Editorial

THE WORLD HEALTH ORGANIZATION AND LEPROSY

The Report of the Director General to the 30th World Health Assembly (1977) is a substantial document extending to 20 pages and covering the wide range of concern which WHO now has with leprosy control and research. This is surely an appropriate occasion to appreciate the services WHO has rendered in the fight against leprosy during the first generation of its existence.

It is interesting to look back over the past 30 years and notice how far leprosy has figured on the Agenda of previous World Health Assemblies. The first reference to leprosy appeared in the Report of the Director General to the 3rd Assembly (1950) and consisted of a short paragraph regarding the appointment of a leprosy consultant in Ethiopia. During the next 10 years references to leprosy continue to be meagre. In many quarters leprosy was still regarded as a highly specialized subject, outside the range of government health planning, and still very much the concern of voluntary agencies and dedicated individuals. Although change was on the way, the attitude to leprosy in some instances was not merely apathetic but was actively negative, regarding leprosy as something to be ashamed of, a skeleton in the cupboard not to be exposed to the light of world publicity. All honour therefore to Ethiopia, Sri Lanka and Burma who opened themselves to the influence of WHO at an early stage and became the scene of major developments in leprosy research and control.

The WHO Leprosy Secretariat was established in 1958. The task confronting them was formidable. By definition, WHO was concerned primarily with *health.* In relation to a neglected and emotive sphere such as leprosy, there could be no speedy and co-ordinated programme of eradication on a global scale. WHO is an international and not a supranational organization and has no authority other than that entrusted to the Director General by Member States. Lacking any authority, WHO could only stimulate concern and action by suggestion, advice and example. Nevertheless, in the 1950s there was considerable activity in WHO behind the scenes. At first, the Leprosy Secretariat were clearly feeling their way, but their activities indicate a pragmatic approach which time has amply endorsed. From early reports and publications it is apparent that the task of WHO in relation to leprosy was seen to include the establishment and publication of the facts, encouraging and drawing attention to points of growth; broadening isolationist attitudes by facilitating the movement of leprologists and government medical administrators; organizing international conferences and seminars; giving very positive support to reasearch projects relevant to health, and to training at all levels; and actually engaging where invited in specific field projects. Once developed this policy was pursued with skill and determination. WHO's involvement with malaria, tuberculosis and other infective diseases meant that

leprosy could be seen in its wider context, and expertise and experience gained in other directions could be applied to leprosy. The benefits of this have been obvious, helping the building up of a world approach from an impregnable situation of knowledge in the wider context of health.

The WHO Expert Committee on Leprosy

A basis of expert judgment in relation to leprosy was the first priority. This led to the formation of the first WHO Expert Committee on Leprosy, which met in 1952, its members carefully selected on an international basis. This Panel concerned itself with: leprosy control and treatment, the contagiousness of different forms of leprosy; prophylaxis by BCG; the standardization of the lepromin test and the classification of the different forms of leprosy. The Committee met subsequently at intervals of approximately five years, the latest being the 5th Meeting in October 1976. The reports of these Meetings have been of the highest significance, giving guidance and stimulating discussion which have been of great value both to WHO itself and to governments and workers generally. If WHO had done nothing beyond this, its contribution to the understanding and control of leprosy would have been considerable.

Epidemiology and Control

The International Leprosy Congress at Madrid in 1953 became a watershed in the outlook for leprosy treatment by its endorsement of domiciliary chemotherapy with dapsone as a routine procedure. The expansion of WHO involvement in leprosy control dates from that time, with its emphasis on epidemiological surveys, out-patient treatment with dapsone and sustained field studies. All the same, the reports of the Director General continued to be brief into the 1960s but rapidly expanded during the second half of that decade.

(a) ADVISORY SERVICES

The direct involvement of WHO in national leprosy situations began with the request from Ethiopia in 1950 for an Adviser in planning leprosy control, the first of many such requests, response to which was limited only by the shortage of available specialists. The presence of a WHO Adviser meant that international thought was brought to bear on the local problem and a door opened for international aid in practical measures. Many leprosy programmes were initiated as a result of this primary response on the part of WHO, and the benefit was mutual, WHO building up an increasing breadth of experience from which other nations were destined to benefit in their turn. In 1964, technical advice and guidance was given to 35 countries in planning their leprosy control programmes.

An important aspect of this was the organising by WHO of regional seminars and conferences where technical advances in leprosy were publicised, health ministries could share problems, discover common ground, the more dilatory in leprosy control be stimulated by the example of others. Regional events of this nature have been held in many parts of the world.

(b) EPIDEMIOLOGICAL STUDIES

The need for careful epidemiological studies to establish the prevalence, incidence and trend of leprosy, has been a consistent emphasis of WHO, and its influence in this sphere has been considerable, establishing and demonstrating standards of work and analysis. The importance of this is apparent from the numerous published findings of leprosy surveys in which the help of WHO is acknowledged, two of them in this issue of *Leprosy Review.* In 1960 a WHO Advisory Team started work in Africa "to assist countries in determining the prevalence, trend and endemicity and frequency of deformities and disabilities". In the following year field studies were initiated in different parts of the world to evaluate attack rates.

Leprosy survey work poses difficult problems, and the experience gained by WHO in one country often proved useful elsewhere. The successful combination of leprosy with yaws surveys in E. Nigeria led to similar approach in The Gambia, Sierra Leone and Togo. Another example is the combination of leprosy with tuberculosis surveys in Nepal and Upper Volta (1974).

(c) THE PROMOTION OF OUT-PATIENT TREATMENT PROGRAMMES

It was realised very early that leprosy surveys were positively harmful unless combined with facilities for treatment. WHO did much to publicise DDS therapy and promote out-patient treatment programmes, either through financial aid or direct involvement in field projects, e.g. in Burma, Thailand and Pogiri, India. The involvement of UNICEF in leprosy by providing dapsone for out-patient treatment was another service encouraged by WHO. This began in Nigeria in 1953, and the writer was one of those involved in it. The example there set was extended throughout much of the world, until in 1967, 38 leprosy control projects were being assisted by WHO and UNICEF, and many millions of dapsone tablets were being supplied free of cost. As early as 1964, in projects assisted by WHO and UNICEF, 2,854,197 cases were registered, and 1,826,688 patients were attending.

(d) EVALUATION OF LEPROSY CONTROL PROGRAMMES

The need for careful evaluation of leprosy control programmes in order to improve quality of work was another principle for which WHO was especially responsible, setting standards which have been widely accepted. In 1973 evaluations of leprosy control programmes were undertaken in Botswana, Central African Republic, Chad, The Gambia, Upper Volta, also Burma and Thailand.

There must now be very few countries where leprosy is endemic who have not benefitted from the many facetted aid of WHO in leprosy control. The 1973 list for instance includes, Bangledesh, The Maldives, Indonesia, Nepal and Sri Lanka. Relationships have not always been easy, but co-operation with WHO has in fact transformed the leprosy situation in many countries.

(e) INTEGRATION OF LEPROSY INTO GENERAL HEALTH SERVICES

Nigeria was one of the earliest countries to embark on a large domiciliary leprosy control programme, and by the 1950s the leprosy problem in E. Nigeria had shrunk to a point where leprosy workers were already being integrated into the general health services, and their colleagues in general medicine were receiving suitable training in leprosy to equip them to take leprosy into their system. This was known to WHO and reference to such integration as a principle appears in the

Director General's Report of 1960. Since then, it has figured increasingly in WHO policy, and in some countries, e.g. Nepal, through the active encouragement of WHO the fight against leprosy has been integrated from the start. At the same time, the 1970 Report cautioned against instituting integration without adequate preparation.

The Training of Leprosy Personnel

The involvement of WHO in national leprosy problems has in general been a short term process, a preparation for the assimilation of leprosy control into the national health programme. The wider training of medical personnel who would have responsibility in this was thus integral to WHO policy from the start, and numerous travelling fellowships were awarded. We at Uzuakoli in Nigeria received a succession of WHO Fellows in the 1950s, certain of whom later became leaders in the campaign in their own countries.

Seminars for the training and orientation of Medical Officers towards leprosy have also been a feature of WHO policy, particularly important where the integration of leprosy into general health services has been under discussion. Early examples were the post-graduate training course in Tokyo in 1961 and the training conference in the Philippines in the same year. The writer recalls a successful orientation seminar for Senior Medical Officers at Katmandu in 1969, which undoubtedly paved the way for later advance in leprosy control in Nepal. The Director General declared in 1973, "The promotion of training of general health personnel is receiving priority attention".

Disability Studies

An important concern of WHO in the care of patients has been the need for action regarding the disabilities caused by leprosy. Reference to this occurred in the Director General's report in 1959, which stated that 25% of patients suffer from disabilities, 90% of which could be prevented in the early stages. The Second Committee in 1959 also made an important statement on this subject. In 1961, WHO was responsible for calling together a Scientific Meeting on Rehabilitation in Leprosy at Vellore, India, notable for the participation of workers in disciplines other than leprology, and important advances followed, not least the encouragement of research outside leprosy institutions. WHO emphasis on leprosy disabilities has been continuous, as is exemplified by the report in this issue of *Leprosy Review* on disabilities in the New Hebrides.

The Director General in his 1976 report said "Disease orientated medicine needs to be complemented by disability orientated medicine, and it should be realised in every country that the objectives of medicine are not only the prevention and cure of disease but also the restoration of the individual to normal social function".

Research and Publications

The distinguished role of WHO in leprosy research is so well known as to need only brief reference here. It has covered all aspects of research which have relevance to the understanding and control of the disease, and through research fellowships, grants in aid, and direct involvement in specific projects has

contributed enormously both to knowledge and to the acceptance of leprosy by governments and research workers alike as a subject of concern and challenge. Positive steps have been taken to promote research in countries where leprosy is endemic. In 1973 WHO co-operated with 42 Institutes in 24 countries in 58 research projects, embracing: epidemiology, leprosy control, biology of *M. leprae,* experimental leprosy, immunology, pathology, experimental and human chemotherapy including chemoprophylaxis and prevention. As the report of the Director General stated, "This is essential work as long as the disease can only be restrained by secondary preventive measures".

The publication of scientific material is an important part of WHO's involvement in research. The *Bulletin of WHO* and *WHO Chronicle* have been media of wide distribution and value.

World Statistics of Leprosy

Yet another service rendered by WHO has been the collection and publication of statistics relating to leprosy on a global scale. The report of the Director General in 1959 included responses to a world wide questionnaire regarding prevalence and registration for treatment. Statistics gathered then gave an estimated total of 10-12 million sufferers, of whom 1,579,532 were registered for treatment. In 1966, out of a total of 11 million estimated cases, 2.8 million were registered, and 1.9 million actually taking treatment. Detailed figures for 1970, collected by Bechelli, gave 10,407,200 as a conservative estimate (Asia 6.5 million, Africa 3.5 million, the Americas 350,000). The 1977 Report gives figures by country for Asia and the Americas. It is invidious here to follow the trend in individual countries. Statistics are often a notoriously unreliable guide to the actual situation, but these are a salutory reminder that leprosy is still a serious problem in many countries.

It is a far cry from the first almost tentative reference to leprosy on the part of WHO in 1950 to the major report in 1977, over 100 times as long. This is the measure of the remarkable change in world opinion which has taken place in recent years, and to which WHO has contributed so profoundly. The miracle had already happened by 1974, when the World Health Assembly, in Resolution WHA 27/58 recommended that Member States should strengthen their leprosy control measures by calling upon all available sources of co-operation. This resolution not only implied that Health Ministries everywhere should be taking leprosy seriously, but also openly encouraged them to seek the cooperation of voluntary agencies, a breakthrough in official attitudes indicative of real concern. From this point it was a small step to the inclusion of leprosy in the 6 diseases selected for the WHO Special Programme for Research and Training in Tropical Diseases, and the development of IMMLEP and THELEP. It is impossible to exaggerate the part played by WHO in this transformation, combining, as it has, a sustained insistence on the need for serious attention to leprosy, a scientific approach in dealing with it, and a humane attitude to patients. The stage is now becoming set for a global anti-leprosy strategy in which leprosy is fully integrated with general medicine, but its seriousness as a leading disabling disease in many countries is equally recognised. We can but express our gratitude to our colleagues in WHO for their great services to sufferers from leprosy during this first generation of the life of WHO.

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Dapsone Alone Compared with Dapsone Plus Rifampicin in Short-term Therapy of Lepromatous Leprosy

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Previously untreated lepromatous leprosy patients were randomly allocated to treatment with either 100 mg dapsone daily or 100 mg dapsone and 600 mg rifampicin daily for 6 months. Patients receiving rifampicin improved more rapidly, but by 6 months the regimens were equivalent. There was no difference in the incidence, severity, and time of onset of erythema nodosum leprosum (ENL) in the 2 groups. Skin smears and histological sections and mouse foot-pad inoculation of biopsy specimens from skin, peripheral nerve, skeletal muscle and dartos muscle demonstrated more rapid killing of *Mycobacterium leprae* in those on combination chemotherapy. In the patients treated only with dapsone, viable *M. leprae* were generally found after 3 months of therapy, and frequently even at 6 months. Even on the combined regimens, viable *M. leprae* were commonly detected at 3 months, but only occasionally at 6 months.

