Editorial

A VACCINE FOR LEPROSY

An effective vaccine for leprosy is undeniably desirable as a prophylactic reagent to prevent the clinical manifestations of infection and perhaps as a therapeutic reagent to upgrade patients at the lepromatous end of the disease spectrum. Besides being effective, such a vaccine would have to be safe, cheap, easy to administer and a real improvement over BCG.

Taken at its simplest, an effective vaccine for leprosy will be a reagent that induces a circulating clone of thymic lymphocytes capable of instructing macrophages in the art of destroying leprosy bacilli. In principle a vaccine will consist of the antigens (x) of *Mycobacterium leprae* necessary for the induction of protective immunity together with an adjuvant which will particularly enhance the cell mediated rather than humoral immune mechanism. The obvious adjuvant is BCG and alternatives should only be considered if for some reason BCG proves unsuitable. Nevertheless, during the development stages of the vaccine in which vaccinated animals are experimentally challenged a non mycobacterial adjuvant such as *Corynebacterium parvum* could be used to advantage. Leaving aside the practical aspects of experimentation let us assume the vaccine to be BCG + x which could replace BCG alone in the vaccination programme against tuberculosis in leprosy endemic countries. If this is to be the case then not only do we have to find and prove the effectiveness of x against leprosy, but we must also show that it is stable in a freeze dried preparation with BCG and does not impair protection from tuberculosis.

Mycobacteria possess at least 4 groups of antigens (Fig. 1) those which they share amongst themselves and with related genera such as *Nocardia* and *Gordona* (group i antigens); those shared by slow growing mycobacterial species (group ii antigens); those shared by fast growing mycobacterial species (group iii antigens) and those limited to individual species (group iv antigens) (Stanford, 1973*a*). So far as we know there is little or no cross protection between *Nocardia* and *Mycobacterium* or between fast growing and slow growing mycobacteria. There appears to be considerable cross protection between slow growing species which also show some cross reactivity to Tuberculin PPD, but so far there is no evidence of cross protection between fast growing species. The best protection, however, is afforded by members of the same species. Thus BCG immunization affords somewhat better protection from tuberculosis than does the so-called "non-specific" sensitization to Tuberculin PPD attributed to contact with *M. avium* and *M. gordonae,* and immunization of mice with *M. avium intracellulare* affords better protection from *M. lepraemurium* than does BCG vaccination (Brown, personal communication). One may conclude from this that antigens inducing protective immunity amongst slow growing mycobacterial species may belong to

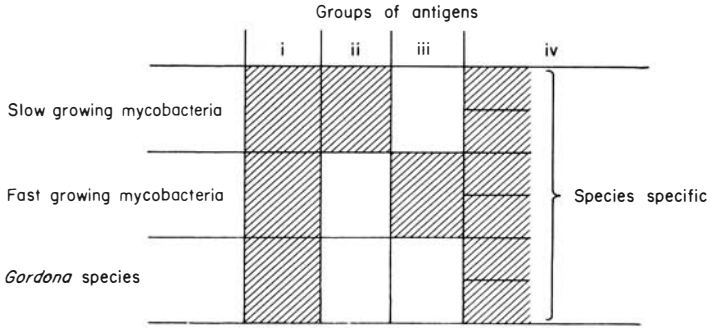

Fig. 1. The antigens of *Mycobacterium* and *Gordona* species demonstrable by immunodiffusion arranged in groups. The antigens of group i are shared by all members of both genera and the group iv antigens are limited to individual species.

the antigenic groups ii and iv, although this does not necessarily mean that the protective antigens are themselves precipitated in immunodiffusion analysis.

On the basis of these observations it would be best to use the antigens of *M. leprae* itself in any proposed vaccine since the use of antigens obtained from related culturable species might be expected to afford less good protection. Until such time as the leprosy bacillus can be readily cultured *in vitro* it will be necessary for the organism to be extracted from tissues. It is not only necessary to free the organism of host tissue antigens, but it is also necessary to leave the leprosy antigens chemically intact and not complexed with host antibody. Even if a suitable extraction technique is used there is still the problem of the majority of leprosy bacilli in tissues, even armadillo tissues, having been dead for some considerable time. If any parallel can be drawn from experience with BCG we can expect little immune protection to be induced by the antigens of long dead organisms. Thus a lysate of bacilli extracted from tissue will contain a comparatively small proportion of the desired antigens, possibly necessitating the use of some fractionation and concentration procedure before a useful product is obtained.

Induction of cellular or humoral immunity to the wrong antigens of *M. leprae* may itself be hazardous since in some forms of the disease these very phenomena are a part of pathogenesis. Their superimposition on a person already subclinically infected with the leprosy bacillus might precipitate a worse form of the disease than would otherwise have developed. Because of the many difficulties associated with the production of a vaccine from tissue derived leprosy bacilli serious consideration should be given to alternative approaches.

It has already been pointed out that a vaccine from a related culturable species might be expected to be less effective than one prepared from *M. leprae* itself. Nevertheless, such a vaccine might provide a very useful amount of protection. What then do we know of the relationships existing between *M. leprae* and other mycobacterial species?

Immunodiffusion analyses have not so far demonstrated the presence of group ii or iii antigens in the leprosy bacillus so that it cannot clearly be related to either the fast or slow growing subgenera of *Mycobacterium* (Stanford *et al.*, 1975). This

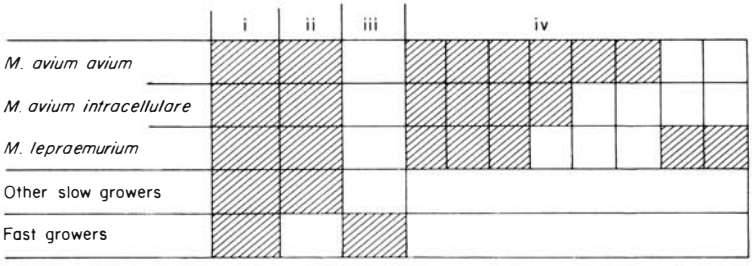

Fig. 2. The group iv (species specific) antigens of *M. avium* variants shown in relation to the antigens they share with other species. The group iv antigens are shared vertically where this is indicated by hatching.

lack of groups ii and iii antigens is also a feature of *M. vaccae* and of members of the genus *Gordona.* Studies on the mycolic acids of these organisms have shown *M. leprae* and *M. vaccae* to possess those of the mycobacterial type whereas *Gordona* species possess mycolic acids with smaller numbers of carbon atoms, similar to the nocardomycolic acids (Etemadi and Convit, 1974; Alshamaony *et al.,* 1976). Studies of delayed hypersensitivity in leprosy patients and their family contacts using a range of very specific skin test reagents produced from 2 *Gordona* species and 20 mycobacterial species have shown the leprosy bacillus to be more closely related to *M. vaccae* and *M. nonchromogenicum* than with the other species tested (Paul *et al.,* 1975). Similar conclusions have been reached from studies of delayed hypersensitivity in experimentally immunized animals.

I have it on the authority of Dr S. Browne that there is no evidence for the existance of leprosy prior to 600 B.C. If this is so and if we allow a margin of 5 millenia then the leprosy bacillus has only been with us some 8000 years—a very short time indeed compared with the antiquity of man himself. Presumably *M. leprae* arose as a naturally selected mutant of another mycobacterial species. It is highly likely that this progenitor is still in existence and there is no reason to think that it need be a pathogen. In fact there is good reason to believe that it was not. With the exception of *M. tuberculosis* and possibly *M. lepraemurium,* which is passed directly from the infected to the uninfected, the other mycobacterial pathogens of mammals are all opportunists coming from the environment. In many cases strains causing infections are probably the same as environmental strains, but in one species, *M. fortuitum,* the serotype usually involved in human infections differs from those generally present in soil and it has been shown that the soil serotypes throw off the potentially pathogenic type at a low rate, probably by a process of deletional mutation (Grange and Stanford, 1974). With the exceptions of *M. fortuitum* and *M. chelonei* which are fast growing species giving rise to infections unaccompanied by the development of positivity to Tuberculin PPD, all the culturable pathogens of mammals are slow growing species infection with which does produce positivity to Tuberculin PPD. *M. lepraemurium* belongs to the slow growing mycobacteria possessing antigens of group ii. This species is closely related to *M. avium* from which it almost certainly arose, possibly by a process of deletional mutation (see Fig. 2) (Stanford, 1973*b*).

Thus the leprosy bacillus does not appear to be closely related to the other pathogens. However, it may well bear a relationship to a culturable environmental

species similar to that of *M. lepraemurium* to *M. avium* or the pathogenic to the nonpathogenic serotypes of *M. fortuitum.*

It is particularly unfortunate that the two organisms found to be related to the leprosy bacillus, *M. nonchromogenicum* and *M. vaccae* are themselves little understood. Both are common in certain natural environments and both were first described relatively recently. There has been only one reported case of a human infection with *M. nonchromogenicum* and none are known with *M. vaccae.* Unfortunately both species are incompletely characterized and so variable that in fact each may really comprise several species.

Research is currently going on to try to sort out the various strains of these species and to determine which of them is most closely related to *M. leprae.* This should shortly be completed and then animal protection experiments can begin. Both organisms are so easily cultivated that large quantities can be readily prepared. Their lack of pathogenicity makes them easy to handle and even the possibility of a live vaccine might be considered.

The numbers of persons producing positive reactions to skin tests with the antigens of *M. nonchromogenicum* or *M. vaccae,* in regions where these organisms are common in the environment is low in comparison with those reacting to other environmental mycobacteria suggesting that, like the leprosy bacillus itself, they are not readily allergenic (Stanford *et al.,* 1976). Perhaps they lack some of the adjuvanticity associated with other mycobacteria, however, this could readily be provided by BCG. A small study of the environmental mycobacteria of Uganda found *M. nonchromogenicum* to be widely distributed, but strains of *M. vaccae* were only encountered around Lake Kyoga in regions close to those where the trial of BCG against leprosy was carried out (Brown, *et al.,* 1969). Perhaps the good results obtained in the trial were in part due to enhancement of reactivity to these environmental species by BCG.

In conclusion it is likely that a vaccine for leprosy will consist of BCG. together with antigens able to induce specific protective immunity from the disease. Although these antigens would theoretically be best obtained from *M. leprae* the practical difficulties in their extraction and purification from infected tissues—even of armadillos—may be difficult to overcome. In view of this an alternative source should be sought amongst the leprosy bacillus' closest culturable relatives. Some success in identifying these organisms has already been achieved and experimental vaccines employing them will shortly be tested in animals. This in itself will be problematical since the intact rather than the immunologically suppressed mouse will have to be used and there is very little latitude for protection in such animals. In view of this the vaccine may well have to be assessed in the only animal known to be naturally susceptible to leprosy—man.

J. L. Stanford

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

MARIAN RIDLEY, W. H. JOPLING AND D. S. RIDLEY

Hospital for Tropical Diseases, London NW1 0PE

In over 30 long-treated patients with lepromatous leprosy the fingers were found to be the skin site with the highest bacterial load and with the highest number of solid-staining bacilli. It was also the site at which bacilli, solid or otherwise, were most frequently detected. In these patients the nose, as expected, was not a very productive site for bacilli. No clinical lesions were present on the fingers examined. In one amputation specimen of a finger the only site at which bacilli were seen was in a fibrosed structure thought to be a Pacinian corpuscle.

Introduction

Relapse in the lepromatous case is only too well known, and in the past has usually been due to the fact that the patient has stopped treatment against medical advice, but in recent years an additional factor responsible for relapse has been the development of bacterial resistance to dapsone. Both these possibilities (premature cessation of treatment and drug resistance) are likely to occur at a stage in the disease when the patient's skin lesions have disappeared, and it is therefore important that the physician should insist on taking skin smears each time the patient reports for medical check-up so that early intimation of relapse can be obtained, long before any clinical evidence of relapse can be observed. This is shown by the appearance of one or more solid-staining bacilli at one or more sites where previously all skin smears were negative or had shown the presence of granular bacilli only. Our policy is to take skin smears (by the scraped incision method) regularly every 6 months on lepromatous patients in whom the disease appears arrested, the sites for smears being the 2 ear lobes and 4 or 6 sites on face, trunk or limbs at the precise locations where lesions had originally been observed and from which smears had been taken in the past. Ear lobes have always been included because we had formed the impression that these two sites have tended to harbour granular bacilli after other sites (and nasal scrapings) have become negative, and, in addition, have been the most likely sites at which to find early evidence of relapse.

Recently, following a conversation between one of us (M.J.R.) and Dr J. M. H. Pearson, who was interested in the subject of oedema in fingers in leprosy even when there is no clinical lesion there, it was decided to carry out a pilot trial in which 2 skin smears from fingers would be taken in addition to the routine 6 or 8 smears.

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Material and Methods

An unselected series of 30 lepromatous (LL) patients attending this hospital was used for the trial. All patients had received treatment for periods of 6 months to 25 years. Twenty-six of the 30 had received treatment for at least 5 years. Slit skin smears were taken from the following sites in all cases: 2 earlobes, lesions (healing or healed) on trunk and limbs (up to 4 if there were 4 lesions) and 2 fingers. The dorsum of the first phalanx of the middle finger of both hands was the site, provided there was no lesion apparent. If a lesion was present a neighbouring, apparently normal, finger was chosen instead. Nasal scrapings were taken in 10 of these patients, and smears from toes in 8.

Smears were fixed and stained with carbol fuchsin at 42°C for 15 min. The Bacteriological Index (BI) and the Solid, Fragmented and Granular (SFG) Index were determined as described by Ridley (1964, 1971). The SFG is a ratio of solid to fragmented to granular bacilli, 10 representing all solid forms and 0 all granular. Below 3 there are never any solids. The presence of any solid forms was invariably noted.

Results

The results are shown case by case in Table 1, and summarized in Table 2. In patients with only a short period of treatment bacilli in the fingers were found to be comparable with those at other sites in respect of numbers and morphology, even though there were no clinically apparent lesions on the fingers. In long standing cases the fingers were found to be the most productive site for bacilli in respect of total numbers of bacilli and also of solid bacilli.

These observations were confirmed by further cases that were examined following the termination of the unselected series. The fingers were the sole site for bacilli in 3 out of 12 cases, and the sole site for solid forms in 2 out of 12. The fingers in these cases were again more productive than any other site, the advantage, however, being confined to long treated patients.

As regards the patients in the series of 30 who received nasal scrapes and smears from the toes, the fingers were more productive of bacilli than the nose in 9 out of 10 cases, and more productive than the toes in 8 out of 8 cases.

AMPUTATED FINGER

A finger amputation specimen, part of the terminal phalanx of the index finger from a long treated lepromatous (LL) patient, became available as a result of an accident. This patient gave bacteriological evidence of early relapse at some sites, but there were as yet no clinical signs of relapse. The finger was gangrenous with a fairly heavy neutrophil infiltrate which involved amongst other structures the Pacinian corpuscles, which were otherwise histologically normal. The nerves were mildly fibrosed as frequently happens in this type of leprosy and were free of infiltrate. A search for acid-fast bacilli was made in serial sections. The only site in which they were found was a fibrosed structure of approx. 1½ × ½ mm, which appeared to be a fibrosed Pacinian corpuscle, which was free of cellular infiltrate. There were many (5+) bacilli in the peripheral zone of this structure, which was about 60 μm deep, but none in the central area. These bacilli were predominantly short solid forms. No AFB were found in the other Pacinian corpuscles or in nerves.

TABLE 1

Distribution of leprosy bacilli at various skin sites

Patient	Ears		Lesions on trunk or limbs		Fingers		Toes		Nose	
	BI[a]	SFG[a]	BI[a]	SFG[a]	BI[a]	SFG[a]	BI[a]	SFG[a]	BI	SFG
1	0	–	0	–	0	–				
2	0	–	0	–	0	–				
3	0	–	0	–	0	–				
4	0	–	0	–	0	–				
5	0	–	0	–	0	–				
6	0	–	0	–	1+	1	0	–	0	–
7	0	–	0	–	1+	1				
8	0	–	0	–	2+	1				
9	0	–	0	–	1+	10				
10	0	–	1+	1	1+	10			0	–
11	2+	2	0	–	3+	2				
12	1+	1			3+	3	1+	1	1+	10
13	3+	0	3+	1	4+	2	3+	2	0	–
14	3+	3	4+	3	3+	5	3+	2		
15	2+	1	2+	1	4+	3				
16	3+	0	2+	0	3+	3	0	–	0	–
17	4+	2	4+	2	4+	2			0	–
18	5+	2	5+	3	5+	3	5+	2		
19	4+	1	5+	3	5+	3				
20	5+	4	6+	6	6+	5				
21	1+	1	0	–	1+	1			1+	1
22	1+	10	1+	1	1+	10				
23	3+	4	0	–	2+	4	0	–		
24	4+	3	3+	1	3+	2				
25	6+	4	5+	4	4+	2			3+	1
26	4+	8	4+	4	4+	7				
27	4+	5	5+	4	4+	4	3+	5	0	–
28	0	–	3+	3	0	–				
29	4+	2	5+	2	4+	2			0	–
30	4+	2	4+	2	3+	2				

[a]Highest readings given.

TABLE 2

Relative values of smears from various skin sites (derived from Table 1)

Skin site	Number of cases	Mean BI	Mean SFG, Index	Sole site showing bacilli	Sole site showing solid bacilli
Ear lobes	30	2.0	1.8	0	1
Lesions (healing or healed)	29	2.0	1.3	1	1
Fingers	30	2.5	4.0	4	4

Discussion

The reason why the fingers of all the sites tested should contain the most bacilli, solid or otherwise, is unexplained; but coolness of the site and exposure to trauma are obviously possible factors. It would be interesting to compare the results between fingers and toes in bare-foot patients.

Another possibility is that the persistence of bacilli in fingers might be connected with their rich supply of nerve endings. Nerve endings in the skin in leprosy have been the subject of a number of studies by earlier authors who are quoted by Klingmüller (1930). Sudakewitsch found the Pacinian corpuscles to be normal or atrophic without bacilli, or swollen with granulations when bacilli were numerous between the lamellae. Bernucci found only a few Meissner or Pacinian corpuscles or free nerve endings in the finger pulp in lepromatous leprosy; they were swollen, clubbed or degenerate, while in other cases they had virtually disappeared. Saijo and Takino noted that the degeneration of Meissner corpuscles was related to lepra globi in them or in contact with them. In our amputation specimen we found only one Pacinian corpuscle to be degenerate and fibrosed. Others were involved in the gangrene but not atrophic. The degenerate corpuscle was the only site for bacilli in the whole specimen, and in it bacilli were abundant and probably viable, but only at a distance from the central capillary and axis cylinder. It could be that it was fibrosis in the nerve ending, brought about originally in response to leprosy bacilli, which later protected these bacilli by preventing access of drugs to them.

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

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Does Droplet Infection Play a Role in the Transmission of Leprosy?

J. C. PEDLEY AND JOHN G. GEATER

Experiments are described aimed at repeating in the context of modern knowledge the long neglected work of Schaffer on the release of *Mycobacterium leprae* from the upper respiratory passages during sneezing, coughing and normal speech. In two Bhutanese patients large numbers of *M. leprae,* including some of normal morphology, were projected during sneezing up to a distance of 30 cm from the face and smaller numbers to a distance of 50 cm. None could be recovered during 20 min of normal speech. Only patients with untreated or relapsing lepromatous leprosy are implicated, as distinct from borderline cases, the criterion being the presence of a highly bacilliferous nasal discharge.

Does Droplet Infection Play a Role in the Transmission of Leprosy?

