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Editorial

LUCIO'S PHENOMENON: AN OVERVIEW

This paper is intended for leprologists outside of North and Central America who have had little or, more likely, no clinical experience with Lucio's phenomenon. The purpose of this paper is to delineate the features which establish Lucio's phenomenon as a distinctive reactional state. The data base for this paper is the experience with Lucio's phenomenon at the University of Southern California/Los Angeles County Medical Center. This experience has been more elaborately detailed in three other publications: a retrospective chart study (Rea and Levan, 1978), a report of an immunologic investigation (Quismorio *et al.,* 1978), and a report of a comparative histopathological study (Rea and Ridley, to be published). For further reading in English the paper of Latapi and Zamora (1948) and the monograph by Frenken (1963) are particularly recommended.

Historical Background

In 1852 Lucio and Alvarez described a necrotizing skin reaction complicating the course of non-nodular leprosy. Although this finding was confirmed by their contemporaries, knowledge of the reaction was lost until rediscovered by Latapi and his co-workers. Latapi and co-workers' contributions included recognition that histopathologically the necrotizing reaction was a vasculitis and that clinically the reaction was restricted to patients with a form of diffuse, non-nodular lepromatous leprosy. These investigators named the necrotizing reaction Lucio's phenomenon eponymically and erythema necroticans descriptively, and designated the form of diffuse lepromatous leprosy as pure and primitive diffuse lepromatous (PPDL) (Lapati and Zamora, 1948).

Definition and Prevalence

Any patient who had a clinically characteristic haemorrhagic infarct and diffuse, non-nodular lepromatous leprosy was considered as having Lucio's phenomenon. Eleven such individuals have been clinic patients in the past 9 years, approximately one out of 6 lepromatous patients.

The Anlage, PPDL

In this series patients with PPDL were truly without nodules. In 2 of our patients the earlobes were definitely thickened and in one, the only atypical

case in the 11 patients, the skin of the forehead was folded, suggesting leonine faces, but without loss of normal skin markings. Total alopecia of eyebrows (and often of the eyelashes) was present in all. Acral distal symmetrical anaesthesia of some degree was also present in all. Trophic changes, attributable to sensory loss, were present in 3 patients, but motor palsies as evidenced by contractures of fingers, interosseous atrophy, or weakness were absent. Destructive rhinitis was present in all and septal perforation common. In contrast, only one patient demonstrated beading of a corneal nerve, the same atypical patient. A profound telangectasia of the face was present in one patient.

The Reaction, Lucio's Phenomenon

The earliest observed lesion was a slightly indurated light blue plaque with an erythematous halo. Lesions soon evolved into typical haemorrhagic infarcts with or without bulla formation (Fig. 1). Lesions were painful but not tender, and arose in crops on the extremities. Large lesions below the knees frequently ulcerated. Small lesions below the knees and most other lesions elsewhere crusted, without overt ulcer formation but healed with scarring. The typical well-developed haemorrhagic infarct had a serrated border, with the convex margin lying within the lesion. Lesions ranged from 2 mm to 5 cm in diameter.

In this series, the initial onset of Lucio's phenomenon has not been observed in patients on dapsone. Three of the 11 patients had had dapsone prior to the onset of Lucio's phenomenon, but in all of these 3 dapsone had been stopped for at least 6 months before developing this reaction.

SYSTEMIC SIGNS AND SYMPTOMS

Fever was not associated with Lucio's phenomenon in these 11 patients, in marked contrast to patients with ENL (Rea and Levan, 1975). Arthritis was present in one patient, and nephritis in another, but it is uncertain if these changes were related to Lucio's phenomenon or even to lepromatous leprosy. Splenomegaly was present in 3 patients. Orchitis and iritis were not present.

LABORATORY FINDINGS

None of the 11 patients with Lucio's phenomenon had a leukocytosis or absolute neutrophilia, in contrast to patients with ENL (Rea and Levan, 1975).

Routine laboratory abnormalities which did not differ greatly from those of other lepromatous patients included a mild normochromic, normocytic anaemia, high erythrocyte sedimentation rate, hypergammaglobulinemia and positive cardio-lipin antigen tests for syphilis.

HISTOLOGICAL CHANGES

Early lesions of Lucio's phenomenon showed ischaemic epidermal necrosis, necrosis in the walls of superficial vessels of the dermis, and endothelial proliferation in the medium-sized vessels of the mid-dermis (Figs 2 and 3).

Abundant AFB were found in endothelial cells, both in proliferating and in apparently normal cells (Fig. 4). These large numbers of AFB in endothelial

cells have been emphasized by others (Obermayer *et al.*, 1949; Derbes *et al.*, 1960; Donner and Shively, 1967; Kramarsky *et al.*, 1968).

Granuloma development in the dermis was variable, particularly in the superficial dermis; in two cases no perivascular granulomas were found.

Using the system of Ridley (1974) patients with Lucio's phenomenon were classified as lepromatous (LL). Because of the inflammatory infiltrate associated with the Lucio reaction, it was not possible to distinguish between polar (LLp) and subpolar (LLs) disease.

IMMUNOLOGIC RESPONSES

No immediate responsivity to lepromin was found in the four patients tested, the only finding at variance with the report of Latapi and Zamora (1948). (The variable composition of lepromin is a likely explanation for this difference.) No Mitsuta type of lepromin responsivity was found.

Tuberculin responsivity did not differ from that of controls, but dinitrofluorobenzene and dinitrochlorobenzene responsivity was slightly (statistically insignificantly) diminished.

Direct immunofluorescence studies of skin lesions demonstrated immunoglobulin and complement components in vessel walls (Quismorio *et al.*, 1978), changes not demonstrable in patients with ENL (Rea *et al.*, 1977).

Evidence for circulating immune complexes in the serum of patients with Lucio's phenomenon included positive Raji cell tests, positive latex fixation tests and cryoglobulinaemia, up to 37 mg/100 ml. The cryoglobulins were of the mixed type, consisting of IgG, IgM, IgA and complement components.

THERAPEUTIC RESPONSES

Of the 10 patients observed for 3 months or more, in 7 new lesions of Lucio's phenomenon ceased in association with dapsone as the sole therapeutic agent. Three patients continued to have new lesions while on dapsone; none of these 3 remitted in association with thalidomide therapy, but in each case new lesions ceased within one week of beginning rifampin.

Ulcerated lesions began to heal within 6 weeks of beginning antilepromatous chemotherapy and were completely re-epithelized by 6 months; only bland topical therapy was used.

Perspectives

Lucio's phenomenon is a distinctive reactional state as judged by clinical, histopathological and therapeutic criteria. The reaction occurs in patients with a variant of lepromatous leprosy, PPDL. Circulating immune complexes are associated with Lucio's phenomenon and may be important in its pathogenesis.

The restriction of Lucio's phenomenon to patients with PPDL can be partially understood by hypothesizing that these patients have a singularly deficient defence mechanism (Rea and Ridley, to be published). Thus this nadir of resistance permits the replication of *M. leprae* in endothelial cells, enhancing the exposure of bacterial antigen to circulating antibody, eventually resulting in

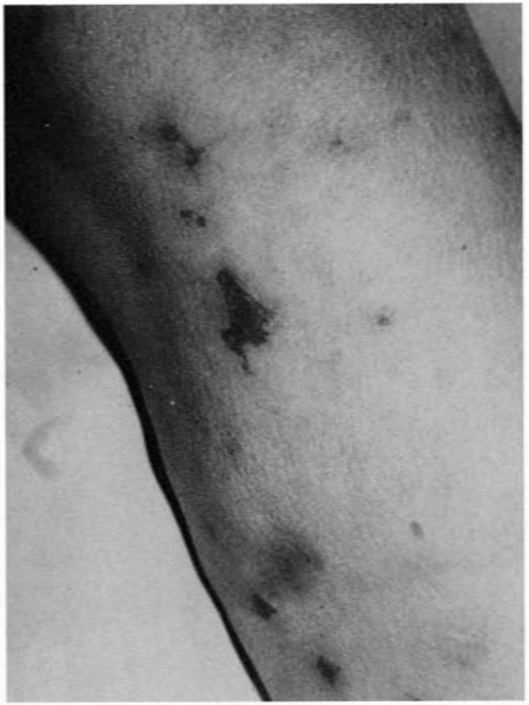

Fig. 1. Well developed haemorrhagic lesions of the Lucio reaction. Note the variation in size and the serrated margins.

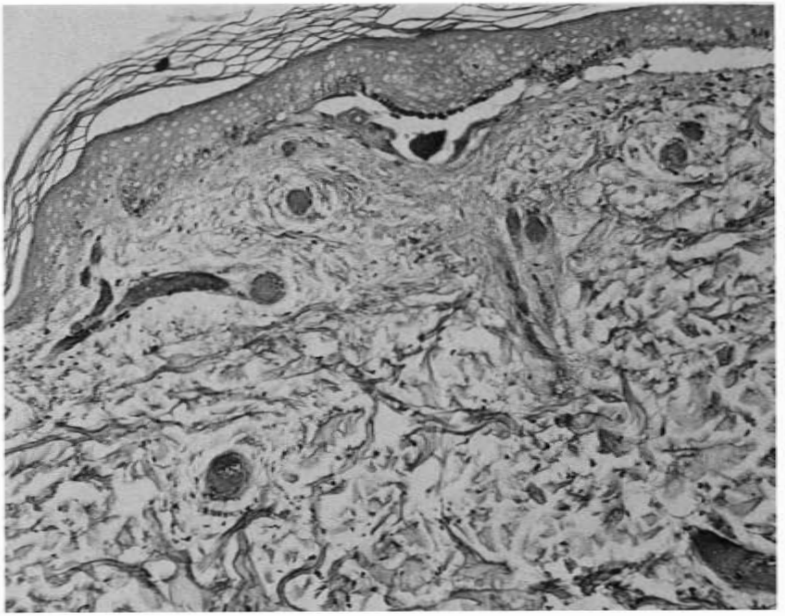

Fig. 2. Ischaemic epidermal necrosis and necrosis of vessel walls is demonstrated by loss of nuclear detail. Note the intense passive congestion of the necrotic vessels. Haematoxylin and eosin. × 150.

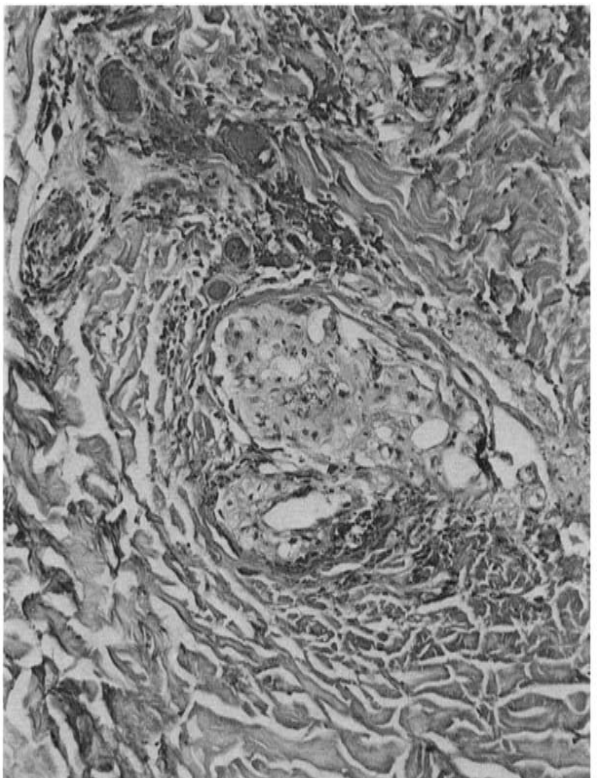

Fig. 3. Well developed endothelial proliferation in a mid-dermal vessel. Note the sparse inflammatory infiltrate and the absence of granuloma development. Haematoxylin and eosin. × 150.

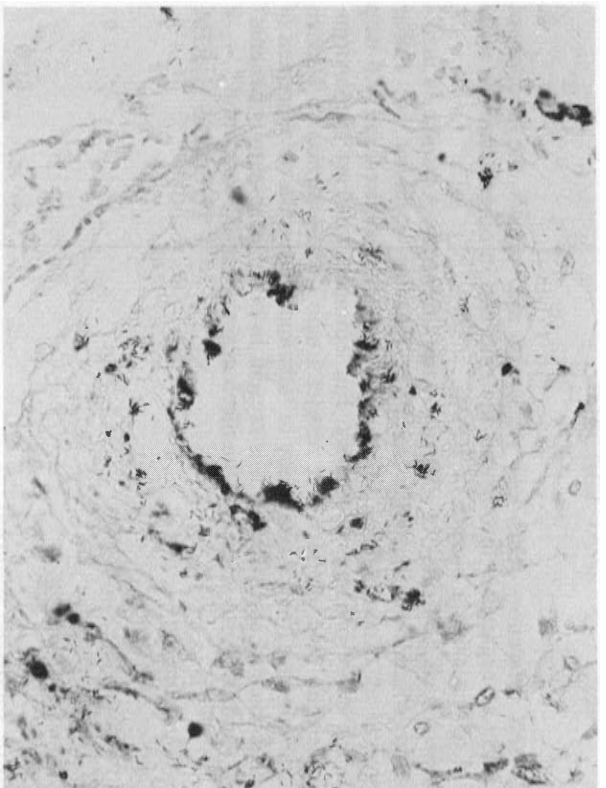

Fig. 4. Abundant AFB in endothelial cells of a vessel which appeared to be normal on routine section. Fite-Faraco. × 300.

vasculitis and infarction. This low resistance also allows the unopposed dissemination of organisms throughout the skin and in other tissues as well, giving rise to the clinical picture of PPDL.

For leprologists outside of Mexico and Central America, Lucio's phenomenon should not be regarded as a faraway curiosity but rather approached as an experiment of nature, one that when understood will help illuminate the entire problem of leprosy. For example, what are the environmental or genetic determinants that restrict Lucio's phenomenon to Mexico and Central America? What deficiency in resistance allows the development of Lucio's phenomenon and PPDL but is present in other lepromatous patients? Why do no nodules form or what is the mechanism of nodule formation?

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Antibody Activity Against *Mycobacterium leprae* Antigen 7 in Leprosy: Studies on Variation in Antibody Content Throughout the Spectrum and on the Effect of DDS Treatment and Relapse in BT Leprosy

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Antibodies against *Mycobacterium leprae* antigen 7 were determined by a specific radioimmunoassay. The median value of 4 groups of patients decreased gradually from the lepromatous to the tuberculoid end of the spectrum, but there was a striking variation between the antibody content of individual sera in each group. Prolonged DDS treatment led to only a moderate decline of this antibody activity in lepromatous leprosy. In borderline tuberculoid leprosy, DDS treatment led to a marked decrease in antibody activity and a relapse is associated with renewed synthesis and increased antibody content.

Introduction

Research into the cellular immunity in leprosy has had major emphasis during the past few years (Myrvang *et al.,* 1973; Bjune *et al.,* 1976). Humoral immunity has also been studied, but to a lesser extent. Until recently, sensitive methods have not been applied to evaluate changes in its parameters during long term studies in leprosy.

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Rees *et al.* (1965) found a gradual fall in the amount of precipitating antibodies in lepromatous patients during DDS treatment. Melsom *et al.* (1978) used a specific radioimmunoassay for demonstration and quantitation of antibodies against *Mycobacterium leprae* antigen 7 and demonstrated a slight decline in the antibody activity in sera from lepromatous patients during the first year of DDS treatment. They noted that the fall in the antibody activity was small and contributed this to the enormous amount of antigen present in these lepromatous patients.

This paper describes our studies on antibodies against *M. leprae* antigen 7 throughout the clinical spectrum of leprosy. The effect of prolonged treatment with DDS was investigated in groups of patients with borderline tuberculoid (BT) leprosy with the intention of exploring whether changes in antibody activity against *M. leprae* antigen 7 could be used as an indicator of the effect of treatment or of relapse in tuberculoid leprosy.

Materials and Methods

Sera were obtained from patients attending the Addis Ababa Leprosy Hospital. The patients were classified clinically and in most cases histologically according to the Ridley Jopling scale (1966). For studies of antibody activity throughout the spectrum, sera were obtained from patients who were untreated or had been treated with DDS for less than half a year. The patients were divided into 4 groups; the LL group included patients with polar and subpolar lepromatous leprosy, the BT group included patients with BT and BT/TT leprosy.

The patients who were under treatment received DDS in doses of 50–100 mg daily.

To study the effect of prolonged DDS treatment in lepromatous leprosy, sera were obtained from 16 patients who had been treated with DDS for at least 10 years and whose skin smears had been negative for at least 5 years. Sera from 17 untreated lepromatous patients were tested for comparison.

To study the effect of DDS treatment in BT leprosy, antibody activity was determined in sera from groups of individuals. The control group consisted of sera from 18 patients with newly diagnosed BT leprosy. Sera were also obtained from 13 BT patients treated for half a year, 17 treated for 1 year, 11 treated for 2 years, and from 27 patients treated for 3 years or more. All these patients received DDS at the time the sera were obtained.

Another group of 7 patients had been "released from control" (RFC) which means that their disease had been considered to be cured after DDS treatment for at least 5–6 years, and they subsequently had no DDS medication for at least 2 years. The last group of 14 sera was obtained from BT patients released from control, but with clinically suspected or histologically proven relapses.

The sera were stored at −25°C in order to be tested as a group towards the same labelled *M. leprae* antigen 7 preparation. The preparation and labelling of *M. leprae* antigen 7 and the radioimmunoassay were performed as described previously by Melsom *et al.* (1978). All sera were tested in dilutions 10^{-3} and

10^{-4}. Comparison between groups gave the same overall results when these two dilutions were used. In the BT group, many sera from untreated patients gave low values at dilution 10^{-4}; this dilution was thus less suitable for demonstration of decrease in antibody activity in BT patients. In lepromatous leprosy, however, many values are very high at dilution 10^{-3}. In these figures, the findings at dilution 10^{-4} are therefore recorded for characterization of antibody activity throughout the spectrum and in lepromatous leprosy, whereas 10^{-3} is used for illustrating the effect of DDS treatment in tuberculoid leprosy. All values are given as mean values of double tests. To permit comparison between tests on different days, an internal standard was used and the activity expressed as radioactivity bound to staphylococci in per cent of the maximum binding activity by a reference serum pool containing strong anti-*M. leprae* antigen 7 activity.

The Wilcoxon test for two samples was used for calculation of statistical significance of the differences between groups of sera.

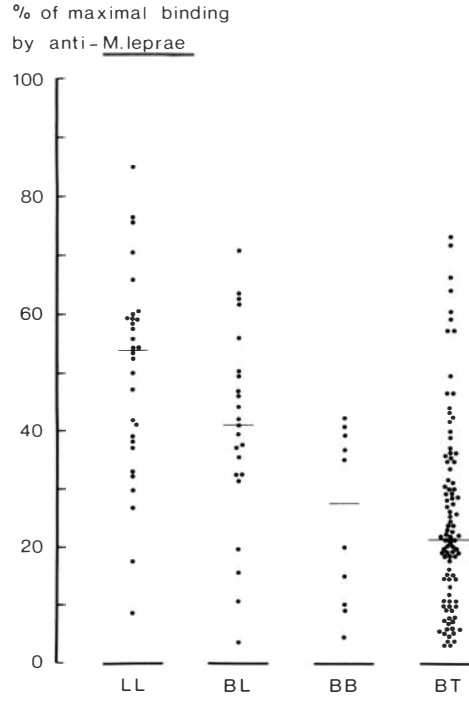

Fig. 1. Antibodies against *M. leprae* antigen 7 throughout the clinical spectrum of leprosy. Each point represents one patient. The activity is shown as binding of labelled antigen by serum diluted 10^{-4} and expressed as per cent of maximal binding by anti-*M. leprae*. The horizontal bars show median values in all figures.

Results

Figure 1 shows anti-*M. leprae* antigen 7 activity in sera from patients throughout the clinical spectrum of leprosy. Two findings are apparent: the median value decreases gradually from the lepromatous to the tuberculoid end of the spectrum, and there is a striking variation between the antibody activity of individual sera within each of the four groups of patients. These findings confirm and extend our previous observations (Harboe *et al.,* 1977; Melsom *et al.,* 1978).

Analysis of the case records of the patients in the BT group showed that the antibody content was not significantly different in groups separated on the basis of sex, age and duration of disease. Neither did it appear to be correlated with the presence or absence of reaction, nor with the response to sonicated or whole *M. leprae* in the lymphocyte transformation test. Further data and analyses are needed to see whether there is a correlation with severity of the disease, e.g. as graded by a combined measure of bacillary content and extent of lesions.

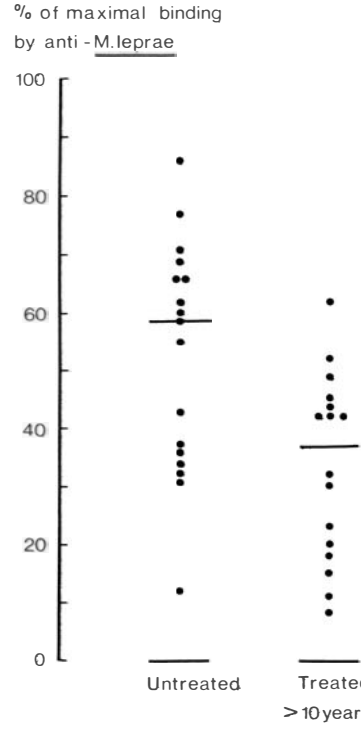

Fig. 2. Effect of prolonged DDS treatment on antibodies against *M. leprae* antigen 7 in lepromatous leprosy. Each point shows the activity in serum from one patient diluted 10^{-4}.