Introduction

Rees *et al.* (1970) reported that rifampicin was active against *M. leprae* infection of the mouse foot-pad and at the same time demonstrated in lepromatous leprosy patients that 600 mg rifampicin daily by mouth killed organisms more rapidly than dapsone or any other antileprosy drug studied thus far. The evidence for the rapid bactericidal activity of rifampicin was extended by a series of reports from Shepard *et al.* (1972, 1974). Mouse inoculation of skin biopsy specimens from previously untreated lepromatous leprosy patients became negative 3 to 4 days

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after daily 600 mg rifampicin or after a single dose of 1500 mg. In contrast, biopsy material from patients treated with daily dapsone on the average is not rendered non-infectious for mice for 3 months (Shepard *et al.*, 1968).

In recent years the dual processes of bacterial resistance and persistence have emphasized the need for combination chemotherapy of lepromatous leprosy.

Sulphone resistance was first proven by Pettit and Rees (1964) in Malaysia in 1964. Recently, the Malaysian experience with the first 100 proven cases of dapsone resistance has been published (Pearson *et al.*, 1975). Both irregularity of therapy and low sulphone dosage appear to predispose lepromatous leprosy patients to dapsone-resistant relapse. Estimates of the risks of developing dapsone resistance in lepromatous leprosy have ranged from 2.5% in Malaysia (Pearson *et al.*, 1975), 6.8% in Costa Rica (Peters *et al.*, 1976) and something like 40% in Ethiopia (Pearson, 1975; Pearson *et al.*, 1977). As in the chemotherapy of tuberculosis, the obvious remedy is treatment with a combination of agents.

Waters *et al.* (1974) reported the results of mouse foot-pad inoculation of skin, skeletal muscle, peripheral nerve and dartos muscle from 12 Malaysian lepromatous patients who had completed a minimum of 10 years of supervised dapsone therapy in full dosage. Ten of the 37 specimens and 7 of the 12 patients still harbored persisting viable *M. leprae* which when passaged to mice were shown to be fully sensitive to dapsone. Evidence that bacterial persistence might be a problem in the treatment of lepromatous leprosy also came from a study of the Karimui of Papua New Guinea in which 5 of 28 lepromatous patients were found to have solid-staining bacilli in their skin smears despite regular treatment with acedapsone for 3 to 5 years and expected blood sulphone levels (Russell *et al.*, 1975). These results emphasize that monotherapy with dapsone is not sufficient treatment for lepromatous leprosy.

It appears inconsistent that viable *M. leprae* cannot be detected after a few months of dapsone or even a few days of rifampicin, but are regularly found after some years of dapsone therapy. This is most likely a methodological paradox. In the mouse foot-pad infection 5×10^3 are inoculated, and if more than 5 viables are present in the initial inoculum, these grow yielding 10^6 *M. leprae* by 6 months. It is estimated that an untreated lepromatous leprosy patient harbors 10^{12} organisms in his body, of which 10^{10} to 10^{11} are viable. If initial antimicrobial therapy reduces the viables by 99.9% to 10^7 to 10^8 organisms, inocula of 5000 organisms may contain no viable bacilli. However, as dead organisms are preferentially cleared from the tissues, the proportion of viable organisms increases so that detection of *M. leprae* by mouse foot-pad inoculation again becomes possible.

As a first study of the efficacy of combined chemotherapy, we, therefore, initiated a short-term study of dapsone plus rifampicin therapy compared to dapsone alone in previously untreated patients with lepromatous leprosy.

Patients and Methods

Previously untreated patients who were clinically lepromatous and classified histologically as LL or LI by Ridley were hospitalized for the trial period at the Leprosy Research Unit, National Leprosy Control Center, Sungei Buloh, Malaysia, and randomly assigned to one of 2 treatment regimens. Six patients, 4 Chinese males, one Chinese female and one Malay male ingested 100 mg dapsone and placebo resembling rifampicin daily for 6 months. Five patients, 2 Chinese males,

2 Malay males and one Chinese female ingested 100 mg dapsone and 600 mg rifampicin daily for 6 months.

Patients were followed by clinical, histological and bacteriological criteria for the duration of the trial. Clinical response was assessed by the clinical investigators and by an independent experienced leprologist. Smears from the same 6 skin sites were taken prior to therapy, every 2 weeks for 6 weeks and at 3, 4, 5 and 6 months for assessment of the bacteriological index (BI) and morphological index (MI). Biopsies were taken prior to therapy and at 3 and 6 months after the initiation of treatment from skin (S), peripheral nerve (N), skeletal muscle (M) and, from the men, dartos muscle (D) for histological examination and mouse foot-pad inoculation. Each biopsied tissue was homogenized and inoculated into both hind foot-pads of 6 female CBA mice. Doses of up to 10^4 acid-fast bacilli from the pretreatment biopsied tissues and up to 10^5 acid-fast bacilli from the tissues biopsied after starting treatment, were inoculated into normal and thymectomized-irradiated mice respectively.

Results

There was a decrease in lepromatous infiltrate in all patients in the study. Patients treated with dapsone and rifampicin generally showed more rapid clinical improvement than those receiving only dapsone. In particular, patients receiving rifampicin were noted to have more rapid reduction of erythema of skin lesions, alleviation of nasal congestion and, where present, healing of primary lepromatous ulceration. However, at the completion of 6 months of therapy, no discernible difference between the 2 regimens was found. Four of the 6 patients receiving dapsone alone developed ENL during the course of the trial, in 3 instances the ENL was mild and in one moderate, while 4 of the 5 patients that also were treated with rifampicin had mild ENL. The addition of rifampicin did not result in earlier or more severe ENL.

The average BI and MI were derived by first averaging the results of the 6 skin smears from each patient at each time interval, and these in turn averaged for the 6 patients receiving dapsone alone and the 5 on the combined regimen. In those patients receiving dapsone alone, the average pretreatment BI was 4.55 and was still 4.47 after 6 months of therapy. On the other hand, the BI prior to therapy averaged 4.56 in those on the combined regimen but fell significantly ($P<0.01$) to 4.06 after completion of the 6 month trial period. The results of the morphological indexes are presented in Table 1. The average MI prior to therapy in those receiving dapsone alone was 22.7, which was not significantly different from the average MI of 23.8 found in those patients who subsequently received dapsone plus rifampicin. The MI fell more rapidly in those on the combination

TABLE 1
Average morphological index (MI)

	Pretreatment	2 weeks	4 weeks	6 weeks	3 months	4.5 months	6 months
Dapsone	22.7	19.5	16.2	7.9	3.1	0.5	0.2
Dapsone+ rifampicin	23.8	4.4	0.4	0.6	0.4	0.3	0.3

TABLE 2

Infectivity (viability) in the mouse of M. leprae *from skin (S), nerve (N), striated muscle (M) and dartos muscle (D) of patients treated with dapsone 100 mg daily either alone or combined with rifampicin 600 mg daily*

Treatment regimen	Duration of treatment	Proportion of foot-pads showing multiplication (by biopsy site)					Proportion of sites yielding positive foot-pads					Proportion of patients yielding positive foot-pads from at least one tissue site
	(months)	S	N	M	D	Totals	S	N	M	D	Totals	
Dapsone	3	22	15	9	5	51	5	3	2	1	11	5
		54	50	54	44	202	6	6	6	5	23	6
Dapsone+	3	1	2	5	4	12	1	1	1	2	5	3
rifampicin		52	50	48	38	188	5	5	5	4	19	5
Dapsone	6	1	8	4	6	19	1	2	2	2	7	3
		53	52	48	46	199	6	6	6	5	23	6
Dapsone+	6	1	0	1	0	2	1	0	1	0	2	1
rifampicin		40	42	30	40	152	5	5	4	4	18	5

regimen. The MI was found to be significantly lower in those receiving rifampicin plus dapsone than in those treated with dapsone alone at 2, 4 and 6 weeks, and at 3 months ($P<0.01$ at all these intervals). These results suggest that rifampicin plus dapsone kills *M. leprae* significantly more rapidly than does dapsone alone.

After the initial pretreatment biopsy, histological sections showed no solid-staining bacilli in any of the sampled tissues from those receiving combination chemotherapy except an occasional solid-staining organism from the skin of a single patient at 3 months. On the other hand, histological sections from patients receiving dapsone alone revealed solid-staining bacilli from at least one site in 4 of the 6 patients at 3 months and 3 of the 6 patients even at 6 months. Skin and nerve were the most common source of these solid-staining organisms.

In Table 2 are presented the results of the mouse foot-pad inoculations. At 3 months 5 of the 6 patients receiving dapsone alone and 3 of the 5 patients receiving dapsone plus rifampicin were found to harbor viable bacilli from at least one tissue site. Though not statistically significant, a greater percentage of tissues after 3 months of therapy contained viable *M. leprae* from patients receiving dapsone (11 of 23, 48%), compared to those from patients on combined therapy (5 of 19, 26%). Of particular interest is that at 3 months, 5 of 6 skin biopsies contained *M. leprae* viable for mice from those receiving dapsone alone, while only one of 5 skin biopsies from those on the combined regimen harbored viable bacilli. A statistically highly significantly ($P<0.0001$) greater number of total foot-pads showed multiplication at 3 months of therapy from those receiving dapsone alone (51/202, 25%) compared to those receiving rifampicin in addition (12/188, 6%). Skin and peripheral nerve particularly accounted for those differences ($P<0.01$ for each compared independently). At 6 months after the initiation of therapy 3 of 6 patients receiving only dapsone yielded *M. leprae* from at least one tissue site that grew in the mouse foot-pad, compared to only one of the 5 patients treated with dapsone plus rifampicin. From the patients receiving combined chemotherapy only 2 of 18 (11%) tissues, skin and skeletal muscle from the same patient, showed multiplication of *M. leprae* in the foot-pads of mice. Though not statistically significantly different, 7 of 23 (30%) sampled tissues from patients on dapsone alone contained *M. leprae* that grew in the mouse foot-pad. As at 90 days, a highly significantly ($P<0.0001$) greater number of total foot-pads showed multiplication from tissue of patients on dapsone alone (19 of 199, or 10%) compared to those on the combined regimen (2 of 152, or 1%). Nerve and dartos muscle particularly appear responsible for this difference.

Discussion

These studies resulted in clinical, histological and bacteriological evidence that dapsone plus rifampicin is more effective than dapsone alone in the therapy of patients with previously untreated lepromatous leprosy. Whether this combination merely kills organisms more rapidly and whether more prolonged dapsone therapy would result in equally efficacious results, albeit more slowly, remains for further trials. Certainly such combination chemotherapy should prevent future relapse with resistant organisms. Because of the expense of rifampicin for most developing countries where leprosy is a problem, finding the minimal amount of rifampicin necessary is most important. From the frequency of recovery of viable *M. leprae* in this study, it appears that 3 months and possibly even 6 months of daily therapy may not even be sufficient. This does not rule out the utility of

rifampicin in some intermittent regimen. However, because of the potential for serious toxicity when rifampicin is given intermittently (Aquinas *et al.*, 1972), such trials should be entertained with great caution.

One of the major goals in leprosy chemotherapy is to find sufficiently potent antimicrobial regimens to reduce the therapy for lepromatous leprosy from lifelong to a finite and practical period of time. Rees (1975) and Rees *et al.* (1976) recently reported a study of 28 dapsone-resistant lepromatous leprosy patients who had relapsed, that were subsequently treated with 600 mg rifampicin daily and in most thiambutosine as well for 0.5 to 5 years. *M. leprae* were isolated from one or more of the 4 tissue sites sampled in 20 of these patients. All 11 of those patients treated from 2 to 5 years with daily rifampicin yielded *M. leprae* that multiplied in mice. Pessimistically, one might ask if lepromatous leprosy can ever be cured by chemotherapy alone. On the other hand, just as the duration necessary for the therapy of pulmonary tuberculosis has been significantly reduced by the use of regimens containing 2 or 3 bactericidal agents (Fox and Mitchison, 1975), might lepromatous leprosy be similarly responsive? Clearly, the search for new bactericidal drugs and regimens against *M. leprae* in experimental animals and man must continue to be pursued.

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Viability of *Mycobacterium leprae* Outside the Human Body

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It is important to recognise whether *Mycobacterium leprae* discharged from the body will remain alive after they settle down over articles of daily use, and if so the duration of their viability. The common belief is that the organisms die soon after they are discharged from the body, particularly in tropical countries. In order to verify this concept, an experimental procedure has been designed using the mouse foot-pad model. It has been found that the organisms remain alive for more than 9 days. This finding has an important bearing on the epidemiology of leprosy.

Introduction

Mycobacterium leprae are believed to be killed soon after they are expelled from the body since they are obligatory intracellular organisms. For this reason, the mode of transmission of leprosy was thought to be through direct skin contact, excluding the possibility of an indirect route through articles of daily use. Since it was not possible to culture the organisms, no experimental method could be designed to simulate the natural processes and check the viability of the organisms in the human discharges or excreta, either in a fresh state or after subjecting the material to drying and desiccation. However, with the advent of the mouse foot-pad model, it has been possible to grow the organisms in the experimental animal and verify their state of viability. This paper presents the results of an experimental study in which bacterial suspensions dried for different periods of time were inoculated into mouse foot-pads to assess their viability.

Material and Methods

Suspensions of *M. leprae* from two sources were prepared viz. from nose blows and from skin biopsy. (1) The patient was asked to blow his nose into a plastic bag. The bag was rinsed with normal saline and the contents transferred to a 50 ml flask. (2) A piece of skin obtained at biopsy was minced with scissors, homogenized and suspended in saline, carrying out all procedures aseptically at a low temperature over ice. The large particles were allowed to settle for 2 to 3 min. The supernatant fluid was collected.