At the first International Leprosy Congress at Berlin, Schäffer (1898) described experiments in which sets of microscope slides were placed at distances up to 50 cm in front of 2 patients with severe lepromatous leprosy during the process of talking, coughing and sneezing. Large numbers of acid-fast bacilli were found on the slides. At that time it was impossible to identify these as *Mycobacterium leprae,* and Schäffer's work suffered from the neglect which for so many years surrounded nasal infection in leprosy, on the grounds that authentic *M. leprae* could be confused with contaminating acid-fast bacilli at this site.

The attention drawn by one of us to nose blows (Pedley, 1973) once again stimulated interest in Schäffer's findings. His original paper was written in German. Dr R. J. W. Rees arranged for its translation into English by Dr Bodingius, and the relevant sections are as follows.

"20-30 glass slides, closely adjacent, were placed in front of the patient. The patient talked for 10 min, reading or counting, after which time the slides had on them specks of mucus of different sizes. The slides were left till dry, fixed over a flame, and stained by the Ziehl-Neelsen method. For counting slides were divided into 8 quadrants, numbers of acid-fast bacilli in each quadrant were counted using oil immersion lens, and the total number of bacilli then calculated. Mistakes were avoided by decolourising with acid alcohol, bacilli about which there could be no doubt showing characteristic cigar shaped bundles and the occurrence of conglomerates (globi). No bacillary complexes were counted, only single organisms. It was found that if the patient stood upright, droplets were projected as far as 30-50 cm onto surfaces held in front of the patient.

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Results. One patient released 10,000 to 25,000 bacilli. The other patient released 75,000 to 120,000 bacilli and on one occasion 185,000 bacilli. In both patients investigated the secretion from the nose contained very many bacilli. Extremely large numbers of bacilli were released in sneezing (patients were given sneezing powder) . . . in one sneeze a patient released 110,000 bacilli.

Conclusions. Leprosy patients with mucous membrane affection of the respiratory tract . . release thousands of bacilli during speech, coughing and sneezing. Are the released bacilli viable? Some authors think they are dead. This is still unproved because no culture or animal inoculation has been possible up till now. We should not worry too much because clinical experience has shown that the danger of leprosy transmission is in fact extremely small. Cases of close contact for years do not acquire leprosy. Bacilli in great masses reach healthy persons without leading to disease. We may however not conclude that bacilli released by the respiratory tract do not play a role in the transmission of leprosy."

Nowadays patients with untreated florid lepromatous leprosy are not easy to find, but it seemed to us worthwhile to repeat Schäffer's work against the background of modern knowledge. An opportunity arose when a suitable patient attended at Mongar Hospital, Bhutan. The patient, a Bhutanese patient about 35 years of age, had been suffering from lepromatous leprosy for 5 years and was untreated. The disease was well advanced, and smears of the noseblow showed that the mucus was heavily infected with acid-fast bacilli and numerous globi. The B.I. of skin smears was 5.0.

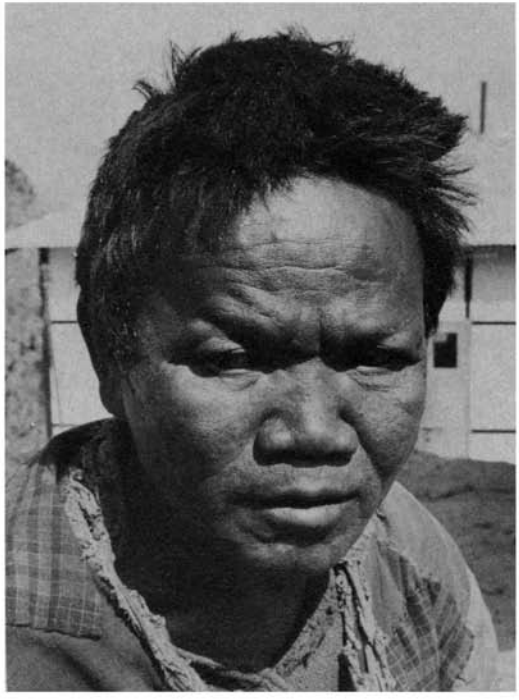

Fig. 1. Name: Sonam. Nationality: Bhutanese. Age: 35. Untreated lepromatous leprosy 5 years.

Method

Sneezing was induced by tickling the nasal mucosa. The patient directed his sneeze towards microscope slides placed at distances of 20, 30 and 50 cm from the face. Slides were fixed, stained by the Ziehl-Neelsen method and examined for acid-fast bacilli.

Findings

SNEEZE AT 20 CM

Two slides with a total area of approximately 39 cm^2 were examined systematically and revealed the presence of 500 droplets of sizes varying from 0.2 mm to 0.7 mm in diameter. Fifty droplets (i.e. 10% of the total) were examined in detail in succession as they occurred on the slides using the oil immersion lens. In 35 of the 50 droplets (i.e. 75%) bacilli were found, arranged as follows:

Globi	20
Smaller aggregates (cigar shaped bundles, clusters, etc.)	32
Single bacilli	50-100

Figure 2 shows a single field from a slide at this distance.

SNEEZE AT 30 CM

Three slides from which a total area of approximately 35 cm^2 was systematically searched revealed the presence of about 340 droplets with the same variation in size as recorded above. Fifty droplets were examined under oil immersion. Thirteen showed the presence of acid-fast bacilli, classified as follows:

Globi	8
Smaller aggregates	16
Single bacilli	20

Figure 3 shows a single field from a droplet which was 0.4 mm in diameter at this distance.

SNEEZE AT 50 CM

A second patient, a Bhutanese youth aged 22 years, suffering from untreated and well advanced lepromatous leprosy (B.I. of skin 3.5, B.I. of nasal mucus secretion 4.0) sneezed towards a slide held at 50 cm from the face. A search of the slide revealed the presence of 7 droplets, in 6 of which acid-fast bacilli were found, occurring singly, in groups and in globi.

At all distances individual bacilli were encountered which preserved the stain uniformly.

Figure 4 shows a single field from a slide at 50 cm.

The photomicrographs from both patients are filed at the Leprosy Study Centre, London.

Further experiments were undertaken with the first of these two patients in order to ascertain the release of bacilli in talking, snoring (simulated with the mouth open), and panting after vigorous exercise. Table 1 summarizes the findings in all these experiments.

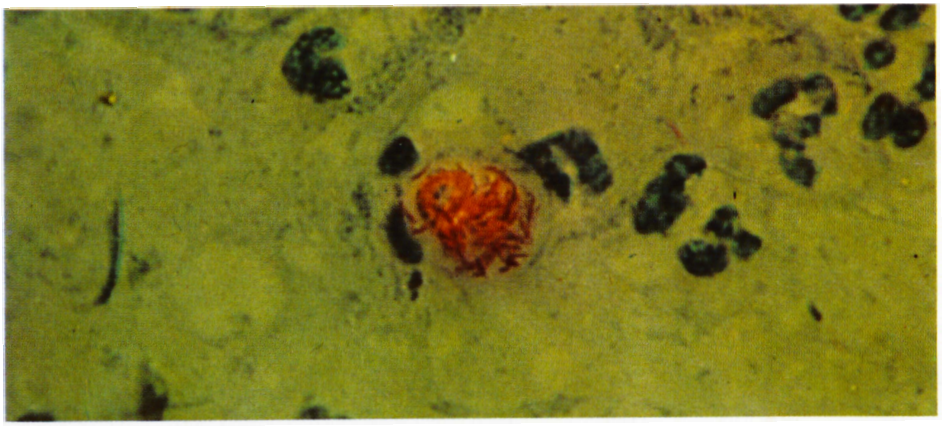

Fig. 2. Sneeze at 20 cm.

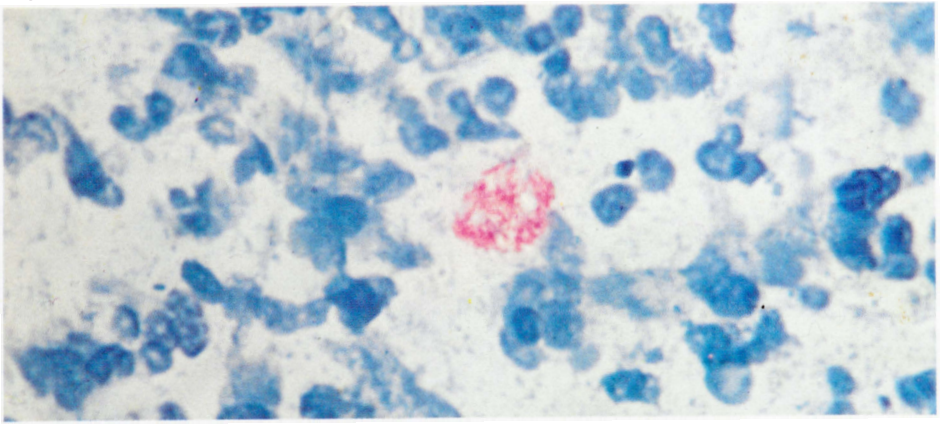

Fig. 3. Sneeze at 30 cm. Large globus in droplet (diameter 0.4 mm).

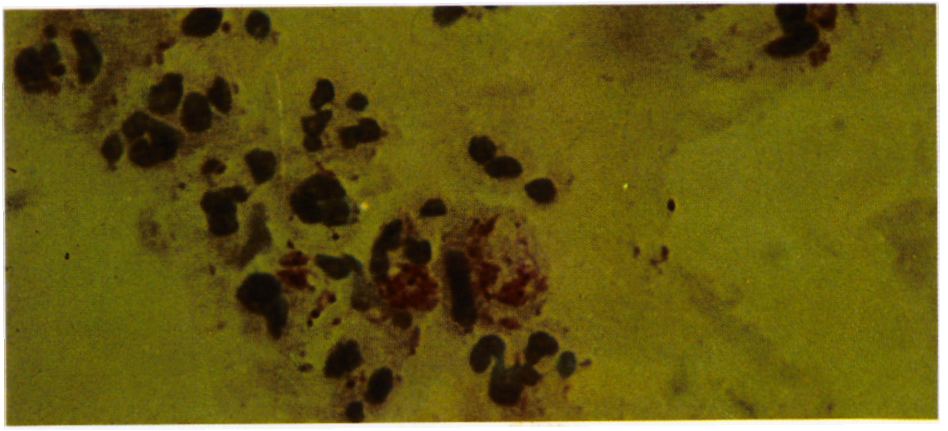

Fig. 4. Sneeze at 50 cm.

TABLE 1

Release of acid-fast bacilli from the nose and mouth

Experiment	Number of slides	Distance from face (cm)	Time (min)	Number of droplets	AFB present
Sneezing	2	20		500	large numbers
Sneezing	3	30		340	large numbers
Sneezing	1	50		7	numerous
Talking	3	10	10	10	nil
Talking	2	5	20	15	nil
Snoring	3	10	?	nil	nil
Panting	2	20	?	nil	nil
Panting	2	5	?	nil	nil

Discussion

These findings confirm those of Schäffer where sneezing is concerned. In the case of untreated patients with severe lepromatous leprosy enormous numbers of acid-fast bacilli are projected from the nose during sneezing to distances at any rate up to 50 cm from the face, including bacilli morphologically normal. Taken in conjunction with Rees's findings on the viability of *M. leprae* outside the body (Davey and Rees, 1974) our findings strongly suggest that droplet infection could play a significant role in the transmission of leprosy.

It is probable that only patients with untreated lepromatous leprosy and heavy involvement of the nasal mucosa will yield positive findings in droplets, and it is surprising how non-apparent such cases can sometimes be (Pedley, 1970). It is most unlikely that borderline leprosy even in reaction is associated with the presence of acid-fast bacilli in the nasal secretions (Pedley, 1973). Enormous numbers are however found in the nasal discharge in untreated lepromatous leprosy at all stages (Davey and Rees, 1974), and this is the criterion for any selection of patients in the expansion of the studies reported here which is clearly desirable. Finally, it is probable that both of Schäffer's patients were also suffering from heavy involvement of the throat and larynx, and possibly of the palate as well, and this is likely to have contributed to his findings. It is a cause for thanksgiving that with the advent of present day treatment such advanced cases of lepromatous leprosy are rarely seen, and that with modern treatment bacilli can rapidly be eliminated from the nasal secretion.

Acknowledgements

Our grateful thanks are due to Dr R. J. W. Rees for much advice and encouragement. Thanks are also due to Dr D. J. Harman of the Leprosy Study Centre for the photomicrographs, and to the Leprosy Mission for covering the cost of colour photographs and for all their support without which this paper could not have been written.

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Lepr. Rev. (1976) **47**, 103-106

Studies of the Mouse Foot Pad Technique for Cultivation of *Mycobacterium leprae*

3. Doubling Time During Logarithmic Multiplication

LOUIS LEVY

Leprosy Research Unit, Public Health Service Hospital, San Francisco, California 94118, U.S.A.

The doubling time of a strain of *Mycobacterium leprae* during logarithmic multiplication in the mouse foot pad was estimated by inoculating mice with serial dilutions of a bacterial suspension and measuring the time from inoculation to multiplication to 10^6 organisms per foot pad. The doubling time was found to be 11.1 ± 1.92 (mean ± 95% confidence limits) days, about 15% shorter than an earlier estimate based on measurements of the slopes of many single growth curves of *M. leprae*.

Introduction

Shepard has estimated that the doubling time of *Mycobacterium leprae* during logarithmic multiplication in the mouse foot pad infection is 12 to 13 days (Shepard and McRae, 1965). Work in this laboratory has yielded a similar estimate of 13 days (Levy, 1970). Both estimates, however, are imprecise because they depend upon measurements of the slopes of growth curves, which cannot be measured with precision.

A better approach for measuring the rate at which *M. leprae* multiply was suggested by the results of an experiment performed to ascertain the minimal number of *M. leprae* required to infect mice. Mice were inoculated with serial 10-fold dilutions of a bacterial suspension. The strikingly parallel character of the resulting growth curves suggested a more precise method that has subsequently been employed in a systematic study of the rate of doubling of *M. leprae* during logarithmic multiplication in the mouse foot pad.

Methods

The strain of *M. leprae* studied in these experiments is the standard strain that has been used for most of the studies performed in this laboratory. Inocula were

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prepared, locally-bred BALB/c mice inoculated, and harvests of *M. leprae* from mouse foot pad tissues performed by published methods (Shepard, 1960; Shepard and McRae, 1968). For these experiments, suspensions of *M. leprae* harvested from mouse foot pads were diluted serially to provide inocula of 5000, 500, 50 and, in most experiments, 5 organisms per foot pad. Each of the inocula was used to inoculate both hind feet of 10 or 15 mice. Harvests of *M. leprae* from pools of at least 4 foot pads were performed at intervals thereafter, and growth curves were constructed.

Results

The results of the first experiment are shown in Fig. 1, in which the $\log^{10}$ number of AFB per foot pad found at harvest is shown as a function both of the number of days elapsed from inoculation to harvest and the size of the inoculum. The time intervals between pairs of adjacent growth curves at $\log^{10}$ number AFB = 6.0 are 40 and 45 days for the 3 larger inocula and 72 days for the 2 smaller inocula. Because a 10-fold increase in the number of *M. leprae* represents 3.32 doublings, the mean number of days per doubling is 12.8 when only the

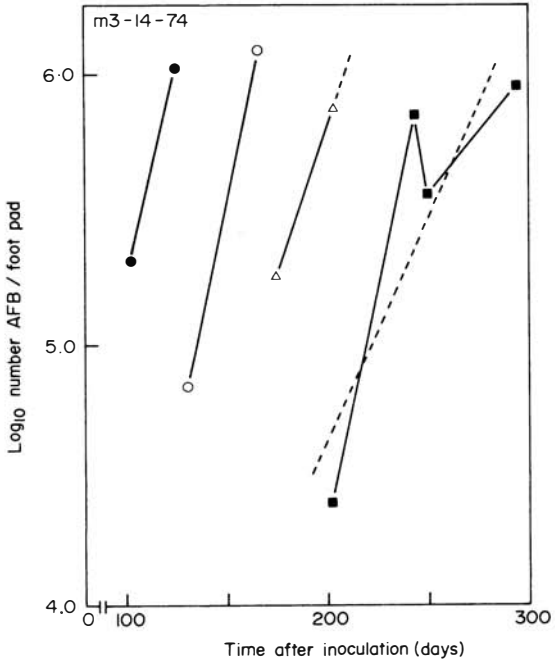

Fig. 1. The $\log^{10}$ number of acid-fast bacilli (AFB) per foot pad as a function of the number of days from from inoculation to harvest and the number of AFB inoculated. Points representing the harvests of *M. leprae* from each group of mice; the best-fitting straight line used to measure the time from inoculation to multiplication to the level of 10^6 organisms per foot pad. Mice were inoculated as follows: (●) 5000 organisms per foot pad; (○) 500 organisms per foot pad; (△) 50 organisms per foot pad; (■) 5 organisms per foot pad.

three largest inocula are considered. The irregularity of the growth curve representing the smaller inoculum and the large time interval between the growth curves derived from the 2 smaller inocula suggest that the smallest inoculum did not infect all of the foot pads.

The results of this experiment and of 6 subsequent experiments are summarized in Table 1, in which the numbers of days elapsed from inoculation to multiplication of *M. leprae* to the level of 10^6 per foot pad in mice inoculated with 5000, 500, 50 and, in some experiments, 5 organisms per foot pad are listed. In addition, the doubling times, calculated from the linear regression of the time to 10^6 organisms per foot pad on the $\log^{10}$ number of *M. leprae* inoculated, are shown. The mean doubling time for the seven experiments is 11.1 days; the 95% confidence limits are 9.2 and 13 days.

TABLE 1

Doubling time of M. leprae *during logarithmic multiplication in the mouse foot pad*

Experiment No.	Time from inoculation to multiplication to 10^6 AFB per foot pad (days)				Doubling time (days)
	Number *M. leprae* inoculated per foot pad				
	5000	500	50	5	
m 3-14-74	123	163	208	280[a]	12.8
m 9-19-74	126	177	208	248	12.0
m 10-16-74	144	186	199	ND[b]	8.28
m 12-10-74	123	159	207	261	13.9
m 12-23-74	134	140	191	ND	8.58
m 1-14-75	121	159	190	236	11.3
m 4- 3-75	125	178	198	ND	11.0
Mean ± 95% confidence limits					11.1 ± 1.92

[a] This value was not used for calculation because the growth curve suggested irregularity of infection.
[b] Not done.

Discussion

The purpose of this study was to measure more precisely the rate at which *M. leprae* multiply during the logarithmic phase in the mouse foot pad. Previous estimates of this rate were derived from measurements of the slopes of growth curves of *M. leprae* in mice. Although the typical growth curve represents at least 200-fold multiplication (7.3 doublings) from the inoculum of 5000 *M. leprae* per foot pad to the ceiling of somewhat more than 10^6 organisms per foot pad, the entire length of the growth curve cannot be used for calculating the slope. A harvest of 5000 *M. leprae* per foot pad from a pool of 4 foot pads results when only a single organism has been counted in the examination of 60 microscopic fields with a magnification of x 1250, and a harvest of 100,000 organisms per foot pad results when only 20 organisms have been counted. Assuming that the distribution of the organisms is random and described by the Poisson distribution (Goldstein, 1964), the 95% confidence limits around a count of 20 are 11 and 39 organisms. This broad confidence band implies that one may overestimate the

number of organisms by two-fold (one doubling), or underestimate it by one-half. The confidence band may actually be somewhat broader, because *M. leprae* tend to clump and probably are not distributed randomly. Thus, only the upper portion of the growth curve—from 1 or 2×10^5 to 10^6 organisms per foot pad, equivalent to only 2.3 to 3.3 doublings and constructed from only 2 or 3 harvests—can be used to measure the slope with confidence.

