value inferred from several public policy decisions ranges from £50 (minimum) to £20,000,000 (maximum) (Card and Mooney, 1977). Moreover, at present basic health needs increasingly appear to be judged in the context of human rights.

(B) Present Methods of Leprosy Control

Two basic principles of leprosy control are :

(1) early detection of cases, and

(2) treatment to cure or arrest the disease.

Both principles are hampered by a number of problems:

(a) EARLY CASE DETECTION

Although close contacts of lepromatous patients are at higher risk of developing leprosy than non-contacts, the great majority of patients are found among non-contacts. Thus, surveys cannot be limited to any identifiable high risk group.

The social stigma of leprosy puts pressure on patients to abstain from seeking medical assistance until the disease is advanced and easily recognizable. Because of the stigma, integration of leprosy into general health services is problematic, other patients may protest against being treated in the same place as a "leper", and overextended primary health care systems will have to make tough decisions on priorities.

(b) TREATMENT

Dapsone remains the major first-line drug in leprosy. It has been used for more than 30 years, is generally well tolerated with few side-effects, and it is inexpensive, costing only a few dollars per year per case.

However, it has a slow action; lepromatous patients remain bacteriologically positive for several years, and acute reactions may occur in patients on treatment. Case holding is therefore a significant problem. In addition, after 30 years of monotherapy, an alarming increase in DDS-resistant bacilli has been reported from various parts of the world (see *Leprosy Review,* 1977). This world epidemic is still apparently only in its beginning.

Combined chemotherapy is now recommended for multibacillary leprosy (World Health Organization, 1977*a*). However, even when applying combinations which include rifampicin, a most potent antileprosy drug, viable bacilli (so called "persisters") may be detected in patients after 4–5 years of treatment (Waters *et al.,* 1978). Thus cures after short-term treatment regimens do not seem in sight at present.

(c) LEPROSY AND SOCIO-ECONOMIC DEVELOPMENT

Leprosy declined rapidly in Norway during the period from 1870 onwards (Hansen and Looft, 1895). This decline is generally assumed to be due to

TABLE 1
*Selected comparisons of GNP, health parameters and birth rates**

	GNP per capita	Life expectancy years	Death rate per 1000	Infant mortality per 1000	Birth rate per 1000
Low income countries	$152	48	17	134	40
India	$140	50	15	139	35
Kerala State (India)	$110	61	9	56	30
Sri Lanka	$130	68	8	45	28
Taiwan	$810	68	5	26	23
Iran	$1250	51	16	139	45
U.S.A.	$6670	71	9	17	15

*Bloom (personal communication).

socio-economic development, but whether any factor associated with socio-economic development — like nutrition or education — is of special importance or not, remains unknown.

Since socio-economic development in countries where leprosy now is endemic has different patterns, as epidemiological investigation of leprosy in various developing countries could perhaps throw light on this question. In particular it would seem of interest to learn about leprosy in Kerala state, India, and in Sri Lanka, where health care appears to be of high standards, in spite of low gross national product per capita ratios (Table 1).

This, however, remains at present a hypothesis for exploration, which does not alter the fact that there is no evidence of decline in leprosy on a world-wide basis, and that the prospects of controlling leprosy with the presently available methods appear remote. Research into the development of new tools is therefore an urgent matter.

(C) If Developed, is a Vaccine Likely to Have Any Place in a Leprosy Control Programme?

The most important question in this regard is the cost/effectiveness of a potent vaccine. Costs may be considered at three levels:

(1) Cost of development: The vaccine component of the IMMLEP programme has been estimated to cost £1.5–2.5 million from start to the end of the first field trial. This is less than 25 pence per patient today.

(2) Production costs: These cannot be estimated at present.

(3) Delivery costs: Since the prevalence of leprosy in endemic areas is low, the delivery costs per case protected are likely to be high if isolated leprosy vaccination campaigns on a mass scale were to be undertaken. However, since multiple vaccines (at least six) may be given simultaneously without negative interference, a leprosy vaccine could be incorporated into larger vaccination programmes.

Here I have merely pointed to some factors, at present largely unknown, which will have to be considered in due course and balanced against the costs of chemotherapy and other forms of treatment on a per case basis. However, in my view a place for a vaccine in leprosy control cannot be ruled out by presently available cost/effectiveness considerations.

(D) Is Immunoprophylaxis, If Applied, Likely to Have Any Impact on the Infectious Reservoir of Leprosy?

Since man is the only significant source of *M. leprae,* this question first requires a description of the clinical manifestations in leprosy.

(a) CLINICAL MANIFESTATIONS

The leprosy bacillus is a slowly growing organism with a generation time of 12–13 days (Shepard, 1971). The incubation period of the disease is also long, ranging from 2 or 3 to more than 10 years. Just as with many other infectious diseases, such as tuberculosis and poliomyelitis, leprosy appears to cause disease in only a minority of those who become exposed to the germ (Godal, 1974*a*). Most subjects appear to control the infection effectively at a pre-clinical stage. In those who develop disease, a wide spectrum of clinical manifestations is encountered. They range from a single, often self-healing skin lesion in so-called tuberculoid leprosy to a disseminated, diffusely infiltrated form called lepromatous leprosy. While tuberculoid leprosy patients are

TABLE 2
*Some histological and immunological features in leprosy**

	TT	BT	BB	BL	LLs	LLp
Epithelioid cells	++	++	++	±/−	—	—
Non-vacuolated giant cells	++/−	+/−	—	—	—	—
Histiocytes/foamy macrophages	—	—	—	++	++	++
Lymphocytes	+±/+	+±/±	±	++/+	+/±	±/−
Dermal nerve, maximum diameter in μm	1000	400	250	200	200	80
Acid-fast bacilli in granuloma	−/+−	−/+	++	+++	++++	++++
Acid-fast bacilli in nose	—	—	—	+−	++	++
Lepromin (Fernandez) reaction	+++	++/−	+/−	—	—	—
Lepromin (Mitsuda) reaction	+++	++/+	—	—	—	—
Lymphocyte transformation test (% transformation)	15	5.7	2.0	0.4	0.3	0.2
Leucocyte migration index	0.76	0.84	0.89	0.92	0.92	0.96
Antimycobacterial precipitins	—	—	−/+	−/++	++	+++
Anti-*M. leprae* antibodies	−/+	−/++	++	+++	+++	+++
Immunological stability	++	±	—	±	+	++
Borderline reactions	—	+	++	+	±	—
Erythema nodosum leprosum	—	—	—	±	++	++
Approximate distribution of cases (%)	9	24	8	10	31	18

*From Godal, 1978 (modified from Ridley, 1974).

negative on bacteriological examination, billions of bacilli may be found per g tissue of the skin from lepromatous leprosy patients. These two polar types are interlinked by a range of sub-groups comprising borderline leprosy (see Table 2).

Apart from the skin, the bacilli also thrive in other tissues, especially the nerves. This leads directly, or more often indirectly by the patients' immunological attack on the bacilli inside the nerves, to nerve damage (Godal, 1974*b*). The resulting paralysis and hyposensitivity over the years — under low socio-economic conditions — produce deformity, mutilation, and in some patients blindness.