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The bacterial suspension prepared by either of the above two methods was processed as follows: (a) About 1 ml of the suspension was processed for immediate inoculation. To the nose-blow material was added an equal volume of 2% NaOH. It was shaken vigorously, left for 10 min and then titrated with 2% sulphuric acid, using phenol red as indicator. The suspension was further sterilized by the addition of 200 I.U. crystalline penicillin per ml. (An earlier experiment wherein the nose blow material was inoculated without the addition of penicillin, resulted in the death of all the animals in 24 hours.) Enumeration of bacilli was done in this as well as in the skin tissue suspension. The material was diluted with Hanks' balanced salt solution (BSS) so that 0.03 ml contained 10^4 bacilli. A batch of 4 mice was inoculated with each specimen, the animals receiving 0.03 ml into each hind foot-pad. These animals served as positive controls. The remaining suspension was then autoclaved for 15 minutes at 15 lbs/in^2 pressure. The autoclaved material was inoculated into 4 mice, 0.03 ml into each hind foot-pad. These animals served as negative controls. (b) The rest of the original suspension was distributed to 5 sterile petri dishes. The petri dishes were left on the table in the laboratory and the material was allowed to dry. The dried material was scraped from the petri dishes after 15, 40 and 65 h, and 6 and 9 days. The scrapings were suspended in Hanks BSS to which crystalline penicillin was added. Bacterial counts were done and each specimen was inoculated into the hind foot-pads of mice so that 10^4 bacilli were introduced to each foot-pad.

The inoculated animals (controls and experimental groups) were housed in an air conditioned room at a temperature around 22° C. After 6 months, the mice were sacrificed, one at a time at monthly intervals. Harvests were performed from the inoculated foot-pads and bacterial counts were done. The method of inoculation, harvesting and bacterial counts were those described by Desikan and Venkataramanaiah (1976). All the observations were double blind, the smears prepared from the harvested material from several experiments being examined together after having been given coded numbers.

Results

The results of the experiment are given in Table 1.

TABLE 1

Viability in mouse foot-pads of M. leprae *derived from noseblows or skin and allowed to dry for varying periods**

Experiment number	Name/Source	Fresh specimen	Dried specimen					Autoclaved specimen
			15 h	40 h	65 h	6 days	9 days	
1	2	3	4	5	6	7	8	9
1	K.J./Nose blow M.I. 4%	2/4	0/4	1/4	1/4	2/4	1/4	0/4
2	K.P./Nose blow M.I. 7%	4/4	1/4	2/4	3/4	4/4	1/4	–
3	K.P./Skin M.I. 7%	3/4	2/4	2/4	1/4	0/4	4/4	0/4

* The figures indicate the number of mice showing multiplication of bacilli (numerator) out of the mice inoculated (denominator).

It could be seen that *M. leprae* remained alive and multiplied in the foot-pad even when the material containing the organisms was dried for 15, 40 and 65 h, 6 and 9 days. The negative findings in the foot-pads inoculated with autoclaved material showed that the positive finding was not due to any technical error. The infected material was allowed to dry inside a room in the shade but not in total darkness. The experiments were carried out under the fairly hot climatic conditions of a coastal town in South India. Table 2 is a weather chart showing the temperature and humidity on the days when the experiments were being carried out.

TABLE 2
Temperature and humidity chart at time of experiments

Date	Maximum (°C)	Minimum (°C)	Humidity (%)	Rain (mm)
May, 16	35.1	26.8	75	–
May, 17	36.0	27.2	79	–
May, 18	35.2	27.5	80	–
May, 19	36.9	26.5	77	–
May, 20	37.6	26.0	78	–
May, 21	37.2	26.8	74	–
May, 22	34.0	27.8	80	–
May, 23	35.0	27.6	77	–
May, 24	34.0	26.5	70	–
May, 25	37.4	26.5	73	–
May, 26	38.9	24.6	90	7.2
May, 27	37.6	24.8	78	–
May, 28	37.3	23.8	78	–
May, 29	37.4	25.8	70	–
May, 30	38.2	27.9	79	–
May, 31	38.6	25.4	83	–

Experiment 1 from May, 16 to 24
Experiment 2 from May, 20 to 28
Experiment 3 from May, 22 to 30

The mean maximum and minimum temperatures were 36.7° C and 26.3° C respectively and the humidity ranged from 70% to 90%. Since bacteria were found to be alive even on the 9th day of drying, the experiments have not established the end point of viability of the organisms outside the body. This apparently seems to be more than 9 days under the climatic and experimental conditions described above.

Discussion

In the experiment described above, nasal discharge and suspensions of *M. leprae* from skin lesions dried in the shade at an average maximum room temperature of 36.7° C and humidity of 77.6% were found to be viable up to 9 days. Since the bacilli were demonstrated to be alive even on the last day of the experiment, the end point was not established. The bacilli are therefore likely to resist conditions of drying for more than 9 days under the climatic conditions described. This was a very important finding and quite contrary to what was believed and expected. Davey and Rees (1974) first reported results of the experiments conducted in

London to demonstrate the viability of *M. leprae* after desiccation. They showed that nasal discharges allowed to dry for 24 h and 1.75 days contained viable bacilli. With one exception, no bacilli were found to be alive after drying the nasal discharges for 3 days or more. (In one instance, however, there was evidence of multiplication after drying for 7 days, the material containing less than 1% viable bacteria compared to the organisms in the fresh material.) It was therefore thought that in a tropical country, the organism would remain viable for a much shorter period outside the body. Chingleput, where the present experiments were carried out, has a much warmer climate, being located on a latitude of 13°N. The mean temperature at the time of our experiment was much higher than the temperature in London where the experiments of Davey and Rees were conducted. However, the mean humidity was 77.6% compared to 43.7% in London. The high humidity is perhaps responsible for the survival of *M. leprae* at a higher temperature.

The results of these studies are very significant and have an important bearing on the epidemiology of the disease. Since it has been shown that the organisms are viable in the discharges for several days, the possibility of infection due to indirect contact has to be seriously considered. Infection through inhalation is another possible route as shown experimentally by Rees and McDougall (1977).

It is regrettable that in this part of the country, as in many parts of the world, many people have the unhygienic habit of blowing their noses anywhere out of doors and wiping their fingers on any convenient nearby object. Bacilli could thus settle on such objects and also be sprayed over articles in daily use, from which they could be transmitted to other persons. Muir (1948) was of the opinion that indirect transmission occurs at times through the wearing of a patient's clothes, using his furniture and other appliances or living in a house vacated by a patient. The chances of indirect contact with a leprosy patient are quite high, particularly in a metropolitan city in India. It must be remembered, however, that while the possibility of transmission of the disease by an indirect method certainly does exist, there is no need to become unduly alarmed, since the frequency of clinical leprosy is much less than one would expect if this were the only factor involved. Obviously there are also other factors that influence the epidemiology of leprosy, especially in an endemic country like India.

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Post-script

The question has been raised whether dilution of nose-blow material and decontamination with 2% sodium hydroxide might possibly destroy or dilute some constituents of nasal secretions detrimental to the survival of *M. leprae.* While such a hypothetical possibility might be considered, it would be relevant to mention in this connection that treatment with sodium hydroxide was considered necessary and was done for the fresh specimen in order to destroy the other organisms in the nasal secretions. However, this procedure was not adopted while preparing suspensions of dried material since the other organisms are likely to be killed during the process of drying. As such, the question of destruction of inhibiting factors in nasal secretions with sodium hydroxide does not arise as far as the dried material is concerned. The possibility of dilution may also be ruled out since the material was desiccated again.

The validity of the experiments is further confirmed by the results of inoculation with skin biopsy material which was not subjected to these procedures.

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Some Characteristics of the Action of Dapsone on Multiplication of *Mycobacterium leprae* in the Mouse*

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In a number of experiments, male BALB/c mice were inoculated with *Mycobacterium leprae* and administered dapsone (4,4′-diaminodiphenylsulphone, DDS) incorporated into the mouse chow in concentrations of 10^{-2} to $10^{-4.5}$ g% for periods of about 90 days during logarithmic multiplication of the organisms. Both the duration of the delay between beginning treatment and the onset of inhibition of bacterial multiplication and the duration of the delay between cessation of treatment and resumption of bacterial multiplication were dependent on the dosage of DDS. The number of doublings of *M. leprae* after the start of DDS treatment appeared more sensitive to minor variations of DDS concentration than the duration of the delay of resumption of multiplication after treatment was stopped.

Introduction

The activity of dapsone (4,4′-diaminodiphenylsulphone, DDS) against *Mycobacterium leprae* has been intensively studied in mice. When DDS, incorporated into the mouse chow, is administered for periods of 60-90 days during logarithmic multiplication of the organisms in the mouse foot-pad [Shepard's "kinetic" method (Shepard, 1967, 1969)], the antimicrobial activity of the drug may be characterized according to 2 criteria:

(1) the duration of the delay between beginning treatment of the mice with an effective dose of DDS and the onset of inhibition of bacterial multiplication; and
(2) the duration of the delay between cessation of treatment and the resumption of bacterial multiplication.

The delay between beginning treatment and the onset of inhibition is shorter, and

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that between cessation of treatment and the resumption of multiplication is longer when DDS has been administered in a larger dosage (Shepard, 1967, 1969).

During the past 8 years, we have conducted a number of experiments in which DDS was administered to *M. leprae*-infected mice. Although we observed the same characteristics of antimicrobial activity of DDS noted by Shepard (1967, 1969), it was also apparent that the quality of inhibition of multiplication of *M. leprae* varied from experiment to experiment in which the dosage of DDS, the strain of *M. leprae,* and the strain of inbred mice were not varied. We have analysed the results of these experiments in an attempt to explain the variation of drug effect. An important cause of the variation of drug effect appears to be minor variation of the dosage of DDS revealed by measurements of the concentration of DDS in the plasma of mice sacrificed for harvests of *M. leprae.*

Materials and Methods

DDS, purchased from K & K Laboratories, Inc., Hollywood, California, U.S.A., was incorporated into the mouse chow (Wayne Lab-Blox, Allied Mills, Inc., Chicago, Illinois, U.S.A.) by means of a liquid-solid twin-shell blender (Patterson-Kelly Co., East Stroudsburg, Pennsylvania, U.S.A.). The strain of *M. leprae* used in all experiments was a "fast" strain (Shepard and McRae, 1971) that had been isolated by C. C. Shepard, Center for Disease Control, Atlanta, Georgia, U.S.A., from an untreated patient with lepromatous leprosy, and was subsequently carried through many mouse passages both in Shepard's laboratory and in ours. Locally-bred weanling male BALB/c mice were employed in all of the experiments.

Mice were inoculated and *M. leprae* were harvested and enumerated by established methods (Shepard, 1960; Shepard and McRae, 1968). Administration of DDS in concentrations of $10^{-4.5}$ to 10^{-2} g% was carried out for periods of about 90 days, beginning usually about 60 days after inoculation; in 4 experiments, DDS administration was begun about 75 days after inoculation. Harvests of *M. leprae* were carried out from the pooled tissues of 4-8 foot-pads of untreated mice at intervals beginning about 100 days after inoculation, in order to define the logarithmic portion of the growth curve. Similar harvests were carried out from the foot-pad tissues of DDS-treated mice at least once late during the period of treatment, and at intervals thereafter until the *M. leprae* had multiplied to the level of 10^6 organisms per foot-pad, or until no mice remained. The regression of the $\log_{10}$ number of acid-fast bacilli (AFB) per foot-pad on the time in days after inoculation was calculated (Goldstein, 1964), assuming a constant doubling time during logarithmic multiplication of 12 days (Levy, 1976), to represent the phase of logarithmic growth of *M. leprae.* When mice were to be sacrificed for harvest of *M. leprae* during DDS treatment, the mice were first exsanguinated and plasma was separated and stored frozen for later analysis. DDS analyses were carried out by the chromatographic-fluorometric method (Murray *et al.,* 1971, 1975).