The upper end of the growth curves also poses problems. At some time after multiplication passes the level of 10^6 organisms per foot pad, the rate slows, and one cannot be certain whether a harvest of 2×10^6 *M. leprae* per foot pad, for example, represents the peak of logarithmic multiplication or the stationary phase of bacterial growth.

An alternative method for measuring the doubling time of microorganisms was suggested by Youmans and Youmans (1949). These investigators inoculated liquid media with serially diluted suspensions of *M. tuberculosis* and took as the end point the first appearance of subsurface growth in the cultures. A plot of the logarithm of the inoculum against the time from inoculation to visible subsurface growth yielded a straight line; the doubling time was readily calculated from the slope of the line. This method, which depends simply on the appearance or non-appearance of an event, yields a better estimate of the doubling time than does a method that depends upon the measurement of some variable quantity that cannot be measured with great precision. In growth curves of *M. leprae*, we can determine with much greater precision that time at which multiplication reaches the level of 10^6 per foot pad than we can the slopes of growth curves.

The doubling time of the strain of *M. leprae* studied in these experiments, 11.1 days, is 15% shorter than our previous estimate of 13 days, based on repeated studies of the same strain (Levy, 1970). More importantly, it is a better estimate, because each of the seven experimentally-derived values shown in the sixth column of Table 1 was based on from 8 to 12 harvests.

Acknowledgements

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Tissue Levels of Clofazimine in a Case of Leprosy

K. V. DESIKAN AND S. BALAKRISHNAN

Central Leprosy Teaching and Research Institute, Chingleput 603 001, India

A quantitative assessment of clofazimine in some of the organs obtained at autopsy is reported. Although 40 days had elapsed since stopping treatment with the drug, significant quantities of the substance were found in the organs of the reticulo-endothelial system. The intestinal mucosa also showed a heavy concentration of the drug. Attention is drawn to the heavy accumulation of the drug during prolonged treatment.

Introduction

Clofazimine, a phenazine derivative, was synthesized in 1954 and found to have anti-tuberculosis activity (Barry *et al.*, 1957). It was first used in the treatment of leprosy by Browne and Hogerzeil (1962). Subsequently, there have been several reports of its use in the treatment of leprosy, as well as lepra reaction. (For review see Theophilus, 1975.) A characteristic feature of this compound is that it is concentrated within the cells of the reticulo-endothelial system, being taken up by macrophages throughout the body (Conalty *et al.*, 1971). Consequently the organs are coloured bright yellow-orange or brick-red. These changes in the organs have been studied in mice (Conalty and Jackson, 1962). The corresponding changes in human viscera have recently been described (Desikan *et al.*, 1975). The concentration of the drug in body fluids and tissues has been estimated in experimental animals by Barry *et al.* (1960). Mansfield (1973) has studied the tissue concentration of clofazimine in leprosy patients at autopsy.

Recently a quantitative assessment of clofazimine in various organs obtained at autopsy has been carried out on a patient with lepromatous leprosy. The autopsy findings in this case were similar to those reported earlier (Desikan *et al.*, 1975). The findings are presented in this communication.

Materials and Methods

The material for the present study was collected during an autopsy on a patient of lepromatous leprosy who was aged 16 years and weighed 21 kg at the time of the death. He had treatment with clofazimine continuously for an initial period of 6 months on a dose of 300 mg a day. During the next 6 months, he did not

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receive the drug. Subsequently he had a second course of treatment with clofazimine for 2½ months on a dose of 200 mg a day. The drug was stopped 40 days before his death. The patient also had severe diarrhoea and recurrent convulsions for which he received symptomatic treatment.

At autopsy, samples of various organs were collected for estimation of clofazimine. The method employed for the estimation of clofazimine was essentially the same as described by Barry *et al.* (1960) with minor modifications. About 1 g of the tissue was weighed and minced thoroughly to a paste with about 3 ml of 10% acetic acid. The minced tissue was extracted with 20 ml instalments of benzene till the benzene layer became colourless. The pooled benzene extracts were made up to a known volume with benzene. Ten ml of this benzene extract was treated with 1 ml of concentrated hydrochloric acid and shaken vigorously. The layers were allowed to separate. The acid extract was removed to a graduated measuring cylinder. This acid extraction was repeated with 1 ml instalments of concentrated acid, till no more colour was extractable. The acid extracts were pooled and made up to 10 ml with distilled water. A stock standard solution of clofazimine containing 1 mg/ml was made with benzene as the solvent. 0.1 ml of this stock standard was diluted to 10 ml with benzene. This was extracted with concentrated hydrochloric acid in 1 ml instalments till the clofazimine extraction was complete. The total volume of the pooled extract was made up to 10 ml with distilled water. The optical densities of the standard and test solution were read in a photoelectric colorimeter using green filter (540 mμ) and the concentration of clofazimine per gram of the tissue was evaluated.

Representative samples from the organs were also processed for histological examination. For detection of clofazimine crystals, special care had to be taken in preparing the sections, since the crystals are readily dissolved in alcohol. The bits of organs were fixed in warm 10% formalin for 10 min. Frozen sections of 10 to 12 μm thickness were prepared and mounted on slides. The sections were dehydrated in the incubator for a period of 1 to 2 h. After rapidly rinsing the sections with xylol they were mounted using Permount or any other mounting medium. The crystals could easily be recognized and the preparations made in this way were good for photography. Paraffin sections were also made for routine histological study and the sections were stained by haematoxylin eosin method and Fite-Faracco method.

Results

The colour changes in the skin were not obvious due to post-morten lividity. Subcutaneous fat and fat in the omentum were stained bright orange yellow. The loops of small intestine appeared reddish brown from the peritoneal surface. The mucosa of the intestines was stained intensely red with marked oedema and several ulcerations. The liver and spleen were reddish brown in colour on the external as well as on the cut surface. The liver was large for the size of the body and weighed 740 g. The spleen was of normal size. The lymph nodes (both superficial and deep groups) were discrete and dark brown in colour. The mesenteric lymph nodes were stained intensely and had a bluish-brown hue. The bone marrow of the lumbar vertebrae was examined and found to be dark brown in colour. The lungs had a bright red coloration. The skeletal muscles showed a brick-red colour.

Apart from the colour changes, the other gross post-mortem findings were the extensive pleural adhesions, multiple sub-diaphragmatic abscesses and the occurrence of a circumscribed area of caseation in the brain measuring 2.5 x 1.5 x 0.5 cm in the left cerebral hemisphere adjacent to falx cerebri.

The levels of clofazimine in various organs are given in Table 1.

TABLE 1

Serial No.	Organ (g)	Concentration (mg/g)
1	Liver (740)	0.18
2	Spleen (60)	1.00
3	Small Intestine	2.10
4	Lungs: Right (330)	0.17
	Left (260)	
5	Kidney: Right (60)	0.04
	Left (60)	
6	Omentum	0.35
7	Lymph nodes (mesenteric)	3.30
8	Brain (1100)	Not detected

It could be seen that clofazimine was found in all organs studied except the brain. High concentrations were noticed in the mesenteric lymph nodes, small intestine and spleen. A relatively smaller concentration of the drug was found in the omentum, liver and lungs. The kidney showed only traces.

Histological examination of the frozen section of the small intestine showed a heavy deposit of the crystals in the mucosa (Fig. 1). Large clumps of the crystals were seen in the liver also (Fig. 2) but it was difficult to define the exact location of these crystals. In the lymph nodes, the crystals were densely packed in the macrophages (Fig. 3). A relatively smaller amount was found in the spleen and lungs and appeared to be located in the macrophages. Frozen unstained sections of kidney, adrenals, testes, heart, aorta, pancreas and thyroid did not reveal any crystals. Histological examination of the paraffin sections confirmed the lesion in the brain to be a tuberculoma. The subdiaphragmatic abscesses were also tuberculous and the smears made from the pus showed acid-fast bacilli. There was massive fatty infiltration of the liver with scattered lepromatous leprosy lesions in the parenchyma. Yellowish-brown pigments were seen in the liver cells. The pigments were also seen in macrophages in the spleen, lungs and lymph nodes. These could possibly be due to clofazimine after partial dissolution during processing the tissues. Clumps of dark brown material were also seen within the blood vessels of several organs. The intestinal mucosa showed "ghosts" of clofazimine crystals. There was ulceration and marked infiltration of all the layers with mononuclear cells. The inflammatory exudation and ulceration is most likely due to accumulation of clofazimine crystals in the intestinal mucosa.

Discussion

A gross examination of the organs at autopsy showed that in addition to fat in all the locations, the liver, spleen, lymph nodes, bone marrow and lungs had taken

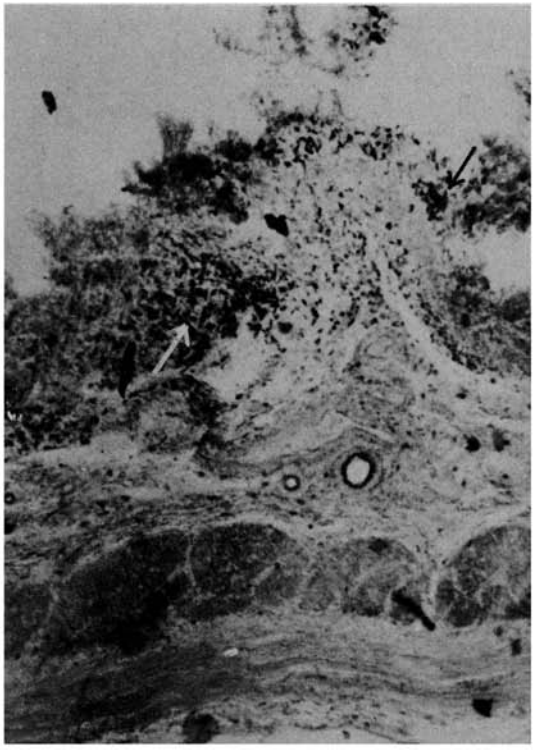

Fig. 1. Frozen section of small intestine. The arrows indicate a heavy deposit of clofazimine in the mucosa. (×42).

up the colour of the drug. Frozen sections of liver, spleen, lymph nodes and lungs showed clofazimine crystals mainly within the macrophages. The omentum showed the dye as droplets rather than as crystals, since clofazimine is a fat soluble substance. On a quantitative estimation, the drug was found to be concentrated to a significantly high level in all these organs. The lymph nodes from the mesentery contained the maximum concentration of 3.3 mg/g of the tissue. In other words, the drug had accumulated in the lymph node, constituting as much as 0.33% of the weight of the organ. Judging from the depth of the coloration, the concentration of the drug could not have been high in other groups of lymph nodes. Of the other organs of the reticulo-endothelial system studied, the spleen contained the next highest concentration, the drug forming 0.1% of the weight of the organ. Liver and lungs were next in order, the concentration nearing 0.02%. The concentration of the dye substance in the macrophages of these organs is consistent with the finding in mice by Conalty and Jackson (1962), who have shown that clofazimine is taken up by reticulo-endothelial cells. The lungs, which contain a large number of macrophages, also contain the drug in these cells. The

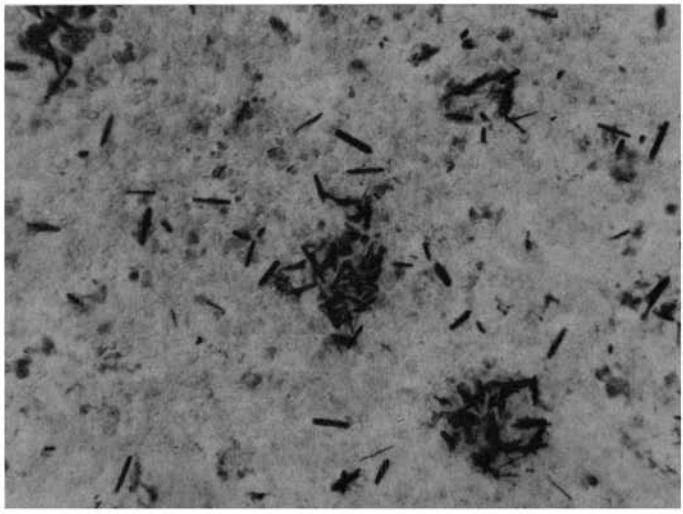

Fig. 2. Photomicrograph showing clofazimine crystals in liver. (×120).

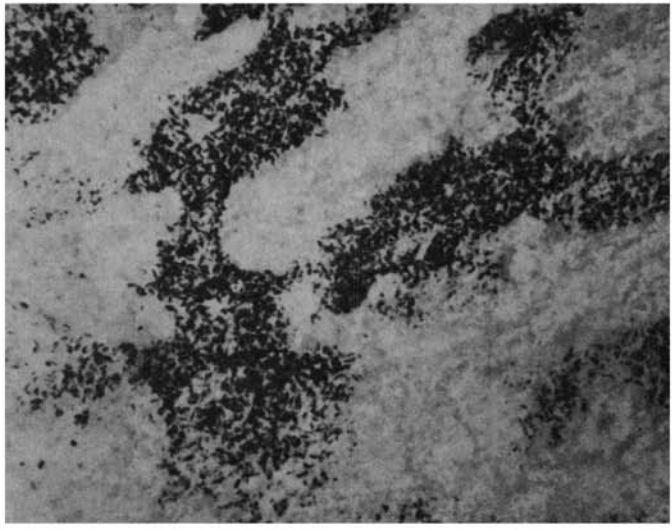

Fig. 3. Frozen section through a mesenteric lymph node showing massive deposits of clofazimine. (×42).

very low concentration of the drug in the kidney (0.04 mg/g) indicates that the accumulation of the drug is proportional to the number of macrophages that the organ or tissue contains. This could be the reason for the drug becoming concentrated heavily at the sites of the leprosy lesions in the skin, which are composed mainly of macrophages.

The heavy concentration of the drug in the intestinal mucosa is of special note. The drug is absorbed through the intestines and therefore is accumulated in the mucosa. Such an accumulation in the intestinal mucosa would cause diarrhoea which is commonly associated with clofazimine therapy (Desikan *et al.*, 1975). The case presented here also had severe diarrhoea.

Although the concentration of the drug per gram of tissue is less in liver compared to lymph nodes and spleen, it must be realized that the total quantity of the substance in the liver is quite high, in view of its size. In the case reported, the total amount of the drug in the liver works out to 133.2 mg since the organ weighed 740 g. It could be presumed that the drug was uniformly distributed in the organ because the cut surface showed uniform coloration. The corresponding total amount in spleen (which was also uniformly stained and weighed 60 g) was only 60 mg. Although the concentration of the drug in the mesenteric lymph nodes was very high, the drug was not uniformly distributed in all the lymph nodes, so that the total amount of the dye in the lymphoid tissues of the body taken as a whole would have been less than the amount in the liver.

In the present study, the organs listed in the table were selected for quantitative assessment of clofazimine, because these organs showed distinct coloration due to the drug. The quantities of clofazimine estimated chemically roughly corresponded with the intensity of coloration as judged by gross examination of the organ. The brain had not taken up any colour nor were any crystals seen in the frozen sections. Even so, the tissue was processed chemically to detect the presence of the drug and to check whether the dye could pass the blood-brain barrier. Such a possibility has been ruled out by the absence of the dye in the brain. The peripheral nerves were not examined for the presence of the drug in this case.

The present study provides some idea of the quantity of the drug that could accumulate in human tissues during regular treatment with clofazimine. It has been shown that in liver alone as much as 133 mg of the drug had accumulated in the course of 8½ months of interrupted treatment with clofazimine. Taking into account that the patient weighed only 21 kg the amount of the drug in the liver appears substantial. Further, it has been mentioned that the adipose tissue all over the body also contained the drug. The drug was also present in the bone marrow and to a lesser extent in the skeletal muscles as judged by the coloration of the organs. Since this was a case of lepromatous leprosy, the drug could presumably be distributed throughout the skin. All this added up would constitute a sizeable amount of the drug in the body. The implications of such an accumulation of the drug, particularly in organs like liver and small intestine, are not clear at the moment, but this fact has to be borne in mind when a patient is subjected to prolonged treatment with clofazimine.

Acknowledgement

Clofazimine therapy of the patient was under the supervision of Dr K. Ramanujam and Dr G. Ramu who have kindly supplied the clinical details. Technical assistance provided by Sri P. B. Nath in preparation of tissue sections and by Sri C. Samuel in photography is acknowledged as also is the secretarial help of Sri M. Nagarethinam.

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The Incidence of Leprosy Between 1943 and 1973 in a Hyperendemic Area, Before and After the Introduction of Leprosy Control Measures

D. L. LEIKER*

Royal Tropical Institute, Amsterdam, The Netherlands

P. FISCHER

Leprosy Control Officer, Miei, Wandamen Bay, Irian Jaya, Indonesia

A leprosy incidence study in a hyperendemic area (prevalence 7%) is presented, based on whole population surveys at intervals, and covering a period of 30 years (1943-1973). The effect of three measures, introduced at different times, segregation of patients, mass chemotherapy and BCG vaccination, was assessed.

In the period 1943-1952 segregation of a proportion of the infectious patients was the only control measure. It was found that the incidence of leprosy remained nearly stable. Apparently this measure was virtually ineffective. In 1950 sulphone treatment was introduced. All segregated patients were treated. After 1952 an intensive casefinding, mass-treatment and caseholding programme was implemented. In the period 1958-1960 a very marked decline in the incidence was found. The incidence decreased by 74%, as compared with the preceding 3-year period.

In 1957 a mass BCG vaccination campaign was carried out. The epidemiological data are not compatible with a spontaneous "natural decline". The decrease has to be ascribed to the control measures. If the mass treatment campaign alone was responsible for the decline in incidence one would expect a proportionally similar decline in the incidence of progressive forms of leprosy and of tuberculoid leprosy. It was found, however, that the decline in incidence of tuberculoid leprosy was much more marked and more sudden immediately following the BCG vaccination campaign. In 1958-1960 the incidence of B + L cases had decreased by 41% as compared with the preceding 3-year period, but the incidence of tuberculoid leprosy had decreased by 86%.

It is concluded that the decline of progressive forms of leprosy and a proportionally similar decline of tuberculoid leprosy was due to the mass treatment campaign, but that the BCG vaccination campaign had contributed additionally and significantly to the decline of tuberculoid leprosy. It is encouraging to learn from this example that with conventional leprosy control measures, provided that they are conscientiously applied, rapid and impressive results can be obtained. The leprosy case load was reduced to such low proportions that general basic health services should be able to cope with the remaining case load.

* Dermatologist, former head of Leprosy Control Division, Department of Health, West New Guinea.

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Introduction

Wandamen Bay is located in the south west corner of Geelvink Bay in Northern Irian Jaya, Indonesia. Between 1952 and 1957 an intensive study on leprosy was carried out by the first author. In 1972 and 1973 whole population surveys were repeated by the second author. Together, the data give a reliable picture of the course of leprosy in a row of villages during a period of 30 years. Since, in general, incidence studies on leprosy are scarce and incidence studies prior to and after the introduction of leprosy control activities are even more scarce, the results are published in some detail.

Demographic Data

The population of the east coast of Wandamen Bay is living in a row of villages shown in Fig. 1. The northern villages are located at the coast. A few villages in the south are located inland. The distance between the villages is, on the average, only a few kilometres. The main occupation is agriculture and fishing. The staple food is sagoe, cassave and sweet potatoes. The economical level is a subsistence economy.

