Lepr Rev (1981) **52**, 293–298

Editorial

THE USE OF CORTICOSTEROIDS IN LEPROSY

Cortisone was first used in medicine at about the same time that dapsone was introduced for the treatment of leprosy, and prednisone (the first of the less salt retaining synthetic corticosteroids) was introduced a few years later, in about 1956. The first report of their use in leprosy appears to be that of Lowe.[1] He reported that 5-day courses gave immediate benefit in acute manifestations of leprosy, warned that they might recur (sometimes more severely) on stopping treatment, and warned also of the possibility of aggravation of the underlying disease. He advised them unreservedly for drug allergy and (as local applications which are devoid of systemic toxicity) for eye complications.

In 1953 the report of the 6th International Leprosy Congress[2] confirmed the dramatic effect of the corticosteroids in relieving the acute manifestations of leprosy, but commented that there were wide differences of opinion on the late results, particularly in the treatment of recurrent reactions. The risk of deterioration of the underlying disease was mentioned, but the use of corticosteroids for drug allergy and eye complications was supported.

By 1957 Jopling and Cochrane[3] were able to make general recommendations for the use of corticosteroids. They advised cortisone 100–200 mg daily as the initial dose, to be tapered off as a course lasting 5–10 days. Such courses were to be repeated as necessary. They advocated intraneural injections of hydrocortisone (with procaine and hyaluronidase) for neuritis, and noted that treatment for a year or more might be required in cases of erythema nodosum leprosum (ENL).

At the 7th International Leprosy Congress in 1958,[4] almost all those participating in the 'Section of Therapy' used and recommended corticosteroids for reactions: the report, however, makes little mention of the dosage or duration of treatment.

By 1964 the indications of their use had been well worked out. Jopling's[5] recommendations have a modern flavour to them, and remain the basis of current treatment. They can be summarized as follows:

In 'reversal' reactions (Type 1 lepra reaction, RR) corticosteroids should be

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avoided in the absence of neuritis or ulceration of skin lesions. If used, the initial dosage should be cortisone 200 mg daily (equivalent to prednisone 40 mg daily) till improvement starts, then slow reduction of dosage. A course should last at least 10 days.

In ENL (Type 2 lepra reaction) corticosteroids should be avoided except in severe cases, when the dosage advised was cortisone 100 mg daily (equivalent to prednisone 20 mg daily) reducing rapidly and stopping after 5 days. The dosage should be sufficient to control the worst features of the reaction, but no attempt should be made to suppress it completely, and the patient should be warned that such attacks would continue to occur, and might require repeated courses of treatment. In neuritis (dealt with by Cochrane in a separate chapter[6]) it was suggested that in tuberculoid and borderline cases treatment with cortisone (initially 100–200 mg daily) should continue in reducing dosage for 1–5 weeks and sometimes longer.

These recommendations were supported in general by Browne[7] in 1964. In RR he advised that corticosteroids should be used only for acute reaction and particularly neuritis, and recommended a 10-day course, tapering the dosage from cortisone 75 mg daily initially. Longer treatment, however, would be required if the reaction continued, and he emphasized that, if used at all, 'enough for long enough' must be prescribed. He also pointed out the need for the early use of corticosteroids in reaction involving the face if permanent nerve damage was to be prevented. In ENL cortisone should be used only if there was severe systemic illness, severe ulcerating skin lesions, general oedema, eye involvement, or neuritis. The dosage was the same as for RR. Browne also pointed out the value of corticosteroids for less severe but prolonged (over 2 weeks) attacks of ENL.

Since 1964 few papers on the use of corticosteroids in leprosy have been published; this might imply general acceptance of their value and of the indications for their use. Nevertheless, teaching the practical use of these drugs very often provokes interesting, stimulating and controversial discussion, indicating that this remains one of the uncertain areas of leprosy therapy. Certainly wide differences of practice exist, even between those who agree on the theoretical indications for the use of corticosteroids.

Non-steroid drugs are available to treat reactions. In particular clofazimine and thalidomide have proved effective in the management of ENL. Thus, in 1973 Karat and Ramanujam[8] suggested that corticosteroids were only indicated for treatment of the Lucio phenomenon, for severe toxic states in reaction, for acute eye complications that threatened vision, for acute neurological catastrophes, and for the initial 2–4 weeks period when clofazimine was being used to treat ENL. However, the cost of clofazimine (and its pigmentation, often unacceptable to pale skinned out-patients) and the limited availability of thalidomide make this advice unrealistic, even for the treatment of ENL. Moreover, clofazimine and thalidomide are of little or no value in the

management of RR. In most leprosy programmes, and for most patients, the corticosteroids must be the backbone of anti-reaction therapy: they must therefore be used in such a way that they exert maximum benefit while producing the minimum of harmful effects.

The obvious problem in the use of corticosteroids is their toxicity. A short list of their toxic effects includes hypertension, diabetes mellitus, peptic ulceration, osteoporosis, psychosis, exacerbation of infections such as tuberculosis, and adrenal suppression. The risk of short courses (1–2 weeks) is slight, even if high dosage is employed; but the risks increase greatly with prolonged treatment at dosage levels higher than 10–15 mg prednisone daily. Clearly corticosteroids are potentially dangerous.

There are, however, two other, less obvious problems in the use of corticosteroids to treat reactions. The first is the variable clinical pattern of leprosy reactions. Severe ENL often has such a fluctuating and unpredictable course that it is not easy to decide whether clinical improvement is the result of treatment or merely due to the natural history of the condition
more predictable course. The rational use of corticosteroids therefore demands knowledge of the natural history of the reaction that is being treated.

The second problem concerns the results of treatment. The methods used in leprosy control programmes to assess the improvement or deterioration of neuritis (the most common indication for corticosteroid therapy) are generally so crude as to be of little or no value. Comparison of groups of patients receiving defined courses of corticosteroids with those receiving non-steroid drugs has hardly been attempted. Therefore, the hazards of corticosteroid treatment are well known, but the penalties the patients must pay when corticosteroids are withheld or prescribed 'too little, too short or too late' are not clearly seen. The rational use of these drugs requires the introduction of more accurate ways of measuring the results of treatment, both short term and long term.[9]

Interestingly, the natural history of reactions has seldom been in doubt. Even before the immunological mechanisms of reactions began to be understood, there was general agreement[10] that ENL reaction in lepromatous leprosy usually consisted of short episodes with symptom-free intervals which often continued for a year or longer. The reversal reaction in non-lepromatous leprosy, on the other hand, was seldom recurrent (except in untreated cases, when recurrent reactions marked the progress of the disease) and lasted for weeks or sometimes months continuously. Thus, when corticosteroids were first introduced, the use of short repeated courses to treat ENL reactions was logical, but the general avoidance of longer courses for RR was less logical.

The immunological mechanisms of ENL have been much studied but are as yet undefined. By contrast, the immunological basis of reversal reactions is better understood.[11] There is a transient increase in the cell mediated immune response to antigens of *Mycobacterium leprae*; this increase persists for weeks or months, but gradually declines. It may be sufficient to cause tissue damage,

particularly in nerves (where the bacillary concentration tends to be higher than elsewhere). This neuritis is therefore logically treated by immunosuppression during the period of the increased immune response.

Naafs[12] was the first to apply this knowledge to the treatment of RR. He used continuous steroids and adjusted the dosage and duration of treatment according to the clinical response, measured by frequent sensory, motor, and conduction velocity tests of the affected nerves. He found that most patients with BT leprosy required treatment for 6 months or less (most of the time with prednisolone 15 mg daily or less). Patients with BL leprosy needed longer, usually about 9 months, but a few developed persistent severe neuritis which took 12–18 months to subside. He demonstrated very accurately the neurological improvement achieved by his treatment and (by a limited retrospective comparison) showed that the results of short-course treatment were not so good. Few patients developed steroid toxicity. His results are probably the best that can be obtained by the use of corticosteroids on a largely out-patient basis.

The principles of the use of corticosteroids to treat reaction can therefore be defined as:

Reversal reaction: There is a transient increase in the immune response, which starts suddenly but fades away slowly over weeks or months. Corticosteroids should therefore be employed in initial high dosage (such as prednisolone 30 mg daily) gradually tapering off, the course lasting for weeks or months continuously.

Erythema nodosum leprosum: The reaction usually takes the form of acute episodes lasting about 2 weeks with reaction free periods between them. Corticosteroids should therefore be employed in repeated courses of about 2 weeks, each course being very rapidly tapered off (from, say prednisolone 20–30 mg daily); indeed tapering may not be required.

Neuritis: In the absence of skin reaction, neuritis should be considered as a manifestation of reaction in the nerve, and treated as for the appropriate skin reaction. The longer steroid treatment for neuritis is delayed, the less satisfactory is the result likely to be.

Patients with ENL who require frequent, almost continuous courses of corticosteroids for periods of months should receive continuous clofazimine and/or thalidomide. These drugs will make it possible to reduce or discontinue the use of corticosteroids.

In both RR and ENL the dosage of corticosteroids should be adjusted to the severity of the reaction. There is, however, need to define standardized courses of treatment which, while reasonably effective, have a low risk of toxicity and are therefore suited for field use. Individual (and possibly geographical) variations in the duration and severity of reaction, however, make it unlikely that any completely standardized regimens can be evolved.

The problem of steroid toxicity is linked with that of 'steroid addiction'.

There are patients who, after taking corticosteroids for some months, find it almost impossible to stop, even if their reaction has subsided. They frequently develop steroid toxicity. In many cases these patients purchase corticosteroid drugs themselves following initial medical prescription and experience of their benefit. It is noticeable that such cases are seldom seen by doctors who, while prescribing steroids rather freely, do so according to the proper indications. 'Steroid addiction' is more commonly found by doctors prescribing corticosteroids for insufficient indication or else in too low dosage to be effective when they are badly needed, so that the patient experiences only intermittent relief of his symptoms on the prescribed medication. This suggests that a combination of health education (on the risks of corticosteroids) and prescription of adequate dosage soon enough and for long enough offers the best hope of preventing 'steroid addiction'.

In addition to their systemic use, corticosteroids can be used as topical applications in the treatment of iritis, iridocyclitis and scleritis. Systemic toxicity is not encountered, though there is risk of uncontrolled viral and bacterial eye infections. Depot injections, which can be administered subconjunctivally, are also available. This use of corticosteroids in the treatment of eye complications, however, requires more space than is available here.

A further, currently neglected use of corticosteroids is by local injection around inflamed nerves. Such injections usually take the form of a local anaesthetic/hyaluronidase/hydrocortisone mixture and may be repeated daily if necessary. They may be particularly valuable in the management of severe mononeuritis, but no reports of long-term functional results are available.

Perhaps the major problems concerning the use of corticosteroids in leprosy are administrative. Most leprosy patients do not attend hospital clinics and are not seen by doctors. They attend small village clinics, and are seen by paramedical workers; increasing numbers of patients attend integrated clinics and are liable to be seen by staff who have little training, experience or interest in leprosy. Defining empirical corticosteroid regimens for treating reaction may be fairly simple. Ensuring that the need for corticosteroid treatment is recognized and that the drug is actually available is certainly difficult. Defining a chain of rapid referal to a centre with staff qualified to prescribe corticosteroids and able to supervise treatment will be very hard indeed. But corticosteroids are still the normal drugs to treat severe reactions and neuritis. If these tasks are avoided, patients will continue to become unnecessarily anaesthetic, deformed, and blind during the course of treatment.

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Errata

Please note the following corrections to the paper by G A ELLARD, *Editorial. Drug compliance in the treatment of leprosy, Lepr Rev* (1981) **52**, 201–213, for which we apologize.

page 206, fourth paragraph, first line, for *page 125* read *page 215.*

page 208, fourth paragraph, last line, for *page 147* read *page 237.*

page 209, reference 3, for *147–53* read *237–43.*

reference 5, for *125–30* read *215–20.*

page 210, reference 6, for *131–38* read *221–28.*

reference 7, for *139–45* read *229–35.*

Editor

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A brief review of experiences with short-term clinical trials monitored by mouse-foot-pad inoculation*

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Summary Beginning in 1964 we used mouse-foot-pad inoculations to monitor the loss in numbers of viable *Mycobacterium leprae* that occurs when the patient begins antileprosy therapy. Our studies eventually involved patients at the US Public Health Service Hospital in San Francisco and the Leonard Wood Memorial facilities in Cebu, Philippines and mouse-foot-pad laboratories in San Francisco and Cebu, as well as Atlanta. We found that to monitor short-term therapeutic trials, the mouse-foot-pad method was the most efficient one available, in the sense that it required the smallest number of patients. All the results are compiled here in a standard form of presentation to facilitate comparisons between trials and regimens. A table is provided for statistical consideration of results such as these.

Introduction

Most of the results to be presented have already been published, but their collection in one place in a standard form may be helpful. Beginning in 1964 Levy and I, in collaboration with Fasal, (Levy and Fasal were then at the US Public Health Service Hospital in San Francisco) began to employ mouse-foot-pad inoculations to monitor the decrease in numbers of viable *Mycobacterium leprae* that occur when the patient begins antileprosy therapy. We already knew from the earliest mouse-foot-pad days that the bacilli from untreated patients were regularly infective for mice and that those from patients who had been

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treated with sulphones for months or years were not, and we were curious about the timing of the loss of detectable viability. All of the work could have been carried out in San Francisco, but by doing the inoculations in Atlanta we could ensure a collaboration that we correctly sensed would be productive.

Eventually we found that with mouse-foot-pad inoculations the early loss in viability of *M. leprae* could be followed much more satisfactorily than with existing methods. True, 12 months had to pass before a negative result could be registered, but we were measuring the solid ratios (morphological indices, MIs) of the *M. leprae* in the specimens at the same time anyhow. With measurements of the solid ratios we could monitor a decrease in number of viable *M. leprae* by about 90% (conveniently expressed as a loss of one 'log' because the logarithm to the base of 10 of the number of viable *M. leprae* is reduced by one). With mouse inoculation we would monitor two or three logs of loss and could do so with more accuracy near the end point. Thus, it seemed clear that this was the most efficient available method of monitoring short-term trials in man. Later, under the United States–Japan Cooperative Medical Science Program, it became possible to start clinical trials in collaboration with Leonard Wood Memorial personnel in Cebu, Philippines, and a mouse-foot-pad facility was developed there. These trials started in 1969 and continued until administrative difficulties led to their loss in 1974.

Materials and Methods

Skin-punch biopsy specimens (5–6 mm) were removed at appropriate intervals, a tissue suspension prepared, and the bacilli counted. Usually, 20 mice were inoculated. The inoculum was diluted, if necessary, to contain not more than 5×10^3 *M. leprae*. CFW mice were used in Atlanta, BALB/c in San Francisco, and usually CBA in Cebu. Systematic comparisons failed to show differences between CFW and BALB/c, or between BALB/c and CBA. Biopsy specimens from San Francisco patients were shipped by air to Atlanta, and those from Cebu patients were divided in two for parallel inoculation in San Francisco and Cebu in the beginning. Later, only a sample of the Cebu specimens were shipped to San Francisco. From 3 through 12 months after inoculation, a mouse was taken each month for histological sections. When a section contained acid-fast bacteria (AFB), four mice were taken for counts of AFB in their pooled foot-pad tissues. In San Francisco and Cebu, additional harvests were frequently carried out at about 12 months if all the sections were negative.

With these data, one can calculate the incubation period and generation time and construct an *M. leprae* killing curve for the drug in each patient. Of course, the lepromatous patient has a total of 10^{11} or 10^{12} viable *M. leprae* in his tissues and we are following only the initial two or three logs of the killing in this type of short-term trial. The most important point of this *M. leprae*

killing curve is the lowest point we can detect; that is, the time when the number of viable *M. leprae* decreases to subdetectable numbers. Consequently, the most important feature of the response in each patient can be shown by two points, the time of the last positive specimen and the time of the next negative specimen. In the figures each line represents a patient and the two symbols on each line represent these two critical times. Results are not shown when the inoculum contained less than 1×10^3 AFB, or when the pretreatment specimen gave weak or negative results in the mice.

For the statistical analysis in the later trials where the specimens were taken at regular times after treatment, the comparisons could be made between the number of specimens positive or negative at particular times. In the early trials, however, when the optimum times for collection were not yet known, the patients were counted as positive any time before the last positive specimen and as negative any time after that (even though the next negative specimen had not yet been taken). When a negative specimen was never obtained (marked with question marks at the end of a patient's line), the patient was included in the analysis only for the times before the last positive specimen. The times selected for analysis were determined by the speed of response to a regimen. For example, in Figure 1 the results were analysed at 50, 100 and 150 days. For all trials the differences between regimens were analysed by Fisher's exact test, specifically, for the time of treatment to be analysed a fourfold table was constructed to show the number of positive and negative patients for the two regimens. The *P* values given are for a one-tailed test. Of course, when the patients are not assigned to regimen by random selection there is an increased risk that factors other than differences in drug regimen are responsible for the observed differences between groups. Nevertheless, the analysis determines what the probabilities are that the difference observed would occur by chance alone.

Results

The early results in San Francisco[1, 2, 3] are presented in Figure 1. The B663 and the ethionamide patients had received earlier sulphone therapy and were in relapse. The others were new patients. There was no attempt to randomize the assignment of patients to regimen. The differences between regimens were analysed statistically at 50, 100 and 150 days. All of the differences between groups could be explained as statistical variation except those between DDS and DADDS at 100 and 150 days.

We then turned to rifampicin in a series of trials, starting in 1970. (Figure 2) The first was a randomized trial comparing 600 mg rifampicin with 50 mg DDS daily.[4, 5] The DDS patients are included in Figure 1. Note that the time scale in Figure 2 is changed. Rifampicin killed *M. leprae* so rapidly that the difference

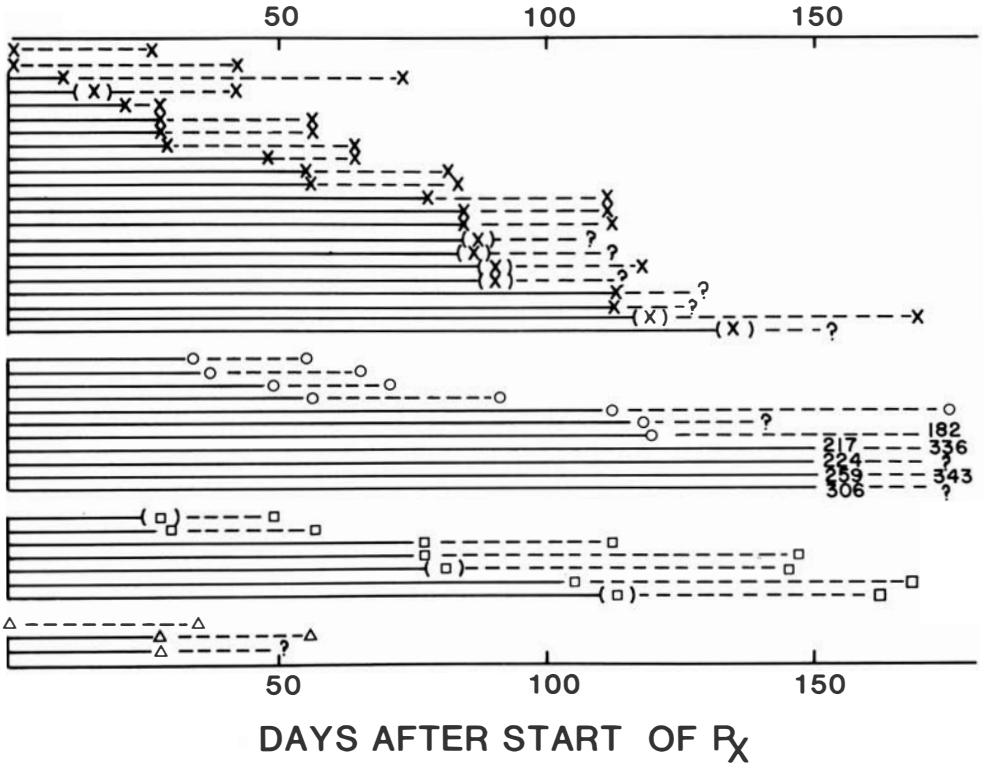

Figure 1. Results of mouse-foot-pad inoculation of *M. leprae* from serial skin-punch biopsy specimens taken from lepromatous patients in San Francisco.[1, 2, 3] Each line represents a patient and the two symbols represent only the last positive specimen (last specimen with *M. leprae* infective for mice) and the next negative specimen. Parentheses indicate a weakly positive result; that is, either the monthly histological section or the harvest (count of AFB in a pool of usually four mice) was negative. A single parenthesis indicates a harvest less than 1×10^5. A question mark indicates that the last specimen taken was still positive. DDS = dapsone, DADDS = acedapsone, B663 = clofazimine, ETH = ethionamide. x, DDS to 50 mg/d; ○, DADDS, 225 mg/77 d; □, B663, 200 mg/d; △, ETH, 259 mg tid.

was dramatic, with no overlap between the rifampicin and DDS results at 14 days. The *P* value here is $\ll 0.001$.

The second rifampicin trial in San Francisco was a trial of a single dose of 1,500 mg[5, 6] (Figure 2). Actually the regimen included 10 mg DDS daily, but it seems very unlikely that the DDS had detectable effect by 3–5 days, the time the second specimen was taken.