Figure 2 shows the findings in the two groups of patients with lepromatous leprosy. The median value at dilution 10^{-4} in the group of untreated patients is 59%, with again a striking variation in the antibody content of the individual sera. In the group treated with DDS for over 10 years and with negative skin smears for at least 5 years, the antibody activity was lower, with a median value of 37%. There was also a wide scatter between the individual sera in this group. The difference between the two groups is statistically significant ($P<0.005$). At dilution 10^{-3}, the median values were 87% and 75% respectively. The latter value is virtually the same as the median value of the group of untreated BT leprosy patients (74%), shown in the extreme left column of Fig. 3.

Figure 3 shows the findings in the various groups of borderline tuberculoid (BT) leprosy, each point representing the activity in the serum from one patient diluted 10^{-3}. The median value in the untreated group is 74% and there is a striking variation in antibody content in individual sera. The same variation is

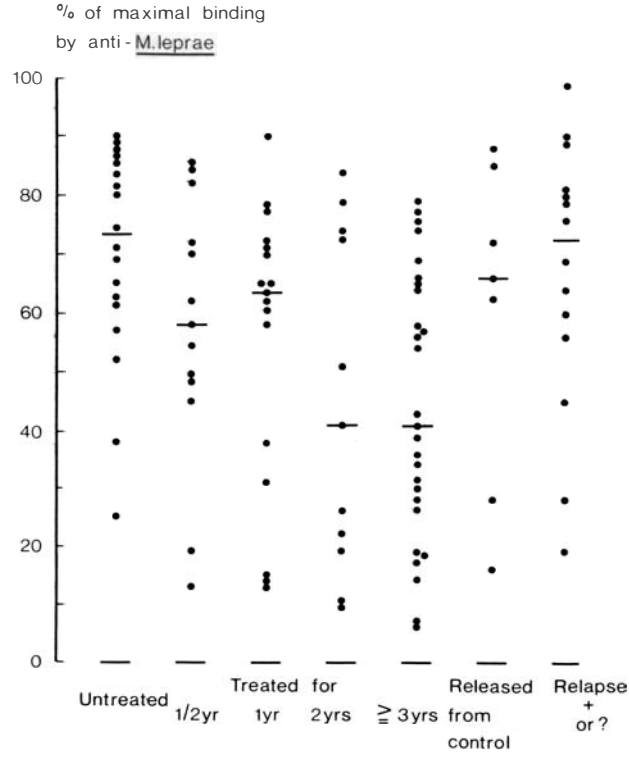

Fig. 3. Effect of DDS treatment and relapse on antibodies against *M. leprae* antigen 7 in borderline tuberculoid (BT) leprosy. Each point shows the activity in serum from one patient diluted 10^{-3}.

evident in the other groups, but the median value decreased markedly during DDS treatment to 41% in the groups who had been treated for 2 years and 3 years or more. The difference between the untreated group and the group treated for 3 years or more is statistically significant ($P<0.005$). The median value of the group of RFC patients is higher, but the number of sera tested is small. The extreme right column shows the findings in sera from 14 patients released from control after prolonged DDS treatment, but who were seen at the hospital with a clinically suspected or histologically proven relapse. The antibody content varied markedly also within this group, but the median value was virtually identical to the untreated group. The difference between the group treated for 3 years or more and the group with relapse is statistically significant ($P < 0.005$).

Discussion

When the median values of distinct groups of patients are compared, there is a gradual decrease in antibody content against *M. leprae* antigen 7 from the lepromatous to the tuberculoid end of the leprosy spectrum (see Fig. 1). Within each group of patients, however, there was a striking variation in antibody content, both when distinct groups in the spectrum were tested and within groups of BT patients treated for different periods. These findings confirm and extend the previous findings of Melsom *et al.* (1978) and Harboe *et al.* (1977) who used a radioimmunoassay with labelled BCG antigen 60 which cross-reacts with *M. leprae* antigen 7. The reason for this wide variation in antibody content within groups of patients with similar classifications based on clinical and histological criteria has not been established. It may be noted that studies of cellular immunity have provided similar results; the mean response in the lymphocyte transformation test, with *M. leprae* as the stimulating antigen, decreased continuously from the tuberculoid to the lepromatous end of the spectrum, but there was a wide variation within each of the groups close to the tuberculoid end (Myrvang *et al.,* 1973).

A slight fall in antibody activity during DDS treatment of lepromatous leprosy was demonstrated by Rees *et al.* (1965) and Melsom *et al.* (1978). That the fall over a 10 year period or more is not more marked is indeed striking (see Fig. 1). In fact, we found that the median value of lepromatous leprosy patients treated for more than 10 years and with negative skin smears for more than 5 years was the same as for untreated BT patients. This can probably not be explained only on the basis of stimulation by cross-reacting antigens present in environmental mycobacteria. Since antibody production continues to be so high, a significant stimulus should be looked for and probably comes from persisting *M. leprae* in these lepromatous patients. Persisting, viable *M. leprae* have been demonstrated in such cases by Waters *et al.* (1974). Krieg and Meyers (1978) studied serial biopsy specimens from lepromatous leprosy patients during treatment. With effective chemotherapy, the bacilli became granular, and eventually lost their acid-fastness completely. When comparable sections, which contained no acid-fast bacilli, were stained

by Gomori's methenamine silver technique, large numbers of bacilli were frequently detected. They concluded that these persisting carcases are probably a continuing source of *M. leprae* antigens long after the patients are considered bacteriologically negative by routine studies of skin smears. Another source of *M. leprae* antigen which cannot be ruled out is that a number of the lepromatous patients may harbour DDS-resistant bacilli. In Ethiopia, 3% of these patients have developed DDS resistance each year during the last 4 years (Pearson *et al.*, 1977).

In tuberculoid leprosy the bacillary load is much less, and it could be expected that effective DDS treatment together with the ability of the tuberculoid patient to dispose of the bacilli might lead to elimination of *M. leprae* antigen. This assumption seems to be confirmed by our results, showing a marked fall in anti-*M. leprae* antigen 7 activity during the first 3–4 years of DDS treatment. The possibility that DDS, as such, is responsible for the decrease in antibody content, must also be considered. However, we consider this explanation improbable. In DDS-treated lepromatous patients, the decrease occurs very slowly, and a high antibody content is seen in many patients even after more than 10 years of DDS treatment. In tuberculoid leprosy the variation between individual patients in the groups is as marked after 3 years of DDS treatment as in untreated patients, and this would not be expected if DDS had a marked suppressive effect on antibody production against *M. leprae* antigen 7.

The demonstration of increased antibody content in the group of patients with suspected or proven relapse is important since it indicates that we may obtain a useful immunological indicator of relapse in tuberculoid leprosy. This is particularly valuable since criteria for effect of treatment and relapse are few in these patients with little or no detectable acid-fast bacilli in the skin lesions.

In relapse, with an increasing number of bacilli, increased antigenic content in the lesions is probably a very potent stimulus for antibody formation. These observations indicate that the occurrence of persisting *M. leprae* should not only be considered in lepromatous leprosy, but also in tuberculoid patients. Their number may be low, but they must be present as shown by the high relapse rate found by Touw-Langendijk and Naafs (1979) among borderline tuberculoid leprosy patients in Ethiopia, especially in the first 2 years after "release from control". It may be assumed that many BT patients who are considered to be clinically cured after DDS treatment and are released from control may harbour viable *M. leprae* which in most instances are adequately controlled by the host's immune system. If this fails, the infection will be reactivated. Duncan (1977) found an increased relapse rate after delivery in BT female patients who were released from control before pregnancy. This indicates that the persisting, previously dormant, bacilli start to multiply during pregnancy due to insufficient control by the immune system. This is analogous with endogeneous reactivation of tuberculosis (Ustvedt, 1947; Stead, 1965). A few of our patients may be DDS resistant since some of them who were released from control and then restarted on DDS treatment did not respond adequately, i.e. the disease was not arrested within a year (Naafs, unpublished observations).

In this study, groups of patients, treated for different periods, were compared. Additional studies are now being carried out, in which blood samples are obtained from individual BT patients at regular intervals during DDS treatment to see if there is a gradual and regular fall in antibody content in patients who start with a high antibody concentration and respond clinically to treatment with DDS. In addition, serum is taken from BT patients when DDS treatment is terminated and stored at –25°C. New samples will be taken at a later date to permit simultaneous testing of the serum obtained at termination of treatment and later samples, to see whether an increased antibody content in individual patients is correlated with other criteria for relapse.

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Relapses in Leprosy after Release from Control

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In 1974, 678 patients, originally classified as suffering from various types of leprosy from LL to TT, were released from control. During the next 3 years, 105 of them reported back on their own accord, with evidence of relapse which was confirmed by clinical, bacteriological and electrophysiological observations. During this period the overall relapse rate was 15%, but patients in the LL/BL group, the indeterminate group, and the BT group treated for less than 5 years, had a relapse rate of over 30%. Reasons for these disconcertingly high figures are discussed and a plea is made for the collection of more data on relapse rates in similar groups of patients from different countries, in order to revise the criteria for releasing patients from treatment.

Introduction

Since the introduction of dapsone in the treatment of leprosy, both the dose and duration of treatment have changed considerably. In the early years of treatment dapsone was stopped immediately when a state of inactivity was achieved. However, a large relapse rate was encountered (Erickson, 1950; Rodriguez, 1958) and it soon became evident that even after clinical arrest of the disease continuation of treatment was necessary (Cochrane and Davey, 1964), the duration of treatment after inactivity being dependent on the original classification of the patient.

At present (1977) WHO continues to advise treatment for tuberculoid patients at least $1\frac{1}{2}$ years after inactivity, for indeterminate patients, 3 years after inactivity, and for borderline-lepromatous (BL) and lepromatous cases, 10 years after this state is achieved, or maybe even better on a life-time basis in the last two categories. Dharmendra (1976) has reviewed the important and difficult matter of length of treatment after inactivity, with conclusions which are similar in principle.

In this study we checked the clinical records of 678 patients suffering from various forms of leprosy, who were released from control (RFC) in 1974. The number of relapses in the following 3 years, the cause, and the seriousness of the relapses are studied.

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Patients and Methods

Clinical records of patients who were released from control in 1974 were reviewed. The original classification according to Ridley and Jopling (1966), biopsy results and skin smears were recorded. Dapsone treatment and dose were noted. Before 1974, patients were usually treated with 300 mg DDS in a single weekly dose, this being gradually achieved over a period of 3–6 months. When a reaction occurred, or when a patient defaulted for a longer or shorter period, the treatment was initiated again with low doses.

During their treatment period these patients, all living in Addis Ababa, attended regularly, and every half year their progress was recorded in the clinical records. In 1974, 678 of them were released from control and dapsone was stopped. After RFC there was no regular follow-up of the patients, but those who suspected that their disease had come back, reported on their own initiative to the hospital. The method of detection and confirmation of relapse are shown in Table 1.

TABLE 1

Signs of relapse	Method of detection
(1) New skin lesions	Clinical examination and biopsy
(2) New numbness of extremities	Sensory testing
(3) New paralysis	Voluntary muscle testing
(4) Tenderness of nerves	Clinical examination and electromyography
(5) Presence of leprosy bacilli	Skin smears

Results

From the 678 patients who were RFC in 1974, 105 patients reported with proven signs of relapse. Many others have been seen with general complaints including fear of relapse. Of the 105 patients, many had to report more than once before relapse could be confirmed.

Table 2 presents the relapse rate according to the original classification. It can be seen that 3 groups especially have a very high relapse rate in this 3-year period: the BL/LL group, the indeterminate group and the BT group treated for less than 5 years, have a relapse rate of over 30%. In the other groups the relapse rate is lower than a more or less acceptable 15%.

A large number of patients came with new nerve involvement as the first sign of relapse. Figure 1 shows the cumulative number of relapsed patients according to the time after RFC, and the cumulative number of patients who relapsed with nerve damage.

This figure shows: (1) that from the 105 patients who relapsed, 48 patients (46%) did so with new nerve damage: anaesthesia, palsy and neuritis; (2) year by year, the relative number of patients relapsing with nerve damage is 40% of

TABLE 2

Classification, number and percentage of relapses in 105 patients reporting back within 3 years of release from control (RFC)

Classification	Number of patients	Relapses	
		Number	Percentage
TT, treated for at least 1½ years	239	33	14%
BT, treated for at least 5 years	204	31	15%
BT, treated for less than 5 years	50	14	28%
BL/LL, treated for at least 10 years after inactivity	37	12	32%
Indete	27	8	30%
Classification not known; treated for more than 15 years	121	7	6%
TOTAL	678	105	15%

the total number of relapsed patients; (3) the majority of the patients relapse within 2 years after RFC, but relapses can be expected for a much longer period.

Discussion

Within 3 years, 15% of the patients RFC came back to the hospital with signs of active leprosy. This relapse rate is slightly higher than reported by other authors (Browne, 1965; Kandaswamy, 1968; Ramu and Ramanujam,

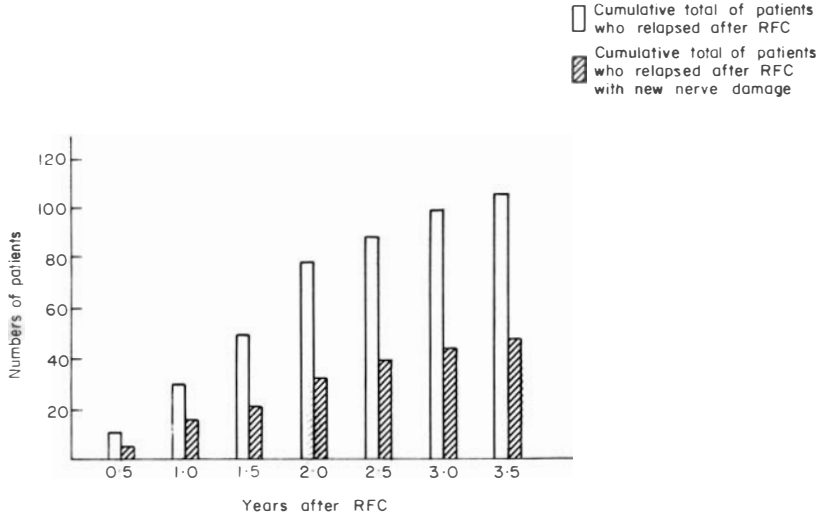

Fig. 1

1974). It must be borne in mind that the actual percentage may be higher, since many patients may not have reported with their relapse. We believe that over-diagnosing of relapse in this study has been avoided by adhering to a definite set of criteria (Table 1).

The cause of relapse may be a reinfection, but we consider that it is more likely to have been caused by a multiplication of persistent organisms which escaped leprosy treatment, for the following reasons —

(1) The dose of DDS is what we now consider an insufficient and low dose (WHO, 1977).
(2) A number of patients would not have been RFC if their records had been better scrutinized.
(3) In others, the original description and classification were not accurate.
(4) The date of inactivity on which the date of RFC should be based could not always be determined.

The number of relapsed patients discovered in this study is disturbing in view of the fact that so many report with new and often well-established nerve lesions. Very early lesions are reversible with treatment, but it is difficult to detect these early signs in relapsing patients. To differentiate old lesions from new lesions it is necessary to have good clinical records of the residual signs of leprosy at the time of RFC. Besides this clinical description of the skin, eyes, nerves and extremities of the patients, voluntary muscle testing (MRC War Memorandum, No. 7, 1943; Goodwin, 1968) and sensory testing (Naafs and Dagne, 1977) are extremely valuable. The results at the time of RFC can then be compared with the results at the time of check-up and relapse can be detected more accurately.

It is frightening that relapses of 30% in some groups are occurring in a well-staffed and well-equipped centre like ALERT in Addis Ababa. Higher rates probably occur, but may pass unnoticed, in less sophisticated centres which nevertheless follow the WHO criteria.

Dapsone is a relatively safe drug which can be taken with hardly any side-effects for years. However, from the leprosy control point of view a large number of "cured" patients in the programme represent a heavy work load. In order to diminish this work-load, patients should be RFC when it is virtually certain that they are indeed cured. Theoretically a T patient is healed after a certain, relatively short, period of treatment and continuation is then unnecessary. But as shown in this report, the rules for RFC as used in ALERT in 1974 are not sufficient to prevent a considerable number of relapses, about half of whom present with new disabilities.

Clinical information and statistical studies on relapses in leprosy from many different countries are needed in order to update international rules for RFC and to prevent grave disappointment to patients with leprosy and the doctors who treat them.

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Variability of Urinary Dapsone/Creatinine Concentration Ratios in Leprosy Patients Fully Compliant with Dapsone Therapy

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A highly sensitive and reproducible assay procedure for the determination of dapsone (DDS) and hydrolizable metabolites in urine is described. DDS/creatinine (D/C) concentration ratios, which are used to monitor compliance with DDS therapy, have been determined on samples of all urine voided throughout a 24-h period by 7 leprosy in-patients fully compliant with their therapy. The D/C concentration ratios varied both within and between patients over the 24 h and the time-course of variation showed no closely predictable pattern. Urinary excretion of DDS over the 24 h was found to be 74.8%±5.7% (S.E.M.) uncorrected or 90.2%±6.8% corrected for recovery. Our results indicate an unreliability in the use of single urine samples to determine D/C ratios and hence compliance by individual patients with their DDS therapy.

Introduction

A quantitative method by which dapsone (DDS) self-administration in leprosy patients can be monitored has been evaluated (Ellard, Gammon, Helmy and Rees, 1974*a*). The ratios of DDS to creatinine (D/C) concentrations in urinary samples are determined and a comparison made between the D/C concentration ratios of patients taking DDS under strict supervision and those who administer their own medication. Ellard, Gammon and Harris (1974*b*), Low and Pearson (1974) and Huikeshoven *et al.* (1976) have applied this technique to determine the regularity of dapsone self-administration.

Prior to assessing in a large number of patients the regularity of DDS self-medication based on measurement of D/C concentration ratios, the reliability of the use of D/C concentration ratios obtained on single urine samples has been examined. This paper describes the results of determinations on samples of all urine passed in 24 h by 7 patients. All patients are resident in a leprosarium in England where their DDS administration is strictly supervised.

Methods

PATIENTS

Seven leprosy patients (6 male, 1 female), resident in a leprosarium, volunteered for this study. All had been on long-term DDS therapy and had

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received their current dosage regimen (25 mg or 50 mg once daily) for at least 6 weeks. Five of the patients (numbers 1, 2, 5, 6 and 7) were receiving other drugs listed in Table 1.

URINE SAMPLES

All urine was collected during one 24-h period. At each voiding the time was noted, a 25-ml sample separated and the remainder placed in a collection bottle. Creatinine and DDS were determined in each voiding and in the 24 h save.

CREATININE AND DDS DETERMINATIONS

Creatinine was determined by the alkaline picrate method (Jaffe, 1886), using an automated procedure (Technicon Method No. SE4–0011FH4, 1974). DDS, as total diazotizable compounds, was determined in duplicate by the following method which is similar to that recommended by Varley (1967) and is a modification of the Bratton and Marshall (1939) procedure. Two-ml portions of each sample were acidified by addition of 2 ml 2 N HCl and immersed in a boiling water bath for 15 min to ensure hydrolysis of dapsone metabolites (Ellard, 1966). After cooling, 0.4-ml volumes of 0.1% sodium nitrite, 0.5% ammonium sulphamate and 0.1% naphthylethylenediamine dihydrochloride (in 95% ethanol) were added successively at 5-min intervals. The optical density at 540 nm was measured 5 min after addition of the last reagent against a reagent blank using 5 μg/ml DDS standards. Urinary blank values were determined on each sample by substitution of water for sodium nitrite.

Recovery of DDS added to urine was 82.9% ± 2.8% (S.E.M.) (range 69–91%) and duplicate determinations showed satisfactory repeatability [Fisher's (1970) intrapair correlation coefficient $r > 0.98$]. Urine from 13 normal untreated subjects yielded apparent DDS/creatinine concentration ratios of 1.10 ± 0.20 (range 0.20–2.95) μg/mg.

All of the drugs listed in Table 1 and also the metabolites N-demethylclindamycin and desmethyldiazepam were tested for interference with the DDS assay procedure. None of the drugs, except desmethyldiazepam, was found to react.

Results

Total DDS and creatinine excretion in 24 h and D/C concentration ratios of these totals, together with the ranges found among all urine samples, are given in Table 1. Urinary DDS excretion over 24 h was found to be 74.8% ± 5.7% (S.E.M.) of the dose administered. After correction for an average recovery of 82.9% in the determination, this amounts to 90.2% ± 6.8% of the dose.