The two northern villages, Wasior and Miei, differ slightly from the others. Wasior is the civil administration headquarters of the area. A number of civil servants from other parts of Irian Jaya are employed in the various departments. Miei is the headquarters of the Mission, the site of the only health centre and of the only secondary school in the area. (Recently a district hospital was built in Wasior.) The presence of a few Chinese shops makes these villages the main shopping and trading centre of the area, frequently visited by people from other villages. The third village in the row is the leprosarium, consisting of a row of houses on pilings at the beach, a small hospital, an occupational therapy building, a shop, a school and a church. Communication between the villages is via a single north-south track through the villages; or at low tide via the beach, or by sea.

A part of the population of Wandamen Bay is temporarily or semi-permanently absent. The majority of the emigrants are living in the nearest town, Manokwari, or are employed by the oil company at Sorong (usually on a 1 year contract basis). These emigrants too were examined between 1952 and 1957. A large proportion returned to Wandamen Bay after 1962, and have been re-examined since.

History of Leprosy

The history of leprosy was studied in detail between 1952 and 1955. Genealogical tables, comprising 5 generations, were compiled of all patients. The origins of the clans and the family relationship were studied.

Data were established by referring to events which were well known to everybody and at the same time are fixed by records, e.g. beginning and end of the war, arrival of the first civil administrator, opening of the first school.

All information on patients who had died prior to the survey was cross-checked with other informants, frequently with informants from other villages too. In 1952 a high proportion of the patients with onset of the disease after 1942 were still alive and were examined. However, a number of lepromatous and borderline

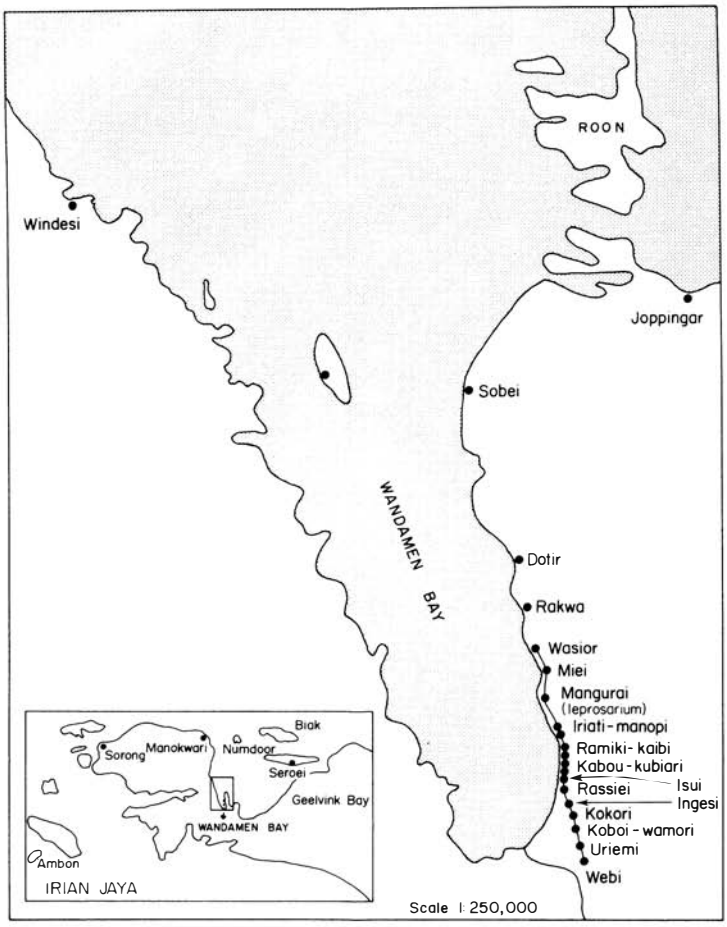

Fig. 1. Villages of Wandamen Bay, Indonesia.

patients had died, but with the exception of some early cases, their case histories could still be completed. No attempt was made to collect information on deceased tuberculoid and indeterminate patients, as such information would necessarily be too unreliable. The data presented in this report are regarded as nearly complete, with the exception of some under-registration of tuberculoid and indeterminate leprosy in the period between 1943 and 1952.

The first known patient in Wandamen Bay, a man in Miei, showed the first signs of the disease in 1904. Our informant, his son, confirmed that a few years earlier his father had visited Manokwari and had stayed for some months with immigrants from Numfor, living in Manokwari. The clan name of the first patient indicates that this clan originated from Numfor and this explains why he stayed with the Numfor immigrants at Manokwari.

Leprosy was introduced in Manokwari around 1870 and was reported to be spreading markedly in 1879. Around 1900 the disease had become highly endemic in this area.

The second patient in Wandamen Bay, a man in Wasior and a relative of the mother of the first patient, was seen in 1907. This patient was living in a large clan-house (several closely related families living together in a large, turtle-shaped house on pilings at the beach). The disease spread rapidly in this house. The first civil administrator, who arrived in 1906, induced the people to move from the large clan-houses to smaller family houses. Soon leprosy patients were found in many houses in the village.

In 1935 a visiting medical officer (Bierdrager, unpublished) found a leprosy prevalence rate of 16% in Wasior. The spread of leprosy to the other villages was relatively slow and irregular. In 1925, a married couple, both with leprosy, originating from Manokwari, introduced the disease in Manopi. In 1927 the first patient was seen in Kubiari in a house which was frequently visited by sagoe traders from Windesi (leprosy was introduced in Windesi between 1915 and 1920). A lepromatous patient from Windesi lived in this house for some time.

In 1928 a woman from Miei married in Wamori (Tandia) and developed lepromatous leprosy.

Around 1930 a man in Sirabi (Rassiei), who had lived in Wasior, developed leprosy.

In 1934 the first patient was seen in Ramiki-Kaibi, a relative of the first patient in Manopi.

In 1935 the first patient was seen in Isui, a member of a clan which came from Wasior.

In the same year the first patient was seen in Kabon, a woman originating from Kaibi.

Between 1930 and 1940 in most villages the disease was spreading rapidly to many other houses. An analysis of the genealogical tables, however, shows that the spread was not even. Frequently, no new cases were seen in neighbouring houses, while outbreaks of leprosy were recorded in more distant houses. A very high proportion of the new cases was seen in houses which were not marked by proximity to houses with sources of infection, but in other houses connected by family relationship with known patients and by inter-marriage. Apparently the chance of infection in this area was markedly influenced by the degree of contact with the sources of infection. The social customs in this area limit significantly the degree of contact between non-relatives. Even in 1952 when the first whole population survey was carried out it was found that, though leprosy was found to be highly endemic in all villages, the distribution of the cases was still uneven.

Statistics

The first whole population survey was carried out in 1952 by Sloan and Leiker.

In 1955 a house to house census and survey was carried out again, and 92% of the population were examined. The remaining 8% were temporarily absent from the area. They were examined soon after return to the area in the following years. A leprosy prevalence rate of 7.7% was found, not including

patients from outside the area, who had developed the first signs of leprosy prior to immigration to Wandamen Bay. It may be assumed that in 1957 virtually all patients were registered. In 1962 the medical officer left and casefinding and treatment were continued by a trained Papuan leprosy control officer. In 1973 a house to house census and survey was carried out again by the second author of this article. The fact that in this survey only a few unregistered patients were found confirmed the opinion that most new patients had been registered fairly soon after the onset of the first symptoms of the disease.

It is therefore believed that, with the exception of registration of a number of patients with mild selfhealing tuberculoid leprosy in the period between 1943 and 1952, virtually all patients in the period between 1943 and 1973 have been registered.

Though in the great majority of the patients the year of onset of the disease is regarded as fairly accurate, the possibility exists that in a proportion of the patients signs of the disease were already present before they were noticed. The data are therefore grouped in 3-year periods. Table 1 shows the average incidence of leprosy in 3-year periods between 1943 and 1973. A fairly stable pattern of leprosy in the first 15 years is followed by a dramatic decline in incidence in the next 3-year period, not followed by a marked further decline in the next 10 years, and a slight increase in the last few years of the period. Age at onset is given in Table 2, and sex and type indices are given in Table 3.

Leprosy Control Activities

Before 1942 groups of patients were segregated at a few sites outside the villages. However, they used to live together with other members of the family. In 1934 a few patients were sent to a leprosy colony at Seroei and a few were sent to the leprosarium at Ambon.

In 1949 the patients were largely concentrated in one village at the site of the present leprosarium. After 1950 the number of segregated patients increased gradually, but by 1955 a relatively high percentage of bacteriologically positive patients were actually living in the leprosy colony. Even then segregation was not strict. Relatives were visiting the patients regularly, not seldom staying in the colony and patients frequently visited the trading centres at Miei and Wasior or visited relatives in other villages.

The second leprosy control measure was the introduction of sulphone therapy in 1950, initially with diasone, followed in 1952 by DDS. In 1950 all patients in the leprosy colony and many patients in the northern villages were on treatment. From 1952 onwards most registered patients in other villages too were treated fairly regularly.

The third factor which may have influenced the incidence of leprosy is a BCG mass vaccination campaign carried out in 1957. More than 80% of all tuberculin negative people, children as well as adults, were vaccinated. The fourth factor which deserves consideration is a "natural change" in the pattern. It was found in other studies, carried out in New Guinea, that epidemics of leprosy may be followed by a rapid spontaneous decline in the incidence of the disease.

TABLE 1

Incidence and type of leprosy in 3-year periods

	L	B	L + B	T	I	T + I	Total	Population	Average annual		
									Incidence	L + B incidence (%)	T + I incidence (%)
1943-45	11	2	13	19	2	21	34	Est. 2200	0.52	0.20	0.32
1946-48	17	1	18	22	2	24	42	2300	0.61	0.26	0.35
1949-51	14	5	19	21	5	26	45	2400	0.63	0.26	0.36
1952-54	15	1	16	25	1	26	42	2500[a]	0.56	0.21	0.35
1955-57	8	5	13	43	5	48	61	2600[a]	0.78	0.17	0.62
1958-60	8	0	8	6	2	8	16	2700	0.20	0.10	0.10
1961-63	5	1	6	5	0	5	11	3000	0.12	0.07	0.06
1964-66	3	1	4	9	0	9	13	3300	0.13	0.04	0.09
1967-69	1	0	1	2	0	2	3	3400	0.03	0.01	0.02
1970-72	4	3	7	7	1	8	15	3600[a]	0.14	0.04	0.08
1973	0	2	2	3	0	3	5	3600	0.14	0.02	0.03

[a] Census.

TABLE 2

Age at onset (in 3-year periods)

(a)

	0-4	5-9	10-14	15-19	20-29	30-39	40-49	50+	Total	Child index
1943-45	0	6	3	3	8	11	3	0	34	26%
1946-48	1	14	4	4	6	9	4	0	42	45%
1949-51	4	8	3	2	11	9	8	0	45	33%
1952-54	0	7	11	7	12	2	3	0	42	43%
1955-57	3	13	9	8	10	10	6	2	61	41%
1958-60	0	2	2	1	7	2	2	0	16	25%
1961-63	0	0	0	2	1	4	4	0	11	0%
1964-66	0	2	2	3	0	5	1	0	13	30%
1967-69	0	1	0	0	0	1	1	0	3	33%
1970-72	1	2	2	1	1	6	1	1	15	33%
1973		1		1	1			1	4	25%

(b)

1943-57	8 (3.7%)	48 (22.3%)	21 (9.8%)	24 (11.2%)	47 (21.9%)	41 (19.1%)	24 (11.2%)	2 (0.9%)	215	36%
1957-73	1 (2.6%)	8 (20.8%)	6 (15.6%)	8 (20.8%)	10 (16.1%)	18 (46.8%)	9 (23.4%)	2 (5.2%)	62	24%
1958-63	0 (0%)	2 (7.4%)	2 (7.4%)	3 (11.1%)	8 (29.6%)	6 (22.2%)	6 (22.2%)	0 (0%)	27	15%
1964-73	1 (2.9%)	6 (17.1%)	4 (11.4%)	5 (14.3%)	2 (5.7%)	12 (34.3%)	3 (8.6%)	2 (5.7%)	35	31%

TABLE 3

Sex and type in 3-year periods

(a)

	Males			Females			Total m + f	Sex index		
	L + B	T + I	Total	L + B	T + I	Total		all cases	L + B	T + I
1943-45	10	9	19	3	12	15	34	56%	77%	43%
1946-48	14	8	22	4	16	20	42	52%	78%	33%
1949-51	10	12	22	10	13	23	45	49%	50%	48%
1952-54	12	10	22	4	16	20	42	52%	75%	38%
1955-57	7	18	25	6	30	36	61	41%	54%	38%
1958-60	6	5	11	2	3	5	16	69%	75%	63%
1961-63	5	3	8	1	2	3	11	73%	83%	80%
1964-66	1	3	4	3	6	9	13	31%	25%	33%
1967-69	0	2	2	1	0	1	3	67%	—	66%
1970-72	5	1	6	2	7	9	15	40%	71%	46%
1973	1	2	3	1	0	1	1	75%	50%	100%
(b)										
1943-57	53	57	110	27	87	114	224	49%	66%	40%
1958-73	18	16	34	10	18	28	62	55%	64%	47%

Discussion

The leprosy situation between 1943 and 1957 is best represented by the data of the period between 1955 and 1957 when surveys had been completed and all new cases were registered in an early stage of the disease.

If it is taken into account that in the previous years some tuberculoid patients had died and that in others with a mild selfhealing form of tuberculoid leprosy, e.g. a single superficial lesion, the diagnosis could no longer be confirmed during the surveys, the data show that the incidence of leprosy had been rather stable in these 15 years. The epidemiological pattern is not compatible with a recent epidemic of leprosy. Epidemics of leprosy are characterized by a very low type rate, a low child index, and a rather even distribution of cases in the community. Epidemics have exclusively been found in areas with a very low tuberculin index. Of 224 patients registered in the period 1943-1957, 65 were lepromatous, a type index of 29%. Out of the 224 patients, in 86 (38%) the disease started before the age of 15. The disease was found to be markedly focalized into particular families in the community.

Tuberculosis is highly endemic in Wandamen Bay. In a tuberculin survey carried out in 1957, 15% of the 0-9 years old children, 51% of the age group 10-19 years, and 78% of the adults showed a positive Mantoux reaction to 5-TU PPD. The sudden decline in incidence in the period between 1958 and 1960 therefore cannot be explained by a "natural decline" following an epidemic of leprosy. Segregation has been practised. In the period before 1952 only a fairly small proportion of the bacteriologically positive patients were to some extent segregated. In the period between 1952 and 1957 the number of segregated patients increased gradually, but only in the last few years a very high proportion of the bacteriologically positive patients were segregated soon after the diagnosis had been made. Even then segregation was far from strict. The segregation of patients does not seem to have had a significant effect on the incidence of the disease, which remained remarkably stable in the whole period between 1943 and 1957. Between 1950 and 1952 many bacteriologically positive patients and between 1952 and 1957 the great majority of the bacteriologically positive patients and a high proportion of the nonlepromatous patients were regularly treated with sulphones. In the period of 1955-1957 already a slight decline in the incidence of lepromatous and borderline patients was seen, followed in the next 3-year period by a marked decline in incidence.

If 4-5 years is accepted as the average incubation period of leprosy, the time of decline corresponds with the elimination of sources of infection by chemotherapy. It is believed that the intensive casefinding, treatment and caseholding activities in the period between 1952 and 1957 are the most important factors responsible for the decline. However, in 1957 a very large proportion of the tuberculin negative population were vaccinated with BCG. Table 1 shows that in the period 1958-1960 the average annual incidence of lepromatous and borderline patients as compared with the following 3-year period decreased from 0.17% to 0.10%, a decrease of 41%, but that the incidence of tuberculoid and indeterminate leprosy decreased from 0.62% to 0.10%, a decrease of 84%.

The explanation cannot be that lepromatous leprosy is diagnosed on the average one or a few years later because of the less conspicuous symptoms in the early phase of the disease, because the figures do not change essentially if

the next 3-year period too is taken into account. If treatment should be the only factor responsible for the decline of leprosy one would expect that the decline in e.g. the period 1958-1965 would be about the same in all types of the disease. The much greater decrease in incidence of tuberculoid leprosy as compared with lepromatous leprosy, immediately following the BCG vaccination campaign, therefore indicated that BCG vaccination contributed significantly to the decline of incidence of leprosy by preventing the development of tuberculoid leprosy.

The decline in prevalence continued slowly but steadily, in the period between 1963 and 1969. In the last 3-year period, however, the incidence of tuberculoid as well as lepromatous cases shows an increase again. Also, the average age of onset of the disease, which had shown a marked shift towards higher age groups in the period 1958-1963 as compared with previous years, shows a shift to the lower age groups again in the period 1964-1973, particularly in the last few years. This indicates that leprosy is not being kept under control. Part of the increase may be caused by the return of many emigrants to Wandamen Bay after the administration was taken over by Indonesia.

Among the immigrants were patients who were not on regular treatment when they arrived. Another cause may be that after the medical officer left in 1962 active casefinding and caseholding has diminished and the initiative for reporting for treatment has been left too much to the patients. The present study shows that an intensive casefinding, treatment and caseholding programme may result after about 5-7 years in a very marked decrease in the incidence of leprosy, and that BCG vaccination may contribute significantly to reducing the caseload of mild tuberculoid leprosy. The way towards eradication of the disease however is a very long one, requiring at least the maintenance of a very intensive approach for very long periods and most probably additional measures such as e.g. prophylactic treatment of a whole population or even more effective tools than at present are available.

Notwithstanding the conclusion that leprosy has not been finally controlled in this area, it is however encouraging to learn from this example that with the conventional methods, if conscientiously applied, in a short period of time impressive results can be achieved. The survey of 1973, including bacteriological examination of nontuberculoid patients, has shown that resistance to sulphones has not yet become a problem. No definite cases of sulphone resistance were found. Patients who had been discharged untimely or who had absconded from treatment and had relapsed, still responded to sulphone treatment. The explanation may be that a relatively high dosage of DDS, 600 mg weekly, in most patients given in divided dosages, has been maintained and that the great majority of the bacteriologically positive patients have been treated very regularly. The prolonged success of the scheme after the medical officer had left must be ascribed to the activities of the single auxiliary worker, who carried on with the distribution of DDS and to the initiative of the population who, after a number of years of intensive health education and other control activities, had become very leprosy conscious and cooperative to the extent that most patients spontaneously reported for treatment soon after onset of the first symptoms. At present a few hospital beds only are sufficient for taking care of the complications of the disease. There is, in fact, no longer a need for a special leprosy centre.

The caseload has been reduced sufficiently to enable complete integration of leprosy work into the general medical service. Since the basic general health service is still very weak, however, the objective of the leprosy activities should not be the eradication of the disease but the maintenance of a very low incidence of the disease and the available resources should be primarily used for strengthening the general basic health service.

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Leprosy Endemicity in Bombay: An Assessment Through Surveys of Municipal Schools*

R. GANAPATI,† S. S. NAIK,‡ M. Y. ACHAREKAR§ AND S. S. PADE¶

Acworth Leprosy Hospital, Wadala, Bombay 400 031, India

Leprosy surveys of randomly selected municipal schools in Greater Bombay during 1970-71 revealed the existence of pockets where the endemicity was expected to be high (of the order of 10 per 1000). It became possible to identify these pockets, essentially located in the northern suburbs of the city, by arbitrarily grouping some schools in which a prevalence rate of more than 5 per 1000 was encountered.

This experience led to a second phase of intensive surveys of all the schools situated in 10 such endemic pockets. Results of these surveys form the subject of this presentation. Out of 83,413 children on the rolls, 67,857 (81.4%) were available for examination, among which 733 leprosy cases could be identified. The overall prevalence rate of 10.8 per 1000 has confirmed our impression gained through previous surveys as regards the high endemicity in these localities.