Next there was a comparison of single doses of 600, 900 and 1,200 mg rifampicin with randomized assignment of patients to treatment group.[7] The differences between the groups were not significant, but in view of the previous experience with larger intakes, it is probably important that one of the patients

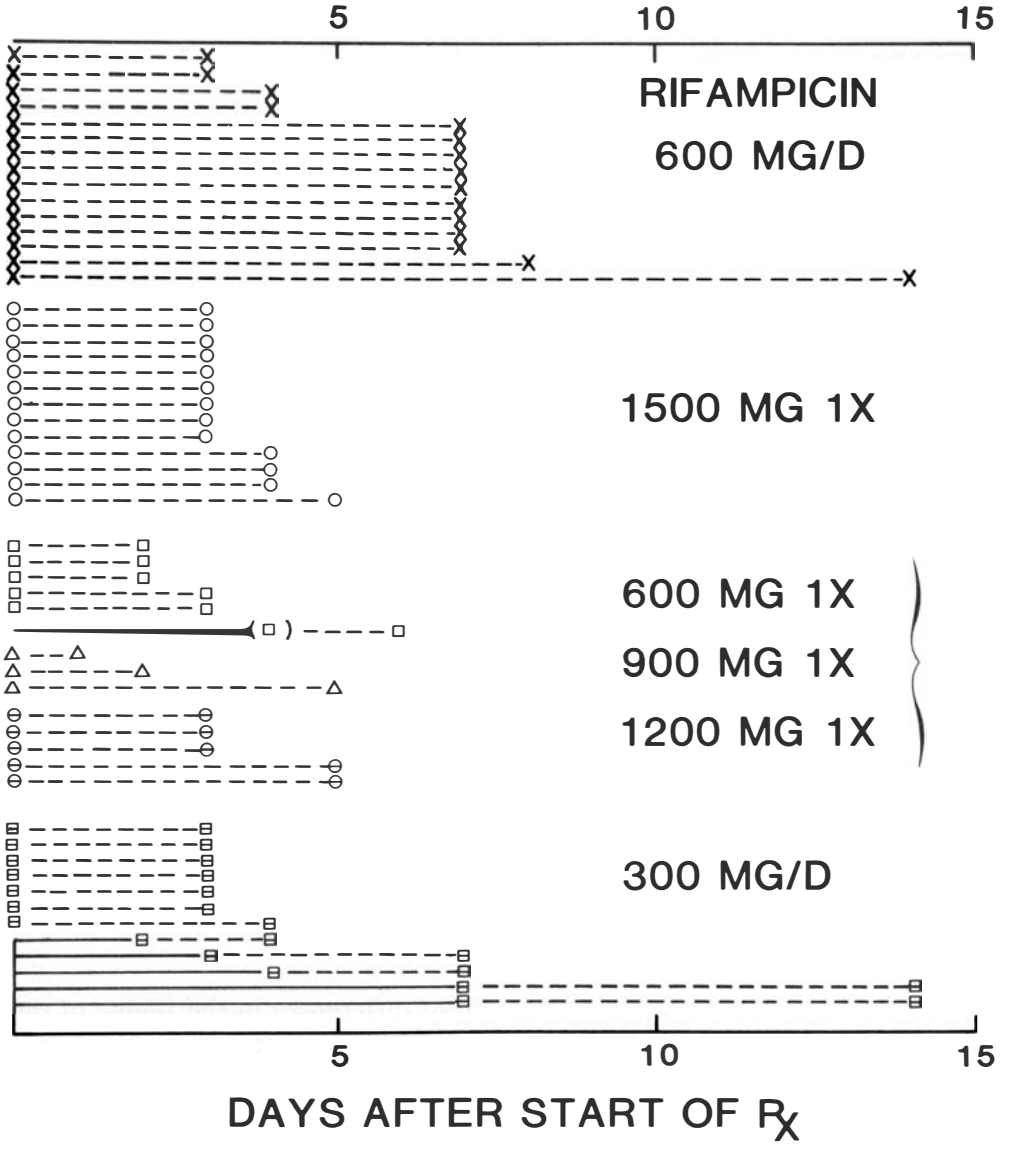

Figure 2. Results with rifampicin treatment in San Francisco.[4–7]

receiving 600 mg had a weakly positive result at 4 days (positive section but negative harvest, which indicated that the inoculum contained very few viable bacilli).

Finally, in an attempt to reach the end point for rifampicin, we tried 300 mg a day.[7] Here 5 of 17 patients had positive specimens after the start of treatment, so that these patients had received a total of 300–1,800 mg rifampicin before the last positive specimen was collected. Comparisons with

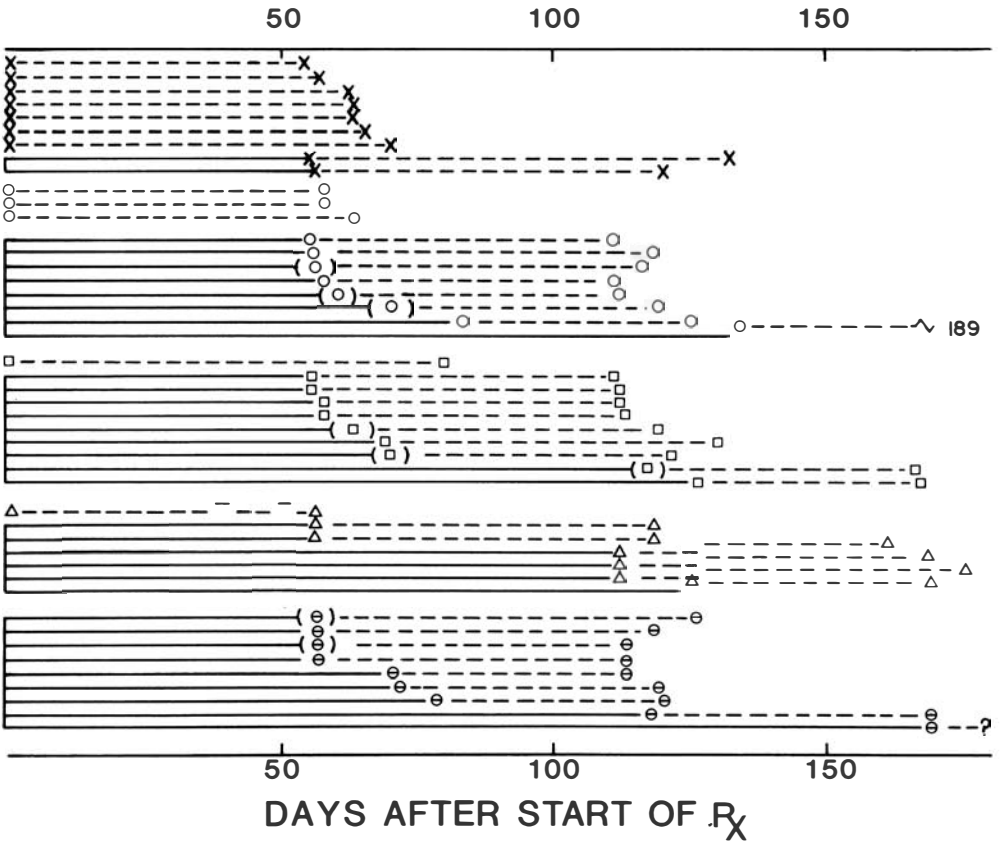

Figure 3. Results with B663 trial in Cebu.[8] B663 II trial: ×, 200 mg, 6 times per week; ○, 100 mg 6 times per week; □, 300 mg once a week; △, 600 mg, once every 2 weeks; ⊖, 600 mg, 2 consecutive days Q 4 weeks.

the 600 mg/day group are difficult because of differences in the timing of the collection of specimens. A comparison with the single dose 600 mg group is possible, but the differences are not statistically significant.

The results of the first trial in Cebu monitored in this way[8] are shown in Figure 3. Regimen I was 200 mg B663 6 days a week and the others involved 4-week totals of 1,200 mg, spaced at various intervals. By inspection, Regimen I appears to be more effective than the others, and the differences among Regimens II, III, IV and V appear to be small. Because the patients were randomly assigned to the five regimens, we may be more confident about the meaning of statistically significant differences. At 50 days, the results with Regimen I are significantly different from those with other groups (for I vs II, $P = 0.035$), but the differences among II, III, IV and V are far from significant. At 100 days, the only significant differences are between I and IV ($P < 0.019$) and II and IV ($P < 0.047$). The differences between the combined II and III and combined IV and V are not significant at either interval.

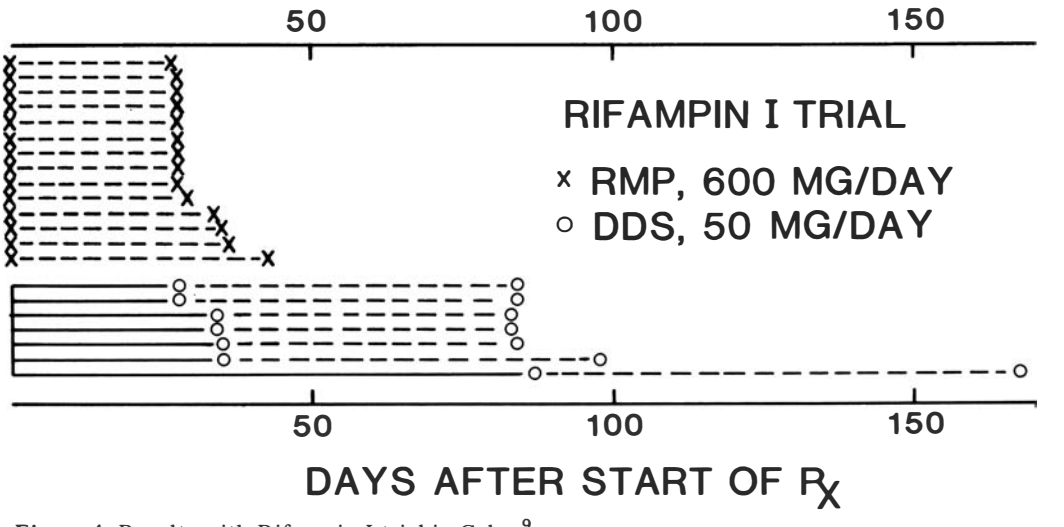

Figure 4. Results with Rifampin I trial in Cebu.[9]

The next use in Cebu was the Rifampin trial[9] (Figure 4), which compared the daily administration of rifampicin to DDS, with patients assigned to regimen on a randomized basis. As one would expect, the difference was marked ($P \ll 0.001$).

The final use in Cebu under the US–Japan Cooperative Medical Science Program was the Rifampin II trial (unpublished results) (Figure 5), in which there were three groups: DADDS alone, DADDS + 1,500 mg rifampicin at the time of the DADDS injection, and 600 mg daily rifampicin. There were no detectable differences between the second and third groups, but as expected, the differences between the first group and the other two were marked (for 1 vs 2, $P \ll 0.001$; for 1 vs 3, $P \ll 0.001$).

The reader might wonder why the Rifampin I and II trials were so large when they were comparing regimens whose efficacy had already been studied in short-term trials. In fact, the Rifampin I and II trials were designed to supply patients for trials of maintenance regimens by long-term followup. The long-term maintenance regimens involved comparisons between DADDS and DDS, with visits to the clinic every 12 weeks. Rifampin I started in early 1971 and Rifampin II in late 1971, so if the trials had not been lost (because of administrative difficulties) they would now be supplying information of critical value to leprosy care.

Discussion

This has been a brief review of short-term leprosy trials monitored by mouse-foot-pad inoculations. A simplified method for presenting the data was used to facilitate comparisons of all the trials to date.

In examining the results obtained with a single regimen, one is struck by

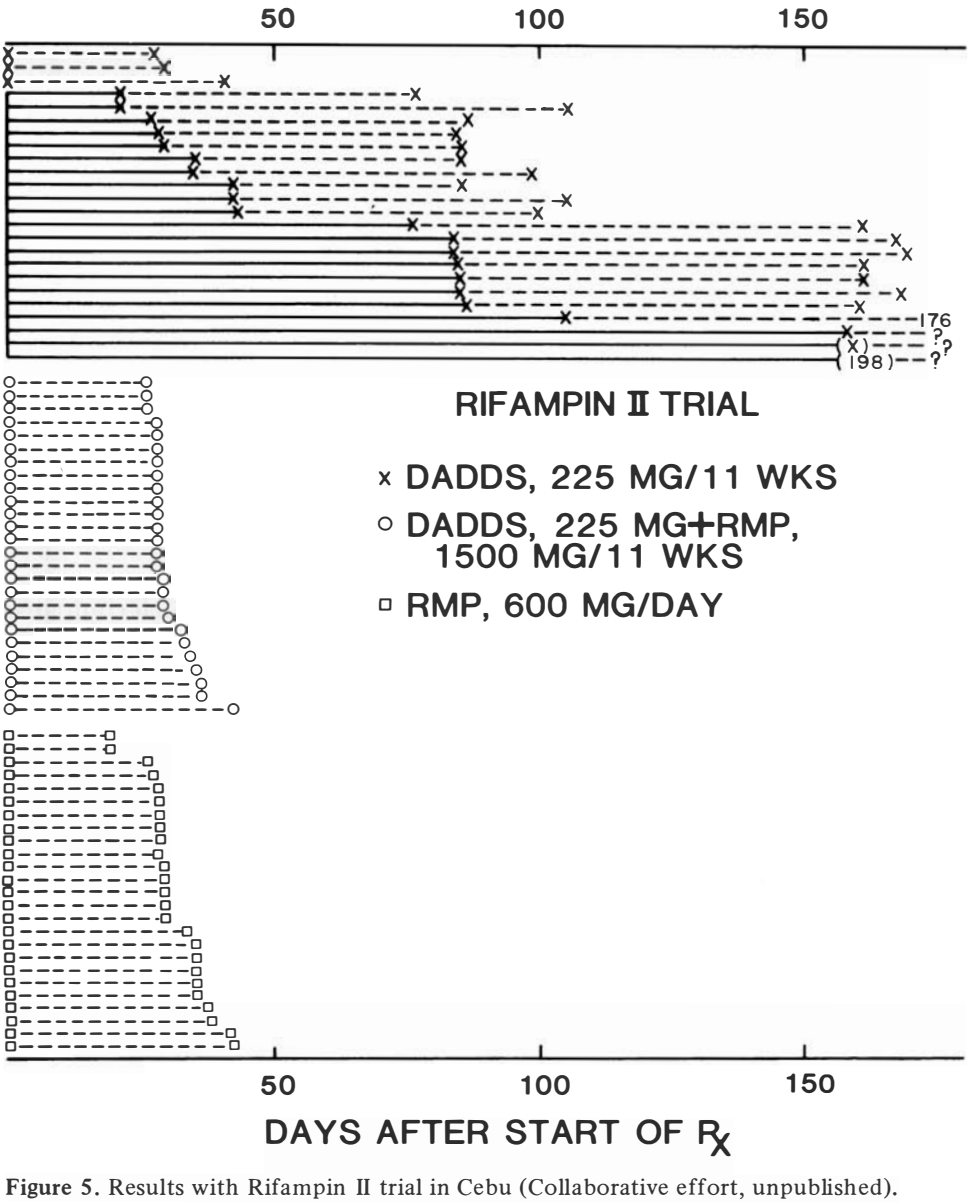

Figure 5. Results with Rifampin II trial in Cebu (Collaborative effort, unpublished).

the large differences in rate of response between different patients. These differences do not appear to be caused by differences in the determined sensitivity of the patient's *M. leprae* to drug. Thus, in the DADDS trial in San Francisco the *M. leprae* from the last positive specimen from the slowest responding patients were shown to be fully sensitive to DDS (0.0001% in the mouse diet), and in the Rifampin II trial some of the isolates from the patients responding most slowly to DADDS were found sensitive to 0.00003% and

Table 1. Critical[a] *P* values by Fisher's exact test in fourfold tables[b].

a + b	c + d	a	c	*P*	a + b	c + d	a	c	*P*
3	3	0	3	0.050	10	10	0	10	0.000005
4	4	0	4	0.014			1	10	0.00006
							2	10	0.0004
5	5	0	5	0.004			3	10	0.001
		0	4	0.024			4	10	0.005
6	6	0	6	0.001			5	10	0.016
			5	0.008			6	10	0.043
							0	9	0.00006
							1	9	0.005
							2	9	0.003
		1	5	0.040			3	9	0.010
		0	4	0.030			4	9	0.029
							0	8	0.0004
7	7	0	7	0.0003			1	8	0.003
		1	7	0.002			2	8	0.012
		0	6	0.002			3	8	0.035
							0	7	0.002
		1	6	0.015			1	7	0.010
		0	5	0.010			2	7	0.035
8	8	0	8	0.00008			0	6	0.005
		0	7	0.0007			1	6	0.029
		1	7	0.005			0	5	0.016
		2	7	0.020			0	4	0.043
		0	6	0.003					
		1	6	0.020					
		0	5	0.013					
		0	4	0.038					

[a] Includes all instances where $P \leqslant 0.05$ by one-tailed test.

[b] Tables constructed as follows:

	Positive[c]	Negative[c]	
Regimen 1	a	b	a + b
Regimen 2	c	d	c + d

[c] Interchange positive and negative columns if necessary to provide fit to the table.

0.00001% DDS, dosages producing about 3 and 1 ng of DDS, respectively, in the plasma of the mice. Because of these unaccountable variations between patients, statistical analysis needs to be applied to the data. The method we have used here is simple. The calculations involve factorials, but tables are widely available, for example, in older editions of the *Handbook of Chemistry and Physics* and some, even inexpensive, hand calculators have a key for factorials. Moreover, the formula can be programmed into certain, moderately priced, hand calculators.

Table 1 is provided for results with (equal) group sizes of 3–10. The use of the table is given in its footnote. As an example, we might consider a comparison of two groups of 10 patients in which, at a particular interval, 'regimen

1' gave 0 positive and 10 negative results and 'regimen 2' gave 6 positive and 4 negative results. In the fourfold table shown, there would be the following entries: for a, 0; b, 10; a + b, 10; c, 6; d, 4; c + d, 10. The one-tailed test may be used when the difference is in the expected direction; in this example, P would be <0.043. The two-tailed test must be used when one cannot predict which drug will be more effective; here P would be twice the value shown in the table, or <0.086.

Of the available procedures for short-term trials, the foot-pad method is the most efficient, in the sense that it needs the fewest patients. The number of patients required for a test of a new drug cannot be set without knowing the activity of the drug, and when the drug is new, the information may be limited to results from studies in mice, for example, by the kinetic method or the proportional bactericidal method. The group size needed can be estimated with the aid of Table 1. With two drugs that have as different short-term activity as DDS and rifampicin, only two groups of three patients are needed to discriminate with a P value of <0.05. If there is apt to be some overlap between the results with the two drugs, and it is important to detect a statistically significant difference between the drugs, and group sizes need to be at least 6–10.

The timing of the specimens varies with the drugs. For rifampicin, we learned from kinetic method results in mice that the second specimen could be taken as early as 2–3 days. For drugs with a short-term killing rate similar to that of DDS, a schedule of 0, 4, 8 and 12 weeks would probably be suitable.

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Qualitative studies of serum lactate dehydrogenase isoenzyme patterns in leprosy

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Summary Serum lactate dehydrogenase isoenzyme patterns were studied in polyacrylamide gel disc electrophoresis in 72 cases of leprosy to define correlation with clinical varieties and presence of specific pattern. The cases were classified on the basis of history, clinical examination, bacterial and morphological indices, lepromin test and biopsy according to Ridley and Jopling into lepromatous 41: 15 active, 23 regressing and 3 ENL, borderline lepromatous 5 cases, borderline tuberculoid seven cases, tuberculoid 18 and indeterminate, 1 case. Serum LDH zymograms showed a diversity of patterns but there was no correlation with the clinical form of the disease. The commonest abnormalities affected isozymes 4 and 5. Thus in 28 cases both isozymes were depressed or absent and in a further 18 cases one or other of these isozymes were depressed or absent. 4 cases showed other abnormalities and in 11 cases each the LDH zymogram was normal or showed a generalized increase in density of all 5 LDH bands. In 25 healthy controls, 23 showed a normal isozyme pattern and in 3 LDH 5 was absent.

Introduction

The term isoenzyme was coined to describe multimolecular forms of enzymes showing electrophoretic heterogeneity but having the same biological catalytic function.[1] Electrophoretic separations using starch or polyacrylamide gels became routine for the characterization of isoenzymes and the methods have found frequent application in diagnostic laboratories. Lactate dehydrogenases are perhaps the best studied. LDH catalyses the interconversion of pyruvic and lactic acids and is an essential enzyme in both anaerobic and aerobic glycolysis.[2] Human serum LDH shows 5 isoenzymes. These were designated by the numbers 1–5 in terms of decreasing electrophoretic mobility, 1 being the fastest moving in European system.[2] Human LDH consists of H or M

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polypeptide chains in varying ratios the individual isoenzymes being as follows: (1) H_4, (2) H_3M_1, (3) H_2M_2, (4) H_1M_3 and (5) M_4. The H unit typifies the cardiac variety and M the muscle though all tissues contain most of the LDH isozymes albeit in varying proportions. Qualitative and quantitative studies of LDH isoenzymes have been useful in diagnosing necrotic parenchymal diseases of the heart (raised 1 & 2) and liver and muscle[2] (raised 4 & 5).