(b) THE INFECTIOUS RESERVOIR

The Fifth Expert committee on leprosy (World Health Organization, 1977*a*) considered that while multibacillary leprosy (BL to LL) was likely to represent the major infectious reservoir, it was also considered that borderline tuberculoid and indeterminate patients in certain areas where the relative proportion of multibacillary leprosy is low, could play a non-negligible part in the transmission of leprosy. Since non-polar lepromatous leprosy patients (BL–LI) may revert immunologically, simply by antileprosy chemotherapy, it would seem likely that immunization at a pre-infection (and pre-clinical?) stage would have a significant effect on this population (I, BT–LI). This group of patients may well represent 50% or more of the infectious reservoir in a majority of endemic areas. Then remains the question whether or not vaccination could influence lack of resistance in subjects prone to develop polar lepromatous leprosy. If genetic factors should turn out to be of major importance for the development of their immunological defect, vaccination even at a pre-infection stage could be of little value. However, the data supporting the involvement of overriding genetic factors in this defect is in my view limited, e.g. the studies by Chakravartti and Vogel (1973) showed that the concordance for lepromatous leprosy in monozygous twins was not more than 50%, a low figure, particularly in the light of the present views on the transmission of leprosy. Moreover, the nature of the defect in lepromatous leprosy, which will be discussed in more detail, indicates that the defect has features in common with so-called immunological tolerance. This type of immunological unresponsiveness can be restored by immunization with cross-reactive antigens. For these reasons, it would seem likely that vaccination could have a significant impact on the infectious reservoir of leprosy.

(E) Technical Considerations

(a) MECHANISMS INVOLVED IN HOST RESISTANCE TO INTRACELLULAR BACTERIA

Immunity to intracellular bacteria is dependent on cell-mediated immune mechanisms rather than humoral antibodies (Mackaness and Blanden, 1967).

Furthermore, studies in experimental animals have revealed that the carrier of this immunity is the thymus-dependent lymphocyte (T cell) (Rees *et al.*, 1967; Gaugas, 1968; Lane and Unanue, 1972; North, 1973). However, the T cell itself appears incapable of killing the parasites directly (Tripathy and Mackaness, 1969; MacGregor and Koster, 1971), but accomplishes this function through the mononuclear phagocyte (macrophage). At least two mechanisms seem to be involved:

(1) When encountering foreign antigens in the tissues, the T cell may increase the antibacterial activity of the surrounding macrophages (Mackaness, 1971); this phenomenon has been called "macrophage activation" and may, at least in part, be accomplished through the release of molecular mediators (lymphokines) by stimulated T cells (Fowles *et al.*, 1973; Godal *et al.*, 1971).

(2) In addition, chemotactic substances (Bloom, 1971; David and David, 1972; Pick and Turk, 1972) are released which increase the influx of macrophage precursors (monocytes) into the lesion; this phenomenon has been called "macrophage mobilization" (World Health Organization, 1973; Mackaness, 1974).

While macrophage activation may represent an important defence mechanism against some infectious agents such as intracellular bacteria (World Health Organization, 1973), macrophage mobilization may be more important against others, such as viruses (Blanden, 1971). The possible contribution of bactericidal factors released by activated macrophages (Bast *et al.*, 1974) has yet to be established.

In addition, macrophage/T cell co-operation apparently takes place at the afferent level of the immune response to intracellular bacteria. This recognition of antigens from intracellularly growing bacteria by T cells is restricted by I region genes of the major histocompatibility complex (Zinkernagel *et al.*, 1977).

Experimentally, significant levels of cell-mediated immunity can be induced by live infection or by the help of adjuvants. Consequently, the two main possibilities for inducing cell-mediated immunity to *M. leprae* would appear to be (1) the use of an attenuated strain of *M. leprae* or closely-related live mycobacterium — or (2) non-viable antigens in an adjuvant.

Among these alternatives, an attenuated strain of *M. leprae* is unlikely to be produced before *M. leprae* can be cultivated on artificial media. This approach therefore appears to be unrealistic at present. The two other approaches are being pursued at present at various research centres.

With regard to a live cross-reactive mycobacterium, taxonomic studies on *M. leprae,* particularly by Dr Stanford's group in London, have indicated that *M. leprae* is more closely related to rapidly dividing mycobacteria, especially *M. vaccae* and *M. non-chromogenicum,* than to slowly growing mycobacteria (World Health Organization, 1977*b*). In the later studies, Stanford and his group have mainly used skin-reactivity in human populations with ultrasonicates of bacilli in their taxonomic studies. However, more information is needed on cell wall and surface antigens, since these may well be important in relation to protective immunity. Whether the cross-reactive strains are sufficiently safe to be used in viable form in man and also whether they would

be capable of inducing cell-mediated immunity, remains unknown. If not, they may be considered for use as killed bacilli in an appropriate adjuvant. If a killed vaccine is to be used, it would seem more logical, at least at first sight, to use *M. leprae* itself. This has now become a realistic possibility because of the large number of organisms that can be harvested from armadillos, if these bacilli appear to contain the most important antigens for protective immunity. The potential of a killed vaccine depends on whether sufficiently strong and lasting cell-mediated immunity can be induced in man.

(b) SOME RECENT ADVANCES MADE IN THE IMMLEP PROGRAMME TOWARDS THE DEVELOPMENT OF A VACCINE

The scientific plan for development of a vaccine was adopted by the 1st Scientific Working Group in 1974 (World Health Organization, 1974)

The main steps were conceived as follows:

(1) Secure the supply of abundant *M. leprae* from infected armadillos.
(2) Develop methods for purifying *M. leprae* from tissues.
(3) To establish optimal methods for the killing of *M. leprae*.
(4) Antigenic and taxonomic relationship between *M. leprae* and other mycobacteria.
(5) Induction delayed type hypersensitivity to *M. leprae*
    (a) in experimental animals
    (b) in man.
(6) Induction of resistance to experimental infection.

IMMLEP has put great emphasis on the first point and will by 1978 have a "farm" of 250–300 animals reserved for *M. leprae* production. R. J. W. Rees at National Institute of Medical Research has taken responsibility for the IMMLEP "bank" and store, and distribution of *M. leprae* according to the directions of IMMLEP's Steering Committee. P. Draper, also at NIMR, rapidly developed a method based on a two-phase polymer system for purification of *M. leprae* (World Health Organization, 1977*b*). This method gave high purity and good yields, but the use of proteolytic enzymes raised the question if important antigens could be destroyed by the procedure. This question has not been entirely resolved, but recent investigations by P. Draper suggest that the method may be modified in such a way that bacilli of high purity can be produced without the use of proteolytic enzymes. By studies carried out by Shepard, Bloom, Lefford and Rees (World Health Organization, 1977*b*) *M. leprae* has been found to have two remarkable features which may turn out to be very advantageous in relation to a vaccine based on killed *M. leprae*. First, killed *M. leprae* without adjuvants can induce delayed type hypersensitivity in guinea pigs and mice and protect mice against experimental infection with *M. leprae*. Second, autoclaved *M. leprae* appear to be as good, or possibly better, both with regard to immunogenicity and protective immunity in mice.

With regard to taxonomy, as reported above, *M. leprae* seems to be more closely related to rapidly growing mycobacteria than to slowly growing mycobacteria, but a cultivable mycobacterial strain with an intimately close

TABLE 3
Classification of T cells *†

Cell	Symbol	Thy-1	ALS	Ly-1	Ly-2,3	Ia‡	FcR	Life span	Special characteristics
Initiator	T_I	High	R§	+	+	+	+?	Short	Adheres to nylon wool. Present in afferent lymph. Absent from nodes. Binds suppressive and enhancing factors.
B cell helper	T_{HB}	Low	S	+	—	+	—	Long	Low density. Becomes Ala-1$^+$ if activated.
T_C cell helper	T_{HC}	Low	S	+	—	+	+	Long	
Delayed hypersensitivity	T_{DHT}			+	—	—?			
Effector		Low	S					Long	Becomes Ala-1$^+$, FcR$^+$ if activated
MHC allogeneic?	T_C			—	+				
Non-MHC?	T_E			+	+	+			
Suppressor	T_S								High density. Abundant in spleen.
Specific?			S	—	+	1-J$^+$			
Nonspecific?				+	+				

* This classification, especially the separation into T cell subdivision, is based on imperfect evidence. It should be regarded as tentative. See text for sources and details.