In our opinion intensive surveys of schools located in presumably endemic zones should be given high priority in urban control programmes.

Introduction

The ample evidence available from the records of the Acworth Leprosy Hospital as regards the high endemicity of leprosy in Bombay, and the striking incidence of the disease among children of school age attending the leprosy clinics (Ganapati *et al.*, 1971) prompted large scale leprosy surveys of municipal schools after making the selection of schools by random sampling (Ganapati *et al.*, 1973). While the overall prevalence rate in schools in general was found to be 3 per 1000 we were struck by the existence of groups of schools where the prevalence was much higher than the general prevalence rate. The identification of 10 such "endemic spots", essentially located in the northern suburbs of the city (see map) was possible by arbitrarily grouping schools in which prevalence rates ranging between 5 and 17 per 1000 were encountered. Intensive surveys of all the schools situated

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† Present address: Medical Director, Greater Madras Leprosy Treatment and Health Education Scheme, 29/C Gajapathy Naidu Street, Shenoynagar, Madras 6000 30, S. India.

‡ Research Assistant.

§ Assistant Medical Officer.

¶ Assistant Medical Officer.

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in these localities were deemed necessary to confirm the impression of high endemicity in these areas. The results of these surveys, which were restricted to municipal schools, form the subject of this presentation.

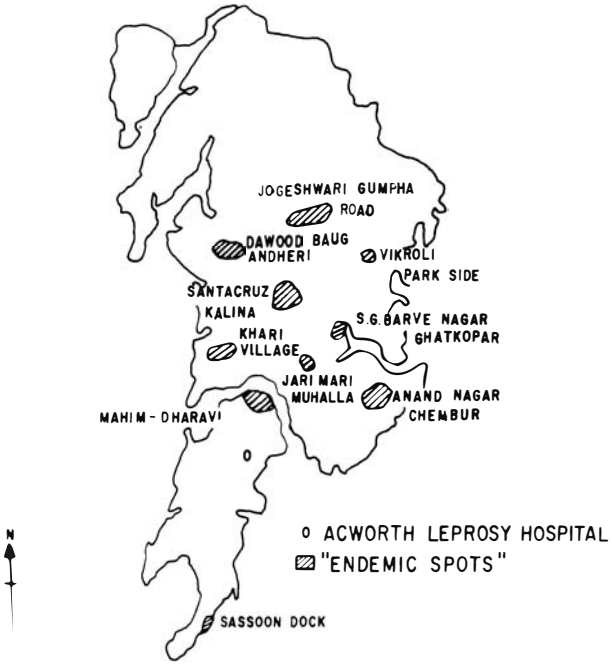

Fig. 1. Map of Greater Bombay showing "endemic spots" detected through school surveys.

Material and Methods

A total of 83,413 children were on the rolls in 148 schools situated in 10 presumably endemic localities. The operational methods of survey and technique of examination and case confirmation, etc. have been detailed in an earlier paper (Ganapati *et al.*, 1973). As in the previous study, the presence of a BCG scar on the deltoid region was noted down, with a view to studying the relation, if any, between the scar and the occurrence of leprosy lesions. Facilities were provided to bring all the suspected as well as diagnosed cases to the clinic of the Acworth Leprosy Hospital for examination and confirmation by senior doctors. While 57.4% of the cases were confirmed in this way, the remaining were examined in the schools by senior workers and the diagnosis confirmed.

Results and Discussion

Table 1 shows the extent of coverage of students in the 10 groups of schools and the prevalence of leprosy in each group.

TABLE 1
Area-wise distribution of cases

No.	Endemic pockets	No. of students on roll	No. of students examined	% covered	Leprosy cases	Cases kept under observation	Prevalence rate per 1000
1	Mahim-Dharavi	11891	9266	77.9	131	26	14.1
2	Khar-khari village	7366	5897	80.0	84	9	14.3
3	Santa Cruz-Kalina	17824	14794	83.0	215	35	14.5
4	Andheri-Dawoodbag/Tata compound	9324	7566	81.0	88	16	11.6
5	Jogeswari-Gumpha Road	13328	10418	78.2	120	16	11.5
6	Kurla-Jarimari Mohalla	2442	1872	76.6	11	2	5.9
7	Chembur-Anandnagar	974	745	76.6	9	1	12.2
8	Ghatkopar-S. G. Barve Nagar	8087	6999	86.5	51	8	7.3
9	Vikhroli-Park side	6717	5530	82.4	11	17	2.0
10	Colaba-Sasson Dock	5460	4770	87.3	13	12	2.7
	Total	83413	67857	81.4	733	142	10.8

Tables 2-4 show the distribution of cases according to age, sex, language groups, etc.

TABLE 2
Age distribution

Age	Number examined	Leprosy cases	Prevalence rate per 1000
5-7	18,555	157	8.4
8-10	26,152	304	11.6
11-13	16,956	193	11.4
14-16	5,461	72	13.2
17-19	682	7	10.3
20-22	51	–	–
Total	67,857	733	10.8

TABLE 3
Sex distribution

Sex	Number examined	Leprosy cases	Prevalence rate per 1000
Male	36,943	453	12.3
Female	30,914	280	9.1
Total	67,857	733	10.8

TABLE 4

Distribution according to language groups

Language	Number of students examined	Cases kept under observation	Leprosy cases	Prevalance rate per 1000
Marathi	40,109	82	453	11.2
Tamil	1,607	5	24	14.9
Gujarati	5,514	7	43	7.8
Telugu	525	2	3	5.7
Hindi	7,770	19	77	9.9
Urudu	9,024	17	86	9.5
Sindhi	14	0	1	-
English	645	3	4	6.2
Kannada	2,649	7	42	15.8
Total	67,857	142	733	10.8

These surveys have revealed an overall prevalance rate of 10.8 per 1000 in the groups of schools situated in the areas referred to and this conforms with the impression gained through our earlier surveys as regards the high endemicity in these localities. Bechelli *et al.* (1973) have correlated the prevalence rates in children and in the total population obtained from studies from various parts of the world and have concluded that the rate found among children 5-14 years old usually reflects the degree of endemicity for planning purposes, as it is easier and less costly to examine school children than other groups. Recent observations in Bombay (Ganapati *et al.*, 1975) from a total population survey of a large closed colony, as well as a survey of schools situated in the same colony, have confirmed the usefulness of such a procedure

The findings of lesser prevalence in the 5-7 year age group as opposed to the maximum prevalence in 14-16 year group (statistically significant: $\chi^2 = 10.06$; $P < 0.005$) and the higher prevalence among male children are similar to our observations in the earlier surveys. As regards the prevalence among various linguistic groups, rates of more than 10 per 1000 were encountered among Marathi, Tamil and Kannada speaking children, Marathi being significantly different from Kannada ($\chi^2 = 4.5, P < 0.05$).

Table 5 shows the relation between the presence or absence of BCG vaccination marks and the number of leprosy cases detected.

As in our previous study, the number of cases in the BCG vaccinated group is less than that in the non-vaccinated group; but unlike our earlier finding, this difference in incidence is highly significant ($\chi^2 = 22.8$ with $P < 0.01$).

TABLE 5

Relation between BCG scars and cases detected

BCG vaccination scar	Number of students examined	Number of leprosy cases	Prevalence rate per 1000
Present	37,669	343	9.0
Not present	30,188	390	12.80
Total	67,857	733	10.80

It was however not possible to obtain data on the vaccination and its relation to the occurrence of lesions, etc.

Out of 733 cases, 715 belonged to the non-lepromatous type. Of the 18 suspected infectious cases 12 could be confirmed to be smear positive by bacteriological examination, the remaining not being available for confirmation. A detailed analysis of the clinical features of these cases will form the subject matter of a future presentation.

The results of this investigation have strengthened our belief that intensive survey of schools located in presumably endemic zones should be given high priority in urban control programmes.

It is suggested that this technique of judging the general prevalence rates through detection of endemic foci after random sample surveys of child population should be applied especially in urban areas where whole population surveys cannot be done easily.

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Leprosy Among School Children in Greater Bombay: Clinical Features

R. GANAPATI,* S. S. NAIK† AND S. S. PANDYA‡

Acworth Leprosy Hospital, Wadala, Bombay 400 031, India

Clinical observations on 1265 cases identified as suffering from leprosy in the course of 4 studies based on surveys covering a total population of nearly 180,000 school children are presented.

94.1% of the cases were of the non-lepromatous type. While 75.3% had early single lesions, 24.7% had either the potential to develop into progressive forms in view of the multiplicity of lesions or were already in an advanced stage of the disease. Polyneuritic leprosy together with intermediate and lepromatous types representing 5.8% of all cases (24 cases were confirmed to be smear positive) belonged to the groups posing therapeutic as well as public health problems. In general the morbidity due to the disease was more marked in children attending municipal schools as compared to private schools.

Analysis of 953 cases with single lesions revealed greater frequency of distribution (58.4%) of patches in parts of the body which are generally covered. It is striking that 26.4% of the solitary lesions was found in the gluteal region and thighs, emphasizing the need for thorough examination of these parts during surveys.

Introduction

This presentation summarises the clinical observations on the large series of leprosy cases detected through school surveys in Greater Bombay during the years 1970 to 1975. The 180,000 children from whom these data are derived represent a significant section of the child population of the city. The surveys reflect not only the extent to which children are exposed to the disease but also the morbidity due to childhood leprosy.

Material

Results of clinical examination of 1265 children identified as suffering from leprosy in the course of 4 studies based on surveys of municipal and private schools were available for analysis. All the cases have been pooled for final assessment. The details of various groups of child population surveyed and the prevalence figures are shown in Table 1.

* Present address: Medical Director, Greater Madras Leprosy Treatment and Health Education Scheme, 29/C Gajapathy Naidu Street, Shenoynagar, Madras 6000 30, S. India.
† Research Assistant
‡ Research Officer, R.R.E. Society.
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TABLE 1

Prevalence rates in the various samples of population

Sample No.	Sample	Child population examined	No. of leprosy cases detected	Prevalence rate per 1000	Reference
I	1. Random sample survey of all municipal schools in Bombay	50,697	152[a]	3.0	
	2. Municipal schools in Dharavi, a known endemic area in Central Bombay	2,932	33	11.3	Ganapati *et al.* (1973)
	3. Municipal and private schools in Abyudaya Nagar, an industrial colony in Central Bombay	10,460	25	2.4	
II	Muncipal schools situated in 10 presumably endemic pockets	67,857	733	10.8	Ganapati *et al.* (1974)
III	Private schools in Andheri, a northern suburb of Bombay	21,508	141	6.5	Pandya *et al.* (1974)
IV	Private schools in Chembur, a northern suburb of Bombay	29,293	181	6.2	Unpublished data
	Total	182,747	1265	6.9	

[a]To the 151 cases reported in the reference cited one case has been added which was a doubtful case under observation, later confirmed as tuberculoid leprosy.

The clinical examination of the children in all these surveys was essentially done by the medical staff from the Acworth Leprosy Hospital, well trained in the out-patient clinic of the hospital. The children were examined in a properly lighted room or in an open space within the premises of the schools, after stripping them to the maximum extent possible. A majority of the cases diagnosed in the field as well as suspected cases attended the hospital clinic for confirmation by senior doctors and for skin smear examination. Remaining cases were registered in the field.

Observations and Comments

The age distribution of 1265 cases (811 males and 454 females) is given in Table 2.

Clinical data in respect of municipal schools (catering almost exclusively to the poorer sections of the community) and private schools are given in Table 3, in which Parts I and II (vide Table 1) represent the findings from the municipal group and Parts III and IV (vide Table 1) those from the private school group.

The non-lepromatous cases have been divided into those with skin manifestations alone and those showing involvement of nerve trunks, since the latter group

TABLE 2

Age (years)	No. of cases	%
5-7	232	18.3
8-10	476	37.6
11-13	363	28.7
14-16	175	13.9
17-21	19	1.5
5-21 years	1265	100

carries a less favourable prognosis. It is seen that 94.3% of the cases were of the non-lepromatous type, the vast majority of them (75.3% of the total) having solitary early lesions of the indeterminate, tuberculoid or maculo-anaesthetic types. Even granting that many such early single lesions may possibly show a tendency to regress spontaneously (Noordeen, 1975, Browne 1975), a significant proportion of cases (24.7%) had either the potential to develop into progressive forms in view of the multiplicity of lesions or were already in an advanced stage of the disease.

Polyneuritic leprosy in an early or advanced stage was encountered in 3%. The higher prevalence of this type in the municipal groups is of concern since these children need careful management to prevent or arrest progressive deformities. It should be noted that polyneuritic leprosy was 3 times more frequent in these children than in those attending private schools. It is also noteworthy that 11 children had primary polyneuritis without any obvious skin lesions and 3 such cases were in the early stages, detectable only by palpation of nerve trunks and careful examination for sensory changes. If, as is all too common, examination for skin patches alone is given importance in leprosy surveys, such cases will be missed. We have grouped intermediate and lepromatous types together as these were suspected on clinical examination to be bacteriologically positive and hence important from the public health point of view. Out of 34 such cases (2.8%) referred for bacteriological examination, only 24 attended the clinic and their

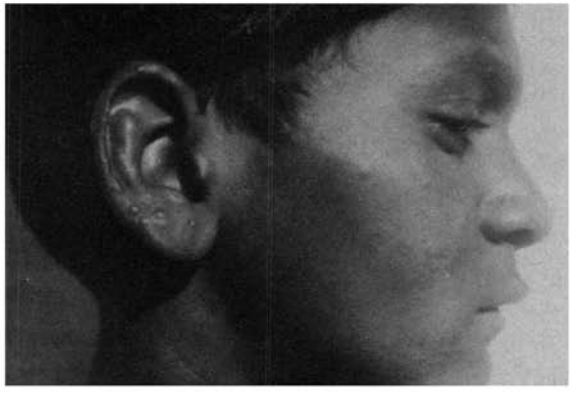

Fig. 1. Moderately advanced lepromatous leprosy in a school child.

skin smears were confirmed to be positive for AFB in all cases. Eight cases showed frank lepromatous features, 5 out of which had moderately advanced (L2) stages of the disease (Fig. 1). It is interesting that in one class in a municipal school, we encountered a pair of twins aged 5 years, suffering from borderline leprosy (smear-positive).

Although borderline and lepromatous types were about 1½ times more frequent in municipal schools than in private schools, it is important to emphasize the presence of previously unrecognized (or misdiagnosed) cases belonging to these types of leprosy even in children whose parents have access to consultant medical opinion. In fact 2 such patients were encountered among the children of well-to-do parents, attending private schools.

Polyneuritic leprosy together with intermediate and lepromatous types, representing 5.8% of all the cases detected, constitute a comparatively difficult group to treat and the infectious cases among them also pose a hazard to contacts.

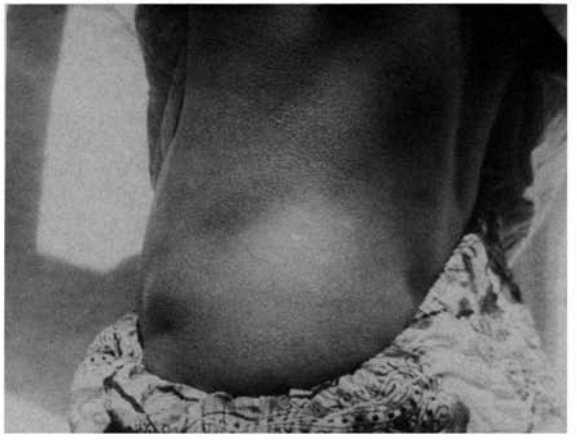

Fig. 2. Leprosy lesion on the loin.

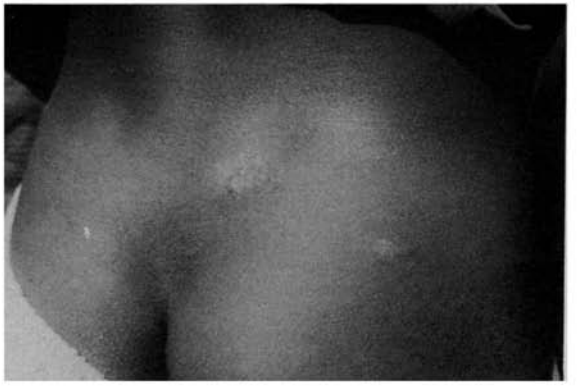

Fig. 3. Leprosy lesions on the waist.

TABLE 3
Clinical details

Sample (vide Table 1)	No. of Cases	Non-lepromatous group								Lepromatous and intermediate (or borderline) groups			
		Without Polyneuritic Involvement				With Polyneuritic Involvement							
		Early	Advanced	Total No.	Total %	Early	Advanced	Total No.	Total %	Early	Advanced	Total No.	Total %
I and II (municipal schools)	943	688	193	881	93.4	20[a]	14[b]	34	3.6	3	25	28[d]	2.9
III and IV (private schools)	322	265	47	312	96.9	2	2	4	1.2	–	6	6	1.9
Total	1265	953	240	1193	94.1	22	16	38	3.0	3	31[c]	34[c]	2.8

[a] 3 cases in this group had primary polyneuritis without skin lesions.
[b] 8 cases in this group had primary polyneuritis without skin lesions.
[c] 24 cases in this group were confirmed to be positive by smear examination. The remaining 10 cases were not available for smear examination.
[d] 8 cases showed frank lepromatous features out of which 5 were in a moderately advanced stage (L2).

TABLE 4

Distribution of single lesions in 953 cases of childhood leprosy

Site of lesion	No.	%
Face and neck		
Cheeks	79	8.3
Forehead	7	0.7
Orbital region	3	0.3
Mandibular and mental regions	24	2.5
Ears	6	0.6
Neck	2	0.2
Total	121	12.6
Trunk		
Upper part of the back (Scapular, infrascapular regions)	73	7.7
Lumbar regions	37	3.9
Chest	17	1.8
Abdomen	26	2.7
Total	153	16.1
Lower limbs		
Thighs	168	17.6
Buttocks	84	8.8
Knees	51	5.4
Legs	41	4.3
Feet	2	0.2
Total	346	36.3
Upper limbs		
Arms	120	12.6
Deltoid region	31	3.2
Elbows	91	9.6
Forearms	67	7.1
Wrist	18	1.9
Hands	6	0.6
Total	333	35.0

TABLE 5

Distribution of single lesions on covered and uncovered parts

Site of lesion	No.	%
Covered parts		
Chest and back Abdomen and lumbar regions	153	16.1
Shoulders and arms	151	15.8
Thighs	168	17.6
Gluteal region	84	8.8
Total	556	58.3
Uncovered parts		
Face and neck	121	12.6
Elbows	91	9.6
Forearms and hands	91	9.6
Knees	51	5.4
Legs	43	4.5
Total	397	41.7

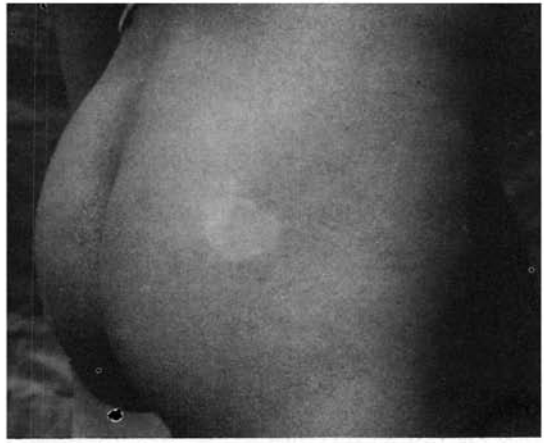

Fig. 4. Leprosy lesion on the buttock.