A careful survey of the literature disclosed only two studies of serum LDH isoenzymes in leprosy.[3, 4] Isozymes 1 and 2 are prominent in well-oxygenated tissues and 4 and 5 in tissues capable of anaerobic metabolism. Leprosy is a unique example of host parasite interactions in which host immune reactions rather than parasite attributes determine the clinical spectrum of the disease. Moreover, in lepromatous leprosy the bacillary load is unique and enormous. We describe here a study of the serum LDH isoenzyme patterns in patients of leprosy.

Materials and methods

CASES

Seventy-two cases of leprosy attending the Sir J. J. Group of hospitals, Bombay, were each studied as follows: a detailed history and clinical examination were recorded; the bacterial (BI) and morphological (MI) indices determined;[5] a lepromin test with armadillo lepromin carried out; and, a biopsy of a cutaneous lesion studied for structural changes and for acid fast organisms. Cases were then carefully classified according to the schema of Ridley and Jopling.[6] Lepromatous leprosy (LL) was subdivided into active, regressing, and erythema nodosum leprosum (ENL) on the basis of clinical features, MI and therapeutic history.

CONTROLS

Sera from 25 normal healthy adults served as the control.

QUALITATIVE ASSAY OF SERUM LACTATE DEHYDROGENASE (LDH) ISOENZYMES

This was carried out in polyacrylamide gel disc electrophoresis[7] in a miniaturized system using gels cast in glass tubing with an internal diameter of 2 mm.[8] Briefly the details were as follows: a 5% monomer was the spacer gel and 7% the separator gel. The buffer was tris-glycine (pH 8.5, 0.1 M). A trace of 1% aqueous bromophenol blue was added to the serum sample and 5 μL of the coloured serum with an equal amount of 40% sucrose was layered on the spacer

gel. Electrophoresis was at a constant current of 1 mA per tube and this was continued till the albumin-stained marker had moved to the lower end of the separator gel. Gels were removed and stained for LDH.[9] The staining solution contained lithium lactate (substrate), nicotinamide adenine dinucleotide (coenzyme), phenazine methosulphate and nitro blue tetrazolium. Gels were incubated in the staining solution at 37°C in the dark for 1 hour. Purple-coloured bands of formazan indicated the site of LDH isoenzymes. Patterns were scrutinized visually and an arbitrary judgement arrived at in terms of normal, absent, increased or reduced, and the Ef values calculated by use of the conventional formula:

$$\text{Ef of LDH isoenzyme} = \frac{\text{Distance travelled by LDH isoenzyme band}}{\text{Distance travelled by albumin marker}}.$$

RESULTS

Figure 1.

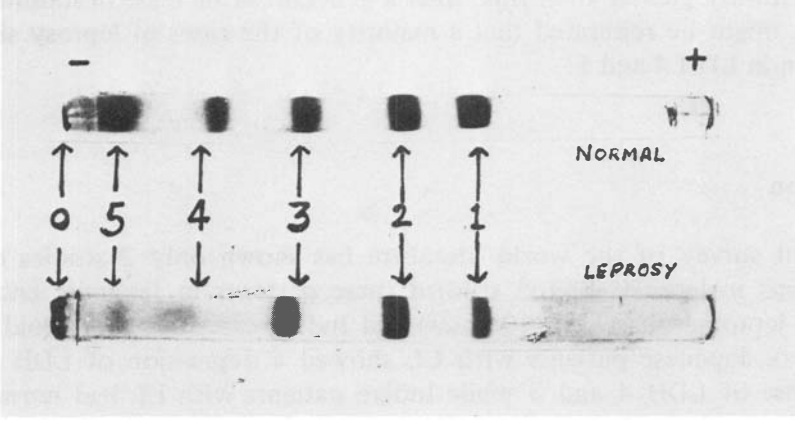

Figure 1. Lactate dehydrogenase isoenzyme separators of sera on polyacrylamide gel disc electrophoresis. Two separations – normal and a case of leprosy – are illustrated. The 5 bands 1–5 in decreasing order of electrophoretic mobility are marked. 0 = origin. Note the diminution in LDH 4 and 5 in the serum from a case of leprosy; this was the common pattern.

CONTROLS

A normal pattern of LDH isoenzymes was obtained in 22 samples. The LDH isoenzyme bands 1–5 in decreasing order of electrophoretic mobilities had Ef values of 0.66, 0.5, 0.37, 0.22 and 0.08 with a variation of ± 0.04. As described in the literature[2] the relative intensity of the bands in decreasing order was $2 > 1 > 3 > 4$ and 5. The remaining three samples showed four bands the missing band always being LDH 5.

CASES

Sera from the patients with leprosy exhibited a diversity of LDH zymograms. Only 11 cases showed the normal pattern. There was no correlation between the clinical type of disease and any particular LDH isoenzyme pattern. However, the dominant feature of all the cases as a whole was a deficiency of the two cathodal LDH isoenzymes 4 and 5 in as many as 28 cases (39%); in 7 cases these bands were absent and in 21 they were faint (Figure 1). In 13 cases faint LDH 4 and 5 bands were associated with prominent bands 1 and 2. Table 1 summarizes the results. The miscellaneous group of patterns seen in 22 cases consisted of: 18 cases with an isolated reduction or absence of either LDH 4 or 5 the other being normal; one case with reduction of both LDH 1 and 2; one case with an elevation of LDH 1 and 2; and 2 cases showing only a single band LDH 1. Eleven cases showed an isomorphic pattern characterized by an increased staining density of all five LDH isoenzymes, though this result could be the result from an inadvertant increase in the sample size, because it is difficult to pipette 5 μl with absolute precision. If the volume on occasion is inadvertantly greater than this, then a generalized increase in staining would occur. It might be reiterated that a majority of the cases of leprosy showed a reduction in LDH 4 and 5.

Discussion

A careful survey of the world literature has shown only 2 studies on LDH zymograms in leprosy. Saito[3] studied these patterns in Japanese and Indian cases of lepromatous (LL) (10 cases) and Indian cases of tuberculoid leprosy (13 cases). Japanese patients with LL showed a depression of LDH 1 and 2 with a rise of LDH 4 and 5 while Indian patients with LL had normal LDH 1, 2 and 3 and an elevation of LDH 4 and 5. In contrast the Indian cases of TT showed a fall or an absence of LDH isoenzymes 4 and 5. The changes were ascribed to damage of the skin, muscle or liver or on account of faulty clearance of LDH from the blood stream to a deranged reticuloendothelial system. The other study[4] noted a normal LDH zymogram in 18 cases of leprosy.

The present study indicates marked differences in the LDH zymograms between patients with leprosy and normal individuals. The commonest observation was a deficiency of the two slow-moving (cathodal) LDH isoenzyme bands 4 and 5 with or without a corresponding rise in the fast-moving (anodal) 1 and 2 bands. Leprosy granulomas have been shown to have a depressed anaerobic glycolysis.[10] It is therefore possible that the deficiency of LDH 4 and 5, noted in the present study, indicates a general shift in the metabolic pattern in leprosy towards aerobic preponderance. This might be reflected in an elevated

Table 1. Serum LDH isoenzyme patterns in 72 cases of leprosy

Type of leprosy	Total no. of cases	Results of serum LDH isoenzyme analysis						
		Normal LDH pattern	Increase of all bands (isomorphic)	Depressed or absent LDH 4 and 5				Other pattern* (miscellaneous)
				Normal LDH 1 and 2		Prominent LDH 1 and 2	Total	
				Absent 4 and 5	Diminished 4 and 5			
ENL	3	1	1	0	0	1	1 (33)	0
LL (active)	15	1	2	1	1	4	6 (40)	6
LL (regressing)	23	5	4	2	2	5	9 (39)	5
BL	5	2	1	0	1	0	1 (20)	1
BT	7	0	3	0	1	0	1 (14)	3
TT	18	2	0	4	3	3	10 (56)	6
ID	1	0	0	0	0	0	0	1
Total	72	11 (15)	11 (15)				28 (39)	22 (31)

*Details of these patterns are given in the text.
Figures in brackets are percentages.

LDH 1 and 2 which was observed in some of the cases. The isomorphic (general elevation) pattern seen in 11 cases, if it is not a technical artefact, could be due to damage to the cleaving or degradation mechanisms of LDH catabolism.

Tissue LDH have also been studied in leprosy. Zuravieva[10] analysed leprosy granulomas in 69 cases by histochemical methods and noted a loss of LDH activity in the lesions; this was ascribed to a depression of anaerobic glycolysis. Saito[11] studied homogenates of tissues from 18 cases of leprosy by agar gel electrophoresis. This author found LDH 3 was increased in ENL leprosy and both 3 and 4 in LL. We described anomalous (additional) LDH isoenzymes in tissue homogenates of cases of leprosy. These correlated with presence of viable *Mycobacterium leprae* in the tissues and were thought to originate from the parasite.[12]

Acknowledgement

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Pharmacologically-active mediators of hypersensitivity reactions in the blood of lepromatous patients with erythema nodosum leprosum

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Summary A bioassay technique was employed to study the mediators of hypersensitivity reactions (MHR) in the blood of 9 control subjects and 20 borderline and polar lepromatous patients including 8 patients with erythema nodosum leprosum (ENL). MHR were isolated from blood and studied on virgin rat uterus following the technique originally described by Brocklehurst. The contractions of uterus were recorded, compared with a stock bradykinin solution which was taken as the reference standard and the levels of MHR were expressed as ng bradykinin equivalent 1 ml blood. The mean level of MHR in lepromatous patients without ENL was 6.69 ng bradykinin equivalent 1 ml blood, but was significantly elevated in patients with ENL (18.09 ng bradykinin equivalent 1 ml). It was postulated that during the attack of ENL, *Mycobacterium leprae* or its broken products were released in the circulation containing high levels of anti-mycobacterial antibodies and thereby triggered the formation of circulatory immune complexes (CIC), activation of complement, deposition of CIC in various tissues and release of pharmacologically-active mediators of hypersensitivity reactions.

Introduction

A number of patients with lepromatous leprosy having high bacilliary load suffer from erythema nodosum leprosum (ENL). Some authors have advanced evidences as to the involvement of immune complexes in the pathogenesis of ENL, since deposits of immunoglobulin and complement have been identified in skin lesions[1] and vessel walls.[2] Recently bacilli, morphologically resembling

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Mycobacterium leprae along with IgG, IgM, IgA and C3 were detected in the circulatory immune complexes (CIC). CICs were separated from the sera of polar and borderline lepromatous patients with or without ENL by the simplified polyethylene glycol technique.[3] Most immune complexes, that are formed *in-vivo*, can activate humoral enzyme systems, fix the first component of complement, C1, and initiate a sequence leading to the formation of anaphylotoxin, a histamine-releasing substance, and a trimolecular complement factor, C567, which is chemotactic for polymorphonuclear leucocytes. Proteolytic enzymes released by the polymorphs also damage adjacent structures.[4] In the kinin-forming system, they can form kinins by splitting its precursor, kininogen. This occurs through the activation of the Hageman (XII) factor of the coagulation system which initiates clot formation.[5] In this preliminary communication we have turned our attention to the study of the pharmacologically-active mediators of hypersensitivity reaction (MHR) in the blood of lepromatous patients with or without ENL and have compared their levels with normal subjects.

Materials and methods

HUMAN MATERIALS

Twenty polar and borderline lepromatous patients including 11 cases with ENL from a leprosy village at Faridabad near Delhi and 9 normal subjects formed the basis of the study. In the patient group there were only 4 females. The diagnosis was based on clinical history, physical findings, lepromin test with armadillo-derived lepromin (WHO) and skin biopsy.[6] Since our leprosy patients were of lower socio-economic status, our control group were also selected from the identical section of the society and their age and sex were matched with the patient group. All patients were on standard dapsone chemotherapy.

COLLECTION OF BLOOD SAMPLES

The procedure described by Brocklehurst[7] was followed. Briefly, one volume of blood (5 ml) was collected in a cold plastic syringe from the patient or control subject by venepuncture with minimum trauma and then forcibly squirted in a plastic vial containing 4 volumes (20 ml) of chilled ethanol with vigorous mixing. Formation of large clumps was thus avoided. Thereafter the mixtures were kept for 4 h, centrifuged, precipitates discarded and the supernatant stored at $-20^{\circ}C$ in stoppered plastic containers for assay of the pharmacologically-active substances.

PURIFICATION OF TEST SAMPLES TO REMOVE INTERFERING SUBSTANCES

The alcohol extracts, besides kinins, also contained potassium from erythro-

cytes, some 5 HT from platelets and catechol amines. To remove these interfering substances, the supernatants were boiled to remove ethanol completely, dilute HCl (pH 1.5) added, saturated with NaCl, extracted twice with *n*-butanol, butanol evaporated, shaken with warm de Jalon solution and assayed for the pharmacologically-active substances.[7]

ESTIMATION OF THE PHARMACOLOGICALLY-ACTIVE MEDIATORS OF HYPERSENSITIVITY REACTIONS

Stilboestrol (1 mg/kg body weight) was injected subcutaneously in a virgin rat weighing about 120 g. After 24 h, the rat was sacrificed, the uterus was removed, and kept in de Jalon's solution at − 27°C–29°C. The uterus was mounted in a 5-ml tissue bath and the contractions of the uterus were recorded first with a standard stock bradykinin solution (100 ng/ml) and then with the test samples. The contractions of the uterus following the addition of the test samples were compared with the contraction due to the standard solution of bradykinin and the levels of the pharmacologically-active substances in the test samples were expressed as a ng bradykinin equivalent 1 ml blood. The sensitivity of the assay of bradykinin varied from 200, 500 pg 1 ml. Recovery experiments showed recovery of bradykinin of the order of 70–90%.

Results

The virgin rat uterus preparation which has been employed as our assay system is readily stimulated to contract by many substances other than plasma kinins.[8]

The blood levels of the pharmacologically-active substances in the controls and patients have been shown in Table 1. The mean level in the patients without ENL was 6.69 ng bradykinin equivalent 1 ml, which was not significantly different from that (4.77 ng bradykinin equivalent 1 ml) in the controls. However, the average level (18.08 ng bradykinin equivalent 1 ml) in the patients with ENL was significantly higher than that in the controls as well as patients without ENL (Table 2).

Discussion

The virgin rat uterus assay technique, employed in the present study, not only detects bradykinin, but also responds to 5 HT and prostaglandins (E1, E2, F2α).[8] These substances would make the usual assay on the rat uterus inaccurate. Thus the responses of the rat uterus observed by the addition of our test samples is most likely due to the kinins and/or prostaglandins present in the samples. However the surest method to characterize bradykinin in a test sample is to inactivate the polypeptide by incubation with chymotrypsin. Further if the uterine contraction is due to the polypeptide, the characterization may be further narrowed by showing that it will cause relaxation of the rat

Table 1. Blood levels of the pharmacologically-active substances in normal subjects and lepromatous subjects

Serial No.	Type of subjects	ENL	Levels of the pharmacologically-active substances ng bradykinin equivalent/ml blood
1	Control		2.0
2	Control		4.5
3	Control		8.3
4	Control		6.0
5	Control		5.1
6	Control		3.0
7	Control		5.0
8	Control		<2.8*
9	Control		6.3
10	Leprosy	+	7.3
11	Leprosy	−	<3.2*
12	Leprosy	−	11.9
13	Leprosy	+	32.3
14	Leprosy	+	6.8
15	Leprosy	−	7.6
16	Leprosy	+	12.6
17	Leprosy	+	40.0
18	Leprosy	−	<3.8*
19	Leprosy	+	16.2
20	Leprosy	−	10.9
21	Leprosy	+	36.8
22	Leprosy	+	28.6
23	Leprosy	+	<4.3*
24	Leprosy	−	6.8
25	Leprosy	+	14.6
26	Leprosy	+	8.6
27	Leprosy	−	<2.9*
28	Leprosy	−	3.5
29	Leprosy	+	9.3

*The minimum sensitivity varied from experiment to experiment.

duodenum.[8] We in our present study have not performed these 2 control experiments. Thus one may precisely conclude that the observed rat uterus contraction by the samples taken from the lepromatous patients might be either due to the presence of kinins, or prostaglandins or both.

The release of bradykinin from mast cells has recently been demonstrated.[9] Kumar *et al.*[10] have demonstrated in leprosy patients an appreciable alteration in the morphology of mast cells and significant rises of serotonin and histamine as compared to the controls. However, they had not studied the bradykinin or prostaglandin levels during such an event. In man, bradykinin causes slow, sustained contraction of smooth muscles, increased vascular permeability, increased secretion of mucous glands and stimulation of pain fibres. Thus,

Table 2. Mean levels of the pharmacologically-active substances in the blood of normal subjects and leprosy patients

Groups	Type of subjects	No	Levels of the pharmacologically-active substances: ng bradykinin equivalent/ml blood — Mean	S.D.	Range
A	Normal	9	4.77	1.98	2– 6.3
B	Lepromatous leprosy	20	13.40	11.58	2.9–40.0
C	Lepromatous leprosy without ENL	8	6.69	3.71	3.2–11.9
D	Lepromatous leprosy with ENL	12	18.09	12.80	4.3–40.0

	Statistical evaluation: *t* value	*p* value
A and B	10.03	< 0.001 significant
A and C	1.72	> 0.2 not significant
C and D	2.89	< 0.01 significant

bradykinin could be responsible for the painful swelling and nodule formation during ENL episodes. Prostaglandins, which on the other hand comprise a number of naturally occurring aliphatic acids with a variety of biologic activities including increased permeability and dilation of capillaries, smooth muscle contraction and alteration in the pain threshold[11] could also be released during lepra reactions. Bioassay on gerbil colon and chick rectum and radio-immunoassay of polypeptides may distinguish between kinins and prostaglandins.[8]

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A preliminary investigation of the responsiveness or otherwise of patients and staff of a leprosy hospital to groups of shared or species specific antigens of mycobacteria

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Summary In an attempt to classify skin-test responsiveness of leprosy patients according to the groups of antigens, rather than the individual mycobacterial species to which they respond, we have tested patients and staff members at Anandaban leprosy hospital in Nepal with Burulin (made from *Mycobacteria ulcerans*) and 3 specially mixed reagents. Ability to make a positive response to group i, common mycobacterial antigens, was almost absent and to group ii, antigens associated with slow growers, was markedly impaired in the patient groups. However, positive responses to group iv, species specific, antigens of slowly growing species were retained. Non-specific skin-test unresponsiveness (Category 2) due either to sequestration of the relevant cells outside the circulation or to circulating suppressor factors was present in 2 out of 27 staff members, 9 out of 24 TT/BT patients, 11 out of 18 BL patients and 10 out of 22 LL patients. Evidence of a suppressor mechanism possibly triggered by group iv antigens of fast growers and operative on positive responses to slow growers, was demonstrable in 3 out of 12 staff members, 8 out of 14 TT/BT patients, 7 out of 7 BL patients and 6 out of 12 LL patients.

It cannot at the moment be proved whether these observations are related to susceptibility to the disease, or are consequences of it. However, the presence of the same, or similar, suppressory phenomena amongst staff members argues against the latter.

Introduction

The soluble antigens present in sonicate preparations of mycobacteria which are demonstrable in immunodiffusion analysis with hyperimmune rabbit anti-

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sera can be divided into 4 groups.[1] Group i consists of antigens common to all species of mycobacteria and nocardiae. Group ii antigens are shared by slowly growing species and absent from rapid growers. Group iii antigens are shared by most rapidly growing species and absent from slow growers. Group iv consists of those antigens limited to individual species. We have prepared 4 reagents with which to attempt to assess the part these groups of antigens may play in skin-test reactivity in leprosy patients. The results of a preliminary investigation of their use are presented.

Materials and methods

REAGENTS

These were prepared from the stock concentrates of our New Tuberculins:[2]

1. Pooled slow grower reagent (SG). Equal volumes of filter sterilized sonicate preparation of 12 different slowly growing mycobacteria were pooled. Each reagent used contained 1 mg of protein/ml.
2. Pooled fast grower reagent (FG). This was produced as described above from sonicates of 12 fast growers, again each at a concentrate of 1 mg protein/ml.
3. Fast grower/slow grower mixtures (F/S). This was prepared by mixing equal volumes of SG and FG (see Table 1).

   For use each reagent was diluted in borate buffer at pH 8.0 ($Na_2B_4O_7 . 10H_2O$, 3.36 g; H_3BO_3, 5.25 g; NaCl, 6.19 g; Tween 80, 0.0005%, distilled water to 1 litre) to a concentration of 2 μg protein/ml, and dispensed into 5 ml tuberculin vials through a sterile 0.2 μm membrane filter.
4. Burulin (B). This was our standard new tuberculin preparation from *M. ulcerans*,[3] dispensed as described above at a concentration of 2 μg protein/ml.

Table 1. Contents of the reagents mixtures

FG	SG
Chitin	Aviumin A
Diernhoferin	Aviumin B
Duvalin	Aviumin C
Flavescin	A*-in
Gilvin	Burulin
Neoaurumin	Gordonin
Nonchromogenicin R507R	Kansasin 8
Nonchromogenicin R812R	Kansasin 1129
Ranin	Marinin
Rhodesin	Scrofulin
Vaccin R859R	'Talwin'
Vaccin R877R	Xenopin

0.1 ml volumes of the 4 reagents were injected simultaneously, 2 on each forearm, on groups of staff members and patients at Anandaban leprosy hospital in Nepal. Diameters of induration were measured after 72 hours, a mean diameter of induration of 2 mm or more was taken as positive. Twenty-seven staff members and 64 patients agreed to take part.