† From Snell (1978).

‡ All T cells except the T_{DHT} cell have been reported as carrying Ia antigens. Ia antigens may ultimately be found on all T cells, and are likely to be different on each cell category (Murphy *et al.*, 1977).

§ R = resistance; S = sensitive.

relationship to *M. leprae* has yet to be discovered. However, based on skin-test data from various leprosy endemic areas, Stanford and his colleagues have come up with a new hypothesis with relevance to immunoprophylaxis in leprosy. They have found that sensitization to *M. marianum* is common in areas with high prevalence of leprosy and therefore suggest that certain environmental mycobacteria, such as *M. marianum,* may interfere with the induction of protective immunity induced by BCG or *M. leprae* itself.

Their hypothesis may explain several epidemiological findings, including the protective effect of BCG in children under the age of 4 in the Burma trial, but would seem to be in opposition to earlier studies in tuberculosis where atypical mycobacteria were found to give a partial protection against *M. tuberculosis* (Palmer and Long, 1966). Such a sensitization did not interfere with the protection provided by BCG in experimental animals, but would simulate such an effect in vaccine trials by reducing the differences between the vaccinated and the control group.

It would seem most important if Stanford *et al.* can substantiate their hypothesis by experimental studies. Thus, right now the most promising path appears to be the use of killed *M. leprae.*

However, one should bear in mind that these investigations to a large extent are based on delayed type hypersensitivity (DTH) investigations in mice and guinea pigs. The sensitivity of the growth of *M. leprae* in the mouse footpad to various immunological interventions, such as BCG and graft versus host reactions, limits its value as an assay for protective immunity.

These studies, therefore, raise the question of the relationship between DTH and protective immunity. Although Rees *et al.* (1967) more than 10 years ago showed that immunity to *M. leprae* was T cell dependent, more recent basic immunological research has been able to dissect the T cell compartment into functionally distinct sub-compartments (see Table 3), which raises the possibility that DTH and protective immunity is mediated through different T cells. My own biased view is that this is unlikely to be the case because the DTH reaction appears to me a most suitable device for dealing with intracellular parasites. Nevertheless, a note of caution should be made with regard to extrapolations from DTH reactions to protective immunity. The antigenic heterogeneity, only a few of which may be important for induction of protective immunity, underlines this reservation.

Studies in armadillos susceptible to disseminated leprosy may turn out to be most important. It is encouraging that Kirchheimer's group has reported protective effects with heat-killed *M. leprae* in Freund's complete adjuvant in this species (Kirchheimer *et al.,* 1978).

In my view, the data obtained in the IMMLEP programme, so far, are sufficiently promising to make a start with the planning of a field trial. The first step in this endeavour is to ask what kind of epidemiological information is required to design a vaccine trial. Since a vaccine is unlikely to have any effect in subjects which have already converted immunologically to *M. leprae,* one such question is, at what age do such conversions take place?

The BCG trial in India has shown that a very large proportion of TB cases occurs in subjects tuberculin positive at the beginning of the trial (Guld, personal communication). Together with observations made in the British

BCG trial (Hart and Sutherland, 1977) and epidemiological information about TB in industrialized countries, such as Norway, it suggests that reactivation is not an infrequent phenomenon in tuberculosis. What is the situation in leprosy? The age-related distribution of cases from Burma (Bechelli *et al.*, 1973) may perhaps suggest that borderline leprosy occurs as result of "reactivation" or immunological deterioration from tuberculoid or sub-clinical leprosy. Information of this nature would seem necessary for determining the appropriate size of such a trial. How will chemotherapy affect the size?

Another question is how to secure a uniform classification of cases, especially indeterminate patients? Will a biopsy from all suspected cases be required?

These are only indications of the variety of important questions which have to be considered before a trial can be precisely designed. Obviously, several of them may require investigations in the field in order to be resolved. Thus, it would seem most important to start the planning now in order to avoid considerable delays when the experimental studies have been finished.

In fact, epidemiology would appear to be the area where more information is most needed for more precision in the future attacks on leprosy.

Ernest Fritchi once called the 1950's the decade for rehabilitation in leprosy, the sixties the decade for leprosy control and the seventies the decade for immunology. May I extend this and suggest that we make the 1980's the decade for epidemiology!

Conclusions

From what has been stated above, it is clear that there are many unanswered questions concerning both the development of an antileprosy vaccine and its potential use in leprosy control. Nevertheless, significant progress has been made over the last few years and now the possibility of using killed *M. leprae* appears most promising.

Many of the questions facing us in the coming years may only be answered by a field trial. This may for example be the only way of determining whether or not a vaccine can protect against lepromatous leprosy. Thus, such a trial may be viewed as an experiment to answer important scientific questions and not turned down *a priori* because of a prohibitive cost per dose of the vaccine to be tested. It has been estimated that 6–12 years are required to fully evaluate the effect of a vaccine trial. I therefore sincerely hope that this year's Clayton Memorial Lecture does not nourish the misconception that an effective antileprosy vaccine will shortly be at hand.

The long time needed and the uncertainties in this area of research, as discussed above, require that other areas of leprosy research, such as chemotherapy, should be given top priority and proceed parallel to vaccine-related research.

After all, leprosy is caused by a mycobacterium, and the best we can hope for is that leprosy research will provide a number of weapons such as new, inexpensive drugs, an effective vaccine and epidemiological tools, all of which may play their part in the fight against this crippling disease.

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*Available on request to World Health Organization.

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Leprosy and the Community

LEPRA — ANNUAL REPORT FOR 1977

The 54th Annual Report of Lepra, presented at the Annual General Meeting in June 1978, covers the year 1977. It condenses into 20 pages the interest and concern for sufferers from leprosy felt by many people in all walks of life in Great Britain.

1977 was a record year for income. The total of £551,376 was achieved by Broadcast appeals, house to house collections, flag days, exhibitions, donations and an astonishing range of social events involving much generous and sacrificial service and often a great deal of enterprise and ingenuity. This is hinted at by a page of illustrations in the Report, but one really needs to turn to *Lepra News,* Lepra's quarterly publication, to gather details of the range of all this interest on the part of so many members of the general public, an interest stimulated by 10 Regional Organizers and 150 Honorary Representatives scattered across England, Scotland and Wales.

All these contributors may be more than satisfied by the way their gifts have been used. Pursuing the well publicized 5 main guidelines for support, Lepra has first continued to sustain major leprosy control projects in Malawi and Sierra Leone and given new grants in aid for development projects in India, Guyana and the Philippines.

In the sphere of research, Lepra is supporting in very practical ways the World Health Organization Special Task Forces IMMLEP and THELEP. Dr Rees, Chairman of Lepra's Medical Advisory Board, is a member of the Steering Committee of both Task Forces. Grants have been given for maintaining an armadillo colony in Britain under the care of Dr Rees as a vital element in the IMMLEP project, also to the Medical Research Council, The Royal College of Surgeons and the All India Institute for Medical Sciences, New Delhi.