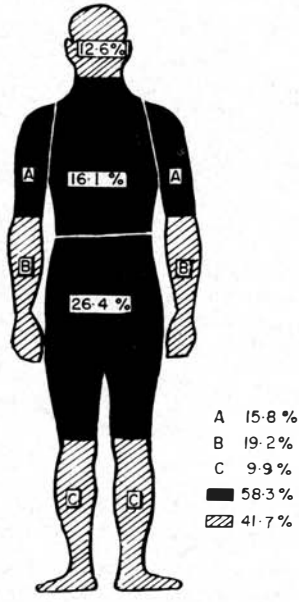

Fig. 5. Distribution of single lesions.

An earlier analysis (Ganapati *et al.*, 1971) of 1000 children attending clinics showed that this group formed 31.3%. The difference is attributable to the fact that the survey sample comprises a large number of children whose disease was diagnosed at a very early stage. This proves the advantage of detecting the vulnerable groups through surveys before they pass on to a stage likely to pose therapeutic as well as public health problems.

SINGLE LESIONS

The data obtained from these surveys are admirably suited for analysis from the point of view of occurrence of first lesions in the body in view of the large number of children (953 cases) exhibiting single lesions. Analysis of this nature has been done by a few authors in the past to find out whether the cutaneous distribution of lesions supports the theory that the portal of entry of *M. leprae* is the skin.

Table 4 shows the distribution of single lesions in various parts of the body:

In Table 5 and Fig. 5 we have attempted to split up the data into two groups, (viz) the lesions noticed in the generally covered parts, i.e., trunk, shoulders, arms, gluteal regions and thighs, and those seen in mostly uncovered areas of the body, i.e. face, elbows, forearms, hands, knees and legs.

The early lesions are seen to a greater extent in the generally covered parts. If such lesions were to have developed at the point of entry of *M. leprae*, one would have expected greater frequency of occurrence in the exposed parts of the body. Our findings are in line with those of Bechelli *et al.* (1973), who made their observation on single lesions in 469 children in Burma. Bedi *et al.* (1975) however, were able to establish a correlation between the clothing pattern and the distribution of single tuberculoid lesions in adults.

Apart from the credibility of the inference from such studies on the portal of entry of the organism, one cannot but be struck by the significant proportion of cases (252 out of 953 or 26.4%) with solitary lesions on the gluteal regions and the thighs. The importance of careful examination of these parts of the body cannot be over-emphasized. Lesions have come to light in several instances by stripping the child to expose the waist and upper parts of the buttocks properly (Figs 2, 3 and 4).

Acknowledgement

The surveys were conducted by the following institutions and we thank the respective authorities for permission granted to make use of the data for clinical analysis: Acworth Leprosy Hospital, Wadala, Bombay 31; Acworth Leprosy Hospital, Society for Research, Rehabilitation and Education in Leprosy, Wadala, Bombay 31; Maharashtra Lokahita Samithi, Santa Cruz, Bombay 54.

Part IV (vide, Table 1) of the survey was possible through the kind donation from the Rotary Club Chembur, Bombay.

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News and Notes

BCG VACCINATION

A recent Editorial in the British Medical Journal (13.12.75) quotes interesting information regarding the BCG campaign against tuberculosis in Britain. Over 9 million BCG vaccinations have been carried out. The risk of tuberculosis infection in Britain is halving every 5 years. The 100,000 BCG vaccinations of school children in 1966-71 prevented an estimated 15 notifications of persons aged 15 to 19 in 1973. It is estimated that one notification would be prevented by 750 vaccinations in 1968, by 1500 vaccinations in 1973, by 3000 vaccinations in 1978 and by 5000 to 10,000 vaccinations in the 1980's. The need for the continued large scale use of BCG is rightly questioned.

These figures will be of interest to leprosy workers. The undoubted contribution of BCG towards reducing the incidence of all forms of tuberculosis to a very low level gives some indication of what we may hope from a corresponding vaccine in leprosy. The appearance of this may be delayed. Meanwhile tuberculosis remains a serious problem in most countries where leprosy is endemic, and while encouraging the widest use of BCG, leprosy workers at the same time will be able to learn much from the experience of our colleagues in tuberculosis control.

PSYCHOSOCIAL FACTORS AND HEALTH

Leprosy workers will find encouragement in the WHO Press Release WHO/8 of 26 January 1976, which includes the following:

Many serious health problems are strongly influenced by psychosocial factors, such as the individual's behaviour. It is also being increasingly realized that these factors determine to a large extent the success of health efforts or social action.

This was recognized by the WHO Executive Board in a recommendation to the World Health Assembly that WHO implement a programme in the field of psychosocial factors and their effects on health. Dr T. Adeoye Lambo, Deputy Director-General of WHO, presenting the programme, stressed that psychosocial factors are of essential importance in the resolution of major public health problems. He said: "Technology alone is not enough to improve health; it can often create a social barrier between the health worker and the people he serves ... WHO is seeking ways of reducing the discord between man's psychological, social and cultural needs, and the technological facts of his environment."

The first objective of the new programme is to apply existing knowledge in the psychosocial field to improve health care, particularly for those most in need; the second, to develop methods in collaboration with countries, so that relevant psychosocial information can be made available to health planners; and the third, to acquire new knowledge on which health action can be based, particularly concerning the needs of uprooted people and changes in family functioning under conditions of rapid social change.

URBAN LEPROSY CONTROL IN INDIA

Another city in India has become the scene of an intensive cooperative programme against leprosy. In April 1975 the Poona District Leprosy Committee were able to launch such a programme with financial assistance from the Leprosy Relief Association of West Germany and Emmaus Suisse.

The main objective of the project is to offer efficient treatment to the maximum number of leprosy cases in the greater Pona area through a chain of out-patient clinics and a mobile clinic. Hospital care, whenever necessary, will be provided through the Dr Bandorawalla Leprosy Hospital. A case finding programme has been launched through surveys of slums and schools up to Higher Secondary level. There are about 250 slum areas in the project area comprising a population of over 150,000. The 110 High Schools and over 300 primary schools have a total enrolment of about 200,000. Both these groups have been selected for total coverage.

Health education will constitute an important activity to cover such population groups as are not covered by surveys. The work done so far reveals that about 8 to 10 per thousand persons in slum areas and about 3 to 4 per thousand school children suffer from leprosy. Further information is available from Dr J. M. Mehta, Hon. President, Poona District Leprosy Committee, 593/2 Rasta Path, Poona 411 011 Maharashtra, India.

INTERNATIONAL ASSOCIATION OF THE FRIENDS OF DR AUJOULAT

At a meeting held in Paris on 8 November, 1975, and attended by 62 people, representing 22 countries, the *Association Internationale des Amis du Docteur Ajuoulat* was founded. Those present were a cross-section of the many interests of Dr Louis-Paul Aujoulat during his long and extremely fruitful life: doctors from France and francophile countries of Africa; high-ranking French diplomats and Ministers of State from many African countries; leaders in health education activities; the Church; and those engaged in the leprosy campaign, from France itself and from the Medical Commission of ILEP.

An international Executive Committee was elected, which includes four members of the Medical Commission of ILEP (Drs Browne, Lechat, Richet and Wegener). The President is Monsieur Raoul Follereau. The Committeewill draw up plans for perpetuating the memory of Dr Aujoulat, who died on 2 December, 1973. This remarkable man–doctor, diplomat, writer, counsellor–was held in the highest esteem in French-speaking medical circles throughout the world. He exerted an influence second to none on the health policies and programmes of the French colonies in Africa and Asia and America as they became transformed into independent countries that continued to look to France for medical expertise and financial help.

As Chairman of the Medical Commission of ELEP from 1968 till 1971, he brought his vast and intimate knowledge of the health problems of the francophone countries, to bear on the programmes of the his vast and intimate knowledge of the health problems of the francophile countries, to bear on the programmes of the Dr Aujoulat, in which leprosy will doubtless have a prominent place.

DR ELEANOR E. STORRS

Dr Eleanor E. Storrs Director of the Department of Comparative Biochemistry of Gulf South Research Institute, New Iberia, Louisiana, was presented the Griffin Award of the American Association for Laboratory Animal Science at the annual meeting of the Association which was held in Boston the week of November 17. The award cites Dr Storrs for outstanding accomplishments in the improvement of the care and quality of animals used in medical and biologic research. She has specialized in the development of the armadillo for studies on leprosy and other biomedical research. In May of 1975, Dr Storrs was presented the Distinguished Alumni Award of the University of Connecticut, and received Special Recognition from Gerard B. Lambert Awards for the discovery of the nine-banded armadillo as a model for the study of leprosy. Dr Storrs was also recently awarded a grant of $50,000 from the Estate of Mrs Esther H. Woodward by the National Executive Council of the Protestant Episcopal Church in support of her research on the armadillo.

XVIII INTERNATIONAL COURSE IN LEPROLOGY AT FONTILLES

The 18th International Course in Leprology for medical auxiliaries has been planned at the Fontilles Sanatorium, Spain, from 13th September to 9th October, 1976. Further information may be obtained from Dr J. Terencio de las Aguas, the Director of the Sanatorium.

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Leprosy and the Community

The World Health Organisation and Leprosy

The inclusion of leprosy in the World Health Organisation Special Programme for Research and Training in Tropical Diseases is a major event in the history of leprosy control and eradication. We are happy to reprint here, with the special permission of WHO, relevant extracts from the Strategy document, including the Summary Report of the First Meeting of IMMLEP, describing the foundation of the leprosy vaccine task force.

LEPROSY

3.1 *Magnitude of the Problem*

Leprosy is a public health problem in more than 70 countries, mostly developing ones. Some 11-12 million cases of leprosy are estimated to exist in the world, with little fluctuation over the past 15 years. In Africa, the estimated number of cases is about 4 million, with more than one million disabled patients. Strong prejudice against leprosy, the long duration of the disease, as well as the frequency of disabilities and their steady aggravation create special problems not found with other communicable diseases.

3.2 *Reasons for Inclusion in the Special Programme*

(a) Need for a specific vaccine (BCG cannot be recommended).
(b) Need for improved methods for the detection of the disease, particularly of its contagious forms in the pre-clinical phase.
(c) Need for improved chemotherapy of established cases. Dapsone, introduced some 30 years ago, is still the drug of choice. It is cheap and well-established, but its action is slow, relapses are frequent in the severe (lepromatous) forms, and resistant strains of *M. leprae* have been demonstrated. No satisfactory alternative drug for mass treatment is at present available.

3.3 *Priorities for Research*

3.3.1 *Short-term* (up to 5 years)

(a) Development of a simple skin test permitting the identification of individuals at high risk of developing the disease, particularly in its severe infectious form.
(b) Development of a more active drug, or combination of drugs, for treatment (including animal screening and short-term trials in man).
(c) Study of the biochemical requirements of *M. leprae,* with a view to achieve mass *in vitro* cultivation of the pathogen.

3.3.2 *Long-term* (over 5 years)

(a) Confirmation of the possible therapeutic effect of new drugs in long-term trials in man.

(b) Development of a vaccine for the prevention of leprosy.

The developments referred to above under 3.3.1 (a) and 3.3.2 (b) can now be envisaged with some reasonable chance of success, mainly because of the availability of large amounts of bacilli from armadillo tissues.

APPENDIX

Summary Report of IMMLEP*

A pure, specific antigen from *M. leprae* would be of inestimable value as a diagnostic and epidemiological tool, as an immunological reagent for incorporation into a vaccine, and as a therapeutic weapon that could perhaps be used to prevent some of the most adverse of the immunological consequences of leprosy, or to restore a state of natural resistance to patients cured of lepromatous leprosy but still at risk of relapse.

Certain logical steps can now be taken towards these goals because of the major contribution made by Kirchheimer and Storrs when they demonstrated that an abundant supply of *M. leprae* could be had from tissues of infected armadillos. Moreover, their generosity in supplying others with infected tissues has permitted the critical first steps to be taken to recover *M. leprae* in preparation for the more exacting task of fractionating the bacillus and purifying its antigenic components. The job of separating the many irrelevant antigens of *M. leprae* from those of diagnostic, immunoprophylactic and therapeutic importance has begun; and from it has come an early indication of what it means to have unprecedented amounts of *M. leprae* with which to plan a concerted attack on this ancient disease.

It was agreed that a plan for developing anti-leprosy tools would have the best chance of success if programmed and implemented in collaboration with the WHO Immunology and Leprosy units and several laboratories and centres in different countries under the Special Programme for Research and Training in Tropical Diseases.

The accompanying chart (the Strategic Plan) depicts a carefully considered approach to the problem of using immunological methods for the control and treatment of leprosy. It can be seen that certain problems must be solved in a logical sequence. For this reason, some aspects of the plan need special emphasis. The first priority is to secure an adequate supply of *M. leprae* from infected armadillos. This is a *sine qua non,* for every phase of the IMMLEP project depends upon the uninterrupted flow of bacilli for the purification, fractionation and antigenic analysis involved in creating the immunological reagents that will be needed at every step of the undertaking.

The rest of the plan, as outlined in the protocols, does not represent merely progression from one problem to the next, since many aspects of the plan can be undertaken concurrently once the supply of *M. leprae* begins to flow. Thus, those charged with responsibility for characterizing the organism antigenically will be preoccupied with its antigenic profile while others are seeking to place *M. leprae* in its proper relation to other mycobacterial species for reasons that are stated

* These plans form the foundation of the leprosy vaccine task force.

elsewhere. At the same time, still other participants in the project will be engaged on the equally important objective of learning how to potentiate the immune response to *M. leprae* and its constituent antigens in ways best calculated to induce resistance. It is not possible to give assurances, however, that an effective vaccine will emerge from all this effort, but there is ample precedent for believing that adjuvants selected for their capacity to modulate the immune response to tumour-associated antigens can do as much and more to enhance the immune response to *M. leprae,* as they have been shown to do with other infectious agents.

There is less uncertainty about other benefit that will soon materialize—a specific skin-test antigen which can provide valuable information. Firstly in the epidemiological field; secondly as an important adjunct to immunological studies; and thirdly in the planning of a vaccination trial and as a preliminary parameter for the measurement of its success.

The protocols, with their crude estimates of cost, provide only a forward-thinking sketch of anticipated problems and suggested solutions. They do, however, open the door to many questions that have engaged the interest of frustrated leprologists for many years. The prospect of analyzing with new-found precision the nature of the defect in lepromatous leprosy, or of devising a rational means of controlling the damage done to nerves in tuberculoid leprosy, are striking examples of the less obvious advantages that deeper immunological insight will bring to the management of this disease.

If the fruits of IMMLEP could be foreseen, the projected costs might seem extremely small. But even in ignorance they are still not large in comparison with what has often been spent on less promising projects. A relatively small investment is needed, however, to bolster budgets that are already committed to one or other aspect of the project by a number of interested agencies. Costs are likely to increase as the project advances, but they will grow only in proportion to its success.

Members of the IMMLEP Task Force at its First Meeting, November 1974

Dr B. R. BLOOM, Albert Einstein College of Medicine, *Bronx,* New York 10461, USA.
Dr J. CONVIT, Institute Nacional de Dermatologia, Apartado Postal 4043, *Caracas,* Venezuela.
Dr T. GODAL, The Norwegian Radium Hospital, Montebello, *Oslo 3,* Norway.
Dr H. C. GOODMAN, Chief, Immunology, WHO, *Geneva,* Switzerland.
Dr M. HARBOE, Institute for Experimental Medical Research, Ulleval Hospital, *Oslo 1,* Norway.
Dr W. S. KIRCHHEIMER, Laboratory Research Branch, United States Public Health Service Hospital, *Carville,* Louisiana 70721, USA.
Dr G. KRONVALL, Armauer Hansen Research Institute, P.O. Box 1005, *Addis Ababa,* Ethiopia.
Dr G. LAVOIPIERRE, Special Programme for Research and Training in Tropical Diseases, WHO, *Geneva,* Switzerland.
Dr G. B. MACKANESS, Trudeau Institute Inc., P.O. Box 59, *Saranac Lake,* New York 12983, USA.
Dr R. J. W. REES, Medical Research Council, National Institute for Medical Research, *London NW7 1AA,* England.
Dr H. SANSARRICQ, Chief, Leprosy, WHO, *Geneva,* Switzerland.
Dr C. C. SHEPARD, Leprosy and Rickettsial Branch, Virology Division, Center for Disease Control, *Atlanta,* Georgia 30333, USA.
Dr J. L. STANFORD, School of Pathology, Middlesex Hospital Medical School, *London W1P 7LD,* England.
Dr G. TORRIGIANI, Medical Officer, Immunology, WHO, *Geneva,* Switzerland. (Secretary).

Dr G. P. WALSH, Gulf South Research Institute, P.O. Box 1177, *New Iberia,* Louisiana 70560, USA.
Dr J. WALTER, Medical Officer, Leprosy, WHO, *Geneva,* Switzerland.

First Meeting of IMMLEP Task Force

List of Protocols

Number	*Title*
1	Supply of *M. leprae* from the armadillo
2	Purification of *M. leprae* from tissues
3	Antigen fractionation of *M. leprae*
4	Taxonomic studies
5	Induction of cell-mediated immunity to *M. leprae*
6	Resistance to experimental infection
7	Immunopathology
8	Sensitization of human volunteers
9	Development and trial of a specific soluble antigen for skin testing
10	Preliminary considerations for a vaccine field trial

Erratum

As the result of a printing error the author of the article "Death and Rebirth of a Leprosy Service" on page 69 of *Leprosy Review* Vol. 47 No. 1 wrongly appears as Richard C. Browne. The author was Dr Richard C. Brown, and we apologise for any inconvenience caused to him.

ASSESSMENT OF EFFORTS TO INDUCE MEDICAL PRACTITIONERS TO PARTICIPATE IN URBAN LEPROSY CONTROL PROGRAMMES*

M. S. NILAKANTA RAO†

The cooperation of private practitioners in the urban leprosy control programme in India is considered essential. Doctors are subject to the inhibitions and prejudices of the general population. Methods adopted to encourage the participation of doctors are described. An individual approach, the provision of literature, and in particular, refresher courses have been shown to lead to changes in attitude, while informal group meetings have also proved helpful.

The urban leprosy control programme differs in approach, though not in aim, from the leprosy control programme in rural areas, mainly because the people are more educated and the environment more sophisticated. The social structure is such that the privacy of the family is something that cannot be violated, and any measures to bring about leprosy relief or change in attitudes must be designed against this background.

When the Gandhi Memorial Leprosy Foundation introduced health education on an experimental basis in 1961 its prerequisites and objectives were in tune with the social psychology of the urban community. The objectives were to make people aware of leprosy, suspect it in the early stages, consult the family physician and take treatment if necessary.

While the whole community was our concern, there were two groups in it which we felt had to be tackled as a priority. The first consisted of school teachers, a large, homogeneous and highly relevant group. The second consisted of the doctors, also a priority group because they were directly concerned with the health of the community, and it is to the family physician that most people in cities go with their medical complaints.

If doctors participated in the leprosy control programme there would be distinct advantages:

1. Patients would not normally hesitate to go to their family physician because this would not reveal their identity as leprosy patients.
2. This would avoid problems created by ostracism and fear.
3. Many patients who would otherwise have remained undetected and untreated would be put on treatment.

There are more than 100,000 doctors working in leprosy endemic areas in India. If each doctor treated 10 cases of leprosy, 1 million patients, or nearly one third of the estimated total of leprosy sufferers in India, would get the benefit. Not only this, but the quantum of infection in the community would correspondingly be reduced.

* Paper read at the Indian Association of Leprologists Seminar held at Bombay on 29 and 30 November 1974.

† Director (Honorary), Gandhi Memorial Leprosy Foundation, Wardha, Maharashtra, India.