Results

Percentages of positive responses to each reagent and mean positive reaction sizes in each of the groups tested are shown in Table 2. Within each of the patient groups responses were fewer and, in general, smaller than in the staff group. Six staff members, 1 BT, 4 BL and 2 LL patients had BCG vaccination scars, but these persons did not seem to have any particular pattern of response.

Table 2. Numbers tested in each study group, numbers and percentages of persons producing positive responses within each group, and mean positive reaction sizes

	No. and % positive					Mean positive reaction size			
	No.	FG	SG	F/S	B	FG	SG	F/S	B
Staff	27	13 48%	24 89%	22 81.5%	23 85%	11.7 mm	14.5 mm	14.7 mm	11.7 mm
Patients									
TT & BT	24	4 16.7%	15 62.5%	9 37.5%	5 21%	7.0 mm	12.1 mm	11.3 mm	11.2 mm
BL	18	2 11%	7 39%	1 5.5%	0	11.5 mm	12.0 mm	3.5 mm	–
LL	22	1 4.5%	10 45.5%	6 27%	2 9%	3.5 mm	11.3 mm	10.5 mm	12.0 mm

Thirteen (48%) of the staff members responded positively to all 4 reagents with a mean response size of 13.3 mm (range 3.5–25 mm) and 2 (7.4%) of the staff were negative to all reagents. Amongst tuberculoid (TT) and borderline tuberculoid (BT) patients one (4.2%) was positive to all reagents and 9 (37.5%) were negative to all reagents. Of the borderline lepromatous (BL) and lepromatous (LL) patients none were positive to all 4 reagents and 11 (61%) and 10 (45.5%), respectively, were negative to all reagents. The results for those individuals who responded positively to 1 or more, but not all, reagents are shown in Table 3.

Discussion

Previous studies[4] have shown that multiple skin-testing divides any population into three categories. Category 1 persons respond to all new tuberculins even

Table 3. Individual skin test responses expressed as mean diameters of induration in mm in persons of Category 3

	Individual No.	FG	SG	F/S	B		Individual No.	FG	SG	F/S	B
Staff	3	0	12	20	0	BL	2	0	8	0	0
	5	0	16	15	12		3	0	17	0	0
	8	0	26	19	16		4	0	9	0	0
	9	0	15	0	14		6	0	9	0	0
	11	0	8	0	9		12	13	13	0	0*
	12	0	0	16	0*		16	8	18	0	0*
	13	0	15	10	8		18	0	8	4	0
	15	0	13	0	11						
	31	0	13	13	15						
	34	0	17	14	13	LL	3	0	0	0	12*
	35	0	12	14	4		5	0	15	8	0
	36	0	12	11	9		6	0	14	0	0
							7	0	15	0	0
							16	0	5	0	0
BT	1	0	9	0	0		17	0	11	0	0
	6	4	13	7	0		19	0	16	14	0
	7	0	10	15	0		20	0	13	9	12
	8	0	9	0	0		22	0	10	0	0
	9	0	12	0	0		23	0	7	9	0
	14	0	8	10	9		24	0	0	11	0*
	15	10	12	14	0		25	4	8	9	0
	18	0	8	0	0						
	27	0	11	0	4						
	28	0	14	0	0						
	30	4	11	5	0						
TT	2	0	20	6	0						
	4	0	11	16	0						
	6	0	17	12	18						

those prepared from species unlikely to have been met. For example, *Mycobacterium leprae* in Great Britain and *M. ulcerans* in Nepal. Thus these individuals are responding to common (probably group i) antigens or combinations of these and species specific (group iv) antigens of those species that have been met. Category 2 persons fail to respond to the normal test dose (0.2 μg protein) of any of the new tuberculins even though many of the species used to prepare them will have been met and perhaps transitorily responded to in the past. For example, such persons are usually temporarily positive responders to Tuberculin after BCG vaccination. Category 2 individuals either have sequestration of competent lymphocytes outside of the free circulation, perhaps in the spleen or lymph nodes, or have a cell mediated suppressor mechanism triggered by group i antigen or a circulating blocking substance, perhaps an antibody. The third and largest category is of persons responding positively to some new tuberculins and not to others. Such persons respond to group iv antigens of

the species they have met in most cases and perhaps sometimes to group ii antigen.

Reagent SG in this study contains the normal concentrations of groups i and ii and twelvefold dilutions of each of the group iv antigens of the organisms included. Similarly the FG reagent contains normal concentrations of groups i and iii antigen and a twelvefold dilution of the group iv antigens of the fast growing organisms. The combined reagent F/S contains the normal concentration of group i antigen, half concentrations of groups ii and iii antigen and twenty-fourfold dilutions of all the group iv antigens. The single reagent Burulin contains approximately normal concentrations of groups i and ii antigen plus the group iv antigens of *M. ulcerans* that none of our study group should have met. It should be pointed out as a rough rule of thumb, that tenfold changes in reagent concentration produce approximately twofold changes in diameters of induration in positive responses.

Figure 1 shows the apportionment to the different categories of responders achieved in our study groups. Except for one person out of 24 in the TT/BT group, none of the patients belong to Category 1; thus it can be concluded that the ability to produce a positive response to group i antigen is almost

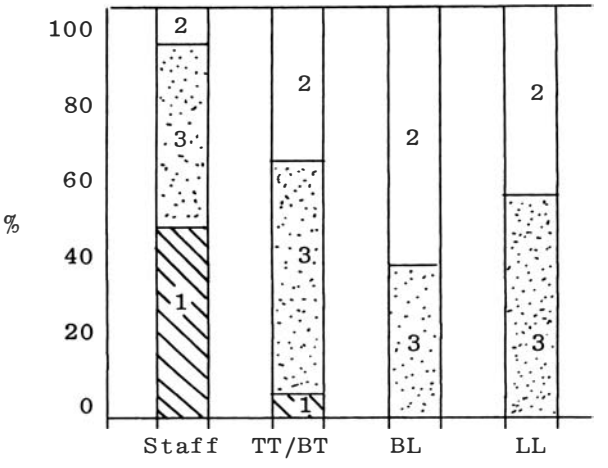

Figure 1. Division of the study groups into the categories of skin test responsiveness.

completely suppressed or absent in leprosy patients.[4] Conversely, Category 2 is markedly expanded in each of the disease categories, in principle supporting previous observations.[5] This non-specific unresponsiveness to mycobacterial antigens in patients with a mycobacteriosis has to be due to either active suppression or the absence of circulating clones of relevant lymphocytes.

The expansion of Category 3 to show the responses of each individual in Table 3 allows further insight into the mechanisms operating. It is significant

that of the 45 individuals listed, 6 responded to FG and 42 responded to SG, but only 25 responded to F/S. This demonstrates active suppression of some response to SG by the addition of FG. This suppression is not always complete and halving of the response to SG in response to F/S can also be taken as evidence of fast grower triggered suppression. This phenomenon appears in 3 out of 12 staff members, 9 out of 14 TT/BT patients, 7 out of 7 BL patients and 5 out of 12 LL patients. The mechanism of this suppression might be due to suppressor cells or suppressor complexes in which the antigens involved might be the group iii or the group iv antigens of fast growers. Our previous studies showing an almost normal distribution in responses of leprosy patients to some fast growing species[6] containing group iii antigen shows that in most cases at least, this suppression must be triggered by the group iv (species specific) antigens of particular species, or by a unique presentation of group i antigens.

Responses to Burulin indicate recognition of groups i and/or ii antigens. These are strikingly missing from all patient groups, only 5 out of 33 patients responding, compared with 10 out of 12 staff members. This means that the responses shown by most leprosy patients to SG are directed against the group iv antigens of those slowly growing species that they have met.

Table 3 also gives results of five individuals (one staff member and four BL/LL patients), that we cannot yet explain with any confidence. These are marked in the table with asterisks.

In summary the majority of leprosy patients appear incapable of producing a positive skin-test response to groups i and ii antigen. They recognize slow growing species by response to their group iv (species specific) antigens and have suppressor mechanisms triggered by the group iv antigens of particular fast growing species. These phenomena are present in all the parts of the leprosy spectrum studied, although there is some variation between them. Whether the observed phenomena are a prerequisite for the development of disease, or a consequence of it, is difficult to answer. However, it may be of significance that some staff members also display the same phenomena. One tentative conclusion might be that ability to recognize group i antigen is crucial to the early detection and successful limitation of infectious challenge with the leprosy bacillus.

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Kveim Test in leprosy: a clinical and histopathological evaluation

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Summary The gross appearances and microscopic features of Kveim tests were studied in 21 North Indian leprosy patients. Of 6 patients with tuberculoid leprosy, 2 showed positive reactions and a close correlation between nodule formation and granulomatous histology. Of 15 patients with lepromatous leprosy, only 1 patient (who showed no evidence of a papule or induration at the Kveim test site) yielded a positive response microscopically. These findings suggest the occurrence of a low level of Kveim reactivity in North Indian leprosy patients. However, it is suggested that further studies with proper controls should be carried out to eliminate the possibilities of chance inclusion of subclinical leprotic skin lesion at the site of Kveim antigen injection and needle trauma in triggering or accelerating granulomatous inflammation.

Introduction

The specificity of Kveim test in sarcoidosis has been debated and challenged for years.[1–9] More recently, a number of publications have strongly supported its specificity in sarcoidosis.[10–13] However, using validated Kveim preparations, it has been concluded that positive Kveim reactions do occur in all varieties of leprosy but are infrequent, except in Chinese and Japanese patients who show a higher frequency of positive tests.[14–18] This study was undertaken to test validated Kveim antigen CR-I[11] in North Indian leprosy patients.

Material and methods

Twenty-one patients of different types of leprosy[19] attending the leprosy clinic of the Nehru Hospital attached to the Postgraduate Institute of Medical

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Education and Research, Chandigarh, India, were tested with validated Kveim antigen CR-I. 0.15 ml of the test material was injected on the forearm. The exact site was identified by measuring the predetermined distance from the India ink spot tattoed in the forearm skin. All of the patients had been tested with 1 unit of PPD (Serum Institute, Copenhagen), and only negative reactors were included in the study. The patients were thoroughly screened for evidence of active tuberculosis, sarcoidosis, or any other chronic disease.

Lepromin test was carried out with 0.15 ml of standard lepromin (having 160–200 million bacilli/ml) on all the patients and was read after 4 weeks, and if negative, after 6 weeks. The test was considered negative if there was less than 4 mm induration.

Age, sex, duration of the disease, and treatment were not taken into consideration. None of the patients had received any steroid, immunosuppressive or other anti-inflammatory drugs within the past 3 months.

Biopsy specimens from Kveim antigen sites, irrespective of the induration, were taken after 40 ± 2 days and were stained with haematoxylin and eosin stains, and Fite-Faraco stain for the demonstration of acid-fast bacilli. The biopsies were graded as positive, equivocal, or negative according to the criteria of Siltzbach and Ehrlich[20] and those of Mitchell.[21] Biopsy specimens were separately screened by 2 different pathologists who were not aware of the type of study.

Results

Out of the 21 patients studied, 4 were polar tuberculoid (TT), 2 were borderline (BT), 10 belonged to the borderline lepromatous (BL) group, and 5 were of the polar lepromatous (LL) type. For purposes of discussion, BT patients have been included in the TT group and BL in the LL group, as shown in Table 1. Duration of the disease was more than 3 years in all patients, and each patient had taken the treatment for over 2 years.

Lepromin reaction was positive (induration of 4.5 mm or more) in all the TT and BT patients, and negative in all BL and LL patients.

The Kveim test was positive in 3 patients, 2 in the TT group (Figure 1) and 1 in the LL group (Figure 2). In the TT group both patients showed a nodule formation and positive histology, whereas in the LL group the positive histology was seen in the absence of any detectable induration (Table 1). In addition, the biopsies in 1 patient in the TT group and 2 in the LL group showed moderate chronic inflammatory cellular response with no specific granuloma formation.

Table 1. The age, sex, type of leprosy, positive reactions, and histopathology

No.	Name/Age/Sex/Type of Leprosy/Duration of disease	Reaction to Kveim Antigen	Grouping of patients for study	Histo-pathological findings
1	L/40/M/BT/4 yrs	+	TT	—
2	RSS/35/M/TT/3 yrs	—	TT	±
3	D/25/M/TT/5 yrs	+	TT	+
4	RN/35/M/BT/3 yrs	—	TT	—
5	SK/35/F/TT/5 yrs	—	TT	+
6	AK/45/F/55/4 yrs	+	TT	—
7	AR/45/M/BL/8 yrs	—	LL	—
8	SL/40/M/BL/3 yrs	+	LL	—
9	MPN/50/M/BL/6 yrs	—	LL	—
10	RD/45/M/BL/4 yrs	—	LL	—
11	JS/55/M/BL/3 yrs	—	LL	—
12	S/20/F/BL/4 yrs	—	LL	—
13	SS/50/M/BL/4 yrs	—	LL	—
14	K/35/F/BL/5 yrs	—	LL	±
15	BS/60/M/BL/10 yrs	—	LL	±
16	L/20/F/BL/4 yrs	—	LL	+
17	H/35/M/LL/5 yrs	—	LL	—
18	KD/45/F/LL/5 yrs	—	LL	—
19	LB/20/M/LL/5 yrs	—	LL	—
20	RR/30/M/LL/5 yrs	—	LL	—
21	BR/40/M/LL/10 yrs	—	LL	—

BT Borderline tuberculoid. LL Polar lepromatous.
BL Borderline lepromatous. TT Polar Tuberculoid.
— Negative + Induration up to 5 mm.

Histopathological changes:
— None to mild. Nonspecific inflammation.
± Equivocal. Moderate inflammation with no classical granuloma formation.
+ Positive. Classical epithelioid granuloma with or without giant cells.

Discussion

Since the first use of test material reported by Williams and Nickerson,[22] subsequently named Kveim antigen,[23] conflicting reports appeared in the literature regarding the specificity of Kveim test. While some authors accepted false positive Kveim test rate in the range of < or = 3%[6,24,25] others claimed much higher positive rates in a variety of diseases other than sarcoidosis.[4,14,15,24,26–29] The lack of specificity of Kveim test was, in most part, attributed to unvalidated Kveim preparations.[30] Further, careful testing of Kveim antigens prepared from different sarcoidosis tissues have shown that less than half of these Kveim preparations may turn out to be specific enough as to warrant its use as a diagnostic reagent.[17] Although a number of recent publications strongly support the specificity of Kveim test,[10–13] the response

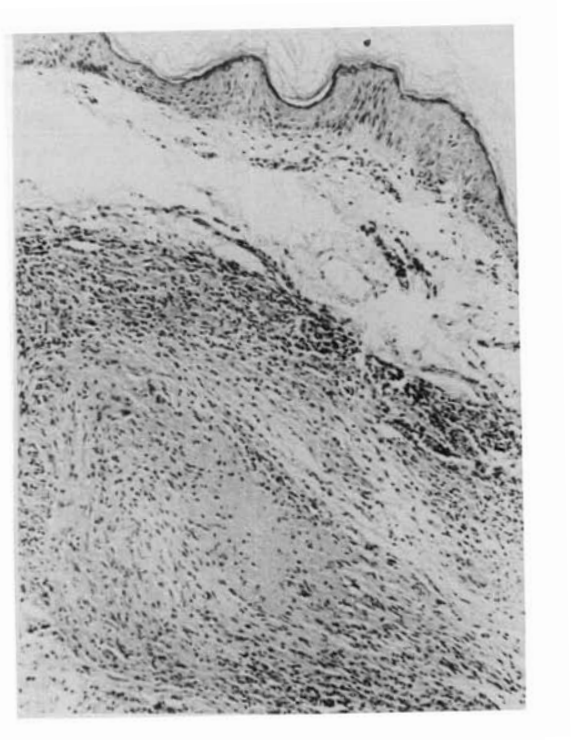

Figure 1. Typical granuloma in a tuberculoid case.

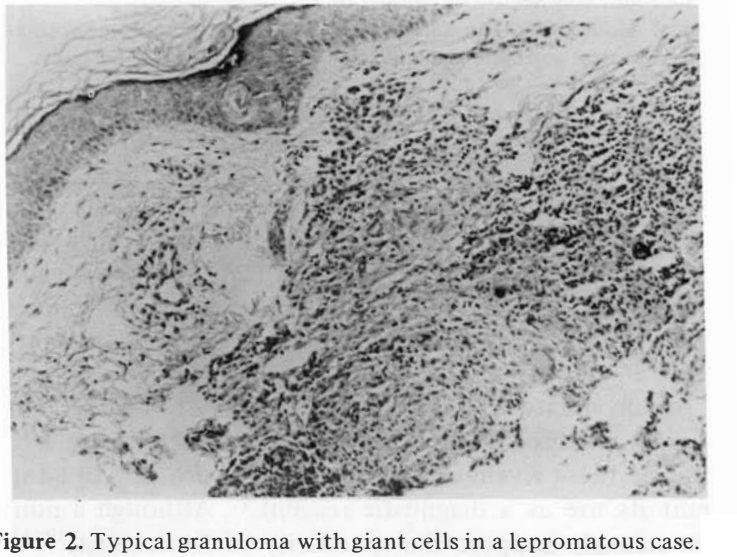

Figure 2. Typical granuloma with giant cells in a lepromatous case.

of leprosy patients to intradermal injection of Kveim antigen is a special matter because in an international study[6,7] in which a validated Kveim material was used, it showed a high frequency of positive Kveim test reactions among Japanese. Similar results were reported by Pearson *et al.*[14] and Rees[15] in Japanese and Malay patients with lepromatous leprosy, and by Hurley *et al.*[31] in lepromatous leprosy and ENL. In contrast, Pearson *et al.*,[14] Rees[15] and Hopper and Stuettgen,[32] using validated Kveim material, found no positive reactions among European, and Mendes *et al.*[27] in the Brazilian leprosy patients.

In the present study, 2 of the 6 tuberculoid patients (33%) gave positive histopathological response and 1 gave an equivocal result, whereas in the lepromatous group only 1 patient out of 15 (6.6%) gave positive reaction and the result was equivocal in 2. In the only study available from India, Krishnamurthy *et al.*[18] found positive rates of 36% among tuberculoid patients and 25% among lepromatous patients. Thus, our results show lower frequency of positive Kveim tests than those in Japanese[6,14,15] and South Indians.[18]

There is no clear explanation for the positive Kveim test reported in leprosy patients. It will be interesting to note that Bedi *et al.*[33] examined skin biopsies from clinically normal looking skin of the scalp, axillae and groins in 20 treated lepromatous leprosy patients and found that up to 25% of the patients had well-formed foam cell granulomas. Further, Klokke *et al.*[34] performed skin tests similar to Kveim tests on 7 patients with tuberculoid leprosy with a suspension of non-sarcoid human spleen and found that 3 of these patients had histologic evidence of granulomatous inflammation at the test site.

It appears that positive Kveim tests in leprosy patients could very well be due to the presence of occult granulomas present in the normal looking skin of these patients. The needle trauma could also be triggering or accelerating the granulomatous inflammation. It is suggested that further studies be carried out with inactivated Kveim antigen and normal saline as controls to finally settle the controversy of positive Kveim tests in leprosy.

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Leprosy in the Cape Verde Islands

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Summary After a general profile of the country, information is given concerning the history of leprosy in the Cape Verde Islands, with data related to the control activities of the years 1950–77. Finally the authors present the data collected during the first 2 years of activities under the new National Leprosy Control Project.

General information

The Cape Verde Islands are located in the Atlantic Ocean, 445 km off the coast of Senegal. Ten islands and 5 islets, between 17°12′5 & 14°18′ N. and 22°44′ & 25°22′ W., they are divided into 2 groups: Barlavento, North, 6 islands, and Sotavento, South, 4 islands. Total area is 4.033 km².

Three of the islands, closer to the African continent, are sandy and flat. The others, of volcanic origin, are characterized by very high cliffs and ridges and deep, narrow valleys. The highest peak of the archipelago is that of the volcano of Fogo (active, last eruption 1952), reaching 2.829 m above the sea.

Climate is hot and dry. Temperature oscillates between 17°C and 34°C. Average rainfall is 300 mm/year, concentrated in 1–13 days, between August and October.

Drought is a permanent problem in the islands; still, albeit poor, rainfall contributes heavily to soil erosion.

Total population, according to June 1980 National Census,[1] is 296,093. The majority of the population is of mulatto stock, of mixed West African and European (Portuguese) descent.

The population lives in 2 major towns (about 40,000 inhabitants each), in several smaller centres and in isolated homesteads. Nine of the islands

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are inhabited; population density varies, from 5.47 hab/km^2 (Boa Vista) to 184.10 (S. Vicente).

Eighty per cent of the people live by agriculture. This fact, coupled with the climatic conditions, easily explains the strong and persistent trend to emigrate.

