Editorial

"RELEASE FROM CONTROL" IN LEPROSY

Up till 10 years ago the "criteria for discharge" in leprosy were regarded as a logical, necessary and relatively clear-cut aspect of patient care. The menacing psychological atmosphere which surrounded leprosy, both for patient and doctor alike, gave enormous importance to the concept of an end-point, when after prescribed courses of chemotherapy, and the attainment of a condition of "inactivity", a further period of observation and treatment could lead to the day when the disease would be regarded as arrested, and, hopefully, overcome. At that point chemotherapy could be suspended, a medical certificate given, and with the safeguard of regular but occasional follow-up, the patient could be restored to normal life, This was a day of great emotional content for patients.

During the past decade several aspects of this approach to leprosy have been challenged by events and by better understanding of the bacteriology and immunology of *Mycobacterium leprae.* The idea that a line can be drawn between infection and no infection has been rudely shattered. The very natural bacillus-orientated approach made it easy to pontificate and even legislate on behalf of patients in the belief that they would meekly follow our advice. We have had to learn that the final arbiter on how much chemotherapy is taken and when treatment is stopped is not the doctor, but the patient himself. All our well laid plans and carefully considered judgments fall to the ground if the patient on whose behalf they are made simply fails to co-operate. He, as well as the germ, must be at the centre of our concern, and our approach be such that our well meant programmes are not frustrated.

The judgments of the WHO Expert Committee on Leprosy on this subject are highly relevant. The Report of the 4th Expert Committee (1970) included the following:

> "A leprosy patient without any sign of clinical activity, and with negative bacteriological findings should be considered as an 'inactive case'.
>
> Once inactivity is achieved, *regular treatment* should be continued for varying periods of time before a patient is 'released from control' (rfc). These periods should be $1\frac{1}{2}$ years for tuberculoid, 3 years for indeterminate, and at least 10 years for lepromatous and borderline cases. Since data on relapse after rfc are scarce, it is advisable and important to continue the follow-up of lepromatous cases but without treatment. Some leprologists consider that this should be done for life."

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This statement was endorsed by the 5th Expert Committee (1976) with an interesting proviso. "The Committee strongly recommended that inactive tuberculoid and indeterminate cases be promptly released when they meet the criteria. This action is not only in the interest of the patient but has an important bearing on operational efficiency and would release resources for other activities of the programme."

Clearly in 1976 wider issues came within the purview of the Committee than the earlier approach, but the endorsement of the 1970 statement means that the views then expressed are carried forward as the recommended norm for today. Some aspects of this invite discussion.

It must first be said that for patients with types of leprosy towards the tuberuloid end of the spectrum the traditional approach remains valid. With such patients the question of ostracism and isolation should not have arisen, and following chemotherapy, inactivity and continuing therapy for the times suggested by the Committee, an end-point can be envisaged and a discharge certificate be given with minimal prospect of relapse. The key here is surely the existence of cell-mediated immunity as the limiting factor in the infection, holding the promise of continuing ability to deal with the bacillus, and monitored by a positive reaction to lepromin, whether this was there from the start or develops in association with reversal reactions.

Continuing Chemotherapy and Surveillance

When we turn to patients with bacilliferous leprosy the position is rendered much more difficult by the discovery that even in spite of long periods of chemotherapy viable *M. leprae* may persist, notably in the skin, bone marrow, lymph glands and nerves. Clearly it is very important that the types of patient in whom such persister bacilli are found should be identified as accurately as possible. At present they must be assumed to include all patients with established lepromatous leprosy. How far this phenomenon extends into the borderline part of the spectrum remains to be determined. The crucial question is the extent to which such persister bacilli are responsible for relapse. A lot more data are needed on the whole subject, but there seems to be no logical reason why persister bacilli, granted favourable conditions, should not recommence reproductive life, the only possible exception being the small minority of such patients who ultimately attain lepromin positivity.

It is not difficult to envisage such favourable conditions. We already encounter them in relation to downgrading reactions. Clearly the discovery of persister bacilli has an important bearing on chemotherapy. With such patients there can surely be no magical moment when after 10 years of inactivity we can say, "Now it is all over, you can stop taking dapsone". At present the only defence we have against relapse is continuous chemotherapy. As long as we are dependent on dapsone for maintenance therapy it would seem to be obvious advice to the patient with LL or BL leprosy that he should continue to take dapsone at therapeutic dosage indefinitely, even though he appears to be clinically inactive. This means that in present circumstances there should be no discharge from treatment for such patients, and the "criteria for discharge" have become irrelevant.

By the same token there can be no discharge from regular surveillance. The whole purpose of surveillance is to monitor the possibility of relapse, whether this is caused by dapsone-sensitive or dapsone-resistant bacilli. As long as we accept the reasonable possibility of relapse, then surveillance must continue indefinitely, and is indeed very important.

It would appear therefore that in LL and BL leprosy, with present chemotherapy and with present day knowledge, discharge from treatment or from surveillance should not be advised, both in the best interests of the patient and of the community.

The Personal Factor

Acceptance of this principle immediately poses a difficult question: How can we expect the co-operation of patients in such procedures? Careful studies in recent years have indeed exposed the truth that frequently only a minority of patients continue to take dapsone as prescribed [e.g. *Malawi:* Ellard, Gammon and Harris (1974); *Ethiopia*: Low and Pearson (1974); *Bombay*: Naik (1977)]. The same applies to attendances at treatment clinics. Many patients after longer or shorter periods of attendance simply discharge themselves and make nonsense of the medical criteria for discharge. It so happens that patients with LL and BL leprosy are often the most faithful in their attendance, but there is a problem here which must be resolved.

Now it is a fact of medical experience that people in general like to take medicines, whether they are Africans, Asians or Europeans, and will continue to do this as long as they feel that prescribed medicines are doing them good, the medicines are easy to obtain, and there are no economic or social problems involved. The taking of tablets indefinitely holds no intrinsic problem. Millions of people do it, e.g. for hypertension, rheumatic conditions, or diabetes. Exactly the same is true of periodic medical examinations, provided the doctor–patient relationship is what it ought to be. Why then do we expect something different where leprosy is concerned? The reason cannot lie simply in the need for protracted treatment. It lies in the way the patient regards his illness and in the way he feels that other people, including the doctor, regard him, the sufferer from leprosy. All too often in the minds of patient, community and doctor alike, leprosy continues to hold a special anxiety-creating position, the natural reaction to which is to turn away from it, fail to face it, or forget it as quickly as possible.

The WHO Committee recommends 10 years of chemotherapy after inactivity in bacilliferous leprosy. If a patient has persisted for 10 years, he must so have got into the habit that there should not be the slightest difficulty in his taking it for 11, 12 years or indeed indefinitely. This is not the problem. The real problem is the desire to escape from the association with leprosy. This is something that deserves much more careful consideration than is usually given to it.

The best likelihood of maintaining continuity of treatment and surveillance, of encouraging the patient to persevere, will occur if three things are safeguarded.

(1) The patient must be helped to understand the nature of his illness.
(2) The doctor–patient relationship must be good. So much depends on this. It is the experience of the writer that where patients believe they are going to be welcomed and treated with understanding and consideration they are prepared to face the facts of their disease and respond with continuous co-operation.
(3) Dapsone must be available as simply and unobtrusively as possible, *not* in the context of time consuming frequent visits to special clinics labelled in everyone's minds as reserved for people with active leprosy.

These principles apply during the first 10 years as well as subsequently. If they can be achieved there seems to be no logical reason why a patient should not of his own choice, continue to remain under chemotherapy and surveillance indefinitely.

It appears to the writer that the sustained co-operation of patients with LL and BL leprosy is made unnecessarily difficult by the perpetuation of old ideas and emphases.

The WHO definition of inactivity includes *negative bacteriological findings,* a feature which condemns many patients at the lepromatous end of the spectrum to long years of carrying the anxiety, and usually the stigma, of active leprosy. The traditional attitude would maintain that as long as acid-fast material, regardless of its morphology, is found in routine skin smears, the patient is still suffering from active disease, and by inference other people are at risk.

Ever since the work of Rees and Valentine (1962), the judgment has continuously built up at centres of the highest excellence in leprosy research, that viability in *M. leprae* is associated with the intact rod-shaped, uniformly staining organism. Various attempts have been made to cultivate *M. leprae* from fragmented bacillary material. None has been authenticated.

If we are ready to accept that it is the morphologically intact normal staining form of the bacillus which is responsible for the disease leprosy and for transmitting that disease, then any basic anxiety we have concerning leprosy *as a transmissible disease* should centre around that form of the bacillus and not around dead fragmented forms of no significance in the transmission of the disease. The role of dead bacilli in relation to ENL and neurological aspects of leprosy is an important but quite different question. From the angle of the patient's capacity to transmit the disease, can it not be generally accepted that if the morphological index is zero, i.e. no bacilli of intact shape and staining can be found on careful bacteriological examination, then the numbers of such bacilli are so slight, that as with tuberculosis the patient may be regarded as non-infective to others. Persister bacilli in deep organs are not capable of leaving the body and have no relevance to this matter. The important point is that if the patient is in practice regarded as not infective to others, then we should say so. This would give an enormous boost to the morale of patients with these types of leprosy. So often the consciousness of being infective to others creates deep anxiety in the minds of patients where their children are concerned, and is a potent factor in the

depression that so easily leads to despair and non-co-operation. Furthermore, the logic of the situation should be followed through. The patient should surely be regarded as in no way different from any other sick person. He should be able to attend general out-patient's departments, occupy any appropriate hospital bed, be employed in any suitable capacity and have no social restrictions placed on him whatever. The idea that these normal prerogatives of people in community are to be denied until the traditional routine smears are totally negative for any acid fast-material is unscientific and indeed may even be considered uncharitable. This suggestion is not inherent in the WHO statement, but it is very much the common interpretation of what "release from control" really means, an echo of earlier rigid attitudes to this disease.

A Liberal Outlook Must be Backed by Sound Technology

If we are looking diligently for viable bacilli, our technology must be reliable. This means first, that the nose must be included in our attention. This is still frequently neglected, or if included, nasal examination often takes the form of old-fashioned septal smears, taken less than 2 cm within the anterior nares and calculated to yield nothing important. The inferior turbinate must engage our attention, and if as frequently happens it does not seem at first glance to be there, we need to realise that its anterior end has already been eroded by serious lepromatous disease. A bacteriological examination of the nasal discharge, choosing saneo-purulent areas is a *sine qua non.*

Secondly, relapse commonly first manifests itself by the appearance at maybe a single site in the skin of large numbers of normal-staining bacilli in a patient elsewhere and previously exhibiting only fragmented bacilli. Three months later normal viable bacilli are likely to be widespread, but by then it is certain that intranasal infection will have been re-activated, maybe worse than before initial treatment, and the patient be already discharging large numbers of viable bacilli from the nose. Early discovery of relapse is thus extremely important. There is no guarantee that common methods of skin smears, selecting fixed sites in an inflexible routine, will identify relapse in its earliest stages, though careful clinical examination might well have aroused suspicion. This is particularly important if the relapse as is very common, takes the form of histoid lesions. An important feature of histoid leprosy is its capacity to appear in areas of the body not usually selected for routine bacteriological examination, e.g. the buttocks, lower abdomen, upper thighs and genitalia. Histoid lesions readily ulcerate and discharge enormous numbers of viable bacilli. To the uninitiated a well defined histoid lesion might even be mistaken for a reversal reaction or unusual form of ENL. Clinical acumen and skill in taking and reading smears are essential if relapse is to be detected early. Failure on either side brings surveillance into disrepute and leads to the pessimistic dictum that inactivity in lepromatous leprosy cannot be accurately assessed by routine bacteriological methods. There is comfort in the fact that relapse is far more common among patients who are not taking regular chemotherapy than among those who are, and this particularly applies to relapse with histoid leprosy.

Wider Issues

In all our judgments affecting the life and well being of patients, the preservation and protection of the patient's place in community life is a long-term priority and there is no escape from our responsibility in this direction. Some separation during the stage of the disease when the patient is discharging viable bacilli must be acceptable, but as the morphological index is usually zero within 6 months or thereabouts of starting treatment, this is the sort of limit that needs generally to be visualized. There is, of course, no harm in some sort of "disease arrested" certificate following the criteria enunciated by the WHO Committee, but far more important in practice for the patient with LL or BL leprosy would be some form of medical certification given on request when the stage of negative MI had been attained, and indicating that the patient could be regarded as non-infective to others. Such a certificate would indeed release the patient from his primary anxieties and restrictions, encourage his continuing co-operation and promote a much more open and healthy attitude to leprosy generally.

It must be admitted that to secure such conditions considerable re-orientation and re-education of both patients and the community are needed, regarding the nature of leprosy, the delivery of chemotherapy, and the meaning of surveillance. It can however be done, as Antia (1977) has shown.

The fear that leprosy may be transmitted by forms of the bacillus other than the intact rod-shaped bacillus may be hypothetical, but it dies hard, especially in relation to leprosy that appears to have been traced to patients considered bacteriologically negative. Davey and Rees (1974) showed that *M. leprae* could remain viable in air for up to 7 days. Recent work by Desikan (1977) extends this period to 11 days. These findings pinpoint possible unsuspected sources of such infections. The basic plea of this paper is that our sense of responsibility for patients with LL and Bl leprosy should help us to accept with courage the facts regarding the viability of *M. leprae* which have been authenticated, and apply them resolutely.

There is one final point. Is "Release from Control" a phrase worth retaining in its present context? In common English usage "release" suggests a previous state of bondage or imprisonment. "Control" suggests a restriction on movement. Both words, used in relation to patients who have been under chemotherapy for years and exhibited no sign of viable bacilli for a long time are not only irrelevant but psychologically harmful to patients, workers, and community alike. Are they really necessary?

T. F. DAVEY

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The "Proportional Bactericidal Test": A Method for Assessing Bactericidal Activity of Drugs Against *Mycobacterium leprae* in Mice

M. J. COLSTON, G. R. F. HILSON AND D. K. BANERJEE

St George's Hospital Medical School, London SW17 0QT, U.K.

A new method for assessing the bactericidal activity of antileprous drugs against *Mycobacterium leprae* using the mouse footpad technique is described. This approach, referred to as the "proportional bactericidal test", has been devised to overcome some of the problems of interpretation caused by drug persistence or prolonged bacteriostasis after drug administration has ended. The bactericidal activity of several drugs against *M. leprae* has been determined using this approach and the results obtained compared with those previously reported using alternative methods.

Introduction

The first attempt to detect and assess bactericidal activity of a drug against *Mycobacterium leprae* in the mouse footpad was made by Shepard and Chang (1967), who fed mice with an established *M. leprae* infection on 4,4′-diaminodiphenylsulphone (DDS, dapsone), and measured the viability of *M. leprae* by subinoculation at intervals into new groups of mice. Although this technique is considered reliable for detecting the presence of a bactericidal effect, it is tedious and time-consuming to perform, and the rate of bacterial killing by drug is difficult to distinguish from that due to the concurrent killing effect of the host's acquired immunity.

An alternative technique, the "kinetic method", was devised (Shepard, 1967), in which drug was given for a limited period of time early in the growth cycle, and the bactericidal activity of the drug assessed by comparing the delay in appearance of growth of *M. leprae* with that in untreated controls, with allowance for the delay due to inhibition during drug administration. The *absence* of bactericidal activity is reliably demonstrated by this approach; however, most bactericidal drugs are known to exert a "bacteriopausal" effect: i.e. a prolonged bacteriostasis after removal of drug due to the recovery of reversibly damaged cells (Dickinson and Mitchison, 1966)—while other drugs, such as clofazimine, persist in the host's tissues after drug administration has ended (Barry, 1958; Barry *et al.*, 1959, 1960; Conalty and Jackson,

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1962), making the presence and extent of bactericidal activity difficult to detect (Banerjee *et al.*, 1974; Levy, 1974).

A modified approach, devised to overcome these difficulties and referred to as the "proportional bactericidal test", was reported by Hilson and Banerjee (1974) using *Mycobacterium lepraemurium*. This involved the inoculation of groups of mice with serial dilutions of a bacillary suspension, treating them for a limited period, and then sampling for bacillary growth after sufficient time had elapsed for the development of detectable growth arising from one or more surviving bacilli. This approach has now been adapted for the assessment of bactericidal activity of a number of antileprous agents against *M. leprae*.

Materials and Methods

Two strains of *M. leprae* were used (SBL 16220 and TG) both of which were originally derived from untreated lepromatous leprosy patients and subsequently maintained in mouse passage in our laboratory. The inoculation of female ASH/CSI mice (Charles River U.K. Ltd), harvesting and counting of *M. leprae* from mouse footpads were performed according to previously reported methods (Hilson and Elek, 1957; Holmes and Hilson, 1972). Inocula were prepared and diluted in Bacto TB Broth (Difco).

Assessment of bacillary growth was carried out by "scoring" for the presence or absence of growth; growth was assumed to have occurred in mice in which the number of bacilli harvested was significantly greater than the number originally inoculated. In practice, scoring for the presence or absence of bacillary growth was straight-forward since growth was either undetectable (less than 10^4 *M. leprae* harvested), or had reached more than 10^5 *M. leprae* per footpad, with no equivocal results.

The drugs used were dapsone (DDS), rifampicin (RMP), clofazimine (B663), thiambutosine, thiacetazone, ethionamide, and prothionamide, and their incorporation into mouse diet was performed as described by Holmes and Hilson (1972).

Results

In the first experiment, *M. leprae* (TG) was inoculated into the footpads of groups of 10 mice using inocula of 10^4, 10^3, 10^2 and 10^1 AFB per footpad. Drug treatment with 0.003% B663, 0.003% RMP, 0.01% DDS, 0.1% thiambutosine and 0.1% thiacetazone was started on the day of inoculation and continued for 60 days, and mice were scored for the presence or absence of growth 12 to 18 months after inoculation. The results are shown in Table 1.

The results were analysed by determining the "most probable number" of viable bacilli (MPN) (Halvorson and Ziegler, 1933; Taylor, 1962). This analysis indicates that the original inoculum contained at least 16% viable organisms, though this figure does not take into account the fact that more than one viable bacillus may be required to initiate an infection (Levy *et al.*, 1974). In the drug-treated mice, this analysis gives an estimate of the MPN of viable bacilli remaining after drug treatment. It can be seen from the table that treatment with thiambutosine produced no bacterial killing, whereas RMP,

TABLE 1

The proportional bactericidal test: the bactericidal activity of thiocarlide, thiambutosine, thiacetazone, DDS, RMP and B663 against M. leprae *(strain TG)*

Drug regimen	Inoculum size (*M. leprae* per footpad) 10^4	10^3	10^2	10^1	MPN* of viable *M. leprae*	Survival (%)	*P*§
Control	10/10†	10/10	9/9	6/8	1600	—	—
DDS (0.01%)‡	10/10	7/7	8/8	2/7	350	22	<0.01
RMP (0.003%)	2/8	1/9	0/8	0/9	0.2	0.01	<0.01
B663 (0.003%)	8/9	5/8	3/7	0/8	14	1	<0.01
Thiocarlide (0.1%)	9/9	8/8	10/10	8/10	1600	100	1
Thiambutosine (0.1%)	10/10	10/10	8/8	10/10	>1800	112	1
Thiacetazone (0.1%)	9/9	7/7	7/7	4/8	920	58	0.24

* Most probable number per 10^4 bacilli injected.

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

‡ All 6 drugs given for 60 days.

§ Probability of the difference in MPN in the drug-treated group and that in the control group having arisen by chance.

B663 and DDS all showed varying degrees of bactericidal activity, with 99.99%, 99% and 78% killing respectively. The analysis of the results with thiacetazone gives an MPN of 920 viable *M. leprae*, which is equivalent to a 42% killing effect; this reflects a "score" of 4/8 positive in the 10^1 group, compared with 6/8 in the control mice.

In the second experiment mice were inoculated with 10^4, 3×10^3, 10^3, 3×10^2, 10^2, 3×10^1, and 10^1 *M. leprae* per footpad, and B663 (0.01% and 0.003%), RMP (0.01%) and DDS (0.01%) administered for 30 days. Harvests of *M. leprae* were made 12 to 18 months after inoculation. The results are shown in Table 2.

The viability of the original inoculum was rather low, with only about 2.5% of the bacilli viable. All 4 drug regimens produced some bactericidal effect, with 0.01% B663 producing a 98% kill, 0.003% B663 a 96% kill, 0.01% DDS a 72% kill, whilst 0.01% RMP totally eliminated the infection in all the mice.

In the final experiment, ethionamide and prothionamide were assessed for bactericidal activity against *M. leprae*. Treatment with 0.1% ethionamide and prothionamide was started on the day of inoculation and continued for 45 days; treatment with 0.2% ethionamide was stopped after 30 days. Mice were sacrificed and *M. leprae* harvested from footpads 12 to 14 months after inoculation. The results are shown in Table 3.

Treatment with either 0.1% ethionamide or 0.1% prothionamide for 45 days produced identical bactericidal activity with survival of 1.4% of the inoculum, while 30 days' administration of 0.2% ethionamide resulted in survival of 2.6% of the inoculum.

Discussion

The events which are assumed to take place in the proportional bactericidal test are shown in Fig. 1. The assumption is made that the rate of fall in viable

TABLE 2

The proportional bactericidal test: the bactericidal activity of B663, RMP and DDS against M. leprae *(SBL 16220)*

Drug regimen	Inoculum sizes (*M. leprae* per footpad)							MPN* of viable *M. leprae*	Survival (%)	*P*§
	10^4	3×10^3	10^3	3×10^2	10^2	3×10^1	10^1			
Control	5/5†	5/5	5/5	5/5	5/5	2/5	0/5	250	—	—
B663 (0.01%)‡	6/9	5/8	4/8	1/10	0/7	0/8	0/8	4	2	<0.01
B663 (0.003%)	8/8	7/7	5/8	2/9	0/10	0/8	0/9	10	4	<0.01
RMP (0.01%)	0/10	0/7	0/9	0/10	0/8	0/9	0/9	0	0	<0.01
DDS (0.01%)	9/9	7/7	9/9	8/10	6/10	1/9	0/10	70	28	<0.01

* Most probable number per 10^4 bacilli injected.

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

‡ All 4 drugs given for 30 days.

§ Probability of the difference in MPN in the drug treated group and that in the control group having arisen by chance.

TABLE 3

The proportional bactericidal test: the bactericidal activity of ethionamide and prothionamide against M. leprae *(strain TG)*

Drug regimen	Inoculum size (*M. leprae* per footpad) 10^4	10^3	10^2	10^1	MPN* of viable *M. leprae*	Survival (%)	*P*§
Control	5/5†	5/5	5/5	3/5	920		
Prothionamide (0.1% for 45 days)	5/5	4/5	0/5	0/5	13	1.4	<0.01
Ethionamide (0.1% for 45 days)	5/5	4/5	0/5	0/5	13	1.4	<0.01
Ethionamide (0.2% for 30 days)	5/5	5/5	0/5	0/5	24	2.6	<0.01

* Most probable number per 10^4 bacilli injected.

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

§ Probability of the difference in MPN in the drug-treated group and that in the control group having arisen by chance.

numbers of bacilli under the action of a bactericidal drug is independent of inoculum size; though it is not possible to demonstrate that this is so for *M. leprae*, it has been shown to be true for cultivable organisms *in vitro* (Garrett, 1971). On withdrawal of drug, this period of "proportional" killing may be followed by a prolonged bacteriostatic action in some cases, or a slow

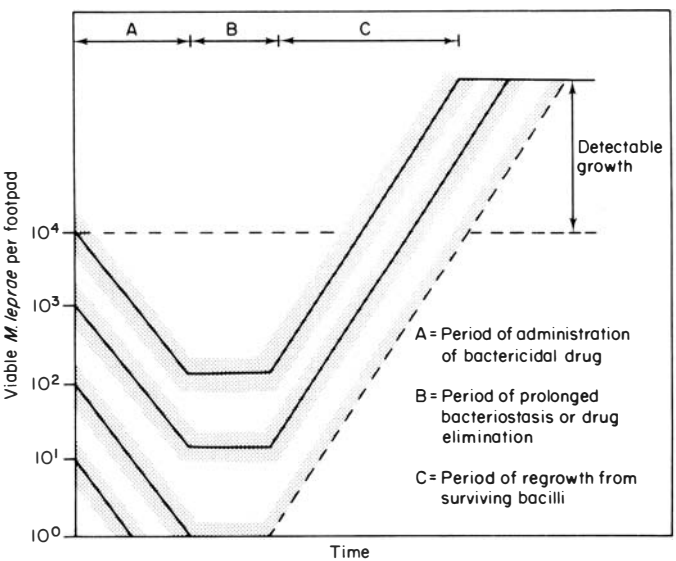

Fig. 1. Schematic representation of events occurring in the proportional bactericidal test. Inoculum sizes are 10^4, 10^3, 10^2, and 10^1 *M. leprae* per footpad. The shaded areas represent the variability inherent in the inoculum size and in the response to drug. The observed results in this example are: 10^4 group—all footpads positive, 10^3 group—all footpads positive, 10^2 group—some footpads positive, 10^1 group—all footpads negative.

elimination of drug in others. In those footpads in which viable bacilli still remain (10^4, 10^3 and in some 10^2 inoculated mice in the example shown in the figure), growth of the survivors then occurs at a rate independent of the numbers of remaining viable bacilli; the independence of growth rate and size of bacillary population has been demonstrated for cultivable organisms *in vitro* (Youmans and Youmans, 1949) and for *M. leprae* in the mouse footpad (Levy, 1976). The mice are assessed for the presence or absence of growth at the end of the regrowth period, and the proportion of mice which are positive in a particular group (i.e. the number of mice which still had viable bacilli remaining after drug treatment) is a reflection of the amount of bacterial killing which occurred during drug administration and hence of the rate of bactericidal action of the drug.