Personal Approach

The method adopted to enlist the cooperation of doctors was to approach each doctor individually, and try to convince him of the need and importance of his participation in leprosy work as part of his routine medical practice. It soon became apparent that doctors had certain inhibitions regarding the diagnosis and treatment of leprosy patients. At one stage of our health education campaign we asked people to approach their family physician if they saw signs simulating leprosy on their bodies. Naturally, these persons expected their doctor to be as competent to treat leprosy as he was with their other ailments. The doctor's dilemma was that although he had some theoretical knowledge of leprosy, he did not feel confident enough to say whether a patient was or was not suffering from the disease. Another predicament was that if he labelled the case as leprosy, the patient might suffer from psychological trauma. In order to escape from this embarrassing situation, many doctors who were contacted by the Foundation suggested that if the Foundation brought out some handy literature and arranged refresher courses on leprosy, they would welcome it. They expected answers to their problems to be elicited during refresher courses.

Literature

As a result of the first suggestion the Foundation brought out a booklet entitled *Hints on Diagnosis and Treatment of Leprosy*. At about the same time the Foundation also prepared a film, suitable for medical and paramedical groups with the title *Diagnosis of Leprosy*. Both the booklet and the film turned out to be very useful.

Refresher Courses

The Foundation then worked out a methodology for organizing refresher courses. The Paramedical Officer of the Foundation would visit a town and make a complete list of the doctors with the help of the local Secretary of the Indian Medical Association. The doctors were then approached through 3 letters. The first gave the doctor an idea of the leprosy problem in India and the need for his participation; the second gave information regarding refresher courses; the third letter in the series requested a personal interview with the doctor. Then in consultation with the doctors and the Secretary of the Indian Medical Association refresher courses would be organized. Originally the course consisted of four lectures each of 1½ hours' duration and spread over a period of 4 days. Later on the course was condensed to 2 days to suit the convenience of doctors.

The Foundation has so far conducted 83 refresher courses for 2810 doctors in six States. Details are on opposite page.

Evaluation of Refresher Courses

We sought to assess the usefulness of these refresher courses by sending questionnaires to doctors in two places, Midnapur and Poona. The first information sought was, how many persons came to the doctor with suspicious skin lesions during the previous 2 years; it was not how many cases did he detect among his clientele. The letter was sent to 50 doctors at Midnapur, of whom only

Refresher courses

Name of unit	Number of courses	Doctors attending
Poona (Maharashtra)	20	905
Midnapur (West Bengal)	31	748
Khurda Road (Orissa)	10	342
Kottyam (Kerala)	13	365
Wardha (Maharashtra)	2	76
Dharwar (Karnataka)	4	218
Tiruchirapalli	3	156

9 responded by giving information. Eight doctors out of the 9 who responded were approached by their clientele for diagnosis of suspicious lesions. At Poona, according to the answers we received, 11 out of 23 doctors were approached by their clientele for diagnosis of suspicious lesions. The overall impression gained by this method of analysis was that the questionnaire method was unsatisfactory for the purpose of evaluation. All the same some encouraging trends in changes of attitude among doctors could be discerned.

Analysis by Social Scientist

At our request a social scientist of Poona University undertook an analysis of the results of refresher courses held at Poona. This step was taken because however much we may try to be objective in our self-evaluation, we are likely to be very biased because of our own involvement.

The social scientist undertook his study at two comparable towns, namely Poona and Jalgaon. At Poona refresher courses had been conducted. At Jalgaon no refresher courses had been conducted. The sample was selected by a statistician by the method of stratified random sampling without replacement. The universe in Poona consisted of 475 doctors who had attended the refresher courses. In Jalgaon the entire medical population was taken as the universe. In each town 47 doctors were selected. The doctors from both towns had graduated from medical colleges where the teaching of leprosy had been similar. Both groups had been exposed to the same information regarding leprosy through medical journals, the press and other sources. Further details are as follows

	Poona	Jalgaon
Doctors selected at random	47	47
Male	40	39
MB BS	17	12
Post Graduate Diploma and Degree	23	22
General practitioners	87.2%	74.4%

The main points of similarity were:

(i) The samples showed a preponderance of degree holders in both towns
(ii) At both places there was a preponderance of general practitioners in the sample.

INSTRUMENT OF EVALUATION RESEARCH

The interview schedule was designed and used with a view to test awareness of the facts of leprosy, to note the prejudices, practices and opinion about leprosy. The schedule was not designed to test the knowledge of the doctor.

The results of the enquiry are interesting.

(i) At both places the doctors examine suspicious skin lesions for leprosy, 74% in Poona, 76% in Jalgaon. In Poona this may be due at least in part to refresher courses (and health education). In Jalgaon this may be due to the proximity of the town to leprosy centres at Amraoti and Wardha, whose influence cannot be ruled out.

(ii) In Pona 81% of patients are treated openly, as against 45% in Jalgaon, where they are treated confidentially.

(iii) In Poona more patients are treated in private dispensaries and less are referred to skin specialists as compared with Jalgaon.

(iv) 21% of doctors at Jalgaon feel that the disease will spread to others if patients are treated at their clinics, as compared with 0.5% at Poona.

(v) 25% of doctors at Jalgaon believe that all leprosy patients should be sent to leprosy colonies in order to check the disease, as compared with 4.4% in Poona.

(vi) At both places doctors were of the opinion that refresher courses in leprosy are essential.

The social scientist commented that he could not ask technical questions for obvious reasons, even though he was aware of areas of ignorance and prejudice. "Moreover there are no universal truths available in leprosy" he adds.

It becomes clear that health education has a definite impact in changing the outlook of doctors on leprosy. It may be commented that in stating this health education has been equated with refresher courses. It must however be understood that preceding the refresher course the Paramedical Officer had spoken to the concerned doctors a number of times, and this was also true subsequently to the refresher course. Thus the refresher course was a part of the educative process.

Those medical men who have been exposed to health education and have undergone a change in attitude in consequence definitely assist in urban leprosy control work. It cannot be surmised at this stage to what extent their cooperation will influence leprosy control. This is material for further assessment in the years ahead.

In terms of cost, it may be mentioned that on an average the cost per doctor attending refresher courses is around Rs 40/- (*c.* £2). This includes expenses incurred by the Paramedical Officer in organizing the refresher courses and those incurred in sending a leprologist from Wardha to conduct the courses.

Group Meetings

The Foundation has conducted a large number of group meetings for doctors. These are on opposite page.

These are not refresher courses in the sense that the subject was not covered according to a pre-determined method. The subject was nevertheless covered in all its essentials, including the projection of slides and wherever possible showing the film *Diagnosis of Leprosy* in the time that was available. Such gatherings were subjected to post-lecture analysis by the speaker and the Paramedical Officer who

Group meetings for doctors

Unit	No. of meetings	Attendance	
		Doctors	Students
Poona	44	1333	395
Midnapur	20	655	–
Khurda Road	16	295	1010
Kottyam	9	149	294
Wardha	6	168	–
Bardoli	28	985	3550
Dharwar	5	101	–

organized the group. The criterion to determine whether a group meeting had been successful or not was the number and range of questions put to the speaker at the end of his talk. By that criterion the impression gained was that such gatherings were beneficial. A number of the doctors who attended such group meetings were practitioners from rural areas.

Book Review

Leprosy, Diagnosis and Management, by Dr C. K. Job, Dr A. J. Selvapandian and Dr P. V. Kurian. pp 92 with 16 pages of illustrations. Published by Hind Kusht Nivaran Sangh, 1 Red Cross Road, New Delhi 110001, India.

This book, written by distinguish Indian leprologists, is directed to general practitioners and senior students of medicine who may encounter leprosy in their practice. It follows an earlier edition of lecture notes given over 15 years, circulated privately and quickly exhausted.

While essential information on all aspects of leprosy is included, the book concentrates its 92 pages, as its title suggests, on clinical features, diagnosis and classification (25 pages) and management (52 pages). It contains many valuable features. Against the background of leprosy as seen in India it is not surprising that nerve damage and its resultant disabilities, their prevention and correction receive detailed attention. This is entirely as it should be, and the chapters concerned will appeal to a wide audience. The chapters on medical management are well written and up to date. Eye complications are the subject of a chapter on their own. There is a valuable chapter on occupational therapy, written by Miss D. Hopkins.

Nilakanta Rao has estimated that there are 100,000 doctors working in areas of India where leprosy is endemic. For many of them a separate textbook on leprosy would need to be clear, concise and inexpensive. This last requirement has limited the illustrations which on the face of it seem rather unbalanced. While photographs and diagrams relating to disability and its care total 32, entirely justifiably, those illustrating the skin lesions of leprosy total 5, not of top quality. It is a moot point whether the small increase in price needed to include a more comprehensive selection of clinical photographs would not fully have justified itself.

The leprologist might raise other issues, e.g. the use of the "Indian" version of the Bacterial Index (maximum figure 4) but the omission of the Indian classification with its Maculoan-aesthetic type of leprosy. These are perhaps academic questions for the reader for whom the book is intended, and who is not a leprologist, but nevertheless these could be considered weaknesses capable of adjustment, along with printing errors, in a later edition. All the same this book meets a real need both in India and wider afield, and at the price of Rs 10/- (50p) paperback, it is excellent value. There is also a hardback edition.

T. F. DAVEY

Lepr. Rev. (1976) **47**, 157-166

Abstracts

MICROBIOLOGY

1. BERGEL, M. Reproducción del *Mycobacterium leprae* inoculado a ratas alimentadas con carne vacuna en estado de putrefacción. **[Multiplication of *Mycobacterium leprae* in rats fed on meat in a state of putrefaction.]** *Revta Lat.-am. Microbiol.,* 1975, v. 17, No. 1, 5-8. English summary.

A group of 12 rats was fed on a standard rodent diet, which consisted of pellets of dehydrated green vegetables; a group of 18 were fed on beef muscle, bought daily at the local market, which had been kept at room temperature for 48 hours and in which the smell of putrefaction was noticeable. After 30 days on these diets, the animals were inoculated in the plantar pad of the right foot with 0.1 ml of a fresh suspension of *Mycobacterium leprae* taken from the leproma of an untreated patient with leprosy. Diets were continued for 7 months. Throughout the experimental period the test animals showed deterioration in their general condition and mortality was greater than in the control group. All the surviving animals (9 in the control and 11 in the test group) were killed 9 months after inoculation. In the control group 5 had 0-0.04 million bacilli per pad, 2 had 0.04-0.2, 1 had 0.2-0.5, 1 had 0.5-1; in the test group 1 had 0.2-0.5, 2 had 0.5-1, 1 had 1-2, 3 had 2-5 and 4 had over 5 million bacilli. This difference was statistically significant.

A diet of putrefied meat closely resembles that on which rats normally feed. Such meats would include amines, such as putrescein, which are known to favour the growth of *M. leprae.* Experimentally BERGEL (*Acta Leprologica,* 1967, Jan., 5) found that necrotic tissue favoured *M. leprae* growth, whereas other authors consider putrescein or tetramethylenediamine may be a *M. leprae* metabolite.

E. Agius

2. FIELDSTEEL, A. H. & GARTNER, S. **Effect of thymectomy and anti-lymphocyte serum on *Mycobacterium leprae* infection in mice.** *Infection & Immunity,* 1975, v. 12, No. 4, 733-737.

"BALB/c mice thymectomized at 3 to 5 days of age were studied to determine if this procedure would result in enhanced susceptibility to infection with *Mycobacterium leprae* and, if so, whether or not administration of antilymphocyte serum would further increase this susceptibility. The plateau for growth in the footpads of intact mice occurred 4 months after inoculation, whereas in the thymectomized and thymectomized plus antilymphocyte serum-treated groups the plateau occured between months 11 and 12 after inoculation. Thymectomy resulted in at least a 10-fold increase in the number of *M. leprae* found in the footpads. Antilymphocyte serum did not appear to further enhance the *M. leprae* infection in the thymectomized mice. Although growth of *M. leprae* in the testes of both intact and thymectomized mice was erratic, the number of organisms reached a higher ceiling in the thymectomized groups. *M. leprae* harvested from all groups was passaged into intact mice at various intervals after inoculation to test for viability. Viable *M. leprae* were found at all intervals tested including 22 months after infection in the intact mice, suggesting that a chronic infection occurred that probably lasted during the entire life of the animals."

3. PATTYN, S. R. & VERDOOLAEGHE-VAN LOO, G. **Effect of quinacrine, chloroquine and primaquine on the multiplication of *Mycobacterium leprae* in mice.** *Int. J. Lepr.,* 1975, v. 43, No. 1, 14-15.

"Quinacrine administered at 100 mg per kg body weight to mice had a bacteriostatic activity on *M. leprae* in the mouse, chloroquine at 15 mg per kg and primaquine at 0.25 mg per kg were without activity. These findings could point to the presence of a functioning direct oxidative pathway of glucose catabolism in *M. leprae.*"

4. OLITZKI, A. L. & MULLER, S. **Further investigations on *M. leprae*. Growth promotion and inhibition by organic substances and observations on antagonistic and synergistic effects.** *Boll. Ist. Sieroter. Milan,* 1975, v. 54, No. 1, 5-12.

"The multiplication of 2 strains of *M. leprae* on a medium containing a sonic extract (SE), prepared from *M. smegmatis,* was promoted by cysteine, tryptophane and dimethylsulfoxide (DMSO), while glutamic acid, glutamine and histidine exerted variable effects. The final effects of glutamic acid and glutamine were determined by the total concentration of both compounds together. The presence of cysteine and glutamic acid alone or together with DMSO abolished all inhibitory effects. Desferal did not enable the multiplication of *M. leprae* on media devoid of SE prepared from *M. smegmatis.* However with SE and 0.005% and 0.002% concentrations of Desferal its initial growth was accelerated. Its final counts, noted after an 8-month incubation, did not exceed those observed without Desferal.

"Purine and pyrimidine compounds promoted markedly the multiplication of *M. leprae* (counts $> 3 \times 10^7$/ml). The highest counts were observed with pyrimidines (thymine, thymidine, cytosine) applied single or combined."

5. KIRCHHEIMER, W. F. & SANCHEZ, R. M. **Survival of *Mycobacterium leprae* in cutaneous inoculation sites of armadillos.** *Lepr. India,* 1975, v. 47, No. 1, 5-8.

By studying the effects of inoculating 15 nine-banded armadillos intradermally with similar quantities of a suspension of *Mycobacterium leprae* obtained from a single human source, the authors show that there are considerable individual differences in susceptibility to experimental leprosy infection among these animals. Thus, after 1095 days, 5 had died, and autospy revealed disseminated leprosy. Four of the survivors had signs of disseminated leprosy at this stage, despite good clinical condition. The authors found evidence that survival of bacilli at the inoculation site for more than 400 days was a good indication of their ultimate widespread dissemination.

[No reasons are advanced for non-survival and non-dissemination of *Myco. leprae* in the other 6 armadillos. Would they eventually develop some form of high-resistant leprosy, or would the introduced bacilli fail to multiply and disappear without causing any histologically recognizable lesions?]

S. G. Browne

6. PRABHAKARAN, K., HARRIS, E. B. & KIRCHHEIMER, W. F. ***o*-Diphenoloxidase of *Mycobacterium leprae* separated from infected armadillo tissues.** *Infection & Immunity,* 1975, v. 12, No. 2, 267-269.

7. DELVILLE, J. & PICHEL, A. M. Microbiologie de la lèpre. Existe-t-il une phase cultivable *in vitro* du bacille de Hansen? [**Microbiology of leprosy. Does an *in vitro* cultivable phase of the leprosy bacillus exist?**] *Ann. Soc. Belg. Méd. Trop.*, 1975, v. 55, No. 2, 109-118. English summary (8 lines).

The authors provide a further interim report on their investigations of organisms isolated from leprosy lesions. By omitting penicillin and all other antibiotics from the specially adapted culture media used, and taking material from leprosy patients with rigorous aseptic precautions, they have succeeded in isolating slow-growing non-acid-fast diphtheroid-like organisms. Material has been obtained, both from circulating blood and from skin lesions, from patients who have been resident in Zaire, Ethiopia and Senegal.

From 32 skin biopsy specimens obtained from patients with different forms of leprosy, 18 cultivable strains have been isolated up to date, as well as 8 strains from blood culture.

From mouse footpads inoculated directly with material from leprosy patients, 8 strains of non-acid-fast bacilli have been isolated. Apparently identical organisms have been isolated from mouse footpads injected with material obtained from leprosy patients. (The authors guarantee that their mice are free from *Corynebacterium kutscheri* infection.)

The initial cultures require a period of several weeks to several months before growth is evident, but thereafter multiplication appears to become much more rapid, with a generation time of apparently only about 3 hours.

The taxonomic position of these isolates is difficult to establish; they have affinities with the corynebacteria, but anti-*C. hofmanni* has no reactivity with them.

A welcome addition to the investigative techniques now introduced is the inoculation of isolates into mouse footpads and observing the development of acid-fastness in the organisms. Another is the use of immunodiffusion techniques to establish relations with mycobacteria, nocardia, etc.

The authors do not claim that they have yet proved that the organisms they have been studying represent phases in a complex life-cycle of *Mycobacterium leprae,* but they obviously are still thinking along these lines.

[See *Trop. Dis. Bull.*, 1975, v. 72, abstr. 1389.]

S. G. Browne

BIOCHEMISTRY, PATHOLOGY, IMMUNOLOGY

8. MEYERS, W. M., KVERNES, S. & STAPLE, E. M. **Failure of levamisole to alter the lepromin reaction.** *Am. J. Trop. Med. Hyg.*, 1975, v. 24, No. 5, 857-859.

"In a study of 37 leprosy patients, the oral administration of levamisole failed to provoke an increase in both the Fernandez and Mitsuda reactions to lepromins of human and armadillo origin. We interpret this as evidence against an effective specific immunostimulatory capability of levamisole in leprosy patients under the conditions of the study. Current knowledge of the mechanism of levamisole action supports the concept that the fundamental immunologic defect in lepromatous leprosy may reside in the lymphocyte and not the macrophage, or the respective related functions of these two cell forms."

9. ABALOS, R. M., TOLENTINO, J. G. & BUSTILLO, C. C. **Histochemical study of *erythema nodosum leprosum* (ENL) lesions.** *Int. J. Lepr.*, 1974, v. 42, No. 4, 385-391.

A histochemical study of *erythema nodosum leprosum* (ENL) skin lesions in 14 patients with lepromatous leprosy demonstrated the presence of PAS-positive diastase resistant substances, acid mucopolysaccharide, neutral fat, phospholipid, aryl sulphatase and acid phosphatase. These were situated around the periphery of the reaction centre, scarcely at all within it. This was taken to indicate a leakage of hydrolytic enzymes from the area of acute inflammation into

the surrounding tissues. Substances which inhibit the release of enzymes (*e.g.* cortisone and chloroquine) are sometimes used therapeutically against ENL. It is suggested that these enzymes may play a role in the pathogenesis of ENL.

D. S. Ridley

10. MCADAM, K. P. W. J., ANDERS, R. F., SMITH, S. R., RUSSELL, D. A. & PRICE, M. A. **Association of amyloidosis with erythema nodosum leprosum reactions and recurrent neutrophil leucocytosis in leprosy**. *Lancet,* 1975, Sept. 27, 572-576.

In Papua New Guinea, where amyloidosis is common, 16 out of 190 leprosy inpatients were found by rectal biopsy to have amyloidosis, including 20% of patients of the LL type who had had leprosy for more than 2 years, all of whom had had recurrent bouts of erythema nodosum leprosum (ENL). Five patients of the borderline or tuberculoid type in whom amyloid was found did not have ENL but they all had severe chronic neurotrophic ulcers. 8 of the 16 amyloid patients died from renal failure within a year.