DDS/creatinine concentration ratios of different urine samples varied widely both between and within individual patients. The variability encountered is shown in Fig. 1; it ranged from 1.44-fold (patient no. 7) to 4.49-fold (patient

TABLE 1

Urinary excretion of DDS and creatinine and D/C concentration ratios in 7 patients: (a) 24 h excretion; (b) values for individual urine samples during 24 h

Patient	Sex	Age	DDS dosage (mg/day)	Other drugs	(a) 24 h excretion			(b) Range of individual values		
					DDS (mg)	Creatinine (g)	D/C ratio (μg/mg)	DDS (μg/ml)	Creatinine (mg/ml)	D/C ratio (μg/mg)
1	M	62	25	Diazepam	14.9	1.30	11.5	3.1–19.3	0.26–1.36	9.4–16.2
2	M	46	25	Erythromycin	21.5	1.39	15.5	6.4–28.7	0.40–2.10	7.1–21.0
3	M	82	25	nil	16.6	1.31	12.7	3.1–39.8	0.51–2.19	5.4–24.2
4	F	76	25	nil	23.0	0.74	31.1	8.2–61.0	0.28–2.27	19.5–33.3
5	M	50	50	Clindamycin Indomethacin	17.5	1.44	12.2	9.9–57.9	0.91–2.04	9.1–28.3
6	M	54	50	Diazepam	56.5	1.70	33.2	18.7–35.2	0.64–1.73	13.7–47.2
7	M	20	50	Clofazimine	36.8	1.21	30.4	23.0–58.4	0.86–1.52	26.6–38.3

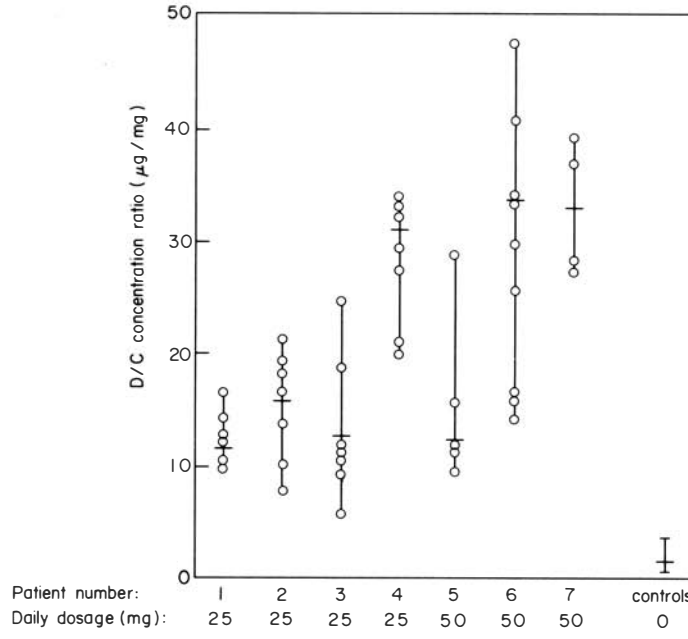

Fig. 1. Urinary DDS/creatinine concentration ratios (μg/mg) of all samples voided by 7 patients during 24 h. Horizontal lines indicate 24 h values.

no. 3). In one subject (patient no. 3) D/C concentration ratios were found to differ 3-fold in urine samples voided within one 2-h period. Analysis of variance, using a nested classification, revealed that the differences observed were highly significant: viz. between patients, $P < 0.01$; between times within patients, $P < 0.001$ (Table 2). Inspection of the time course of D/C ratios

TABLE 2
Analysis of variance of urinary DDS/creatinine concentration ratios. Values shown in Fig. 1

Source of variation	d.f.	Sum of squares	Mean square	*F*	*P*
Between doses	1	1871.92	1871.92	2.41	—
Between individuals within doses	5	3888.77	777.75	11.85	<0.01
Between 12-h periods within individuals	7	459.55	65.65	0.62	—
Between times within 12-h periods	36	3843.47	106.76	529.58	<0.001
Within times (error)	50	10.08	0.2016		
TOTAL	99	10073.79			

through the 24-h period of collection revealed no clear pattern of variation and there was no significant difference between ratios during the first and second 12-h periods following drug administration.

Discussion

A highly sensitive and reproducible assay procedure for the determination of DDS and hydrolizable metabolites in the urine has been described. Attempts were made in our laboratory to follow the adaptation of the Bratton and Marshall method described by Ellard *et al.* (1974*a*). The formation of a fine purple precipitate in standard solutions of 30 μg/ml and over led to interference with spectrophotometry, making the assay imprecise. If the precipitate is due to the insolubility of the azo dye so formed, then a certain amount of alcohol must be added with or just before the coupling component, as suggested by Bratton and Marshall (1939). Our modification of the assay procedure showed highly satisfactory reproducibility. Urine from untreated subjects yielded apparent D/C ratios of less than 3 μg/mg; some published figures using other modifications have yielded ratios up to 10 μg/mg. The present method therefore appears to be particularly applicable in studies of patients, such as ours, on low dosage regimens.

It was found that recovery of DDS added to urine samples of 10 normal subjects averaged 83%. The recovery rates varied between samples, however, to an extent which might be expected to influence DDS concentrations in clinical samples to a minor degree, calculated as less than 30%. No attempt has been made to measure recovery of the drug's acidic metabolites, which account for much of its total excretion (Ellard, 1966), so the clinical implication of this finding is at present incalculable.

DDS/creatinine concentration ratios of our patients were subject to substantial variability over the 24 h, the greatest difference between D/C concentration ratios within any one individual being $4\frac{1}{2}$-fold. This range is somewhat greater than that indicated by the repeat sample study performed by Low and Pearson (1974), and it is too great to be explained by differences in recovery in the method. No clear reason for such variation is apparent. In particular we found no consistent diurnal change such as would be expected from once daily drug administration.

Two of the patients (nos 1 and 6) were treated with diazepam, the first metabolite of which, desmethyldiazepam (Hillestad *et al.*, 1974) was found to yield colour with the assay procedure. Such interference is, however, unlikely to have contributed to the total variation in apparent DDS output because the metabolite has an elimination half-life of over 90 h and in such a case the urinary appearance of this compound and its further degradation products can change only minimally over the 24-h period.

Our results demonstrate that with determinations on single urine samples errors in classifying individual patients as taking their dapsone regularly or irregularly will arise in those who normally have quite variable D/C concentration ratios through the 24 h. The reliability of using one urine sample obtained

from the patient at a surprise visit to his home, as suggested by Ellard *et al.* (1974*b*) and carried out by Huikeshoven *et al.* (1976), is thus questioned. Our findings, however, do not invalidate the use of such samples in population studies from which general levels of patient compliance are deduced.

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Lamprene (Clofazimine) in Leprosy

Basic information. Compiled by
S. J. YAWALKAR and W. VISCHER

Pharma Division, CIBA-GEIGY Limited, Basle, Switzerland, October 1978

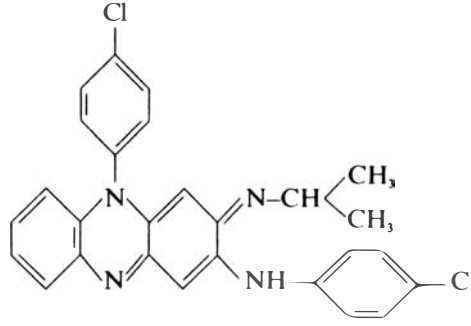
We are extremely grateful to CIBA-GEIGY Limited for permission to reproduce in full this 15-page booklet on a drug of increasing interest and value in the treatment of leprosy.

Introduction

In 1962, Browne and Hogerzeil[1] first reported on the efficacy of ®Lamprene (B 663, G 30,320, clofazimine) in leprosy patients in Nigeria. At present, Lamprene is one of the extensively used antileprosy drugs; it is effective in the prevention[2–4] and treatment of lepra (ENL) reactions[5] and is also useful for the treatment of dapsone-resistant leprosy cases[3, 6, 7]. To date, Lamprene is the only major antileprosy drug which displays an anti-inflammatory effect and to which resistant strains of leprosy bacilli have not been reported.

Composition

The active ingredient in Lamprene is a substituted iminophenazine dye. This bright red dye, the result of progressive molecular manipulation of aniline aposafranine, was synthesized in 1954 by Vincent Barry *et al.* in Dublin[8]. Its structural formula and chemical designation are:



3-(*p*-Chloro-anilino)-10-(*p*-chlorophenyl)-2, 10-dihydro-2-(isopropylimino)-phenazine (= clofazimine).

Presentation

Each Lamprene capsule contains 100 mg of micronized clofazimine suspended in an oily base. The product should be protected from humidity and heat. Its shelf-life is 5 years. The capsule shell consists of gelatin, which is known to be sensitive to humidity. Hence, the preparation is supplied in a humidity-resistant container, which should be closed again immediately after use. The capsules may occasionally stick together, but they remain usable.

Absorption, Tissue Distribution and Excretion

ABSORPTION

Clofazimine absorption varies appreciably from one patient to another. It is more complete from micronized material and from oily preparations. When the active substance is given in the form of coarse crystals, it is absorbed only to the extent of about 20%, whereas, if taken orally in the form of a microcrystalline suspension in an oil-wax base, an absorption rate of about 70% has been achieved[9]. This is the reason why Lamprene is supplied in this formulation.

SERUM CONCENTRATIONS IN LEPROSY PATIENTS

In leprosy patients the following serum concentrations have been reported with various dose schedules[10]:

Oral dose	Average serum concentration
100 mg thrice weekly	0.5 µg/ml
100 mg daily	0.7 µg/ml
300 mg daily	1.0 µg/ml
400 mg daily	1.4 µg/ml

TISSUE DISTRIBUTION

Lamprene is highly lipophilic and tends to be deposited predominantly in the fatty tissue and in cells of the reticulo-endothelial system. It is taken up by macrophages throughout the body. At autopsies performed on three leprosy patients, clofazimine was found predominantly in mesenteric lymph nodes, adrenals, subcutaneous fat, liver, bile, gall-bladder, spleen, small intestine, muscles, bones, and skin. In these patients, who had received Lamprene in varying dosages of up to 300 mg daily for 35–243 days, the brain concentration was near zero[11]. In another autopsy study "ghosts" of clofazimine crystals were observed in histological sections of the intestinal mucosa[12].

EXCRETION

The exact manner in which clofazimine is metabolized by the mammalian body is still not completely known. The drug tends to remain a long time in

human tissues and is eliminated from the body very slowly. Its half-life ($t_{1/2}$), following oral administration, is at least 70 days in man[14]. Urinary excretion of clofazimine in lepromatous leprosy patients is negligible, accounting on the average for 0.1% of the dose in 24 h (range: 0.01–0.43%), while faecal excretion varies considerably, amounting in some cases to as much as 35%. Part of the ingested drug recovered from the faeces may represent excretion via the bile rather than failure of absorption from the gut[11]. A small amount is eliminated in the sebum and sweat[9].

Therapeutic Effect

Lamprene exerts a potent inhibitory effect on the growth of *Mycobacterium leprae* (Hansen's bacillus). Its precise mode of action, however, remains to be elucidated. Clofazimine does not show cross-resistance with dapsone or rifampicin.

It is not possible to determine the MIC of clofazimine against leprosy bacilli in animals, since the drug is not very homogeneously distributed in the tissues. Neither blood nor tissue levels necessarily reflect clofazimine concentrations in the immediate environment of *Mycobacterium leprae*[13]. The determination of the MIC of clofazimine against leprosy bacilli *in vitro* is not yet feasible.

In the mouse footpad system, the multiplication of *Mycobacterium leprae* is inhibited by feeding 0.0001%–0.001% clofazimine in the diet[15]. Although bacterial killing begins immediately in lepromatous leprosy patients treated with 50 mg dapsone daily, but only after about 50 days in patients receiving 100–200 mg Lamprene daily, the rates of bacterial killing are identical[6]. The reason for the slower onset of action of Lamprene is obscure. Initial killing of leprosy bacilli, monitored by inoculating mice with organisms from skin biopsies taken during the first 24 weeks of treatment, occurs at the same rate whether Lamprene is administered in a dose of 100 mg three times weekly or in one of 200 mg daily on 6 days a week[16].

Several reports indicate that the overall antibacterial effect of clofazimine in lepromatous leprosy patients is of the same order as that of dapsone[17–21]. In a multicentre double-blind trial carried out in patients with lepromatous leprosy with the aim of comparing the antibacterial effects of low dosages of clofazimine (100 mg) and dapsone (50 mg), both administered twice weekly for 48 weeks, the morphological index (MI) reached zero by the 18th week in both treatment groups[20]. In previously untreated lepromatous cases, the rate of fall in the MI in response to clofazimine is in general similar to that obtained with dapsone treatment[17].

Plock and Leiker, however, reported a slightly slower average annual decrease in the bacteriological index (BI) in skin smears and biopsies — i.e. 13% and 14%, respectively — in patients receiving clofazimine in dosages of 100–600 mg daily than that reported in patients on sulphone treatment (on the average about 17%)[22].

In lepromatous cases clofazimine produces a clinical effect similar to that of dapsone[19, 23]. Clinical improvement is visible between the first and third months

of treatment and is clearly evident by the sixth month. Neuritis and sensory loss also respond well to Lamprene[4, 42, 44, 45].

Lamprene also displays an anti-inflammatory effect[9, 17, 24] which is clinically valuable in controlling erythema nodosum leprosum (ENL) reactions occurring in multibacillary forms of leprosy. It is a drug of choice for the management of ENL in females of child-bearing potential, in whom thalidomide is contra-indicated, and it is a useful means of controlling reversal reactions in borderline leprosy, in which thalidomide is not effective[25]. Lamprene, however, has a slower onset of action than thalidomide and corticosteroids[26]. Although a combination of clofazimine and dapsone does not hasten clinical or bacteriological improvement in patients with lepromatous leprosy, it leads to a considerable reduction in the incidence of ENL reactions[5] and improves treatment acceptance and patient cooperation.

Combined therapy with clofazimine and dapsone is likely to prevent the emergence of dapsone resistance. Lamprene, given in a dosage of 100–200 mg daily, is effective in proven dapsone-resistant lepromatous leprosy cases[3, 6, 7, 26]. From 1963 to 1968 it was the first alternative for the treatment of dapsone-resistant patients[27]. At present, a combined drug regimen comprising two or three drugs is recommended for such cases.

Although clofazimine is believed to stimulate the phagocytic activity of polymorphonuclear leucocytes and to enhance their oxygen uptake, to date there is no confirmatory evidence of its immunostimulant properties[28]. Moreover, in recent investigations in 5 healthy women it was found to have no effect either on reticulo-endothelial phagocytosis or on the leucocytic index, which suggests that a mechanism of action other than reticulo-endothelial stimulation must be responsible for the therapeutic effect of this drug[29].

Lamprene has also been reported to be effective in Buruli skin ulcers caused by *Mycobacterium ulcerans*[30].

Indications

Lamprene is indicated as a part of combined therapy for the prevention or treatment of secondary dapsone resistance in lepromatous and borderline leprosy and for the treatment of erythema nodosum leprosum (ENL) and reversal reactions.

(1) For the prevention of secondary dapsone resistance, Lamprene should be administered to lepromatous (LL) and borderline (BL, BB) leprosy patients in combination with dapsone given in full dosage.
(2) For the treatment of established dapsone resistance, Lamprene should be given in combination with rifampicin.
(3) Lamprene prevents the occurrence of ENL in reaction-prone lepromatous patients. It can also be used when ENL occurs in patients treated by other drugs and especially in females of child-bearing potential, in whom thalidomide is contra-indicated[25].
(4) It is also indicated for treating reversal reactions occurring in borderline leprosy, in which thalidomide is not effective, and when corticosteroids are contra-indicated[25, 33].

Dose Schedules

It is advisable to administer Lamprene daily or on alternate days[15]. The dosage should be adapted to the individual case, i.e. to the patient's body weight, activity of the disease, and presence of dapsone resistance.

The dose schedules tentatively recommended for adults by the WHO Expert Committee on Leprosy[31] (1977) are as follows:

(1) Dapsone non-resistant uncomplicated lepromatous (LL) and borderline (BL, BB) leprosy patients (to prevent dapsone resistance and in an attempt to reduce the incidence of ENL reactions):
100 mg Lamprene orally daily or 3 times a week for the first 4–6 months
+
50–100 mg dapsone orally daily indefinitely.

(2) Established dapsone-resistant cases:
100 mg Lamprene orally daily indefinitely*
+
600 mg rifampicin orally daily for the first 2–3 months.

ENL REACTIONS

The treatment of erythema nodosum leprosum (ENL) depends on the severity of symptoms. ENL is graded severe: if it is accompanied by a high temperature and general malaise; if the skin lesions become pustular and/or ulcerate; if the nerves become painful or if loss of nerve function develops; or if there is evidence of iridocylitis, orchitis, joint swelling, or persistent albuminuria[31]. Severe cases should be referred immediately to hospital, analgesics being given as required for the journey.

In general, the antileprosy treatment should be continued unchanged. The drugs of choice for the treatment of ENL reactions are corticosteroids, thalidomide, and clofazimine. Corticosteroids rapidly control ENL but have to be given continuously and often in increasing dosage, while thalidomide is teratogenic.

In ENL cases, Lamprene should as a rule be given in a dosage of 300 mg daily for about 3 months. The drug has a slow onset of action and therefore takes 4–6 weeks to exert its full effect. In very severe ENL, even at dosages of 300 mg daily (a dose level that should not usually be maintained for longer than about 3 months), clofazimine may not be as effective as corticosteroids or thalidomide[31]. However, unlike corticosteroids and thalidomide, clofazimine not only acts on lepra reactions but also exerts a specific therapeutic effect on leprosy itself. Moreover, its side effects are much less dangerous than those of prednisolone[32].

REVERSAL REACTIONS

Prednisolone is an effective form of treatment for reversal (Type 1) reactions, but as these reactions may persist for weeks or months,

*Regular clinical and laboratory supervision of these patients is advisable

corticosteroid cover has to be continuous in spite of the risks involved. An alternative drug is clofazimine and the dosage required is usually in the order of 300 mg daily[5, 33].

Toxicity

Lamprene is a relatively non-toxic drug[16].

TOXICITY IN ANIMALS

The acute oral LD_{50} of clofazimine was found to be >5 g/kg in mice, rats, and guinea-pigs. In the rabbit it was 3.3 g/kg.

In general, daily oral doses of 30 and 50 mg/kg given for 6 months were well tolerated by monkeys and rats, respectively. Reddish discoloration of the skin, faeces, and urine was observed. Temporary diarrhoea was occasionally reported in rats[34].

Clofazimine accumulates selectively in the fat cells and reticulo-endothelial cells of laboratory animals fed with a diet containing the drug. Long-term consequences, if any, of clofazimine crystal deposits in animal tissues are not known. Experimental studies in mice, rats, and rabbits did not yield any evidence that clofazimine possesses a primary embryotoxic or teratogenic action[34]. Clofazimine does not exhibit mutagenic activity[38].

TOXICITY IN HUMANS

At autopsies performed on leprosy patients clofazimine has been found in various organs. Histological sections of the intestinal mucosa showed "ghosts" of clofazimine crystals[12] at autopsy of a patient who had received 300 mg clofazimine daily for 6 months and later on a second course of 200 mg a day for $2\frac{1}{2}$ months after a drug-free interval of 6 months. After 6 and 18 months' regular intake of Lamprene (100 mg t.i.d. for the first 3 months followed by a maintenance dose of 100 mg daily), a non-specific granuloma, comprising foreign-body giant cells and lymphocytes together with crystals of clofazimine, was found on laparotomy in the terminal ileum of 2 out of a total of 120 patients in the reactive phase of leprosy. No AFB were grown on culture[35].

A case of eosinophilic enteritis is reported in a 29-year-old woman with leprosy who had been receiving clofazimine for 3 years in a dose of 600 mg daily. At laparotomy there was nodular thickening of the upper ileum with blackish-brown pigmentation of the ileal wall. Ileal biopsy revealed the presence of eosinophilic enteritis, and red crystals of clofazimine were observed in unstained sections of the small bowel mucosa and submucosa, as well as in mesenteric lymph nodes[36]. Clofazimine crystals have been found in lymph nodes almost 4 years after treatment with the drug had been discontinued[37].

A long-term study in 51 patients receiving Lamprene for periods of up to 8 years (comprising 220 patient-years of observation) showed that, despite the deposition of the drug in various tissues in man, Lamprene appears to be remarkably free from serious toxic effects in clinical use. The advantages of

clofazimine outweigh its known disadvantages in those leprosy patients for whom it is indicated[25].

Clofazimine crosses the human placenta, since infants born to females who had received the drug during pregnancy were more deeply pigmented at birth[17]. No evidence of teratogenicity has been found[5].

General Tolerability

In general, Lamprene is well tolerated and virtually non-toxic. The following side effects have been reported.

SKIN

Reversible dose-related pink to brownish-black skin discoloration, especially on exposed parts, is the most commonly observed side effect of Lamprene. Discoloration of sweat, hair, sputum, urine, and faeces may occur during clofazimine administration. General dryness of the skin (xeroderma), ichthyosis, pruritus, phototoxicity, acneiform eruptions, and non-specific skin rashes have also been described.