In all 3 experiments described here the distribution of results in each of the groups is statistically acceptable ($P' > 0.05$) using the analysis recommended by Taylor (1962).

Thiambutosine showed no bactericidal activity at all, confirming previous findings (Shepard, 1967; Colston and Hilson, 1976). RMP proved to be the most rapidly bactericidal of the drugs tested, with 0.003% for 60 days producing 99.99% killing (Table 1) and 0.01% for 30 days producing 100% killing (Table 2). If the assumption is made that the bactericidal effect is exponential in character, the bacterial survival half-life ($T_{\frac{1}{2}}$) for 0.003% RMP was 4 days, and for 0.01% less than 2 days. The rapid bactericidal effect of RMP against *M. leprae* in mice has previously been reported (Shepard *et al.*, 1971; Holmes and Hilson, 1972; Shepard, Levy and Fasal, 1972), with an estimated $T_{\frac{1}{2}}$ of 0.6 days at a dosage of 0.01% (Holmes and Hilson, 1974).

The bactericidal effects of DDS and B663 have proved difficult to demonstrate. In Shepard and Chang's original work (Shepard and Chang, 1967), DDS was shown to produce killing in the mouse footpad, but in subsequent studies it has been suggested that administration of DDS produced prolonged bacteriostasis rather than bactericidal activity (Levy, 1970, 1972). DDS showed a slow bactericidal activity, with 78% killing at a dosage of 0.01% for 60 days against strain TG ($T_{\frac{1}{2}} = 27$ days), and 72% at 0.01% for 30 days against strain SBL 16220 ($T_{\frac{1}{2}} = 18$ days).

The bactericidal effect of B663 has proved even more difficult to estimate due to its marked tissue accumulation in both the mouse and in man (Barry, 1958; Barry *et al.*, 1959, 1960; Conalty and Jackson, 1962; Banerjee *et al.*, 1974; Levy, 1974). In combined bacteriological and pharmacological studies, Levy (1974) suggested that its action was probably bactericidal and Holmes, Banerjee and Hilson (1976) have confirmed this by studying its effect on the solid ratio of an established infection. The results reported here confirm the bactericidal activity of B663, with a dosage of 0.003% for 60 days killing 98% of the inoculum (strain TG), and the same dosage for 30 days producing 96% killing (strain SBL 16220). The difference between the bactericidal activity of 0.01% and 0.003% B663 was not significant, but in each case B663 was significantly more bactericidal than DDS ($P' < 0.01$). Clinical experience with B663 suggests that during continuous treatment, its bactericidal activity in man is similar to that of DDS (Pettit and Rees, 1966; Pettit, Rees and Ridley, 1967; Levy, Shepard and Fasal, 1972). The relationship between the degree of

tissue accumulation of B663 and its bactericidal activity against *M. leprae* is unknown; different accumulation properties in man and in the mouse could account for its different bactericidal properties in the 2 species. Alternatively, the significantly greater bactericidal effect of B663 as compared with DDS reported here could be due to drug accumulation and persistence, resulting in leprosy bacilli being killed after drug administration has stopped. Thus although in this experiment the extent of bacterial killing was markedly different, the rate of killing may well have been similar.

The killing effect seen with thiacetazone suggests that 60 days' treatment with 0.1% produced 42% killing of the inoculum with a $T_{\frac{1}{2}}$ of 68 days. However, the difference between the MPN of the thiacetazone-treated group (930 viable bacilli) and the control group (1600 viable bacilli) is not significant at the 95% level.

The bactericidal effect seen with ethionamide and prothionamide is supported by further findings (Colston *et al.*, 1978) and the results with ethionamide confirm previous findings using the kinetic technique (Shepard, 1969). The results obtained when both drugs were administered at 0.1% were identical, with 98.6% killing in 45 days, representing a $T_{\frac{1}{2}}$ of 7.5 days. The amount of bacterial killing produced by 30 days' administration of 0.2% ethionamide was less than that produced by 45 days of 0.1% though the difference was not significant. However, the *rate* of bactericidal action was greater with 0.2% ethionamide ($T_{\frac{1}{2}} = 6.0$ days) than with 0.1% ($T_{\frac{1}{2}} = 7.5$ days). This value of $T_{\frac{1}{2}}$ is twice that obtained by the kinetic approach (Colston, unpublished data) and perhaps demonstrates the way in which the kinetic technique may exaggerate bactericidal activity by not differentiating between prolonged bacteriostasis and bactericidal action.

The results suggest that the proportional bactericidal test is a reliable method for assessing the bactericidal activity of antileprous drugs. All the results were statistically acceptable ($P' > 0.05$) and there is agreement with other techniques in which the purely bacteriostatic action of thiambutosine, the rapid bactericidal effect of RMP and the intermediate bactericidal effect of ethionamide, have been demonstrated. The method of bacillary growth assessment (simply scoring for the presence or absence of growth) has obvious advantages over the kinetic technique in which bacillary counts are made, and the problems of interpretation due to prolonged bacteriostasis or slow drug elimination are overcome.

Acknowledgements

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Antibody Activity Against *Mycobacterium leprae* Antigen 7 During the First Year of DDS Treatment in Lepromatous (BL-LL) Leprosy

REIDAR MELSOM,* BEN NAAFS, MORTEN HARBOE AND OTTO CLOSS

Armauer Hansen Research Institute (AHRI) and All-Africa Leprosy and Rehabilitation Training Centre (ALERT), Addis Ababa, Ethiopia, and University of Oslo, Institute for Experimental Medical Research, Ullevaal Hospital, Oslo 1, Norway

A specific radioimmunoassay was developed for demonstration and quantitation of antibodies against *Mycobacterium leprae* antigen 7 which cross-react extensively with a similar antigen in many species of mycobacteria, including BCG-antigen-60.

The antibody activity against *M. leprae* antigen 7 showed only a slight tendency to decrease in 15 patients with lepromatous leprosy during their first year of treatment with dapsone associated with marked clinical improvement.

Introduction

Sera from patients with lepromatous leprosy contain strong antibodies against various mycobacterial antigens. The stimulus for their formation is probably antigens released from *Mycobacterium leprae in vivo* both during the subclinical stage and during the period with overt clinical disease. Prior stimulation by cross-reacting antigens originating from environmental mycobacteria may also be of importance for the intensity and the specificity of the antibody response. By double-diffusion tests in gel against a culture filtrate of *Mycobacterium tuberculosis*, Rees *et al.* (1965) found a gradual but steady fall in the amount of precipitating antibodies in lepromatous patients during dapsone (DDS) treatment.

Harboe *et al.* (1977*a*) have developed a specific radioimmunoassay for demonstration and quantitation of antibodies against BCG-antigen-60, a prominent antigenic component of BCG bacilli which cross-reacts with similar components in many mycobacterial species including *M. leprae* and *M. tuberculosis*. In a lepromatous serum pool there was anti-BCG-60 activity with

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* Requests for reprints should be addressed to: Dr R. Melsom, Institute for Experimental Medical Research, Ullevaal Hospital, Oslo 1, Norway.

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a titre of 10^5, whereas the titre in a tuberculoid serum pool was 10^4. In tests of individual lepromatous sera, a striking variation in antibody content was observed. It has not yet been established to what extent variation in antibody content is related to particular clinical features. In tuberculoid leprosy, the median antibody content was distinctly lower than in lepromatous leprosy. Again there was a wide variation in antibody content in individual sera, and 5 out of 20 sera from patients with tuberculoid leprosy had a higher anti-BCG-60 antibody content than the median value of the lepromatous group (Harboe *et al.*, 1977*b*).

The purpose of the present investigation was:

(1) To develop a radioimmunoassay for antibodies against the corresponding antigen of *M. leprae* called *M. leprae* antigen 7 (Harboe *et al.*, 1977*c*)
(2) To initiate a long term study of anti-*M. leprae* 7 antibody activity during DDS treatment of patients with lepromatous leprosy.

Materials and Methods

PATIENT SERA

Fifteen patients attending the Addis Ababa Leprosy Hospital were selected for the study. The patients were classified clinically and histologically according to the extended Ridley-Jopling scale (Ridley and Jopling, 1966; Ridley and Waters, 1969; Myrvang *et al.*, 1973), 5 patients having LL, 5 patients having LI and 5 patients having BL leprosy. One patient (No. 11), included in Fig. 5, had a dual mycobacterial infection, BB/BL leprosy and tuberculosis. All the patients started treatment with DDS at the point of inclusion into the study, except one (patient No. 13) with a disease history of 10 years. He had been treated with DDS for 2 years and then had no treatment for 8 years before inclusion into the study. The first bacteriological index was determined and the first serum sample was obtained at the beginning of the study. The median observation period was 12 months, with a range of 10 to 16 months.

Treatment consisted of DDS in a dose of 100 mg daily, except in patient No. 1, a 13-year-old boy, who received 50 mg DDS daily. The patients were seen regularly and evaluated by clinical criteria for regression of nodules, decrease of infiltration in the skin, nerve conduction velocity and bacteriological index.

IMMUNOLOGICAL TECHNIQUES

Preparation and labelling of M. leprae *antigen 7*

The methods used were based on previous experience with purification and labelling of BCG-antigen-60 (Harboe *et al.*, 1977*a*).

M. leprae was provided by IMMLEP as freeze-dried bacilli (the A/10 preparation) purified from liver tissue of an infected armadillo by Draper's procedure (Draper, 1976). *M. leprae* (60 mg dry weight) was suspended in 10 ml 0.1 M phosphate buffer pH 7.4 and sonified on ice for 20 min with the

Branson B-12 sonifier at 80 W effect (Branson Sonic Power Co., Danbury, Conn., U.S.A.). After centrifugation for 15 min at 20,000 **g** at 4°C, the supernatant fluid was collected and served as unlabelled, crude *M. leprae* antigen. An aliquot of this preparation was labelled with ^{125}I by electrolytic iodination as described previously (Harboe *et al.*, 1977*a*). Free iodide and non-covalently bound iodide were removed by extensive dialysis against phosphate-buffered saline at 4°C, and the iodinated preparation was diluted in immunoassay buffer and stored at −25°C until used.

Radioimmunoassay (RIA).

The procedure previously described for assay of antibodies against BCG-antigen-60 (Harboe *et al.*, 1977*a*, *b*) was used. The technique is based on the separation of antibody-bound labelled antigen from free antigen by the use of protein A containing staphylococci which serve as a solid phase and have a marked capacity to bind IgG antibodies (Jonsson and Kronvall, 1974). Briefly, each tube contained 100 µl of the appropriate serum dilution and 100 µl of labelled *M. leprae* antigen 7 providing around 20,000 counts/400 s. The mixtures were incubated for 30 min at room temperature before addition of 2 ml 1% formalinized staphylococci of the Cowan I strain (NCTC 85308). All dilutions of unlabelled (cold) and labelled proteins and of sera were made in immunoassay buffer of the following composition: phosphate-buffered saline of pH 7.4 with 0.03 M NaN_3, 0.001 M EDTA, and 0.2% human serum albumin (Reinst, Behringwerke, Marburg-Lahn, Germany). After the reagents had been mixed, the tubes were spun at 1500 **g** for 20 min, the supernatant was carefully sucked off and the radioactivity determined in the bacterial pellet. All values are given as mean values of double tests and in experiments where this is appropriate expressed as radioactivity bound to staphylococci in per cent of maximum binding activity by a reference serum containing strong anti-*M. leprae* antigen 7 activity. To establish maximum binding activity, this serum pool was tested in dilutions 1:10, 1:20, 1:40 and 1:80. All these dilutions showed the same binding activity indicating antibody excess.

TECHNICAL PROCEDURES

The following procedures have been described previously: crossed immunoelectrophoresis (CIE) with intermediate gel (Axelsen *et al.*, 1973; Harboe *et al.*, 1976); radioautography (Harboe *et al.*, 1977*a*); gel filtration (Harboe *et al.*, 1977*a*); immunization procedures and antisera (Harboe *et al.*, 1977*c*).

Results

DEVELOPMENT OF THE ASSAY FOR ANTIBODIES AGAINST *M. LEPRAE* ANTIGEN 7

Among the constituents of a BCG sonicate, antigen 60 has a particular affinity for iodine during electrolytic iodination. When crude preparations of BCG-antigen-60 with several contaminating antigens were iodinated, selective labelling occurred and the product could therefore be used for a specific assay

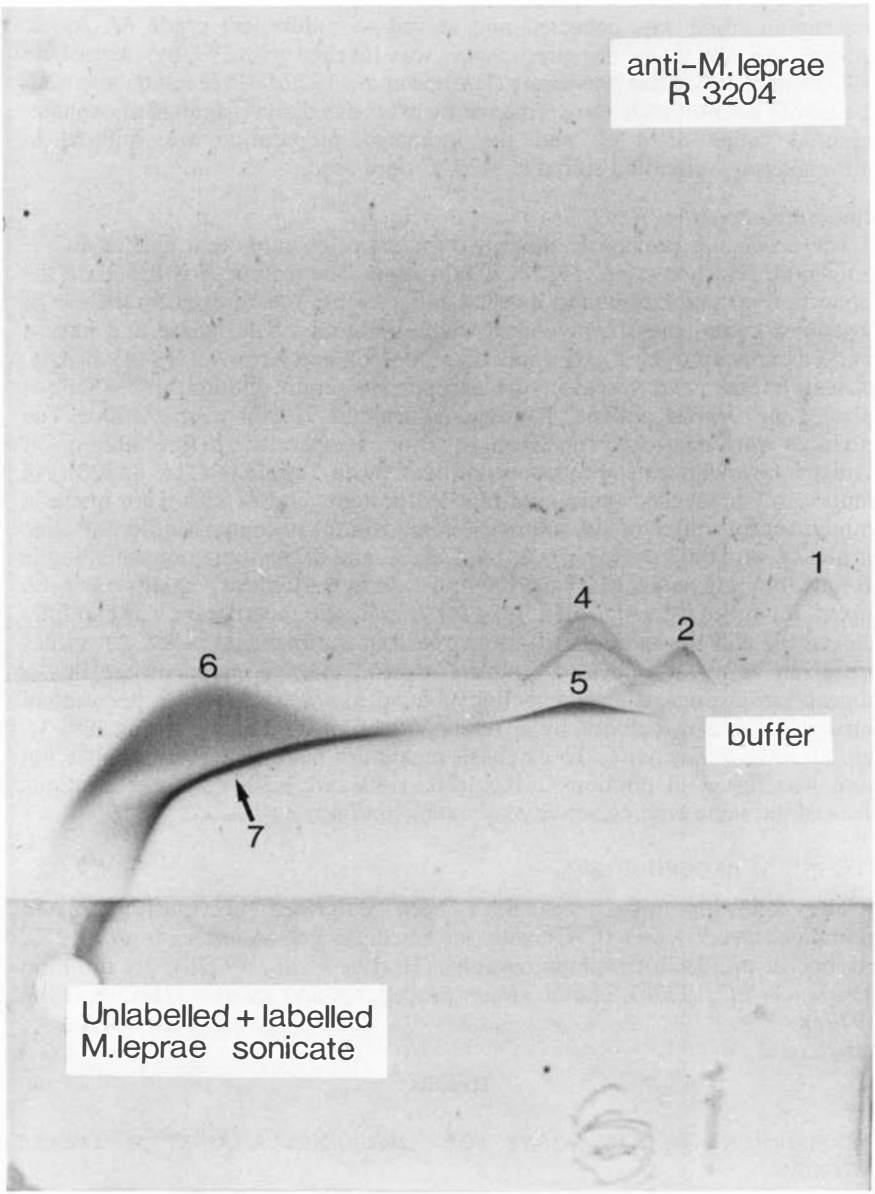
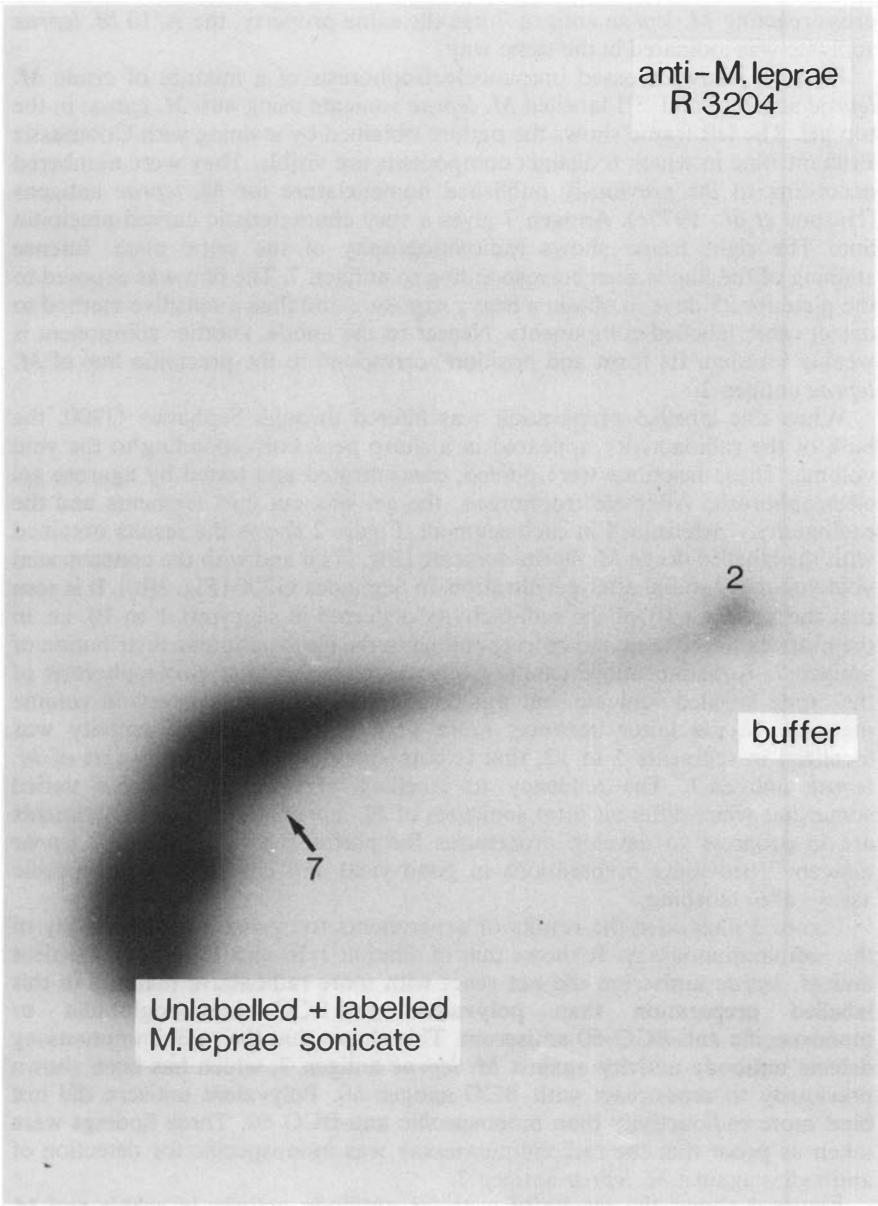


Fig. 1. Crossed immunoelectrophoresis of *M. leprae* sonicate mixed with ^{125}I-labelled *M. leprae* sonicate. The left frame shows the plate after protein staining, the right frame after



radioautography. The bulk of the radioactivity was localized in a single precipitin line corresponding to antigen 7. Weak radioactivity also occurred in component No. 2.

of anti-BCG-60 antibodies (Harboe *et al.*, 1977*a*). To examine whether the cross-reacting *M. leprae* antigen 7 has the same property, the A/10 *M. leprae* sonicate was iodinated in the same way.

Figure 1 shows crossed immunoelectrophoresis of a mixture of crude *M. leprae* sonicate and ^{125}I-labelled *M. leprae* sonicate using anti-*M. leprae* in the top gel. The left frame shows the pattern obtained by staining with Coomassie Brilliant Blue in which 6 distinct components are visible. They were numbered according to the previously published nomenclature for *M. leprae* antigens (Harboe *et al.*, 1977*c*). Antigen 7 gives a very characteristic curved precipitin line. The right frame shows radioautography of the same plate. Intense staining of the film is seen corresponding to antigen 7. The film was exposed to the plate for 28 days to obtain a heavy exposure and thus a sensitive method to detect other labelled components. Nearer to the anode, another component is weakly labelled. Its form and position correspond to the precipitin line of *M. leprae* antigen 2.

When this labelled preparation was filtered through Sephadex G200, the bulk of the radioactivity appeared in a sharp peak corresponding to the void volume. These fractions were pooled, concentrated and tested by agarose gel electrophoresis. After electrophoresis, the gel was cut into segments and the radioactivity determined in each segment. Figure 2 shows the results obtained with the labelled crude *M. leprae* sonicate [Fig. 2(a)] and with the concentrated void volume material after gel filtration on Sephadex G200 [Fig. 2(b)]. It is seen that the greater part of the radioactivity occurred in segments 1 to 10, i.e. in the most cathodic area and corresponding to the electrophoretic distribution of antigen 7. A distinct more anodic peak was obtained after electrophoresis of the crude labelled sonicate, but this fraction was smaller in the void volume material. In the latter instance, more than 95% of the radioactivity was localized in segments 1 to 12, that is corresponding to the major part of *M. leprae* antigen 7. The tendency to labelling of other components varied somewhat when different total sonicates of *M. leprae* were used. Experiments are in progress to develop procedures for partial purification of *M. leprae* antigen 7 providing preparations in good yield and consistent monospecific assays after labelling.

Figure 3 illustrates the results of experiments to evaluate the specificity of the radioimmunoassay. It shows that in dilution 1:10 and 1:100, a polyvalent anti-*M. leprae* antiserum did not react with more radioactive material in this labelled preparation than polyvalent anti-BCG immunoglobulin or monospecific anti-BCG-60 antiserum. This shows that the radioimmunoassay detects antibody activity against *M. leprae* antigen 7, which has been shown previously to cross-react with BCG-antigen-60. Polyvalent antisera did not bind more radioactivity than monospecific anti-BCG-60. These findings were taken as proof that the radioimmunoassay was monospecific for detection of antibodies against *M. leprae* antigen 7.

Figure 4 shows the results of tests for antibody activity in rabbit anti-*M. leprae* antisera and in various pools made from human sera. It may be seen that the lepromatous serum pool contains potent antibodies against *M. leprae* antigen 7. The pool of sera from patients with tuberculoid leprosy also had strong antibody activity, but with a distinctly lower titre. To compare the

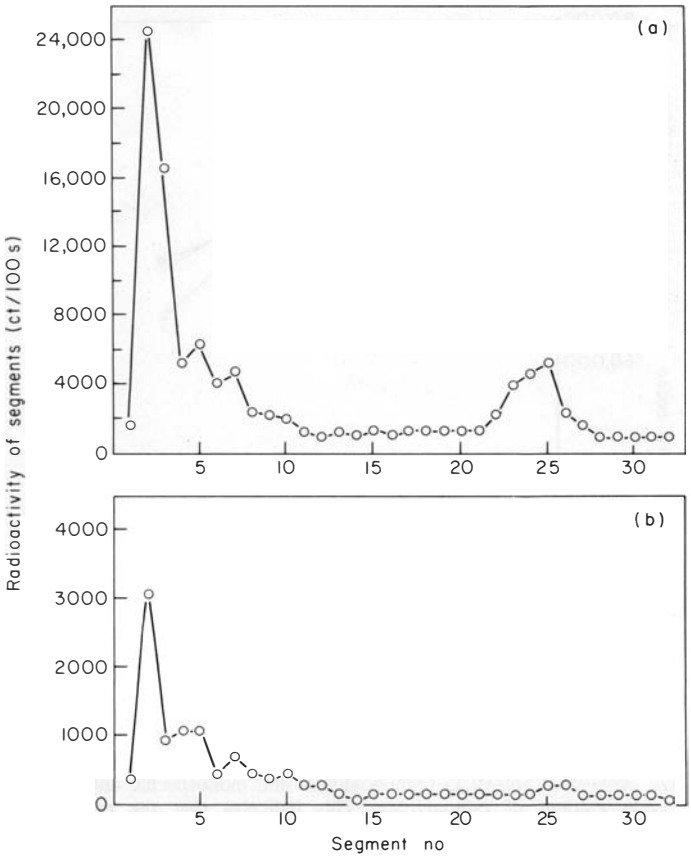


Fig. 2. Agarose gel electrophoresis of labelled *M. Leprae* sonicate (a) and concentrated void volume material after gel filtration through Sephadex G 200 (b). The bulk of the radioactivity occurred in segments 1 to 10 corresponding to the electrophoretic distribution of antigen 7. A small, but distinct peak occurred in later segments. After electrophoresis of the void volume material, the second peak was smaller amounting to less than 5% of the total radioactivity.

antibody content of different serum samples taken from the same individual, several principles may be used. We decided to test a single dilution made simultaneously from all serum samples obtained from a given patient and to test them against the same labelled antigen preparation. A dilution of 1:10,000 was selected to provide an assay sensitive for variation in antibody content. Many lepromatous sera will give maximum binding activity at dilution 1:1000 and at this dilution the system is rather insensitive to changes in antibody concentration particularly with regard to the strongest reacting sera.