The serum component (SAA), thought to be a normal serum protein in trace amounts as well as a precursor of amyloid AA fibrils, was detected in 29% of LL patients, 15% BL and 12% of BB/BT cases. The SAA titre rose as patients went into ENL reactions, and there was a parallel rise in the leucocyte count; it is suggested that neutrophils may be associated with the production of SAA. Subsequently the SAA titre fell, depending on the severity of the ENL, and was found in only 35% of the patients with amyloidosis. Most of the non-lepromatous patients with SAA had trophic ulcers. The significant association between SAA and amyloid was in striking contrast to the influence of diet and other factors which appeared to be irrelevant.

D. S. Ridley

11. SKINSNES, O. K. & MATSUO, E. **Acid mucopolysaccharide metabolism in leprosy. 1. Storage of hyaluronic acid and its possible significance in the pathogenesis of leprosy** [SKINSNES & MATSUO). *Int. J. Lepr.,* 1974, v. 42, No. 4, 392-398. **2. Subcellular localization of hyaluronic acid and β-glucuronidase in leprous infiltrates suggestive of a host-*Mycobacterium leprae* metabolic relationship** [MATSUO & SKINSNES]. *Ibid.,* 399-411.

I. In a study comprising 102 skin biopsies of leprosy patients of various types, an acid mucopolysaccharide with the characteristics of hyaluronic acid was found in lepra cells in amounts that were inversely proportional to the level of immunity of the patient, being maximal in lepromas, especially those of short duration, and minimal in the granulomas of tuberculoid leprosy, especially those of long duration. Hyaluronic acid enhanced the growth of *Mycobacterium leprae* in mice (this is the subject of another study).

II. An elegant combined histochemical-electron microscopy study of β-glucuronidase and hyaluronic acid was made with the object of unravelling the metabolism of the latter. The enzyme is responsible for the second stage in the degradation of hyaluronic acid (it has not so far been possible to study hyaluronidase activity, which is responsible for the first stage). Hyaluronic acid was found in the phagosomes of active lepromas and β-glucuronidase was found there in and around *M. leprae.* The enzyme alone was present also in the lysosomes of epithelioid cells and giant cells. It is suggested that *M. leprae* uses hyaluronic acid derived from histiocytes as a nutrient and that, in tuberculoid types of infection, bacilli may have to compete with the epithelioid cells for it, whereas in lepromas there is no competition.

D. S. Ridley

12. MATSUO, E., SKINSNES, O. K. & CHANG, P. H. C. **Acid mucopolysaccharide metabolism in leprosy. 3. Hyaluronic acid mycobacterial growth enhancement, and growth suppression by saccharic acid and vitamin C as inhibitors of β-glucuronidase.** *Int. J. Lepr.*, 1975, v. 43, No. 1, 1-13.

"A series of pilot studies are presented utilizing mouse and human infections with *M. leprae* and mouse infections with *M. lepraemurium* relating to the previously reported finding that hyaluronic acid seems to be a major nutrient substrate for these bacilli. The 'feeding' of hyaluronic acid to the bacilli enhanced the growth of *M. leprae* in mouse abdominal walls and increased the Morphologic Index of *M. lepraemurium* infection. Saccharic acid, an inhibitor of β-glucuronidase previously reported as present in these leprosy bacilli, caused marked regression of advanced *M. lepraemurium* infection, inhibited early infections and was accompanied by marked morphologic changes in the bacilli. Ascorbic acid (vitamin C), also an inhibitor of β-glucuronidase, given at a level of 1.5 g day for 4.5 months to one lepromatous patient without other treatment and for up to 24 months to four other lepromatous patients receiving DDS, was accompanied by lesion regression and changes in bacillary morphology similar to those seen in the inhibitor treated mice.

"If these observations are confirmed the possible use of β-glucuronidase inhibitors as a useful adjunct to other leprosy therapy is raised as is also the likelihood of developing new therapies."

13. PANDYA, S. S. & CHULAWALA, R. G. **Innervation of muscle in leprosy with special reference to the muscle spindle.** *Int. J. Lepr.*, 1975, v. 43, No. 1, 32-35.

"The pattern of extrafusal and intrafusal innervation was studied in muscle biopsies from the flexor carpi ulnaris and biceps brachii muscles, which were clinically unimpaired. Smudginess and enlargement of the motor end plates were the most definitely abnormal feature of the extrafusal innervation pattern; the intrafusal fibers, on the other hand, were either unremarkable or showed increased tortuosity, beading and in more extreme cases a grossly complicated intertwining pattern. Bacilli were frequently found in the spindles, no component being spared. The study emphasizes the significant involvement of striated muscle in leprosy, a fact not always revealed by clinical examination alone."

14. AGARWAL, D. P., SRIVASTAVA, L. M., GOEDDE, H. W. & ROHDE, R. **Biochemical, immunological and genetic studies in leprosy. I. Changes in serum lactate dehydrogenase isoenzymes, creatine phosphokinase and aldolase activity in different forms of leprosy.** *Tropenmed. Parasit.*, 1975, v. 26, No. 2, 207-211.

"Serum lactate dehydrogenase isoenzymes, creatine phosphokinase and aldolase activity were determined in healthy control subjects and in lepromatous and tuberculoid leprosy patients from Ethiopia. Sera from lepromatous patients showed a higher total LDH activity compared with control subjects. The values for tuberculoid leprosy patients were similar to those of controls. Sera from normal healthy controls showed a higher proportion of LDH-H form (72%) while lepromatous leprosy patients' sera exhibited a higher proportion of LDH-M form (55%). Tubercuoid leprosy patients showed a pattern similar to that of healthy controls. A possible significance of these observations is discussed. No significant variations were observed in fructose-1,6-diphosphate aldolase activity within the different types of disease and controls. Although creatine phosphokinase levels in different types of leprosy decreased significantly from those of normal healthy persons, they fall within the reported variation of the activity in normal sera."

15. SRIVASTAVA, L. M., AGARWAL, D. P., GOEDDE, H. W. & ROHDE, R. **Biochemical, immunological and genetic studies in leprosy. II. Profile of immunoglobulins, complement components and C-reactive protein in sera of leprosy patients and healthy controls.** *Tropenmed. Parasit.*, 1975, v. 26, No. 2, 212-218.

"Various classes of immunoglobulins (IgA, IgM, IgG, IgD and IgE), complement components (C3 and C4) and C-reactive protein (CRP) were estimated in sera from normal healthy controls and leprosy (lepromatous and tuberculoid) patients from Ethiopia. Higher levels of IgA, IgM, IgG and IgD were found in lepromatous leprosy compared with normal healthy people while in tuberculoid leprosy only IgM, IgG and IgD levels were increased. Borderline leprosy patients showed increase in IgG level only.

"Although an increase in IgE was noted in lepromatous leprosy, it was not significant; the variations in IgE levels could be due to different socio-economic background and exposure to intestinal parasites.

"C3 component was significantly reduced in leprosy patients compared with healthy controls while no difference in C4 component was observed. The results point towards an involvement of the 'alternate pathway.' A positive test against C-reactive protein antiserum was given by about 20% of the normal healthy controls while more than 60% lepromatous and tuberculoid leprosy patients were CRP positive.

"The results are discussed in relation to the status."

16. WATSON, S. R., SLJIVIĆ, V. S. & BROWN, I. N. **Defect of macrophage function in the antibody response to sheep erythrocytes in systemic *Mycobacterium lepraemurium* infection.** *Nature, London,* 1975, July 17, v. 256, 206-208.

Mice infected with *Mycobacterium lepraemurium* showed an impaired antibody response to an injection of sheep erythrocytes. Macrophages from these mice functioned poorly in that they did not properly augment the production of plaque forming cells *in vitro.* These experiments suggest that the defective humoral response to sheep erythrocytes might be associated with a macrophage defect, and possible mechanisms for this link are discussed.

A. Bryceson

17. SEBILLE, A. L'unité motrice chez les lépreux: résultats d'une étude électromyographique et histologique, comparée aux données cliniques et aux vitesses de conduction motrice. [**The motor nerve-muscle unit in leprosy: the results of an electromyographic and histological study compared with clinical data and motor condition time.**] *Méd. Trop.,* 1975, v. 35, No. 3, 231-237. English summary (9 lines).

This report of an investigation into the correlation of nerve trunk damage and its distal motor and histological effects, is both interesting and important.

Electromyography in 20 leprosy patients (17 lepromatous, 2 tuberculoid and 1 borderline) of the external popliteal nerve and the muscles it supplies, was supplemented by microscopical examination of muscle specimens. Damage to muscle was mainly due to impairment of nerve function, and not to the rare presence of *Mycobacterium leprae* in the muscles themselves. No correlation was found between the presence and degree of nerve trunk damage and the presence of *Myco. leprae* in either the muscles or the nerve sheath.

Signs of nerve trunk denervation were found in early lepromatous leprosy and in the absence of any clinically detectable abnormality of the nerve trunk. These signs revealed by electromyography also preceded histological signs of nerve damage in the muscles supplied.

However, where enlargement of the nerve trunks was already established, then definite reduction in conduction time was evident, accompanied by histologically discernible muscle damage. Slowing of nerve conduction times was most noticeable in the segments of the nerve

clinically subject to enlargment, but the actual impairment of the conduction time bore no relation to the presence or absence of enlargement of the nerve trunk in these situations.

Subclinical muscle damage was demonstrated by electromyography in 90% of patients, a finding that suggests to the author that such damage may be occurring at the time of the early skin rash of lepromatous leprosy.

S. G. Browne

18. BEIGUELMAN, B., PINTO, W., Jr, EL-GUINDY, M. M. & DRIEGER, H. **Factors influencing the level of dapsone in blood.** *Bull. Wld. Hlth. Org.,* 1974, v. 51, No. 5, 467-471.

"The level of dapsone in the blood 4 and 6 h after the ingestion of the 7th daily dose of 100 mg of the drug was investigated in 36 adult males with leprosy who had normal renal function and were free of diarrhoea and emesis. The bimodal distribution of the dapsone levels at 6 h was shown by multiple regression analysis to be due to a negative correlation between this trait and the haematocrit value. Among the patients with high dapsone blood levels, 81.8% presented haematocrit values under 36%, whereas only 20% of those with low levels showed low haematocrit values. Partial regression coefficients, calculated for the dapsone level on the age, weight of the patient, estimated number of years since the onset of leprosy, number of years under sulfone treatment, and blood levels of haemoglobin, albumin, and globulins, did not show statistical significance."

19. PETERS, J. H., GORDON, G. R. & KARAT, A. B. A. **Polymorphic acetylation of the antibacterials, sulfamethazine and dapsone, in South Indian subjects.** *Am. J. Trop. Med. Hyg.,* 1975, v. 24, No. 4, 641-648.

"A group of South Indian subjects was studied for their capacities to acetylate sulfamethazine (SMZ) and dapsone (DDS) and to clear DDS from the circulation. An apparent trimodal distribution of acetylator phenotypes was found in 49 subjects (51% slow, 12% intermediate, and 37% rapid acetylators) from measurements of the percentage acetylation of SMZ in 6-hour plasma samples after administration of 10 mg SMZ/kg. The intermediate phenotype was not discernible from either the percentage acetylation of SMZ in urine (collected concurrently with the plasma after SMZ) or that of DDS in plasma after the ingestion of 50 mg DDS by the same subjects. The latter two measurements yielded a bimodal distribution of 59% slow and 41% rapid acetylators, nearly identical to earlier reported distributions of isoniazid inactivator phenotypes in larger numbers of South Indian tuberculosis patients. In the current group, acetylation of DDS and SMZ was positively correlated. The half-time disappearance (T½) of DDS, an expression of the rate of clearance from the plasma, ranged from 13 to 40 hours. No correlation was found between the subject's capacity to acetylate DDS and the T½ value for DDS. These results were generally consistent with earlier observations made during similar studies of American and Filipino subjects."

[See *Trop. Dis. Bull.,* 1973, v. 70, abstr. 304.]

20. ALLEN, B. W. *et al.* **The penetration of dapsone, rifampicin, isoniazid and pyrazinamide into peripheral nerves.** *Br. J. Pharmacol.,* 1975, v. 55, No. 1, 151-155.

"1. Dapsone, rifampicin, isoniazid and pyrazinamide were shown to penetrate readily into the sciatic nerves of the dog and sheep.

"2. These findings suggest that the continued persistence of viable drug-sensitive leprosy bacilli in the peripheral nerves of patients treated for long periods with either dapsone or rifampicin is not due to inadequate intraneural drug penetration."

THERAPY

21. PALANDE, D. D. & AZHAGURAJ, M. **Surgical decompression of posterior tribial neurovascular complex in treatment of certain chronic plantar ulcers and posterior tibial neuritis in leprosy.** *Int. J. Lepr.,* 1975, v. 43, No. 1, 36-40.

"Seventy-one cases of posterior tibial neurovascular surgical decompression in leprosy are analyzed and reviewed. Thirteen had chronic refractory posterior tibial neuritis while 58 had chronic nonhealing plantar ulcers. The plantar ulcers were associated with posterior tibial neuritis and/or vascular insufficiency. The clinical and operative findings together with the results are presented and the physiopathology of neurovascular compression is discussed. The operative procedure is described. The presence of pale granulation tissue in a nonhealing ulcer seems to be a characteristic finding in these cases. Neurovascular compression in the tunnel, behind and also below the malleolus, was present in all. In operative procedures, the importance of incising the inferior calcaneal bands is stressed. The results show that the neuritis was cured in all cases, while in 53 of 58 cases the plantar ulcers healed in a short period after the decompression. This stresses the value of this procedure. The prophylactic potential of this procedure needs to be evaluated."

22. NEBOUT, M. Résultats d'un essai contrôlé de l'extrait titré de *Centella asiatica* (E.T.C.A.) dans une population lépreuse présentant des maux perforants plantaires. [**Results of a controlled trial of a titrated extract of *Centella asiatica* in leprosy patients with perforating plantar ulcers.**] *Bull. Soc. Path. Exot.,* 1974, v. 67, No. 5, 471-478.

Having been impressed by the experimental demonstration that extracts of *Centella asiatica* had a stimulating effect on reticuloendothelial cells and induced tissue hypervascularization, the author arranged a trial of the drug in 90 leprosy patients with perforating plantar ulcers, to evaluate its effect (if any), and to find out if the parenterally injected extract had any advantages over locally applied ointment containing the extract.

The patients were divided into three groups, the members of which were comparable in age, sex, type of leprosy, anti-leprosy treatment received, and duration of leprosy. The only criterion of exclusion from the trial was the presence of some bony involvement shown radiologically.

The trial was conducted blind, with frequent clinical and monthly photographic control, and lasted for two months. An "index of regeneration" was established mathematically to indicate the rate of regeneration of lost tissue within the ulcer.

Both the injections and the applications were well supported, with no side-effects.

There was no statistically significant difference between the group having the injected extract in addition to the locally applied ointment, but there was a considerable difference between these two groups taken together and the third control group, the members of which received only the basic local care common to all groups, which was essentially rest and the application of dressings of Dakin's solution.

The author recommends that on grounds of cost and practicability the local treatment of chronic perforating ulcers of the foot with an ointment containing a titrated extract of *C. asiatica* should be further investigated.

S. G. Browne

23. BEDI, B. M. S., NARAYANAN, E., DOSS, A. G., KIRCHHEIMER, W. F. & BALASUBRAHMANYAN, M. **Distribution of single lesion of tuberculoid leprosy.** *Lepr. India,* 1975, v. 47, No. 1, 15-18.

The unresolved question of the portal of entry of *Mycobacterium leprae* into its human victim may find a partial answer in this study of the distribution of single lesions of tuberculoid

leprosy in the skin. The extremely scanty observational indications that the portal of entry is the site of the first or only skin lesion, are supplemented by the conclusions of the authors. Up to the age of 12 years, the male: female ratio of tuberculoid leprosy in a small group of 103 children in an area around Pondicherry (south India) was almost 1 : 1, and the distribution of the single tuberculoid lesions was very similar. In 212 adults (above the age of 12), however, the male: female ratio was 2.2 : 1, and females showed fewer lesions on the trunk and lower limb than males. The authors conclude that this discrepancy may be related to the wearing of clothing by females which protects the skin from the bites of arthopods that might transmit leprosy bacilli.

S. G. Browne

24. RUSSELL, D. A., SHEPARD, C. C., MCRAE, D. H. SCOTT, G. C. & VINCIN, D. R. **Acedapsone (DADDS) treatment of leprosy patients in the Karimui of Papua New Guinea: status at six years.** *Am. J. Trop. Med. Hyg.,* 1975, v. 24, No. 3, 485-495.

Since 1967, patients with leprosy in Karimui have received acedapsone 225 mg every 75 days. After four years, in 5 of the 28 multibacillary patients evenly-stained *Mycobacterium leprae* reappeared, but were dapsone-sensitive. Clinical response was good. In 1973 "most of the multibacillary patients" received 600 mg rifampicin daily for 90 days.

C. S. Goodwin

25. U.S. LEPROSY PANEL: LEONARD WOOD MEMORIAL. **Rifampicin therapy of lepromatous leprosy.** *Am. J. Trop. Med. Hyg.,* 1975, v. 24, No. 3, 475-484.

15 patients with lepromatous leprosy were given rifampicin 600 mg daily, and 9 patients were given dapsone 100 mg daily. After one year they received acedapsone 225 mg every 12 weeks or oral dapsone 50 mg daily. Mouse footpad inoculation of skin specimens showed that after four weeks of rifampicin therapy *Mycobacterium leprae* was "nearly undetectable", but after 12 weeks of oral dapsone viable *Myco. leprae* were present. Clinical response was good.

C. S. Goodwin

EPIDEMIOLOGY AND CONTROL

26. HERTROIJS, A. R. **A study of some factors affecting the attendance of patients in a leprosy control scheme.** *Int. J. Lepr.,* 1974, v. 42, No. 4, 419-427.

This paper reports a detailed and careful investigation into the reasons for irregular attendance of patients registered in the Mwanza Regional Leprosy Scheme, Tanzania. In an area of 19,600 sq km, in which the prevalence of leprosy is estimated to be 14 per 1000, 8655 patients have been diagnosed as suffering from leprosy, a figure representing about 55% of the probable numbers needing treatment. Since the inauguration of the scheme in 1966, and complete coverage of the area some 5 years later, 2800 patients have defaulted. A "defaulter" is a patient who has not attended a treatment centre for a year or more; an "irregular attender" is one who has made fewer than 9 visits to the centre out of a total possible of 13 (4-weekly) in a year.

It was found that the most important differences between defaulters and irregular attenders on the one hand and regular attenders on the other, were that the former tended to be younger in age (*i.e.,* below 20 years), single rather than married, rather better educated (and hence migrating from the area), suffering from indeterminate or early tuberculoid leprosy rather than from lepromatous leprosy, with or without deformity. Patients registered for treatment after a survey tended to default, lacking the motivation of those who reported for diagnosis and treatment. Social and economic factors were important in determining irregularity of attendance for treatment and then ceasing attendance altogether. The desire for secrecy and anonymity prompted many patients to give false addresses to cover up their tracks.

Home visits to trace defaulters and irregular attenders were found to be expensive in terms of man-hours and relatively unproductive, although of some value when the patient was young and male and suffering from lepromatous leprosy, perhaps with severe disabilities.

The paper concludes with a very practical list of recommendations which, if followed, would increase the effectiveness of many leprosy control/treatment schemes by reducing the proportion of those patients who for one reason or another fail to persevere with treatment for as long as they should.

S. G. Browne

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CONTENTS

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