Results

The results of 2 typical experiments, portrayed in Fig. 1, demonstrate the application of the 2 criteria to characterize the antimicrobial activity of DDS when the drug administered in a 90-day "pulse" beginning during logarithmic

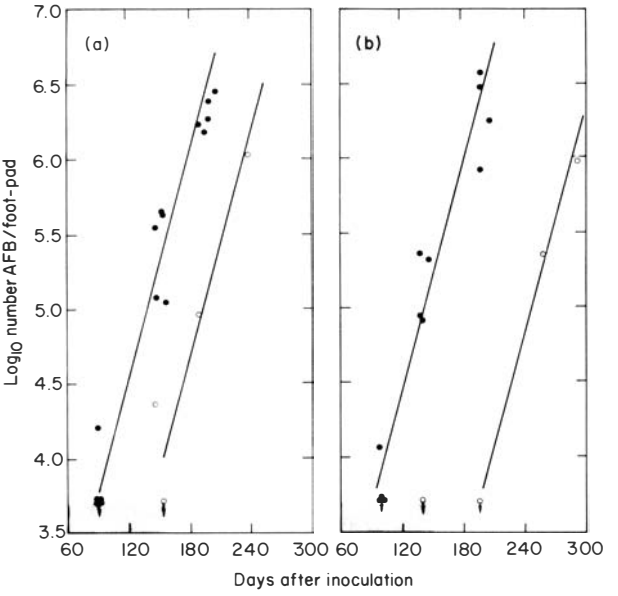

Fig. 1. Log_{10} number of AFB (*M. leprae*) per foot-pad as a function of the time after inoculation of mice. Mice were inoculated with $10^{3.7}$ organisms in both hind foot-pads on day 0. Those of experiment m6-12-68 (a) were administered 10^{-4} g% DDS incorporated into the mouse chow; the mice of experiment m4-2-69 (b) were administered 10^{-2} g% DDS. The drug was administered for the time indicated by the shaded bars along the abscissae. In each experiment: (●) results of harvests of *M. leprae* from pools of the tissues of 4 foot-pads of untreated control mice; (○) results of harvests of *M. leprae* from the foot-pads of treated mice. The solid lines, the best-fitting straight lines drawn through the collections of points with a slope equivalent to a doubling time of 12 days, represent the logarithmic phase of bacterial multiplication. No organisms were found in the harvests represented by the points with the downward-extending arrows; the points were calculated as if one organism had been encountered in the counting procedure.

multiplication of *M. leprae*. In experiment m6-12-68 (experiment no. 1 of Table 1), 10^{-4} g% DDS was administered for 95 days, beginning 61 days after the mice were inoculated. The regression line representing logarithmic multiplication of the organisms in untreated mice yields values of 178 days for the time after inoculation at which multiplication achieved the level of 10^6 *M. leprae* per foot-pad, and $10^{3.02}$ for the number of organisms per foot-pad at the time DDS administration was begun. Harvests of *M. leprae* from the foot-pads of treated mice during the period of DDS administration 146 and 153 days after inoculation yielded $10^{4.38}$ and fewer than $10^{3.70}$ AFB per foot-pad respectively. The geometric mean of these 2 values, $10^{4.04}$, represents the level to which *M. leprae* had multiplied in treated mice after DDS administration was begun. This level was reached in untreated mice 102 days after inoculation and 41 days after treatment had been started. Thus, there was a delay of 41 days between beginning treatment and the onset of inhibition. The number of doublings of *M. leprae* during this delay may be determined:

$$10^{4.04}/10^{3.02} = 10.5\text{-fold multiplication; } \log_2 10.5 = 3.39 \text{ doublings.}$$

The regression line representing logarithmic multiplication of *M. leprae* in treated mice after withdrawal of DDS yields a value of 233 days for the time at which multiplication reached the level of 10^6 AFB per foot-pad. Multiplication of the organisms in untreated mice had reached this level 55 days earlier. DDS had been administered for 95 days, but the *M. leprae* had continued to multiply during the first 41 days of administration, leaving a period of 54 days during which DDS inhibited multiplication of the organisms. Thus, the *M. leprae* appear to have resumed multiplication virtually immediately upon cessation of DDS administration. Therefore, in this experiment, in which mice were treated with 10^{-4} g% DDS beginning during logarithmic multiplication of the *M. leprae,* the organisms continued to multiply through about 3.4 doublings before the onset of inhibition, and multiplication resumed immediately when DDS treatment was stopped.

In experiment m4-2-69 (experiment no. 4 in Table 1), 10^{-2} g% DDS was administered for 88 days beginning 61 days after inoculation. At this time, the calculated number of AFB per foot-pad was $10^{2.97}$. A harvest of *M. leprae* from the foot-pads of treated mice on day 139 yielded fewer than $10^{3.70}$ AFB per foot-pad. Because multiplication of *M. leprae* in untreated mice appears to have reached the level of $10^{3.70}$ AFB per foot-pad 90 days after inoculation and 29 days after beginning DDS administration, multiplication of *M. leprae* in the treated mice could have continued for no longer than 29 days after treatment was begun. During this time, no more than 2.4 doublings of *M. leprae* could have occurred, assuming a doubling time of 12 days. Once DDS treatment had been stopped, multiplication to the level of 10^6 AFB per foot-pad appears to have occurred 105 days later in treated than in untreated mice. At least 46 days—105-(88-29)—represents a delay of resumption of multiplication that cannot be accounted for by the presence in the mouse tissues of DDS in an effective concentration. Thus, in this experiment in which mice were treated with 10^{-2} g% DDS, multiplication of *M. leprae* probably ceased immediately upon the institution of treatment, and resumed only after a considerable delay, once treatment was stopped.

The results of 20 experiments in which DDS was administered to *M. leprae*-infected mice are presented in chronological order in Table 1. The data in this table were derived by means of the calculations just described. As shown by the second column of the table, the drug was administered in a dosage of 10^{-4} g% in 18 experiments, and in other dosages in 5 experiments. For each of the 20 experiments, the number of AFB per foot-pad at the time DDS administration was started is shown in column 3. In the fourth column are entered the actual results of harvests of *M. leprae* from the foot-pads of treated mice about 90 days after beginning treatment; DDS was stopped at this time in all but one experiment. The fifth column of Table 1 shows the number of days elapsed between inoculation and multiplication of *M. leprae* to the level of 10^6 per foot-pad in untreated mice. The number of days between the start of treatment and multiplication of *M. leprae* to the level of 10^6 AFB per foot-pad in untreated mice, which is the difference between the values in column 5 and the number of days elapsed between inoculation and the start of DDS administration, is shown in the sixth column. The purpose of the data of columns 5 and 6 is to permit the consideration of the point on the growth curve of *M. leprae* at which the administration of DDS was begun. The concentration of DDS measured in the plasma of mice sacrificed for harvest of *M. leprae* during treatment is shown in the

TABLE 1

Characteristics of the effects of treatment with DDS on the multiplication of M. leprae *in the mouse foot-pad*

Experiment no.	Dosage of DDS* (10^{-4} g%)	Log_{10} AFB/foot-pad		Time to 10^6 AFB/foot-pad From inoculation† (days)	From start of DDS† (days)	Plasma DDS (μg/ml)	No. of doub-lings	Delay § (days)
		Start of DDS†	End of DDS‡					
1	1.0	3.01	<4.03	178	117	<1.0	<3.4	1
2	1.0	3.82	4.85	148	86	–‖	3.4	17
2	10	3.82	3.76	148	86	–‖	0	31
2	100	3.82	<3.70	148	86	–‖	0	68
3	100	2.96	4.33	180	120	–‖	4.6	103
4	100	2.97	<3.70	181	120	–‖	<2.4	46
5	1.0	3.73	5.39	150	89	–‖	5.5	>156
6	0.3	3.97	5.36	155	80	<1.0	4.6	8
6	1.0	3.97	5.48	155	80	2.0	4.9	39
7	1.0	3.55	4.61	171	96	1.8	3.5	–¶
8	1.0	4.40	5.51	139	63	4.0	3.7	60
9	1.0	5.06	5.87	114	38	1.5	2.7	>328
10	1.0	4.94	5.96	103	42	6.4	3.4	<1
11	1.0	4.21	5.09	129	70	5.2	2.9	106
12	1.0	4.43	5.30	120	61	6.9	2.9	72
13	1.0	4.73	5.66	110	50	6.2	3.0	191
14	1.0	4.43	4.88	115	53	4.2	1.5	92
15	1.0	4.43	5.42	121	61	3.1	3.2	53
16	1.0	4.33	4.76	128	66	9.2	1.4	55
17	1.0	3.94	4.27	143	81	6.5	1.0	22
18	1.0	4.46	5.33	123	62	6.8	2.9	76
19	1.0	4.12	4.73	134	74	8.4	2.0	27
20	1.0	4.24	4.70	131	69	6.2	1.5	37

* DDS was administered incorporated in the mouse chow for about 90 days, beginning about 60 days after inoculation in all experiments except nos 6-9, in which drug administration was begun about 75 days after inoculation.

† Calculated from the regression line representing the logarithmic phase of bacterial multiplication in untreated control mice.

‡ Actual number recovered at harvest from treated mice.

§ Delay = the difference between the time to 10^6 AFB per foot-pad in treated mice and that in untreated mice (column 5), from which has been subtracted the difference between the duration of treatment and the duration of continued multiplication after beginning DDS.

‖ Not measured.

¶ Not applicable, because treatment was not stopped after 90 days.

seventh column. In the eighth column of Table 1 is presented the number of doublings of *M. leprae* that occurred in treated mice after treatment had been started. In the last column is shown the duration of the delay of resumption of multiplication in treated mice after cessation of treatment that cannot be attributed to the presence of DDS in the tissues in effective concentration.

Multiplication of *M. leprae* appears to have ceased immediately after beginning treatment with 10^{-2} g% DDS in experiment no. 2 and probably also in experiment no. 4. In experiment no. 3, the harvest of *M. leprae* performed just before withdrawal of treatment yielded $10^{4.34}$ AFB per foot-pad, representing 24-fold multiplication or 4.6 doublings. However, 2 subsequent harvests performed 194 and 233 days after inoculation yielded fewer than $10^{3.70}$ and $10^{3.70}$ AFB per foot-pad respectively. These data suggest that the yield of the first harvest was not representative, and that multiplication of *M. leprae* had indeed ceased immediately after treatment with 10^{-2} g% DDS had been begun in this experiment also. In each of these 3 experiments, once treatment had been withdrawn, multiplication of *M. leprae* resumed only after a delay.

In the one experiment in which mice were treated with 10^{-3} g% DDS (experiment no. 2), multiplication appears to have ceased immediately after treatment had been started, and resumption of multiplication of *M. leprae* appears to have been delayed significantly after cessation of treatment. In contrast, in the one experiment in which mice were treated with $10^{-4.5}$ g% DDS (experiment no. 6), *M. leprae* continued to multiply through almost 5 doublings after treatment had been begun, and multiplication resumed without significant delay after DDS administration was stopped. Thus, the results of treatment of mice with DDS in dosages of $10^{-4.5}$, 10^{-3} 10^{-2} g% appear consistent with those reported by Shepard (1967, 1969): the larger the dosage, the fewer the doublings after beginning treatment and the longer the delay of resumption of multiplication after withdrawal of treatment.

The major problem to which this study is addressed is the lack of uniformity of the results of treatment with 10^{-4} g% DDS. Multiplication of *M. leprae* was inhibited in all 18 experiments. The number of doublings of *M. leprae* after beginning DDS administration varied fron 1.0-5.5, with a mean of 2.93 doublings. The relationship of the number of doublings to several characteristics of bacterial multiplication is shown in Table 2. It is apparent that the time required from inoculation to multiplication to 10^6 AFB per foot-pad in untreated mice varied from experiment to experiment, probably as a result of variation of the proportion of viable organisms in the inoculum or of the duration of the lag phase. Because treatment was started at about the same time after inoculation in all experiments, the portion of the logarithmic phase during which DDS administration was started also differed considerably from experiment to experiment. Neither the time from inoculation to multiplication to 10^6 AFB per foot-pad nor the time from beginning treatment to multiplication to this level was correlated with the number of doublings of *M. leprae* after beginning treatment. The number of doublings was negatively correlated with the concentration of DDS measured in the mouse plasma, and also with the date on which the experiments were started.

The duration of the delay of resumption of multiplication of *M. leprae* also varied from experiment to experiment in which 10^{-4} g% DDS was administered. There was no delay in experiments no. 1 and 10; the duration of the delay was barely significant in experiments no. 2, 17 and 19; and the delay was longer than

TABLE 2

Correlation of the number of doublings and the delay of resumption of multiplication with several characteristics of multiplication of Myco. leprae

Correlation examined	*r**	*t**	*P**
Number of doublings versus:			
Log_{10} AFB foot-pad:			
At start of DDS	−0.244	1.01	> 0.05
At end of DDS	0.435	1.93	> 0.05
Time to 10^6 AFB foot-pad:			
From inoculation	0.352	1.51	> 0.05
From start of DDS	0.271	1.12	> 0.05
Plasma DDS concentration†	−0.587	2.71	< 0.02
Date experiment initiated‡	−0.760	4.68	< 0.01
Number of days delay versus:			
Log_{10} AFB foot-pad:			
At start of DDS§	0.490	2.18	< 0.05
At end of DDS‖	0.521	2.36	< 0.04
Time to 10^6 AFB/foot-pad:			
From inoculation	−0.379	1.59	> 0.05
From start of DDS¶	−0.482	2.13	0.05
Plasma DDS concentration	−0.269	1.01	> 0.05
Date experiment initiated	−0.033	0.13	> 0.05
Number of doublings	0.126	0.49	> 0.05

* *r*, The correlation coefficient; *t*, Student's "*t*"; *P*, probability.

† Number of doublings = 2.74 − (0.24 ± 0.19) (DDS concentration in ng/ml − 4.96). In this and the subsequent regression equators, the expression for the slope includes the 95% confidence limits around the estimate of the slope of the regression line.

‡ Number of doublings = 2.93 − (0.36 ± 0.16) (date experiment initiated − 7.3).

§ Number of days delay = 78.4 + (83.8 ± 81.8) (log_{10} AFB per foot-pad at start of DDS − 4.24).

‖ Number of days delay = 78.4 + (79.8 ± 72.2) (log_{10} AFB per foot-pad at end of DDS − 5.12).

¶ Number of days delay = 78.4 + (2.084 ± 2.081) (number of days from start of DDS to 10^6 AFB per foot-pad − 68.4).

100 days in experiments no. 5, 9, 11 and 13. The duration of the delay may be seen in the lower panel of Table 2 to have been correlated with the numbers of AFB per foot-pad at the beginning of DDS administration and at the end of the period of treatment in treated animals, and to have been negatively correlated with the time elapsed from start of treatment to multiplication to the level of 10^6 AFB per foot-pad in untreated mice. None of these correlations is striking, however. The duration of the delay was not correlated with plasma DDS concentration, the date experiments were initiated, or the number of doublings that occurred after beginning treatment.