GASTRO-INTESTINAL TRACT

At present no accurate assessment can be made of the incidence and nature of gastro-intestinal side effects. Symptoms reported include nausea, vomiting, abdominal pain (usually epigastric, but occasionally described as "abdominal cramps" or "colicky"), intermittent loose stools, diarrhoea, anorexia, and weight loss. According to the available literature, there is a possibility of two separate entities:

(1) An early syndrome, commencing within a few days or weeks of starting clofazimine[5] and possibly due to a direct irritant effect of the drug. This syndrome was commoner in response to a high dosage, especially when the drug was given in a single dose, e.g. 300 mg once daily, than when it was administered in divided doses, e.g. 100 mg three times a day. It was possibly more frequent in patients suffering from other concurrent gastro-intestinal diseases, such as amoebiasis and intestinal bacterial infections[22]. The symptoms subsided once the dosage had been reduced or the drug discontinued.

(2) A late syndrome, commencing after some months or years on high dosage (more than 300 mg daily), with persistent diarrhoea, loss of weight, and abdominal pain. This was considered to be the cause of death in one patient who received 100–600 mg clofazimine daily for 6 years because of continued ENL reactions[39]. The syndrome was associated with deposition of clofazimine crystals in the tissues, usually in the submucosa of the small intestine and in the mesenteric lymph nodes[12, 37, 40, 41]. Some of these patients were complex (one had concurrent amyloidosis[41] and another a tuberculoma of the brain[12]). Differing radiological abnormalities and jejunal biopsy findings have been reported, but only a few patients have so far been thoroughly

studied. No peritoneal fibrosis following clofazimine administration has been observed. In the case of the late syndrome, withdrawal of clofazimine was not necessarily followed by an improvement.

Severe gastro-intestinal side effects are rare; they are likely to occur only following prolonged treatment with the high doses recommended for ENL reactions.

EYE

Except for conjunctival pigmentation[5, 42], interfering neither with the treatment nor with visual acuity, no other ocular side effects have been reported in leprosy patients. However, in 10 out of a total of 26 non-leprosy cases treated with Lamprene in Sweden, reversible linear brownish corneal streaks were observed[43]. These streaks disappeared within 2 months of stopping the drug. In this series 2 cases of macular pigmentation were also noted.

Precautions

The unwanted reactions to Lamprene are mostly benign, reversible, and often dose-related. A dosage of more than 100 mg daily should be given for as short a period as possible (3 months) and only under supervision.

The most common side effect is skin discoloration, which can be prevented by reducing the dosage or duration of treatment and by taking protective measures (anti-solar lotions, umbrellas).

As far as possible clofazimine should not be given:

— in the first 3 months of pregnancy

— to patients subject to recurrent abdominal pain and diarrhoea

— to patients with liver or kidney damage.

Lamprene capsules should be taken with meals or with a glass of milk. The dose should be reduced, and if necessary the interval between the doses increased, if the patient complains of colicky or burning pain in the abdomen and/or nausea and vomiting. If diarrhoea or vomiting persists, the patient should be hospitalized.

In patients receiving Lamprene indefinitely for dapsone resistance, or in those with a history of liver or kidney disease, clinical check-ups and laboratory tests, such as routine blood and urine examination, serum bilirubin, serum albumin and globulins, blood urea nitrogen (BUN), and fasting blood sugar, should be carried out at 3-monthly intervals.

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Leprosy and the Community

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LEPROSY CONTROL

Review of technical cooperation and the available funds

The actual number of leprosy cases requiring treatment in the world is not known. In 1970, there were close to 3 million registered patients but a conservative estimate of the total number of cases was over 10 million (6.5 million in Asia, 3.5 million in Africa, and 350,000 in the Americas)*. During 1976/77, questionnaires were distributed to countries through WHO Regional Offices and the results, when available, will give an up-to-date appraisal of the leprosy situation. The article below, which is based on the Director-General's report to the World Health Assembly this year†, describes WHO's efforts in technical cooperation to control leprosy in the various regions and the available resources for carrying out this work.

Guidelines on Leprosy Control

The WHO Expert Committee on Leprosy, in its fifth report published recently‡, laid down guidelines on the strategy of leprosy control and on the formulation and management of a leprosy control programme. Particular emphasis was given to manpower training and deployment of staff, to programme supervision, and to evaluation by the fixing of operational milestones and output targets and by the definition of the most important operational and epidemiological indicators.

In the area of chemotherapy, the Committee was confronted with two major problems: dapsone resistance and the persistence in some treated patients of undestroyed dapsone-sensitive bacilli. Reported rates of secondary dapsone resistance in lepromatous cases range from 2% to 8%, and in one country it is estimated that as many as 30% of infectious cases could cease to respond to treatment within 10 years because of dapsone resistance. To meet these hazards and keeping in mind the economic considerations, the Committee recommended combined drug therapy with clofazimine and rifampicin for multibacillary cases only.

The vital need for adequate information on leprosy prevalence and morbidity in individual countries was also reflected in the Committee's recommendations. As a first step towards meeting this need, an analysis was made by a collaborating centre of the various clinical records and reporting forms

*Bechelli, L. M. and Martinéz-Domínguez, V. (1972). *Bull. Wld. Hlth. Org.* **46:** 523.
†Unpublished WHO document A30/14.
‡WHO Technical Report Series, No. 607, 1977.

used by 78 leprosy control services in 45 countries in Africa, the Americas, Asia, and Oceania. The development of a system providing basic standardized information (collected by health staff at the peripheral level) is planned, from which national figures could be derived and used by Ministries to assess the programmes.

From the Committee's recommendations, it is clear that an effective approach to leprosy control will require:

— improved programming and management of control activities
— development of multidisciplinary manpower
— gradual build-up of an integrated information system, by countries
— strengthening of research activities, particularly those to be carried out within the research component of WHO's Special Programme for Research and Training in Tropical Diseases.

Technical Cooperation in Leprosy

GLOBAL AND INTERREGIONAL ACTIVITIES

In recent years many countries have built up their own institutions for training both general health staff and specialized staff, and particularly paramedical and auxiliary personnel. From 1960 to 1974, 389 WHO fellowships were awarded in the field of leprosy; by 1976, only 6 awards were made in this field. With the establishment of a regional training and research centre in leprosy and tropical diseases in South America (in Caracas) and centres in Africa (in Addis Ababa, Dakar, and Ganta in Liberia) and South-East Asia (in India at Chingleput and Karigiri), well-organized training courses are available for the health staff of all endemic countries.

Since 1958, regional seminars and intercountry group educational courses have been conducted for training senior public health staff and for the exchange of views on the strategy and management of leprosy control activities. In 1969 and 1974 the WHO Regional Office for the Western Pacific held combined seminars on leprosy and tuberculosis. However, the need for long-term manpower training plans in most countries and for up-to-date trained teachers in leprosy control — important areas of technical cooperation — has led to provision being made for them in the regular budgets for 1978 and 1979.

An international workshop on leprosy training in Asia and a workshop on the chemotherapy of leprosy were held, respectively, in Bangkok in November 1976 and in Manila early this year. Both workshops were sponsored by the Sasakawa Memorial Health Foundation (SMHF), jointly with the government of the host country, and WHO participated on the technical side. It is the intention of the SMHF to sponsor further workshops in cooperation with governments in Africa, Asia, and South America.

THE AFRICAN REGION

Leprosy control services in the African Region have been integrated into epidemiological or strengthening of health services projects (or both) and do not appear in the WHO programme budget separately.

In Nigeria (70 million population) the leprosy problem is large and ill-defined, particularly in the northern and central states. In three northern states, Bornu, Kano and Kaduna (total population of 28 million), there were 155,199 registered patients undergoing treatment. The total number of registered patients for the whole country may well be over 300,000.

From 1974 till March 1977 the government in Upper Volta and WHO cooperated with a number of voluntary agencies in a combined leprosy-tuberculosis random sampling survey, which confirmed a 75% reduction in the prevalence of active leprosy cases. This achievement was the result of intensive antileprosy work carried out by mobile units in past years. The results of this survey indicate that a significant decline in prevalence may be occurring in other countries where similar antileprosy programmes have been pursued, e.g. Benin, Central African Empire, Chad, Congo, Ivory Coast, Mali, Mauritania, Niger, Senegal, Togo, and the United Republic of Cameroon.

The combining of leprosy and tuberculosis field activities, the feasibility of which was examined in Upper Volta, is an approach that has been adopted (e.g., in Bangladesh, Maldives, Nepal, and Venezuela) and may find wide application in other countries in Africa and elsewhere.

THE AMERICAN REGION

In the Ten-Year Health Plan, 1971–80, the countries where leprosy was considered to be a national problem set themselves goals for 1980 in the reduction of prevalence. Technical cooperation for the development and evaluation of leprosy control services is provided by a WHO leprologist and through the PAHO/WHO Center for Research and Training in Leprosy and Tropical Diseases, both based in Caracas. With funds from a voluntary contribution by the Order of Malta, a consultant was appointed to review and advise on the leprosy control services in Argentina; a small grant was also made to the leprosy control programme in Colombia.

THE SOUTH-EAST ASIA REGION

In 1975 the WHO Regional Committee adopted a resolution emphasizing "the urgent need for coordinated and concerted efforts on the part of the governments, international and voluntary organizations, and bilateral agencies to come to grips with the problem of leprosy within a short time". Consequently, an intercountry consultative meeting on leprosy was held in New Delhi in December 1975, at which participants from 7 Member States reviewed the magnitude of the problem, strategies for control, and areas for research. Targets were laid down for case detection in endemic areas, for delivery of treatment, and for widening the population coverage. Collaborative field studies were planned on the bacterial reductions in lepromatous cases produced by different drug regimens including combined therapy.

Leprosy control activities in individual countries in the Region are as follows:

(a) The WHO trial in Burma of BCG vaccination of children against leprosy (see below) was terminated in 1975 and the long-term results are being

evaluated. The design of a clinical trial for rifampicin was prepared by consultants with support from the WHO Regional Office.

(b) The review of the leprosy services in Nepal, which was carried out in 1975, is an example of the way in which WHO assists countries develop effective programmes for early detection and closely supervised treatment of the disease. Detailed leprosy project formulation was undertaken as part of the country health programming within the fifth 5-year development plan. A WHO consultant cooperated during 1976 in the initial stages of the implementation of the programme and conducted training courses of field auxiliaries and supervisors.

(c) Bangladesh is now engaged in a combined leprosy/tuberculosis project which health personnel are being trained to operate an integrated field programme for mycobacterial control. A WHO medical officer is cooperating in the field programme.

(d) India has intensified its case-finding and caseholding programme in order to extend present services to hitherto unsurveyed areas of high and moderate endemicity. It is estimated that the total number of untreated cases is two million.

(e) Indonesia has an integrated programme for leprosy control and is now developing, with the cooperation of a WHO consultant, a national training centre for health staff with a view to strengthening case-finding and case-management throughout the country.

(f) Maldives has begun a multipurpose total population survey, which will define the leprosy/tuberculosis problem, with the ultimate aim of developing primary health care.

(g) In Burma and Thailand, operational studies are being conducted to ascertain the best way of integrating the leprosy control services with the health services. In a highly endemic area in Burma, for example, studies on the integration of separate disease programmes — leprosy, tuberculosis, trachoma, and malaria — are in progress. A recent assessment suggests that the retraining of field workers from the separate programmes into a multipurpose worker has to be improved to ensure satisfactory results.

THE EASTERN MEDITERRANEAN REGION

In the course of 1976, three countries in the Eastern Mediterranean Region benefited from technical cooperation in leprosy:

— Democratic Yemen received consultant services, WHO fellowship awards, and supplies and equipment

— Direct field assistance was provided by a medical officer to the leprosy control project in the Sudan and is planned to continue until 1979

— Supplies and equipment for leprosy control were received by Pakistan.

THE WESTERN PACIFIC REGION

Starting this year and until 1980, a regional leprosy advisory team will continue epidemiological and assessment surveys and will guide health authorities in the operation of leprosy programmes in the South Pacific, where

the territories are widely dispersed. An efficient information system, with the prospect of regular appraisals, will be created.

In the Socialist Republic of Viet Nam, the strengthening of the leprosy control programme is considered to be of prime importance in the reconstruction of the health services, for which substantial resources have been and will be made available through voluntary funds from the government of Switzerland (during 1976–80), the Japan Shipbuilding Industry Foundation, and some member associations of the International Federation of Anti Leprosy Associations (ILEP). Technical cooperation in the field of leprosy was also extended to the Republic of Korea and to Papua New Guinea.

Operational Studies and Research Activities

In the last two decades WHO has supported collaborative research on various aspects of leprosy, including studies on the biology of *Mycobacterium leprae* and attempts at its cultivation, development of animal models, drug trials, and diagnostic procedures. Special consideration was given to the possible preventive action of BCG vaccine through a trial carried out in Burma from 1964 to 1975, covering about 28,000 children under 14 years of age and still being followed up. In this trial, protection was found to be limited to about 20% of the children aged 0–14 years old; in addition, the trial enabled valuable epidemiological data to be collected.

Operational studies have been an important feature in a number of national programmes in recent years. For example, sample surveys have provided not only essential information and operational data for evaluation, but also led to improvement of field strategies and diagnostic methods and contributed to the strengthening of health education and an understanding of the psychosocial consequences of the disease.

RESEARCH IN IMMUNOLOGY AND CHEMOTHERAPY

Within WHO's Special Programme for Research and Training in Tropical Diseases, priority is being given to research in the immunology of leprosy (IMMLEP) and chemotherapy for leprosy (THELEP).

The objectives of the IMMLEP programme are (i) development of vaccines, (ii) development of diagnostic tests for subclinical infection, and (iii) exploration of immunotherapy. The need for adequate supplies of *M. leprae* for experimental purposes has been met by increasing the supply of this organism from infected armadillo tissue. Other achievements of this programme so far include purification of *M. leprae* and preparation of antigenic fractions and their evaluation, induction of immune responses in animals, and studies on other mycobacteria (in the environment) antigenically related to *M. leprae*. Although recent progress in research strengthens the hope that an effective vaccine against leprosy will be developed, practical large-scale applications cannot be expected in the near future.

The THELEP programme has four objectives:

— to assess more accurately the risk of the emergence of drug-resistant *M. leprae* in lepromatous patients during single-dose regimens with dapsone

— to develop new laboratory methods for chemotherapeutic trials on patients with leprosy
— to develop effective new drugs against *M. leprae*
— to plan the training of additional laboratory and clinical staff recruited from leprosy endemic countries.

At its first meeting in April 1977, the THELEP scientific working group reviewed and revised the draft standard protocol for chemotherapy trials in lepromatous leprosy and recommended lists of drug regimens and priorities for trials in the following groups of patients: previously untreated, proven dapsone-resistant, and previously responsive to dapsone.

The revised IMMLEP budget for 1976 amounted to $173,736 and the tentative 1977 budget for THELEP is $478,000.

OTHER COLLABORATIVE RESEARCH

For technical cooperation in 1976 with 32 research centres or principal investigators in 20 countries the Organization provided $76,885 from the regular budget and nearly $70,000 from other sources; these amounts are separate from the funds made available for the IMMLEP and THELEP programmes.

The wide range of research studies and the number of centres involved at present (given in parentheses) are as follows: epidemiology of leprosy (7 centres), pathology (2), histological identification and classification of leprosy (1), immunology of leprosy (10), drug trials (3), research on *M. leprae* (26), and systems analysis approach to leprosy control (1).

Funds for Leprosy Activities; Cooperation with Other Organizations and Agencies

During the past 3 years in particular there has been a wide extension of activities — in research in the multidisciplinary approach to leprosy control, and in coordination with other international organizations and agencies for the mobilization of additional resources.

In Table 1 are given details of contributions from WHO's regular budget and extrabudgetary funds for leprosy activities in 1976. The actual funds were approximately $725,000 from the regular budget, $528,000 from the Special Account for the Leprosy Programme (from WHO's Voluntary Fund for Health Promotion), and $198,000 from the Special Programme for Research and Training in Tropical Diseases (for the IMMLEP and THELEP programmes). In 1975 and 1976 substantial contributions were made to the Special Account for the Leprosy Programme by the Japan Shipbuilding Industry Foundation.

UNITED NATIONS CHILDREN'S FUND (UNICEF)

UNICEF assistance to leprosy programmes has two components: a major one of supplies and equipment (comprising transport, medical equipment, and drugs) and a smaller one in cash (representing stipends for trainees in the lower grades of health services).

TABLE 1
Funds from WHO for leprosy activities in 1976 (expressed in US$)

Activities	Regular budget	Other sources*	Total
WHO headquarters:			
Leprosy unit†	176,890	3,659	180,549
Global and interregional activities:			
Expert Committee on Leprosy	18,203		18,203
Programme promotion		17,288	17,288
Publication "Leprosy in Children"		5,676	5,676
Collaborative research	76,885	69,949	146,834
Collaborating centres	8,500	3,962	12,462
Sub-total	280,478	100,534	381,012
Special Programme for Research and Training in Tropical Diseases:			
IMMLEP programme		173,736	173,736
THELEP programme		23,956	23,956
WHO Regional activities:			
Africa (15 countries)	227,032	42,828	269,860
Americas (1 country and 1 inter-country)		79,620	79,620
Eastern Mediterranean (1 country)	13,508		13,508
South-East Asia (6 countries)	176,888	120,871	297,759
Western Pacific (3 countries and 2 inter-country)	26,717	66,958	93,675
TOTAL	724,623	608,503	1,333,126
Percentage attributable to direct technical cooperation	(61.29%)	(83.48%)	(71.42%)
Other headquarters' and global and interregional activities (percentage of grand total, in parentheses)	280,478 (38.71%)	100,534 (16.52%)	381,012 (28.58%)

*Voluntary Fund for Health Promotion (Special Account for the Leprosy Programme) provided $528,883 and the Pan American Health Organization regular budget provided $79,620.

†Leprosy unit staff: 2 medical officers, 1 technical officer, 1 clerk, and 1 clerk-stenographer. Costing based on 1976 average costs.

The UNICEF expenditure on leprosy (including drugs) over the period 1970–75 reached a peak, in real terms of value to countries, in 1972 with $644,000. During 1973–74 the cost of dapsone, the standard drug, almost doubled in price so that the $764,000 spent by UNICEF in 1974 does not represent an increase in real terms of assistance in kind. The countries of the African and South-East Asia Regions were the main recipients of UNICEF assistance during 1970–75, 50% going to Africa and 42% to South-East Asia.

NONGOVERNMENTAL ORGANIZATIONS

A close relationship has been maintained for many years between the International Leprosy Association (ILA) and WHO. Although the ILA has a limited budget, it has considerable and important connexions with other

foundations and voluntary agencies. Expert assistance for both WHO and ILA are drawn from the same professional pool. Technical and scientific committees of the ILA (and those of voluntary agencies also) have a deep interest in the public health approach. The *International Journal of Leprosy and other Mycobacterial Diseases,* an ILA publication, and ILA-sponsored meetings are routinely used for publicizing WHO's policies, objectives, and programmes.

It is of special interest that the International Union against Tuberculosis, a nongovernmental organization, has recently begun cooperation with the International Federation of Anti-Leprosy Associations (see below) and other voluntary organizations with the aim of supporting programmes of either tuberculosis and leprosy combined activities or integrated public health programmes with tuberculosis and leprosy components.

VOLUNTARY AGENCIES

There is also close cooperation and liaison between WHO and the International Federation of Anti-Leprosy Associations (ILEP), which represents over 24 voluntary agencies from 16 donor countries. The total expenditure of these agencies reached $15.3 million in 1975. There is now a general understanding among voluntary agencies seeking to help patients that their action should be integrated with, or closely coordinated with, government programmes. In several countries, e.g., India, Indonesia, Maldives, Nepal, and Sudan, ILEP member agencies are providing valuable contributions to the development of rural and urban community-based health facilities.

Research is given high priority ($1.3 million in 1975) and also training ($1.5 million in 1975 in support of 7 training projects, of which 3 were in institutions

TABLE 2

Distribution of resources other than government inputs, by Regions, for 1976 (expressed in US$)

Region	WHO regular budget	Other sources			ILEP*		Total
		PAHO	VL†	Total	Coordinated with government	Direct assistance	
Africa	227,032		42,828	42,828	3,961,664	1,836,727	6,068,251
Americas		79,620		79,620	280,655	319,117	679,392
Eastern Mediterranean	13,508				1,443,094	2,465,015	3,921,617
Europe						351,742	351,742
South-East Asia	176,888		120,871	120,871	550,499	4,112,120	4,960,378
Western Pacific	26,717		66,958	66,958	583,277	218,531	895,483
TOTAL	444,145	79,620	230,657	310,277	6,819,189	9,303,252	16,876,863

*ILEP: International Federation of Anti-Leprosy Associations.

†VL: WHO's Voluntary Fund for Health Promotion (Special Account for the Leprosy Programme).

(in Ethiopia, India, and Liberia) providing courses at international level). Rehabilitation continues to be a particular concern of ILEP member associations; over $1 million was spent on 24 technical cooperation programmes. Table 2 gives details, by WHO Region, of some of the resources directed in 1976 into country-level programmes.

The efficacy of the services provided by voluntary agencies in the context of public health depends greatly on the support and recognition given by governments to their work. Full participation by the agencies' staff in the planning and organization of countrywide leprosy services fosters good cooperation and coordination of effort. The latter can often be achieved by the establishment of a national leprosy advisory board or committee, which would heighten interest in leprosy control as a national goal and lead to a better appreciation of the needs of each area, and hence to a wiser allocation of total resources.