Figure 5 shows the results of tests of 9 different patients whose curves were typical of all the patients observed.

Patients No. 8 and 10 showed a continuous and slight decrease in antibody

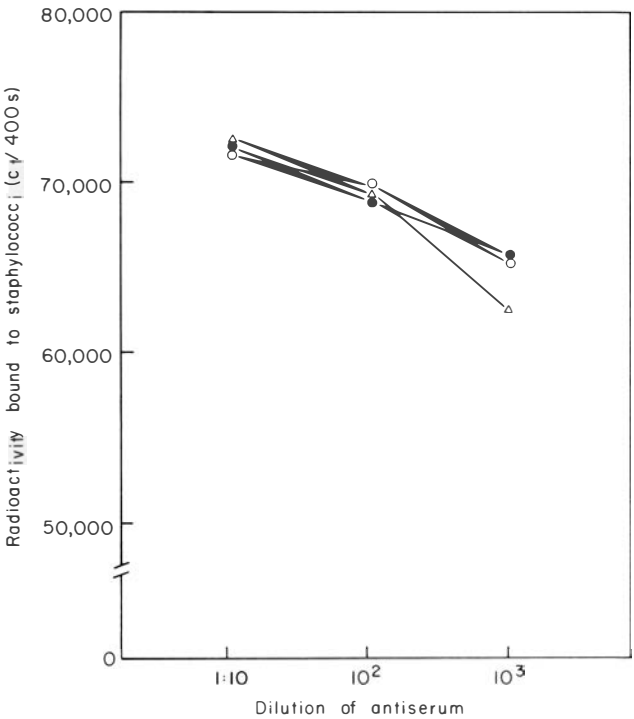


Fig. 3. Radioimmunoassay with ^{125}I-labelled *M. leprae* sonicate. At dilution 1:10 and 1:100, anti-*M. leprae*, polyvalent anti-BCG immunogloblin and monospecific anti-BCG-60 antibody bound the same amount of radioactivity. This indicates that the radioimmunoassay is monospecific for antibodies against *M. leprae* antigen 7 which cross-reacts with BCG-antigen-60. (△—△) Anti-*M. leprae*; (○—○) anti-BCG; (●—●) anti-BCG-60.

activity during the observation period. Patient No. 6 showed a marked fluctuation in antibody activity and patients No. 7, 16 and 17 showed patterns with less fluctuation. Taken as a whole, the findings showed that there is a tendency to slowly decreasing concentration of antibodies against anti-*M. leprae* antigen 7 during the first year of DDS treatment in lepromatous leprosy. Careful clinical observations with demonstration of resolving nodules, decreasing infiltration in affected skin areas, decreasing bacteriological index, and marked improvement in nerve conduction velocity demonstrated a clinical effect of the DDS treatment as expected in patients with DDS sensitive bacilli. The form of the curves did not show any consistent pattern related to clinical improvement or to development of reactions which were observed in 11 of the patients. Nine of them experienced slight to moderate erythema nodosum leprosum (ENL), and 2 had severe ENL.

Patient No. 11, included in Fig. 5, is the only one in whom antibody activity increased slowly and steadily throughout the observation period. He was entered into the study in May 1975 with a diagnosis of BB/BL leprosy and

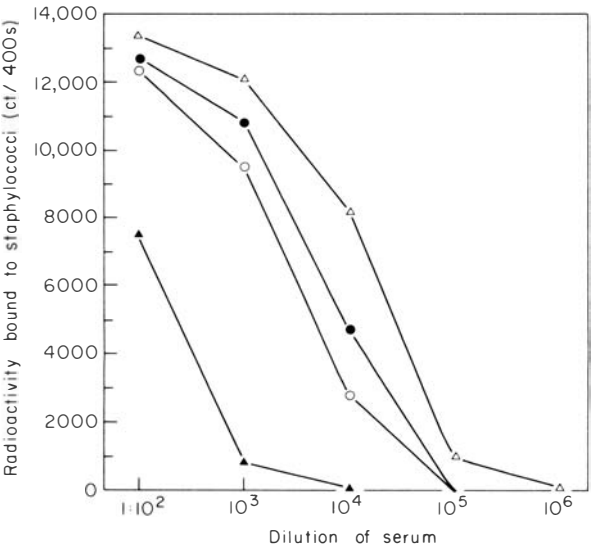


Fig. 4. Radioimmunoassay for antibodies against *M. leprae* antigen 7 in 4 serum pools. (△—△) Anti-*M. leprae*; (●—●) lepromatous pool; (○—○) tuberculoid pool; (▲—▲) contact pool.

developed a typical reversal reaction. In August 1975 treatment with prednisolone had to be started and he was given 30 mg daily for 1 week, 20 mg daily for 2 weeks and 10 mg daily for 7 months. In October 1975 he developed clinical and X-ray features of active pulmonary tuberculosis. Since he suffered from a dual mycobacterial infection he was excluded from the calculation of the decrease in antibody activity in Table 1. The demonstration of a steady increase in antibody concentration in this patient should be related to the previous observation that sera from patients with active pulmonary tuberculosis often contain strong anti-BCG-60 antibodies (Harboe *et al.*, 1977*b*).

Discussion

Recent studies with CIE have provided new information on the antigenic structure of mycobacteria. In several mycobacterial species, e.g. *M. tuberculosis, M. smegmatis* and *M. lepraemurium,* more than 40 distinct antigenic components have been detected (Closs *et al.*, 1975; Kronvall *et al.*, 1975; Janicki *et al.*, 1976). Immune reactions in mycobacterial disorders should therefore be studied in terms of reactions against defined antigenic components of the mycobacteria. This requirement is difficult to fulfil in studies of cell-mediated immune reactions since this would require studies using highly purified antigenic components of the mycobacteria.

For characterization of antibody specificity in mycobacterial infection, crossed immunoelectrophoresis with intermediate gel containing patient serum is a particularly valuable technique (Axelsen *et al.*, 1974; Closs and Kronvall,

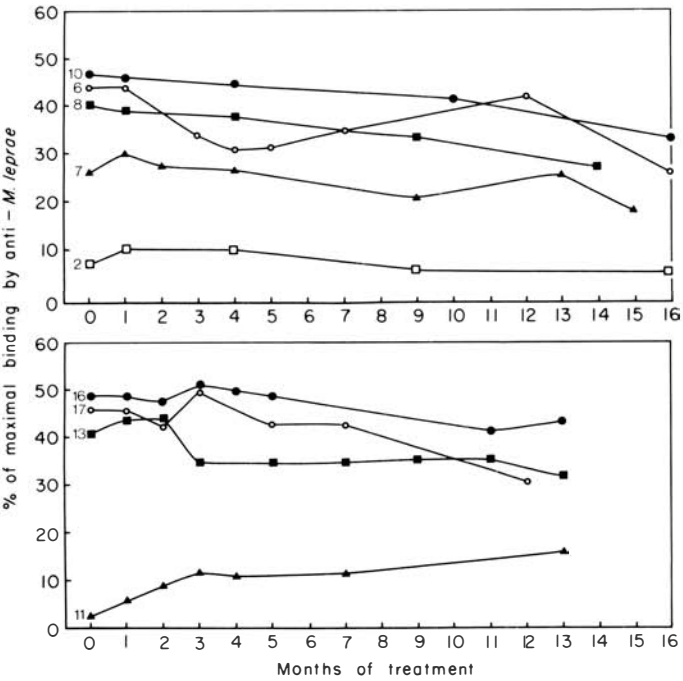


Fig. 5. Radioimmunoassay for antibodies against *M. leprae* antigen 7 in serial serum samples obtained from 9 patients during the first year of DDS treatment for lepromatous leprosy. The ordinate shows antibody activity expressed as percent of maximal binding by a polyvalent anti-*M. leprae* antibody.

1975, Kronvall *et al.*, 1975; Harboe *et al.*, 1977*c*). For quantitative and sensitive studies of antibody formation against defined antigenic components, radioimmunoassays may be used. Monospecific test systems can be established provided that an antigenic preparation is available in which only one component is labelled. In this case the test will only detect antibody activity against this component even though other antigen antibody reactions may take place simultaneously in the tube, but against unlabelled components.

Harboe *et al.* have developed a specific radioimmunoassay for antibodies against BCG-antigen-60 and have used the assay to study antibody formation against this antigen in rabbits during experimental immunization (Harboe *et al.*, 1977*a*), and in leprosy and in various types of control sera (Harboe *et al.*, 1977*b*). In the present paper, we describe a similar test for demonstration and quantitation of antibodies against the cross-reacting antigen 7 of *M. leprae.* To the best of our knowledge this is the first quantitative test for antibodies against a defined protein component of *M. leprae.*

Figure 5 and Table 1 show that there is a slight decrease in antibody activity against this antigen during the first year of DDS treatment in lepromatous leprosy. On the whole, the startling observation is that anti-*M. leprae* antigen 7 activity remains strong in patients with lepromatous leprosy during the first

TABLE 1

Antibody activity against M. leprae *antigen 7 in 15 patients with lepromatous leprosy before and after 10 to 16 months treatment with DDS*

Patient No.	Antibody activity		Difference
	At the start of the study	At the end of the study	
1	25	24	−1
2	7	6	−1
3	31	32	+1
6	44	28	−16
7	26	19	−7
8	40	30	−10
9	41	35	−6
10	47	35	−12
12	43	37	−6
13	41	32	−9
14	45	42	−3
16	49	44	−5
17	46	32	−14
18	44	32	−12
20	49	27	−22
		Median value	−7.0

year of DDS treatment even when they show marked clinical improvement. Our observations regarding a single, although widely cross-reacting antigen of *M. leprae* are very similar to those of Rees *et al.* (1965). By double-diffusion tests in gel against a culture filtrate of *M. tuberculosis*, they found a gradual but steady fall in the amount of precipitating antibodies in lepromatous leprosy during DDS treatment.

Bjorvatn *et al.* (unpublished observations) used serial serum samples from individual patients with lepromatous leprosy in the top gel of CIE against an *M. leprae* sonicate. The precipitate pattern, i.e. the antibody specificity, varied from patient to patient but it was remarkably stable in each patient during the first year of DDS treatment.

Currently available *M. leprae* sonicates contain fewer antigenic components than similarly prepared sonicates from cultivable mycobacteria. These components in *M. leprae* are characterized by extensive cross-reactions with other species of mycobacteria (Harboe *et al.*, 1977*c*). *M. leprae* is characterized by a long generation time. Several years of bacterial growth are therefore required after the initial infection to produce the clinical features observed in our patients. The immune system of these patients has thus been exposed to antigens released from live, dying or dead leprosy bacilli during several years. This prolonged exposure is probably a very potent stimulus for the immune system. In addition, these patients are also exposed to antigens from other environmental mycobacteria. The latter stimulus may induce antibody formation in normal individuals (Harboe *et al.*, 1977*b*) and may also be important to sustain the antibody production in patients treated for

mycobacterial disease. Acid-fast bacilli are destroyed very slowly in humans and in experimental animals, even during effective treatment of mycobacterial infections. Taken together, these features indicate that it may take several years before anti-mycobacterial antibodies disappear during DDS treatment of leprosy. *M. leprae* antigen 7 cross-reacts with a similar antigen in many other species of mycobacteria. Additional information concerning the stimulus for antibody formation in leprosy should be obtained by comparing the behaviour of antibodies against widely cross-reacting antigens with antibodies reacting with antigenic determinants specific for *M. leprae* in long term studies.

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The Epidemiology of Leprosy in the New Hebrides

R. C. RATARD* AND L. L. BRAVO†
**Chief Medical Officer, Rural Health Service, Vila, New Hebrides, and †WHO Leprologist*

This epidemiological study of leprosy in the New Hebrides was based on a survey of the population (41% coverage), and the results of 20 years of case finding. The annual incidence of new cases is 0.45 per thousand. Thirteen percent are of lepromatous type. Leprosy predominates among males. The incidence of leprosy cases increases with age until the age group 30 to 44. Leprosy is concentrated in families, in villages and in foci in which the prevalence is high. The prevalence is also very high among contacts. Most of the foci are well under control but some are still developing. In some areas there is a possibility of a small outbreak occurring. Leprosy being one of the major public health problems in the New Hebrides, a careful and selective control programme is indispensable.

Introduction

The New Hebrides is a group of islands in the Southwest Pacific 1200 miles off the eastern coast of Australia, lying between 13° and 21° south. There are 12 major islands (500 to 3000 sq. km each) and 100 tiny islets. Around the volcanic frame the coral reefs have built up low platforms, hence a mixture of mountainous areas surrounded by small coastal plains and corallian islets. The climate is tropical, hot and humid with rainy season from December to May. The indigenous people are Melanesians. Several hundreds of years ago there were migratory waves of Polynesians who settled on the coasts and islets. In these areas the indigenous population is a mixture of the original Melanesians and of Polynesians.

Although the New Hebrides was "discovered" in 1606, the first important contacts with Europeans took place during the 19th century. The epidemics that swept over the country during this period were the causes of an intense depopulation. The trend was reversed only during the 1920's . The population density is low, only 6 per sq. km, and some islands are still very scarcely populated.

Most of the people live in the rural areas in small villages of 20 to 50 inhabitants. Their main occupation is farming. Males spend most of their time working in the gardens, taking care of the harder tasks. They also cut copra, which is the main source of wealth. Hunting, fishing and pig farming are other sources of income. Women divide their time between gardening, where they perform the less strenuous tasks, and the household. Children are often raised in the extended family, including grandparents, uncles, aunts, and cousins. From age 6 to 14 the children attend the village schools. Girls do not spend as much time in schools as boys.

The living standards and the level of hygiene are low. The average family unit has 3 buildings, including at least one kitchen and one sleeping room. In the more primitive areas there are communal houses where 10 to 20 people sleep. The most common building materials are bamboo, corrugated iron sheets and thatch. Water is available from wells, springs, or rainwater drums. The majority of the people are Christian. There is an intense circular

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migration of young adults, mostly male, going to work for several years on the plantations or in the towns.

Very little is known about leprosy in the New Hebrides in the 19th and early 20th centuries. Leprosy is commonly thought to have been introduced by European ships or labour traffic between 1820 and 1870. The only earlier mention of leprosy was made by the French explorer Bougainville (1768) who named Aoba island the "Isle of Lepers" because of "the wounds with which these people were covered" (Dunmore, 1965). In Aoba there were many highly prevalent skin diseases that could have been mistaken for leprosy, such as ulcerative tertiary yaws, pityriasis versicolor and tinea imbricata.

In 1883 the first cases of leprosy officially notified in New Caledonia were among 4 New Hebrideans (Ragusin, 1951). However, at that time it was not widely spread. Missionaries from both Epi and Tongoa reported the absence of leprosy in their respective islands in 1894 (Cantile, 1927). In *"The History of the Melanesian Mission"* no mention was made of leprosy, even in Mota Lava where it became highly prevalent (Armstrong, 1900).

In 1925 Buxton and Lambert noted that "leprosy is distributed all over the New Hebrides, but it is nowhere common" (Buxton, 1927). Twelve cases were found on Tanna.

In 1932 Placidi mentioned the existence of a single case in a southeastern plantation of Santo and of a small focus on Tanna island. This focus on West Tanna vanished with the deaths of the lepers, but 10 years later in 1946 a girl from the same area developed the disease (Davies, 1951). Meanwhile in 1940 a lepromatous male working on a ship came back to his village in Port Resolution, East Tanna, From this case stemmed a new focus of leprosy. In 1962 to 1963 among 3100 people examined 39 had leprosy, i.e. a prevalence of 12.6 per thousand. Most of the cases were intrafamiliar (Mahé, 1964). On West Tanna there was only one case left.

In 1940 only one case was reported on Paama (Balzeau, 1940).

The first comprehensive survey was done by Davies from 1948 to 1951 (Davies, 1951). 21,514 persons, representing 43% of the whole population were examined (Table 1). Ninety-six leprosy cases or 4.4 per thousand examined were discovered. Some foci of leprosy were already well established on Mota Lava, West and South Santo, Malekula, Pentecost, Ambrym and East Tanna.

In the next 10 years leprosy spread in the Mota Lava focus and all over the Banks group.

TABLE 1
Davies leprosy survey of the New Hebrides 1948 to 1951

Island–area	Total population	Population seen	Cases discovered	Discovered cases per thousand examined
Torres	160	102	0	0
Banks Mota Lava	639	365	13	36
Other island	1955	1135	0	0
Santo & islets	4820	1498	32	22
Aoba	4203	2076	2	1.0
Maewo	850	475	0	0
Malekula	7500	4256	10	2.3
Pentecost	5400	2133	12	5.6
Ambrym	4100	1591	9	5.7
Paama	1400	1042	5	4.8
Lopevi	150	137	0	0
Epi Lamen	1400	838	2	2.4
Sheperds	2500	1683	5	2.9
Efate & islets	5000	2121	2	0.9
Tanna	7400	1252	4	3.2
Sthern islands	1080	810	0	0
Total	48,557	21,514	96	4.4

TABLE 2

Age group distribution at diagnosis by sex and types

		0–14		15–29		30–44		45–59		60+		Total known		Unknown		Total		Total
		M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	
Number of	I	25	15	7	2	4	2	0	0	0	0	36	19	11	2	47	21	68
new cases	T & B	76	67	85	40	42	26	26	12	11	5	240	150	97	41	337	191	528
1957–1976	L	8	7	15	8	23	6	5	2	0	0	51	23	16	6	67	29	96
	Total	109	89	107	50	69	34	31	14	11	5	327	192	124	49	451	241	692
% of cases	I	20		6		6		0		0		11		8		10		
per age	T & B	72		79		68		84		100		75		80		77		
group	L	8		15		26		16		0		14		12		13		
	Total	100		100		100		100		100		100		100		100		
Sex ratio	L	1.1		1.9		3.8		2.5		–		2.2		2.7		2.3		
M/F	Total	1.2		2.1		2.0		2.2		2.2		1.7		2.5		1.9		

Eight new cases had appeared in Mota Lava, bringing the total to 20 known cases (prevalence of 28.6 per thousand, incidence of new cases per year of 2.9 per thousand, Quentin, 1956).

From 1957 to 1972 the government and mission medical services carried on the case detection, treatment and follow-up of leprosy patients. A leprosarium was established in Aoba and most of the leprosy patients from the northern district were taken care of through the leprosarium. In 1973 a national leprosy control programme was established within the Rural Health Service.

Material and Methods

In order to assess the epidemiological situation of leprosy in the country, 2 methods were used:

(1) A systematic case-finding survey was undertaken from October 1973 to 1976. The objectives of the survey were to establish leprosy prevalence rates in some islands, to complete the date on the leprosy patterns in known foci of leprosy and to assess the situation in unknown areas. The survey was not based on a random sampling of the population, but rather on the following criteria: (a) examination of the entire population in the known foci of leprosy; (b) examination of as many leprosy contacts as possible; (c) examination of the entire population in areas where the situation was unknown; (d) examination of a small sample of population in areas where it was already established that leprosy was not prevalent.

(2) The establishment of a central register of all cases found. These cases were found during systematic case finding surveys carried out from 1957 to 1976. It is estimated that for this period of 20 years that at least 90% of the leprosy cases were registered. Because of this the epidemiological situation described in this paper can be considered as accurate.

The ages of patients mentioned throughout this work are the ages given at the time of diagnosis. For some patients ages were not recorded in years but as either children, adolescent, adult or elderly. These ages were recorded as unknown in Table 2, but since age group divisions of 15 years were used it seemed reasonable to include them in their age group to estimate the incidence of new cases.

Results

NUMBER OF LEPROSY CASES

In this period of 20 years, 1957 to 1976, a total of 692 cases were found. The average annual incidence for the period calculated with the population of 1967 was 0.45 per thousand per year. It is estimated that at least 80% to 90% of the new cases were registered.

During the 1973 to 1976 survey 40,789 people were examined (41% of the total population) and 119 new cases were found (2.9 new cases per thousand population examined). In December 1976 there were 253 leprosy patients considered as active and receiving treatment. This number of patients depends on the criteria used to release or keep patients on control.

TYPES OF LEPROSY

The distribution of the leprosy cases according to type is presented in Tables 2 and 3. The average incidence of new cases per thousand per year is also presented. Thirteen per cent were

TABLE 3
Distribution of leprosy according to types

	I	T	B	L	Total
Number of cases	68	322	206	96	692
Percentage	10	47	30	13	100
Incidence of new cases per yr per 1000	0.04	0.21	0.13	0.07	0.45

lepromatous, 10% indeterminate, and 77% borderline and tuberculoid. The criteria of distinction between borderline and tuberculoid varies with successive surveys. Due to this the distinction between these 2 types is not very meaningful.

The proportion of lepromatous cases is low as in the African countries. It is also low in comparison with other countries of the South Pacific. The low proportion of indeterminates indicates that diagnosis is made late when the disease has already developed into a more polar type. The average incidence of the lepromatous type is 0.07 per thousand per year. With such a low incidence a wide proportion of the population is not exposed to infectious cases.

LEPROSY AND SEX

Leprosy is more common in males than in females as shown by the incidences of new cases per year per thousand. There is an incidence of 0.56 among males and 0.34 among females using as a denominator the population in 1967. The male/female ratio is 1.9:1. The distribution of leprosy types is similar among males and females and the ratios are 2.2:1 for indeterminate, 1.8:1 for tuberculosis and borderline, and 1.9:1 for lepromatous.

TABLE 4
Distribution of leprosy according to sex

		M	F	Total
Number of cases	Total	451	241	692
	I	47	21	68
	T & B	337	191	528
	L	67	29	96
Incidence of	I	0.06	0.03	0.04
new cases per yr per	T & B	0.42	0.27	0.34
thousand	L	0.08	0.04	0.07
	Total	0.56	0.34	0.45

It has been commonly observed that the ratio between male and female lepromatous is 2:1 but in non-lepromatous leprosy, the ratio is not as high. This predominance of male lepromatous is thought to be due to a higher susceptibility of males.

LEPROSY AND AGE

The data on distribution of leprosy by age groups of 15 years are presented in Tables 1 and 5. The incidence was calculated using as a denominator the population in 1967.

The incidence of new cases increases with age up to a peak at age 30 to 44 and then slowly decreases (Fig. 1).

TABLE 5
*Distribution of leprosy according to age**

		0–14	15–29	30–44	45–59	60+	Total
Est. number of cases		264	209	137	61	21	692
Incidence	I	0.07	0.03	0.03	0.00	0.00	0.04
of new cases	T & B	0.28	0.42	0.38	0.37	0.27	0.34
per thousand	L	0.03	0.07	0.16	0.13	0.00	0.07
	Total	0.38	0.52	0.57	0.50	0.27	0.45

* In this table an estimation was made about the age of the unknown to get rid of this category.

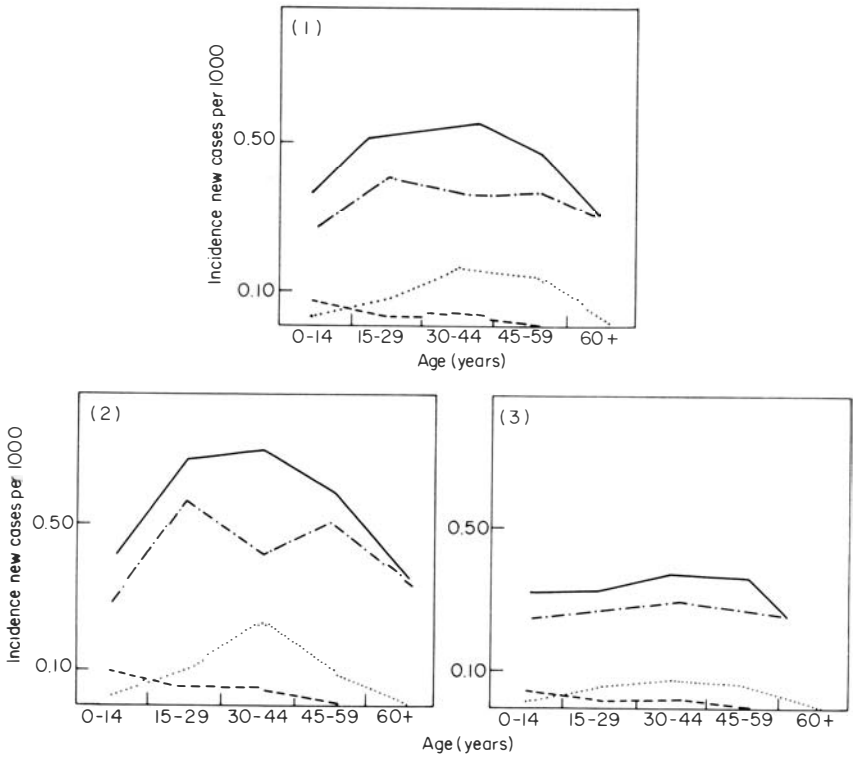


Fig. 1. Distribution of leprosy according to age. (———) total; (.–.–) B & T; (. . . . . .) L; (– – – –) I.