Discussion

The purposes of this study were to describe the manner in which multiplication of *M. leprae* in the mouse foot-pad was affected by a 90-day course of DDS begun during the logarithmic phase of bacterial growth, and to find an explanation for

the variation of the effects of treatment from experiment to experiment. Our results appear to confirm those reported earlier by Shepard (1967, 1969). Administration of DDS in a concentration of 10^{-4} g% inhibited multiplication of this strain of *M. leprae.* The bacterial strain used in this study proved also to be susceptible to $10^{-4.5}$ g% DDS; in an earlier, unpublished study, it was found to multiply in mice during the administration of 10^{-5} g% DDS. These results are consistent with the earlier demonstration that *M. leprae* recovered from untreated patients are uniformly susceptible to DDS in this dosage, and that many strains of *M. leprae* recovered from untreated patients are susceptible to $10^{-4.5}$ g% DDS, whereas only a few are susceptible to 10^{-5} g% DDS (Shepard *et al.,* 1969; Levy and Peters, 1976).

Our results also demonstrate the relationship described earlier (Shepard, 1967, 1969) between the dosage of DDS on the one hand and characteristics of drug action on the other—the lag between beginning treatment and the onset of inhibition of multiplication, and the delay of resumption of multiplication of *M. leprae* after the cessation of DDS administration. These 2 phenomena are of particular interest because of the variable effects noted to follow the administration of DDS in a concentration of 10^{-4} g%.

Multiplication has been reported to continue through several generations after the addition of sulphonamides to cultures of susceptible organisms (Wolff and Julius, 1939). The authors speculated that the lag between addition of drug and onset of growth inhibition depended upon the presence within the organisms of a store of an essential substance, the supply of which is affected by the drug. The concentration-dependence of this phenomenon was not described in this report, however. Our demonstration that the duration of the lag in the case of inhibition of *M. leprae* by DDS is related to the concentration of DDS appears more consistent with the presence within the organisms of a store of a precursor of di- or tetrahydrofolic acid than with a store of the end-product itself.

The results of administration of 10^{-4} g% DDS demonstrate considerable variation of the 2 characteristics of DDS action from experiment to experiment. The number of doublings of *M. leprae* that occurred after the start of DDS administration was inversely related to the concentration of DDS in the plasma of mice sacrificed near the end of the period of treatment, and also to the date on which the experiments were started. That the number of doublings was smaller when a larger DDS concentration was measured is not unexpected. That the number of doublings was smaller in more recent experiments requires explanation. In another study, conducted during a portion of the time covered by this study, variation of the plasma DDS concentration from experiment to experiment was noted, although no trend could be discerned (Levy and Peters, 1976). However, in the present study, the plasma DDS concentration was positively correlated with the date on which the experiments were begun (r, the correlation coefficient = 0.744; Student's $t = 4.17$; $P < 0.0003$). Thus, the relationship between the number of doublings of *M. leprae* after beginning treatment and the plasma DDS concentration at the time mice were sacrificed for harvest is consistent with the relationship between the number of doublings and the date on which mice were inoculated in each experiment. The date on which the experiments were started is also correlated negatively with the time from inoculation to multiplication to the level of 10^6 AFB per foot-pad in untreated mice ($r = 0.615$; $t = 3.12$; $P < 0.002$). Although this relationship may suggest that our technique has drifted during the course of the past 8 years, no relationship could be discerned between the number of doublings that occurred in treated

mice after treatment had been started and the time from inoculation to multiplication to 10^6 AFB per foot-pad of untreated mice.

The duration of the delay of resumption of multiplication of *M. leprae* after administration of 10^{-4} g% DDS was stopped also varied among experiments. The duration of the delay was positively correlated with the number of AFB per foot-pad at the beginning of treatment and negatively correlated with the time from beginning of treatment to multiplication to the level of 10^6 *M. leprae* per foot-pad of untreated mice. These findings are consistent, because both measurements are made from the same regression line. On the other hand, the duration of the delay was found to be correlated with the number of AFB per foot-pad of treated mice measured near the end of the period of treatment, whereas it was not correlated with the number of doublings between the start of treatment and the onset of growth inhibition. These findings are inconsistent, because the number of doublings is determined by the difference between the number of AFB per foot-pad of treated mice mice at the end of the period of treatment and the number of AFB per foot-pad at the time DDS administration was begun. The duration of the delay was correlated neither with plasma DDS concentration (in the case of those experiments in which 10^{-4} g% DDS was administered) nor with the date experiments were begun.

Taken together, these results are consistent with the explanation that both characteristics of DDS effect—the lag between beginning treatment and onset of inhibition, and the delay of resumption of multiplication after the end of treatment—depend upon the dosage of DDS. However, the number of doublings of *M. leprae* after the start of DDS treatment appears to be more sensitive to relatively minor variations of the concentration of DDS in the neighbourhood of 10^{-4} g% than is the duration of the delay of resumption of multiplication once treatment has been stopped.

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Leprosy Disabilities in the New Hebrides

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The proportion of disabled among leprosy patients is 39% in the New Hebrides. This proportion is higher among lepromatous cases (67%) than among tuberculoid and borderline cases (38%). The disability index is higher among disabled lepromatous (1.2) than among disabled tuberculoid and borderline (0.8). Males are more often disabled than females (47% for males, 33% for females), but females seem to be more seriously disabled than males. There is an increase in the proportion of disabled and in the disability index with age. Disabilities are more frequent among positive cases, among patients taking irregular treatment or no treatment at all and among patients with leprae reaction. The proportion of disabled among tuberculoid cases increases 4 to 6 years after diagnosis and then decreases. For lepromatous patients there is a high and stable proportion of disabled from the beginning of the disease; there is also a steady increase in the severity of the disabilities. The nature of the initial symptoms influences the future occurrence of disabilities among tuberculoid and borderline cases. Only 13 to 16% will develop disabilities if there is no nerve involvement, 35 to 38% will do so if nerves are already involved. Bilateral lesions are more common among lepromatous than among tuberculoid or borderline cases. The prevalence of disabled for the whole population was estimated to be 2.7 per thousand.

Introduction

The Second Report of the WHO Expert Committee on Leprosy (WHO, 1960) estimated that about 25% of all leprosy patients have some degreee of disability. This figure was later considered as an underestimation of the disability problem at the Scientific Meeting on Rehabilitation in Leprosy (WHO, 1961), held at Vellore, India, in 1960 because "in many surveys anaesthesia of the hands and feet, which constitute severe disability, has not been recorded except when accompanied by deformity".

Percentages of disabled leprosy patients from different countries vary widely, as do the criteria for their classification and definition: 26.6% in Burma, 40.3% in Taiwan, 25.8% in Japan (Intl. Soc. Rehab. Lep., 1965), 42.9% in South India (Rao, 1970).

Studies on prevalence of leprosy disabilities in different countries (Martinez Dominguez and Bechelli, 1966) and studies of disabilities in relation with other factors as sulphone treatment (Wardekar, 1968), socio-economic problems (Frist, 1973), etc., have been done using once again different criteria for the definition and evaluation of disabilities.

The writers assess the disability problem among the New Hebridean leprosy patients from the epidemiological and clinical points of view, evaluating the different factors that could influence the development of disabilities. The estimated prevalence of disabled leprosy patients for the whole country is also given.

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The following objectives have been chosen:

(1) The problem of leprosy disabilities in relation with the whole population (prevalence).
(2) Distribution of disabilities by sex, age, and type of leprosy.
(3) The relation between disabilities and bacteriological results, regularity of treatment and lepra reaction.
(4) The evaluation of disabilities with time.
(5) Prognosis of disabilities according to the initial lesions (skin, nerve, or both).
(6) Frequency of type of disability.
(7) Distribution of hand and foot disability according to the leprosy type (laterality of disabilities).
(8) Geographical distribution of disabilities in the group of islands and possible reasons for this.

Material and Methods

The data on disabled patients were collected from the clinical examinations made during leprosy surveys and periodic follow-ups.

Data on previous disabilities, initial symptoms, bacteriology and regularity of treatment were collected from the central register of the leprosy control unit of the New Hebrides.

The WHO form (WHO, 1970) for the recording of disabilities and the Disability Index DI-2 (Bechelli, 1971) was used because it is the most elaborated.

To describe the disability situation in any given group 2 data are presented:

(1) percentage of disabled;
(2) mean disability index of disabled patients.

Results

FREQUENCY OF DISABILITIES

Out of a total number of 700 leprosy patients alive in the New Hebrides, detailed data were available for 329 patients studied for disabilities. Among these, 128 (39%) were found to suffer from some kind of disability. In comparison with other countries this percentage of disabled among leprosy patients is rather high. From this it may be estimated that there are about 270 disabled leprosy patients in the country, i.e. a prevalence rate of 2.7 per 1000.

DISABILITIES IN RELATION TO THE TYPE OF LEPROSY

The data are presented in Tables 1 and 3 and Figs 3 and 4. No disabled were found among indeterminate cases. According to the WHO Classification for Disabilities (Bechelli, 1971), indeterminate cases have disabilities only if at least anaesthesia was present on hands or feet. Anaesthesia of indeterminate macules located elsewhere in the body is not considered as a disability. Among the other types there were:

(a) a higher percentage of disabled among lepromatous (67%) than among tuberculoid and borderline (38%) (difference significant at $P = 0.05$);
(b) a higher disability index among disabled lepromatous (1.2) than among disabled tuberculoid and borderline (0.8) (difference significant at $P = 0.05$).

High percentages of disabled and high disability indices among lepromatous cases were also found in other studies (Martinez Dominguez and Bechelli, 1966; Novreen and Srinivasan, 1966). It can be explained by the widespread and progressive nature of lepromatous leprosy. The other types are more localized and have a shorter evolution.

The observations made on the tuberculoid and borderline groups were similar regarding the disabilities. Most of the boderline cases examined were close to the tuberculoid pole.

DISABILITIES ACCORDING TO SEX

The data are presented in Tables 1 and 2 and Figs 1 and 2. Males are more often disabled than females (47% for adult males, 33% for adult females; difference significant at $P = 0.05$).

TABLE 1
Disabilities by sex, age and leprosy types

	Males				Females				Children				Total			
	No. of cases	No. of disabled	% disabled	D.I.	No. of cases	No. of disabled	% disabled	D.I.	No. of cases	No. of disabled	% disabled	D.I.	No. of cases	No. of disabled	% disabled	D.I.
Indeterminate	14	0	0	–	9	0	0	–	8	0	0	–	31	0	0	–
Tuberculoid	77	36	47	0.7	61	20	33	0.9	26	5	19	0.4	164	61	37	0.8
Borderline	62	26	42	0.8	22	8	36	0.8	4	2	50	0.2	88	36	41	0.8
Lepromatous	31	24	77	1.0	15	7	47	2.4	0	0	–	–	46	31	67	1.2
Total	184	86	47 1	0.8	107	35	33	1.1	38	7	18	0.3	329	128	39	0.8

D.I., Disability Index.

TABLE 2
Disabilities by age and sex

		Males				Females				Total			
		No. of cases	No. disabled	% disabled	D.I.	No. of cases	No. disabled	% disabled	D.I.	No. of cases	No. disabled	% disabled	D.I.
	0-14	16	5	31	0.3	22	2	9	0.3	38	7	18	0.3
Adults	15-29	82	28	34	0.7	48	14	29	0.7	130	42	32	0.7
	30-44	59	30	51	0.9	31	9	29	1.4	90	39	43	1.0
	45+	43	28	65	0.9	28	12	43	1.4	71	40	57	1.0
	Sub-total	184	86	47	0.8	107	35	33	1.1	291	121	41	0.9
Total		200	91	45	0.8	129	37	29	1.1	329	128	39	0.9

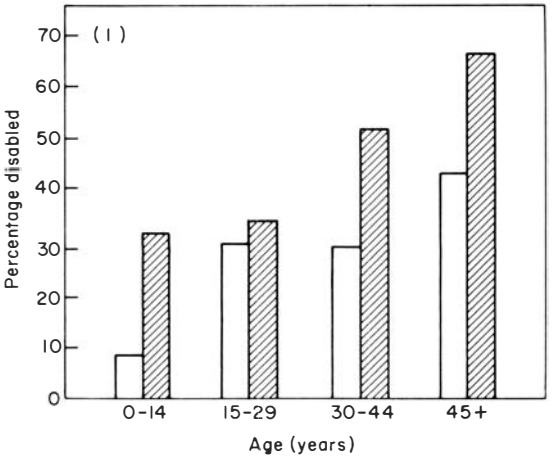

Fig. 1. Percentage of disabled according to age and sex; (▨) male; (□) female.

The same difference is observed in each type of leprosy, but it is more evident in the lepromatous type.

Although less often disabled, females seem to be more seriously disabled (D.I. = 0.8 for males, 1.1 for females, difference not significant at $P = 0.05$). This difference is most prominent for the lepromatous type (D.I. = 1.0 for males, 2.4 for females).

It is difficult to find a full explanation of these differences according to sex. Leprosy in the New Hebrides is almost entirely limited to the rural areas (only 2 cases were detected in the urban population). New Hebrideans are farmers, both the males and the females. Males spend more time working in gardens, hence a greater exposure to traumas of gardening and a higher proportion of disabled. Females do the easier gardening jobs along with housework and cooking. While cooking they are exposed to more severe disabilities. Male children have rougher activities than females.

It is not fully understood why there should be a difference between male and female lepromatous D.I. (0.8 *versus* 1.4) and no difference between male and female tuberculoid or borderline (0.8 *versus* 0.8).