There are strong Capoverdean communities abroad: in the USA 200,000; Portugal, 40,000; Angola, 35,000; Senegal, 25,000; S. Tomé & Principe, 8,000; Italy, 8,000; France, 7,000; Holland, 7,000; Brasil, 3,000; Luxemburg, 3,500; Argentina, 2,000. There are other communities in Sweden, Norway, Switzerland, Mozambique, Gabon and Ivory Coast. From 1900 to 1973 the total number of official emigrants was 267,363.[2] One of the many results of this phenomenon is an M/F ratio of 0.86.

There is no great difference in housing and living conditions from island to island. The majority of the families (average 6 members), live in stonebuilt houses, 1–2 rooms, 15–30 m^2. Hygiene standards are naturally low, due to lack of water, while nutrition is a top priority problem in the country.

Discovered by the Portuguese in 1460, the Cape Verde Islands were populated by European settlers but, mostly, by West African slaves. The islands remained for some time a breeding station on the slave trade route.

The population has been periodically ravaged by epidemics and famines: in 1773, 50% of the population died of starvation; in 1831, 20%; in 1863, 40%; in 1900–4, 25%; in 1922, 20%; in 1942, 13%; in 1947–9, 16%, in 1952, 10%; in 1959, 5%.[2]

A Portuguese colony for 500 years, Cape Verde obtained independence on 5 July 1975.

Leprosy in Cape Verde

Leprosy seems to have arrived in the Cape Verde Islands with the first inhabitants.[3] The first official reference to the disease appears in a letter by the King of Portugal, appointing 'Francisco de Araujo, accountant. . . caretaker of orphans, hospitals, chapels, monasteries and leprosaria ('gafarias' in the text) of the Islands of Cabo Verde' on 31 January 1531.[4] Fifty years later, in 1587, another similar appointment was issued. There are eighteenth-century references, and still possible ruins, of a leprosarium then standing on an islet in the Harbour of Praia.

In 1913 a special law established a leprosarium in the island of S. Antâo, and ordered a census of the leprosy patients living in the islands.[5] Famines, in 1941–9, seemingly claimed many victims among the leprosy patients.

Promin was introduced into Cape Verde in 1950; prior to that date treatment was based on hydnocarpus oil. Free, government supplied treatment (DDS, by fortnightly injections) was established in 1952.

In 1954 Teixeira de Sousa published data collected the previous year in Fogo: 131 patients (prevalence 7.27‰): of these, 49 L, 5 T, 77 I ('Indiferenciada ou Indeterminada'). Fourteen cases were less than 12 years old, 21 between 13 and 20 years, 96 were older. Male/female ratio was 59/72.[6]

In 1957 the local health services[7] announced 356 registered patients in the islands: 8 in S. Vicente, 176 in Fogo, 163 in S. Antâo, 2 in Brava. In 1959 two new leprosaria were opened, in S. Antâo and in Fogo. In that same year the WHO Bureau in Brazzaville had a figure of 13 leprosy cases in Cape Verde.[8]

In 1961 Pinto examined, mostly by mass survey, a fair share of the whole population (25% in Fogo, 10% in Santiago, 23% in S. Nicolau, 38% in Sal, 46% in Maio, 1,502 people in Brava, 5,823 in S. Antâo; in S. Vicente only contact survey) 247 patients were observed (92 in Fogo, 14 in Brava, 80 in S. Antâo, 30 in S. Vicente, 21 in Santiago); among the findings, the high proportion of L form (35% in Fogo, 40% in S. Antâo). Prevalences were estimated for Fogo, Brava and S. Antâo: 18, 1.99 and 7.04‰ respectively. The report stressed the inexistence of treatment records, while suggesting measures for the control of the disease.[9]

The following year official dispositions for a 'Campaign of Eradication (of leprosy) in Cape Verde' were issued (1962). The total number of patients was then estimated at about 800–850. Rules were set for the definition of clinical inactivity and for the length of treatment. Chemoprofilaxis – DDS 5 mg/kg/Wk – was advised for the patients' household contacts, and standard doses were fixed for DDS treatment, with gradually increasing induction of therapy.[5]

In 1964 in S. Antâo there were 160 patients treated 'irregularly',[10] of these 27.5% L, 77.06% I, 3.66% T. In the same year the 2 leprosaria were closed, and the local health services reported 27 cases in Santiago, 8 in S. Vicente, 403 in Fogo, 13 in Brava and 340 in S. Antâo.[7]

In 1965 the same source[7] reported 27 patients in Santiago, 403 in Fogo, 20 in S. Vicente, 140 in S. Antâo: total 590. Data concerning the same year, published in 1966 in *Int J Lepr* and quoted by Bechelli and Dominguez,[11] give a total of 625 cases.

The situation in 1968 was: 556 cases, distributed in Boa Vista (2), S. Nicolau (1), S. Vicente (42), Brava (20), Santiago (70), S. Antâo (132), Fogo (289).[7]

In 1970 the local missionaries unofficially re-opened the leprosarium in Fogo. In 1971 Pina[12] reported 293 patients registered and treated in Fogo.

In 1972 and 1973, Leite and Sobral[3] in two visits to the islands, observed 303 patients, suspending treatment ('Alta Provisoria') for 194 of them. They found the following proportions: L, 115 cases; I, 154 cases; T, 24 cases. 'Incidence', calculated out of 250,000 inhabitants – but the authors probably meant prevalence – was 1.21‰. In the same year Cambournac reports[13] 626 leprosy cases in the Cape Verde Islands.

In 1975 WHO gave a figure of 303 cases.[14]

In 1977 the Ministry of Health and Social Affairs of the new Republic of Cape Verde, estimated 600 cases of leprosy, distributed among Fogo, Brava, S. Vicente and S. Antâo.[15]

In the same year Silva Picoto[16] examined 159 patients among those registered. Findings: 19% T, 49.3% L, 24.7% I, 3.2% D, 3.8% NC. Invalidity Rate 61.9%; patients regularly treated 66.9% (Lepromatous regularly treated 61.7%).

In February 1978, on a fact-finding visit prior to the start of the present National Leprosy Control Programme, 355 of the registered patients were examined, together with 1.090 contacts, among whom 27 new cases were found. Of the patients observed, L form accounts for 57.7%; 50% of the patients were found to be clinically active, Invalidity Rate was calculated around 60%.[14]

The new Leprosy Control Programme

The new Leprosy Control Programme is fully integrated within the National Health Services. It is oriented by a leprologist and staffed with 3 PMWs: 1 with laboratory practice and 2 charged with the running of the small specific centre in Fogo (32 beds).

Materials and methods

In order to assess the prevalence of leprosy in the islands and thus set conditions for control, case-finding activities were conducted during 1978 and 1979: contact survey, selected survey and, in a few areas, mass examination of the population. These activities were accompanied by health education and updating courses for health professionals. Few *vestigia* were found of the old local registers, and none of the central one. So a central and local register were established anew of all cases: these registers now keep records of cases detected between 1951 and 1979, and are periodically updated by medical examination. For the Central Register the OMSLEP recording system was adopted.[18] The ages shown in the tables are those of the last examination.

Total number of cases. Coverage rates

The total number of registered cases on 31 December 1979 was 781. Of these, 547 had been detected and treated before 1978 (average age 47.94); 136 have been detected in 1978, and 98 in 1979 (average age of the new cases 29.39).

Of the 781 registered cases, 695 are under treatment.

Field activities developed in four campaigns, covering 7 of the 9 inhabited

islands. In the islands of Maio and S. Nicolau no case has been notified so far; the case registered in S. Nicolau in 1968 having left the island in 1970.

Between February 1978 and December 1979, 69.8% of the contacts of the registered patients have been examined at least once.

School surveys covered 22,395 students, that is 41.46% of the national school population (7–16 years); other selected survey – barracks, prisons etc. – included roughly 1,000 people; mass surveys covered about 2,800.

Altogether during these 2 years 29,151 people have been examined, once or more: 10.47% of the population of the 7 islands submitted to the control.

Types of leprosy

The distribution of cases according to types appears in Tables 1 and 2. Lepromatous form accounts for 36.1% of cases, I for 11.26%, T for 25.99% and Dimorphous for 25.48%. The proportion of L cases is much higher than found along the neighbouring African coast, and rather brings to mind European or Latin American figures. Lepromatous rate in the total population is 0.97‰.

The absence of active case finding prior to 1978 can explain the low proportion of indeterminate forms: of the 88 I cases, 75 have been detected during the last 2 years.

Table 1. Distribution of registered cases at 31 December 1979 according to type and sex

Type	Male	%	Female	%	Total	%
I	49	11.06	39	11.53	88	11.26
T	108	24.37	95	28.10	203	25.99
D	116	26.18	83	24.55	199	25.48
L	164	37.02	118	34.91	282	36.10
Not classified	6	1.35	3	0.88	9	1.15
Total	443	100%	338	100%	781	100%

Table 2. Distribution of registered cases at 31 December 1979 according to type and age

	0–14 years				15 years or more			
Type	Male	Female	Total	%	Male	Female	Total	%
I	23	21	44	50.00	26	18	44	50.00
T	12	11	23	11.33	96	84	180	88.66
D	1	4	5	2.51	115	79	194	97.48
L	4	2	6	2.12	160	116	276	97.87
Not classified	–	–	–	–	6	3	9	100.0
Total	40	38	78	9.98%	403	300	703	90.01%

Leprosy and sex

Looking at the total of the registered patients, leprosy seems to affect more males than females (443 M, 338 F); the ratio though is inverted among new cases (111 M *v.* 123 F).

Distribution of forms does not vary greatly with sex: there is a slight prevalence of T forms among females and of D and L forms among males.

Leprosy and age

90.01% of the registered cases belong to the over-14 group. There is though an even distribution, 1/1, of I form between the under 14 and the over 14 group.

The analysis of the new cases (Table 3) which have been divided into groups of age roughly according to different periods of social life, shows an important concentration of cases in the first group (0–14: 38.46% of the new cases), while the other groups hold respectively 25.64% (15–29), 15.81% (30–49), 20.08% (50 and beyond) of the total 234 new cases. In the 1st, 2nd and 3rd group the M/F ratio keeps approximately 1/1, while it shifts clearly in the 4th group (18 M *v.* 29 F).

Prevalence and geographical distribution (see Figure 1 and Table 4)

The general prevalence of leprosy in the Cape Verde Islands is 2.63‰. As seen elsewhere in analogous geographical situations,[19] the distribution of the diseases varies greatly from one island to another: 2 islands appear to be untouched, while others present severe prevalence rates. Fogo, for instance, has a prevalence of 10.76‰. In the affected islands leprosy is not evenly distributed, and some areas can present very high rates: Relva, in Fogo, counts 42 patients among its 700 inhabitants; Tarrafal and Monte Trigo, in S. Antâo, have a prevalence of 12.33‰.

Within a given area, leprosy presents a clear intrafamiliar character. For 71.05% of the new cases it has been possible to recognize at least another patient, known or unknown, within the household.

Case finding activities

Contact survey have given 59.4% of the new cases detected in 1978–9: 64% of the first age group, 40% of the second, 14% of the third and 21% of the fourth.

Selected survey have given 7.6% of the new cases: 18 cases total, 17 in the first group and 1 in the second.

Notifications have given 13.67% of the new cases: 32 cases, 2 in the first group, 8 in the second, 9 in the third, and 13 in the fourth.

Table 3. New cases, 1978 and 1979. Distribution according to type, sex and age group

	0–14		15–29		30–49		50 or more		Total		
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Combined total
1978											
I	16	19	5	5	–	1	–	–	21	25	46
T	6	6	10	10	5	7	3	10	24	33	57
D	1	–	3	2	–	2	2	2	6	6	12
L	1	1	4	3	3	1	1	6	9	11	20
NC	–	–	–	–	–	–	1	–	1	–	1
Total	24	26	22	20	8	11	7	18	61	75	
Combined Total	50		42		19		25		136		
1979											
I	11	11	4	1	–	–	2	–	17	12	29
T	8	6	3	8	4	2	4	4	19	20	39
D	1	1	–	1	3	4	2	4	6	10	16
L	1	1	1	–	3	2	3	2	8	5	13
NC	–	–	–	–	–	–	–	1	–	1	1
Total	21	19	8	10	10	8	11	11	50	48	
Combined Total	40		18		18		22		98		

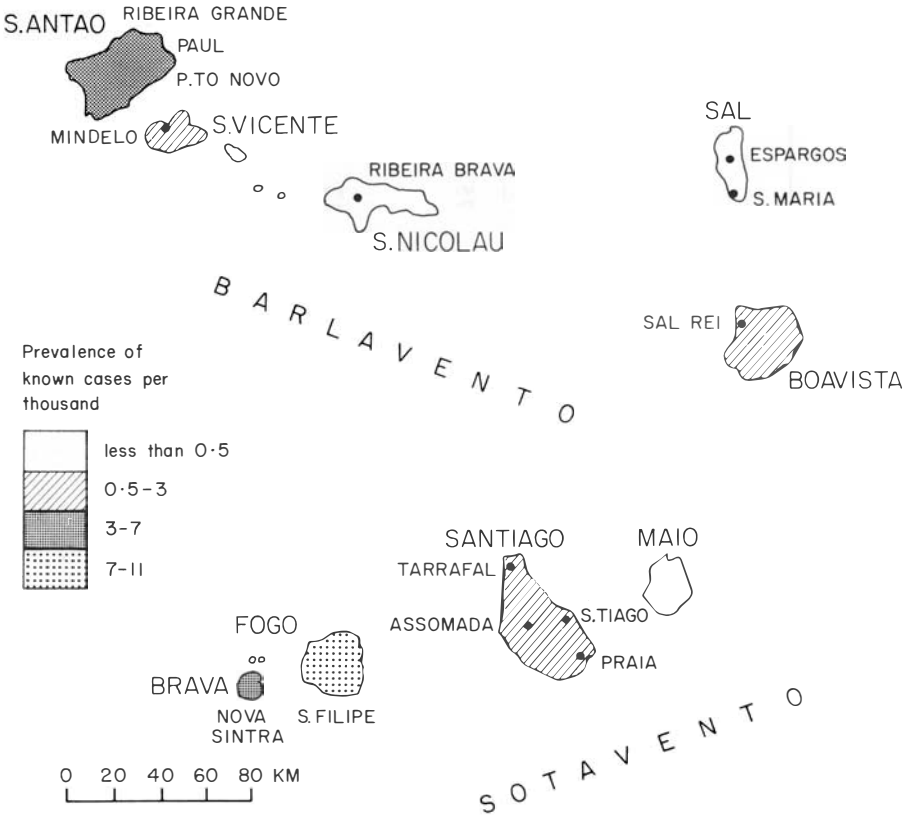

Figure 1. Distribution of leprosy in the Republic of Cape Verde.

Voluntary presentations account for 15.81% of the new cases: 37 cases, 6 in the first group, 9 in the second, 10 in the third, 12 in the fourth.

Mass survey have given 3.4% of the new cases: 1 case in the first group, 2 in the second, 4 in the third, 1 in the fourth.

Remarkably, notifications and volunteers together account for only 3 of the new indeterminate cases. In our opinion, with lack of staff and moderate prevalence rates, the only case-finding activity of objective value is confirmed to be the contact survey, integrated by health education and training and information of general health, to increase the voluntary presentation and the notification quotas.

Clinical status

Table 5 shows the distribution of patients by type, age and clinical status. For the definition of Active, Inactive under treatment, Inactive under observation,

Table 4. Geographical distribution. Registered leprosy cases on 31 December 1979

Island	Population (1980)	Registered cases					Total	Prevalence/1000
		I	T	D	L	NC		
Santiago	145,923	11	19	21	28	4	79	0.54
Fogo	31,115	39	110	76	107	3	335	10.76
Brava	6,984	2	5	11	16	–	34	4.86
Maio	4,103	–	–	–	–	–	–	–
(Sotavento	188,125	52	134	108	150	7	452	2.40)
S. Vicente	41,792	15	14	15	40	–	84	2.01
S. Antão	43,198	25	54	71	87	2	239	5.53
S. Nicolau	13,575	–	–	–	–	–	–	–
Sal	6,006	–	–	2	–	–	2	0.33
Boa Vista	3,397	–	1	–	3	–	4	1.17
(Barlavento	107,968	40	69	88	130	2	329	3.04)
Cape Verde	296,093	92	203	196	280	9	781	2.63

we referred to the standards expressed by the WHO Expert Committee on Leprosy in 1970. 'Unknown' means a patient, whose clinical conditions have not been assessed during the last 12 months.

The follow-up of the new cases 1978–9 shows that 13 indeterminate patients, 6 T, and 1 D got inactive. In the same period 13 I passed to T, 1 to D and 1 to L. Eight tuberculoid downgraded to D and 1 D upgraded to T. It needs to be stressed here that classification was done on clinical and only partially bacteriological basis.

Deformity rate (Table 6) is quite high compared to that currently found in literature. Understandably, in the order, D, L, and T forms appear to be affected differently. Out of 431 cases affected by deformities, only 1 is under 14. Deformity rate among the new cases is 20.94%.

Among possible causes of the phenomenon are distortion due to emigration, the geophysical character of the islands and general working conditions. It can be assumed that there are a number of patients not yet affected by deformities and at present undetected.

Treatment

At present 695 patients are under treatment (mostly monotherapy, DDS 50 or 100 mg/die). Treatment is distributed fortnightly by general health staff, at health posts or by mobile units (in Fogo only).

Supervised, combined treatment is available only for patients admitted to the specific center of Fogo.

Treatment attendance rates are far from satisfactory: 65.61% of patients are regularly treated. Practical measures are being studied to improve the situation (see Table 7).

Table 5. Registered cases. Clinical status on 31 December 1979

	0–14				15 or more			
	Active	Inactive under treatment	Unknown	Inactive under observation	Active	Inactive under treatment	Unknown	Inactive under observation
I	35	8	1	–	22	13	2	7
T	16	6	1	–	59	68	7	46
D	5	–	–	–	84	84	8	18
L	5	1	–	–	150	109	5	12
NC	–	–	–	–	–	4	2	3
Total	61	15	2	–	315	278	24	86

Table 6. Distribution of disabilities according to type, age group, sex (Grade 2 and 3 WHO)

	Total cases	0–14		15 or more		Total disabilities	Type (%)
		Male	Female	Male	Female		
I	88	–	–	–	–	–	
T	203	–	1	54	45	100	49.26
D	199	–	–	91	73	164	82.41
L	282	–	–	101	63	164	58.15
NC	9	–	–	2	1	3	33.33
Total	781	–	1	248	152	431	55.18

Table 7. Patients under treatment at 31 December 1979. Attendance rates

	0–14				15 or more			
	Treated	Reg.	Irr.	Reg. (%)	Treated	Reg.	Irr.	Reg. (%)
I	44	33	9	75.00	37	20	14	54.06
T	23	16	7	69.56	134	68	56	50.7
D	5	3	2	60.00	176	129	40	73.2
L	6	6	–	100.00	264	180	71	68.1
Not classified	–	–	–	–	6	1	2	16.6
Total	78	58	18	74.35%	617	398	183	64.5

There are cases suspected of DDS-resistance: 4 at least have been confirmed by BI and MI under supervised treatment with DDS 100 mg/die.

Discussion

Leprosy seems to have been present in the Cape Verde Islands since the beginning of their colonization, 520 years ago. Leprosy can be considered a major health problem in 3 of the islands. It is still seen to be a health hazard, although it has lower prevalence rates, in 2 major urban centres, where internal migration concentrates.

The situation is made worse by the high lepromatous rate and by the generally deficient conditions of treatment. The latter has been lasting now for about 30 years, and sets a good background for DDS-resistance.

Deficient standards of control undoubtedly contribute to the high invalidity rate. In our opinion, emigration is equally important in shaping the profile of leprosy in Cape Verde, probably setting a filter only for the patients affected by the most obvious signs of disease. We lack information concerning leprosy among the numerous and considerable Capoverdian communities abroad.

The geographical setting of the country may help in limiting the spread of the disease, but raises serious operational problems for leprosy control.

Acknowledgements

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Lepr Rev (1981) **52**, 349–354

SPECIAL ARTICLE

Report of the Third Meeting of the Scientific Working Group on Chemotherapy of Leprosy (THELEP) of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, Geneva, 20-22 October 1980*

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Since its first meeting in April 1977, the Scientific Working Group (SWG) on Chemotherapy of Leprosy (THELEP) of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases has promoted activities in 5 major areas: (1) field studies; (2) controlled clinical trials; (3) laboratory studies; (4) drug development studies; and (5) biological studies.

In addition, the decision was taken at the second meeting of the THELEP SWG, in March 1979, to embark on large-scale field trials of chemotherapy of lepromatous leprosy. The third meeting of the THELEP SWG was convened, 20–22 October 1980 in Geneva, to consider progress made in these areas. In addition, the SWG reconsidered the subject of trials in non-lepromatous leprosy.