Fig. 2. Distribution of leprosy according to age among males. (———) total; (.–.–) B & T; (. . . . . .) L; (– – – –) I.

Fig. 3. Distribution of leprosy according to age among females. (———) total; (.–.–) B & T; (. . . . . .) L; (– – – –) I.

The sex distribution is not the same in all groups. The ratio of males to females is around 1:1 in the age group 0 to 14, then around 2:1 in the older age groups. This applies for all types of leprosy. In most surveys lepromatous leprosy was shown to have a male predominance only in persons over 14 years of age (Bechelli and Martinez Dominguez, 1963).

GEOGRAPHICAL DISTRIBUTION OF LEPROSY IN THE NEW HEBRIDES

Leprosy is distributed in foci with very high incidence and prevalence in some islands or areas and very low in others (Tables 6 and 7). In some islands, such as Mota Lava, the incidence may be as high as 3.25 per thousand per year. An incidence of new cases above 1 per thousand per year may be considered as high incidence in the New Hebrides.

There is a good correlation between the number of new cases per year and the number of active cases, with the number of active cases being about 5 times the number of new cases. In areas with a high proportion of lepromatous, the number of active cases tends to be higher since lepromatous patients are kept on treatment for years.

There is also a good correlation between annual incidence of lepromatous cases and annual incidence of all leprosy cases. In Fig. 4 each island or area was plotted according to their

TABLE 6
Geographical distribution of leprosy. New cases 1957 to 1976

Island	Area	Population 1967	New cases I	B + T	L	Total	Incidence New cases per 1000 per year L	Total
Torres	Mota Lava	200	0	0	1	1	0.25	0.25
Banks	Mota Lava	816	7	30	16	53	0.98	3.25
	Vanua Lava	747	1	12	4	17	0.27	1.14
	Mota	269	1	11	2	14	0.37	2.60
	Other	1,449	1	13	0	14	0	0.48
Santo	N.E. & C	4,932	4	44	8	56	0.08	0.56
Rural	South & Islets	2,504	12	94	15	121	0.26	2.37
	West	917	1	29	2	32	0.10	1.74
	Malo	1,594	0	3	1	4	0.03	0.12
Aoba		5,971	4	28	7	39	0.05	0.28
Maewo		1,196	0	5	0	5	0	0.21
Malekula		11,182	1	4	1	6	0	0.03
Pentecost		6,801	15	67	6	88	0.04	0.65
Ambrym		4,246	11	61	6	78	0.07	0.91
Paama		1,947	3	49	9	61	0.23	1.67
Epi Lamen		2,032	5	44	3	52	0.06	1.28
Sheperds		3,594	0	5	1	6	0.01	0.08
Efate	Rural	6,699	0	4	4	8	0.03	0.06
Tanna		10,476	2	21	6	29	0.03	0.14
Aniwa		227	0	4	3	7	0.66	1.54
South islets		1,110	0	0	1	1	0.04	0.04
Towns		7,673	0	0	0	0	0	0
Total		76,582	68	528	96	692	0.07	0.45

TABLE 7
Contact tracing

		Contacts examined	New cases	New cases per thousand
Index case	I	62	0	0
	T and B	555	5	9.0
	L	147	17	115.6
	Total	764	22	28.8

incidence of lepromatous cases and total leprosy cases. One would expect such a situation where the lepromatous prevalence is low (Newell, 1966).

Leprosy is not evenly distributed in these areas of endemicity. The distribution of leprosy at village level is as follows:

Villages with no cases at all	1753	87%
One case only	158	8%
2 to 5 cases	78	4%
5 to 10 cases	20	1%
More than 10 cases	11	0.5%
Total number of villages	2000	

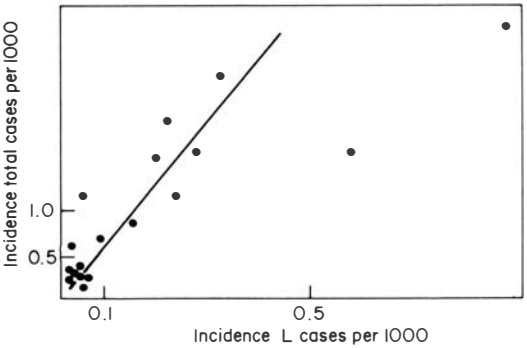


Fig. 4. Correlation between lepromatous and total cases.

The highest annual incidence may be quite high in some villages. It ranges from 5 per thousand to 20 per thousand in these 10 most endemic villages. This is 10 to 40 times more than the national average. This concentration of cases in villages has been observed in most endemic areas.

CONTACT TRACING, INTRAFAMILIAR CASES

For 405 cases data was available on the presence of other cases in the family. "Family" is considered to include father, mother, children, grandparents, and single aunts or uncles. There are about 10 persons in such a family and about 8 to 10,000 families in the country.

Families with a single case	110
2 cases	78
3 cases	22
4 cases	11
5 or more cases	7
Total	228

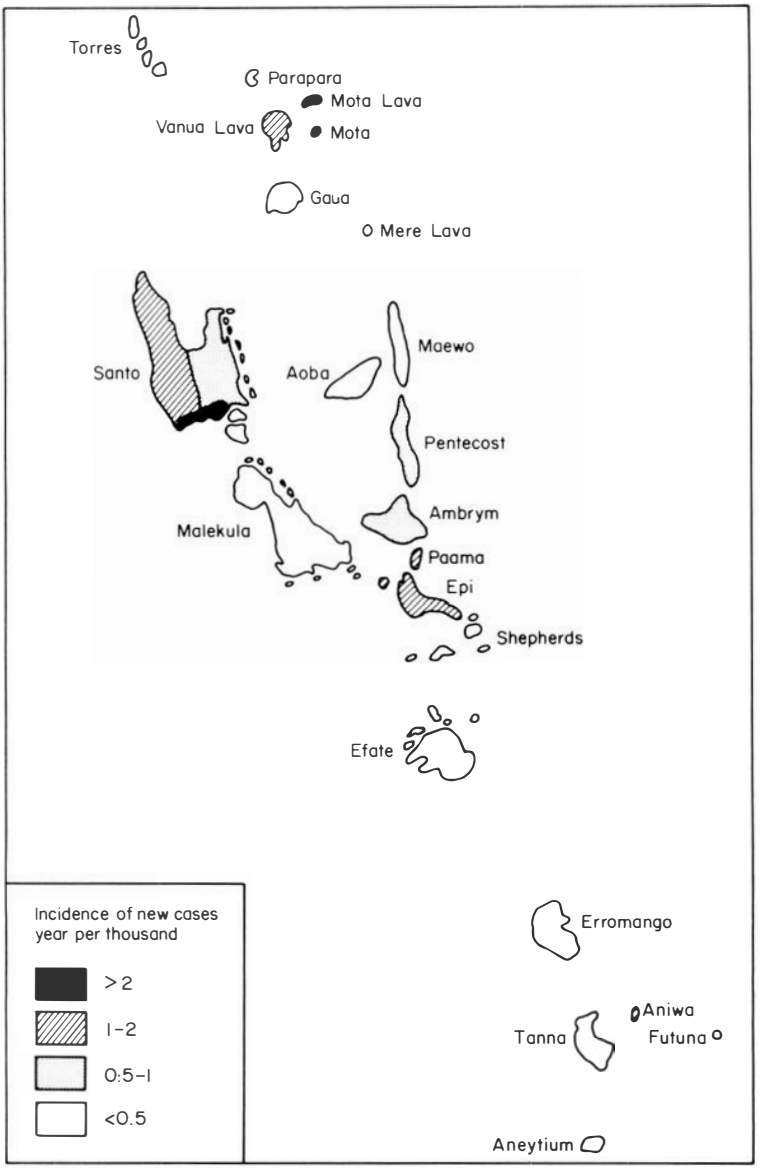
Contact surveys prove to be the most useful way to find new cases as shown in Table 7.

The rate for new cases discovered per examined (thousand) was 2.9 in the whole population, 9.0 among contacts of tuberculoid and borderline cases or 3 times more, and 116 among contacts of lepromatous cases or 40 times more. Similar observations in other countries showed twice the annual attack rate of the general community among contacts of tuberculoid cases and 8 times among contacts of lepromatous cases (Doull, 1961).

CLINICAL AND BACTERIOLOGICAL CONDITION OF PATIENTS

The data are presented in Table 8. The classical clinical patterns of leprosy types hold true for the New Hebrides. The percentage of disabled is high in comparison with other countries of the South Pacific [39% in the New Hebrides, 22% in French Polynesia, 17% in Tonga (Bechelli and Martinez Dominguez, 1972)]. The percentage of positive cases is 38% of the total cases, 100% of the lepromatous, 20% of the tuberculoid and borderline, and 4% of the indeterminate. The percentage of bacteriological positive cases for total cases is biased because more positive cases were examined.

The average duration of symptoms before diagnosis was 3 years 5 months for lepromatous, 2 years 7 months for tuberculoid and borderline. and 1 year 10 months for indeterminate cases.



Map of leprosy in the New Hebrides.

TABLE 8

Clinical and bacteriological status of patients at diagnosis

	Total number of cases	Cases studied	Clinical condition (%)								Disability			Bacteriology	
			Macules	Infiltrate	Nodules	Anaesthesia	Pain	Paralysis	Enlarged nerve	Ulcers	Cases studied	% dis.	D.I.	Cases*	Positive %
I	68	30	100	0	0	7	0	0	0	0	31	0	–	24	4
T + B	528	285	44	39	0	40	2	18	44	6	252	38	0.8	249	20
L	96	42	43	48	14	64	5	21	48	17	46	67	1.2	83	100
Total	692	357	49	36	2	68	2	19	46	7	329	39	0.8	356	38

* This distribution is biased, more L cases were studied.

Death rates cannot be presented since deaths of patients released from control are not recorded. However, the number of deaths among lepromatous seems to be 2 times greater than among other leprosy patients.

Discussion

Leprosy may be considered as a major public health problem in the New Hebrides. The number of active cases is 2.5 per thousand population, the number of lepromatous is 0.7 per thousand population. The incidence of new cases is 0.45 per thousand per year. These rates are low in comparison with other countries of the South Pacific. However, active measures of control have to be continued since the situation is not at all stabilized.

Due to a lack of previous data it is difficult to ascertain the evolution of the disease. Leprosy was believed to have been introduced about a 100 years ago in a few places. Foci of the disease developed slowly and the spread to other islands was hesitant and uneven. This illustrates the very slow progression of the disease due to a long incubation period, the scarcity of highly contagious cases, and the widespread resistance among the population. Leprosy is increasing in some islands. The existing pockets of lepromatous cases of Mota Lava and the northern half of Santo have maintained an active source of contagion. New cases are to be expected among the younger age groups.

In some islands of the southern half of the group, Epi, Paama and Eniwa, leprosy foci became established only within the last 20 years. A high number of new cases might be expected there in all age groups. Even in islands with no leprosy, such as Futuna and Anatom, or where leprosy was recently imported, as in Erromango, the possiblity of leprosy epidemics cannot be ruled out. In Pentecost, Malekula and Ambrym, the central islands, known foci are on the decline and have lost their potential of contagiousness. The present control programme must be flexible enough to adapt the preventive measures according to each area.

Area	Control measure to be specially recommended
(1) Any focus	Contact survey and follow up of patients
(2) Disappearing focus (Pentecost, Ambrym, Malekula)	No supplementary measure
(3) Old focus, still active (Mota Lava, West Santo)	Contact survey Case finding among children
(4) Recent focus, very active (Paama, Epi)	Contact survey Case finding among all age groups
(5) Recent focus, few imported cases (Erromango)	Contact survey
(6) Non-endemic area	No supplementary measure

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Associated Cases in the Families of School Children with Leprosy

R. GANAPATI AND C. R. REVANKAR

R.R.E. Society of the Acworth Leprosy Hospital, Wadala, Bombay 400 031, India

and

CHRISTINA AND ROMANO

Vimala Dermatological Centre, Versova, Bombay 400 061, India

The screening of 190 families in which children suffering from leprosy discovered through school surveys were present, yielded a total of 41 cases. Though the prevalence rate among the contacts was 44 per thousand, only in 14% of the families visited, another associated case could be found, and only in 2 instances out of 27 families, the associated case belonged to L type. The school surveys as well as contact examination yielded predominantly cases belonging to non-lepromatous type mostly with single lesions whose contribution to the pool of infection in the community is questionable.

Introduction

In recent times school surveys have come to be given an important place in several urban leprosy control projects. Even in rural areas where the proportion of school going children is comparatively small, screening of pupils regularly has been looked upon as an effective method of controlling leprosy, (Kurian *et al.*, 1975).

Working under constraints of limited resources and personnel, the exact order of priority which school surveys should be given in relation to other techniques of case detection and case holding in a leprosy control programme is not quite clear.

Views have been expressed (Noordeen, 1975*a*) that school survey may prove to be an important means of source case detection in the community, if examination of household contacts of school-detected cases is done methodically. This presupposes that a large number of intrafamilial "source cases" may be found through this means. Though school surveys are carried out extensively, no data are available from any of the projects proving the utility of this technique to detect source cases in the household. Ganapati *et al.* (1977), working on a small sample of children attending schools situated in the

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midst of a well demarcated and somewhat isolated slum showed that although school and family contact examination may be more economical with time, money and personnel, it may not result in the disclosure of a significant proportion of the cases in the community, and, more importantly, of infectious cases.

Subsequent to the above study larger samples were available from a few leprosy control projects in Bombay, and it was thought that the material could be pooled to assess the following features.

(i) prevalence rate of leprosy among household contacts of school-detected cases,
(ii) relation of the types of associated cases with those of index cases and
(iii) extent of yield of "progressive types" of leprosy from the school as well as contact samples.

Material and Methods

The children found to be suffering from leprosy through school surveys derived from the following 3 sources were considered as index cases.

(i) Vimala Dermatological Centre (schools in Versova and Andheri).
(ii) Bombay Leprosy Project (schools in Khar-Danda).
(iii) R.R.E. Society of Acworth Leprosy Hospital (schools in Janata Colony, Chembur) (Ganapti *et al.*, 1977).

The families of index cases were screened in order to detect the "source cases" if any. The material from the 3 sources was pooled for analysis.

The surveys of schools as well as families were conducted by trained para-medical workers, and case confirmation was done by medical persons experienced in leprosy after bringing the patients for examination at the clinic.

The simple field classification of N (non-lepromatous), L (lepromatous) and N?L (intermediate forms) as recommended by the National Leprosy Control Programme of India was followed. (Operational Guide and Guidelines of Assessment of Leprosy Control Work in India, 1969.) Bacteriological examination was done in the lepromatous type of cases.

Results

The following tables show the types of index cases and those of associated cases in the families.

TABLE 1
Cases in relation to families visited

No. of families visited	Proportion of coverage of family contacts	No. of leprosy cases in family contacts	Prevalence rate in contacts
190	930/1196 (77.7%)	41 (including 2 lepromatous cases)	44/1000

TABLE 2
Types of index cases and associated cases

Sr. no.	School case (index)		Contact case (associated)	Sr. no.	School case (index)		Contact case (associated)
1	N	—	N	14	N	—	N
2	N	—	N + N	15	N	—	N
3	N	—	N	16	N	—	N
4	N?L	—	N + N + N	17	N	—	N
5	N?L	—	N	18	N	—	L
6	N	—	N	19	N	—	N
7	N	—	N + N	20	N	—	N
8	N	—	N	21	N	—	N + N
9	N	—	N + N	22	N	—	N
10	N	—	N + N?L	23	N	—	N + N
11	N	—	N + N + N	24	N	—	N + N
12	N	—	N + N	25	N	—	N
13	N	—	N	26	N	—	L + N
				27	L	—	N + N

(1) Out of a total pool of 312 index cases (from school surveys), 190 families could be visited. A total of 1196 household contacts were identified, out of whom 930 were available for examination, representing a coverage of 77.7%.

(2) Forty-one cases were detected among these contacts, the prevalence rate among contacts being 44 per 1000.

(3) These 41 cases were actually found in 27 families owing to the existence of multiple cases in many families.

(4) In 14% of the families (27 out of 190) a single and multiple associated cases were found.

Discussion

(1) A prevalence rate of 44 per 1000 among contacts (taken as a group) is strikingly higher than the prevalence rate generally obtained from whole population surveys. This is to be expected and stresses the value of contact examination in general. Where facilities for whole population survey are limited, this technique may therefore be recommended.

(2) However only in a small proportion of cases i.e. 14% (27 out of 190) was another associated case found and only 2 instances were associated with L cases (Table 2; nos 18 and 26). So if our object is to unearth infectious sources in the whole community and bring them under treatment as an effective control measure in the community, this technique is poor as compared to mass surveys.

(3) Among the highlights were 2 instances, in which 4 case-families were present including the index case (Table 2; nos 4 and 11) and in 12 instances (Table 2), there were 3 or more cases in the family (including the index school case).

(4) The fact should be stressed that out of 190 families carefully searched, there were only 2 instances where associated lepromatous cases were found. In the remaining 25 instances only non-lepromatous cases were unearthed.

(5) Also the school survey itself yielded only 1 lepromatous case and 2 N?L cases; the remaining 24 were non-lepromatous mostly with single lesions and hence probably not of great public health significance. Studies by Browne (1974) and Noordeen (1975*b*) indicate the benign and non-progressive nature of single lesions belonging to the tuberculoid type.

(6) From Table 2 it is seen that in 3 instances (nos 4, 5 and 27) among the multiple case-families index cases were of N?L and L types, whereas family contact cases belonged to N type. The significance of this association in a larger sample of multiple case-families is being studied and will form the subject of a future communication.

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Encouraging Results From DDS Urine Analysis Among Registered Leprosy Patients in the Wangas, Kenya: An Exception That Challenges the Rule

HAN HUIKESHOVEN AND IMAN BIJLEVELD

Royal Tropical Institute, Mauritskade, Amsterdam, The Netherlands

From previous research among the Wangas (Kenya), it appeared to be the standard of medical services, and in particular the leprosy fieldworker's approach, rather than sociocultural factors, which accounts for failure of leprosy control.

The present investigation adds weight to these findings. Urine samples were taken from 39 patients of one highly reputable leprosy fieldworker, and analysed for DDS/creatinine ratios. Comparison with data from elsewhere demonstrates their scrupulousness in weekly DDS-taking at home.

Introduction

In 1975 to 1976 a sociological research project was carried out in Western Province, Kenya, in an attempt to better understand the rapid turnover of registered leprosy patients in the West Kenya Leprosy Control Project (WKLCP).

Erratic attendance appeared to put effective control out of the question. Although before researchers entered the field it was believed that social and cultural variables would account for patients' problematic behaviour, eventual findings demonstrated that the failure of control efforts were more easily attributed to short-comings in the quality of those administering leprosy care services than to consequences of the values system adhered to by those receiving these services (Varkevisser, 1977; Bijleveld, 1976, 1977). This conclusion was reached in part after a study in the Wangas of patients and ex-patients of 2 leprosy fieldworkers (LFW) of vastly different calibre, one a model of conscientiousness and the other somewhat lax in job performance. There was virtually no defaulter problem at any of the superior leprosy fieldworker's clinics. Some irregularity of attendance did occur, but of acceptable proportions. The fieldworker's success must first and foremost be ascribed to his holding of clinics on schedule without fail, and his ability to demonstrate personal concern for the well-being of his patients. The contrasting fieldworker did not always appear at his clinics; when he did, his

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behaviour towards patients was abrupt and authoritarian. Defaulters from his clinics, and even patients who continued to attend had built up grudges against the man. He did not seriously attempt to give health education or to motivate patients to ingest medicine punctually. If one endeavours to characterize the leprosy treatment available at clinics throughout the WKLCP, one must admit that the inferior LPW was more typical than his colleague.

Apart from the question of how regularly patients attended their clinics and received their monthly allotment of diaminodiphenyl sulphone (DDS), essential doubt remained whether they swallowed their DDS faithfully as instructed between clinic dates at home. Urine analysis of patients who were "regular attenders" at clinics in Malawi, Ethiopia and Tanzania has shown that such regularity does not guarantee satisfactory intake of DDS without supervision at home (Ellard *et al.*, 1974*b*; Low and Pearson, 1974; Huikeshoven *et al.*, 1976). Would the same pattern emerge from analysis of the urine of the "regular attenders" of the superior LFW in the Wangas? Or would the extra attention which he devoted to health education and patient motivation prove sufficient to produce satisfactory at-home DDS swallowing patterns? Ideally, such urine analysis would also have been conducted among regular attenders at the clinics of the second fieldworker in the Wangas. Collection of urine took place, however, several months after the conclusion of sociological research. In the interim the second fieldworker had died and his clinics, after a period of disruption, had been entrusted to a public health technician whose merits were not yet known. Differences or similarities in the DDS content in patients' urine samples would thus have been impossible to interpret.

Methods

COLLECTION OF URINE SAMPLES

Urine samples were collected by 2 interpreters employed earlier during the sociological research project. They now worked under the supervision of senior staff at Alupe Leprosy Hospital. All patients treated by the superior fieldworker who had been part of the sociological research sample and who were scheduled to receive 300 mg DDS/week were visited. This sample had been selected to be representative (age, sex, degree of deformity, registration at tree clinic* or health centre) of leprosy patient caseloads in Western Province. Additional patients of the same fieldworker receiving 300 mg DDS/week were chosen at random from all his clinics which brought the total of urine samples to 39: 17 from men, 22 from women. Surprise visits were the occasion for collection, 2 days after scheduled home medication. No reason was offered to patients to explain why their urine was wanted.

ANALYSIS OF URINE SAMPLES

The samples were analysed for their DDS/creatinine ratio in keeping with the method described by Ellard *et al.* (1974*a*). Samples thus examined were evaluated according to the positive/negative classification laid down in Huikeshoven *et al.* (1976), based on comparison with urine from 65 supervized

* This is a clinic held in the open under a mango tree.

patients and 62 blank controls from Tanzania. Urine samples with a DDS/creatinine ratio greater than 10.0 (male) or 12.0 (female) were classified as positive.

Results

Table 1 summarizes the ratios of DDS/creatinine found in the 39 urine samples examined, compared to blank, control and field statistics calculated for urine samples in Mwanza, Tanzania (Huikeshoven *et al.*, 1976).

TABLE 1
DDS/creatinine ratios in urine samples

Type of urine samples		Number	%	DDS/creatinine (μg/mg) Range	Mean ± S_m
From men					
Blanks		32	—	1.4– 9.8	5.3 ± 0.5
2nd day supervized		32	—	14.8– 68.8	50.1 ± 2.0
Wanga	Field samples < 10 (negative)	4	24	5.0– 9.5	7.8 ± 1.0
	Field samples > 10 (positive)	13	76	11.4– 70.8	49.6 ± 4.4
	All field samples	17	100	5.0– 70.8	39.8 ± 5.5
Mwanza	Field samples < 10 (negative)	21	26	2.6– 9.9	6.4 ± 0.5
	Field samples > 10 (positive)	59	74	10.4– 88.3	38.8 ± 2.5
	All field samples	80	100	2.6– 88.3	30.3 ± 2.4
From women					
Blanks		30	—	0.0– 12.5	6.0 ± 0.5
2nd day supervized		33	—	38.9–107.6	64.9 ± 0.3
Wanga	Field samples < 12 (negative)	2	9	10.7– 11.9	11.3 ± 0.6
	Field samples > 12 (positive)	20	91	12.1–125.4	63.3 ± 5.7
	All field samples	22	100	10.7–125.4	58.6 ± 6.1
Mwanza	Field samples < 12 (negative)	27	35	0.0– 11.6	6.9 ± 0.6
	Field samples > 12 (positive)	51	65	12.5–105.8	43.4 ± 2.9
	All field samples	78	100	0.0–105.8	30.8 ± 2.9

Indicated are percentages of positive and negative results, ranges of values found in each group, and mean values with the standard error of the mean (S_m) for each group.

As a consequence of the limited number of urine samples from the Wangas, the S_m values are considerable. Results should therefore be interpreted with caution. Statistical analysis reveals, however, that the difference between the mean ratio found in positive urine samples from Wanga men and from Mwanza men is, apparently, significant. On the other hand the difference between the mean ratio found in all urine samples from Wanga men and from Mwanza men is not clearly significant and the difference between the percentages of positive results in both male groups is clearly not significant. Differences found between the urine samples of the 2 female groups, however, is much more convincing: the means of positive samples, the means of all samples, and the percentages of positive results all display significant differences in favour of the Wanga women ($P < 0.005$).