Lepra's direct involvement in leprosy research is also personified in Dr Colin McDougall and his outstanding histopathological work at Oxford, related to THELEP and also to the Ciba-Geigy Rifampicin trial. An important research event in 1977 was the Heathrow Meeting sponsored by Lepra, to which representatives were invited from WHO and the Medical Commission of ILEP to consider the importance of dapsone resistance in relation to the control and treatment of leprosy.

Over 22,000 children suffering from leprosy benefited from Lepra's Children Fund in 1977. In the face of dapsone resistance financial provision has been made for combined therapy in appropriate cases.

One of the historic aspects of Lepra's work has been the fostering of

contacts between researchers, and enriching the experience of leprosy workers through fellowships and travel grants. The writer benefited from this as long ago as 1938, and over the years the cause of leprosy eradication has been greatly furthered by the involvement in leprosy research of specialists whose interest was first strengthened in this way. Several such grants were given in 1977.

Finally we pay tribute to the continued encouragement and support of Lepra in the publication of *Leprosy Review,* and especially to Mr G. F. Harris, the Director. With this issue the Journal has completed its 49th Volume, and its distribution of around 900 copies carries it into the hands of many a doctor and field worker for whom it is the only source of up to the minute information on matters of leprosy research and organization. From the beginning, Lepra has been responsible for this Journal, drawing together the specialists concerned in its production and providing essential financial undergirding. An important aspect of this has been the policy of generously subsidizing the distribution of the Journal to doctors engaged in field or hospital work where resources are limited, a service of great value. The status enjoyed by the Journal is evidenced by the number, range and quality of the original contributions submitted for publication. One of its features is the effort which is made to publish those which are accepted by the Editorial Board with a minimum of delay. In its sponsorship of *Leprosy Review* Lepra makes a contribution to the cause of leprosy eradication of great importance.

We offer our best wishes to Lepra for the year ahead.

T. F. DAVEY

"SET APART" — THE ANNUAL REPORT OF THE LEPROSY MISSION FOR 1977

"Set Apart", the Report of The Leprosy Mission for 1977, is a record of another year of remarkable progress. Attractively produced and very well illustrated, the front cover of the Report immediately invites the right kind of interest as it portrays patient, national doctor and expatriate physiotherapist all deeply concentrating on the care of the patient's hand, a scene in sharp contrast to the ghoulish pictures so frequently associated with leprosy publicity.

During the past 4 years the annual income of the Mission has increased from £1,000,000 to more than double that amount. Now very much an international organization, the financial support of the Mission from England and Wales is exceeded by support from Continental Europe, while giving by people in New Zealand, Australia and Canada is quite outstanding in relation to the population of those countries.

This great increase in resources has made expansion possible in every aspect of the worldwide commitments of the Mission. This report focuses upon *people,* set apart to seek, to heal, to restore and to care, to teach, to help and to witness, and so the many-faceted work of the Mission is covered.

The historic commitment of The Leprosy Mission to the Indian sub-continent continues. Emphasis on the quality and efficiency of field workers has led to major developments in training facilities, first at Karigiri, but also including Salur, Purulia and Miraj, with many Government sponsored trainees taking part in the courses provided. Thirty-five full-time doctors are now engaged in the extensive S.E.T. work supervised by the Mission, and more are needed in this, by far the largest Voluntary Agency leprosy control organization in India. It is the standing which the Mission enjoys in India which opened the door to developments in Bhutan, Bangladesh, and in lesser degree, in Nepal.

The Leprosy Mission has always fostered research in leprosy, from the highly sophisticated procedures associated with electron microscopy and mouse footpad inoculation to field studies and the enormous developments in corrective surgery, physiotherapy and occupational therapy. There is world-wide recognition for the great services of members of The Leprosy Mission staff in these fields, services which are still continuing, especially in India.

In Africa The Leprosy Mission supports leprosy control work in 15 countries and is a partner in the All Africa Research and Training Centre (ALERT) at Addis Ababa. In East and South East Asia the Mission has a key role in several countries, in close relation with University authorities at Taegu in Korea, and with Government in Thailand, Indonesia and Papua New Guinea.

Characteristic of The Leprosy Mission are the dedication of its workers and the open-minded generosity which the writer first experienced in 1938 at the Cairo Conference, when the General Secretary of the Mission offered financial assistance to Uzuakoli hospital, then just embarking on a major leprosy control programme. In 1977 no less than £214,000 was given in grants to centres run by societies other than those under the direct management of the Mission. This great international organization channels the concern of Christians in many lands who believe that "it is more blessed to give than to receive".

This review would be incomplete without a special reference to Dr Victor Das, for 15 years Secretary of the S.E. Asia Region of the Mission, who retired at the end of 1977 and is succeeded by Dr R. Thangaraj. During my years in India I had many contacts with Dr Das and had first hand knowledge of the dedication, skill and wisdom which he brought to his exceedingly onerous duties. His retirement after a lifetime of service for sufferers from leprosy in India is a great loss. We think of him with admiration and affection and offer best wishes for the years ahead to Mrs Das and himself.

T. F. DAVEY

EMMAUS-SWISS PALAMANER LEPROSY PROJECT, CHITOOR DISTRICT, ANDHRA PRADESH, INDIA, FIRST ANNUAL REPORT, FEBRUARY 1978

This 21-page report describes the growth of the Project, from the opening of the first clinic at Palamaner in September, 1977, to the end of that year. In an

introductory message from Dr M. Phaineua, Regional Director for WHO in New Delhi, we are reminded that leprosy is a major health problem in India, with 372 million people at risk and 3.2 million estimated to have the disease, of whom about 1.6 million have so far been registered for treatment; 10% of these are infectious.

The test describes Andhra Pradesh as one of the hyper-endemic zones, with 628,000 estimated cases, of whom 253,000 have been registered for treatment; the average prevalence for the State has been estimated at 14.8 per thousand. Within this, the Project has concentrated on the Chitoor District, with an overall estimated prevalence of 17.8 per thousand and the Report describes the steps taken in case-detection, classification, registration of disabilities and rehabilitation. So far, 13 peripheral clinics have been established, registering 1314 cases for treatment.

Clearly these are early days in an area where there is an immense amount of work to do in "reducing the incidence of leprosy within the area selected for control activities in a most efficient and economic way", and we look forward to further reports of this Project, which is sponsored by Leprosy Relief Work Emmaus-Switzerland, while wishing it every success.

A. C. McDOUGALL

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News and Notes

APPROPRIATE TECHNOLOGY FOR HEALTH — WHO NEWSLETTER NO. 1

WHO have recently initiated a novel new series of Newsletters, published by the Appropriate Technology for Health (ATH) programme. The object is "to describe developments in this field both within WHO and amongst the many individuals and organizations interested in this subject throughout the world".

The extensive development of primary health care services calls for simple inexpensive technologies, some of which have already been in operation in limited areas for a long time. These Newsletters are envisaged as a medium whereby on the one hand practical problems can be publicized and on the other hand where suggestions and possible solutions to them can be shared.

Already WHO have published 2 useful monographs in this field: "Excreta Disposal for Rural Areas and Small Communities" and "Water Supply for Rural Areas and Small Communities", both by E. G. Wagner and J. N. Lanoix. Special terms for developing countries are obtainable on application to WHO Distribution and Sales Service, 1211 Geneva 27, Switzerland.

The intention now is to invite as many contributions to the Newsletters as possible, and we have been asked to draw the attention of our readers to this. No. 1 includes details of a portable radiographic unit; a simple qualitative test to detect the presence or absence of Vitamin A in dry skimmed milk; the use of bamboo for pressure piping in rural water supplies; flow charts as an aid to diagnosis, with vomiting in the first month of life as one example in a series which should be of practical value to the field worker with only limited training.