Prevalence surveys of dapsone resistance

The first cases of proven dapsone resistance, represented by relapse after many years of clinical improvement under supervised dapsone monotherapy, and despite continued therapy, were reported in 1964. Subsequently, dapsone resistance has been reported from many parts of the world. Country-wide surveys in Costa Rica and Israel reported prevalences of, respectively, 7/100 and 4/100 patients at risk. More than 200 proven cases have been recognized in Malaysia. And an annual incidence of 3/100 was reported from one centre in Ethiopia. Thus, the situation as the THELEP programme was organized was one of concern. If the situation in Ethiopia were representative of large parts of the world, we faced the alarming prospect of being required to control leprosy without dapsone. If, on the other hand, the situation in Costa Rica, Israel and Malaysia (where a prevalence slightly in excess of 2/100 was calculated) were more representative, there was cause for concern but no emergency. To clarify the situation, THELEP embarked on a programme of prevalence surveys of dapsone resistance. A standard protocol for prevalence surveys of secondary (acquired) dapsone resistance was prepared, and formal surveys were initiated in Burma, two districts in South India and Upper Volta. In addition, a survey of primary resistance was initiated in the Philippines.

*In addition to this report, a further paper presented at the October 1980 meeting of the THELEP Scientific Working Group appears in this issue of *Leprosy Review*. It is our understanding that this report, together with other papers presented at the meeting, will appear in the December 1981 issue of *International Journal of Leprosy*. Editor

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The incomplete results were reported of a prevalence survey of secondary dapsone resistance in Gudiyatham Taluk, South India, where a leprosy control programme employing dapsone in full dosage and enjoying 80% attendance has been in place for 16 years. Of a total of 1,580 known patients with lepromatous leprosy, 1,431 were re-examined, of whom 46 were found to have clinical and bacteriologic evidence of relapse. Of 26 biopsied for mouse inoculation, 24 were found to harbour dapsone-resistant *Mycobacterium leprae*; adding 9 cases of dapsone resistance previously found in this population, the minimal estimate of prevalence is 2.3%.

The results were reported of a prevalence survey of primary dapsone resistance in Cebu, Philippines, in which consecutive patients with apparently untreated, multibacillary leprosy were biopsied and mice inoculated. Of the first 50 patients, the specimens of 47 contained organisms infective for mice; the organisms were fully susceptible to dapsone in 46 of the 47 cases, low-grade resistance having been demonstrated in a single instance, yielding a prevalence of 2.1%.

In discussion, it was reported that primary dapsone resistance has been recognized among patients with previously untreated multibacillary leprosy in San Francisco and Carville (USA), Burma, Malaysia, Mali and South India.

Controlled clinical trials

The results of short-term trials of a variety of single-drug regimens were reviewed. Patients' organisms were rendered non-infective for mice after treatment for 100 days with dapsone in full dosage; 150 days with clofazimine in a dosage of 200 mg daily; about the same with clofazimine 100 mg 3 times weekly but somewhat longer with clofazimine in dosages of 300 mg weekly, 600 mg every 2 weeks, and 600 mg on 2 consecutive days every 4 weeks; about 30 days on the average in 3 patients with ethionamide 250 mg 3 times daily; and 3 or 4 days with rifampicin in a variety of regimens, including 600, 900, 1,200 and 1,500 mg in a single dose and 300 or 600 mg daily.

Also reviewed were the results of clinical trials in which demonstration of persisting *M. leprae* by inoculation of immunosuppressed mice was attempted. In the first persister study, small numbers of viable, dapsone-susceptible *M. leprae* were detected by inoculation of normal or immunosuppressed mice in at least 1 tissue (skin, nerve, skeletal muscle or dartos) of 7 of 12 patients who had been treated with dapsone in supervised, full dosage for a minimum of 10 years. Subsequent trials revealed evidence of persisting *M. leprae* in patients treated for from 6 months to 5 years with rifampicin 600 mg daily, clofazimine 100 mg daily or rifampicin 600 mg daily *plus* dapsone 100 mg daily.

At the time that the THELEP programme began, it was already clear that even a single dose of rifampicin was maximally effective as measured in short-term trial with inoculation of intact mice, whereas the combination of dapsone and rifampicin, each drug administered daily in full dosage, was inadequate to eradicate the persisting *M. leprae,* detected by inoculation of immunosuppressed mice with large numbers of *M. leprae.* Recognizing the need to employ drug combinations including some dosage of rifampicin, THELEP embarked on 2 controlled clinical trials among previously untreated patients with multibacillary leprosy, in which thymectomized-irradiated mice are inoculated with as many as 10^5 *M. leprae* per foot pad after 3, 12 and 24 months of treatment.

The regimens employed are at the Central Leprosy Teaching and Research Institute, Chingleput, South India:

A_1 dapsone 100 mg daily, rifampicin 600 mg daily and clofazimine 100 mg daily;

C dapsone 100 mg daily *plus* rifampicin in a single initial dose of 1,500 mg;

D_1 dapsone 100 mg daily *plus* rifampicin in a single initial dose of 1,500 mg *plus*

clofazimine in an initial 3-month course of 100 mg daily;

and at the Institut Marchoux, Bamako, Mali:

A_2 dapsone 100 mg daily, rifampicin 600 mg daily and prothionamide 500 mg daily;

C as for Chingleput;

E_2 dapsone 100 mg daily *plus* initial 3-month courses of rifampicin 900 mg weekly and prothionamide 500 mg daily.

About 48 patients have been recruited into the trial at Chingleput, which began recruiting patients in August 1978.

One patient was found to have low-grade dapsone resistance in the pretreatment biopsy specimen, and another patient's organisms failed to infect mice pretreatment. The treatment regimens have been well-tolerated; clinical and bacteriological improvement has been gratifying; the results of inoculation of immunosuppressed mice are as yet too fragmentary to permit analysis.

Thirty-one patients have been admitted into the trial at Bamako since November 1978. Organisms from the pretreatment specimen of 1 patient did not infect mice, and those from the pretreatment specimens of 5 patients exhibited low-grade resistance to dapsone. The results of inoculation of immunosuppressed mice were too fragmentary to permit analysis.

Work with immunosuppressed rodents

The papers in this segment of the meeting were devoted to a review of work in progress on immunosuppressed rodents, with particular reference to the detection of persisting *M. leprae*. Originally, thymectomy of mice was performed at a few weeks of age; a few weeks later, the animals were subjected to whole-body irradiation with 900R, followed immediately by bone marrow replacement. This animal permitted multiplication of *M. leprae* well above the ceiling in normal mice of about 10^6 organisms per foot pad; in addition, systemic spread of the infection and grossly-evident lesions were common. More recently, decreased survival of these 'T900R' mice has required a change of procedure; mice are now thymectomized as before, and subsequently subjected to 200R 5 times at intervals of 2 weeks ('T200 x 5R'). This animal does not require bone marrow replacement, but its immunity is not suppressed to the same degree as is that of the T900R mouse. This animal has been useful in attempts to detect persisting *M. leprae* in biopsy specimens obtained from patients under treatment, and is currently being applied to the ongoing THELEP controlled clinical trials in Bamako and Chingleput.

The results were received of work with neonatally-thymectomized rats (NTR), which are thymectomized within 16 hours of birth and either inoculated intravenously with large numbers of *M. leprae,* to be used subsequently in chemotherapeutic experiments, or for the detection of persisters, either in patients or in *M. leprae*-infected NTR undergoing chemotherapy.

The objective of the chemotherapeutic experiments has been to reproduce in NTR the state of microbial persistence encountered in patients with lepromatous leprosy, and to devise drug regimens that are active against these persisting *M. leprae.* It has been found that 10 daily doses of rifampicin, each 10 mg/kg body weight, administered on a background of dapsone administered continuously in a concentration in the diet of 10^{-5} g%, the minimal effective dose, produces a situation comparable to that seen in patients: subinoculation of small numbers of *M. leprae* to normal mice fails to result in multiplication of the organisms, whereas subinoculation of larger numbers to NTR results in multiplication.

The incomplete results were presented of a clinical trial in which 2 regimens are being compared: daily dapsone *plus* rifampicin either in a single initial 1,500 mg dose or in a

once-weekly 900 mg dose. Skin biopsy specimens are obtained 3 or 4 days, and 1, 2 and 4 weeks after the start of treatment. Normal mice are inoculated with 5,000 AFB per foot pad, and NTR are inoculated with 10^5-10^7 AFB per foot pad. The results appear to confirm the usefulness of the NTR in detecting the presence of persisting *M. leprae.*

Early work was described with the congenitally athymic rat, which is more effectively and more uniformly immunosuppressed than is the NTR. Although the athymic rat appears to possess active non-T-cell mediated mechanisms that account for its ability to survive under conventional conditions of husbandary, it nevertheless appears to permit multiplication and dissemination of *M. leprae* from large inocula.

The results were reviewed of work in which gnotobiotic nude (hairless, congenitally-athymic) mice are infected with *M. leprae.* Intravenous, intraperitoneal and subcutaneous (in the foot pad) inoculation of the organisms appears to result in disseminated infection, and animals inoculated in the foot pad exhibit some swelling of the feet some months later. A comparison of nude, T200 x 5R, and normal mice inoculated with 10^2 fresh *M. leprae* diluted by large numbers of irradiated organisms established the superiority of the nude mouse over both of the others, in terms of permitting multiplication of the viable organisms.

Studies of patient compliance

The background was reviewed of our concern with the compliance of patients with chemotherapy—particularly chemotherapy with dapsone, which is traditionally self-administered. Studies carried out in several parts of the world have demonstrated that compliance of leprosy patients with self-administered dapsone as monotherapy ranged from very poor to poor. The focus of THELEP has been the development of simpler, more specific means of monitoring compliance under field conditions.

The Bratton-Marshall colorimetric method applied to urine has been most widely used. Simultaneous assay of urinary creatinine makes the test more precise, but there remains an important element of lack of specificity for dapsone. An alternative is the addition to dapsone tablets of a readily-detected marker. Such a marker is a small quantity (6 mg) of isoniazid, which can be detected by a simple and specific test. Use of an isoniazid marker would permit recognition of dapsone ingested within the 16 hours preceding the urine collection. Most desired, however, is a specific test that will detect dapsone ingestion during the preceding 5—10 days. After 5 consecutive missed daily 100 mg doses of dapsone, the plasma dapsone concentration has fallen below that required to inhibit multiplication of low-resistant *M. leprae;* after 10 consecutive missed daily doses, the plasma dapsone concentration is insufficient to inhibit multiplication of *M. leprae* fully susceptible to dapsone.

The results of work based on two 'ELISA' techniques were described. Both techniques are capable of detecting dapsone in ng/ml concentrations. The less sensitive technique is capable of recognizing dapsone in the urine as late as 8 days after a single 100 mg dose; the more sensitive technique can detect dapsone in a finger-prick blood specimen as late as 5 days after a dose. These techniques have been made available as 'kits', and have been employed by leprosy workers in endemic areas.

Drug development

Work in progress on clofazimine analogues in 3 laboratories was reviewed. A mass of data has been generated on structural requirements for activity against *Mycobacterium* sp. 607, acute toxicity in the mouse, and mutagenesis; these have been submitted for analysis of the

quantitative structure-activity relationships (QSAR). The 3 major pigmented metabolites in human urine have been separated and identified; these were found not to be mutagenic.

The results of work with cell-free preparations of folate-synthesizing enzymes of *Mycobacterium lufu* and *M. leprae* were reviewed. The action of dapsone in these systems appears to be qualitatively as well as quantitatively different from that in the comparable *Escherichia coli* system. Dapsone is much more potent in the 2 mycobacterial systems. Also, dapsone is incorporated in the *E. coli* system into an analogue of the product of the reaction between dihydropteridine alcohol and *p*-aminobenzoic acid, whereas no analogue is formed in either mycobacterial system.

Work was described on 2 systems that involve the uptake by *M. leprae* in short-term culture (in macrophages or *in vitro*) of various radioisotope-labelled substrates. These systems show promise of usefulness in screening drugs for activity against *M. leprae,* and in testing the drug-susceptibility of *M. leprae.*

Trials of chemotherapy of non-lepromatous leprosy

Trials of chemotherapy of non-lepromatous leprosy have been an objective of high priority since the THELEP Programme was first established. Yet, no such trials have been undertaken, because of the difficulties inherent in measuring the response to therapy of non-lepromatous leprosy, in which *M. leprae* are too few to permit animal inoculation, and also because it appeared more urgent to develop better methods for the control of lepromatous leprosy, the more infectious form of the disease. Because it appeared important to reconsider the priority of these trials within the framework of THELEP activities, a segment of the meeting was devoted to reviews of the importance of non-lepromatous leprosy in leprosy control programmes, and of the methods that have been employed in several trials in the past.

The deformities that characterize non-lepromatous leprosy, which accounts for two-thirds of the world's leprosy patients, have an enormous economic impact. In addition, it cannot be stated that these patients are non-infectious; the attack rate among household contacts to non-lepromatous patients was 3.7 times that among non-contacts in South India, and 1.6 times that among non-contacts in Burma. Finally, a study in Burma revealed that nearly half of the lepromatous borderline cases had evolved from 'paucibacillary' forms of the disease. On the basis of this evidence, control of non-lepromatous leprosy with more effective, short-course regimens appeared to make sense in the framework of leprosy control programmes. Merely preventing deformity and permitting much earlier 'release from control' would free enormous resources that could then be applied to the detection and treatment of patients with lepromatous leprosy.

The results of past trials were then reviewed. The most useful measurement appeared to be that of relapse after initial response and subsequent cessation of therapy. Several short-course regimens of dapsone *plus* rifampicin appeared undoubtedly to have been effective. And it was noted with considerable interest that, in at least 1 trial of a short-course regimen, clinical improvement continued even after cessation of treatment.

Recommendations and conclusions

The SWG felt that it was important to prevent the emergence of strains of *M. leprae* resistant to rifampicin and the thioamides as well as to dapsone. For this reason, every newly-discovered patient with multibacillary leprosy should be treated with combined chemotherapy, and additional drug(s) should be employed in the case of such patients already receiving dapsone as monotherapy.

It was recommended that THELEP conduct field trials of combined drug regimens designed to prevent drug resistance. In addition, THELEP should abandon its programme of formal surveys of the prevalence of secondary dapsone resistance, because those in progress appear already to have accomplished THELEP's purpose—namely, to demonstrate the widespread nature of this problem. In place of the programme of formal surveys, THELEP should promote the establishment of mouse-foot-pad laboratories around the world, and encourage them to monitor primary resistance within leprosy control programmes.

Work in immunosuppressed rodents

The SWG was of the opinion that the nude mouse and the immunosuppressed rat are unlikely to replace the thymectomized-irradiated mouse as a means of detecting *M. leprae*. On the other hand, these other immunosuppressed animals should prove extremely valuable as models of the lepromatous patient for chemotherapeutic studies.

Drug development

The SWG recommended that efforts be continued to improve the existing drugs, in terms of potency, selectivity, convenience (supervisability) and cost. In addition, THELEP should press forward in its attempts to develop screening systems other than that of the mouse foot pad. *M. lufu* has already proved so useful as a model of *M. leprae* for studies of drugs acting on folate-synthesizing enzymes as to suggest the usefulness of other model organisms that might be employed in studies of other drug classes.

Chemotherapy of non-lepromatous leprosy

The SWG felt the issue to be of sufficient urgency to require that the next step be taken—namely, development of a protocol for chemotherapy trials in non-lepromatous leprosy.

Immunopathology of nerve damage in leprosy

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Editorial Note. For nearly 10 years, first in Oxford, later in Birmingham and Edinburgh, and later still for all medical schools in the United Kingdom, the British Leprosy Relief Association (LEPRA) has sponsored prize essay competitions. These have recently been extended to Zambia and India. We present here an abbreviated version of a prize-winning essay in 1979, from a student in one of the London Hospitals. Following a general introduction to the immunopathology of leprosy, including sections dealing with the nature of the immunological defect and the response of the immune system to *Mycobacterium leprae,* the author proceeds as follows.

Nerve damage in leprosy

Often many of the clinical features of a disease are due to local tissue damage as a result of the host's attempts to eliminate the organism. *Mycobacterium leprae* requires CMI for its elimination and this can also cause extensive tissue damage leading to the clinical manifestations of the disease. Interaction between humoral antibody and antigen derived from the organism can cause tissue damage even though the antibody is unable to eliminate the organism.

Nerve damage in leprosy is recognized more easily histologically than functionally; since, due to receptive field overlap, 30% of the fibres in a nerve must be destroyed before decreased sensation in the area subserved can be recognized. Damage occurs more readily in tuberculoid leprosy than lepromatous leprosy. In the former it is a feature early on whereas in the latter damage and partial loss of sensation is a feature of the advanced disease. It occurs either as part of the natural history of the disease or due to reactions.

The peripheral nerves are something of an immunological backwater. The perineurium forms an effective barrier and the endothelial cells of the intraneural capillaries have tight junctions and hence are less permeable than elsewhere in the body. The Schwann cells, which protect and support the axon, have a very long life span and anything which is taken into their cytoplasm may not be exposed to the extracellular environment for years. Soluble antigens may leak out but even so infection in this sheltered zone can escape recognition. Extraneural bacilli are phagocytosed by histiocytes, which have a life span of a few weeks. Again soluble antigens are exposed all the time but when the host cell dies the whole bacilli will be exposed.

M. leprae is the only organism known to parasitize Schwann cells and it is important to understand how it gets there. Possible mechanisms are:

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(1) Phagocytosis by Schwann cells in the upper layers of the dermis and once engulfed the bacteria travel centrally through contiguous Schwann cells or possibly within the axon itself. However there is little evidence that bacilli ever lie free in the dermis and histologically nerves in the middle and deeper layers of the dermis are involved to a greater extent than terminal nerve fibres. Bacilli are seldom seen in axons and when they are seen there the possibility that they are not in the tongues of Schwann-cell cytoplasm invaginating the axon has not been excluded.[1]

(2) By penetration of the perineurium with the inflammatory cells. However when the inflammatory cells enter, the Schwann cells are already laden with bacilli and hence bacillation is a cause rather than a consequence of inflammatory cell entry.

(3) Via the endoneural blood vessels. Bacteraemia is a normal finding in untreated lepromatous patients and histologically, in early nerve involvement, bacilli tend to be close to the endoneural blood vessels.

Much is still unknown, for instance whether the bacteria enter the nerve within macrophages or free, however once inside ultimate phagocytosis by Schwann cells is inevitable.

The predilection of *M. leprae* for nerves is as yet not satisfactorily explained. Other mycobacteria are not seen to enter nerves. It is possible that it represents an immunological phenomenon in that elsewhere in the body *M. leprae* is destroyed whereas since the nerve is an immunological backwater it is able to proliferate there. In lepromatous patients, in whom the immune response to *M. leprae* is generally depressed, bacteraemia is a normal finding and the visceral organs are often involved with granuloma formation. Studies of liver and kidney biopsies from LL patients show that the bacteria are grossly fragmented as opposed to the intact bacteria seen in skin and nerves.[2]

Other theories are that the peripheral nerves and skin are cooler and it is possible that *M. leprae* multiplies more rapidly here or that these sites are subjected to constant minor trauma leading to minor inflammation with consequent increased capillary stickiness and bacillary or monocyte adherence. If the latter is true it is at variance with the hypothesis that the nerve is an immunological backwater.

In the initial stages of the infection Schwann cells are colonized but little affected. However after some time they may be destroyed by either the bulk of organisms or competition with metabolic processes. Job and Verghese[3] found increased numbers of mitochondria, ribosomes and increased endoplasmic reticulum in infected cells. With cell destruction the bacilli are released and may be taken up by neighbouring Schwann cells, hence moving along the nerve, or by intraneural histiocytes, which could transport them via endoneural blood vessels along the nerve. In tuberculoid leprosy the bacilli are far more concentrated in the nerves than elsewhere and this is probably the major route of dissemination in this form of the disease.

The mechanism of tissue damage is different in the different forms of the disease and this will now be discussed.

(1) *Tuberculoid leprosy*. In this form of the disease CMI against *M. leprae* is high and the evidence that this is responsible for tissue damage and the clinical presentation is:

(a) Histological.

(b) The intensity of inflammatory changes is correlated with the strength of delayed hypersensitivity reactions as measured by LTT and LMIT responses to *M. leprae*. Clinical severity of the disease is also related to the spread of *M. leprae*.

(c) Mice made lepromatous develop tuberculoid-type lesions with nerve damage when injected with syngeneic lymphoid cells or thymus transplants.

(d) The localized nature of the lesions makes it unlikely that they are caused by autoimmune responses precipitated by *M. leprae* infection. However involvement of responses to host cell antigens altered by *M. leprae* parasitism cannot be excluded.

The precise nature of tissue damage is uncertain; for instance the exact role of T cell cytotoxicity or cytotoxic mediators remains unknown. Mere infiltration and distortion of the tissues by the inflammatory cells with intra and extracellular oedema may explain most of the features of the lesion. Its chronic nature is probably related to the extremely slow degradation and elimination of *M. leprae*.

The overall picture is of a wave of bacillation spreading slowly through dermal nerves pursued but never quite overtaken by the inflammatory response. Once all the nerve is destroyed the bacilli are finally destroyed with it and resolution by fibrosis occurs leading to the clear centre of the tuberculous lesion.

(2) *Lepromatous leprosy.* In this form of the disease CMI directed against *M. leprae* is depressed and some other mechanism of nerve damage must be sought.