One is also able to estimate the total quantity of DDS swallowed compared to the doses distributed at clinics (Ellard *et al.*, 1974*b*). Such comparison is

illustrated in Table 2. Results from similar proceedings in Tanzania are once again included. The difference between results of Wanga men (77%) and Mwanza men (56%) is almost significant ($P < 0.10$). The difference between results of Wanga women (89%), however, and Mwanza women (42%) is definitely significant ($P < 0.001$).

TABLE 2
Estimated amount of DDS swallowed, relative to the amount received at clinics

Origin \ Sex	Men	Women
Wanga	77% ± 13%	89% ± 10%
Mwanza	56% ± 6%	42% ± 5%

A most interesting picture is obtained comparing Wanga and Mwanza results by means of the frequency distributions of recorded DDS/creatinine ratios (Fig. 1). Figure 1 shows with clarity that for both men and women the positive urine samples from the Wangas have frequency distributions which closely resemble those of supervized groups, whereas positive urine samples from Mwanza do not. The general conclusion appears valid that urine samples from the Wangas indicate more systematic swallowing of correct doses of DDS than was true in Mwanza.

Lastly, a few remarks should be made concerning the 6 Wanga patients whose urine samples proved negative upon analysis. First, 5 of them achieved a result close to the positive border. This suggests that either they took *some* DDS on the proper day, or even all their prescribed medicine (300 mg) during the preceding week. Second, inclusion of the majority of patients whose urine was tested in the sample studied during prior sociological research meant that more information concerning them was available at the time of the urine analysis than merely their names! Participation of those who collected the urine samples in the sociological research project turned out to have distinct advantages: they were all able to make notes concerning the home circumstances of patients they visited to collect urine (illnesses, births, deaths, leprosy reactions, etc.) which helped suggest explanations why 5 of the 6 patients whose urine tested negatively had skipped, wholly or in part, taking their medicine as scheduled (Bijleveld, 1977)

Discussion

Results of the analysis of urine samples from regular attenders at the clinics of a superior leprosy fieldworker in the Wangas confirm the relatively high quality of his job performance. Not only do his patients come to clinics more dependably than most patients in Western Province, but they take their DDS at home with commendable regularity compared with regular attenders at clinics in Mwanza, Tanzania. Because a profile of patients whose urine was

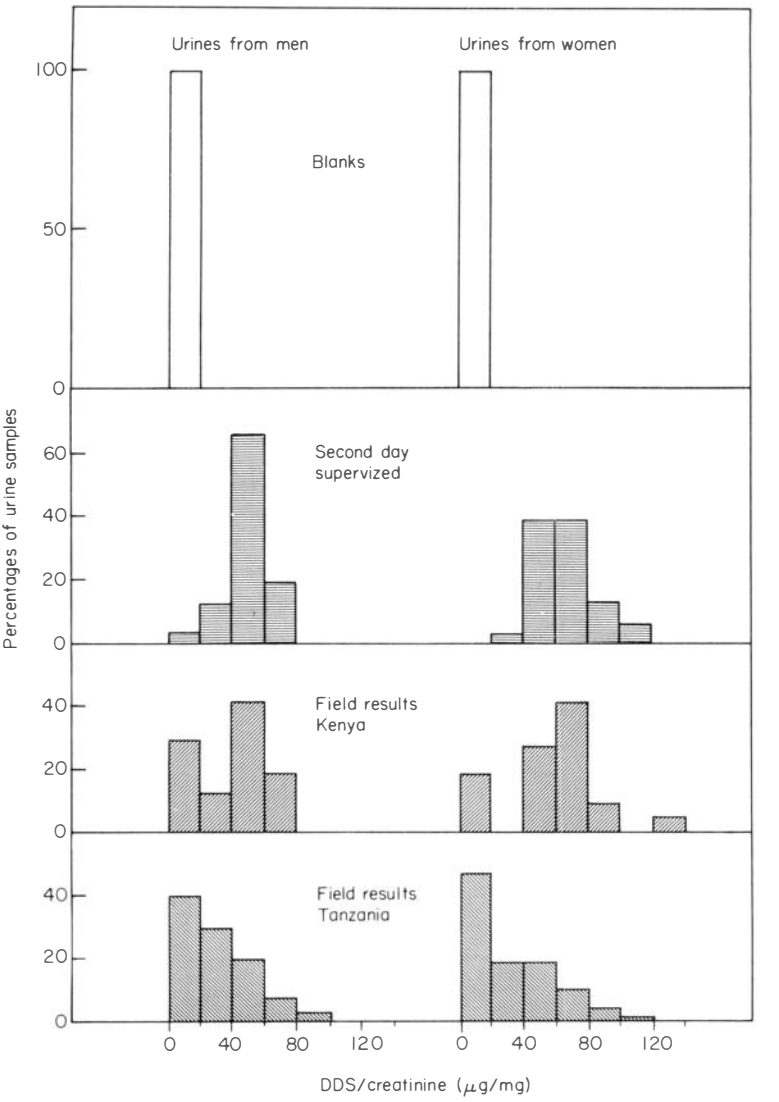

Fig. 1. Frequency distribution of DDS/creatinine ratios.

tested in the Wangas had been compiled previously, moreover, plausible explanations could be advanced why the few patients whose urine tested negatively had, atypically, missed their full medication the week of urine collection. Results also indicate how meaningfully social scientific and physical research can complement each other.

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Elective Surgical Decompression of Nerves in Leprosy— Technique and Results: A Preliminary Study

NARENDRA J. PANDYA*

B.Y.L. Nair Hospital and Jaslok Hospital and Research Centre, Bombay, India

and

NOSHIR H. ANTIA

Tata Dept of Plastic Surgery, J.J. Group of Hospitals, Bombay, India

Elective surgical decompression by extraneural and medial longitudinal epineurotomy was carried out in 45 patients. The ulnar nerve was the commonest, followed by the lateral popliteal, median and posterior tibial which comprised 69 nerves which were biopsied. The maximum period of follow-up was up to 3 years with a mean of 25 months.

Thirty-three patients showed sensory recovery, 3 failed to recover and only 1 deteriorated. Motor recovery was less predictable and seen in 26 patients. Seven failed to show any improvement and 1 deteriorated. Six patients with no sensory and 9 with no motor loss showed no adverse effects when followed for 3 years. The recovery was better seen in the group seeking early treatment and at an earlier age.

It is felt that the beneficial effects may have resulted from the increased vascularity and improved venous return due to relief from the extraneural and intraneural compression.

Introduction

The idea of decompression of nerves is not new. Most procedures tried so far have been primarily used to obtain relief from pain or for evacuation of abscesses. With the help of plastic surgical training in microneurosurgery, we undertook a comprehensive study to ascertain if early elective surgical decompression could be beneficial in preventing any long term deformities. This paper deals in detail with our surgical technique and also briefly mentions the results achieved.

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* Reprints requests should be addressed to: Dr Narendra J. Pandya, F.R.C.S. (E), 1, West Navroze Apartments, Bhulabhai Desai Road, Bombay 400 026, India.

Babcock (1907) was the first to suggest endoneurolysis, by multiple longitudinal incisions. Lowe (1942) recommended desheathing, Callaway *et al.* (1964) suggested external neurolysis with anterior translocation and resection of the thickened sheath. Carayon *et al.* (1964) recommended fascicular neurolysis with excellent results. Palande (1973) described external neurolysis with other procedures and Enna (1974) neurolysis and transposition. Vaidyanathan and Vaidyanathan (1968) advocated division of fascial roof and excision of fibrous arch.

Most procedures were probably too drastic and could interfere with the vascularity of an already inflamed nerve (Babcock, Lowe, Callaway, Enna etc.); while some (Vaidyanathan and Vaidyanathan) appeared too inadequate.

Our technique is simple, can be easily performed in any leprosarium and can achieve the desired results with least interference to the vascularity or the anatomy. The technique is similar to the one described by Said *et al.* (1973) with some modifications. It is carried out with meticulous care and microsurgical technique so as not to damage the inflamed tissue or the vascular pattern. Extraneural decompression to relieve the external, and medial longitudinal epineurotomy to relieve internal pressures throughout the involved segment were carried out. We hoped, in turn, that this may help to retrieve some of the sensory and motor damage and further minimize and/or prevent deformities. The medial side was chosen as it was least likely to damage the vessels (Smith, 1966).

Surgical Technique

The surgical procedure was carried out using a tourniquet, consisting of the inflated cuff of a sphygmomanometer wrapped around the upper arm. Local anaesthesia was preferred for single nerve while general anaesthesia for multiple nerves. The operative time varied from 20 to 30 min. Two times magnifying spectacles were employed during the dissection and especially while undertaking nerve biopsy.

The ulnar nerve at the elbow was exposed through a 10 cm incision placed 7 cm above and 3 cm below the medial epicondyle and running midway between the medial epicondyle of the humerus and the olecranon process of the ulnar. The skin and subcutaneous tissue were incised and the deep fascia of the anterior medial compartment of the upper arm exposed (Fig. 1). This was usually thickened, congested and opalescent and found to compress the enlarged nerve lying underneath. It was divided longitudinally, and when adherent to the epineurium of the underlying nerve had to be dissected off (Fig. 2). The fascia was divided up to the mid-arm with a partially open pair of scissors. This at times had to be carried up to the point where the nerve entered the arm and pierced the medial inter-muscular septum. The nerve may be compressed at this point. A compressing effect of the fascia on the underlying nerve can be demonstrated by the flattened nerve assuming a more rounded shape. Further extraneural decompression was obtained by dividing the roof of the fibro-osseus tunnel formed by the fibrous band connecting the medial epicondyle to the olecranon (Fig. 3). Due care had to be exercised here if the nerve was found adherent to the inner surface of the roof. Division of the

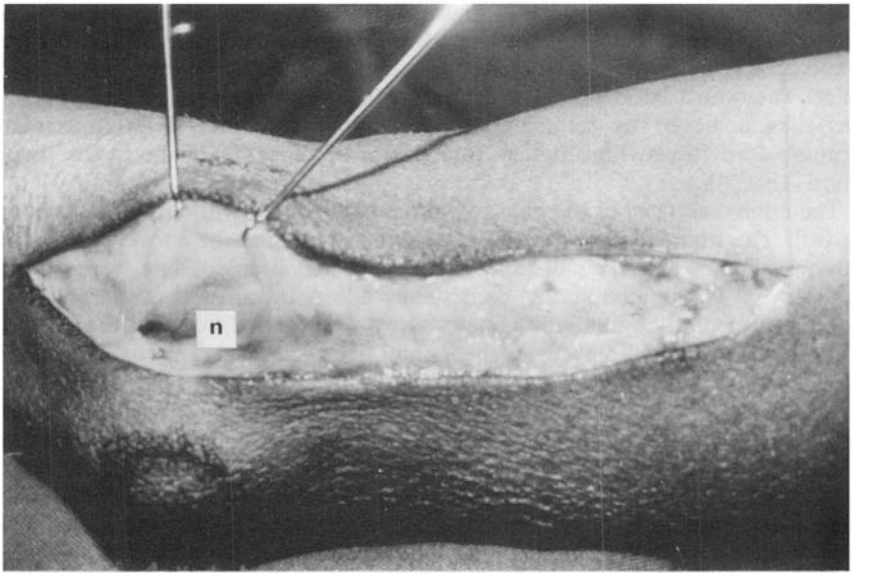


Fig. 1. A tear in the deep fascia of the arm exposing the ulnar nerve (n).

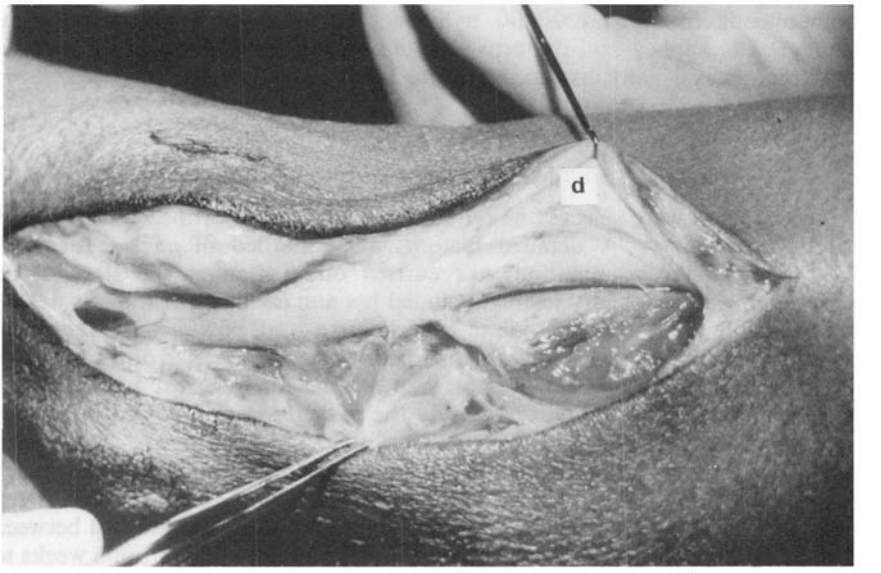


Fig. 2. Division of the deep fascia (d). Note the flattened nerve.

overlying tendinous fibres of the origin of the flexor carpi ulnaris provided a release of the nerve from the constricting effect produced by these fibres. Two branches to the flexor carpi ulnaris from the ulnar nerve are given off at this point. They must be identified and preserved. The extraneural decompression was thus achieved by releasing the pressure due to medial intermuscular septum, deep fascia, fibro-osseus tunnel and the 2 heads of the flexor carpi ulnaris (Fig. 4).

The entire segment of the exposed nerve was cleared without lifting it from its bed. The diameters at the site of maximal enlargement as well as at the narrowest point and their distances from the medial epicondyle were noted. The nerve was palpated and its consistency noted. Intraneural decompression through a medial longitudinal epineurotomy was carried out with the help of fine non-tooth watchmakers forceps and iris scissors. The technique of epineurotomy was simple. The epineurium on the medial side was carefully slit at a relatively avascular area at the site of maximal swelling (Fig. 5). This was extended proximally as well as distally to include the entire involved segment. The epineurium was generally found to be thickened, opaque and inelastic. Due care was taken not to damage the overlying vascular network. This medial longitudinal epineurotomy had an added advantage in not disturbing the vascular supply which came through the mesoneurium on the lateral side of the nerve. As this was completed the nerve seemed to open out exposing the tightly compressed nerve bundles (Fig. 6). Wider opening indicated higher intraneural tension. No attempt was made to separate individual funicules. If an abscess was encountered, it was gently evacuated.

Whenever indicated, a full length of the most involved and diseased funicule was biopsied. The wound was closed in 2 layers using 0000 plain catgut for subcutaneous tissue and 00000 nylon for the skin. A firm compression bandage was applied and the arm elevated during the post-operative period. The patient was usually discharged the next day.

Material and Methods

The patients were selected at random and the nature of the treatment was carefully explained. A detailed history was recorded of each patient. A thorough clinical examination was carried out, including the state of all peripheral nerves. Sensory testing included hot and cold temperature as well as No. 5 and graded nylon studies. Muscle tone and power were recorded. Routine smears, by slit and scrape method, were taken from ear, nasal scraping and skin patch (if present) and stained for acid-fast bacilli by the Ziehl-Neelsen method. Post-operatively the patients were followed at regular intervals.

Neurolysis was performed in 69 nerves from 45 patients (38 males and 7 females) varying from 13 to 50 years old. Thirty-five suffered from tuberculoid, 7 borderline and 3 from lepromatous types. The interval between the appearance of symptoms and the surgical treatment varied from 5 weeks to 5 years. Tingling and numbness were the commonest presenting symptoms in 24 patients; 8 patients had early claw deformity while 7 had dull ache at the

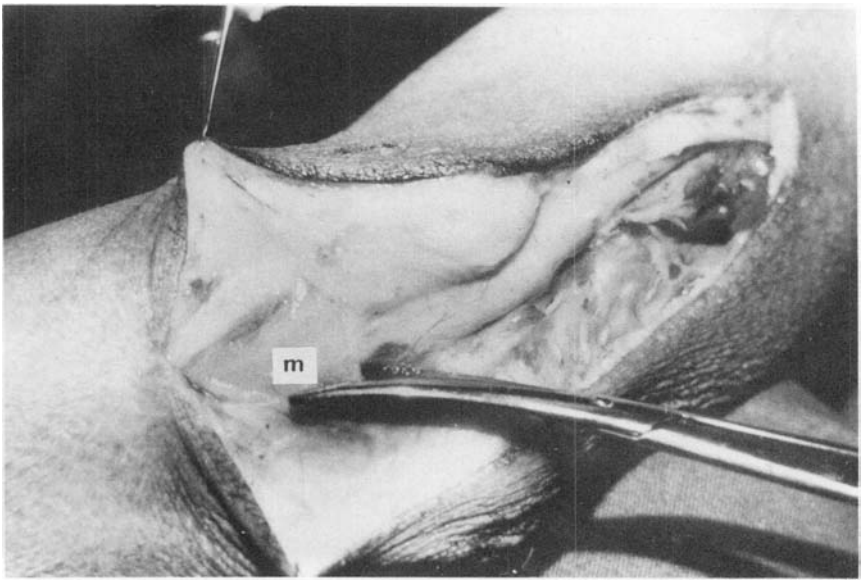


Fig. 3. Division of fibrous tunnel roof and the tendinous origin of the 2 heads of flexor carpi ulnaris (m).

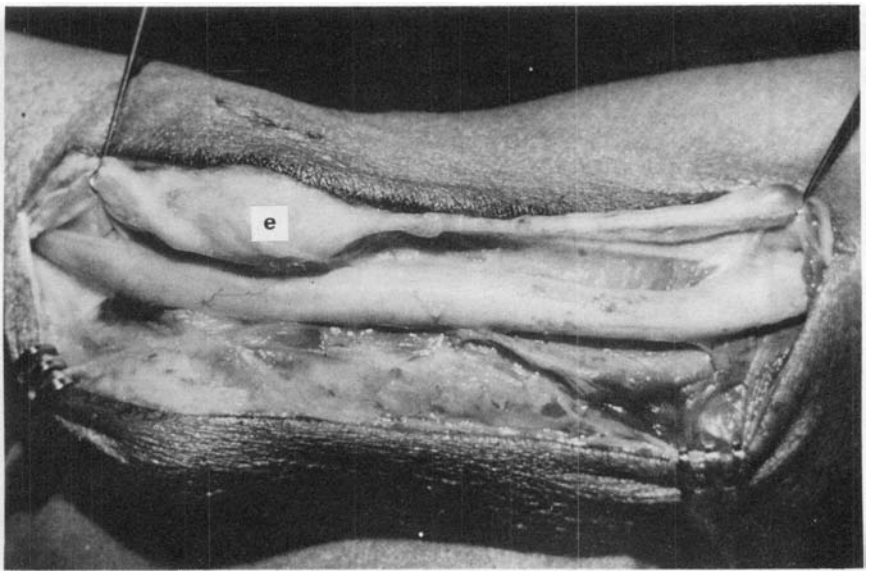


Fig. 4. External neurolysis completed. Note the rounded nerve with thickening extending from the lower arm to the heads of flexor carpi ulnaris. (e) medial epicondyle.

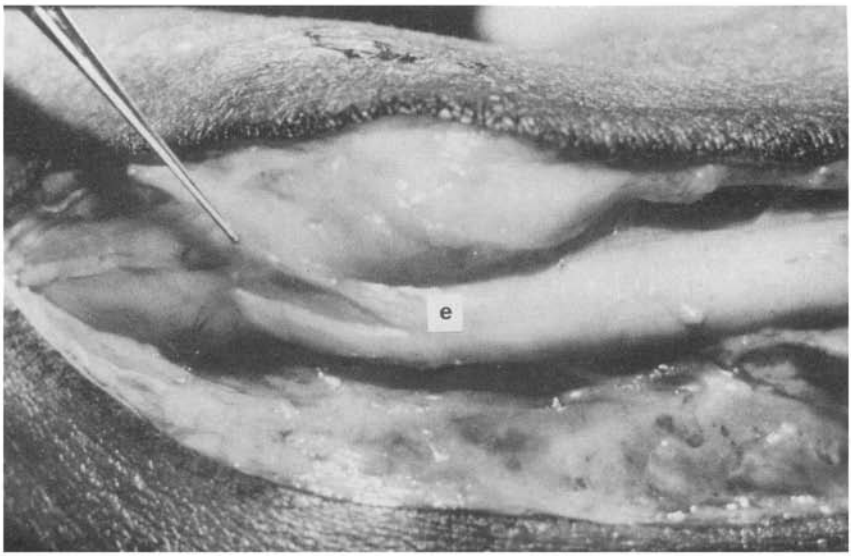


Fig. 5. Epineurotomy—note the thick, opaque epineurium (e).

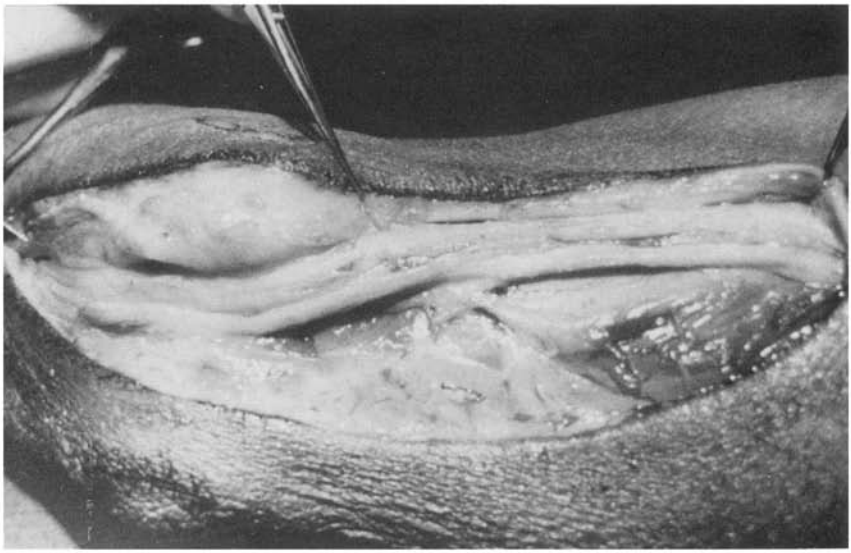


Fig. 6. Medial longitudinal epineurotomy completed. Note the open nerve exposing the bundles.

site of entrapment. Multiple symptoms were seen in 9 patients while pain, experienced by only 4, was not the predominant symptom in our series.

Forty-nine ulnar nerves at the elbow, 9 lateral popliteal at the knee, 7 median at the wrist and 4 posterior tibial at the ankle were decompressed. Post-operative follow-up was maintained at regular intervals.

Findings

The deep fascia of the anterior medial compartment of the upper arm was thickened, congested and opalescent in 35 cases and found to compress the underlying nerve. The thickening of the nerve varied from a minor enlargement to gross thickening of up to 18 mm diameter. A part or sometimes even the entire segment of the exposed nerve was thickened. Nineteen nerves had diameters varying from 6 to 10 mm, 21 from 11 to 15, and 5 more than 15 mm at the level of maximum enlargement. The swelling was generally spindle-shaped, the maximum thickness being located about 4 to 6 cm above the medial epicondyle. The thickening was mostly restricted to the lower third of the arm but in 8 cases extended up to the middle of the arm and downwards into the ulnar groove and between the 2 heads of flexor carpi ulnaris. The thickened portion of the nerve felt firm but palpation of the nerve above the swelling generally revealed a normal, soft consistency. Occasionally the swelling extended within the ulnar groove where it was compressed by the fibrous band connecting the medial epicondyle to the elecranon. When this extended above and below the fibro-osseous tunnel, a dumb-bell effect was produced. This was observed in 11 cases.

After the completion of longitudinal epineurotomy, the nerve bundles could be visualized. Separate funiculi could be identified in most cases while in a few they were found to be pale, matted together and fibrous. Intraneural abscess was found in 4 cases. These were all gently evacuated.

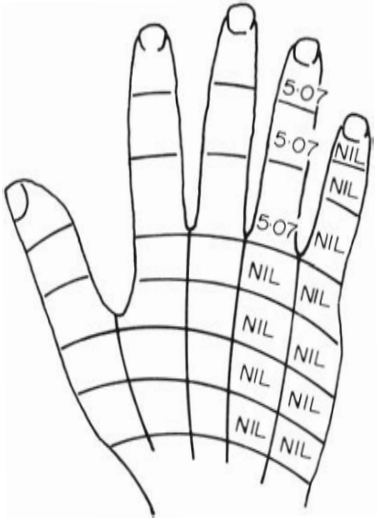
Funicular biopsy was obtained from 39 cases, comprising 30 ulnar, 8 lateral popliteal and 1 median nerves. In early cases, single nerve bundles could be dissected out using the magnifying loupe. In more advanced cases, a wedge-shaped biopsy specimen of the nerve was removed from the site of maximum thickening, including a few of the matted funiculi.