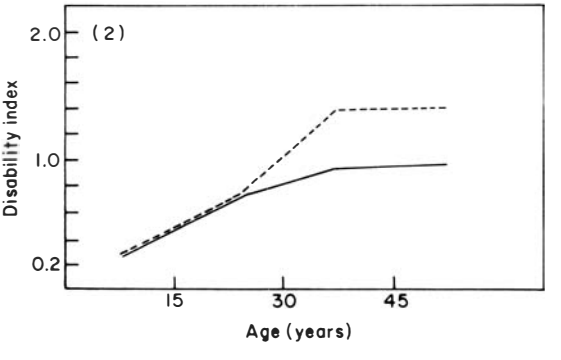

Fig. 2. Disability index according to age and sex. (————) male; (– – –) female.

TABLE 3
Disabilities by age and leprosy type

		Tuberculoid				Borderline				Lepromatous			
		No. of cases	No. disabled	% disabled	D.I.	No. of cases	No. disabled	% disabled	D.I.	No. of cases	No. disabled	% disabled	D.I.
	0-14	26	5	19	0.4	4	2	50	0.2	0	0	–	–
Adults	15-29	61	22	38	0.5	41	16	39	0.9	11	4	36	0.8
	30-44	48	21	44	0.9	21	6	29	0.8	17	12	71	1.2
	45+	29	12	41	1.1	22	12	54	0.7	18	15	83	1.4
	Sub-total	138	56	41	0.8	84	34	40	0.8	46	31	67	1.2
Total		164	61	37	0.8	88	36	41	0.8	46	31	67	1.2

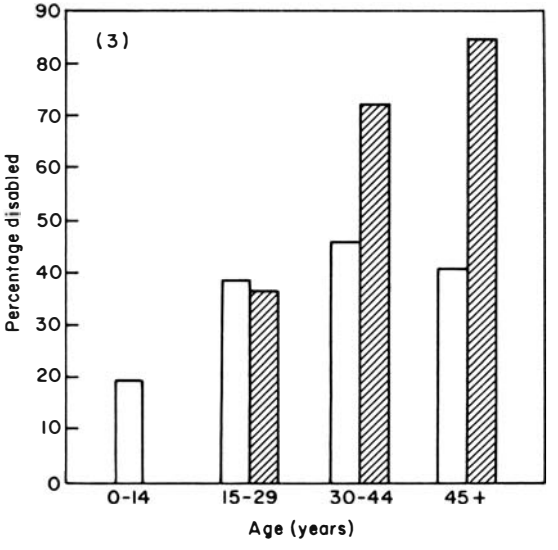

Fig. 3. Percentage of disabled according to age and leprosy type. (▨) LEP; (□) TUB.

DISABILITIES AND AGE

The breakdown by age groups of 15 years is presented in Tables 2 and 3 and Figs 2 and 3. For males and females, for tuberculoid, borderline and lepromatous there is an increase of the percentage of disabled and of the disability index with age.

For tuberculoid and borderline the increase is progressive. The disabilities become more common and more serious with age. For the lepromatous the increase is very rapid until a high plateau is reached at the age of 30. (It will be noted that the samples used are small.)

Males have more disabilities than females in all age groups. In the age group 0 to 14, 31% of the males are already disabled while only 9% of the females show some disability. This difference is less conspicuous in the 15 to 29 years age group (34% for males, 29% for females), but it becomes more obvious in the older age groups. Since there was no random sampling done, the smaller difference in the 15 to 29 age group might be due to random fluctuations.

Fig. 4. Disability index according to age and leprosy type. (———) TUB; (– – –) LEP.

The percentage of disabled children is high (18%) in comparison with some other countries (Martinez Dominguez and Bechelli, 1966). There were no lepromatous cases in the age group below 15, hence this high percentage is observed among tuberculoid and borderline, mostly among males. It is likely that this diagnosis was made in relatively advanced stages of the disease.

DISABILITIES AND BACTERIOLOGY

The bacteriological status (Table 4) of the tuberculoid and borderline types influences the disability problem. There are more disabled among positive cases than among negative cases (67% and 68% versus 41% and 38%, differences significant at $P = 0.05$). However it does not influence the severity of disability since disability indices are equivalent.

TABLE 4
Relation between disabilities and bacteriology

	Positive				Negative			
	No. of cases	No. disabled	% disabled	D.I.	No. of cases	No. disabled	% disabled	D.I.
Tuberculoid	9	6	67	0.8	132	54	41	0.6
Borderline	25	17	68	0.8	77	29	38	0.7
Total	34	23	68	0.8	209	83	40	0.6

TABLE 5
Geographical distribution of disabilities

Island	No. of cases studied	No. disabled	% disabled	D.I.
Mota Lava	37	13	35	1.7
Vanua Lava	9	1	11	0.3
Mota	11	2	18	0.2
Other Banks/Torres	11	6	54	0.8
N. Santo	24	15	62	0.5
S. Santo	63	21	33	0.6
W. Santo	10	8	80	1.2
Islets	9	2	22	0.4
Aoba	20	8	40	0.9
Maewo-Malekula	4	4	100	0.7
Pentecost	21	8	38	1.6
Ambrym	28	6	21	0.7
Paama	30	12	40	0.8
Epi	16	4	25	1.2
CD1 Islets	9	7	78	0.9
Tanna	24	9	37	0.8
Sthn. Islets	3	2	67	1.0
Total	329	128	39	0.8

The geographical difference in the percentage of the disabled among leprosy patients is not significant. However the disabilities are not evenly distributed throughout the group of islands. There are several factors which are thought to influence this distribution by islands: quantity and quality of health posts available; means of communications; proportion of lepromatous; etc. For instance, in Mota Lava the severity of the disability problem (35% of disabled,

(5)

Indices	Number
0.1 – 0.3	38
0.4 – 0.6	15
0.7 – 0.9	27
1.0 – 1.2	18
1.3 – 1.5	11
1.6 – 1.8	7
1.9 – 2.1	2
2.2 – 2.4	2
2.5 – 2.7	2
2.8 – 3.0	1
Over	5

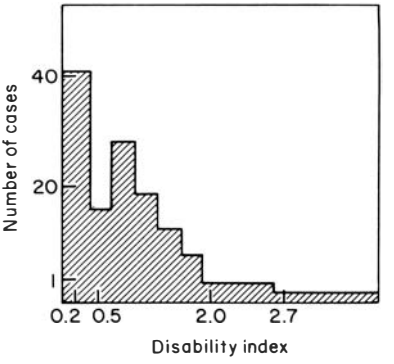

Fig. 5. Distribution of disability indices.

D.I. = 1.7) is probably due to the high prevalence of lepromatous on the island. In West Santo, the main contributing factors to the disabilities are the isolation and the complete lack of adequate facilities and trained personnel.

There is an apparent correlation between the percentage of disabled and the disability index: the higher the percentage of disabled, the higher the disability index. However, in 3 areas the disability index is higher than expected: Mota Lava, Epi and Pentecost islands. There is no obvious explanation for this lack of correlation.

CLINICAL DESCRIPTION

Out of 128 disabled patients, 41 (32%) had only anaesthesia of hands and/or feet and 87 (68%) had disabilities besides anaesthesia.

The majority of disabilities are minor ones as shown by Fig. 5. The different types of disabilities, anaesthesia excluded, are presented in Table 6. The most common disabilities are

TABLE 6
Types of disabilities

		Number	%
Anaesthesia only		41	32
Anaesthesia & deformity		87	68
Total		128	100
Hand	Ulcer & injuries	8	4
	Mobile claw	54	28
	Slight absorption	36	19
	Stiff joint	4	2
	Severe absorption	10	5
Feet	Ulcers	45	23
	Clawed toes	6	3
	Slight absorption	10	5
	Foot drop	3	1.5
	Contractures	1	0.5
	Severe absorption	10	5
Face	Lagophthalmos	1	0.5
	Iritis, keratitis	3	0.5
	Visual impairment	3	1.5
	Facial paralysis	1	0.5

TABLE 7
Hand and foot disability according to leprosy type

	No. of cases	No. disabled*	Hand				Foot			
			No. with hand disability	Monolateral	Bilateral	% bilateral	No. with foot disability	Monolateral	bilateral	% bilateral
Tuberculoid	164	61	38	28	10	26.3	25	21	4	16.0
Borderline	88	36	18	15	3	16.7	18	12	6	33.3
Lepromatous	46	31	16	5	11	68.7	17	6	11	64.7

* Some cases had both hand and foot disabilities.

TABLE 8
Prognosis of disabilities according to the initial lesions

	Skin only				Nerve only				Both involved			
	No. of cases	No. disabled	% disabled	D.I.	No. of cases	No. disabled	% disabled	D.I.	No. of cases	No. disabled	% disabled	D.I.
Tuberculoid	73	12	16	0.2	21	8	38	0.2	22	8	36	0.5
Borderline	61	8	13	0.1	4	0	0	–	20	7	35	0.3
Lepromatous	13	7	54	0.8	0	–	–	–	9	5	56	1.3
Total	147	27	18	0.5	25	8	32	0.2	51	20	39	0.7

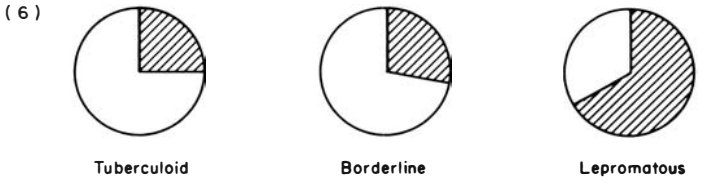

Fig. 6. Laterality of disabilities of hands and feet. (▨)% of bilateral lesions.

the mobile claw hand which represents 28% of all disabilities, foot ulcers with 23% and hand absorption at 19%.

Bilateral lesions are significantly more common among lepromatous than borderline or tuberculoid (Table 7 and Fig. 6). Looking at the distribution of the clinical lesions, the patients classified as borderline are, in the New Hebrides, close to the tuberculoid pole. The distribution of disabilities follows the pattern observed for skin and nerve lesions. The disabilities are localized and asymmetrical in the tuberculoid and widespread and symmetrical in the lepromatous.

Lepra reaction provokes the development of disabilities. For 14 lepromatous cases who had had lepra reaction in the past, the disability index was 1.4. It is only 0.8 among all other lepromatous cases. However the number of cases is too small to provide more detailed information.

EVOLUTION OF THE DISABILITIES

Data regarding initial symptoms were available for 223 cases.

The nature of the initial symptoms (skin symptoms, nerve symptoms, or both) influence the future occurrence of disabilities among tuberculoids and borderline cases. Only 13% to 16% will develop disabilities if there is no nerve involvement, while 35% to 38% will do so if nerves are involved (Table 8).

The evolution of disabilities with time is presented in Table 9 and Figs 6 and 7. For tuberculoid patients the proportion of disabled increases 4 to 6 years after diagnosis and then decreases. The severity of these disabilities is fairly constant (stable index). For lepromatous patients there is a high and stable proportion of disabled with a steady increase of the severity of the disability. The improvement of disabilities of tuberculoid patients may be due to the recovery of Grade 1 disabilities (anaesthesia only, in hands and/or feet, conjunctivitis). Among lepromatous patients Grade 1 disabilities appear at a later stage and the disabilities get worse.

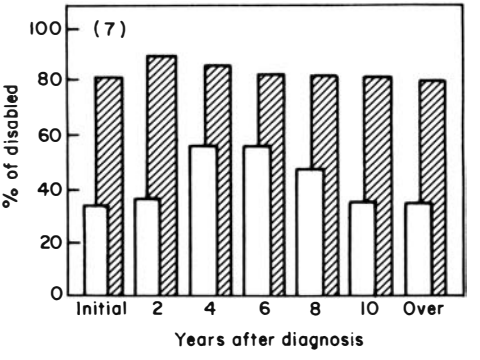

Fig. 7. Evolution of disabilities with time. (▨) LEP; (□) TUB.

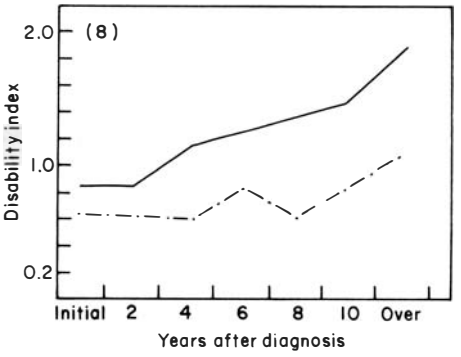

Fig. 8. Evolution of disability index with time. (– – –) LEP; (–.–.) TUB.

TABLE 9
Evolution of disabilities with time

		Years after diagnosis						
		Initial exam.	2	4	6	8	10	Over
T	No. of patients	92	49	17	17	19	20	20
	No. disabled	33	19	10	10	9	7	7
	% disabled	36	39	59	59	47	35	35
	D.I.	0.6	0.6	0.6	0.8	0.6	0.8	2.2
B	No. of patients	86	39	22	27	17	28	15
	No. disabled	26	12	12	16	9	11	10
	% disabled	30	31	54	59	53	39	67
	D.I.	0.9	1.1	1.4	1.1	1.2	1.1	1.1
L	No. of patients	27	23	18	12	14	12	22
	No. disabled	23	21	15	10	12	10	17
	% disabled	85	91	83	83	86	83	77
	D.I.	0.8	0.8	1.1	1.2	1.3	1.4	1.7

TABLE 10
Relation between disabilities and regularity of treatment

	Regular				None or irregular			
	No. of cases	No. disabled	% disabled	D.I.	No. of cases	No. disabled	% disabled	D.I.
Tuberculoid	11	7	64	0.5	39	22	56	0.6
Borderline	22	4	18	1.5	35	16	46	0.9
Lepromatous	10	7	70	1.2	11	11	100	1.5
Total	43	18	42	1.0	85	49	58	0.9

Nerve and bone involvement in lepromatous leprosy are bound to occur and to cause disabilities even under treatment (Jopling, 1971).