The last page of the Newsletter gives short statements of problems for the solution of which ideas are wanted. These diverse problems include two of special relevance to leprosy workers, (a) a simple method of use under field conditions for detecting dapsone in urine, and (b) a simplified technique for distinguishing between viable and dead *M. leprae*. Contributions are invited. The address is: The Editor, ATH Newsletter, World Health Organization, 1211 Geneva 27, Switzerland.

T. F. DAVEY

PERSONAL

Dr S. G. Browne, CMG, OBE

The authorities of King's College Hospital Medical School have recently decided to inaugurate a Fellowship. Not more than three will be awarded in any one year. Among the first three is Dr S. G. Browne, the Secretary Treasurer of the International Leprosy Association.

We congratulate Dr Browne on this honour.

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Letter to the Editor

Cross-resistance Amongst Thiambutosine, Thiacetazone, Ethionamide and Prothionamide with *Mycobacterium leprae*

Thiambutosine and thiacetazone have been quite widely used in the treatment of leprosy, and the rapid emergence of thiambutosine- or thiacetazone-resistant *Mycobacterium leprae,* when the drugs are used in monotherapy, has been well documented (Davey, 1960; Rees, 1967*a*, *b*; Garrod and Ellard, 1968; Waters, Pearson and Rees, 1976). The use of the thioamides ethionamide and prothionamide for the treatment of leprosy has been much less extensive, but in the search for alternative drugs for use in combined drug therapy, interest in these compounds has been renewed (Colston, Ellard and Gammon, 1978). In view of the several reports of cross-resistance with *M. tuberculosis* between thiacetazone and ethionamide (Rist, Grumbach and Libermann, 1959; Bartmann, 1960; Grosset and Benhassine, 1970), it was important to establish whether such a phenomenon exists for *M. leprae.*

Five strains of *M. leprae* were tested for sensitivity to ethionamide, prothionamide, thiambutosine and thiacetazone. Strains L25 and L30 were obtained from patients in North Africa who had relapsed during treatment with ethionamide (Pattyn *et al.,* 1975). Strains 144/62, L21 and 22491, had been shown to be resistant to thiambutosine by mouse footpad testing. These strains of *M. leprae* were inoculated into the left hind footpads of mice and the 4 drugs administered at a dietary concentration of 0.1%. When counts of *M. leprae* in control mice had reached a maximum, drug-treated mice were examined histologically for bacillary growth. In the case of strains L25 and L30, bacillary growth was determined on the basis of counts of total numbers of AFB per footpad. The results are shown in Table 1.

The two strains which were clinically resistant to ethionamide (L25 and L30) were found to be resistant also to prothionamide, thiacetazone and thiambutosine. The 3 thiambutosine-resistant strains, however, were sensitive to prothionamide, and strain L21 was also sensitive to thiacetazone.

For *M. tuberculosis,* cross-resistance between the thioamides and thiacetazone is two-way, at least for strains developing resistance *in vivo* (Bartmann, 1960; Grosset and Benhassine, 1970). Cross-resistance between ethionamide and prothionamide is to be expected since the parts of the molecules responsible for antibacterial activity are identical. Thiambutosine and thiacetazone are also closely related compounds, and cross-resistance is shown by both *M. leprae* and *M. tuberculosis* (Rees, 1967*a*, *b*). Of the small number of strains available for this study, ethionamide-resistant strains (L25 and L30) were also resistant to thiacetazone and thiambutosine, whereas thiambutosine-resistant strains (144/62, L21 and 22491), although not tested

TABLE 1

Sensitivity of thiambutosine- and ethionamide-resistant strains of M. leprae *to thiambutosine, thiacetazone, ethionamide and prothionamide*

Strain of *M. leprae*	Drug treatment				
	Control	Thiambutosine (0.1%)	Thiacetazone (0.1%)	Ethionamide (0.1%)	Prothionamide (0.1%)
L25*	6/6§	6/6	6/6	6/6	6/6
L30*	6/6	6/6	6/6	6/6	6/6
144/62†	6/6	6/6	NT	NT	0/7
L21†	6/6	2/3	0/7	NT	0/9
22491†	9/9	4/8	NT	NT	0/5

*Strains from patients clinically resistant to ethionamide.

†Strains demonstrated to be resistant to thiambutosine by mouse footpad testing. Strains 144/62 and 2249 were isolated from old "lepromatous" cases and details of treatment were not available; patient L21 had been treated for 1 year with thiambutosine.

§Number of footpads showing growth of *M. leprae*/number of footpads harvested.

NT, Not tested.

against ethionamide, were sensitive to prothionamide. This suggests that development of resistance to these drugs is a penicillin-type (multiple-step) process, and that the first step is a small one. The ratio of peak serum level to MIC for thiambutosine is much lower than that for thiacetazone, ethionamide and prothionamide (Colston *et al.*, 1978; Colston, Ellard and Gammon, 1978), thus even a small decrease in sensitivity would result in clinical resistance to thiambutosine, but not necessarily to thiacetazone, ethionamide or prothionamide. On the other hand, the decrease in sensitivity required for clinical resistance to ethionamide would certainly result in resistance to thiacetazone and thiambutosine.

This demonstration of cross-resistance with *M. leprae* amongst thiambutosine, thiacetazone, ethionamide and prothionamide emphasizes that these drugs should be considered as alternatives to each other when devising antileprous drug regimens, and that where past treatment with one of the drugs is known to have occurred, sensitivity testing in the mouse footpad is advisable when considering one of the drugs for inclusion in a treatment regimen.

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M. J. COLSTON

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Book Reviews

A Window on Leprosy. Gandhi Memorial Leprosy Foundation. Silver Jubilee Commemorative Volume, edited by B. R. Chatterjee. January, 1978.

This is a strongly-bound and well-printed book of 395 pages, produced to celebrate the Silver Jubilee of the above Foundation. There are 58 contributors, all experts in the field of leprosy, and the chapter headings include—Epidemiology, Pathology, Microbiology, Immunology, Treatment, Control, together with sections outlining the work of WHO, ILEP, various voluntary agencies and "Trends of Leprosy in India". Many of the contributors are indeed from India yet the overall content and application of this valuable book is decidedly international. By their very nature, some subjects such as the drug treatment of untreated, and dapsone-resistant lepromatous leprosy, and the management of adverse reactions will probably not survive well in the present climate of discussion and change, but others, particularly histopathology and pathology, should stand many years as standard sources of reference. This book should be on the working shelves of all those seriously interested in leprosy. Details of its cost and postal charges may be obtained from—Dr B. R. Chatterjee, Leprosy Field Research Unit, The Leprosy Mission, Silkra Hills, Jhalda, West Bengal, 723202, India.

A. C. McDOUGALL

Essentials of Leprosy, by J. M. H. Pearson and H. W. Wheate, 2nd edit. 1977. All Africa Leprosy and Rehabilitation Training Centre, Addis Ababa, Ethiopia.