Follow-up

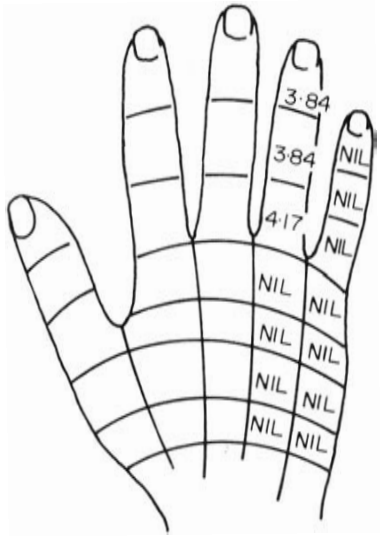
Forty-three patients were followed up for a period varying from 3 months to 3 years with an average of 25 months. Two patients were lost to follow-up.

Pain in all cases when present, was the first symptom to be completely relieved. Sensory improvement was expressed as a percentage of the pre-operatively involved area. Sixteen patients had excellent sensory recovery (75% or more), 5 had very good (50 to 75%), 6 had good (25 to 50%) and 6 had satisfactory (under 25%) recovery. Three patients did not improve and only 1 worsened. Six patients had no preoperative sensory loss and showed no deterioration 3 years after surgery.

Motor recovery was assessed from the patient's comments and also by estimation of tone and power changes in the affected group of muscles, and was



K.P. 14 yrs 4-12-72
RT. DORSAL
Pre op.



K.P. 14 yrs 11-1-73
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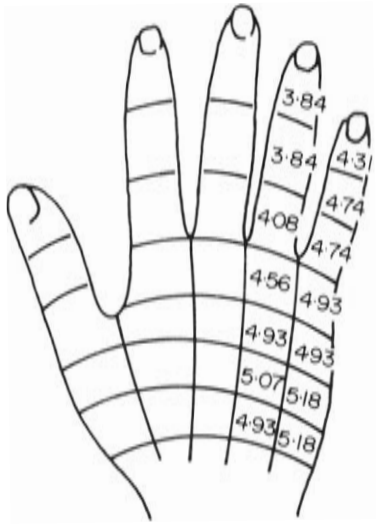
Post op.



K.P. 14 yrs 6-3-75
RT. DORSAL

Fig. 7. K. P. Right hand dorsum. Sensory charting with graded nylon.

expressed as a percentage of pre-operative level. Excellent motor recovery (50%) was seen in 4 patients while 3 showed good (31 to 50%), 19 satisfactory (0 to 30%) and 7 no improvement at all. Nine patients who had no pre-operative motor involvement showed no deterioration after 3 years, while only 1 patient got worse.

It was observed that the recovery was better when treatment was sought within 6 months of the origin of the symptoms and also in the younger age group.

Discussion

Our study was conducted in order to carry out surgical decompression electively with a view to alter favourably the progress of the disease and also possibly minimize and/or prevent the ghastly deformities associated with the disease. This was achieved through meticulous surgical technique with the least disturbance of the anatomy and in particular, its vascularity.

Inflammation of the nerve results in oedema. This leads to compression of the nerve bundles as well as interference with blood circulation leading to hyperaemia and further oedema. The resulting ischaemia promotes fibrosis. Partial ischaemia causes a reversible paralysis without Wallerian degeneration. If, however, the ischaemia becomes absolute or lasts longer, the nerve will be destroyed and the paralysis is then irreversible. The constricting effect of fibrosis due to ischaemia makes this worse. Hence surgical decompression is effective at an earlier stage of the disease when the intraneural oedema is primarily responsible for the yet reversible damage. Once fibrosis has set in, surgery is of little use. The beneficial effects of surgery in our cases can be attributed to this early elective procedure. Thus the extraneural decompression would provide relief to the surface network while medial longitudinal epineurotomy would similarly relieve the interfunicular, perineurial and intrafunicular networks. Weir Mitchell (1872) emphasized the importance of preserving the blood supply of the peripheral nerves.

Early elective extraneural decompression and medial longitudinal epineurotomy has given good results for 3 years. Further work along this line is continuing firmly to establish the importance of this form of surgery in order to influence favourably and minimize the damage to the affected nerves.

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Lepr. Rev. (1978) **49,** 63–68

Extensor Pollicis Brevis Transfer to Flexor Digitorum Sublimis in Hansen's Disease—Follow-up Study for Four Years*

E. P. VAIDYANATHAN† AND P. ANTHONY

Hemerijckx Leprosy Centre, Polambakkam, India

(1) Five cases of tuberculoid leprosy with paralysis of thumb are studied.
(2) Extensor pollicis brevis was anastomosed with ring finger, flexor sublimis at different levels, and cases were assessed.
(3) Case reports, assessments and advantages of the operation are presented.

Introduction

In the action of pinch, the thumb has to be brought forward in front of the hand and rotated to oppose the fingers. In this position the thumb is supported normally by the extensors, flexors, abductors, adductors and opponens. In leprosy, the short flexor of the thumb, the adductor, the abductor and the opponens are all likely to be paralysed. This leaves only the long and short extensors and the long flexor. The only remaining function of the paralysed thumb is the ability to squeeze against the side of the second metacarpal bone.

Opposition is not only a movement. It also gives the widest area of contact between the pulps of the thumb and finger. Three joints are responsible for movements of the thumb: interphalangeal, metacarpaphalangeal and carpometacarpal. The range of mobility increases from distal to proximal.

Instability, a frequent result of combined median and ulnar palsy, must be corrected since it jeopardizes any restoration of function. The first carpometacarpal joint, by virtue of its architecture and the laxity of its capsule, makes opposition possible. Any damage to this joint will cause deterioration of this basic movement. An operation which aims at restoring opposition of the thumb will be successful only if the stability and mobility of these joints are preserved.

A number of procedures have been devised to produce opposition of the thumb. Starting from the principle of the pulley operation described by

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* Work done in Leprosy Centre, Polambakkam, India in 1970.
† Present address: Surgeon, Bababaghi Leprosy Sanatorium, Tabriz, Iran.

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Bunnell, one may modify any of its 3 basic components which are:

(1) the motor muscle;
(2) the pulley;
(3) the point of insertion.

It is preferable to choose a muscle the transfer of which will not produce any appreciable motor deficit.

The purpose of this paper is to describe a new method of reconstructive surgery for the paralysed thumb in Hansen's disease, without sacrificing the powerful flexor digitorum sublimis. For the follow-up study 5 cases with ulnar and low median palsy were chosen.

Technique

EXTENSOR POLLICIS BREVIS TRANSFER TO FLEXOR DIGITORUM SUBLIMIS TENDON

No tourniquet is applied. Locally 1% Lignocaine hydrochloride is given and an inverted "L"-shaped incision is made on the posterior aspect of the lower third of the forearm to expose the extensor pollicis brevis tendon. At the musculo–tendinous junction the tendon is divided.

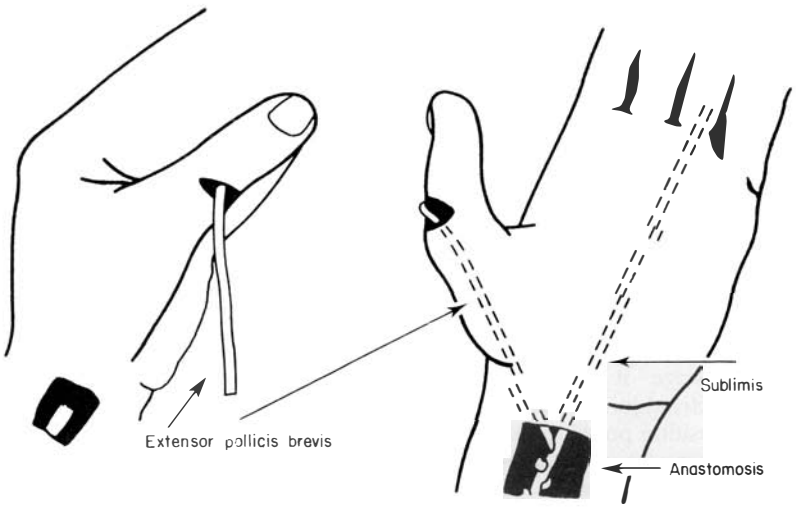

Fig. 1. Operative procedure.

Another transverse incision is made at the posterior aspect of the metacarpophalangeal joint of the thumb. The extensor pollicis brevis tendon is identified and pulled out through the incision.

An "S"-shaped incision is made on the distal third of the anterior aspect of the forearm and the tendon of the flexor digitorum sublimis of the ring finger is

identified. By asking the patient to flex the ring finger, the excursion of the sublimis tendon is noted. In all the cases the maximum excursion was at a point about 1 in proximal to the wrist joint. A subcutaneous tunnel is made between the forearm incision on the anterior aspect and the thumb incision to bring the extensor pollicis brevis tendon to the forearm.

Keeping the thumb fully rotated and abducted the extensor pollicis brevis tendon is anastomosed with the flexor digitorum sublimis tendon about 1 in proximal to the distal wrist crease.

Wounds are closed with continuous stainless steel wire and the hand plastered in the lumbrical position with thumb fully rotated and abducted.

Plaster and the sutures are removed after 3 weeks and exercises started.

Case Reports

CASE NO. 1

Male aged 41 years, an oil merchant, was a case of tuberculoid leprosy with right high ulnar and low median palsy.

On examination of his right thumb, the metacarpophalangeal joint was hypermobile, interphalangeal joint was flexed and voluntary extension was not possible. There was no opposition. He was operated upon in August 1970 and the plaster and sutures were removed after 20 days. Three months after operation action of the tendon was good, rotation and abduction was fair. Tip flexion was present and opposition was possible. Pinch was active, pulp to pulp, and stability was good. Strength was "4".

Four years later rotation was very good, abduction was good, tip flexion was present and opposition was possible. The web was fully stretched. The patient was not able to hold the handle of a bicycle before the operation and was happy that he could do so after the operation.

CASE NO. 2

Male aged 45 years, an agriculturist, was a case of tuberculoid leprosy with bilateral high ulnar and low median paralysis.

On examination of his right thumb the metacarpophalangeal joint was hypermobile. The interphalangeal joint had flexion contracture. Assisted extension was partial, opposition was nil. Pinch was of active adduction type. The web was slightly contracted and there was no rotation. He was operated upon in July 1970. After 5 months, tendon action was good. The metacarpophalangeal joint was stable. Full abduction was possible and opposition was good. Pinch was of nail to nail, as he had clawed fingers. Grip was fair.

After 1 year there was no hyperextension of the metacarpophalangeal joint. Abduction was full and the web was well stretched. Grip was good.

CASE NO. 3

Male aged 40 years, was a case of tuberculoid leprosy with bilateral high ulnar and low median paralysis.

On examination the metacarpophalangeal joint was hypermobile. Rotation, abduction and opposition were nil. Pinch was of adduction type. The web was adequate. He was operated upon in July 1970. Five months after the operation, the metacarpophalangeal joint was not stable. Adduction, flexion and rotation were nil. There was hyperextension of the metacarpophalangeal joint; the interphalangeal joint was flexed. Abduction and opposition were nil. Stability, strength and rotation were good.

In this case the anastomosis was done at 1 cm proximal to the distal wrist crease. The excursion of the sublimis is better at 2.5 cm proximal to the wrist crease and therefore the action was not good.

Before operation the patient used to injure the web near the metacarpophalangeal joint. He was able to use the crowbar and spade without injuring the web, after operation.

CASE NO. 4

Male aged 30 years, washerman by profession was a case of tuberculoid leprosy with bilateral ulnar and median paralysis.

On examination of his right hand, the metacarpophalangeal joint was hypermobile. The interphalangeal joint was flexed. Abduction and opposition were nil. Pinch was of adduction type. The web exhibited borderline contraction.

He was operated upon in March 1970. After 7 months of operation the metacarpophalangeal joint was hyperextended. The interphalangeal joint was flexed. Abduction was moderate and opposition was nil. Pinch, stability, strength and rotation were good.

He had not been able to wash clothes before the operation for about 17 years. After operation he was able to do so.

CASE NO. 5

Male aged 32 years, an agriculturist was a case of tuberculoid leprosy with bilateral ulnar and median paralysis.

On examination he had stiff claw on the left and absorbed fingers on the right hand.

The right hand metacarpophalangeal joint was stable. The interphalangeal joint was flexed. Assisted extension was limited. Abduction and opposition were fair. Pinch was active. Stability and strength were fair. Rotation was partial.

The patient was satisfied and is able to do his work better.

The tension of the extensor pollicis brevis to sublimis is not enough as the anastomosis was done 1 cm proximal to distal wrist crease as was done in one of the previous cases.

Advantages

(1) Operation can be done under local anaesthesia without a tourniquet.
(2) Action of the thumb can be seen by active flexion of ring finger.
(3) Less trauma of the thumb.

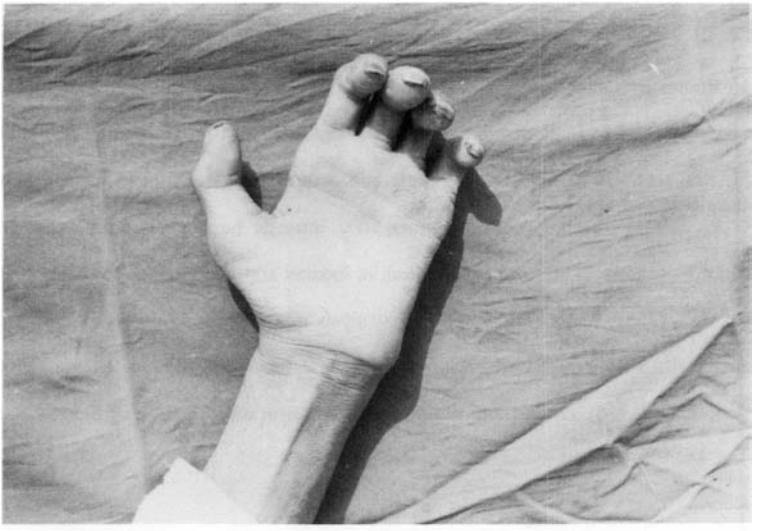

Fig. 2. Pre-operative.

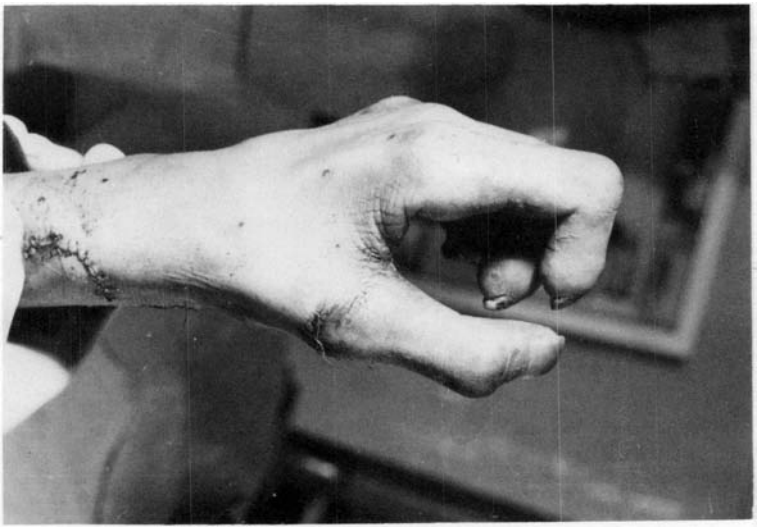

Fig. 3. Post-operative. Thumb-web stretched and with full rotation and abduction.

(4) Easy to perform.
(5) Powerful flexor sublimis need not be sacrificed.
(6) Post-operative education is easier.
(7) Post-operative web stretching is very good.

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Lepr. Rev. (1978) **49,** 69–73

First Meeting of the WHO THELEP* Scientific Working Group

The first meeting of the THELEP Scientific Working Group (SWG) was held in Geneva in April 1977. This meeting had been preceded by 2 earlier THELEP meetings, that of the Planning Committee held in April 1976, and the meeting of the Screening Committee in December 1976. These meetings had established as areas of priority field studies of the prevalence of dapsone resistance, clinical trials in lepromatous leprosy, relevant laboratory investigations and the development of new chemotherapeutic agents, and reviewed applications for support of proposals related to these objectives.

The 78-page report of the first THELEP SWG meeting (WHO document TDR/SWG-THELEP(1)/77.3), which is available on request to the World Health Organization (1211 Geneva 27, Switzerland) includes the "Standard Protocol for Chemotherapeutic Trials in Lepromatous Leprosy". This was prepared by the SGW for use in THELEP-supported studies, and contains a wealth of information on the chemotherapy of leprosy as well as much helpful advice on the treatment of the individual patient.

In the introduction to the report the evidence for the inadequacy of present-day treatment of lepromatous leprosy is reviewed. Present chemotherapeutic methods appear to be inadequate primarily because they fail to prevent the emergence of drug-resistant *Mycobacterium leprae* and because they appear incapable of eradicating persisting viable bacilli. As a consequence patients may relapse during continued treatment or after the termination of very lengthy periods of chemotherapy. The serious shortcomings in the chemotherapy of lepromatous leprosy appear to have resulted not only from a shortage of effective drugs but also from a lack of knowledge of how to use existing drugs in the most effective way.

One of the major objectives of the THELEP programme is therefore to develop more effective therapeutic regimens for the treatment of lepromatous leprosy, and it was to this end that the Standard Protocol was prepared. Estimates of the efficacy of currently available drugs are largely based on measurements in the footpads of immunologically normal mice of the proportion of viable *M. leprae* recovered from skin biopsy specimens of lepromatous leprosy patients obtained at intervals during therapy with these drugs. These studies have demonstrated that rifampicin is maximally effective,

* "THELEP" is the designation of the Programme for Research in Chemotherapy of Leprosy, which, together with IMMLEP (Programme for Research in Immunology of Leprosy), represents at this time the leprosy component of the WHO Special Programme for Research and Training in Tropical Diseases (TDR).

reducing the proportion of viable organisms below the threshold of detectability within a few days of a single 1200- or 1500- mg dose, and suggest no drug combination including rifampicin may be expected by this test to appear more effective than rifampicin alone. A few studies using immunosuppressed mice, in which smaller proportions of viable *M. leprae* may be recognized, have demonstrated the survival of drug-susceptible, "persisting" organisms after years of monotherapy with a number of drugs including rifampicin, and after months of therapy with rifampicin and dapsone in full daily dosage. The principal objective of the chemotherapeutic trials conducted according to this standard protocol is to minimize the proportion of persisting *M. leprae,* and, at the same time to prevent the multiplication of drug-resistant organisms. Furthermore it is believed that those regimens which minimize the number of persisting leprosy bacilli will also be the most effective in preventing the subsequent emergence of drug-resistant organisms. No trial of drug combinations, especially those including rifampicin, will yield meaningful results unless persisting *M. leprae* are measured. Consequently, the inoculation of immunosuppressed rodents is mandatory for compliance with the THELEP standard protocol.

THELEP intends eventually to mount chemotherapeutic trials among three categories of lepromatous leprosy patients: untreated patients with fully drug-sensitive *M. leprae*; patients with proven dapsone-resistant leprosy bacilli; patients who have already responded to a period of monotherapy with dapsone and who may therefore be presumed to harbour larger proportions of dapsone-resistant organisms than are normally encountered in previously untreated patients.

The Standard Protocol prepared by the THELEP SWG has been designed to assess the relative efficacy of different regimens in treating these 3 types of patients, and endeavours to elicit the maximum amount of information while exposing patients to the minimum of risk. The Protocol envisages the trials as having 2 phases—an initial short-term phase of 3 months' intensive treatment followed by a long-term phase of less intensive treatment of 21 months' duration. Depending upon the results of these first 2 phases, a third phase may be envisaged. If no persisting *M. leprae* are detected after treatment for 24 months with one or more regimens, therapy could safely be withdrawn from half of the patients, and all of the patients observed thereafter for a minimum of 5 years. In those patients in whom persisters are detected after 24 months, the effect of a change of regimen on the persisters could be measured.

Eight potential regimens were selected for evaluation in previously untreated patients:

Regimen A_1: Dapsone, 100 mg daily for the duration of the trial; Rifampicin, 600 mg daily for the duration of the trial; Clofazimine, 50 or 100 mg daily for the duration of the trial.

Regimen A_2: This identical to Regimen A_1, except that prothionamide, 500 mg daily, is substituted for clofazimine.

Regimen B: Dapsone, 100 mg daily for the duration of the trial; Rifampicin, 600 mg daily for the duration of the trial.

Regimen C: Dapsone, 100 mg daily for the duration of the trial; Rifampicin in a single initial 1500 mg dose.

Regimen D_1: Dapsone, 100 mg daily for the duration of the trial; Rifampicin in a single initial 1500 mg dose; Clofazimine, 50 or 100 mg daily for the first 3 months.

Regimen D_2: This is identical to Regimen D_1 except that prothionamide, 500 mg daily, is substituted for clofazimine.

Regimen E_1: Dapsone, 100 mg daily for the duration of the trial; Rifampicin, 900 mg once weekly for the first 3 months; Clofazimine, 50 or 100 mg daily for the first 3 months.

Regimen E_2: This is identical to Regimen E_1, except that prothionamide, 500 mg daily, is subsituted for clofazimine.

Four regimens were chosen for potential studies in patients with dapsone-resistant leprosy utilizing daily treatment with clofazimine (50 or 100 mg) or thiacetazone (150 mg) supplemented by the addition of rifampicin or/rifampicin plus prothionamide. The same 4 regimens supplemented with 100 mg dapsone daily were selected for trials involving patients who had already responded to an initial period of treatment with dapsone alone.

All THELEP-sponsored trials require the approval of governmental and institutional authorities. Approximately 30 patients will be recruited into each of the regimens being studied in the collaborating centres. Patients who agree to participate in the trials should be at least 15-years-old and in apparently good health. They should have LL (LLp) or LI (LLs) leprosy by clinical and histopathological classification and have Mitsuda reactions of less than 3 mm in diameter. Patients will however be excluded if they have tuberculosis requiring treatment, a life-shortening disease such as cancer, severe diabetes, severe hypertension, renal, hepatic or cardiac diseases or other significant psychological or organic disease that might adversely affect their compliance with therapy or follow-up. Pregnant patients will also be excluded if they have a history of ENL.

The clinical investigator will carry out a full clinical examination of each patient on his entry into the trial, which will include a complete clinical history and physical examination, anatomical silhouettes that map and give measurements of skin lesions, nerve enlargements, and sensory and joint changes. Pretreatment biopsies will be taken to provide *M. leprae* for inoculating immunologically normal mice in order to establish the presence of viable leprosy bacilli and to determine their susceptibility to dapsone. Further biopsies will then be taken after 3, 12 and 24 months treatment to provide bacilli to inoculate both immunologically normal mice and immunologically suppressed rodents. The results obtained from the biopsies taken at 3 months should demonstrate that the patient's leprosy bacilli have been killed at a satisfactory rate during the initial phase of intensive treatment and confirm that when these combinations of drugs are given they do not antagonize each other's bactericidal action.

The most crucial evidence for assessing the relative potency of the regimens will however be derived from the infectivity for immunologically suppressed rodents of inocula containing large numbers of leprosy bacilli prepared from biopsies obtained after 3, 12 and 24 months treatment, because these determinations should enable measurement and comparison of the proportions of *M. leprae* that survive the initial phase of intensive treatment and persist

during 9 to 21 months of continuing treatment. Portions of the biopsies will also be fixed and processed for histopathological classification according to the Ridley and Jopling system and for measurement of the logarithmic biopsy index.

The therapeutic progress of the patients will also be monitored by carrying out regular clinical examinations, and by measuring the bacterial indices in smears taken from 6 skin sites and prepared from nasal secretions. Throughout the course of treatment the occurrence of ENL and other leprosy reactions will be carefully noted and described, and patients will be regularly questioned to ensure that symptoms suggesting adverse reactions to the drugs they are being prescribed are not missed. Samples of blood, urine and stool will also be collected at specified intervals for routine laboratory studies to monitor haematological parameters and hepatic and renal function, and assess the regularity with which the dapsone prescribed has been ingested.

The THELEP SWG's report also includes with the Standard Protocol detailed appendices describing how the clinical examinations should be conducted, the classification of LL and LI leprosy and the lepromin test procedure. Other appendices describe the methods to be employed for preparing the skin and nasal smears and the measurement of their bacterial indices. Detailed descriptions are also given of the techniques to be used for obtaining the skin biopsies, and of how they should be prepared, packaged and shipped to the reference laboratories for animal inoculation and histopathological examination. The methods for inoculating immunologically normal and immunologically suppressed mice are also described in detail, together with the procedures to be used for the subsequent enumeration of *M. leprae* in their footpads. The urine-test method to be used for monitoring the ingestion of dapsone is described in full. Further appendices provide guidance on the management of ENL and reversal reactions, the monitoring of adverse reactions to drugs and the criteria to be used for removing patients from the controlled clinical trials because of the possibility of drug toxicity.

The report also includes brief descriptions of the facilities and patients available for clinical trials at treatment centres in 10 countries. Summaries are also included of the deliberations of the 2 informal subgroups that were formed during the THELEP SWG meeting. One subgroup considered methods for measuring the prevalence of dapsone resistance and the conduct of clinical trials of non-lepromatous leprosy, while the other subgroup designated 5 areas of laboratory-based research activity that could aid the development and screening of new antileprosy drugs or the more effective use of combinations of established drugs.