The effects of the regularity of treatment on the percentage of disabled is significant in the lepromatous and borderline types (Table 10). Data were available for 128 patients. However, it is difficult to conclude that this is the effect of treatment as these cases were not randomly selected.

The lower percentage of disabled among regularly treated patients has already been mentioned (Wardekar, 1968). However, the opposite observation has also been made (Noordeen and Srinivasan, 1966). DDS in large doses may increase the incidence of lepra reaction, mostly in borderline patients, but this does not counterbalance the beneficial effects of the treatment.

IMPORTANCE OF THE DISABILITY PROBLEM

From the data collected in the sample of 329 patients studied, the prevalence of disabilities among the whole population may be estimated at 2.7 per thousand. The 700 presently living patients would have the following disabilities:

Unable to work	(D.I. $>$ 3)	10
Partially disabled	(1 $<$ D.I. $\leqslant$ 3)	60
Mild disability	(0 $<$ D.I. $\leqslant$ 1)	200
No disability	(D.I. = 0)	430

This does not constitute an economic problem for the manpower of the country. There is also a very small social problem since prejudice against leprosy and/or its deformed victims is minimal. Disabled patients are looked after by their families or by the community.

Conclusion

Although the prevalence of leprosy is rather low in the New Hebrides (2.9 per 100) in comparison to other countries the prevalence of disabilities is rather high, probably due to late diagnosis. The isolation and difficulty of communications in this island group and the scarcity of well-trained medical personnel impair the early diagnosis of leprosy. The primitive living and working conditions contribute to the development of severe disabilities.

It would be justified for the leprosy control programme to put more emphasis on the detection and prevention of disabilities, with males and lepromatous being the groups which have higher risks. Females have less risk of developing disabilities, but the disabilities they do develop tend to be more severe. Case detection and health education could be better utilized after the results of this study.

Acknowledgement

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Results of Five Years of Integration of Leprosy Control into the Provincial Health Service of Phuket Island, Southern Thailand

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Five years experience of integration of leprosy control in Phuket Island, Southern Thailand, showed that known cases of leprosy had increased by 251% from 0.77 to 1.93 per thousand, through the efforts of local health workers, and by 318% from 0.75 to 2.45 per thousand on a second survey conducted in the fifth year of integration. Local health workers detected 43% of total registered cases, remaining cases being found by a specialized leprosy survey team.

The accomplishment of 3 main targets in leprosy control, namely treatment, contact examination and bacteriological smears had gradually declined by 35% from 66 to 31% indicating a great need for better supervision and motivation. Adequate survey before integration was also necessary, followed by regular supervision and field guidance to promote proper efficiency and effectiveness of leprosy control.

Introduction

The Phuket Province is one of the smallest and most hyperendemic in leprosy of the 14 provinces comprising the Southern Region of Thailand. It is an island with an area of 801 km^2 where 103,262 inhabitants live in 3 districts with little mobility of population. The existing health structure covers every area, and the health workers are well motivated. Because of its strategic position in the Region and its available health facilities, Phuket Province was chosen as the pilot province for integration of leprosy control into the Provincial Health Services.

Within 5 years of the integrated leprosy control services, registrations of patients increased from 91 in 1972 to 253 cases in 1976, which brought up the

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prevalence in Phuket Island to 2.45 per thousand, being highest in the South. In 1976, with the support of the Sasakawa Memorial Health Foundation of Japan and the technical advice of the World Health Organization, the Leprosy Division of the Department of Communicable Disease control of Thailand conducted a stratified random sampling survey to assess the epidemiological situation and to evaluate certain aspects of the integrated central operations.

First Survey and Orientation Training Prior to Integration

In 1972, prior to the launching of integration, the Leprosy Division sent a survey team to conduct selective case finding procedures, which included the examination of all known cases, suspects, household contacts and school children. Health education was also conducted on local radio to stimulate voluntary presentation for examination at the Provincial Health Office. The survey lasted about 3 weeks. Eighty-seven leprosy cases were detected and registered with an overall point prevalence of 0.77 per thousand and a lepromatous rate of 0.44 per thousand.

After the survey, a 3 day orientation training course prior to integration was given to 2 groups of 54 provincial health workers. Subsequently, patients were then delegated to the health workers in charge of the existing 14 health centres and 3 midwifery centres. Seven main targets in leprosy control service were assigned to each of the workers. These were as follows:

(a) To carry out examination for leprosy of people voluntarily attending all health and midwifery centres.

(b) To give monthly treatment to all registered cases at the minimal annual treatment rate of 75%.

(c) To examine household contacts once a year at the minimal annual examination rate of 60%.

(d) To examine school children once a year at the minimal annual examination rate of 20%.

(e) To make bacteriological smears of all lepromatous (including borderline) and newly detected cases once a year at the minimal annual smear rate of 60%.

(f) To send a monthly report on leprosy control activities.

Second Survey

The second survey of the province was undertaken in 1976 by the authors. A total of 90 villages in rural areas were covered by the survey and the sampling unit was half of the households of each village (50%). The method of stratified random sampling was used, picking out labels with odd or even numbers. If odd No. 1 was drawn, the survey would be carried out in households Nos. 1, 3, 5, 7, 9 . . . etc., house after house, and vice versa for even numbers, until the target was reached. The survey took 3 months, and a total population of 31,350 were examined from 5,301 households (51.63%) out of a total 10,268 households in a total population of 62,564, and an approximate 51.6% sample and 97.03% coverage of target population were obtained.

Since the method used for the first survey was not the same as that in the second survey, it is not intended in this report to compare the results of these two surveys, but to use the result of the second one as basic data to be in every way comparable to future surveys, using the same frame of households and methods.

The results of the second survey revealed a detection of 31 leprosy cases, a detection rate of 0.99 per thousand with lepromatous cases 0.25 per thousand. When comparing the detection rate of Phuket with the assessment at Khonkaen conducted by the WHO Headquarters Leprosy Advisory Team (L.A.T.) in 1962 and 1972, the most important conclusion which can be drawn from this data the lepromatous detection rate, detection of lepromatous cases among newly detected cases, and prevalence of old leprosy cases are comparable in Khonkaen and Phuket, even though the duration of control operations was completely different (Table 1).

TABLE 1
Comparison of results of epidemiological survey of Khonkaen in 1962, 1972 and Phuket in 1976

Provinces	Year conducted	Duration of leprosy control project prior to assessment	Prevalence of old cases per thousand in assessment year	Detection rate of new cases per thousand	Detection rate of newly lepromatous cases per thousand	Proportion of newly detected lepromatous cases (%)
	1962	7	8.51	3.86	0.30	7.8
Khonkaen	1972	14	2.88	1.42	0.21	8.82
Phuket	1976	5	1.93	0.99	0.18	19.35

TABLE 2
Clinical classification of new leprosy patients found from the second survey of Phuket

Area	Indeterminate	Tuberculoid	Borderline	Lepromatous	Total
Sampling households in rural area	8	15	2	6	31
Outside the sampling households in rural area	2	12	1	0	15
In-municipal area	1	6	0	1	8
Total	11	33	3	7	54

The classification of new cases found on survey is set out in Table 2. Of the 31 new cases found in the sampling households in rural areas, 8 were indeterminate, 15 were tuberculoid, 2 were borderline and 6 were lepromatous. This figure might be of value as baseline data for future survey. Besides 31 new cases found in the sampling households, 15 and 8 new cases were also detected from outside the sampling households in rural areas and municipal areas respectively. These total 54 new cases found in 1976 indicated inadequate case detection effectiveness by local health workers.

Sub-district Prevalence

The present prevalence of leprosy by sub-district (Tambol) together with the prevalence found in 1972, is shown in the map given as Fig. 1. The highest

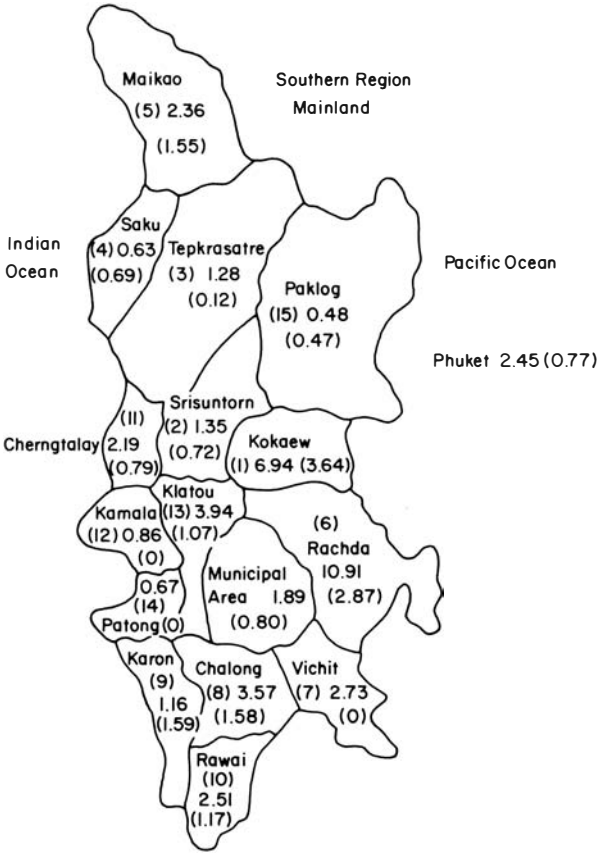

Fig. 1. Phuket Island showing prevalence of leprosy per thousand by subdistrict (Tambol) in 1976; figures in brackets, leprosy prevalence-1972.

prevalence rate (10.91 per thousand) was in Tambol 6 (Rachda) while the lowest prevalence rate (0.48 per thousand) was in Tambol 15 (Paklog).

An increase in point prevalence had occurred in almost all subdistricts (Tambol), but it was most remarkable in Tambol 1 (Kokaew) and Tambol 6 (Rachda), both of which had increased from their previous hyperendemic level of prevalence to well above 5 per thousand. Both Tambols have special tribes of seamen, so called "Chaoley" whose living standard and education are rather low. Total survey of two hyperendemic villages in these 2 Tambols was carried out by the assessment team, with 95.57% population examined. The results showed an increase of prevalence from 52 and 119 per thousand to 56 and 139 per thousand respectively. Since there are now good communications and health structures covering all Tambols, with adequate field guidance and supervision, it is hoped that higher standards of case holding will be achieved here in the future.

Operational Assessment

CASE FINDING

The annual detection of new cases, both overall and for lepromatous cases is shown in Fig. 2.

The overall case finding showed that out of a total 253 cases detected in the 5 year integrated programme, 87 (34.39%) were found from the first survey and 54 (21.3%) were found from the second survey, while local health workers themselves detected 112 cases (44.24%). It is therefore important to conduct adequate case finding programmes before integration of leprosy control into the local health service. However, if 87 cases found from the first survey were excluded, it is noteworthy that 67.47% of newly registered cases in Phuket after total integration were detected by local health workers, therefore, their diagnostic capability should be highly evaluated.

With regard to the mode of case finding (Fig. 3), voluntary case detection was

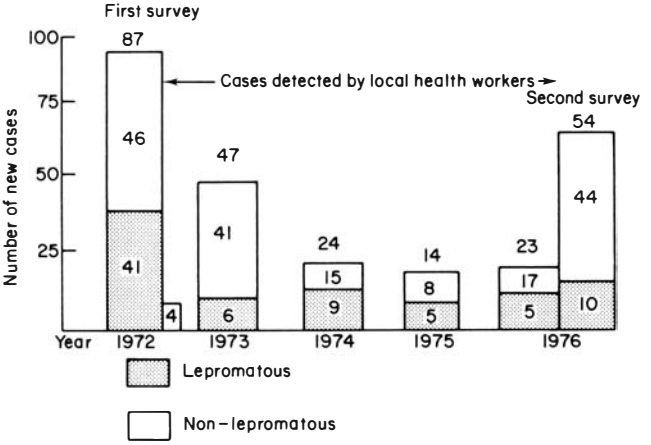

Fig. 2. Annual detection of new cases of leprosy in Phuket, 1972-1976.

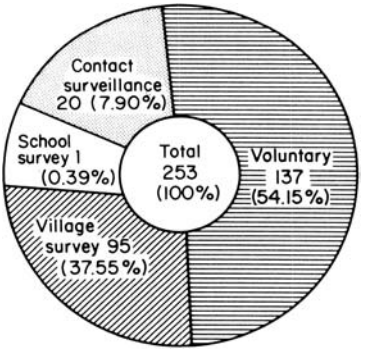

Fig. 3. Showing mode of case finding of total 253 registered cases of leprosy in Phuket (derived from registration records).

TABLE 3

Clinical assessment of 163 old registered cases of Phuket

Type	Total number of registered cases	Number of cases examined	Condition of cases						Transfer out
			Active	Inactive	Released	Misdiag	Misclassification	Dead	
Indeterminate	18	13	3	7	2	3	0	0	3
Tuberculoid	112	100	62	38	2	0	13	0	2
Borderline	1	1	1	0	0	0	1	0	0
Lepromatous	68	49	32	17	0	0	6	1	1
Total	199	163	98	62	4	3	20	1	6

found to be very high (54%) while village survey detected 37% of cases. The high percentage of voluntary cases indicates the value of using health education through radio and bringing treatment close to the patients, but it is also evident that there is still a limited coverage. Contact surveillance has been one effective tool to detect cases. School surveys have appeared, on the whole, not to have been very productive as a routine measure, and more selection in the school, for instance those located in hyperendemic areas, would probably be economical.