LEPROSY. WHO *WEEKLY EPIDEMIOLOGICAL RECORD*, Number 3, (1979), pp. 17–23

The above article from a *WHO Chronicle* of 1977 should be read in close conjunction with detailed information just published by WHO in a *Weekly Epidemiological Record* of 1979. In fact this refers to the world-wide distribution of leprosy as at 1975, but is nevertheless the most up-to-date and authoritative source of data currently available on the estimated and registered numbers of leprosy cases in virtually all countries where leprosy is endemic. The last two paragraphs of the accompanying text are worth quoting in full:

> "Apart from the American Region, where for each country an estimate of the total number of cases accompanies the total of registered cases, less than a third of the countries provided estimates of the total cases. This is to be regretted since the figures which are available suggest that perhaps only one third of the total cases in the world are as yet detected.
>
> It is probable that the total number of cases in 1975 is not substantially different from that of 1968."

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News and Notes

PERSONAL

Award of the C.M.G. to Dr R. J. W. Rees

It is with the greatest of pleasure that we record our congratulations to Dr R. J. W. Rees on the award of the C.M.G. in the recent Honours List. Known perhaps best to readers of *Leprosy Review* as Vice-Chairman of the Editorial Board and Chairman of the Medical Advisory Board of LEPRA, Dr Rees' main professional contributions to medical and scientific research on leprosy have been based on his laboratory work at the National Institute for Medical Research, Mill Hill, London. Much of this work is now closely linked to the WHO Special Programme of research in immunology (IMMLEP) and the therapy of leprosy (THELEP). The value of his own published work is equalled only by the widely-spread and outstandingly effective influence he has in supporting and encouraging leprosy research in this country and abroad. In congratulating him, we wish Dr Rees every possible success — and for many years to come — in an increasingly interesting field of research, to which he has already contributed so much.

A. C. McDOUGALL

LEPRA-SYMPOSIUM, AMSTERDAM, 25 NOVEMBER 1978; THE GASTMANN WICHERS FOUNDATION

Following the XI International Leprosy Congress in Mexico, Professor A. H. Klokke of the Dermatologische Kliniek, Academisch Ziekenhuis, Groningen, The Netherlands, organized a Seminar in Amsterdam, at which invited delegates from the Mexico Congress spoke on various aspects of leprosy. Following introductory speeches by Professors Klokke and Zuidema, the programme was as follows:

(1) *Microbiology;* P. Draper, the National Institute for Medical Research, Mill Hill, London.
(2) *The significance of nasal mucosal changes;* C. J. G. Chacko, Schieffelin Leprosy Research and Training Centre, Karigiri, India.
(3) *Clinical aspects;* the intermediate zone of the spectrum; A. C. McDougall, the Slade Hospital, Headington, Oxford.
(4) *Immunology;* W. R. Faber, Universiteit van Amsterdam, Afdeling Dermatologie, Amsterdam.
(5) *Therapy;* M. F. R. Waters, the National Institute for Medical Research, Mill Hill, London.
(6) *Surgery and rehabilitation;* J. van Droogenbroek, All Africa Leprosy and Rehabilitation Training Centre, Addis Ababa, Ethiopia.

The one-day Seminar was attended by about 200 people, approximately 50 of whom were senior-year medical students. The topics stimulated a number of interesting questions and comments from the floor. Amongst these, Dr D. L. Leiker (The Royal Tropical Institute, Amsterdam) suggested "that in the matter of drug treatment of leprosy patients, the time had come to consider much shorter, well-supervised courses of drug combinations, followed by stopping treatment altogether, as in tuberculosis. This would significantly lighten the burden on the patient and the health services. Such a course would necessarily mean accepting a percentage of relapses, but the relapse rate might not be much worse than it is at present due to the high rate of defaulting patients. Moreover, in case of relapse, treatment could be resumed with the same drugs, since drug resistance is unlikely to develop after treatment with drug combinations for limited periods of time".

[This comment from a very experienced observer is clearly one of potentially great importance to the future of leprosy control. It is hoped that it will be examined and discussed at length in a future number of *Leprosy Review*. Editor.]

BASIC HEALTH SERVICES IN DEVELOPING COUNTRIES

A well-attended International Colloquium on basic health services in developing countries was held at the Institute of Tropical Medicine in Antwerp, 8–10 December 1978. Although specific health hazards (such as leprosy) were not studied in the presentations or working groups, the implications for leprosy treatment and control of the broad principles discussed were never far from the minds of the two leprologists who attended, the President and Secretary respectively (Prof. M. F. Lechat and Dr S. G. Browne) of The International Leprosy Association.

Following current trends and fashions in terminology and concepts, the colloquium considered such matters as coverage of the population concerned, rural or urban, and participation of the general public in making decisions about and taking responsibility for, the health services they need. Participants were not deceived by the politically-motivated slogans and catchphrases that have recently achieved wide publicity, nor deluded by some current assumptions that intractable problems can be solved by repetition of a few emotive words or phrases.

It was insisted that health professionals should themselves be open to the expressed needs of the populations they serve, and that their responsibilities as team-leaders are likely to increase rather than diminish as the "basic health workers" come to be recruited, trained, supervised and linked with a central referring authority.

Leprosy is a chronic disease that may fail to obtain the attention it deserves, and its share of resources and skilled man-hours, since in many countries it still lacks a popular image that it is recognizable in the early stages and can be arrested before deformity has occurred. Without over-emphasizing its importance in any given situation, leprosy calls for an increasing vigilance on the part of all those whose main concern it is.

S. G. BROWNE

MEDICAL EXPERIMENTATION AND HUMAN RIGHTS

An important Round Table Conference on "Medical experimentation and the protection of human rights" was held in Portugal on 30 November and 1 December under the auspices of the Council for International Organizations of Medical Sciences. The International Leprosy Association was among the 46 members of the CIOMS represented there — in the person of its Secretary, Dr S. G. Browne, who is a Vice-President of CIOMS. No fewer than 53 countries sent delegates to the Symposium, and WHO, Unesco, the United Nations, the Council of Europe and the Holy See were also represented.

The subject of the Round Table was of great interest and importance, since the continued advance of medicine and of research depended on the development of new investigative techniques and new therapies. All these posed potential hazards and risks, and unless the ethical and moral implications of research were recognized and respected, the ultimate gain to humanity might be achieved at too high a price.

The general principles embodied in successive codes (Nuremburg, Helsinki, Tokyo) need to be applied in specific situations, through Review Committees that were usually hospital-based. The Symposium recommended that the ethical issues in medicine should be included in medical curricula and continued in the postgraduate education of the doctor who is often during these formative years confronted by the real problems of professional life and practice.

In leprosy, the ethics of the controlled drug trial, the place of placebos, and the practical difficulties of obtaining true "informed consent" for investigations employing invasive techniques (such as vein puncture, skin smears, biopsies, etc.) or mass treatment programmes would have to be considered in the establishment of general guidelines that could be modified to suit the needs of individual countries and situations.

S. G. BROWNE

LEPROSY — AND WATER AND SEWAGE

The International Symposium on the Prevention and Control of Water-related Diseases in the Tropics, held in London from 11 to 14 December 1978, under the joint auspices of the Royal Society of Tropical Medicine and Hygiene, the International Association on Water Pollution Research, and the Institution of Civil Engineers, brought together over 200 experts from over 40 countries. As doctors, engineers, microbiologists, economists, etc, all were concerned in some way with the health of peoples living in the developing countries, and especially with the huge problems of health and hygiene in relation to water. As Dr S. G. Browne (President of the Royal Society of Tropical Medicine and Hygiene) said in welcoming Mr John Tomlinson, Under Secretary in the Ministry of Overseas Development, who opened the Symposium, "bringing good water to and taking soiled water from households in the tropics, is the greatest single benefit that Western science and technology could confer peoples of developing countries".

For leprosy workers, the Symposium provided a salutary reminder that

leprosy is but one among many transmissible diseases common in tropical and subtropical countries, and that water-related diseases take a far greater toll in acute and chronic morbidity and mortality than leprosy. Our very preoccupation with a disease whose victims are still far too often neglected should not blind us to the risk that they too run of contracting intercurrently some water-related disease (like intestinal infections and parasites, malaria and filariasis, hepatitis and schistosomiasis), nor to the principal killing, debilitating and maiming diseases that afflict chiefly the populations that are also exposed to leprosy infection.

S. G. BROWNE

TWO NEW MEDICAL AND SCIENTIFIC JOURNALS

(1) *Parasite Immunology,* published by Blackwell Scientific Publications Ltd, Oxford. This will be published quarterly and the UK subscription is £21 yearly. Its aims and scope are as follows:

> "*Parasite Immunology* is an international journal which will be devoted to research on parasite immunology in the general sense. Emphasis will be placed on how hosts control parasites, and the immunopathological reactions which take place in the course of parasitic infections. The journal will welcome original work on all parasites: helminths, fungi, protozoa, ectoparasites, bacteria and viruses. Each issue will cover the spectrum of parasite immunology through the original papers published, but in addition there will be 'viewpoint' articles, designed to interest as well as instruct."

(2) *Medical Teacher,* published by Update Publications Limited, 33–34 Alfred Place, London WC1E 7DP. This will be published bi-monthly and the UK subscription is £13 yearly. Volume 1, Number 1 for January/February 1979 has already appeared, and the Editorial summarizes the aims of this journal as follows:

> "*Medical Teacher* will aim to provide a readable and enjoyable journal that is readily available to teachers and learners in the health sciences, giving practical, down-to-earth guidance on day-to-day educational problems. It will seek to help teachers to improve their skills, to function more effectively, competently and enjoyably, and to enable them to keep up to date with advances in the field and with new techniques, materials and resources that they can use. Other journals primarily provide a vehicle for publication of educational research and for discussion of issues at an advanced level amongst those already specializing in medical education. Our function will be complementary to these, rather than competitive."

EDITORIAL NOTE: *FIELD WORKERS FORUM*

Hopefully in one of the remaining Numbers of *Leprosy Review*, Volume **50,** we shall be reviving *Field Workers Forum* with invited articles on topics such as physiotherapy, health education, laboratory work and teaching material for various grades of field worker. Contributions on any aspect of the subject with a direct application to field work will be most welcome.

LEPRA; PRIZE ESSAY COMPETITION, 1979; "THE IMMUNO-PATHOLOGY OF NERVE DAMAGE IN LEPROSY"

Since 1972, first in Oxford, then in Birmingham and Edinburgh, the British Leprosy Relief Association (LEPRA) has annually offered prize money of £100 for essays from medical students on various aspects of the leprosy problem. In 1977 it was decided to extend the offer to all universities with a medical faculty in the United Kingdom. The response in that year, and also in 1978, was encouraging, and the competition is therefore being continued in 1979, with the above title. Posters with full details of the conditions of entry are now being printed and will shortly be issued to universities. The closing date is 31 December 1979.

EDITORIAL OFFICE CHANGE OF ADDRESS

Please note that the new address for the Editorial Office of *Leprosy Review* is *The Slade Hospital, Headington, Oxford OX3 7JH. Tel. Oxford 64841, ext. 597.*

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Book Reviews

Dr D. S. Jolliffe very kindly reviewed Dr W. H. Jopling's *"Handbook of Leprosy"* in Number 1, **50,** *Leprosy Review* (1979), but we unhesitatingly include this additional review of a book which has already proved itself to be of great value in many parts of the world.

Handbook of Leprosy, 2nd edit., by W. H. Jopling, 1978. Published by William Heinemann Medical Books Ltd, 23 Bedford Square, London WC1B 3HT. pp. xii–139. ISBN 0 433 17566 4. Price £3.75.

This is a very valuable book, condensing into relatively little space an enormous number of facts regarding leprosy, including many interesting asides not normally associated with a book of this nature.

In his preface to the 2nd edition the author points out the wide-ranging advances which have occurred during the 1970's in our knowledge and understanding of leprosy, and which have called for extensive re-writing. The result is a concise textbook of leprosy, rather more sophisticated than other handbooks on the subject which have appeared recently and are intended primarily for the field worker. This book, written by a distinguished clinician, is written for the medical practitioner who is concerned with leprosy and who desires something more than a nodding acquaintance with it. The serious student will find here a thoroughly up-to-date, authoritative guide, clearly and concisely written.

The immediate relevance of this book is apparent from the start. The opening chapter on epidemiology emphasizes the importance of nasal infection as a source of *Mycobacterium leprae;* also the involvement of flies, arthropods and mosquitoes in the transmission of the bacillus, and the possibility of infection via the respiratory tract. Bacteriological, pathological and clinical aspects are presented together comprehensively in a single chapter, and several aspects in which knowledge has recently advanced are detailed, e.g. in relation to eye, bone, kidney and testicular involvement in lepromatous leprosy. There is an important chapter on modern immunological concepts, including references to immunotherapy and immunoprophylaxis. In a long chapter on management the approach is up to date. The most recent ideas on chemotherapy are given and drug resistance received special mention. A more emphatic approach to the importance of combined therapy in lepromatous leprosy might perhaps have been made, but unresolved problems of cost and organization in the field, and the fact that we still await confirmation of the best forms of combined therapy have doubtless influenced the author's presentation. The present day approach to leprosy control is presented concisely and includes Ellard's test for detecting dapsone in urine.

Some very useful Tables are a feature of this book, and there is an extensive glossary. Each chapter has appropriate references, and double conversion tables are given in an appendix. Twenty illustrations in colour are included, small but adequate, and there are some excellent photographs and diagrams in black and white.

The condensation into a book of this size of a subject as wide in scope as leprosy has now become inevitably involves many problems in the selection of material. Undoubtedly the author has got his priorities right. The surgeon could add considerably to those sections which primarily concern him and would doubtless have welcomed more detailed reference to preventive physiotherapy. From the standpoint of the clinician there is one area in which some expansion would have been welcome, namely differential diagnosis. The positive signs which enable a diagnosis of leprosy to be made receive full attention, but for the doctor working in tropical areas where leprosy is endemic, with no easy recourse to a reliable pathological laboratory, many diagnostic problems arise, especially in relation to dermatology. Let us hope that when a 3rd edition becomes necessary Dr Jopling from his great experience will be able to include a chapter on this subject.

T. F. DAVEY

The Armadillo as an Experimental Model in Biomedical Research, Scientific Publication Number 366. Pan American Health Organization, 525 Twenty-third Street, NW, Washington, DC 20037, USA. Price US$10.00.

This paperback of 140 pages records the Proceedings of a Workshop held at the Pan American Center for Research and Training in Leprosy and Tropical Diseases in Caracas, Venezuela, 23–27 May 1977. Apart from a small group of observers from Venezuela, there were 16 participants, all well-known in the field of experimental work on this model, including those who originally described it. The animal was discussed in detail under the following main headings: Part I, Biology of the armadillo; Part II, Experimental leprosy in the armadillo; Part III, Natural leprosy infection in the armadillo; Part IV, Utilization of the armadillo in biomedical research; plans and programs, and Part V, Future possibilities of the armadillo as an experimental model for biomedical research.

Discussion amongst the participants at each session is reported in full and—as usual—is often as interesting as the formal text. Although the main content of this book perhaps lags a little behind some of the conclusions of the more recent Mexico Congress, it contains much information of general interest to workers in many fields of leprosy research; it would in fact also be read with care, as one of the participants remarks early on, by research workers in other diseases, who may be intrigued by this animal's potential. The recommendations of the workshop were as follow:

"In view of the differences in local facilities, species, and degree of development of research capacities, we have made the following general recommendations:

(1) We strongly recommend that reproduction of armadillos under controlled conditions be given high priority in the immediate future. The armadillo must be bred in captivity before it can be utilized in biomedical research to its full advantage. This program should be carried out with different species of armadillos that have been demonstrated to offer particular promise for biomedical research (see this volume, pages 41–63, 120–136).

(2) We recommend that research on the immunology of the armadillo be pursued. In comparison with other animals, several species of armadillos (*Dasypus novemcinctus, D. sabanicola,* and *D. hybridus*) appear to have sluggish, cell-mediated immune reactions; the humoral response appears to be vigorous. It may be helpful to bring this observation to the attention of immunologists in general.

(3) Use of the armadillo in experimental chemotherapy of leprosy should be encouraged because the armadillo has several advantages not possessed by other animal models. Such advantages lie in the lepromatous features of the experimental disease and the presence of very large numbers of viable *Mycobacterium leprae.*

(4) Studies should be encouraged on the pathogenesis of infection by *M. leprae* in various species of armadillos.

(5) Studies should be continued on the indigenous infections that have been reported in *D. novemcinctus* with *M. leprae*-like bacteria in Louisiana and neighboring states. The geographic extent of the indigenous infection should be determined, and the possibility of such infections in other areas of the Americas and in other species of armadillos should be investigated. Exploration should be continued in various geographic areas in the Americas on possible infections by other mycobacteria of wild armadillos.

(6) Investigations should be made of the suitability of the armadillo as an experimental model for other infections diseases, particularly those caused by infectious agents whose temperature optima may be less than 37°C and for which there are presently no suitable animal models (see this volume, pages 120–136).

(7) We recognize the hazards involved in work with infected armadillos. Conditions for breeding colonies are different from those for laboratories in which the armadillos are infected. The shipment of armadillos from one area to another should be carefully considered in light of the possibility of introducing infectious agents. The degree of infectious hazards of infected armadillos is unknown, so measures for the protection of the personnel should be carefully considered. Strict measures for the containment of infectious material would be necessary.

(8) We recommend that methods for determination of armadillo age be investigated, with consideration of the use of the eye lens and tooth laminae or other methods. We suggest that

collections of eye lenses and teeth be started now from animals of known age and from important experimental animals.

(9) Because of the confusion and overlap in common or local names of armadillos, we recommend that the scientific identifications of armadillos be used exclusively. In some instances it may be necessary to carry out further research on the taxonomy of armadillos.

(10) In view of the differences among facilities, opportunities, and capabilities mentioned initially, all possible means of financial and other support should be sought, particularly for Latin America, where leprosy and armadillos are abundant but where facilities are sometimes defficient.

(11) We strongly recommend that the Pan American Health Organization promote the publication and distribution of the highly useful atlas on the histology of the armadillo, *Atlas sobre histologia del armadillo,* as presented at this meeting by personnel of the Pan American Zoonoses Center."

1978 Year Book of Dermatology, edited by F. D. Malkinson and R. W. Pearson. Published by the Year Book Publishers Inc, Chicago and London.

This book of 383 pages is priced at £19.75 in the United Kingdom and is clearly outside the realm of casual purchase by most individuals, though invaluable in any dermatological department. It is dated 1978 but in fact represents literature reviewed up to December 1977, and is of course merely one of a now famous series providing "in condensed form the essence of the best of the recent international medical literature. The material is selected by distinguished editors who critically review more than 500,000 journal articles each year". In this one on dermatology, the section reviewing Connective Tissue Diseases alone goes from page 9 to page 36 and finishes with a list of 392 references. Those working in leprosy will be impressed to note that this includes a reference (number 136) to the use of clofazimine in the treatment of discoid lupus, with improvement in 17 out of 26 patients, a reminder of the increasing number of publications in the medical literature on the use of this drug in conditions other than leprosy.

The word leprosy does not in fact appear in the index, but there are a few interesting entries under *Mycobacterium.* One of these refers to the paper by Dr Louis Levy in *Proc. Soc. Biol. Med.* **153,** 34–36 (1976) on the Activity of Thiadiazole on *Mycobacterium leprae,* commenting that the drug appears to be one of the few that are bactericidal for *M. leprae* and that it appears to be relatively non-toxic. The main entry on this paper concludes: "Unfortunately it has been withdrawn from human trial because of its carcinogenicity on long-term administration to rats. Perhaps some analogue will be both effective against *M. leprae* and free from carcinogenic effects". The Editors' comment in brackets continues: "We may never know how valuable this promising drug might have been in the treatment of leprosy, though, hopefully, additional observations will be made by workers in other countries. From now, CL 64,855 joins a rapidly enlarging group of drugs condemned on the basis of animal studies showing apparent carcinogenicity. How many potentially usable drugs will be lost on the basis of carcinogenicity tests in animals is not known, but before the list becomes massive, and significant numbers of people suffer because of the lack of development of new drugs, the validity of the animal testing procedures should be established".

A. C. McDOUGALL

Lepr. Rev. (1979) **50,** 162–179

Abstracts

25. WHITE, S. J., STONE, M. M. & HOWLAND, C. **Genetic factors in leprosy: a study of children in Uganda.** *J. Hyg., Camb.,* 1978, 80, 205–215.

The clustering of leprosy within families has led to considerable discussion in the literature, with some authors interpreting it as a reflection of hereditary—i.e. genetically determined—susceptibility, and others claiming that it reflects only the intimate contact of family members within the home. There is now much evidence that each of these factors (genetic and contact) plays a role in determining the distribution of leprosy within communities. On the other hand, most published studies have concentrated on only one of the factors in interpreting data on the distribution of leprosy; and, in so doing, many authors have overlooked the difficult problem posed by the fact that the two are closely confounded. As people generally have closest contact with their closest relatives, a risk associated with one factor will be apparently associated with the other as well. This study by White *et al.* is noteworthy in its effort to measure both factors simultaneously, in an attempt to assess the relative importance of each.