Participants of the THELEP Scientific Working Group at its First Meeting, April 1977

Dr J. BARZELATTO, Special Programme for Research and Training in Tropical Diseases, WHO, *Geneva*, Switzerland.

Dr LE KINH DUE, Clinique de Dermatologie et de Vénérologie, Hôpital Bach Mai, *Hanoi*, SRVN.

Dr G. A. ELLARD, MRC Unit for Laboratory Studies of Tuberculosis, Royal Postgraduate Medical School, *London W12 0HS*, England (Rapporteur).

Dr V. A. EVSTRATOVA, Leprosy Research Institute, *Astrakhan*, U.S.S.R.
Dr A. H. FIELDSTEEL, Stanford Research Institute, *Menlo Park*, California 94025, U.S.A.
Dr R. GELBER, U.S. Public Health Services Hospital, 15th Avenue and Lake Street, *San Francisco*, California 94118, U.S.A.
Dr L. M. HOGERZEIL, Victoria Hospital, *Dichpalli*, Nizambad District, Andhra Pradesh, India.
Dr T. ITO, Research Institute for Microbial Diseases, Osaka University, Yamada-kami, Suita *Osaka*, Japan.
Dr C. G. S. IYER, Central Leprosy Teaching and Research Institute, Chingleput, Tamil Nadu 603001, India.
Dr KYAW LWIN, Ministry of Health, 34/42 Strand Road, *Rangoon*, Burma.
Dr J. LANGUILLON, Institut de Léprologie Appliquéé, B.P. 11.023 CD Annexe, *Dakar*, Senegal.
Dr D. L. LEIKER, Royal Tropical Institute, Department of Tropical Hygiene, Mauritskade 63, *Amsterdam,* Netherlands.
Dr L. LEVY, Department of Comparative Medicine, Hebrew University–Hadassah Medical School, *Jerusalem*, Israel.
Dr D. V. OPROMOLLA, Hospital Lauro Sousa Lima, 17100 Bauru, Sao Paulo, Brazil.
Dr S. R. PATTYN, Universitaire Instellung Antwerpen, *2610 Wilrijk*, Belgium.
Dr J. M. H. PEARSON, MRC Leprosy Project, P.B. 1005, *Addis Ababa*, Ethiopia.
Dr R. J. W. REES, National Institute for Medical Research, Mill Hill, *London NW7 1AA,* England (Chairman).
Dr E. J. SAERENS, 65 Av. de la Nivéole, *B-1020 Brussels*, Belgium.
Dr J. K. SEYDEL, Forschunginstitut Borstel, *2061 Borstel*, Federal Republic of Germany.
Dr C. C. SHEPARD, Leprosy and Rickettsia Branch, Center for Disease Control, *Atlanta*, Georgia 30333, U.S.A.
Dr L. VILLALBA-PIMENTEL, Instituto Nacional de Dermatologia, Apartado 4043, *Caracas 101*, Venezuela.
Dr M. F. R. WATERS, National Institute for Medical Research, Mill Hill, *London NW7 1AA*, England.
Dr J. S. YAWALKAR, Ciba-Geigy Limited, *4002 Basle*, Switzerland.

SECRETARIAT

Dr H. SANSARRICQ, Leprosy Unit, WHO, *Geneva*, Switzerland.
Dr J. WALTER, Leprosy Unit, WHO, *Geneva*, Switzerland.
Dr A. O. LUCAS, Director, Special Programme for Research and Training in Tropical Diseases, WHO, *Geneva*, Switzerland.
Dr E. DE MAAR, Special Programme for Research and Training in Tropical Diseases, WHO, *Geneva*, Switzerland.
Dr K. L. HITZE, Tuberculosis and Respiratory Infections Unit, WHO *Geneva*, Switzerland.
Dr L. REY, Schistosomiasis Unit, WHO, *Geneva*, Switzerland.
Mr T. K. SUNDARESAN, Health Statistical Methodology Unit, WHO, *Geneva*, Switzerland.

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Obituaries

ALBERT DUBOIS
1888–1977

Albert Dubois died in Brussels on 19 August 1977, at the advanced age of 89. In his time, and in advance of his time, he was an outstanding and forward-looking leprologist. His experience embraced both the presulphone era and subsequent years, and he kept abreast of research in his subject.

Born in Ghent (Belgium) in 1888, Dubois graduated brilliantly in Medicine from Louvain University in 1910 and, having taken a diploma in tropical medicine at Brussels, sailed to the Belgian Congo (now known as Zaire) in 1911. He threw himself wholeheartedly into the many-sided work of the Medical Laboratory in Léopoldville (now Kinshasa), his scientific interests ranging from human trypanosomiasis and amoebasis to beri-beri and onchocerciasis. He was early brought into contact with leprosy in the riverside hospital, and began his investigations of the diverse clinical manifestations of the disease and their histopathological basis, which were later to occupy so much of his time and interest. He became associated especially with an area of unbelievably high prevalence in the Uele, and enlisted the interest of the Belgian Red Cross and subsequently other Belgian philanthropic organizations in establishing and maintaining a first-class laboratory in Pawa in 1934, which became the centre of a model leprosy control scheme in the surrounding villages. A series of good papers came from Pawa, associated directly or indirectly with Dubois.

In 1928, Dubois was appointed Professor of Tropical Medicine at the School of Tropical Medicine in Parc Duden, Brussels, and thereafter in Antwerp when the School became the Prince Léopold Institute of Tropical Medicine. When the great Professor J. Rodhain retired in 1947, Dubois was appointed Director of the Institute, a position that he brilliantly filled until his own retirement in 1958. In these two roles, he played a great part in the training of successive generations of doctors and other health workers from various countries, most of whom would serve in the Belgian Congo or Zaire. From its publication in 1947, his textbook *Les Maladies des Pays Chauds*, written in collaboration with Louis van den Berghe, achieved a deserved success.

He was a careful and methodical clinician, quiet and unassuming, and showing a meticulous objectivity.

While his medical interests were many and varied—*Histoplasma duboisii* is of course named after him—his first and foremost love was leprosy, its clinical aspects, its pathology and its treatment. Influenced by the excellent German

and Scandinavian workers, he was early convinced of the importance of the nasal mucosa as the site *par excellence* of the exit of leprosy bacilli; he was equally convinced of the role of cellular—as distinct from bacillary—infiltration as the overriding factor in peripheral nerve damage. His inspiring teaching of leprosy is enshrined in the manual entitled *La Lèpre*, which for several decades was the leprosy Bible for doctors and other health workers (particularly the *agents sanitaires*) working in Central Africa.

Many of Dubois' former students, as well as distinguished admirers from Belgium and other countries, had pleasure in presenting to him a *Liber jubilaris* or *Festschrift* on the occasion of his 75th birthday.

The doyen of Belgian leprologists, Dubois maintained his interest in the subject long after most people would have shown signs of senescence. He will be remembered with esteem and affection by his many students, and by friends and colleagues all over the world.

STANLEY BROWNE and MICHEL LECHAT
(former students at the Institut de Médecine Tropicale, Antwerp)

DR YOSHINOBU HAYASHI
1890–1977

The Japanese Leprosy Association, and indeed the whole world of leprosy, will mourn the death, on 1 November 1977, of the doyen of Japanese leprologists, Dr Yoshinobu Hayashi.

Born as long ago as 1890, Dr Hayashi began his very fruitful service for leprosy sufferers soon after qualifying as a doctor in 1914, when he joined the medical staff of the Tama Zensho-en Hospital. From the outset, his keen mind and wholehearted dedication to his work were abundantly evident. Interested no less in the clinical than in the pathological aspects of leprosy, Dr Hayashi became Head Physician to the Hospital, and then was appointed Head of the Hospital. In 1941, he was made Director of the National Leprosarium of Tama Zensho-en. It was during this period that Dr Hayashi made his greatest contributions to the study of leprosy, pursuing his researches into the host reactions to the invading organisms and paving the way, through his meticulous observations, for the recent spectacular advances in the immunology of the disease.

Retiring from his responsibilities at the National Leprosarium in 1963, he continued very actively his professional work as a member of the medical staff of the Ministry of Health and Welfare. An appointment that gave him great personal pleasure was that of Honorary Director of the National Leprosarium, a position that he graced from 1964 till the time of his death.

For many years, Dr Hayashi maintained close and cordial links not only with the Japanese Leprosy Association and with such personal stalwarts as Dr Mitsuda, Dr Hamano and Dr Yoshie, but also with the International Leprosy Association. He was a much-respected figure at Congresses of the Association and his opinions were always welcomed. The Leonard Wood Memorial valued his co-operation as consultant during 1953 and 1954.

We salute the memory of a great and good man, who devoted himself to the well-being of leprosy sufferers in Japan itself, and who, through his internationally renowned researches, served the larger weal of leprosy sufferers throughout the world.

S. G. BROWNE
Secretary-Treasurer, International Leprosy Association

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Leprosy and the Community

THE 1ST INTERNATIONAL WORKSHOP ON CHEMOTHERAPY OF LEPROSY IN ASIA, MANILA, PHILIPPINES, 26–28 JANUARY, 1977

Published by Sasakawa Memorial Health Foundation, Sabokaikan, 2–7–5 Hirakawa-cho, Chiyoda-ku, Tokyo, 102, Japan, August 1977

The Proceedings of this important workshop have recently become available from the publishing address above in a 213-page document which is well worth study by those who are involved in the treatment of leprosy, whether for individual patients, or nation-wide control schemes.

The workshop was jointly sponsored by the Department of Health, Republic of the Philippines and the Sasakawa Memorial Health Foundation, Japan. Lectures on the most important aspects of anti-leprosy chemotherapy were given by Dr J. Walter (WHO, Geneva), Dr R. R. Jacobsen (U.S.A.), Dr M. F. R. Waters (U.K.), Dr S. Hazama (Japan), Dr S. G. Browne (U.K.), Dr R. S. Guinto (Philippines) and Professor M. F. Lechat (Belgium). These are recorded verbatim in the first half of this report, the second half being devoted to discussions which arose between the main speakers and delegates and observers from various parts of Asia.

The lectures contain much valuable and fully referenced information, but the discussions provide an exchange of views which is even more revealing, especially when the guest speakers are challenged by delegates with considerable clinical experience. Pages 185 to 187 give final recommendations on the chemotherapy of leprosy, with particular reference to sulphone resistance, and bacillary persistence after long periods of effective therapy. Neither in these recommendations nor elsewhere in the proceedings will the reader find a consensus view for the indications and dosage of all the drugs concerned, but the principles are stated very clearly. One thing is made abundantly clear by this workshop—and that is that we are now on the verge of asking field staff, para-medical workers, nurses, medical assistants and their colleagues to undertake work of a higher standard and greater complexity than ever before. This includes the life-long treatment of all lepromatous patients, the use of dual therapy and the prevention and treatment of adverse reactions of both cell-mediated and immune-complex type. The drugs concerned will include dapsone, rifampicin, clofazimine, the steroids and thalidomide. It will be interesting to see, in the next few years, to what extent the advice from this workshop, which is very close to that of the WHO Expert Committee on Leprosy (1976), is put into practice in areas of the world where there are still many patients with leprosy, most of them inadequately supervised.

A. C. McDOUGALL

HIND KUSHT NIVARAN SANGH: ANNUAL REPORT FOR 1976

The Hind Kusht Nivaran Sangh (Indian Leprosy Association) is one of the most important national Leprosy Associations in the world. The Sangh has a long and distinguished record of service to the people of India, and its Annual Report for 1976 comes at a time when leprosy control is forging ahead. With the President of India as its President, and many distinguished leprologists and men of public affairs on its Governing Body, the Sangh is able to play a very important role in bringing together in close relationship the Governmental and Voluntary Agencies engaged in leprosy control, especially in organizing and sponsoring Conferences and Seminars, and through publications, training programmes, scholarships and research. These diverse interests all figure in the 1976 Report, which not only reports the direct activities of the Sangh, but includes summary reports on the work of important leprosy centres in different parts of India and on the State Branches of the Sangh, all together comprising an interesting picture of anti-leprosy activity in India today. The following are some points of international interest.

The National Leprosy Control Programme in India is gaining strength. Enhanced Government funds for implementing it have allowed the introduction of Zonal Leprosy Officers in the States, the establishment of temporary 20-bed leprosy hospitalization wards in District hospitals, and also Reconstructive Surgery Units in various parts of the country. About 372 million people live in endemic zones of leprosy in India. Out of 3.2 million estimated leprosy cases about 25% are infectious and 20% suffer from deformities. About 400,000 patients have suffered socio-economic dislocation and about 200,000 have become itinerant beggars.

There are now 361 Leprosy Control Units, 4460 S.E.T. Centres, 279 Urban Leprosy Centres, 54 Reconstructive Surgery Units, 120 temporary hospitalization wards, 28 Government and 9 Voluntary Agency Training Centres. Every one of these totals represents a substantial increase over 1975.

A syllabus for leprosy teaching has now been prepared for inclusion in the standard MB. BS. at medical colleges throughout India.

XIV All India Leprosy Workers Conference

This important large biennial event, sponsored by the Sangh, was held at Baroda in April, 1976, and as usual was attended by leprosy workers of various types, and not confined to doctors. Resolutions included the request that mass media in India should consult the H.K.N.S. before transmitting information on leprosy, in order to establish scientific accuracy. The avoidance of the word "leper" was advocated, as was the need to make dapsone freely available to all leprosy institutions and in the open market. It was also requested that the basic facts about leprosy should be included in the curriculum of all secondary schools.

"Leprosy in India"

Leprosy in India is making excellent progress under the distinguished editorship of Dr Dharmendra. More than 250 fresh subscribers were enrolled in 1976 and the size of the Journal has been increased to 460 pages for the 4 issues.

(We cordially associate ourselves with these sentiments and congratulate Dr Dharmendra on a great achievement.)

Training Courses

Training courses sponsored by the H.K.N.S. include the Leprosy Physiotherapy Technicians training course at Vellore, refresher courses for the same type of worker, and orientation courses for doctors.

Publicity and Publications

Health education has been for many years an important emphasis of the H.K.N.S. A *Manual for Public Health Nurses in Leprosy* by Dr D. D. Enna has been published in India among several new publications and revisions of others.

World Leprosy Day

World Leprosy Day receives a great deal of attention in India. The H.K.N.S. takes a leading role in organizing and publicizing functions in support of it.

In addition to the statistics given above the Report of the National Leprosy Control Programme, included as an Appendix to the Report, states that the anti-leprosy programme in India is making rapid strides, and most of the high and moderately high endemic areas of leprosy have been brought under the surveillance of the Programme.

The JALMA Centre at Agra has been taken over by the Government of India and is functioning as a training, research and referral centre (CLIL).

There are also very useful concise reports from: The Indian Council of Medical Research; The Leprosy Mission; The Central Leprosy Teaching and Research Institute, Chingleput; Gandhi Memorial Leprosy Foundation; The Christian Medical College and Hospital, Vellore.

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News and Notes

XI INTERNATIONAL CONGRESS OF LEPROSY, MEXICO CITY, MEXICO 11–18 NOVEMBER 1978

The attention of all our readers is drawn to this important Congress.

Registrations, hotel reservations, social events, tours and in general all administrative matters concerning this Congress will be handled by the Local National Committee. Please address to: *XI International Congress of Leprosy, Associacon Mexicana de Accion Contra La Lepra A.C., Dr Vertiz 464, Mexico 7. D. F. MEXICO.*

Scientific Programme

WORKSHOPS

(1) Chairmen and members have been named to participate in workshops on the following themes: experimental leprosy; microbiology; immunology; experimental chemotherapy; epidemiology and control (including field therapy) and social aspects. The respective chairmen will inform the members of their workshop on which day they will meet (9, 10 and 11 November) before the opening day of the Congress. Reports of these workshops will be presented to participants when they register.

ORGANIZATION OF CONGRESS SESSIONS

(2) After the first plenary session (on epidemiology and control), simultaneous scientific sessions will be organized under the following themes: experimental leprosy; clinical aspects; microbiology; immunology; social aspects; experimental chemotherapy; therapy; rehabilitation and clinico-pathological aspects (including nerve damage).

The main presentations at each session will be made by participants who have already been informed by the chairmen of the session at which their paper will be presented.

FREE COMMUNICATIONS

(3) A very limited number of papers (of 10 min duration) on aforementioned themes will be accepted for reading at each of the scientific sessions.

POSTER PRESENTATIONS

(4) It will be an innovation at the Congress.

CLINICAL SESSION

(5) Patients with Lucio Leprosy will be shown at the Pascua Dermatological Centre.

ABSTRACTS

(6) All abstracts of papers, from intending participants only should be submitted before 30 April 1978 to Dr S. G. Browne, 57A Wimpole Street, London W1M 7DF, England. Four copies of the abstract, not exceeding 200 words in length, in one (or more) of the official languages of the Congress, and indicating the Session at which the paper would be relevant, should be submitted.

No participant may figure as the principal author of more than one paper.

For information about the Scientific Programme, presentation of free papers and so on, please write to: *Dr Stanley G. Browne, Secretary General, International Leprosy Association, 57A, Wimpole Street, London W1M 7DF, England.*

INTERNATIONAL YEAR OF THE CHILD (1979)

On 21 December 1976, the General Assembly of the United Nations passed a resolution declaring 1979 the International Year of the Child. The hope is that by placing children in the centre of world attention, the world community will renew and re-affirm concern for the present condition and for the future of its children.

One critical area of concern is stigma. Many millions of children are prevented from growing and developing in normal ways simply because stigmatizing differences have been ascribed to them. In some cases, children themselves are in some way different. In other instances, it is more a matter of "guilt by association"; parents, siblings, or other associates are the immediate victims.

The causes of stigmatization are many, but in as much as thousands of children are directly afflicted with leprosy and millions more suffer from its stigma, the International Federation of Anti-Leprosy Associations and the International Leprosy Association are taking active parts especially in this aspect of the International Year of the Child activities. And, both through these organizations and independently, American Leprosy Missions is extending support.

In order to take best advantage of the opportunity to highlight the plight of children affected by leprosy either directly or indirectly, help is needed in identifying the priorities which will serve children who suffer spiritually and physically from leprosy. Members of ILEP were requested to complete a questionnaire designed to assist in compiling data. Of special concern is the importance of determining what social injustices, if any, children suffer as a result of leprosy backgrounds. If any reader has information which might be valuable in developing a meaningful programme for children of such

backgrounds, or if you have a specific philosophy or goal for this special year which you would like to have made known at the United Nations, it would be most appreciated.

Within the framework of UNICEF, which is co-ordinating the United Nations efforts on behalf of the International Year of the Child, a special committee for co-ordination of world-wide activities was established and Mrs Bernice Gottlieb, because of her well-known interest in children who have leprosy or whose parents have leprosy, has been appointed by the ILA as a member of this committee. If you have information you would like to share, you may write to Mrs Bernice Gottlieb in care of American Leprosy Missions, 1262 Broad Street, Bloomfield, New Jersey 07003.

WORLD LEPROSY DAY

Information regarding World Leprosy Day 1978 arrived too late for inclusion in the December 1977 issue of Leprosy Review. Our readers will recall that the date of this is always *the last Sunday in January*. In 1979, this will be *28 January*.

The concept of a World Leprosy Day was originated in 1953 by M. Raoul Follereau, to bring the needs of leprosy patients before governments and the public. The day is now observed in over 100 countries.

LEPROSY REVIEW VOLUME 49 (1978)

It is greatly regretted that on account of increased printing costs it has once again been necessary to increase the subscription charge for the journal. Through the efforts of Lepra it is hoped that there will be no additional charge for 1979. We thank all our readers for their continued support. *Leprosy Review* is published on behalf of Lepra, without financial profit to Lepra.

THE FIRST INTERNATIONAL WORKSHOP ON LEPROSY CONTROL IN ASIA

The Sasakawa Memorial Health Foundation is endeavouring to make a real impact on leprosy in Asia. Under its auspices, a Workshop was held in Bangkok (November 1976) on "The Training of Leprosy Workers"; in Manila (January 1977) another on "The Chemotherapy of Leprosy"; and now (28 November to 2 December 1977) "The First International Workshop on Leprosy Control in Asia" was held in Jakarta, Indonesia. This Workshop was organized and sponsored by the Department of Health of the Republic of Indonesia in conjunction with the Sasakawa Memorial Health Foundation. The theme of the Workshop being "The role of voluntary agencies in National Leprosy Control Programmes", participants included delegates from voluntary agencies involved in leprosy field work and training in Indonesia itself (The Leprosy Mission, Nederlands Lepra Fonds, Emmaus Suisse, German Leprosy Relief Association), representatives from WHO, Unicef and ILEP, delegates from neighbouring countries (Nepal, Thailand, the Philippines,

South Korea, Japan), as well as resource persons (Drs S. G. Browne, R. S. Guinto and M. F. Lechat).

Taking the advice given in the Fifth WHO Expert Committee on Leprosy, that "continuing consultation between the health authorities and voluntary agencies should be encouraged", the Workshop reviewed the leprosy programmes in the countries represented, and made suggestions for the better application of the principle of co-operation and complementation that has recently been well demonstrated in Indonesia itself and in other countries in Asia.

The success of the Workshop will be judged by the extent to which the countries concerned put into practice the recommendations that were unanimously adopted at the close of the Workshop proper. A successful field trip concluded the proceedings.

S. G. BROWNE

(*Note.* A review of the published Proceedings of this Workshop is presented under "Leprosy and the Community". Ed.)

DRUG RESEARCH AND DEVELOPMENT

A Round Table Conference on "Trends and Prospects in Drug Research and Development", organized by CIOMS (The Council for International Organizations of Medical Sciences) was held at Geneva on 8 and 9 December 1977. Representatives of Member-Organizations of the Council were present as well as spokesmen for the World Health Organization and Pharmaceutical Companies engaged in drug research.

As far as leprosy is concerned, it seems that our demands for a cheap, non-toxic, rapidly-acting drug, effective in all kinds of leprosy and free from the risk of inducing reversal reaction in nerves—are like "crying for the moon". However, since the World Health Organization through its Training and Research programme in Tropical Diseases, and particularly its THELEP (and indirectly, its IMMLEP) programme, is now more than ever actively concerned with leprosy, it is to be hoped that the meeting will have given a real impetus to drug research at this critical stage in the anti-leprosy campaign. Meanwhile, a more enlightened use of the drugs we have available, and a greater insistence on regularity of treatment, should be within the reach of all leprosy control programmes.

S. G. BROWNE

WORLD HEALTH ORGANIZATION

Special Programme for Research and Training in Tropical Diseases

THE SEARCH FOR SCIENTISTS TO SEARCH FOR THE TOOLS TO CONTROL THE TROPICAL DISEASES

The search for new tools to control disease in the tropical countries requires scientists of many disciplines. Molecular and cell biologists, biochemists, immunologists, parasitologists and entomologists are among those whose contributions are needed.

The research areas covered by the Special Programme for Research and Training in Tropical Diseases are:

— malaria, schistosomiasis, filariasis, trypanosomiasis, leishmaniasis and leprosy;
— epidemiology, biomedical sciences, biological control of vectors, and socio-economic research.

Specific fields within these research areas are developed by the Programme's Scientific Working Groups. Scientists from any country are welcome to submit proposals for research grants within the specific fields. All enquiries should be addressed to:

The Special Programme for Research and Training in Tropical Diseases
World Health Organization
1211 Geneva 27, Switzerland.

For those persons seeking contact with Special Programme participants in the United Kingdom, a Special Programme Committee has been set up by a group of interested scientists there to provide such information. The Committee also has research proposal forms available. Correspondence should be addressed to:

Professor David Bradley, Chairman
UK National Committee of the TDR
c/o Mrs J. Beard
Medical Research Council
20 Park Crescent, London W1N 4AL, U.K.

Should scientists in other countries wish to organize such liaison Committees, we should be pleased to collaborate with them and to publicize their activities. Any suggestions in this regard should be addressed to the Director of the Special Programme.

Lepr. Rev. (1978) **49,** 87–88

Letters to the Editor

Dr Pedley's conscientious studies leave no doubt that the nose is far the most important site of release of *M. leprae.* In fact, I wrote: "The importance of the nasal mucosa . . . is not challenged, neither the likelihood that *M. leprae* found on the skin may frequently have originated from the nasal mucosa". So far there is no essential disagreement.

I quantified the number of bacilli which were selected from the skin as "relatively low", Dr Pedley as "practically nil". I believe that the latter is an understatement, at least with respect to reactive lepromatous patients with ulcerating, vesicular or bullous lesions, because I found that such vesicles often are filled up with bacilli. A single vesicle or bulla may contain hundreds to thousands of bacilli, a number which certainly is sufficient for infecting many individuals. The crucial question is not how many bacilli are released, but how many are needed for infection. If we agree that only few bacilli are needed, and that small numbers of bacilli are released from skin defects, sweatducts and hairfollicles, that in addition much larger numbers of bacilli may reach the skin via nasal discharge, then I believe that it is correct to say that "infection via the skin remains a definite possibility".