It is a courageous undertaking to attempt a description of leprosy in 50 printed pages, including epidemiology, bacteriology, clinical features, classification, immunology, reactional phases, differential diagnosis, control, and all aspects of management, and the authors are to be congratulated on the successful outcome of their venture. I stress the authors' courage because of their coverage of so many aspects of such a complex subject, and because of the criticisms that fellow leprologists are sure to make, for it may not be generally appreciated that no statement can be made on any aspect of leprosy without someone challenging it. For my part I find in this text much more to praise than to criticize, but I have reservations about accepting two recommendations on the difficult subject of managing leprosy reactions. Firstly, to give maximal dosage of DDS in borderline leprosy from the very beginning of treatment and to continue throughout reversal (upgrading) reaction, and I would venture to say that this line of treatment may account for the warning on p. 33 that reversal reaction may require steroid therapy for 6–8 months in BT and for a year or more in BL; in my experience reversal reactions in borderline leprosy are not only unusual but are fairly quickly controlled with the help of prednisone in patients given a maximum of 5 mg DDS daily during the first 6 months of anti-leprosy treatment (the period in which reversal reaction is liable to occur), small dosage of DDS being continued throughout the reaction. Secondly, in the management of severe episodes of ENL, the authors break new ground in opposing the generally accepted view that dosage of steroid should be tapered off.

This booklet is not for the beginner—for whom such intensive and condensed instruction will have little meaning—but will prove of value to experienced leprosy workers, whether medical auxiliaries or qualified doctors, as a "refresher" which can be read slowly, from beginning to end, in the space of one hour.

W. H. JOPLING

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Abstracts

68. McDOUGALL, A. C. & ROSE, P. **Integrated leprosy control in Guyana.**

This paper provides much interesting and relevant demographic, economic and medical data concerning leprosy patient care and attempts at leprosy control in Guyana from 1858 to 1975. These facts alone make it a valuable paper.

However, it is tantalising in that it omits data on child rates and deformity rates in new cases, which are available, and which would enable readers to better evaluate the efficacy of the present programme, the validity of the author's estimates of prevalence and the usefulness of their proposals for future action.

Guyana is not unique in having "a nagging yearly incidence of new cases", some known and some suspected foci of "high incidence" and a health education problem made worse by the continued presence of a now outmoded leprosarium. The additional data would have made the article much more useful to others facing the same problems.

The programme as described is partially integrated. Leprosy patients are treated at "skin clinics" run in general health facilities but the staff who run these clinics are specialist staff. General health staff play little or no part in the leprosy control effort. This may well be the right course for Guyana to follow at present but it is not integration. The paper has no proposals to make concerning progress, if it would be progress, toward full integration.

W. Felton Ross

The Abstracts which follow are reprinted from Tropical Diseases Bulletin *through the courtesy of the Director, Bureau of Hygiene and Tropical Diseases. They are classified according to subject.*

1. MICROBIOLOGY

69. NARAYANAN, E., SREEVATSA, KIRCHHEIMER, W. F. & BEDI, B. M. S. **Transfer of leprosy bacilli from patients to mouse footpads by *Aedes aegypti*.** *Lepr. India,* 1977, v. 49, No. 2, 181–186.

"*Aedes aegypti* mosquitoes which were first allowed to feed on untreated lepromatous leprosy patients, and then to refeed on mouse footpads were found to transfer *Mycobacterium leprae* to the footpads as seen by the subsequent multiplication of the bacilli in the footpads. Results presently available are insufficient to come to any conclusion about the actual role of mosquitoes in the transmission of leprosy in the field."

70. ISHAQUE, M., KATO, L. & SKINSNES, O. K. **Cytochrome-linked respiration in host grown *M. leprae* isolated from an armadillo *(Dasypus novemcinctus,* L.).** *Int. J. Lepr.,* 1977, v. †5, No. 2, 114–119.

"The bacilli were isolated from an armadillo (*Dasypus novemcinctus,* L.) and cytochrome systems as well as oxidation of succinate and NADH by *M. leprae* were studied. Cell-free extracts of *M. leprae* contained cytochromes of the $a + a_3$, *b, c* and *o* type. Whole cell suspensions catalyzed the oxidation of succinate. The process was unaffected by rotenone but

was markedly inhibited by thenoyltrifluroacetone, antimycin A and cyanide. Cell-free preparations of *M. leprae* also oxidized NADH with oxygen as the terminal electron acceptor. Although NADH oxidation was completely inhibited by rotenone, the process was inhibited to only 50% by 5 millimols cyanide. The results indicated that complete respiratory system is present in *M. leprae* isolated from leprous tissues of an armadillo. The effect of inhibitors on succinate and NADH oxidations showed that the respiration in host-grown *M. leprae* is mediated through the cytochrome system with oxygen as the final electron acceptor."

71. ISHAQUE, M. & KATO, L. **Oxidation of substrates by host grown *Mycobacterium leprae* and *Mycobacterium lepraemurium* and by *in vitro* grown mycobacteria cultured from human, armadillo and murine lepromas.** *Int. J. Lepr.,* 1977, v. 45, No. 2, 120–131.

"Oxidative activities of armadillo-grown *M. leprae* and rat-grown *M. lepraemurium* as well as of the *in vitro* grown mycobacteria cultured from human, armadillo and murine lepromas were investigated and compared with authentic strains of *M. scrofulaceum* and *M. bovis,* BCG. Yeast extract was oxidized at a slow rate by *in vivo* grown *M. leprae* and *M. lepraemurium,* but was actively utilized by all the cultures cultivated on artificial medium. Although no oxidation of glycerol by host-grown mycobacteria occurred, after a period of 60 minutes it was utilized at a slow rate by *in vitro* grown *Mlm* (M. lm 56) and *M. leprae* (M. Dakar). However, glycerol was actively oxidized by *M. leprae* (M. A6, armadillo derived), *M. scrofulaceum* and BCG. None of the intermediates of the glycolytic cycle as well as of the tricarboxylic acid cycle were oxidized by purified cell suspensions of *M. lepraemurium* but succinate was readily oxidized by *M. leprae* cell suspensions. Resting cell suspensions of all the *in vitro* grown cultures have been shown to increase their oxygen consumption in the presence of several members of the glycolytic and Krebs' cycles. Sulfur compounds, e.g., cysteine, dithioerythritol and penicillinamine were readily oxidized by all the *in vivo* and *in vitro* grown mycobacteria used in this study. While oleic acid was inactive to human and murine bacillary suspensions as well as to BCG, it was readily oxidized by M. lm 56, M. A6, M. Dakar, and *M. scrofulaceum.* All the *in vitro* grown cultures caused considerable increase in oxygen consumption over the endogenous value in the presence of Tween 80 and Tween 20 but the same substrates were slowly oxidized by murine leprosy bacilli. Comparative rates of oxidation of several substrates by host-grown and *in vitro* grown mycobacteria are discussed."

72. KATO, L. **The Janus-face of *Mycobacterium leprae:* characteristics of *in vitro* grown *M. leprae* are not predictable.** *Int. J. Lepr.,* 1977, v. 45, No. 2, 175–182.

The author of this Editorial reviews and comments on six of the many attempts that have been made to culture the leprosy bacillus, from Clegg in 1909 to Skinsnes *et al.* in 1975 and Kato and Ishaque in 1976 and 1977, with emphasis on the scotochromogenic cultures.

Before publication, the author sent copies to a number of people asking for their comments, and the replies which were received in time were published in the correspondence section of this issue of the *International Journal of Leprosy* (pp. 183–185). These from P. Beaulnes and M. Bourque, J. H. Hanks, K. Kanai, and M. Tsukamura, should be read together with the Editorial in the original. [See also abstr. 981 below.]

F.I.C. Apted

73. KATO, L. & ISHAQUE, M. A. **A scotochromogenic slow-growing mycobacterium probably the etiologic agent of rat leprosy.** *Int. J. Lepr.,* 1977, v. 45, No. 2, 139–149.