The data base consists of information on leprosy prevalence at the onset of, and leprosy incidence during the (8 years) course of, the MRC trial of BCG against leprosy, which was begun in Uganda in 1960. The total population at risk consisted of 20,990 children who were related to, or who had been in contact with, a known case of leprosy. Familial relationships between "at risk" children and nearest leprosy cases were expressed in terms of degree of consanguinity: fathers, mothers and full siblings = 1; half siblings of children and full siblings of their parents = 2; etc. (One flaw of the study is the author's insistence on these as "exact genetic relationship" data—a supposition which appears mildly over-optimistic in the light of well-recognized problems in the collection of such data and the absence of their objective verification in this study.) Contact relationships between "at risk" children and nearest leprosy cases were described in four categories: i.e. "house", "compound", "visiting" or "none". All children could then be broken down into subgroups in terms of their genetic and their contact relationships with the nearest known leprosy patient of lepromatous or non-lepromatous type. Analysis of these data consisted of calculating prevalence rates and incidence rates of leprosy within each subgroup, standardizing for age, tuberculin or vaccination status, and for proportion of multiple or lepromatous contacts. It was hoped that these rates would allow separation of the effects of genetic and of contact relationships between source cases and "at risk" groups. The methodology and standardizing procedures are elegant, and should serve as a model for future studies of the epidemiology of leprosy.

The results are well presented and interesting, even though negative. It proved difficult to separate out close genetic from close contact relationships, as these factors were so highly confounded (approximately 90% of first-degree relative contacts were in the home). Considering the data as a whole, however, there was little evidence for a gradient of risk associated with genetic relationship, and this was virtually totally removed when contact was taken into account. The authors recognize that their data do not refute the evidence for some role for genetic determination in leprosy susceptibility; but they are perhaps correct in their conclusion that, despite several shortcomings in this study due to the fact that it was not originally designed as a genetical investigation, it "should have been sufficient to reveal any important genetic influence." One may agree with the authors, therefore, that once an allowance has been made for extent of physical contact, the degree of consanguinity between known cases and apparent susceptibles does not appear to have been a major factor determining the distribution of clinical leprosy in this Uganda population.

P. E. M. Fine

26. AMBROSE, E. J., KHANOLKAR, S. R. & CHULAWALLA, R. G. **A rapid test for bacillary resistance to dapsone.** *Lepr. India,* 1978, v. 50, No. 2, 131–143.

To date, the only laboratory test of drug resistance in *Mycobacterium leprae* is based on the multiplication of leprosy bacilli in the footpads of mice fed with appropriate concentrations of drug in their diet. Such testing takes from 5.5 to 12 months to complete. Therefore a more rapid, and preferably *in vitro,* test is urgently needed, especially as clinical proof of resistance may take anything from 3 months to 5 or more years, requires close supervision of the patient, and may not be practicable in many cases.

Unfortunately, although a number of workers have claimed to have grown *M. leprae in vitro,* the consensus of opinion is that to date no claim has been fully and independently substantiated. Therefore Ambrose and his colleagues decided on a new approach, namely, to maintain leprosy bacilli obtained freshly from the patient in what they considered to be the best medium at present available, for the shortest possible period necessary to assess their rate of metabolism and growth potential, at a stage "prior to the likely emergence of contaminating Mycobacteria . . ."

The medium chosen was that of Murohashi and Yoshida (1975), a simple synthetic medium containing yeast extract. Great care was taken to maintain sterility while obtaining the skin biopsy specimens and extracting the leprosy bacilli. The latter was achieved by a simple two-stage technique; which involved placing the minced tissue in ice-cold distilled water to lyse all the human cell membranes so releasing the intracellular bacilli, and at the same time eliminating host cells. The initial inoculum size was 10^7 bacilli, but with increasing experience (and skill) this was reduced to 10^6 bacilli (containing perhaps 50,000 viable *M. leprae*) thereby enabling 50–100 cultures to be set up from each biopsy.

A radioactive assay was developed, using labelled [^{3}H]thymidine and [^{3}H]DOPA, and read by scintillation counter at 0, 6 and 9 days. Tubes assayed included standard cultures, heat treated samples, and cultures containing various concentrations of dapsone or rifampicin, and in one experiment clofazimine was also studied. It is claimed that good reproducibility could be achieved in the counts from similar tubes. Results obtained with [^{3}H]thymidine correlated well with those using [^{3}H]DOPA. Good correlation was also obtained between the *in vitro* tests now repeated and drug sensitivity tests performed on two patients in mice.

The work recalls the earlier studies of Hart and Valentine (1960) on the growth (but not multiplication) of *M. lepraemurium in vitro.* It is an exciting development, and further reports are awaited with interest. The advantages of obtaining the results of drug sensitivity tests within about 2 weeks are obvious. The method could be adopted for the rapid screening of new drugs against *M. leprae* and already is being applied to the rate of kill *in vivo* of *M. leprae* in lepromatous patients receiving different drug regimens in controlled clinical trials. Confirmation of the method from other centres is eagerly awaited. At the same time it must be remembered that the technique requires considerable expertise, as well as access to radioisotopes and to scintillation counting; and therefore could only be carried out in main universities and research centres possessing such facilities.

Murohashi, T. and Yoshida, K. (1975). *Acta Leprolog.* **58,** 5. Hart, P. D'A. and Valentine, R. C. (1960). *Nature* **185,** 58.

M.F.R. Waters

27. US LEPROSY PANEL (US–Japan Cooperative Medical Science Program) AND THE LEONARD WOOD MEMORIAL. **A statistical analysis of two chemotherapy trials in lepromatous leprosy: I. The response to therapy as measured by inoculation of mice. II. Interactions among patient variables.** *Am. J. trop. Med. Hyg.,* 1978, v. 27, 1005–1014 and 1015–1018.

I. The first paper is concerned with the correlation between certain pretreatment variables and the subsequent rate at which bacilli in skin biopsies were rendered non-infective to mice. The treatment regimen was found to be the most important determinant of the rate of loss of infectivity. In addition, the LAFB (log of the bacterial count in a suspension prepared for inoculation) and the LIB (logarithmic index of biopsies) were found to affect significantly the response to treatment in the early part of the trial, though not after a period of 24 weeks when the effect of the drugs was paramount. The influence of bacterial numbers was most evident when there was

no big difference in the efficacy of the drug regimens to be compared. The possibility that this apparent effect of numerous bacilli might in reality be due to an inhibitory effect of tissue has not yet been excluded. Of the pretreatment variables tested, age had some significance in trial I, clinical and histological classification (BL or LL) in trial II. This influence was noted after periods of 16 and 12 weeks treatment respectively. Age and classification were not related to the pretreatment values of the LIB or LAFB. Stratification of patients by bacterial counts in skin lesions is recommended for future short-term drug trials in lepromatous leprosy.

The conclusion that bacterial numbers in pretreatment biopsies have a bearing on the subsequent rate of killing of bacilli during a drug trial, if confirmed, is obviously important. Killing of bacilli is the measurement of greatest importance in assessing drug activity. By contrast, classification is more closely related to lysis of bacilli and the fall in bacterial numbers, which is a function of immunity. However, there is no explanation of why a high bacterial count should be associated with an apparent delay in reaching non-infectivity. If it is not due to a dilution effect on a tissue inhibitor of multiplication in the mouse, as the authors suggest, one can think only that a large lesion may contain more "persister" bacilli. This much seems to be clear though the regression analysis, as given, is not comprehensible to a non-mathematician.

II. The second paper deals with the inter-relationships between various characteristics analysed at the commencement of the trial. The subsequent progress of the patient and the loss of infectivity are not under consideration. Sex was found to be associated with the age of the patient and his histological classification; disproportionately large numbers of older patients and of BL patients were male. Classification by clinical and histopathological criteria were closely associated, but many patients classified BL histologically were found to be LL clinically (the details given in the text are by no means clear on this point). Similarly, the bacterial indices (LAFB, LIB and BI) were found to be correlated with each other, though not perfectly. Evidence is given for thinking the LAFB to be the most precise representation of numbers, which it should be as it is a direct count. (In one place BI is misprinted as LIB.)

No correlation was found between classification and bacterial indices. This may have been largely due to the requirement that biopsies should contain enough bacilli to make inoculation of mice practicable; thus, small BL lesions with low counts would have been excluded. (It must be allowed that there is considerable overlap between groups as regards bacterial indices; see *Bull. Wld Hlth Org.*, 1974, v. 51, 451.)

D. S. Ridley

28. SHEPARD, C. C., WALKER, L. L. & VAN LANDINGHAM, R. **Heat stability of *Mycobacterium leprae* immunogenicity.** *Infect. Immun.*, Oct. 1978, v. 22, No. 1, 87–93.

The authors have extended their previous observation that the proliferation in mice of a small challenge dose of *M. leprae* (5000 organisms) can be inhibited by "vaccination" with 10^7 *M. leprae*, or 10^7 BCG one month before challenge.

Thus when normal CFW mice are challenged in the footpad with 5×10^3 *M. leprae* bacilli from human, mouse, or armadillo tissues, there is slow multiplication up to a plateau level of about 10^6 organisms after 6 months. The authors monitored this growth curve and killed the vaccinated mice when the controls reached the plateau, and also 90 days later. The organisms in the challenged footpads were counted. In addition, the size of the lymph-node draining the vaccination site was measured at intervals.

The vaccines used with or without the pretreatments described below were 10^7 BCG, grown in a Tween-albumin medium, or 10^7 *M. leprae* from armadillo livers. For most experiments the *M. leprae* was purified by centrifugation, and gentle trypsinisation, but organisms further purified by the two-phase polyethylene glycol/dextran system gave similar results. Vaccines were usually injected intradermally into the right flank, 28 days before challenge, although in one experiment vaccination into a footpad proved equally effective.

The main studied variable in this paper was the effect on protective efficacy of killing the "vaccines". This was done by heating to 60°C, 80°C or 100°C for 30 min; by freeze-thawing; by autoclaving at 15 lb/sq. in. for 15 min, or by incubation in 2% phenol for 16 h at 37°C. It was consistently shown that whereas killing the BCG greatly reduced its efficacy, killed *M. leprae* protected as well as live organisms. Varying the technique used to kill the organisms, or the medium in which they were suspended resulted in small, not always reproducible differences,

attributable in part to aggregation of the organisms, and consequently enhanced retention at the vaccination site.

The degree of enlargement of the lymph-node draining the vaccination site usually correlated with the degree of protection.

In conclusion the authors argue that the mechanism of protection is likely to be a specific cell-mediated immune response to the challenge dose, and imply that since *M. leprae* can be used after autoclaving, their findings point to the possibility of a killed vaccine, safe for use in man.

However, this mouse model must be interpreted with caution. There is at present no evidence that protection in this system is due to T-lymphocyte-mediated recognition of the 5000 bacilli used for challenge. Protection is seen only when the vaccine induces persistent enlargement of the draining lymph-node. This is *not* an expected prerequisite for the generation of a straight forward *M. leprae*-recognizing T-cell population, and strongly implies that protection is largely due to the maintenance of a state of macrophage activation by a continuing response to the vaccine itself. Against this interpretation is an observation which may imply that non-specifically activated macrophages occur *only* at the vaccination site. Thus Patel and Lefford (1978, *Infect. Immun.,* v. 20, 692–697) have reported that following vaccination with killed *M. leprae,* activated macrophages capable of nonspecifically destroying *Listeria monocytogenes* were present at the vaccination site itself but were not demonstrable following intravenous challenge. Nevertheless, the absence of a nonspecific mechanism capable of killing intravenous *Listeria* does not eliminate the possibility that there is one capable of killing subcutaneous *M. leprae.*

Even if *M. leprae*-recognizing T-cells are evoked by the vaccine, it is doubtful whether their presence can be demonstrated by the protocol used. This doubt is derived from certain bizarre features of leprosy infection in the mouse. Thus when other mycobacteria such as *M. lepraemurium* or *M. avium* are injected into normal mice, the larger the challenge dose, the greater is the likelihood of proliferation and dissemination of organisms. With *M. leprae,* the reverse is true. Larger doses, such as 10^6 or 10^7 bacilli, fail to proliferate, and merely immunize the animal, whereas if only 5000 organisms are injected, they will multiply to a plateau of about 10^6 bacilli. Only in the absence of T-lymphocytes will proliferation continue beyond this point. We can conclude that once a sufficient load of *M. leprae* is present, mouse T-cells are perfectly capable of mounting an effective response, without vaccination. Moreover, *M. leprae* proliferates slowly, but evokes a response within a few days so that in a mouse challenged with an *immunogenic* number of bacilli, any accelerated response due to vaccination would be indistinguishable from the response in unvaccinated controls.

The authors avoid this rapidly evoked and effective response by challenging the mice with a subimmunogenic dose of only 5000 bacilli. The available suspensions of *M. leprae* contain notoriously little soluble antigen, of which there can be only about 10 pg in 5×10^3 organisms. The actual quantity of any one specificity released at any one time by 5000 very slowly proliferating organisms may well be below the threshold for effective T-cell recognition, even by a primed population. Thus the use of this tiny challenge dose may bias the system in favour of the non-specific macrophage activation mechanism, which will accompany the persistent reaction to vaccine, occurring in the enlarged draining node.

This is an important objection, but it can be resolved. It will be necessary to prove that T-lymphocytes recognizing *M. leprae* are generated (even by BCG) and that such T-cells will protect when transferred into normal mice, in which macrophage activation is not a problem. It should also be possible to demonstrate effective vaccination using an organism which *does* cause the development of T-lymphocytes capable of recognizing the antigens of the leprosy bacillus, but which does *not* itself cause chronic lymph-node enlargement and macrophage activation. It is at present puzzling that organisms known to have these properties have failed to protect in Dr Shepard's system (Shepard, Walker, and Van Landingham (1978), *Infect. Immun.,* v. 19, 341–394).

The other main point, made in this paper, is the immunogenicity of killed *M. leprae,* which has been confirmed in several other laboratories. This finding has surprised many workers, because the current dogma states that killed mycobacteria are not immunogenic. This dogma has arisen in spite of the fact that killed *M. tuberculosis* has been known to be fully immunogenic in the guinea-pig since the observations of Petroff in the 1920's. It is now clear that most species of mycobacteria are immunogenic when killed, and evoke vigorous T-lymphocyte responses. In this respect they resemble *Corynebacterium parvum,* which is routinely used killed. The erroneous dogma arose because certain members of the slow-growing subgenus, in particular

some (but not all) strains of the *M. avium/M. lepraemurium* group, and of the BCG/*M. tuberculosis* group, and *M. kansasii*, are indeed poorly immunogenic in the mouse, when killed. Usually organisms are pathogenic for those strains of mice in which they lack immunogenicity when killed. Perhaps a hint of the same phenomenon is seen with *M. leprae* in man. Thus *M. leprae* may be pathogenic only in those individuals who respond poorly to killed organisms, and in whom the Mitsuda lepromin reaction is consequently negative. This would suggest that a killed *M. leprae* vaccine will fail in those who need it most, just as killed *M. tuberculosis* or killed *M. kansasii* fail to protect susceptible mice from tuberculosis, or *M. kansasii* infection.

In summary, the fascinating and painstaking data contained in this paper appear superficially simpler to interpret, but are really at the heart of one of the most obscure corners of mycobacterial immunology.

G. A. W. Rook

The abstracts which follow are reprinted from the Tropical Diseases Bulletin, *September–December, 1978, and January, 1979, through the courtesy of the Director, Bureau of Hygiene and Tropical Diseases, London. They are classified according to subject.*

1. MICROBIOLOGY

29. SREEVATSA, SENGUPTA, U., RAMU, G. & DESIKAN, K. V. **Evaluation of bacteraemia in leprosy patients.** *Lepr. India,* 1978, v. 50, No. 3, 381–387.

"Thirty-five patients with leprosy have been screened for bacteraemia by haemolysis (HL), leucocyte adherence (LA) and buffy coat (BC) methods and the results have been compared. The HL method has yielded not only higher number of acid-fast bacilli (AFB) but also has detected more frequently AFB in blood of leprosy patients as compared to other methods. Further, it has been established that the skin over the cubital fossa does not play any significant role in contaminating blood samples while sampling blood by venepuncture."

30. HIRATA, T. **Electron microscopic observations of cell division in *Mycobacterium leprae* by means of serial ultrathin sectioning.** *Int. J. Lepr.,* 1978, v. 46, No. 2, 160–166.

"The division of *Mycobacterium leprae* in skin was studied in the ultrathin sections at the electron microscopic level. A few dividing bacilli were observed. The division seemed to be accomplished by inward extension of both the cell wall and the cytoplasmic membrane into the cytoplasm of the bacillary cell to form a septum. The intracellular membranous organelle (mesosome) is assumed to play a role in division."

31. KIRCHHEIMER, W. F. & SANCHEZ, R. M. **Examination of North American armadillos for mycobacteriosis.** *Lepr. India,* 1978, v. 50, No. 2, 156–160.

"Between 1 January 1974 and 31 December 1977, Carville has found no leprosy-like mycobacteriosis in 373 armadillos. Two hundred and eighty-two of these armadillos were caught in Louisiana, 78 in Florida and 13 in Texas.

"Seventy-five of the Louisiana armadillos were caught by personnel from the Louisiana Wildlife and Fisheries Commission in the area where Walsh *et al.* said they found 10 per cent 'naturally' infected armadillos.

"Two hundred and seven of Carville's armadillos came from the most human-leprosy prevalent part of Louisiana.

"Alleged claim of man to armadillo transmission of leprosy as an explanation for existence of leprous armadillos in nature also is at odds with South American findings and conditions.

"Independent verification of the claim of Walsh *et al.* is called for and if confirmed investigation of the various possible ways such a situation might have arisen."

[See *Trop. Dis. Bull.,* 1976, v. 73, abstr. 896; 1977, v. 74, abstr. 2803.]

32. NAKAMURA, M., CHIBA, K. & TANAKA, Y. **[Multiplication of** *Mycobacterium lepraemurium* **in cell-free liquid and medium. 12. Growth of** *Myco. lepraemurium* **grown on egg-yolk solid medium in the liquid medium.]** [NAKAMURA, CHIBA & TANAKA.] *Jap. J. Lepr.,* 1977, v. 46, No. 3, 92–97. **[13. Growth evaluation; sediment smear method (SSM).]** [NAKAMURA.] *Ibid.,* 98–103. **[14. Initial growth curve of** *Myco. lepraemurium* **in cell-free medium.]** [NAKAMURA & CHIBA.] *Ibid.,* 104–107. [**15. Growth stimulating effects of adenosine and thymidine on** *Myco. lepraemurium in vitro.*] [NAKAMURA.] *Ibid.,* 108–111. [In Japanese.] English summaries.

[For earlier parts see *Trop. Dis. Bull.,* 1978, v. 75, abstr. 514.]

33. MORI, T. **Study of a growth factor for** *Mycobacterium lepraemurium.* **I. Minimal medium.** *Int. J. Lepr.,* 1978, v. 46, No. 2, 125–132.

"A growth promoting factor is contained in the petroleum ether or acetone extracted residue of lyophilized dry egg yolk. Egg white, horse serum, soybean powder, bovine serum albumin, egg albumin and milk were used in *M. lepraemurium* culture attempts as protein sources instead of yolk lipoprotein. None of these substances promoted the growth of *M. lepraemurium.*

"One percent egg white medium was prepared from the mixture of one part 1% Ogawa basal medium to two parts egg white, adjusted to pH 6.1. This medium does not permit the growth of *M. lepraemurium* but permits bacillary survival for two months. This medium is most suitable as a minimal medium to investigate growth factors of *M. lepraemurium.* Utilizing the minimal medium, the following substances were tested for growth promoting activity: lecithin, cholesterol, petroleum ether extracted fraction of yolk, butanol extracted fraction of yolk, retinol, hemin, yeast extract, broth, farnesol and dolichol fraction of chicken liver. None of these supported growth of *M. lepraemurium.*

"The following neutralizing agents of free radicals were tried in the minimal medium: triethylenediamine, β-carotin, potassium iodide, potassium bromide, 2-aminoethyl-isothiouranium-bromide-hydrobromide and cysteamine. None of these supported growth of *M. lepraemurium*".

34. DELVILLE, J. & JACQUES, P. J. **Effect of treatment** *in vivo* **with Triton WR-1339 and Macrocyclon on infection of the mouse foot-pad by** *Mycobacterium leprae. Biochem. Soc. Trans.,* 1978, v. 6, No. 2, 395–397.

One month after the inoculation of *Mycobacterium leprae* into the footpads of mice, the mice were injected intraperitoneally at weekly intervals with Triton WR-1339 or Macrocyclon in normal saline. The footpads were examined between 41 and 96 days after the start of treatment. With both detergents, the counts of acid-fast bacteria and of granular and solid-stained bacteria were significantly decreased. The results are tabulated. The effect of Macrocyclon was significantly greater than that of Triton.

The authors say that it seems likely, from the viewpoint of final impact on intracellular *Myco. leprae,* that "Triton WR-1339 and Macrocyclon belong in that promising class of antileprotic agents that, like enzymic free-radical and singlet-O_2 generators and yeast glucan, are bactericidal and, in addition, accelerate subsequent intracellular destruction of the parasite."

[See *Trop. Dis. Bull.,* 1978, v. 75, abstr. (1573).]

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35. KOHSAKA, K., MAKINO, M., MORI, T. & ITO, T. **[Establishment of experimental leprosy in nude mice.]** *Jap. J. Bact.,* 1978, v. 33, No. 2, 389–394. [In Japanese.]