The main point in my paper was that there is clinical and epidemiological evidence pointing against the hypothesis that the primary lesion, as a result of droplet infection, is located in the respiratory tract and that the modes of spreading of leprosy and of tuberculosis are similar. What I miss in Pedley's comments is either a challenge of the validity of this evidence or an explanation as to how the evidence can be made compatible with his hypothesis. There are no case reports of visitors of leprosy centres who have contracted leprosy. Few expatriate general medical and paramedical workers in endemic countries develop leprosy. The incidence of leprosy in others who work in highly endemic communities is low. Most of these people must have, on one, or more probably on several occasions, inhaled *M. leprae.*

In the Netherlands small outbreaks of tuberculosis are still frequently seen, but in this densely populated country, with a high incidence of sneezing due to common cold, although countless people must have inhaled *M. leprae* originating from untreated, relapsed or even drug-resistant lepromatous patients, only exceptionally an autochthonous case of leprosy was seen. In 1959 I diagnosed highly bacilliferous lepromatous leprosy in a girl who had lived for more than 2 years in a boarding school, undiagnozed and untreated. None of the hundreds of pupils has so far developed leprosy. My only explanation is that although countless people are exposed to dispersal of droplets containing *M. leprae*, the bacilli which are inhaled do not find in the respiratory tract a suitable environment for survival. Therefore I believe that it

is unlikely that the modes of spreading of leprosy and tuberculosis are identical.

D. L. LEIKER

Koninklijk Institut Voor De Tropen,
Amsterdam, The Netherlands

Vitiligo and Leprosy

I would like to put on record the observation that, during my work as a leprologist in London, I have encountered a significant incidence of vitiligo in patients under treatment for lepromatous leprosy. By "vitiligo" I am not referring to the well known hypopigmentation of leprosy but to the classical circumscribed depigmentation that can affect healthy persons of all races but occasionally is found in association with organ-specific auto-immune disorders such as diabetes, pernicious anaemia, thyroid disease, Addison's disease, and alopecia areata. I have found 8 cases of vitiligo among 114 lepromatous patients, an incidence of 7%, but no cases of vitiligo among a larger number of non-lepromatous patients, and I would be interested to know if this association has been noted elsewhere or if it has been reported in the literature.

This observation, when fully investigated by my successor at the Hospital for Tropical Diseases, may lend support to the hypothesis that vitiligo is an auto-immune disorder, having regard to the wide variety of circulating auto-antibodies which have been described in lepromatous leprosy, such as antinuclear, antithyroid and antisperm antibodies, and rheumatoid factor.

W. H. JOPLING

33 Crown Lane Gardens,
Crown Lane, London SW16 3HZ

Lepr. Rev. (1978) **49,** 89–91

Book Reviews

Skin Biopsy in Leprosy by Dennis R. Ridley, 1977. Documenta Geigy, CIBA-GEIGY Ltd, Switzerland.

We should be grateful to CIBA-GEIGY not only for their interest in antileprosy drugs such as thiambutosine, clofazimine and rifampicin, but also for the production of 2 extremely valuable booklets. The first was the now familiar green paperback *Leprosy* by Dr S. G. Browne of the Leprosy Study Centre, London (1970), which is available in several languages and has recently been reprinted, and the second is this booklet of similar format by Dr Dennis Ridley of the Hospital for Tropical Diseases, London, devoted to the histological interpretation and clinical application of skin biopsy in leprosy. In the foreword, Dr M. F. R. Waters pays tribute to the value of the system which Dr Ridley has developed through the years, in association with Dr William Jopling at HTD in London. "A Classification of Leprosy for Research Purposes" was published in *Leprosy Review* **33** (1962), and "Classification of Leprosy According to Immunity" in the *International Journal of Leprosy* **34** (1966), and those interested in this subject may find it profitable to re-read these papers, together with the author's more recent "Histological Classification and the Immunological Spectrum of Leprosy" in *Bulletin of the World Health Organization* **51** (1974).

Skin Biopsy in Leprosy has 57 pages, a full index, comprehensive references under each main section and 73 illustrations, nearly all of them in colour. For the most part, the latter are of high quality and the use of photographs at low power magnification is particularly valuable. A minor point of criticism is that the density and clarity of bacillary staining (for instance, Figs 23, 24, 30 and 61) do not reproduce at all well. Laboratory methods are fully described and there is a separate section on numerical indices. The other subject headings include: the pathogenesis of a skin lesion, the examination and interpretation of a skin section, diagnosis and differential diagnosis, relapse, classification and the spectrum, and reactions. To those still puzzled by some aspects of the histopathology of leprosy, there are 2 areas of particular interest in the text. The first, mainly on pages 18 and 19, concerns the concept of activity, regression and cell turnover, all of importance in view of the increasing prevalence of relapse in this disease. The second deals with the numbers of lymphocytes in the various types of leprosy, mainly on page 39, where it is stated that these cells are in fact most numerous in Borderline-Lepromatous (BL) leprosy and that they show "very little correlation with the lymphocyte transformation test, and not much with the rate of decline under treatment in the absence of upgrading". Their influence and significance in leprosy tissues are undoubtedly much more complex than we previously thought, and the interested reader will find the subject more fully discussed in Dr Ridley's WHO article quoted above.

The author is to be congratulated on the production of a most valuable booklet. Together with a number of short publications on leprosy of similar length and format which have appeared in recent years, it will rapidly prove far more useful than some of the larger and more expensively produced textbooks. It is available on request from CIBA-GEIGY Ltd, Basle, Switzerland or from GEIGY Pharmaceuticals, Hurdsfield Industrial Estate, Macclesfield, Cheshire SK10 2LY.

A. C. McDOUGALL

Doctors and Healers, by Alexander Dorozynski, 1975. IDRC (International Development Research Centre) 043e.

This is a 63-page paperback booklet, profusely illustrated, written by an experienced medical and scientific author who was the founding member, and later the publisher of Médecine Mondiale, a European news magazine for physicians. It deals with a disquieting subject, namely

the gap between medical knowledge and available resources, and their effective application to those people who most need them. There are sections on the distribution (and mal-distribution) of doctors in the world, the cost of medical education, the principal causes of death in children, birth control, the drain of doctors from underdeveloped to developed countries, and the experience of China in creating its barefoot doctor service. Although the views are officially those of the author only, there is a foreword by the Director of the Health Sciences Division of IDRC, in which it is clear that the book is published with the main intention of supporting "innovative programms designed to provide practical approaches to the provision of health care services". *Doctors and Healers* could profitably be read in conjunction with another booklet of similar size, *Tropical Diseases*, which is produced by WHO with the support of IDRC, and deals with some of the problems to be tackled in WHO's Special Programme for Research and Training in Tropical Diseases. Mr Dorozynski's booklet makes uncomfortable yet compelling reading; it should in fact be read by all those interested in improving the application of medical knowledge to the prevention and treatment of disease in developing countries. The current WHO figures for leprosy (11 to 12 million estimated; 3 million known to local authorities, of whom only a fraction attend with any degree of regularity; 8 to 9 million not registered and thus totally untreated) are one part of the implementation gap about which this book is written. It is available on request from IDRC, Box 8500, Ottawa, Canada, KIG 3H9 or 18 Grosvenor Street, London W1X 9FD.

A. C. McDOUGALL

Leprosy Reactional States and their Treatment, by D. S. Jolliffe, 1977. *British Journal of Dermatology* **97,** 345–352.

This Review article, from the Department of Dermatology at the Royal Free Hospital in London, is well worth careful reading, not only by dermatologists who have responsibility for patients in various types of reaction, but also by those working in leprosy. Dr Jolliffe begins by summarizing our present concept of the disease spectrum and then describes the clinical manifestation of the 2 types of reaction in considerable detail, emphasizing the fundamentally different processes involved. He uses the Type 1 and Type 2 terminology originally suggested by Jopling in 1959 and further developed by the same author in correspondence to the *Leprosy Review* in 1970 (**41,** 62–63), linking Type 1 (Lepra) reaction with changes in cell-mediated immunity, and Type 2 (ENL) reaction with the formation of immune complexes. Under treatment, the general principles are outlined, followed by sections on the indications and dosage of drugs for both types of reaction, again based on their differing aetiology.

The adaptation of all this valuable (and very well referenced) information to the patient in the field is a matter of urgent concern to those who have anything to do with leprosy control programmes. Perhaps the most difficult point concerns the continuation of dapsone (or other anti-bacillary drugs) in normal doses in the presence of either type of reaction. Under "General Principles", and referring to dapsone, the author writes: "Despite previous thoughts on the subject, there is in 1977 ample evidence that there is never any indication to stop such therapy or to reduce the dosage to below 1 to 2 mg/kg/day during reactional states" (the reference he gives, Waters and Helmy, 1974, refers to lepromatous leprosy), and in the next paragraph (and the summary) he implies that dapsone should also be continued in unchanged dosage during reversal (Type 1) reactions. In view of the opinion, strongly held by many experienced leprologists, that reversal reactions are not infrequently precipitated by the use of anti-leprosy drugs (usually dapsone), some may feel hestitant about the application of this advice at the cutting edge of leprosy control, where it is the field worker and not the leprologist who is being asked to recognize and treat adverse reactions in leprosy. Steroids are clearly effective in Type 1 reactions, but as Dr Jolliffe rightly points out: "As the natural history of these reactions can span weeks and months so also must the steroid cover be continued with all the risks involved". He recommends clofazimine (B663, Lamprene) as an alternative in this situation, but draws attention to its slow onset of therapeutic effect and to the occurrence of side-effects. Without doubt, the most serious of these concern the accumulation of crystals in the intestine and lymph nodes and many leprologists who have experience of this drug may feel that the stated maximum daily dose of 500 mg is too high and that even at a daily dose of 300 mg it would be wise to include a warning that clofazimine should be used for only a limited period of time for this purpose.

These are minor points. This admirable account of a difficult subject will be of great value to doctors in clinical medicine and dermatology. It should also provide food for thought for those who have to draw up guidelines for the application of these measures to leprosy control in the field. Some may wonder, particularly in the case of thalidomide and the steroids, how this can be accomplished, with safety.

A. C. McDOUGALL

(In order to draw attention to this very important article, it is reviewed here rather than in the next Section. Ed.)

Lepr. Rev. (1978) **49,** 92–96

Abstracts

1. FILICE, G. A., GREENBERG, R. N. & FRASER, D. W. **Lack of observed association between armadillo contact and leprosy in humans.** *Am. J. Trop. Med. Hyg.,* 1977, v. 26, No. 1, 137–139.

In 1971 it was discovered that the nine-banded armadillo (*Dasypus novemcinctus*) could be infected in the laboratory with *Mycobacterium leprae*, and would manifest disease similar to the lepromatous form of leprosy in man. In 1975 several wild armadillos captured in Louisiana were found to have a disease identical to the *M. leprae* infection in laboratory animals. To determine if there is a significant association between contact with armadillos and presence of leprosy in humans, the armadillo contact of persons with indigenous leprosy in Louisiana was compared to the contact of matched controls. No difference in the nature of frequency of contact was found. If this infection of wild armadillos is of recent onset, an association with human leprosy in enzootic areas may not be detectable for several years.

[See *Trop. Dis. Bull.,* 1976, v. 73, abstr. 896.]

2. SHIELD, M. J., STANFORD, J. L., PAUL, R. C. & CARSWELL, J. W. **Multiple skin testing of tuberculosis patients with a range of new tuberculins, and a comparison with leprosy and *Mycobacterium ulcerans* infection.** *J. Hyg.* Cambridge, 1977, v. 78, No. 3, 331–348.

This very detailed study of skin sensitivity to various mycobacterial antigens cannot adequately be abstracted and should be studied in the original by those interested in the subject.

The work was carried out in Burma, Libya, Kenya and Uganda (the last 2 grouped as East Africa). Patients suffering from active tuberculosis and undergoing treatment in hospital were each tested with 4 mycobacterial antigens. Those being given steroid therapy were excluded because of the known effect of such preparations in suppressing tuberculin sensitivity.

Control groups were formed from normal subjects and patients in Burma suffering from leprosy were also tested for comparison.

The antigens were the following:

Organism	Antigen
M. tuberculosis	PPD (RT23)
M. tuberculosis	Tuberculin
M. sp. 'A'	A*-in
M. avium	Aviumin
M. gordonae	Gordonin
M. kansasii	Kansasin
M. marianum	Marianin
M. ulcerans	Burulin
M. xenopi	Xenopin
M. chelonei	Chelonin
M. duvalii	Duvalin
M. flavescens	Flavescin
M. fortuitum	Ranin
M. gilvum	Gilvin
M. neoaurum	Neoaurumin
M. nonchromogenicum	Nonchromogenicin
M. vaccae	Vaccin

The sources of all are stated.

The antigens were injected intracutaneously, the dose being 0.1 ml containing 0.2 μg of protein. Reactions were read after 72 h and measured. The criterion of a positive reaction was induration of 5 mm or over.

(In order to avoid the confusion caused by using the term "tuberculin" for the antigen produced from any mycobacterium the authors use "Tuberculin" with a capital "T" in the specific sense and "tuberculin" with a small "t" in the non-specific sense.)

The results are presented at length in tables, graphs and nomograms.

Among the normal subjects it was found that positive reactions to Tuberculin were associated with an enhanced response to all the other tuberculins except A*-in. In Burma, where non-specific mycobacteria were common, sensitization to mycobacterial species other than *M. tuberculosis* played a role in determining responses to different mycobacterial antigens.

In tuberculous patients, enhanced skin responses were also seen but only in those countries (as Libya) where the prevalence of non-specific mycobacterial species was low. Where such were common, as in Burma, the converse held and tuberculosis was associated with diminished sensitivity to each antigen. Excessive sensitization may lead to the depression of sensitivity so that the skin test becomes negative. The non-reactors may thus include subjects never sensitized as well as those whose previous sensitivity has been abolished by excessive sensitization.

A greater percentage of patients with tuberculosis in each country responded to Tuberculin than did the control subjects and with a greater degree of sensitivity. It was found however that in Burma 13% of the patients did not react to Tuberculin or the other antigens with which they were tested.

Patients suffering from lepromatous leprosy and those infected by *M. ulcerans* were also found to display anergy. The significance of all these findings is discussed.

[See also *Trop. Dis. Bull.,* 1976, v. 73, abstr. 2763.]

H. G. Calwell

3. PREMANATH, M. & RAMU, G. **The association of leprosy and tuberculosis.** *J. Indian Med. Ass.,* 1976, v. 67, No. 6, 143–145.

Observations are made on 40 patients suffering from both leprosy and tuberculosis, 29 of them lepromatous and 11 borderline in leprosy type. The serious prognosis of tuberculosis when co-existing with lepromatous leprosy is stressed, and synergism rather than antagonism between the 2 mycobacteria is thought to be a possibility.

T. F. Davey

4. MERLIN, M., CARME, B. & KAEUFFER, H. Bilan de 25 ans de chimiothérapie anti-lépreuse en Polynésie française. Influence sur l'age d'apparition de la maladie. [**A balance-sheet after 25 years of leprosy treatment in French Polynesia. Its effect on the age of onset of the disease.**] *Bull. Soc. Path. Exot.,* 1976, v. 69, No. 5, 412–422. English summary.

The authors provide a summary of the main features of leprosy in the scattered islands of French Polynesia. The prevalence rates are generally low (about 2.48 per 1000), but in its clinical features and type ratio the disease resembles that found in the more serious situation in Asia, with about half the patients suffering from multibacillary forms. There are indications that leprosy was introduced into the islands in about 1875 by the Chinese.

The efforts at leprosy control—based on accepted principles of early case finding, school surveys, contact examination, the provision of free treatment—appeared to give good results, with progressive reduction of incidence rates (from 0.25 to 0.9 per 1000 in the years 1950 to 1975). Recently, however, vigilance has unfortunately relaxed and newly-diagnosed cases present with well-established infections and a disturbing increased prevalence is noted in the urban zone of Tahiti.

BCG vaccination now reaches 80% of those aged less than 20 years and prophylactic dapsone has been offered over the past 4 years to contacts.

The authors conclude that chemotherapy alone, as provided in the islands studied, is insufficient to guarantee a sustained decline in the incidence of leprosy and that, where the population is increasing rapidly and subject to the health hazards of migration, further measures are imperative to control the endemic.

An interesting sidelight on the changing pattern is given in the figures of the "age at onset" [which is equated with the age on diagnosis]. In the early years of the study (1925 to 1949), the median age at onset was 17 years; more recently (1970 to 1976) it is 27. [The figures cited in this analysis are too small and unreliable for epidemiologically valid conclusions to be drawn.]

S. G. Browne

5. MERLIN, M., CARME, B. & LAIGRET, J. Impact de la modification profonde des structures d'une société sur l'évolution d'une maladie endémique: la lèpre en Polynésie Française. [**Effect of changing environmental structures on the course of an endemic diasease; leprosy in French Polynesia.**] *Bull. Soc. Path. Exot.,* 1976, v. 69, No. 5, 422–433. English summary (7 lines).

The authors describe briefly the rapidly changing picture of life in the Pacific Islands. From the idyllic tranquillity of 25 years ago, economic development has transformed brusquely the economy, the life-style, and the prevalence of leprosy. The construction of the international airport at Tahiti and the establishment of the Atomic Energy Experimental Centre have attracted migrant populations who now earn inflated wages after abandoning their subsistence farming or fishing. In 25 years the population has doubled and the economic transformation has resulted in declining standards of hygiene.

Although leprosy was never a serious public health problem in the islands, with the exception of the Marquesas and Tuamotu, where there were rather higher prevalence rates, the migration of populations that include many undiagnosed and untreated leprosy sufferers who are potentially contagious presents the authorities with a serious situation. An example given is the finding, during routine school surveys, of children suffering from florid lepromatous leprosy. Since about 53,000 people (41% of the population) are now concentrated in Tahiti itself, the existence of the virtually uncontrolled focus in the urban area augurs ill for the future unless vigorous measures are taken.

S. G. Browne

6. ABREU, A., WERTHEIN, L. J., RUIZ DE ZARATE, S. & AYRADO, A. Programa de control de lepra en Cuba: estado actual. [**Control programme for leprosy in Cuba: current state.**] *Revta Cub. Hig. Epidem.,* 1976, v. 14, No. 2, 117–122. English summary.

The programme in force from 1962 to 1971 involved updating the census, ambulatory treatment and annual examination of persons living with patients. A new programme established in 1972 has exploited the improved dermatological and leprological resources of the country and is characterized by decentralization of diagnostic and therapeutic measures. Persons living with patients undergo chemoprophylaxis. Prevention of physical handicaps and rehabilitation of those afflicted are fundamental aims. In 1974, 307 new cases were detected. There were 4672 known leprosy cases, of which 4517 were controlled. 88.2% of 12,530 persons in contact with leprosy were under surveillance.

Ann Grant

7. LANGUILLON, J., CARNUS, H. & ROUX, G. Le test de transformation lymphoblastique chez les lépreux. Sa signification comme indicateur de l'immunité cellulaire. [**The lymphoblastic transformation test in leprosy. Its significance as an indicator of cellular immunity.**] *Bull. Soc. Méd. Afr. Noire Lang. Fr.,* 1976, v. 21, No. 4, 419–424. English summary.

The authors give a useful summary of cellular and humoral immunity in the various types of clinical leprosy, correlating them in immunological and histopathological terms.

In an attempt to resolve the discordancies in published investigations on the subject, they report the results of their studies of the lymphoblastic transformation test in leprosy. The subjects, African under treatment in Dakar (Senegal), comprised 54 with tuberculoid leprosy (all Mitsuda-positive), 91 with lepromatous leprosy (all Mitsuda-negative), composed of 48 in a reactional state and 43 non-reactional, and 10 with borderline ("interpolar") leprosy whose Mitsuda reaction was negative or doubtful.

They found no difference between these groups in the lymphoblastic transformation test, or between the reactional and non-reactional subgroups in patients with lepromatous leprosy. In addition, patients with borderline leprosy showed a similar scatter of reactivity towards phytohaemagglutinin.

They conclude that their results support the supposition that the depression of cellular immunity in leprosy is associated with a limited and specific antigenic structure possibly present on the surface of *Mycobacterium leprae.*

S. G. Browne

8. PETCHCLAI, B., VILAIPRASERT, S., HIRANRAS, S. & RAMASOOTA, T. **Serum IgE levels in leprosy.** *J. Med. Ass. Thailand,* 1977, v. 60, No. 1, 19–21.

Serum IgE level was determined in 23 cases of tuberculoid and 19 cases of lepromatous leprosy, to see if there is any increase corresponding to the increase in other immunoglobulins. Significantly increased levels were found in both groups. The levels were higher in the lepromatous group but there was no statistical significance. Great fluctuations in serum IgE levels were observed in some tuberculoid patients having 2 collections 15 months apart. The results suggest a hyperactive IgE forming system which is occasionally influenced by and which responds to stimuli other than leprosy bacilli.

9. RAMU, G. & BALAKRISHNAN, S. **Plasma fibrinogen levels and fibrinolytic activity in lepromatous leprosy.** *J. Ass. Physns India,* 1977, v. 25, No. 2, 133–138.

A longitudinal study was carried out on plasma fibrinogen levels in patients with lepromatous leprosy in different phases with varying clinical manifestations. Significant increases were noticed in plasma fibrinogen levels in cases with lepra reaction particularly those manifesting necrotizing skin lesions, kidney lesions and sclerodermic lesions. The increase in fibrinogen level was associated with a decrease in fibrinolytic activity. Treatment with steroids lowered the plasma fibrinogen levels. A direct correlation between increase in the plasma fibrinogen level and ESR was noticed. The significance of those findings in relation to prognosis of the disease and treatment of "lepra reaction" is discussed.

[See also *Trop. Dis. Bull.,* 1975, v. 72, abstr. 512.]

10. HERNANDEZ ANGULO, M., FERNANDEZ BAQUERO, G. & FRAGUELA RANGEL, J. V. Informe preliminar sobre una forma histopatológica atípica de una lepra lepromatosa. [**Preliminary report of an atypical histopathological picture in lepromatous leprosy.**] *Revta Cub. Med. Trop.,* 1976, v. 28, No. 2, 93–100.

The English summary appended to the paper is as follows:

"A patient with lepromatous leprosy whose atypical histopathologic picture involved giant vacuoles and cell atypia is presented. The summary of his clinical record is given, and bibliography is reviewed."

11. SRIVASTAVA, K. P. & KESARWANI, R. C. **Management of trophic ulcers in leprosy patients.** *J. Indian Med. Ass.,* 1976, v. 67, No. 11, 250–252.

Thirty-two cases of trophic ulcer of the foot in leprosy patients are reviewed after treatment at the Orthopaedic Department of the S.N. Medical College, Agra, using varied procedures. The best long-term results were obtained by local excision combined with metatarsectomy of the pressuring head. [The acceptance of leprosy patients into the wards of a teaching hospital is commendable.]

T. F. Davey

12. PETERS, J. H. *et al.* **Acedapsone treatment of leprosy patients: response versus drug disposition.** *Am. J. Trop. Med. Hyg.,* 1977, v. 26, No. 1, 127–136.

In 22 Filipino patients with lepromatous leprosy, receiving their first injection of 225 mg acedapsone (DADDS), dapsone (DDS) and monoacetyl DDS (MADDS) were present in plasma in approximately equal quantities. Peak levels occurred between 22 and 35 days. The half-times of disappearance ($T_{\frac{1}{2}}$) from plasma were 43 days for DDS and MADDS and 46 days for DADDS. 17 patients were rapid and 5 patients slow acetylators. The $T_{\frac{1}{2}}$ of DDS after DDS treatment in the patients was directly related to the minimum levels of DDS at 77 days after DADDS treatment and these were 8-fold higher than the minimum inhibitory concentration of DDS for *Mycobacterium leprae* in mice and rats, but not all patients responded satisfactorily. No relationship could be demonstrated between the bacteriological response and any of the pharmacological parameters examined in these Filipino patients. In a companion study of 447 leprosy patients of all disease types from the Karamui District of Papua New Guinea, the type of response and sulphone levels were unrelated. No substantial accumulation of the sulphone in patients receiving continuous DADDS therapy for 5 years was indicated.

T. F. Davey

13. REES, R. J. W. & McDOUGALL, A. C. **Airborne infection with** *Mycobacterium leprae* **in mice.** *J. Med. Microbiol.,* 1977, v. 10, No. 1, 63–68.

This study was designed to investigate the possibility of airborne infection with *Mycobacterium leprae.* The authors used thymectomized irradiated mice exposed to aerosols containing *M. leprae* with an immediate lung retention of 1×10^5 bacteria. Fourteen to 24 months later, 10 out of 30 mice had considerable numbers of acid-fast bacilli with the characteristics of *M. leprae* in one or more homogenates prepared from ears, footpads, nose or lungs. Evidence is presented from the distribution of *M. leprae* that the infection had arisen from the systemic spread of bacilli initially entering the lungs, rather than from multiplication of organisms locally retained there, or in the nose at the time of airborne infection. The relevance of these results to the possible route of infection with leprosy in man is discussed.

T. F. Davey

Thanks are due to the Director, Bureau of Hygiene and Tropical Diseases for permission to reprint Abstracts from *Tropical Diseases Bulletin,* August and September, 1977.

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