Hastings[4] states that the concentration of bacilli in perineural cells is as great as or more than that in Schwann cells and that both sites may be damaged but that perineural damage is the more important. The perineurium plays an important part in stabilizing the intraneural environment, so important for the normal function of the nerve. Bacillary multiplication is thought to initiate perineural breakdown, by some unknown mechanism, leading to perineural incompetence. Because of this ECF can enter the nerve; impairment will be reversible which would account for the improvement in lepromatous leprosy upon treatment. Similarly the nerve is more vulnerable to the entry of inflammatory cells. The histological picture does not support either of these views. Lepromatous lesions are characterized by the lack of inflammatory cells and there are structural alterations in the nerve which do not concur with the view that impairment of nerve activity is purely functional due to alterations in the extraneural environment. If this were true it would be expected that all the axons in the nerve trunk would be similarily affected since they share the same extra axonal environment. This is not so.

Alternatively the structural abnormalities may be due to defective attempts at repairing the damaged perineurium. Experimentally Morris *et al.*[5] found that Schwann cells are involved in perineural repair by putting out pseudopodia, which plug gaps in the perineurium, forming a pseudoperineurium, which becomes organized and indistinguished from the normal. Job[6] found in electronmicrograph studies of radial cutaneous nerve biopsies from 5 untreated LL patients that Schwann cells are hypertrophied and have papillary processes resembling pseudopodia. In the intraneural blood vessels endothelial swelling and hypertrophy leading to narrowed or obstructed lumina was seen. In some cases there was proliferation of perineural cells forming several layers and the number of myelinated nerve fibres was decreased. In others, axons surrounded by bacilli laden Schwann cells looked normal; in between these extremes there was a graduation of degenerative change.

Schwann cells, perineural cells, endothelial cells and macrophages were all bacillated and showed foamy degeneration. Schwann cell bacillation may lead to defective patching of perineural damage and hence it continues unchecked leading to the multilayered perineural appearance.

Loss of function in the axons is probably due to loss of function in the supporting Schwann cells because of bacillary competition for metabolites etc. This will be exacerbated by blood vessel obstruction and perineural incompetence. Nerve damage in lepromatous leprosy is therefore a secondary phenomenon.

(3) *Reversal reactions.* The clinical presentation varies widely but it can be divided basically into 3 groups:

(a) Those with predominantly skin hypersensitivity.
(b) Those with predominantly nerve hypersensitivity.
(c) Those with both.

Barnetson *et al*[7] investigated the mechanisms underlying these 3 groups. In all reactions

it was found that there was an increase in LTT but that nerve and skin involvement are associated with different antigens. Whole washed bacilli failed to elicit high responses in nerve reactions suggesting that cytoplasmic antigens play an important role in this condition, whereas in the skin case, the increased response is chiefly directed at whole washed bacilli and therefore surface antigens are more important. In BT, BB and BL patients, who are reasonably immunologically competent, many bacilli may be present in the nerve but fewer are present in the skin. Cell surface antigens are rarely exposed and soluble cytoplasmic antigens are more likely to be exposed but are released slowly. In reactions there is a sudden increase in release, due to an unknown trigger mechanism, with subsequent destruction of Schwann cells and exposure of bacillary surface antigens. In the skin case LTT results indicated that there may be an increased exposure of surface antigens. In reactions there is a rise in IgG, IgM and IgA levels but this is probably a non-specific effect rather than a cause.

Godal *et al.*[8] studied reversal reactions in 10 BT patients and found that although they showed clinical deterioration, this coincided with a very strong immune response to *M. leprae*. That the reaction is due to an increase in CMI has been confirmed in experiments by Gaugas *et al.* [9] in which implantation of isogeneic thymus tissue caused changes in infected mice similar to those seen in humans.

Also Rees and Wedell[10] took thymectomized, irradiated mice and injected them intraperitoneally with lymphocytes equivalent to those present in the normal mouse 10 months after the injection of *M. leprae,* when macroscopic lesions had already developed in the foot pad. Six to 10 days later, the areas of skin in which *M. leprae* were present became red and swollen. Bacteriological examination showed that the bacilli degenerate and the yield of organisms drops enormously. Histologically there was evidence of increased lymphocytic infiltration. This is similar to what is seen in the lepromatous patient undergoing a reversal reaction.

Factors precipitating reversal reactions remain uncertain though antileprosy drugs and BCG have been implicated; whatever they are the primary feature is increased CMI against *M. leprae* with oedema which is responsible for the early stages of the lesions. Further epithelioid cell formation leads to total tissue destruction.

Reversal reactions represent a serious therapeutic problem. Immunosuppressive drugs may be necessary to control them and prevent extensive nerve damage. Attempts to increase CMI to eliminate the organisms should be carried out very carefully indeed since they may precipitate a reaction.

(4) *ENL.* The nerves are painful and tender for prolonged periods and still show only mild loss of function. The pain is probably chemically induced by release of active substances, e.g. polypeptides from damaged cells in the vicinity of the nerves.

The lesions occur in areas of high bacillary concentration, i.e. perineural cells, and thus surviving Schwann cells are less liable to be damaged. This explains the unexpectedly slight damage caused. However Job[6] says that bacilli are less common in perineural cells than Schwann cells.

ENL is not associated with a shift in cellular immune status and is probably associated with humoral immune mechanisms. There is a decrease in the number of bacilli, which undergo considerable degeneration undoubtedly with release of antigenic material into the circulation.

However direct evidence that ENL is caused by immune complexes is still lacking and it must be explained why one third of patients with evidence of circulating complexes do not develop ENL. Also why do most patients have only a few attacks while others have repeated attacks over a long period? It could be due to variations in the amount of bacilli being killed off by residual CMI, determined by varying host/parasite relationships.

Conclusions

It can be seen that the understanding of the immunopathology of leprosy is far from clear. In an attempt to bring all the evidence and arguments together I will postulate a hypothesis, which seems to fit the evidence. Any theory must explain several important features of the disease:

(a) how the infection becomes established and what determines the subsequent course of the disease;
(b) why the bacteria shows a predilection for nerves and skin;
(c) how tissue damage is brought about?

In the race between the immune system's attempt at elimination and bacterial proliferation the crucial question is who wins and by how much? Due to the complexity and enormous variations in the disease it is doubtful that any one factor will determine this. It is likely that a number of factors make different contributions in different cases.

To establish an infection in experimental mice it was necessary to immunosuppress them which suggests that normally the immune system is able to cope with infection. Specific and non-specific factors are important and anything which decreases the effectiveness of either of these could prove to be important in the establishment and subsequent course of the disease. Non-specific factors include: diet, climate, concurrent infection, general socioeconomic conditions, age, sex, genetic factors, etc.

On the specific side tolerance has been mentioned and it is possible that the frequency, route and inoculum size of infecting organisms as well as the state of the host immune system are very important. For a long time it was thought that prolonged exposure was necessary for infection to occur however this is not compatible with the finding of explosive spread of leprosy when introduced into non-endemic areas. From the study by Godal and Negassi[11] it appears that subclinical infection is the most common outcome of exposure to *M. leprae* and that supraexposure may lead to depression of the host response and establishment of the infection.

In terms of antigen predosage there is high and low zone tolerance. Between these there is stimulation of active immunity. The spectrum is continuous, hence interaction between the immune system and the organism will give a response lying somewhere on this curve and its position will determine subsequent events. Sensitization will result in subclinical infection. Tolerance, depending upon its degree, will lead to clinical infection; where tolerance nearly equals sensitization reactivity is more likely to be regained and hence the disease will be towards the tuberculoid pole. When tolerance is much more firmly established lepromatous leprosy will be the outcome. Tolerance depends upon the continued presence of antigen for its maintainance and it may be that in tuberculoid leprosy *M. leprae* gets hidden away inside nerves and fails to render newly produced lymphocytes tolerant. This primary response would explain the slow time course of damage in tuberculoid leprosy. In reactions, damage occurs much more rapidly by the same mechanism and this could represent a change to 'sensitization'.

The pattern of exposure to the immune system could be determined by non-specific immune (e.g. BCG) and non-immune (e.g. drugs) factors and hence varied by changes in these leading to shifts on the leprosy spectrum.

The inability of lepromatous macrophages to lyse *M. leprae* is a property of live bacilli and suggests that it is resistant to lysis, however the experiments of Convit *et al.*,[12] in which lepromatous macrophages could lyse *M. leprae* when other mycobacteria were administered concurrently, suggests that the macrophage itself is in some way deficient. In granulomata in other tissues the bacteria are fragmented whereas those in nerves are whole. *M. leprae*

is known to be very fastidious in its growth requirements and it may be that Schwann cells are its first choice home but the organism can survive in other tissues, but considerably less well. By this mechanism bacterial proliferation is decreased in extraneural tissue and the immune response is here able to tip the balance in favour of elimination; this explains the fragmentation of bacilli in liver and kidney granulomata seen in LL leprosy. Similarly, lysis of dead but not live bacteria, intraneurally, is explained in this way.

The activation of macrophages by administration of other mycobacterial antigens probably represents a non-specific affect tipping the balance in favour of elimination. The picture is further complicated by the thesis that the nerve is an immunological backwater. The immune response may be sufficient to eliminate bacteria elsewhere but is unable to completely overcome the barriers where the nerve is involved. In lepromatous leprosy the immune response is not even sufficient to eliminate extraneural bacteria. Reversal reactions represent a situation where the balance is tipped strongly in favour of elimination and massive cell-mediated destruction of tissue occurs wherever bacteria are exposed as opposed to the gradual destruction in tuberculoid leprosy where the difference between elimination and proliferation is much less.

Whatever the mechanism of predilection the bacilli become established in the Schwann cells. In lepromatous leprosy they proliferate rapidly and competition for metabolites etc. leads to decreased Schwann-cell function with consequent axon demyelination and, due to inefficient repair of the damaged perineurium, the characteristic histological picture of lepromatous nerves. Decreased Schwann-cell function may lead to defective antigen presentation to T cells making things even worse. The T cells and macrophages probably affect each other reciprocally. Decreased T cell function affecting the macrophage adversely and vice versa. In tuberculoid leprosy the bacilli are much fewer and the host in attempting to destroy the bacilli destroys the Schwann cells with secondary demyelination. However bacillary multiplication outstrips this and the picture is one of a wave of bacillation followed down the nerve by a wave of tissue destruction.

The time after infection that the bacteria enters the nerve is very difficult to ascertain because of the long incubation period of the disease, which is commonly believed to be in the order of 2–5 years. In view of all that has been said it is likely that its length is determined by the relative excess of proliferation over elimination. It is likely, if the endoneural environment is the most favourable for growth and if the infection is to be established, that *M. leprae* colonizes these cells very early on. Subclinical infection represents the situation where the host is sensitized and *M. leprae* is eliminated before it is able to reach the Schwann cells.

Initially the presence or absence of lymphocyte tolerance to *M. leprae* will determine whether the bacteria reaches the Schwann cells, and indeed other cells of the body, but if it becomes established here this further contributes to the immunological defect by decreased macrophage function.

Leprosy can therefore be seen to be a disease in which the immune system plays a major part in the disease process.

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Lepr Rev (1981) **52**, 363–364

Leprosy and the community

ILEP: THE INTERNATIONAL FEDERATION OF ANTI-LEPROSY ASSOCIATIONS: 234 BLYTHE ROAD, LONDON W14 0HJ

Recently, the Coordinating Bureau have kindly sent a number of items of information:

(1) *ILEP FLASH. Printed in French and English.* No 81/2 of July 1981 includes sections on: an appeal for the eradication of leprosy by Mrs Indira Gandhi at the 34th World Health Assembly (Geneva, 6 May 1981); the beatification of Father Damien; 75th Anniversary of American Leprosy Missions; LEPRA's ring fund; a new manager for the German Leprosy Relief Association, Mr Wilhelm Dewald; OCCGE Technical Conference in Bamako, April 1981; the ILEP Calendar; and finally a page of recent publications.

(2) *36th Meeting of the Medical Commission in Copenhagen, June 1981.* Some of the important matters discussed included: combined chemotherapy regimens, ILEP Guidelines for the Campaign against Leprosy, careers in leprosy, post-graduate training leprosy for doctors with particular reference to nationals of endemic countries in Africa, a technical guide for smear examination in leprosy by direct microscopy, teaching materials, a reference centre for teaching material and documents in Amsterdam, ILEP strategy, research, and the International Leprosy Congress to be held in Delhi, 1983.

(3) At its recent meeting in Copenhagen, the International Federation of Anti-leprosy Associations (ILEP) elected 'Secours aux Lépreux' (Canada) a full member of the Federation.

(4) A revised atlas of leprosy distribution in the world has been prepared by the Damien Foundation, Belgium.

(5) ILEP is collaborating with the International Leprosy Association in the planning and financing of the International Leprosy Congress to be held in New Delhi in November 1983.

(6) *The Leprosy Documentation Service, Amsterdam.* ILEP has issued an appeal for copies of all teaching material to be sent to this centre in Amsterdam; we publish the full text of this important request on page 375 of this issue.

THELEP: REPORT OF THE EIGHTH MEETING OF THE STEERING COMMITTEE OF THE SCIENTIFIC WORKING GROUP ON THE CHEMOTHERAPY OF LEPROSY (THELEP), GENEVA, 23–24 OCTOBER 1980

Because it appeared that the widespread nature of the problem of dapsone resistance had been conclusively demonstrated, the decision was taken not to undertake formal surveys of the prevalence of secondary dapsone resistance in addition to those already in progress.

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Rather, THELEP will promote the establishment of regional and national mouse-foot-pad laboratories, and encourage continuing surveillance of primary drug resistance in leprosy control programmes. Two large-scale field trials of chemotherapy of lepromatous leprosy are to be undertaken, employing one multi-drug regimen. A revised draft protocol for short-term trials of chemotherapy of lepromatous leprosy was adopted, and a search for a suitable trial site launched. Preparation of a protocol for trials of chemotherapy of non-lepromatous leprosy was commissioned. Fifteen applications for research support were reviewed; 4 were new, and 11 were for continued support. Twelve were approved for a total of US$ 256 026.

THELEP: REPORT OF THE NINTH MEETING OF THE STEERING COMMITTEE OF THE SCIENTIFIC WORKING GROUP ON THE CHEMOTHERAPY OF LEPROSY (THELEP). GENEVA 8–10APRIL 1981

Progress in 3 ongoing prevalence surveys of dapsone resistance was reviewed, and a new survey in Cuba was approved. The THELEP Field Trial regimen was reconsidered, and once again found to be cost-effective. Progress in the 12 formal controlled clinical trials was again reviewed, and investigation of cases of jaundice at one of the treatment centres was initiated. Proposals for 2 short-term trials of ethionamide and prothionamide were approved. A search for new compounds possibly active against *Mycobacterium leprae* was initiated, and a workshop on the Ridley-Jopling classification of leprosy was re-scheduled. Twenty-one applications for research support were reviewed; 20 were approved, for a total of US$ 326 353. Finally, plans were made for the next SC meeting, to be held in Rangoon in November 1981, in conjunction with a Scientific meeting to be jointly co-sponsored by the Southeast Asia (SEARO) and Western Pacific (WPRO) Regional Offices of WHO and IMMLEP.

TDR: SPECIAL PROGRAMME FOR RESEARCH AND TRAINING IN TROPICAL DISEASES

We gratefully acknowledge receipt of the following documents:

(1) Report of the IMMLEP Subcommittee Meeting on the Planning of Leprosy Vaccine Trials. TDR/IMMLEP (SUB-TRIALS)/80.3.

(2) Methods used for testing potency of vaccine against *M. leprae* in mice at the WHO Collaborating Centre for reference and research on *M. leprae* by Charles C Shepard, Centre for Disease Control, Atlanta, Georgia 30333, USA. TDR/LEP/PRT/80.1.

Lepr Rev (1981) **52**, 365–366

Field Workers' Forum

ALL AFRICA LEPROSY & REHABILITATION TRAINING CENTRE (ALERT) INTERNATIONAL COURSES PROGRAMME 1982

Dr J Warndorff, Director of Training, has supplied the following details:

Monday 11 January–Saturday 13 March:
Course for Senior Rural Area Supervisors on Clinical Leprosy and Leprosy Control. The course will include 2 weeks of field work.

Monday 12 April–Saturday 8 May:
Course for Medical Officers with emphasis on Clinical Leprosy and Teaching of Leprosy.

Monday 10 May–Saturday 29 May:
Course on Dermatology in the Tropics for Medical Officers, Medical Assistants, Nurses.

Monday 13 September–Saturday 30 October:
Course for Physiotherapists in conjunction with the:

Monday 27 September–Saturday 30 October:
Course for Medical Officers with emphasis on Clinical Leprosy and Leprosy Control. The course will include 1 week of field work.

Apply to ALERT, P.O. Box 165, Addis Ababa, Ethiopia.

SASAKAWA MEMORIAL HEALTH FOUNDATION, JAPAN. REFERENCE AND HEALTH LEARNING MATERIALS FOR LEPROSY. MAY, 1981

Dr Yo Yuasa, Executive Director of SMHF, has kindly supplied information about the following list of materials, some of which may be available free of charge to *bona fide* applicants from individuals and institutions *in East and Southeast Asian countries with which SMHF has working relationships – namely Korea, Taiwan, Philippines, Indonesia, Malaysia, Thailand, Burma and Nepal.* It is important to note the geographic restriction of this offer. Applicants in the countries listed should apply to the Executive Director, Sasakawa Memorial Health Foundation, Sabokaikan Building, 2-7-5 Hirakawa-Cho, Chiyoda-Ku, Tokyo 102, Japan, for full details.

REFERENCE MATERIALS. (Available free from Sasakawa Memorial Health Foundation)

Periodicals:

P-1 *International Journal of Leprosy,* International Leprosy Association. Quarterly
P-2 *Leprosy in India*, Indian Leprosy Association. Quarterly

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P-3 *Excerpta Medica: Leprosy and Related Subjects.* Excerpta Medica on behalf of the Leprosy Documentation Service. 10 issues/year
P-4 *Leprosy Review*, British Leprosy Relief Association. Quarterly
P-5 *WHO Chronicle*, WHO, Geneva. Monthly

WHO Publications (except periodicals):

WHO-1 *A Guide to Leprosy Control*, WHO/Geneva, 1980, pp. 96, Sw.fr 15.00
WHO-2 *Leprosy in Children*, WHO/Geneva, 1976, pp. 28, Sw.fr 9.00
WHO-3 *WHO Expert Committee on Leprosy*, WHO/Geneva, 1977, pp. 48, Sw.fr 6.00

AUDIO VISUAL MATERIALS. (Available from Sasakawa Memorial Health Foundation)

Health Education Films

HEF-1 *The Net*, The Leprosy Mission, 25 min, colour, location India, (English) £170 (approx.)
HEF-2 *Leprosy,* Lepra (British Leprosy Relief Association), 36 min, colour, (English) £330 (approx.)
HEF-3 *Morbus Hansen,* NSL (Netherlands Leprosy Relief Association), 25 min, colour, location Indonesia and Kenya, (English) HFL2,100 (approx.)
HEF-4 *Kusta*, NSL, 27 min, colour, location Indonesia, (English) HFL2,100 (approx.)
HEF-5 *Karibu*, NSL, 31 min, colour, location Kenya, (English) HFL21,100 (approx.)
HEF-6 *Siku Moja*, NSL, 27 min, colour, location Kenya, (Swahili) HFL2,100 (approx.)
HEF-7 *Helping Hands,* NSL, 30 min, colour, location Ethiopia, (English) HFL2,100 (approx.)
HEF-8 *Sarva Mangalam*, NSL, 28 min, colour, location Nepal, (English) HFL2,100 (approx.)
HEF-9 *Armauer Hansen – Discoverer of the Leprosy Bacillus*, Svekon Film, 40 min, colour, (English) US$680 (approx.)
HEF-10 *Toward Eradication of Hansen's Disease*, Sasakawa Memorial Health Foundation, 36 min, colour, location Philippines, Thailand, Korea, (English & Japanese)

Scientific Films

SCF-1 *Leprosy*, Science Service Berlin, 30 min, colour, location Ethiopia etc., (English, German, French, Spanish) DM2,200 (approx.)
SCF-2 *Leprosy – Therapy*, Science Service Berlin, 24 min, colour, location Ethiopia etc, (English, German, French, Spanish) DM1,650 (approx.)
SCF-3 *Leprosy – Rehabilitation,* Science Service Berlin, 24 min, colour, (English, German, French, Spanish) DM1, 650 (approx.)

HEALTH EDUCATION IN LEPROSY THROUGH THE MEDIUM OF WRITTEN PERSONALIZED NARRATIVES. ROBIN GRIGGS. THE UNIVERSITY OF LONDON

Mr David Morley of the Institute of Child Health in London has drawn attention to this study which uses a story, based on real life situations in Burma, as a medium for teaching health care in leprosy. His complete manuscript, which formed the basis of a curriculum option on education through the medium of a second language in the Institute of Education in the Universtiy of London, includes an introduction outlining the rationale of such an approach, which the author considers might be adapted for film, radio, travelling shows/ plays comic strips and traditional books. Further details from Mr R Griggs at 'Blakes', Toot Hill, Near Ongar, Essex, U.K.