"A lepromatoid lesion developed in a nude mouse inoculated with *Mycobacterium leprae* was previously reported by the authors. The secondary passage of *M. leprae* which had proliferated in the lesion of the first infected nude mouse into other nude mice was confirmed experimentally. The reproducibility of animal transmission with nude mice was also proved.

"Successive transmission of *M. leprae* was carried out three times by the foot pad technique with the organism which had proliferated in a nude mouse. *M. leprae* derived from 5 lepromatous patients was also inoculated into foot pads of nude mice. Infected animals were maintained in vinyl (plastic) isolators under an SPF condition.

"Swelling was found microscopically in infected foot pads of all the animals in the 10th month after infection. A lepromatoid lesion was seen at the site of inoculation. At the same time, a bacterial harvest amounted to 3.6×10^8 from a foot pad of the mouse. The nude mouse (BALB/c-*nu/nu*) and its normal littermate (BALB/c-*nu*/+) were examined for body temperature with an electronic thermometer. There was no significant difference in body temperature between the nude mouse and the normal. *M. leprae* was detected from the skin of low-temperatured parts of the body, but not from the skin of high-temperatured parts, in the 10th month after infection. It was seen in lung, liver and spleen, but not in the kidney. *M. leprae* organisms derived from 5 different patients were successfully transmitted into the foot pads of nude mice. The maximum yield of *M. leprae* was 1.1×10^{10} in a foot pad in the 8th month after infection."

36. KAUR, S., KUMAR, B. & GUPTA, S. K. **Fine needle aspiration of lymph nodes in leprosy. A study of bacteriologic and morphologic indices.** *Int. J. Lepr.,* 1977, v. 45, No. 4, 369–372.

In confirmation of a previous study, the morphological indices (MI) of leprosy bacilli in inguinal lymph nodes were found to be higher in most cases than in slit skin smears. Lymph node aspirates were compared with impression smears of excised nodes in 16 cases, and found to give comparable results for both morphological and bacteriological indices. Aspiration of lymph nodes is recommended as a routine bacteriological procedure for leprosy.

[See *Trop. Dis. Bull.,* 1976, v. 73, abstr. 343.]

D. S. Ridley

37. KAWAGUCHI, Y., MATSUOKA, M. & KAWATSU, K. **Pathogenicity of cultivated murine leprosy bacilli of Hawaiian-Ogawa strain in mice. I. The pathogenicity of bacilli from rough colonies.** *Jap. J. Exp. Med.,* 1978, v. 48, No. 1, 17–26.

"This paper deals with the pathogenicity of cultivated murine leprosy bacilli from rough colonies of Hawaiian-Ogawa strain in mice. This strain was isolated by Ogawa, in 1970, on Ogawa's 1% egg yolk medium, from mice previously inoculated with Hawaiian strain of murine leprosy bacilli which has been maintained by passages from mice to mice.

"The pathogenicity of Hawaiian-Ogawa strain was found to belong to the same pattern as Hawaiian strain when the subcutaneous inoculation test was carried out in C57BL/6 and C3H mice, the former being representative of the benign type and the latter being representative of the malignant type.

"In KK mice of the intermediate type with Hawaiian bacilli, however, Hawaiian-Ogawa bacilli produced the lesions with malignant features in almost all the male mice, while the female mice were divided into two groups roughly half showing the intermediate or malignant type. In DDD mice of the benign type with Hawaiian bacilli, some cases of the male mice showed the malignant features, whereas almost all the female mice were of the benign type in the same experimental conditions.

"The pathogenicity of Hawaiian-Ogawa bacilli in mice did not revert into that of Hawaiian bacilli even after serial mouse passage.

"There are slight but definite differences in the mouse pathogenicity between Hawaiian-Ogawa and Hawaiian strains."

38. STANFORD, J. L. *et al.* **A study of alleged leprosy bacillus strain H1-75.** *Int. J. Lepr.,* 1977, v. 45, No. 2, 101–106.

Subcultures of the Skinsnes organism (strain H1-75) cultured from a patient with leprosy were examined bacteriologically in Antwerp and London and identified as a variety of *Mycobacterium*

marianum (syn. *scrofulaceum*). The organism grew on ordinary mycobacteriological media. It gave a skin test reaction in 0/27 patients with tuberculoid leprosy. One of the subcultures also contained numbers of a smaller organism, about the size of *Myco. leprae,* which appeared to be dead. Similar studies of other cultures of the Skinsnes organism must be made to confirm or refute its identity as *Myco. leprae.*

The authors reject the view of Skinsnes and Kato that this organism might be a modified form of *Myco. leprae,* as it differed from it in every way except in being a *Mycobacterium.* It might have been present with the leprosy bacillus in the tissues of the patient since similar organisms have been repeatedly cultured in the past. But they think it most likely to have been a laboratory contaminant.

D. S. Ridley

39. MATSUOKA, M. & KAWAGUCHI, Y. **[Observation of *M. lepraemurium* in subcutaneous tissue of mice by spread tissue preparations.]** *Jap. J. Lepr.,* 1977, v. 46, No. 2, 37–43. [In Japanese.]

"Mice of 6 inbred strains (C3H, CF≠1, BALB/C, KK, DDD and C57BL/6) were inoculated subcutaneously in the back with 0.25 ml of a 1:1000 leproma suspension (Hawaiian strain). Spread tissue preparations were made from the inoculation site at about weekly intervals until 10 weeks to observe growth patterns of murine leprosy bacilli in subcutaneous tissues.

"There were no remarkable differences among these 6 strains during the first 3 weeks after inoculation. In 1 week, an acute inflammatory reaction with polymorphonuclears disappeared and elongation of the bacilli without increase in number was observed in mononuclears. The bacilli showed longer and thinner forms with a length of about 2 to 3 times the initial size. At 3 weeks, enlarged mononuclears, being crowded with the long bacilli, could easily be demonstrable by low magnification.

"Four weeks after inoculation, however, significant differences were observed in growth patterns of murine leprosy bacilli among these mouse strains. In C3H and CF≠1 mice, inflammatory cells consisted mainly of mononuclears, most of which were heavily loaded with the long bacilli. On the contrary, in the other four strains, many lymphocytes and polymorphonuclears were found in the subcutaneous inoculation site, surrounding a smaller number of the bacillus-containing mononuclears. Such differences between mouse strains became more remarkable at 5 weeks, because of more pronounced cellular reactions in these 4 strains.

"The significant differences between C3H and CF≠1 mice were manifested in 10 weeks. In CF≠1 mice lymphocyte infiltration, which surrounded the lesions of mononuclear containing the bacilli, was evident, whereas no host cellular reactions were seen in C3H mice.

"From the results of these observations, this experimental method can be recommended for early evaluation of development of mouse leprosy, with special reference to the relation of the host cells to the organism, and these mouse strain differences are presumably due to the cell-mediated immunity developed in the hosts."

40. MORI, T. **[Cultivation of *Mycobacterium lepraemurium* under low oxygen tensions.]** *Jap. J. Lepr.,* 1977, v. 46, No. 2, 44–47. [In Japanese.]

"Cytochrome b_1 and cytochrome a_2 were detected in the *in vivo* grown or *in vitro* grown *Mycobacterium lepraemurium,* however, cytochrome c and cytochrome a were not found. Cytochrome a_2 is a complex of D and C type cytochrome which is mainly seen in *Pseudomonas aeruginosa* grown in anaerobic condition and is not seen in the bacteria grown in aerobic condition. *Mycobacterium lepraemurium* was grown in aerobic condition on 1% Ogawa yolk medium, however, growing place of the organisms might be fairly anaerobic condition because the cytochrome a_2 was found in this organism. When a few bacteria were inoculated on the 1% Ogawa yolk medium, the organism might be unable to make an optimal anaerobic condition on this medium. Then trial of the cultivation of *Mycobacterium lepraemurium* under low oxygen tension was made by the author.

"Media were put in glass desiccator and were exchanged with gas mixutre through sponge gum cap. Mixture gas was added in desiccator once a week. As shown in Table I, the mixture

gas composed of 5% CO_2, 1% O_2 and 96% N_2 gave the best result for cultivating with a few organisms, but no colony formation was obtained in case of the inoculation with 10^5 bacilli. In the primary isolation of *Mycobacterium lepraemurium* 100% success was not obtained, especially primary isolation from infectious tissue containing relatively little numbers of bacilli was very difficult. As seen in Table 2, the low oxygen condition was better than normal air condition. Primary isolation from ten times diluted inoculum was failed in normal air condition, but succeeded on some tubes in 1% condition. Primary isolation of *Mycobacterium lepraemurium* from tissue culture of A31 cells which contained less bacilli than the murine leproma, is also possible in 1% O_2 condition."

41. MORI, T. **[Cultivation of *Mycobacterium leprae* on modified 1% Ogawa yolk media.]** *Jap. J. Lepr.,* 1977, v. 46, No. 2, 48–51. [In Japanese.]

"Follow-up experiments of Ogawa's method for cultivation of *Mycobacterium lepraemurium* were succeeded by Kozeki and Mori. This steadfast method of isolation of *M. lepraemurium* might have been established today. Now it is urgently necessary that this method should be applied to cultivation of *Mycobacterium leprae* encouraged by the success in case of *M. lepraemurium.* As it was already thought from a biochemical study of *M. lepraemurium* that *M. lepraemurium* might be injured by the excess of oxygen and Prabharan reported that *M. leprae* have a diphenol oxidase and the diphenol might have an important role in the metabolism of *M. leprae,* some suitable reducing agents and diphenol compounds must be used in culture of *M. leprae.*

"Inhibition tests for some reducing agents and diphenol compounds were done by using *M. lepraemurium* and 1% Ogawa yolk medium. As seen in Table 1 and Table 2, the suitable concentrations of DOPA, cystein, thioglycolate and adrenalin were respectively 31γ–62γ, 31γ, 15γ–31γ and 10γ per ml. The other reducing and modified reagents were unsuitable to the growth of *M. lepraemurium.* Then the leproma materials were cultivated for one year at 30°–35°C on 1% Ogawa yolk media modified with 33.3 γ/nl DOPA, 33.3 γ/ml l-cystein, 17 γ/ml thioglycolate and 10 γ/ml l-adrenalin. Eight materials from 8 leprosy patients in National Leprosarium Airakuen, 3 materials from one patient in National Leprosarium Nanseien, one material sent from Professor Nakamura, one material given from National Leprosarium Seishoen and 3 materials from 3 new patients in our clinic were cultured. The results of all experiments were negative even cultivating under the 5% CO_2, 1% oxygen and nitrogen condition."

2. IMMUNO-PATHOLOGY

42. KORANNE, R. V., SINGH, R. & IYENGAR, B. *Mycobacterium leprae* **in the striated muscle of tuberculoid leprosy patients.** *Lepr. India,* 1978, v. 50, No. 3, 375–380.

'Striated muscle specimens from 24 untreated proved cases of tuberculoid leprosy and five healthy normal individuals were studied histopathologically for the evidence of leprous pathology. Atrophy or damage to the muscle fibre was not observed in any patient. Nineteen (79.16%) cases showed evidence of leprosy in striated muscles. Seventeen (70.83%) cases showed scanty histiocytic infiltrate between the muscle fibres. Thirteen (54.16%) cases had acid fast bacilli mostly inside the muscle. There was no correlation between the location of the bacilli and that of the histiocytes; in two cases, acid fast bacilli were seen without the histiocyte. The bacilli were solidly staining and were lying singly in the undamaged muscle. There was no evidence of tuberculosis and, in the Control group, none showed any AFB or infiltrate.

"The presence of lepra bacilli did not depend upon the location of the muscle. Two of the muscle specimens not underneath the cutaneous lesions also had acid fast bacilli. 21.05% of these cases also showed simultaneous involvement of liver and lymph nodes. These are strong evidence of systemic nature of disease in tuberculoid leprosy as well."

43. AGARWAL, S. K. & SAHA, K. **Serum alpha-1-antitrypsin in various forms of leprosy.** *Indian J. Med. Res.,* 1978, v. 68, July, 136–139.

"Serum alpha-1-antitrypsin (AAT) levels were estimated by single radial immunodiffusion technique using monospecific antiserum in 55 patients with various forms of leprosy and compared with its levels found in 60 healthy controls and 50 patients with chronic obstructive airway disease (COAD). Although progressive increase in serum AAT level was observed from normal controls (225±84 mg per cent) through tuberculoid (236±67) to lepromatous (247±95) leprosy patients, a significant elevation was noticed only in cases complicated with ENL (351±97). On the contrary, the patients with COAD demonstrated a significant decline (183±73) of serum AAT. It has been postulated that AAT is an acute phase reactant and is released during the reactive phase of the illness to counteract various endogenous as well as exogenous proteases."

[See also *Trop. Dis. Bull.,* 1977, v. 74, abstr. (832).]

See also DELIA *et al.,* abstr. 3132; DUTTA and DUTTA, abstr. 3134.

44. MINAGAWA, F., YOSHINO, Y. & ABE, M. **Early immune responses in nude mouse following intravenous injection of** *Mycobacterium leprae. Jap. J. Lepr.,* 1978, v. 47, No. 1, 37–42.

"For the purpose of elucidating immune mechanism in early stage of leprosy, three strains of mice, conventional BALB/c, SPF BALB/c-*nu*/+ and BALB/c-*nu*/*nu* mice, were injected intravenously with a mixture of 10^7 *M. leprae* and 10^8 sheep red blood cells. All of these mice showed similar degree of antibody response to *M. leprae,* as demonstrated by indirect immunofluorescence, the antibody-*titer* reaching to the maximum within a week after the injection of antigens. The production of IgG antibodies was somewhat delayed and the *titer* reached to a plateau within 2 or 3 weeks. No decline of antibody-*titer* was observed till at least 5 weeks after the injection of antigens. The transfer of thymocytes from immunized *nu*/+ donors to *nu*/*nu* recipients did not influence the antibody-*titer* in the recipient."

45. JOB, C. K., CHACKO, C. J. G. & TAYLOR, P. M. **Electronmicroscopic study of histoid leprosy with special reference to its histogenesis.** *Lepr. India,* 1977, v. 49, No. 4, 467–471.

Biopsy specimens of histoid nodules from 2 patients were examined by electron microscopy. The thin, elongated histoid cells were found to be closely invested by collagen fibrils. Many small finger-like villi were present on the cytoplasmic surface, mitochondria and lysosomes were numerous and rough endoplasmic reticulum was increased. Thus the cells shared the features of both macrophages and fibroblasts. Numerous bacilli were present, both in phagolysosomes and outside them, but electron transparent substance, or foam, was relatively scanty. It was concluded that the histoid cells were histiocytes, and that the differences from the cells in ordinary lepromatous lesions were due to local proliferation of the cells in response to stimulation by rapid multiplication of *Mycobacterium leprae.* Ordinarily macrophages accumulated by the infiltration of monocytes from the blood.

D. S. Ridley

46. GUPTA, J. C., PANDA, P. K., SHRIVASTAVA, K. K., SINGH, S. & GUPTA, D. K. **A histopathological study of lymphnodes in 43 cases of leprosy.** *Lepr. India,* 1978, v. 50, No. 2, 196–203.

47. BAPAT, C. V., MODAK, M. S., DESOUZA, N. G. A. & CHULAWALLA, R. G. **Comparative study of skin reactions in leprosy patients to** *M. leprae*-**lepromin and to ICRCin, an antigen from cultivable acid-fast bacilli from** *M. leprae* **isolated from lepromatous nodules.** *Lepr. India,* 1977, v. 49, No. 4, 472–484.

"Skin test antigens (Dharmendra type) were prepared from fresh *M. leprae* (lepromin) and from a culture of strain C-44 ICRC bacilli (ICRCin) grown *in vitro* from *M. leprae* isolate from

lepromatous nodules. Comparative study of skin reactivity to lepromin and ICRCin—both 'early' and 'late' reactions in 76 leprosy patients was conducted. In 29 lepromatous (LL) cases, 25 exhibited totally negative reaction at the end of the third week. In tuberculoid (TT) 22 and 23 out of 31 were positive (> 4.5 mm) at 3 weeks to lepromin and ICRCin respectively. In the 16 BB group, the reactions were comparable in the same patient. The cellular reaction in tuberculoid cases consisted of lymphocyte infiltration, epitheloid giant cells and Langhan type cells and indistinguishable from each other. These data with characteristic total lack of reaction in 25/29 lepromatous leprosy cases and identical cellular reaction in TT patients, provide strong evidence that ICRC bacillus strain C-44 is antigenically identical with *M. leprae*."

[The "ICRC bacillus" is not a single strain, but consists of a number of isolates of a cultivable *Mycobacterium* obtained from different human lepromas. Its full antigenic profile is currently being studied and results are awaited. The present paper indicates that it is antigenically closely related to *M. leprae,* but it is overstating the case at this stage to claim that it is "antigenically identical with *M. leprae*", because:— a) only Dharmendra and no Wade-Mitsuda type antigen was studied; b) lepromatous patients nos 10, 24 and 53 gave discordant early reactions and patient no. 26 gave a discordant late reaction, the latter being particularly important; c) no biopsies were taken of lepromatous reactions.]

M. F. R. Waters

48. SERJEANTSON, S. & WOODFIELD, D. G. **Immune response of leprosy patients to hepatitis B virus.** *Am. J. Epidem.,* 1978, v. 107, No. 4, 321–327.

The immune responses to hepatitis B virus of 323 Melanesian patients with leprosy in Papua New Guinea and 290 control subjects were studied using sensitive assay techniques. It was found that patients with lepromatous leprosy, whether in institutions or not, tended to have the highest rates of hepatitis B surface antigen and were significantly different from the patients with the tuberculoid form of leprosy. In the multivariate analyses of antigenaemia, severity of the disease remained a significant determinant of the rates of surface antigen. Similarly, when the series was grouped into three immune response categories of surface antigen, surface antibody or no serological evidence of exposure to hepatitis B virus, the severity of leprosy was a significant factor in determining the immune response. For lepromatous and borderline lepromatous patients, the probability of responding antigenically to the virus, given that some measurable response has occurred, is 0.420. The corresponding probability for tuberculoid patients is 0.250 and for healthy control subjects 0.293. These probabilities suggest that the lepromatous patients have an impaired immune response that not only predisposes them to the most severe form of leprosy but also decreases their efficiency in terminating hepatitis B infection with surface antibody. In contrast, patients with tuberculoid leprosy are as efficient as healthy control subjects in mounting an antibody response.

A. J. Zuckerman

49. JOB, C. K., KIRCHHEIMER, W. F. & SANCHEZ, R. M. **Liver lesions in experimenta lepromatoid leprosy of the armadillo. A histopathologic study.** *Int. J. Lepr.,* 1978, v. 46, No. 1, 1–8.

"A retrospective study of liver lesions was made in 13 armadillos infected intracutaneously with 10^7 *M. leprae* from the same inoculum, to evaluate the pathogenesis of the experimental disease. Survival times ranged from 13 to 55 months. In seven armadillos the liver lesions were markedly less severe than in six of these animals. The extent of the lesions was unrelated to the duration of the infection and was interpreted as reflecting individual differences in resistance. In contrast to man, leprosy bacilli were found in the liver cells of both groups of armadillos but to a lesser extent in those of the more resistant armadillos. The latter also had no obvious changes in the liver tissue except for round cell infiltration and prominent Kupffer's cells which contained *M. leprae*. These lesions can be compared to indeterminate leprosy in humans.

"The lesions in the more susceptible (lepromatoid) armadillos were initiated in Kupffer's cells. Later, large collections of bacillated macrophages infiltrated the liver lobules. The liver cells

heavily loaded with *M. leprae* developed a pale granular cytoplasm which became foamy in the late lesions. In three of the lepromatoid livers, lesions compatible with *erythema nodosum leprosum* were seen."

50. NUTI, M., TARABINI, G. C., TARABINI, G. C. L. & THAMER, G. L'antigene *e* (HB_eAg) nella lebbra. [**The *e*-antigen in leprosy.**] *Quad. Sclavo Diagn.*, 1977, v. 13, No. 4, 393–403. English summary.

From a consideration of all the data so far collected by various workers, it can be said that the occurrence of HB_sAg does not differ between lepromatous and tuberculoid leprosy patients, nor does the occurrence differ from that in the rest of the population, though there is a positive correlation between this incidence and the climatic and environmental conditions of the groups studied, HB_sAg being more frequent in patients mostly deriving from tropical countries and closed communities, on whom most of these observations were made. The investigation here reported deals with the incidence of HB_eAg, this antigen being said to be in direct and close relation with infectivity and with the persistence of the B virus in the circulation.

Sixty-six samples of serum from 42 patients with lepromatous and 24 with tuberculoid leprosy, in Somalia, were examined. For HB_sAg and its antibody were radioimmunologically assayed and the Ouchterlony immunodiffusion method was used for HB_eAg and its antibody. HB_eAg was not found in any case; HB_eAb was found in 3 cases of lepromatous leprosy. HB_sAg was found in 10 cases of lepromatous and in 3 of tuberculoid leprosy. HB_s antibodies were found in 16 cases of lepromatous and in 10 cases of tuberculoid leprosy. The 3 patients with HB_eAb also carried HB_sAg. There was no relation with age or sex. The absence of HB_eAg suggests that these carriers present a low degree of risk or none at all. It appears persons with a depressed cell-mediated immunity reaction tend to acquire the B virus antigen more easily and with more difficulty to show the corresponding antibody.