"Culture media were prepared in which yeast extract, succinate and L-cysteine, respectively, served as a source of energy. These substrates were oxidized by *M. lepraemurium* as measured with manometric technics. Glycerol was the only source of carbon in the media. Bacilli were isolated from subcutaneous lepromas of infected rats. After five weeks of latency, a heavy growth developed during a logarithmic growth phase lasting about ten days in media containing any of the substrates for energy generation with glycerol added. In phosphate buffer solution, at

pH 5.5, optimal growth occurred when incubated at 34°C. Bovine, horse, goat, and sheep serum respectively enhanced *in vitro* multiplication. Hyaluronic acid, heparin and serum albumin were toxic and inhibited growth in the primary *M. lepraemurium* cultures. When host grown murine leprosy bacilli were inoculated into Lowenstein or Dubos media no growth occurred.

"The cultures were scotochromogenic and produced a yellow pigment. Young cultures were nonacid-fast. Full acid-fastness developed during the logarithmic growth phase.

"The strains were easily subcultured not only in the homologue media but became rapidly adapted to new substrates. They then became adapted to and grew in the presence of hyaluronic acid, heparin and serum albumin as well as on Lowenstein and Dubos media. With subsequent subculturing, the latency period became as short as two days followed by three to four days of logarithmic growth. The primary cultures and their subcultures on the homologue media retained specific infectivity for rats but lost their pathogenicity and virulence considerably."

74. YAMAGAMI, A. & CHANG, Y. T. **Growth of *Mycobacterium lepraemurium* in cultures of macrophages obtained from various sources.** *Infection & Immunity,* 1977, v. 17, No. 3, 531–534.

"Studies were made on the growth of *Mycobacterium lepraemurium* in cultures of macrophages obtained from various sources, such as bone marrow, spleen, and blood of mice. Macrophages were maintained in good condition for more than 12 weeks. Marked intracellular multiplication of *M. lepraemurium* was observed in cultures from all three sources. Whereas *M. lepraemurium* freshly prepared from the animals showed good growth in the cultures, those that were kept at 4°C for 10 or 14 days showed no growth."

2. IMMUNOLOGY, PATHOLOGY

75. SAHA, K. & DUTTA, R. N. **Subtypes of Australia antigen in persistent Australia antigenemia and sporadic hepatitis among patients with lepromatous leprosy and their segregated children with no apparent clinical illness.** *Int. J. Lepr.,* 1977, v. 45, No. 1, 38–48.

Serum samples from 135 patients with biopsy-proven lepromatous leprosy in India and from 156 apparently healthy children of patients with leprosy were examined for hepatitis B surface antigen and surface antibody by counter-immunoelectrophoresis [an insensitive technique]. The antigen was detected in the serum of 10.3% of the patients with lepromatous leprosy and in 9.6% of their children, whereas the antigen was found in 2.28% of a control group of soldiers and in 2.9% of 34 undernourished subjects who also served as controls. [The antibody findings are quite meaningless in view of the insensitive method used.]

The predominant subtype of hepatitis B surface antigen was *ay* both among the patients with leprosy and their children.

A. J. Zuckerman

76. FRAGUELA RANGEL, J. V., FERNÁNDEZ BAQUERO, G., KRAFTCHENCO BEOTO, T. & HERNANDEZ ANGULO, M. Alopecia de cuero cabelludo en lepra. **[Scalp alopecia in leprosy.]** *Revta Cub. Med. Trop.,* 1977, v. 29, No. 1, 23–31. English summary (3 lines).

Of 270 patients in the El Rincón leprosy hospital in Cuba, 10, nine of whom were men, had alopecia. All the 10 had lepromatous leprosy. The clinical and histopathological features are described and illustrated in photographs.

F. I. C. Apted

77. TAKATA, H., SADA, M., OZAWA, S. & SEKIGUCHI, S. **HLA and mycobacterial infection: increased frequency of B8 in Japanese leprosy.** *Tissue Antigens,* 1978, v. 11, No. 1, 61–64.

"A total of 60 leprosy patients, 28 of lepromatous and 32 of tuberculoid form, and 70 active tuberculosis patients was compared with a control of 184 for 34 HLA specificities. The most interesting finding was an increased frequency (10.0%) for HLA-B8 (corrected $P \times 0.062$, relative risk $\times$ 20.3) in the leprosy patients as compared with the control group, despite the fact that the frequency of HLA-B8 was extremely low in Japanese. Furthermore, all leprosy patients with B8 had leprous member(s) in their family."

78. LIEBERMAN, J. & REA, T. H. **Serum angiotensin-converting enzyme in leprosy and coccidioidomycosis.** *Ann. Intern. Med.,* 1977, v. 87, No. 4, 422–425.

"Serum angiotensin-converting enzyme levels were found to be elevated in 71.4% of 42 leprosy patients, both treated and untreated, but in only one of 13 patients with disseminated coccidioidomycosis. The elevations with leprosy were present in association with each of the three major categories: lepromatous, borderline, or tuberculoid. Sulfone therapy had no immediate effect on the elevated serum levels, although long-term sulfone therapy appeared to result in a lowering of the level. Corticosteroid therapy had a more immediate and dramatic effect on reducing the elevated angiotensin-converting enzyme level in leprosy. This assay cannot distinguish between sarcoidosis and leprosy or between the various categories of leprosy, but it can help differentiate sarcoidosis from fungal or tuberculous disease. Elevated levels of serum angiotensin-converting enzyme have now been associated with three disease states: sarcoidosis, Gaucher's disease, and leprosy."

79. CRUICKSHANK, J. G. & ELLIS, B. P. B. **Leprosy and the serodiagnostic test for tuberculosis.** *J. Clin. Path.,* 1977, v. 30, No. 8, 728–730.

Agglutination tests were made using antigens prepared from *Mycobacterium tuberculosis* H37Rv in a modified Widal technique on sera from 227 subjects with leprosy.

86% of subjects with inactive disease had titres equal to or less than 1 in 250; 58% of those with healing disease had such titres and 20% of those with active disease; and of those in reaction, all had titres equal to or greater than 1 in 500.

One subject with lepromatous leprosy was followed up weekly for 10 weeks. At weeks 1 and 2 the titre was less than 1 in 125. During weeks 4, 5 and 6 the subject was "in reaction" and by week 7 the titre had risen to 1 in 1250. By week 9 it had fallen to less than 1 in 125 again.

It would appear that agglutinating antibody reflects to some extent the activity of leprosy but not with the degree of accuracy of more conventional tests.

P. A. Jenkins

80. SHESKIN, J. & ZEIMER, R. ***In vivo* study of trace elements in leprous skin.** *Int. J. Der.,* 1977, v. 16, No. 9, 745–747.

"The skin of leprous patients at various stages of the disease was investigated by diagnostic x-ray spectrometry. In the active stage raised iron and slightly raised zinc levels were found. The usefulness of the method in skin investigation is foreseen."

3. CLINICAL

81. HASAN, S. **A survey of leprosy deformities among the patients of Hyderabad City.** *Lepr. India,* 1977, v. 49, No. 3, 393–399.

"Neuropathic deformity is a major problem among the patients of Hyderabad city. Nearly 44.3% of the patients have one or the other kind of deformity of the hand, foot or face. 29.1% of

the upper limbs, 30.7% of the lower limbs and 5.2% of the faces were affected. The patients with lepromatous leprosy showed greater tendency to deformity (66.4%). Patients with simple anaesthesia in hand and feet formed the majority among the deformity cases, a total of 41.6%. Education of the patients in the hand and foot care is an essential feature of the clinic physiotherapy technician."