Lepr Rev (1981) **52**, 367–369

News and Notes

HIND KUSHT NIVARAN SANGH AND A M G INTERNATIONAL. SOUVENIR CUM PROCEEDINGS OF THE 2ND SEMINAR ON LEPROSY, SEPTEMBER, 1980, AT HYDERABAD, INDIA

We acknowledge with thanks receipt of this 133-page account of an important seminar, the main subject headings being: bacteriological examination, blood groups, chemoprophylaxis, clinical features, dapsone resistance, deformities, differential diagnosis, discharge from control, health education, immunology, integration of leprosy work, leprosy in children, leprosy control and prevention, leprosy and law, leprosy in medical curriculum, national leprosy control programme, nerve in leprosy, polytherapy in leprosy, reactions, rehabilitation, supervision, surgery, transmission, treatment, types of leprosy, urban leprosy work and WHO.
(The address of HKNS is Andhra Pradesh, 3-4-760, Barkatpura, Hyderabad-500 027)

LEPROSY IN CHILDREN BY DR F M NOUSSITOU; NOW AVAILABLE IN ARABIC & PORTUGUESE

Dr H Sansarricq, Chief Medical Officer, Leprosy, Division of Communicable Diseases, WHO, 1211 Geneva, 27, Switzerland, has kindly drawn our attention to the issue of this excellent book in Arabic. It is available from the Distribution and Sales Service of WHO, as above.

Through Amici dei Lebbrosi, 4 Via Borselli, I 40135, Bologna, Italy, it is now also available in Portuguese, under the title *A Lepra na Crianca*.

JOINT ACTION

Published by the Public Relations Division; the German Leprosy Relief Association, India, quarterly; annual subscription 40 paise.

We are late in congratulating those concerned with this publication, which will carry 'news and views on leprosy for the information of the public'. Volume 1, number 1, January–March 1980 carried messages from Dr Sansarricq in Geneva, the Minister of Education and Culture in New Delhi and Herr Kober, the Executive Director of the German Leprosy Relief Association.

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ALERT AND AHRI; ADDIS ABABA, ETHIOPIA; REQUEST FOR BOOKS AND JOURNALS

Mr Bernt Johannessen, Executive Director of ALERT, has written to say that the joint AHRI library would greatly appreciate any of the following:

(1) Standard textbooks on leprosy for the library; previous editions of older books may be more than acceptable.
(2) Old issues (back numbers) of the *International Journal of Leprosy* and *Leprosy Review* (pre-1970).
(3) Any teaching slides with instructional text.
(4) New books on leprosy, recently produced or published.

(It is clearly important to check with Mr Johannessen before dispatching any of the above, since some items may by now have been submitted. Within reason, heavier material might be taken to ALERT by members of the Medical Committee on their yearly or twice yearly visits, from either Oxford, Oslo, USA or Amsterdam; details from this Office. *Editor*)

***MEDICAL TEACHER*. VOLUME 3, NUMBER 3, JULY 1981**

This is a journal for educators in the health sciences, published quarterly by Update Publications Ltd, 33/34 Alfred Place, London WC1E 7DP. This issue contains valuable contributions on the teaching of nurses, the enhancement of teaching skills in medical schools, and the availability of audiovisual material from a centre in the University of Newcastle-upon-Tyne in the U.K.

***AFRICA HEALTH*. VOLUME 3, NUMBER 10, JULY 1981**

A recent issue carried an excellent article on leprosy. The current one includes sections on leishmaniasis and the establishment of a health centre laboratory for a rural population. Although aimed mainly at readers who are concerned with the importation, specification or purchase of medical and hospital supplies and services, this journal carries a great deal of information on medical subjects in Africa generally and is circulated free of charge to qualified readers in a number of African countries. Apply to Africa Health; Enquiry Service, 429 Brighton Road, South Croydon, Surrey CR2 9PS, U.K.

PROGRAMME NATIONAL DE LUTTE CONTRE LA LEPRE. RAPPORT ANNUEL, 1980

We acknowledge with pleasure receipt of this excellent account of activities in the leprosy control programme of Togo for the year 1980. This 24 page document is introduced by Dr A A Edorh, Chief Medical Officer of the National Service for Infectious Diseases and Endemic Diseases. There is also a statistical annex with detailed figures on all aspects of leprosy in Togo.

AHRI; THE ARMAUER HANSEN RESEARCH INSTITUTE, ADDIS ABABA, ETHIOPIA; ANNUAL REPORT FOR 1980

This 34-page report gives a full account of activities in 1980 under the following headings: Armauer Hansen Research Institute (origin and development); personnel; research activities; publications; conference; training; meetings; library; animal house AHRI property; finance.

PRIMARY HEALTH CARE; NATIONAL COUNCIL FOR INTERNATIONAL HEALTH; CONFERENCE ON THE TRAINING AND SUPPORT OF PRIMARY HEALTH CARE WORKERS, WASHINGTON DC, JUNE 1981

Central themes included: (1) training and support of primary health care workers; (2) implementing PHCWs training in times of economic restraint; (3) the practical aspects of training policies and priorities; (4) technical management and supervision of PHCWs; (5) the challenge of adapting programme support to local realities; and (6) the Year 2000; how will we feel?

THE HEISER PROGRAM FOR RESEARCH IN LEPROSY, 1982

We have received details of the usual awards which are available from this Program in the USA; they include Post-doctoral Research Fellowships, Research Grants and Visiting Research Awards. Information may be obtained from: The Heiser Program for Research in Leprosy, 450 East 63rd Street, New York, New York 10021, USA.

Lepr Rev (1981) **52**, 370–371

Book Reviews

Mycobacterial Diseases, by John M Grange. No. 1 of Current Topics in Infection, 1980. London: Edward Arnold Ltd. Price £9.75.

After a general description of the genus *Mycobacterium,* with special reference to the species which are pathogenic to man and/or animals, Dr Granger goes on to describe the immunology of mycobacterial diseases, including the immune spectrum in tuberculosis and leprosy. He rightly stresses the importance of gaining a full understanding of the immune mechanisms in leprosy if an effective vaccine against the disease is to be developed for, as he says, 'any inappropriate interference with the immune response could be disastrous'. However, the statement that 'leprosy is a disease of low infectivity' is not strictly correct in the light of the high incidence of subclinical infection among leprosy contacts; it would be more appropriate to say that the rate of transmission of *M. leprae* is very significantly higher than the disease attack rate.

Clinical manifestations of tuberculosis and leprosy are described, together with their bacteriology, histology and treatment, and a chapter is devoted to other mycobacterial diseases and their therapy, including *M. ulcerans* infection (Buruli ulcer) and *M. marinum* infection (swimming-pool granuloma).

This very readable book of 115 pages contains a wealth of information and will prove of particular value to students, general physicians and research workers. It is illustrated by a dozen black-and-white photographs, and a well-chosen bibliography is provided for those who may wish to delve more deeply into specific aspects of this complex and challenging subject.

WH JOPLING

Laboratory Services at Primary Health Care Level. WHO. LAB/79.1

This WHO publication begins with the following paragraphs:

'This document follows a World Health Assembly Resolution (WHA29.74) adopted in 1976 which requested WHO to . . .''develop a programme of health technology relating to primary health care and rural development as part of the overall primary health care programme. . .''. This technology also refers to applied laboratory science which should be appropriate, inexpensive, acceptable and easily handled by the laboratory personnel working at the peripheral level and in certain cases some of the tests could be carried out by other members of the health team. The laboratories will provide technical support for the preventive, curative and promotive services for both the community and the individual, shaped around the life pattern of the population.

In many developing countries, four echelons might be considered in the organization and structure of primary health care and rural development. In some countries, certain echelons might be combined (particularly 2 and 3) or simply do not exist:

(1) At village level, health care is carried out by a village health worker, often under the monitoring of a village health committee and technically supported by the next echelons of the village services system, aimed at the total well-being of

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the community. This includes the recognition, control and treatment, where possible, of important communicable diseases, child and maternal welfare, nutrition and hygiene.

(2) Health work in a dispensary or sub-health centre, health post or clinic, which may serve several villages and be staffed by a small team of 2 or 3 health workers.

(3) A health centre which provides support services and is part of the referral for the village and dispensary health workers. The health centre could serve a population of 5,000 to 10,000, though in some countries it covers a larger number of people. The staff could be 4 or more working closely together as a team to promote health development in the area served.

(4) The primary level hospital, acts as the next place of referral. It receives patients requiring medical attention including minor surgery and at risk obstetrical cases and provides technical and logistic support to the health centre team. The primary level hospital may also provide training facilities for health-centre teams and village workers. In certain countries, this hospital is more developed and therefore not considered at primary-care level but at intermediate level.'

It goes on to describe the organization of a laboratory in a health centre and to list the essential tests and methods to be used at this level. This is followed by a similar description of laboratory services at a primary level hospital, again with lists of appropriate tests and methods. The final sections deal with collection and dispatch of laboratory specimens and the training of laboratory workers for primary health-care level. There are detailed annexes on equipment, supplementary tests and reagents. The latter include one or two surprising chemicals, at least to workers in the United Kingdom. Thus o-tolidine (pp. 14 and 18) and l-naphthylamine (p. 18) are both known carcinogens; basic fuchsin (pp. 14 and 18), and gentian violet (pp. 14 and 18) are both suspect carcinogens; potassium cyanide (pp. 14 and 18), and sodium arsenite (p. 18) are both schedule 1 poisons, whilst O-toluidine, phenol, phenyl mercuric acetate, sodium azide, sodium nitroprusside (all on p. 18) and thiosemicarbazide (p. 19) are all poisonous in some degree and should be used carefully. The inclusion in this list of O-toluidine is particularly surprising, especially as the method advised on page 8 for the examination of occult blood recommends aminopyrine. Although this document loses no opportunity to stress the importance of training and supervision, the inclusion of some of the above chemicals, under the conditions described, is open to criticism.

AC MCDOUGALL

Lepr Rev (1981) **52**, 372–375

Abstracts

The following are reproduced with our grateful acknowledgement to the Bureau of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT.

4. Therapy

23. PATTYN SR, BOURALDN J, WARNDORFF J, CAP A, SAERENS EJ (1979) **Short course two months' treatment of paucibacillary leprosy with rifampicin. Preliminary results.** *Annales de la Société Belge de Médecine Tropicale* **59** (1), 79–85.

'The possibility of treating paucibacillary leprosy by a short course rifampicin regimen was investigated in a pilot trial in Bujumbura and a controlled trial in Addis Ababa. Rifampicin was administered once weekly in a dose of 900 mg during 8 weeks.

'Clinical improvement continued after the administration of RMP was stopped and no systematic adverse effects associated with the intermittent RMP administration were observed.

The follow-up period was one year. The clinical observation and examination of biopsies give the impression that this short course RMP treatment is not as good as standard dapsone therapy.

Three patients in the RMP group developed neuritis, this was not significantly different when compared with the dapsone group and the neuritis developed after the RMP treatment had been stopped. Continuing observation of the patients is necessary.

[This in an interesting report on a subject of the utmost importance to all engaged in leprosy control, since it is now abundantly clear, from most parts of the world where leprosy is endemic, that patients do not attend for the periods of treatment, many of them extending over several years, which are advised by expert bodies. Short courses of chemotherapy, followed either by stopping drugs altogether plus intensive observation and follow-up, or by maintenance thereafter with dapsone in the order of 50 to 100 mg daily (similarly followed by close observation), are thus of vital interest. In the absence of an *in vitro* culture for the leprosy bacillus and of readily available animal models, including footpad inoculation, the assessment of these short courses must lean heavily on long-continued clinical observation, slit-skin smears, and the histopathological examination of biopsies. Although this trial was originally intended to have a follow-up period of 3 years, the authors stress that circumstances beyond their control (presumably continued fighting in Ethiopia) have led them to report preliminary results; the maximum follow-up for patients in Bujumbura was 69 weeks, and for patients in Addis Ababa, 64 weeks. There is a minor, but unfortunate misprint in Table 1 and paragraph 3 on page 81, where LI (meaning indefinite lepromatous, synonym subpolar lepromatous) should read Idt, meaning Indeterminate. Although this report is neither complete as yet, nor entirely convincing in the matter of clinical assessment, the authors are almost certainly right in one of their main conclusions, namely that '. . . other short course drug regimens may be imagined which, if successful, could dramatically change the strategy of leprosy treatment'].

A C McDougall

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24. VENKATENSAN K, BHARADWAJ VP, GIRDHAR BK (1979) **Effect of ascorbic acid on blood levels of DDS.** *Leprosy in India* **51** (4), 511–14.

'A study was undertaken to probe into the influence of ascorbic acid on the absorption and metabolism of administered DDS in leprosy patients. Vit 'C' supplementation did not generally exhibit any effect on blood levels DDS except in cases of BB and LL where only 8 hrs DDS values showed a statistically significant increase.'

25. GODOH M, SAKAMOTO Y, TSUTSUMI S, FUNAZU T, KOIDE S, NARITA M (1979) **[Trials for chemoprophylaxis of leprosy by DDS; fundamental studies on an artificial DDS-rice]** *Japanese Journal of Leprosy* **48** (1), 1–6 [In Japanese]

'Thinking about a past trial for the improvement of malnutrition by vitamins annexed to rice grains, the artificial rice grains adsorbing DDS and coating with zeinpalmitic acid were prepared.

The fundamental studies on the artificial rice grains were performed by employing ^{14}C-DDS and ^{35}S-DDS. The coating effect to prevent the flowing out of DDS during washing of grains was noticed and the flowing was also not marked in case of lipoluble [liposoluble?] medicament.

The metabolism of DDS annexed to rice grains was compared with that of DDS by rats and man. The result showed the probable absorption of DDS from stomach wall if it is annexed to rice grains.

In the same time, the distribution of DDS to the embryos of rats was examined.

The suitable usage of the artificial DDS-rice was discussed.'

26. GUPTE MD (1979) **Dapsone treatment and deformities—a retrospective study.** *Leprosy in India* **51** (2), 218–235

This paper describes the findings in 2608 patients with various types of leprosy, seen in the Gandhi Memorial Leprosy Foundation, Maharashtra, India, during the years 1963–72.

There are 14 tables which attempt to correlate regularity of attendance with deformity rates, as also the incidence of reactions and deformities in patients who were originally undeformed. The main conclusions are as follows:

(1) Patients having problems like neuritis and deformities and of the types lepromatous and borderline were the ones who tended to be regular clinic attenders.

(2) Lepromatous and Borderline and Polyneuritic types and N3 group were prone to develop deformities.

(3) There seemed to be association between reaction and causation of deformities.

(4) Because of the neurotoxic effect and ability to concentrate in the affected nerves, dapsone might enhance the risk of deformities.

(5) Low deformity rates in N1 and N2 types of nerve involvement reaffirmed the necessity of early diagnosis of leprosy.

[Few would doubt that adverse reactions, whether of cell-mediated or humoral type, may cause nerve damage, especially if not diagnosed early and treated with steroids or other appropriate drugs. Conclusion (4) above, however, and the main paragraph in the Discussion, imply that the author believes dapsone may have a direct neurotoxic effect on nerves, causing a peripheral neuropathy. He lists most of the publications in the literature where this neuropathic effect has been observed, following the use of dapsone in various conditions other than leprosy. But in fact, the total number of cases is remarkably small and it is a striking fact that of the many thousands of people who have received dapsone for the treatment of dermatitis herpetiformis, often in doses much higher than those used for the treatment of leprosy, and over a period of many years, few have been recorded as developing a neuropathy attributable to the drug.]

A C McDougall

27. GIDOH M, TSUTSUMI S, FUNAZU T, KOIDE S, NARITA M (1979) **On characteristic antiinflammatory effects of several antileprosy drugs.** *Japanese Journal of Leprosy* **48** (1), 7–18

The authors made use of several procedures now available in an attempt to determine and in some cases to quantify the anti-inflammatory action—long-suspected but not demonstrated precisely—of several drugs used in the treatment of leprosy, including drugs used empirically for their alleged anti-inflammatory action. In addition to the carrageen-induced acute oedema observed in rats, they employed such investigations as: Pontamine Sky Blue skin diffusion, the carboxymethyl cellulose pouch, adjuvant-induced arthritis etc.

By comparing and contrasting the diverse results obtained with these various methods of assessing the anti-inflammatory action of several standard drugs used in leprosy, the authors were able to demonstrate a strong action in the case of dapsone in some tests, but weak in other tests; similarly, with clofazimine and thalidomide, the anti-inflammatory effect seemed to vary with the method used for the investigation.

Obviously, more work needs to be done on the suspected anti-inflammatory action of anti leprosy drugs, since the mechanisms may vary from drug to drug, and no single test will show positive results with all drugs having somewhat similar clinical results.

S G Browne

28. MEHTA JM, NIMBALKAR ST, THALAYAN, K (1979) **A new approach in the relief of pain of leprous neuritis.** *Leprosy in India* **51** (4), 459–464

'Transcutaneous Nerve Stimulation (TNS) has been known since the last several decades to relieve pain in many conditions. For the first time it was used in the treatment of the severe and agonizing pain caused by leprous neuritis with highly beneficial results without producing any side effects. This study was made on 40 patients, and in the majority of the cases there was total relief of pain with one application of a few hours' duration. This encouraging result has led the authors to the conclusion that TNS could be a useful tool in a hospital where leprosy patients are treated.'

29. NIGAM P, SIDDIQUE MIA, PANDEY NR, AWASTHI KN, SRIWASTAVA RN (1979) **Irregularity of treatment in leprosy patients: its magnitude and causes.** *Leprosy in India* **51** (4), 521–532

'Irregularity of treatment has been proved to be a general problem and there is scanty information about the reasons for the irregularity. 1970 patients were studied to determine the reasons for irregularity by regularity in attending the clinic as well as by dapsone/creatinine ratio in urine. 52% of the patients were regularly attending the clinic and thereby can be said to be regular in treatment whereas dapsone/creatinine ratio in urine showed that only 47.7% were actually regular in taking the drugs. Therefore, regularity of attendance is no guarantee of regularity of dosage. The patients who were irregular in treatment were interviewed to find out the reasons behind their irregularity. It was noticed that most of them (60.6%) attended the clinic for dapsone treatment but could not come regularly for valid reasons e.g., economic reasons (29.9%), no time to attend clinic (12.5%), ignorance (22.9%), social stigma etc. (1.2%).

'Irregularity in treatment can possibly be avoided by providing them extra amount of drug when need arises, means to contact patients and creating faith in them towards the treatment, educative talks and providing jobs in sheltered workshop till they can be rehabilitated in the society.'

5. Epidemiology

30. ABREU A, WERTHEIN LJ, RUIZ DE DE ZARATE S (1978) Doce años de

vacunación BCG y lepra infantil en Cuba. **[12-year vaccination with BCG vaccine and infantile leprosy in Cuba]** *Revista Cubana de Higiene y Epidemiología* **16** (1), 63–72 English summary

The authors review the effects of BCG vaccination on the incidence of child leprosy in Cuba during the 12-year period 1965 to 1976. Since 1963 every infant born in an institution has been vaccinated with BCG vaccine and revaccinated at 5 years until 1970 but thereafter at approximately 10 years after the first vaccination. 133 (73.9%) of the 180 cases of leprosy occurring in children aged under 15 years during the duodecennium were studied. 60 (45.1%) of these children had been vaccinated while 73 (54.9%) were unvaccinated. 66 members of the group were males and 67 were females. Bacteriological examination was positive in 31 patients (23.3%) but negative in the remaining 102 (76.7%) of those found clinically positive. Anaesthetic patches were observed in 102 cases and cutaneous nodules in 14 cases. 95 children (71.4%) had been in contact with leprosy patients but in 38 others (28.6%) no contact was traceable. There were 28 cases of lepromatous leprosy (21.0%), 4 cases of dimorphous leprosy (3.0%), 56 cases of indeterminate leprosy (42.1%) and 45 cases of tuberculoid leprosy (33.9%). 24 of the cases of lepromatous disease (85.7%) were among unvaccinated children, but there were only 4 in the vaccinated group, which is interpreted as being due to the effect of the BCG vaccination.

Notified cases of tuberculosis in children aged under 15 years diminished during the period in question from 492 in 1965 to 37 in 1975. No new case of leprosy has been reported in children born since 1970. Studies continue.

There are 7 tables, 3 histograms and 3 sector diagrams.

J M Watson

Leprosy Documentation Service, Amsterdam

ILEP and its Medical Commission are very concerned about the shortage of teaching material of all kinds appropriate for the use of health personnel in the Third World.

Many ILEP Member-Associations are devoting substantial funds to the publication of teaching booklets on leprosy, to the provision of audio-visual equipment and material and to regular subsidies to the various leprosy journals. Probably, however, other teaching material is being produced outside ILEP and, in order to provide information about what is available in various languages world-wide, a leprosy documentation service has been established in Amsterdam.

At its recent Meeting in Copenhagen, on 12 June 1981, the ILEP Medical Commission requested that copies of all teaching material in whatever language should be sent to this Centre. The address is:

The Leprosy Documentation Service
Royal Tropical Institute
63 Mauritskade
1092 AD AMSTERDAM.

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Antileprosy drug with anti-inflammatory[1] properties

effective in the prevention[2] and treatment[3] of lepra (ENL) reactions

indicated as a part of combined therapy for the prevention and treatment of dapsone resistance in lepromatous and borderline leprosy[4].

LAM 7479 e

1. Browne, S. G.: Lepr. Rev. *37*, 141 (1966)
2. Azulay et al.: Lepr. Rev. *46* (Suppl.) 99 (1975)
3. Schulz, E. J.: Lepr. Rev. *42*, 178 (1972)
4. Yawalkar, S. J., & Vischer, W. A.: Lepr. Rev. *50*, 135 (1979)