E. Agius

51. POULTER, L. W. **Systemic immunological reactivity in the absence of delayed type hypersensitivity during murine leprosy.** *Cellular Immunol.*, 1978, v. 40, No. 1, 117–127.

"The generation of cell-mediated immunological reactivity has been examined following systemic infection of mice with *M. lepraemurium* (MLM). It has been found that although delayed-type hypersensitivity to MLM is ablated within 2 weeks of infection, resistance, as determined by a containment of the multiplication of the organism at various sites, persists for at least 7 weeks. During this time it was found that a population of lymphocytes sensitized to MLM antigens appeared within these animals and that DTH could be generated if these cells were focused at a footpad site.

"The possibility that these changes in immunological status are determined by increasing levels of antigen, resulting from a systemic killing of MLM is discussed. It is postulated that persistent desensitization eventually results in anergy to MLM."

52. SAHA, K., SARIN, G. S., CHAKRABORTY, A. K. & SEN, D. K. **Ocular immunoglobulins in lepromatous leprosy.** *Int. J. Lepr.*, 1977, v. 45, No. 4, 338–342.

"Immunoglobulin levels in the ocular fluids have been estimated in normal subjects and lepromatous leprosy patients. In the normal tear, IgA is the major immunoglobulin while IgG is the only immunoglobulin detected in the aqueous humor. The immunoglobulin profiles in the tear and the aqueous humor in normal subjects are different. The mean IgA level in the tears of the lepromatous leprosy group is significantly lower than in the control patients. IgA and IgG levels are raised in the aqueous humor of some leprosy cases who had suffered from uveitis in the past and also in all cases with active endogenous uveitis. Therefore, in lepromatous leprosy the pattern of immunoglobulin alteration in the tear and the aqueous humor is not parallel."

53. OKADA, S., KOMURA, J. & NISHIURA, M. *Mycobacterium leprae* **found in epidermal cells by electron microscopy.** *Int. J. Lepr.,* 1978, v. 46, No. 1, 30–34.

"Leprosy bacilli were found in a keratinocyte of the epidermis by the electron microscopic observation of the ultrathin section of a leproma. The possibility of discharge of leprosy bacilli from the skin should be considered even if the lepromatous patient does not have any ulceration."

54. SAOJI, A. M. & MENE, A. R. **Persistence of Australia antigen in leprosy — a frustrating puzzle in immunology.** *Lepr. India,* 1978, v. 50, No. 1, 7–10.

Hepatitis B surface antigen was detected by the electro-immunodiffusion technique (Laurell's rocket method) in the serum of 4% of 100 patients with lepromatous leprosy and in 2% of 100 patients with tuberculoid leprosy or with a positive lepra reaction in India. Surface antibody was found in 3% of the patients with lepromatous leprosy.

A. J. Zuckerman

55. SASIAIN, M. C., CAROSELLA, E. D., BALINA, L. M., BREZAVSCEK, D. M. & BACHMANN, A. E. **A study of cellular and humoral immunity in three species of armadillos. Part I.** *Int. J. Lepr.,* 1977, v. 45, No. 4, 323–326.

"In the present study the membrane receptors of immunocompetent cells and immunoglobulins in three varieties of armadillos were explored for determining, in later studies, the possible differences in inoculated animals developing leprosy. The studies of cellular immunity were performed in five *Chaetophroctus villosus* (Ch.v), one *Dasypus hibridus septecinctus* (DHS) and one *Zaedus pichei* (ZP), while the humoral immunity was studied with a serum pool of 17 Ch.v and 6 DHS. The results obtained demonstrate that the lymphocytes of the three species studied have receptors for SRBC, C3 and Ig-s, and no receptors for Fc segment of immunoglobulins. With reference to immunoglobulins no definite alteration of the humoral immunity was observed with the exception that DHS presents increased IgG levels and Ch.v increased IgM."

3. CLINICAL

56. EKAMBARAM, V. & SITHAMBARAM, M. **Self-healing in non-lepromatous leprosy in the area of the ELEP Leprosy Control Project Dharmapuri (Tamil Nadu).** *Lepr. India,* 1977, v. 49, No. 3, 387–392.

Six years' observation of 432 patients with non-lepromatous leprosy, most of them presenting single lesions, and none of them taking chemotherapy, revealed that self-healing occurred in 72.92%; 20.8% remained stationary; and only 6.25% became worse.

T. F. Davey

57. HANSENOLOGIA INT., 1977, v. 2, No. 1, 94–98. Associação de hanseníase e periarterite nodosa. [**Association of leprosy with periarteritis nodosa.**] English summary.

58. BARNETSON, R. StC. & BRYCESON, A. D. M. **Cutaneous leishmaniasis and leprosy.** *Trans. R. Soc. Trop. Med. Hyg.,* 1978, v. 72, No. 2, 160–163.

"Eight patients who had concomitant leprosy and leishmaniasis are described. Two patients with lepromatous leprosy had high resistance leishmaniasis, implying that immune deficiency in lepromatous leprosy is specific to *Mycobacterium leprae*."

59. DATAR, S. V., PANSARE, M. S. & KATTI, V. A. **Leprosy and ABO blood groups.** *Lepr. India,* 1978, v. 50, No. 3, 388–391.

"Two hundred and fifty patients with lepromatous and non-lepromatous leprosy were studied. The statistical analysis showed that there is no relationship between the blood groups and lepromatous or non-lepromatous leprosy. The results are discussed in comparison with the work of other authors."

60. KORANNE, R. V., SINGH, R. & IYENGAR, B. **Bone-marrow in tuberculoid leprosy.** *Lepr. India,* 1978, v. 50, No. 2, 181–184.

"Twenty-four untreated patients with proved tuberculoid leprosy and five healthy controls were investigated for the involvement of bone-marrow. The cytology was essentially normal and no acid-fast bacilli was seen in the bone-marrow smears."

4. THERAPY

61. MATSUO, Y., UTSUNOMIYA, S., KAJIHARA, N. & KIM, S. K. **Combinations of rifampicin and isoprodian in the treatment of *Mycobacterium leprae* infections in mice.** *Jap. J. Lepr.,* 1978, v. 47, No. 1, 43–47.

"Combinations of rifampicin and isoprodian were tested against *Mycobacterium leprae* in mice. Drugs were given by gavage once daily, 6 times per week, starting from the day of infection to day 21 after infection in the first experiment, and from day 51 to day 80 after infection in the second experiment. Although a few combinations had some increases of the growth delay over single drugs, it is not likely that appreciably additive effect of both drugs has been noticed in the treatment of *M. leprae* infections in mice."

[Isoprodian is a combination of isoniazid, prothionamide and dapsone. See also *Trop. Dis. Bull.,* 1976, v. 73, abstr. 352.]

62. NOORDEEN, S. K. **Long term effects of chemoprophylaxis among contacts of lepromatous cases. Results of an $8\frac{1}{2}$ years follow-up.** *Lepr. India,* 1977, v. 49, No. 4, 504–509.

An $8\frac{1}{2}$-year follow-up after the termination of a controlled study of chemoprophylaxis with dapsone involving 700 children revealed that those who received dapsone continued to show a degree of protection superior by 56.1% compared with children who received a placebo. This protection was seen about equally in all age-groups, and it was much higher among males than among females. Chemoprophylaxis was more effective in the $2\frac{1}{2}$ years after termination of treatment than in later periods. It is suggested that this "carry over" benefit from chemoprophylaxis might be caused by the drug aborting subclinical infections without interfering with the development of immunity.

T. F. Davey

63. BALAKRISHNAN, S. **Monitoring self administration of dapsone by patients.** *Lepr. India,* 1977, v. 49, No. 3, 364–371.

"The urinary DDS/creatinine ratios in the supervised in-patients and out-patients attending the C.L.T. & R.I. clinic were compared. The subjects of this study were receiving dapsone at the daily dosage of 25, 50 and 100 mg or bi-weekly dosage of 25, 50, 75, 100 and 200 mg. The mean urinary DDS/creatinine ratios from out-patients were significantly lower than those of the in-patients in both dosage schedules of treatment and suggest that a certain percentage of out-patients have been irregular in the intake of dapsone in the period immediately prior to the collection of urine specimens. The estimated percentage of gross irregularity of intake is

markedly higher in the bi-weekly as compared with the daily dosage schedule. The gross irregularity of intake was particularly marked in the higher dosage groups such as 100 mg daily or bi-weekly and 200 mg bi-weekly. The implications of the findings are discussed."

64. NAIK, S. S. & PANDYA, S. S. **Dapsone in wheat flour as a possible method of therapy in leprosy. A laboratory report.** *Lepr. India,* 1977, v. 49, No. 4, 516–520.

Dapsone tablets were added to wheat, in the proportion of 400 mg dapsone to 1 kg wheat, and ground in the flour mill. The flour was used for 2 weeks by a family for cooking chapatties and no change in taste was reported. Blood and urine levels of dapsone were comparable to an intake in adults of 50 to 100 mg dapsone daily. [The problems inherent in administering dapsone by this method are not discussed.]

M. F. R. Waters

65. IYER, C. G. S., BALAKRISHNAN, S. & RAMU, G. **A comparison of low and conventional dosages of dapsone in the treatment of lepromatous leprosy.** *Lepr. India,* 1977, v. 49, No. 3, 372–386.

"A therapeutic trial using two dosages of dapsone with a schedule of administration of the drug once a week was undertaken at the Central Leprosy Teaching and Research Institute, Chingleput. Adult males with active lepromatous leprosy who were either previously untreated, or who had no specific treatment for at least three months immediately prior to their inclusion into this study, were the subjects of this trial. Two dosages, viz., 10 mg per kg body weight/week, and 3.3 mg per kg body weight/week, were employed in this trial.

"It was found that dapsone administered orally as a single dose once a week was therapeutically effective in most of the patients, and improvement, clinical or bacteriological, was directly related to the duration of treatment, irrespective of the dosage of dapsone. Blood levels of dapsone in these patients were in general commensurate with the dose of the drug in either group. No adverse effects on any of the visceral functions were encountered during the prolonged use of this schedule of treatment with dapsone."

66. GIRDHAR, B. K., SREEVATSA & DESIKAN, K. V. **Primary sulphone resistance: a preliminary report.** *Lepr. India,* 1978, v. 50, No. 3, 352–355.

"A case of lepromatous leprosy proven to be a primary sulphone resistant one, has been reported. Bacilli from the case were found to be resistant as checked by their continued growth in the foot pads of mice receiving diet containing 0.001% DDS. A study to identify such cases is being systematically pursued."

67. PANDYA, N. J. **Surgical decompression of nerves in leprosy. An attempt at prevention of deformities. A clinical, electrophysiologic, histopathologic and surgical study.** *Int. J. Lepr.,* 1978, v. 46, No. 1, 47–55.

"Forty-five leprosy patients were electively subjected to extraneural decompression and medial longitudinal epineurotomy in anticipation that relief from compression may favorably alter the course of the disease by retrieving reversibly damaged nerve bundles and preventing further progression of disease. Neurolysis was performed in 69 nerves, including the ulnar, median, lateral popliteal and posterior tibial. The period of follow-up was up to three years. Excellent sensory recovery was seen in most patients while motor recovery was less predictable. The recovery seen was better in those patients taking treatment early and also at the age the surgery was carried out. Motor damage appeared more severe in the 10–20 year age group. Most of the beneficial effects can be explained on the basis of increased vascularity due to relief from extraneural and intraneural compression."

5. EPIDEMIOLOGY

68. GANAPATI, R., PANDYA, S. S., NAIK, S. S., DONGRE, V. V. & DESOUZA, N. G. A. **Assessment of school surveys as a method of case detection in an urban area endemic for leprosy.** *Indian J. Med. Res.,* 1977, v. 66, No. 5, 732–736.

"The study was conducted to determine whether school survey and examination of family contacts was an effective method of case detection in a community where leprosy is endemic as compared to whole population survey. The results showed that although school and family contact examination was more economical as regards time, money and personnel involved, it did not result in the identification of a significant number of cases in the community, either in numbers or in the proportion of infectious cases. This observation implied that most children detected to have leprosy in the school were infected from sources outside the home. The whole population survey revealed a serious shortcoming in that only 60 per cent of the adult male group was covered, a lacuna which is of potential epidemiologic importance."

69. KAPOOR, P., DEODHAR, N. S. & YELLAPURKAR, M. V. **Integration of leprosy control work with general health services as planned in Maharashtra.** *Hlth Popul.,* 1978, v. 1, No. 1, 51–61.

"The current literature on integration of Leprosy Control work with General Health Services has been reviewed. In view of the introduction of Multipurpose Workers' Scheme and an experience in a pilot project, the authors feel that the time of integration of leprosy is ripe. The process of involvement of Multipurpose Workers in the Leprosy Control Programme is being introduced in a manner that ensures adequate supervision by the present Leprosy Control staff during the training period and also subsequently for one year so that the transition from unipurpose to integrated service is a smooth one. After the successful integration of leprosy, the leprosy staff, after adequate training, can be used as Multipurpose Supervisors."

70. SAIKAWA, K. [**The epidemiological study on leprosy in the Ryukyu Islands. The 5th report: on leprosy in the urban area.**] *Jap. J. Lepr.,* 1977, v. 46, No. 1, 8–13. [In Japanese.] English summary.

In the main island the leprosy prevalence rate and the leprosy incidence rate were, respectively, 1.34 and 0.059 per thousand in 1975 compared with 1.97 and 0.088 in 1970. However, in Naha City on the Okinawa mainland (population about 300,000) 20 new cases were detected in 1974 compared with only 5 in 1969. In a rural area, in the Miyako Islands (population 69,000 in 1969, 58,000 in 1974), 17 cases were found in 1974 whereas there were 38 in 1969. Further information is provided in tables and figures.

F. I. C. Apted

71. SAIKAWA, K. [**The epidemiological study on leprosy in Okinawa Island. The third report; on the islets.**] *Jap. J. Lepr.,* 1977, v. 46, No. 1, 1–7. [In Japanese.] English summary.

Tables, in English, show the numbers of new cases of leprosy reported on each of 11 islands in the Okinawa archipelago for each 5-year period from about 1936 to 1975. In 7 of the islands leprosy notifications have remained at a low level — nearly all single figures for each 5-year period — over the whole of this time. In the other 4 islands the situation is different. In Kume and Irabu islands some 25–35 new cases have been reported in most of the more recent 5-year periods, and in Yonaguni about 10–15 cases. There were fewer notifications from Tarama Island, but in each of these 4 islands the proportions of lepromatous cases and of infected children are high. Graphs show the leprosy incidence rate, lepromatous ratio, and child ratio for each of 8 islands.

F. I. C. Apted

72. HONEY, N. R. **Leprosy in Hong Kong, past, present and future.** *Bull. J. Soc. Community Med. Hong Kong,* 1978, v. 9, No. 1, 22–28.

"During the past two decades, the incidence of leprosy declined from a peak of 16.2 per 100,000 population in 1956 to a low level of 1.7 per 100,000 population in 1976. The decline appears to be associated with the use of specific antileprotic drugs, improved socio-economic conditions and migration patterns. During the period segregation of patients has almost ceased and management of patients is now based on the knowledge that bacteriologically positive patients become non-infectious after a short period of treatment."

73. LECHAT, M. F., VELLUT, C., MISSON, C. B. & MISSON, J. Y. **Application of an economic model to the study of leprosy control costs.** *Int. J. Lepr.,* 1978, v. 46, No. 1, 14–24.

"The effectiveness of various control methods for reducing the incidence of leprosy have been tested over 20 years and compared with predictions made using the present current control method (early diagnosis and mass treatment). Specific vaccination of the whole population, a control measure yet to be developed, has been identified as the most effective strategy in the long run.

"A cost-effectiveness analysis has been carried out for three indicators, annual incidence, annual prevalence and cumulative prevalence at 20 years, using cumulative costs. The analysis indicates that specific vaccination at high levels of coverage is the most effective method for controlling incidence in the long term. Provided the cost of the vaccination campaign during the first years (roughly fourfold the funds required for carrying out the current strategy) can be supported, specific vaccination is also the most cost-effective method where a high level of effectiveness is required. Specific vaccination is still the most advantageous method if prevalence or cumulative prevalence are taken to indicate the effectiveness of leprosy control. The BCG-type of vaccination is not only less effective, but is also less cost-effective.

"Reducing the rate of abandonment of treatment (which in the model has been simulated by increasing the rate of resuming treatment) and earlier detection both appear as useful methods under conditions of severe budgetary constraints. Their ultimate effectiveness in terms of incidence reduction is, however, very small. As expected, segregation is costly and ineffective compared with other methods.

"In each simulation, the cost of treating the backlog of patients already ill or infected (incubating) at the time the control measures are initiated is high. Methods aimed at reducing transmission, such as vaccination, early treatment or segregation, have long-delayed effects on the cost even if incidence is reduced. The major cost item in these control measures is the prolonged or even life-long treatment of patients.

"The development of fast-acting, effective treatment is likely to be the only way to reduce the cost in the short term. Thus, in addition to research aimed at developing a vaccine for leprosy, resources should also be allocated for developing new therapeutics."

74. NASSERI, K. & KO, Y. H. **Epidemiology of leprosy in Iran.** *Int. J. Lepr.,* 1977, v. 45, No. 4, 355–359.

"A total of 907 cases of leprosy from two sources, records from Baba-Baghi Leprosarium (709 cases) and Ahar case finding survey (198 cases), have been studied. The main characteristics of the cases are: (a) about 50% of all cases are lepromatous leprosy; (b) the leprosarium cases are about 2.5 years younger; (c) about 70% of all cases are male; and (d) the incidence of leprosy shows a steady increase up to 25–30 years of age and levels off thereafter. These and other findings are discussed."

75. NIGAM, P., VERMA, B. L. & SRIVASTAVA, R. N. **Leprosy — a clinicoepidemiological study in a rural population of Bundelkhand.** *Lepr. India,* 1977, v. 49, No. 3, 349–359.

An epidemiological survey for leprosy in a rural area of north India revealed a prevalence rate of 5.41 per thousand, most cases being in an early stage, and 7 of the 18 cases found being of the

lepromatous type. Ninety-one per cent of the people were examined. These facts, combined with the non-acceptance by the community of persons with advanced leprosy, suggest that the true prevalence of the disease is probably higher than the findings indicate. The disease presented no unusual features.

T. F. Davey

76. WKLY EPIDEM. REC. 1978, v. 53, No. 20, 147. **Leprosy.** [In English and French.]

1832 cases of leprosy were reported in Bolivia in 1977. Of these, 855 were notified from the Department of Santa Cruz, and the remainder, in approximately equal numbers, from Beni and Chuquisaca. Of the total cases, 807 were of the lepromatous type, 561 tuberculoid, 303 indeterminate, and 161 borderline. The total number of cases in the country is estimated at 3907, a prevalence of about 1 per 1000 inhabitants. In the three Departments mainly affected surveillance is carried out by a total of 5 leprologists, in another Department it is undertaken by a dermatologist and elsewhere in the country by the provincial medical officers.

F. I. C. Apted

6. MISCELLANEOUS

77. LEPR. INDIA, 1977, v. 49, No. 3, 440–447. **The WORTH Trust. A report on their activities.**

Formerly known as the Swedish Red Cross Rehabilitation Industries, Katpadi, the WORTH (Workshop for Rehabilitation and Training of the Handicapped) Trust manages 4 rehabilitation institutions for leprosy sufferers and others with disabilities. These provide training in light engineering. The report concludes thus:

"The conviction of the Swedish Red Cross, and the determination with which they pursued the cause under difficult conditions, when very little was done in this area, has amply been rewarded by the success of the project . . . It is the belief of the Worth Trust that a centre run for the physically handicapped with no Governmental or private grants can succeed as a business venture. As a humanitarian effort, it has brought relief and solace to over three hundred handicapped persons. Hardworking wage earners, they do not live on charity, but are skilled workmen who pay taxes, and support families."

T. F. Davey

78. PHILLIPS, M. A. **Health education in leprosy: the problem of overcoming fear and misconceptions.** *Int. J. Hlth Educ.,* 1978, v. 21, No. 2, 130–136.

The author, now in leprosy control work in Lesotho, was in Uganda from 1965 to 1976 where she helped to develop the rehabilitation section of Kumi Leprosy Centre. There are 12 references, concerned with East Africa and Ethiopia in particular but of wide significance.

79. LEPR. INDIA, 1977, v. 49, No. 3, 448–452. **Pune Urban Leprosy Investigation Centre. Report for the period April 1975 to December 1976.**

A series of tables summarizes progress made in the Urban Leprosy Control Project in Poona. These include: cases of leprosy found by survey and by voluntary reporting, statistics of treatment and disabilities, and information on a very active health education programme. Urban leprosy control presents many difficulties and the details given are of interest.

T. F. Davey

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References:
1. Browne, S.G., Int. J. Leprosy *34,* 289 (1966)
2. Waters, M.F.R., Leprosy Review *40,* 21 (1969)
3. Hastings et al., Leprosy Review *39,* 3 (1968)
4. Warren, H.A., Leprosy Review *39,* 61 (1968)

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