[This study was based on the first 1000 patients examined by the author between July 1969 and April 1971.]

82. YUMNAM, I. S.; KAUR, S.; KUMAR, B.; RASTOGI, G. K.; BANERJEE, A. K.; SEHGAL, S. **Evaluation of thyroid functions in leprosy. I. Thyroid function tests** [YUMNAM, KAUR, KUMAR & RASTOGI]. *Lepr. India,* 1977, v. 49, No. 4, 485–491. **II. Histopathology of the thyroid** [KAUR, YUMNAM, KUMAR, BANERJEE & RASTOGI]. *Ibid.,* 492–494. **III. Circulating auto-antibodies against thyroid and nuclear components** [YUMNAM, SEHGAL, KAUR, KUMAR & RASTOGI]. *Ibid.,* 495–499.

I. "Twenty-six patients of different types of leprosy were studied for radioactive iodine uptake (I^{131}) and serum levels of triiodothyronine (T_3), thyroxine (T_4) and thyroid stimulating hormone (TSH). None of the patients had clinical evidence of thyroid involvement. No significant difference was found between the values obtained in patients and normals and in different varieties of leprosy."

II. "Open thyroid biopsies from seven patients of bacilliferous leprosy were studied for leprous granuloma or amyloid deposition. None of the patients had clinical evidence of thyroid involvement. Histopathology did not reveal any specific abnormality."

III. "Sera from twenty-six patients of various types of leprosy were tested for the detection of circulating auto-antibodies and nuclear components against thyroid using various methods. Four patients of lepromatous leprosy had higher levels of thyroid auto-antibodies by latex agglutination. Three patients showed the presence of anti-nuclear antibodies, two belonged to the TT and one to the LL group."

83. SAHA, K., MITTAL, M. M. & MAHESWARI, H. B. **An attempt at passive transfer of immunity to leprosy patients by transfusion of allogeneic lymphocytes, inactivated with mitomycin C.** *Vox Sang.,* 1978, v. 34, No. 2, 104–110.

"An attempt was made to repair cell-mediated immunity in 7 patients suffering from lepromatous leprosy and severe erythema nodosum leprosum by intravenous infusion of 400 million allogeneic blood lymphocytes on 3 occasions. The lymphocytes were obtained from lepromin and tuberculin-positive subjects and were inactivated *in vitro* by treatment with mitomycin C. Immunotherapy with inactivated lymphocytes only modified the severity of erythema nodosum leprosum, without altering other aspects of the disease."

4. THERAPY

84. ANTONY, P. **Polambakkam splint for treatment of plantar ulcer in leprosy.** *Lepr. India,* 1977, v. 49, No. 4, 521–525.

"An open type of short leg splint is described and illustrated for the treatment of plantar ulcer in leprosy. Its fabrication, method of application, advantages and disadvantages are discussed as compared to the other methods of immobilization. In our short experience we have found that with the use of this splint, ulcers heal in a period of about 6 weeks and in many cases even earlier than this period."

5. EPIDEMIOLOGY AND CONTROL

85. GURD, C. H. **Leprosy in the Northern Territory.** [Correspondence.] *Med. J. Aust.,* 1977, Nov. 5, 652.

In an Editorial in *Med. J. Aust.,* 1977, v. 2, 345, it was stated that a highly endemic situation with regard to leprosy persists in the Northern Territory, and that no accurate figures are available. The Director of Health, Northern Territory Division, comments on the inaccuracy of these statements and provides information to show that control has largely been effected. Patients with leprosy in the Northern Territory are kept on the register indefinitely; this aids follow-up but does magnify the problem because in most of them the disease is inactive. Measures which have brought leprosy under control include the early detection of cases by rural health centre staff, effective and acceptable treatment, and surgical and self-help care for deformities. All cases are held on a register in Darwin. Figures for 1975 showed a total number of 695 Aboriginals on the register, 10 Aboriginals in whom the disease was still active, and 6 new cases in Aboriginals. A table gives the number of new notifications for each year from 1966 to 1976. In the first 3 years of this period notifications numbered 29, 46, and 39. Between 1969 and 1974, the annual figures ranged from 12 to 21 cases. In each of the years 1975 and 1976 only 6 cases were notified.

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6. MISCELLANEOUS

86. LEPR. INDIA, 1976, v. 48, No. 4, Suppl., 460–895. **Baroda Leprosy Conference, April 10–14, 1976.**

The Biennial Leprosy Conferences conducted by the Indian Association of Leprologists and the Hind Kusht Nivaran Sangh are always an important stimulus to research and the sharing of experience in a country with over 3 million sufferers from leprosy. The Baroda Conference in 1976 was no exception. Among the wide range of subjects covered by original articles and discussion, the following merited special note:

Epidemiology. P. V. Kapoor (p. 490) reported that epidemiological surveys in 3 areas of Maharashtra, where leprosy control is well established, have shown that there has been a definite fall in leprosy incidence in children in all 3 areas, with the lepromatous rate and deformity rate virtually down to zero. Among adults progress after 15 years has become slower. S. K. Noordeen and P. N. Neelan (p. 492) found chemoprophylaxis with dapsone effective in preventing leprosy among household contacts below the age of 15 years exposed to non-lepromatous leprosy, though the efficacy rate was only 35%. B. R. Chatterjee (p. 493), who has followed up over several years clinically normal persons harbouring acid-fast bacilli (AFB) in ear lobes, failed to show incidence of leprosy among them higher than in control subjects. R. Ganapati, S. S. Naik and S. S. Pandya (p. 494) reported important studies in school-children in Bombay [see also *Trop. Dis. Bull.,* 1977, v. 74, abstr. 355].

Experimental studies and pathology. K. V. Desikan (p. 498) reported experiments in which multiplication occurred in mouse foot pads using an inoculum of AFB in which no normal staining rods were found, based on a count of 100 bacilli. E. J. Ambrose, N. H. Antia and S. R. Khanolkar (p. 499) with a view to developing a rapid *in vitro* assay for the viability of *Myco. leprae* combined radioactively labelled metabolites with high resolution autoradiography and found a significant correlation between MI and labelling index. D. K. Dastur (p. 500) reported on the role of the perineurium in leprous neuritis. V. Sengupta, M. J. Worms and R. J. W. Rees (p. 504) presented evidence that *Myco. lepraemurium* can be transmitted mechanically by mosquitoes *(Aedes aegypti).*

One full session was devoted to *Experiences with clofazimine therapy,* and well exposed the established facts with this drug. L. M. Hogerzeil (p. 524) reported that long term steroid therapy had no adverse effect on the bacteriological decline in lepromatous patients provided they were simultaneously treated with clofazimine. In the session on *Immunology,* V. Mehra, S. N. S. Hanjan, Z. Kidwal, L. K. Bhutani and G. P. Talwar (p. 518) presented evidence of an alteration

in the surface characteristics of lymphocytes derived from the peripheral blood of untreated lepromatous leprosy subjects. K. Saha (p. 521) reported dramatic improvement following the transplantation of human foetal thymus tissue in severe reactional cases of lepromatous leprosy. An important session on *Deformities and rehabilitation* concentrated on the long term results of surgical procedures in leprosy. The technical sessions of the conference were succeeded by the very important Leprosy Workers Conference, concerned with many practical problems in the vast undertaking of leprosy control in India, and on this occasion, especially with assessing progress and evaluating control procedures.

T. F. Davey

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