CLINICAL ASSESSMENT OF 163 OLD REGISTERED CASES

A clinical assessment of 163 old registered cases had been made by the second-survey team, the results of which are shown in Table 3.

In the present assessment, only mis-diagnosis of 3 indeterminate cases (2.68%) was found. As local health workers officially registered all leprosy cases detected, the low instance of mis-diagnosis, therefore, indicated high efficiency of their training and diagnostic capability. The high proportion of inactive cases indicated the successful treatment by integrated leprosy control services. The epidemiological importance of these patients has thus been greatly reduced. The instance of misclassification indicated the need for closer field supervision and guidance, by which a higher number of released cases will also be obtained.

TREATMENT, CONTACT-SURVEILLANCE AND BACTERIOLOGICAL SMEARS

The degree of accomplishment of 3 main targets of integrated leprosy control activities is shown in Fig. 4.

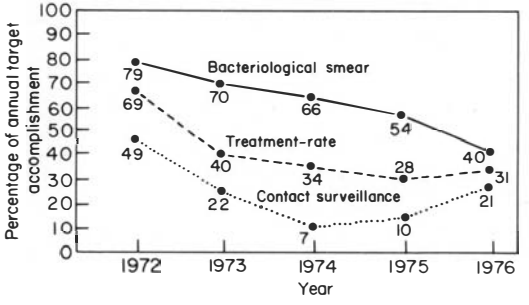

Fig. 4. Showing annual accomplishment of 3 main targets of integrated leprosy control in Phuket, 1972-1976.

The 3 main targets of leprosy control activities, on the whole, were below the standard requirement (treatment rate 75%), contact examination 60% and bacteriological smear 60%), and are not improving. This indicates reduction in interest and willingness of local health workers, and also reflects inadequate supervision. An effort to improve supervision and motivation, therefore, is urgently needed. Further operational study research might be also of great value, so that the result could be applied to other Provinces in Southern Thailand.

BACTERIOLOGICAL STATUS OF "OPEN" CASES

Sixty-eight lepromatous cases registered and treated since 1972 were analysed in respect of their bacteriological status and duration of treatment. This revealed

that 33 cases (48%) who had received treatment for period ranging from 1 to 5 years were still bacteriologically positive by standard skin smears. For the 37 cases who received treatment for fully 5 years, 13 cases (38%) were still positive. In comparison, figures from Khonkaen Province of North-east Thailand, were 37 and 14% respectively. Irregular attendance for treatment might be one of the main factors causing such a difference.

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Report of the Third IMMLEP Scientific Working Group Meeting

The Third Meeting of the IMMLEP Scientific Working Group took place on 21 to 25 February 1977. As in the case of previous Reports we are happy to reprint the Report of this Meeting, minus the Protocols, through the courtesy of the World Health Organisation.

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Summary Abstract

The Third IMMLEP Scientific Working Group (SWG) meeting, held in Geneva, from 21 to 25 February 1977, focused mainly on research projects in the immunoprophylaxis area of the scientific plan. Achievements since the second SWG meeting of December 1975, were reported and included:

(a) increased supply of *M. leprae* to the programme;
(b) further improvement of the method for increasing recovery and purification of bacilli from *M. leprae* infected armadillo tissues (Protocol 3/77);
(c) biochemical chracterization of cell walls from *M. leprae* and characterization of some of its antigens;
(d) identification of mycobacterial strains showing closer antigenic similarities to *M. leprae* than BCG;
(e) induction of cell-mediated immune reactions by killed *M. leprae* in guinea-pigs and mice;
(f) induction of resistance to *M. leprae* infection in mice with killed *M. leprae*;
(g) confirmation of earlier studies showing relatively low reactivity to *M. leprae* antigens in areas non-endemic for leprosy.

Problems which have arisen include the small numbers of *M. leprae* antigens from extracts of armadillo-grown *M. leprae,* the lack of absolute specificity of skin tests for mycobacterial infections and the poor immunogenicity of *M. leprae* related cultivable mycobacteria in some experimental animals. On the basis of these findings new Protocols included:

(a) methods for increased antigenic recovery of *M. leprae* from armadillos (Protocol 4/77);
(b) procedures for enhancing induction of cell-mediated immune reactions to *M. leprae* antigens (Protocol 5/77);
(c) procedures for enhancing induction of CMI and resistance to *M. leprae* related organisms by killed organisms (Protocol 7/77);
(d) procedures for enhancing resistance to *M. leprae* infections in mice (Protocols 5/77 and 6/77);
(e) re-examination of the capability of lepromins to sensitize subjects to *M. leprae* antigens by new methodology (Protocol 9/77);
(f) further improvements of skin-test reagents (Protocol 8/77).

The scientific progress made over the past year strengthens our initial hopes that a vaccine effective against leprosy can be developed; yet it must be recognized that fulfilment of that goal for practical, large-scale applications cannot be expected in the immediate future.

In reviewing the IMMLEP programme as a SWG pilot activity, possible ways by which SWGs may contribute to strengthening of research capability in leprosy endemic countries were discussed. The meeting recommended that:

(a) wherever possible, research fellows in the IMMLEP programme should come from leprosy endemic countries;
(b) there should be increased local training of personnel for field activities which could be important to future epidemiological or vaccine studies;
(c) interlinkage should be made between SWG meetings and training courses in leprosy endemic countries;
(d) WHO regional offices assist in recruiting research fellows and in arrangement of SWG meetings outside Geneva.

Summary Report

(1) INTRODUCTION

At the direction of the Steering Committee, the Third Scientific Working Group (SWG, previously designated Task Force) of IMMLEP met from 21 to 25 February 1977, in Geneva, to consider the results and achievements to date, but to focus particularly on the research projects related to the immunoprophylaxis aspects of the scientific programme. The SWG comprised 19 members in addition to 3 members of the WHO secretariat. With the exception of 3 Steering Committee members, only 4 had attended previous meetings, leaving 12 new members. Thus IMMLEP has again maintained its practice of regularly bringing in new members and selecting them according to the major aspect of the programme under consideration.

General report

Dr Lucas, Director of the Special Programme, stressed the importance and inevitability of the scientific research contributions coming, at least initially, from the developed countries, while underlining the importance of the training and institutional strengthening aspects of the programme for the developing countries in which the 6 selected diseases were major problems.

There followed a general discussion and assessment of the IMMLEP programme, its progress, fulfilment of targets, and balance between research and training as envisaged by TDR. Dr Godal (Chairman, IMMLEP Steering Committee) summarized as follows.

(a) Overall, the planned network programme was on target and progress had been very encouraging.
(b) However, there had been delays in progress due to:
    (i) changes in scientific staff at centres funded by IMMLEP;
    (ii) the discovery that some proteins of armadillos cross-reacted with those from man, a problem now overcome;
    (iii) delay in, and difficulty of, recruiting suitable nationals from countries where leprosy is endemic.

This report is presented in 2 parts: (1) abstracts of the scientific papers and discussions by the participants, and (2) new or modified protocols. As the progress achieved suggests that a "vaccine" worthy of pilot clinical trial may be developed within the next year or two, the SWG considered it essential to begin to consider the safety and ethical factors which this would raise. Therefore, these are included in the general report.

(2) FACTORS TO BE CONSIDERED IN ASSESSING THE SAFETY OF MYCOBACTERIAL LEPROSY VACCINES PROPOSED FOR USE IN HUMANS

Careful consideration must be given immediately to the matter of procedures to be followed in assessing the possible toxic effects or other adverse reactions which may be engendered by any proposed mycobacterial leprosy vaccine. The establishment of such procedures is a matter of urgency as highly purified *M. leprae* from armadillo tissue may be available within the coming year for preliminary testing. These procedures will vary in detail depending upon the nature of the proposed vaccine, i.e. whether it be:

(1) killed *M. leprae*;
(2) a killed cultivable mycobacterium;
(3) a live cultivable mycobacterium, or
(4) a combination of one of these with live BCG.

The tests applied will include all those already specified by WHO Expert Committees on Biological and Human Experimentations.

In addition, since both *M. leprae* and cultivable mycobacteria have inherent adjuvant activity, the safety of these proposed vaccines as *adjuvants* will need to be assessed (see *Immunological Adjuvants, Technical Report Series* No. 595, WHO, 1976, pp. 33-35).

In regard to the use of killed *M. leprae* as a vaccine, it is important that the large literature on lepromin testing in humans be examined for reports of adverse reactions which may have been observed.

It is strongly recommended that the IMMLEP Steering Committee, in consultation with the Secretariat of WHO, prepare a detailed testing procedure to be followed for safety evaluation of each of the four types of vaccines listed above, and that it be made available to members of the Scientific Working Group and other interested individuals before 1 December 1977. This will ensure that the preliminary animal tests can begin as soon as a candidate vaccine is selected.

(3) PURIFICATION OF *M. LEPRAE* FROM HOST TISSUES

Dr Draper described modifications to an earlier method (Protocol 2/75) for purifying *M. leprae* (now Protocol 3/77). Bacteria prepared by the new method had unaltered ability to transform lymphocytes (experiments of Dr Gunnar Bjune). Using *M. lepraemurium* as a model, Dr Stanford and Professor Morten Harboe had been unable to find alterations in antigens (measured by immunodiffusion and crossed immunoelectrophoresis respectively) caused by the method of Protocol 2/75 or the modification. Dr Rees and Mrs Celia Lowe, using skin test in guinea pigs, had found very little armadillo material in bacteria prepared by the modified

method. Professor Talwar emphasized the importance of electron microscopy in judging the purity of *M. leprae* preparations, and the possible use of immunoelectron microscopy to detect the presence or loss of bacterial antigens. Dr Lefford, using a model system of BCG in mice, had shown that the method of Protocol 2/75 did not affect viability, but that large losses of bacteria occurred with the discarding of the low-speed sediment.

Dr Nakayama described a method for purifying *M. leprae,* involving countercurrent distribution in an aqueous two-polymer phase system (Annex 1). The method produced pure bacteria to some of which amorphous material adhered. This material came from the large body described as a sporangium (Annex 2), which could be incubated in a special medium to release further *M. leprae.* Dr Kirchheimer pointed out that the name "sporangium" was misleading for a pyocaryotic organism, and Professor Talwar doubted that the amorphous material was of bacterial origin. Dr Nakayama presented a further paper from Dr G. Matsuki and Dr H. Nakagawa (Annex 3), on purification of *M. leprae.*

Dr Juščenko had studied *M. leprae,* prepared according to Protocol 2/75, in the electron microscope (Annex 4) and showed electron micrographs of *M. leprae* and other mycobacteria. He considered that freeze-drying had little effect on the bacteria, but that proteolytic enzymes were rather harmful as judged morphologically. Dr Rees said that viable *M. leprae* sometimes remained after freezing at -70° C; Dr Kirchheimer reported that DOPA oxidase of *M. leprae* from human tissues, but not from armadillo tissues, resisted freezing.

Dr Closs described crossed immunoelectrophoresis experiments to detect antigens from armadillo and *M. leprae* in purified preparations. He proposed the use of the method to standardize antigen preparations, and demonstrated its use to study 4 preparations. Professor Talwar emphasized the need for good antisera if standardization by the method was to be practicable.

Summarizing, Dr Bloom said that the method in Protocol 3/77 seemed to offer improved yields of *M. leprae* with low contamination with armadillo material. Dr Nakayama's interesting 40 μm particles needed further study and their presence *in vivo* should be investigated. It was unwise to describe them as sporangia. Dr Juščenko had shown the value of electron microscopy in studying possible effects of purification procedures (Annex 4). Cross immunoelectrophoresis was a valuable technique for detecting contamination, but for standardization of antigens it presented difficulties in requiring standard antisera. He asked how skin tests in guinea-pigs compared in sensitivity with the immunoelectrophoretic technique; from discussion they appeared to have similar sensitivity.

It was formally agreed that the modifications to Protocol 2/75, included in and now designated Protocol 3/77, should be adopted (for the present) by IMMLEP as a standard method of preparing *M. leprae* suspensions from armadillo tissues.

(4) CELL WALLS

Professor Lederer described the structure of mycobacterial walls, consisting of mycolic acids, arabinogalactan and peptidoglycan. The latter was unusual in the *N*-glycolylmuramic acid replaced *N*-acetylmuramic acid found in other bacteria. Mycobacterial walls were adjuvants, and the activity seemed to reside in the muramyldipeptide portion of the wall (Annex 5). This substance could be synthesized and was commercially available. The effect of variations of structure on adjuvant activity was known. Two other components of mycobacterial walls, cord factor and polyglutamic acid, affected adjuvant activity.

Dr Draper described some analyses of walls of *M. leprae* prepared by the standard Salton process. They resembled other mycobacterial walls but differed in containing glycine and possibly ribose.

Dr Dawidowicz had studied lipid and carbohydrate composition of *M. leprae* walls prepared without using detergents or proteolytic enzymes. They contained fatty acids, apparently straight chain, with 14, 16, 18, 19, 20, 21 and 22 carbon atoms.

Dr Bloom asked whether walls were important in mycobacterial immunology. Dr Shepard said that in the mouse foot-pad, whole *M. leprae* were antigenic while isolated walls were not. Dr Lefford emphasized the importance of the walls of mycobacteria. He pointed out also that proteins, especially serum albumin, bound strongly to walls, of BCG, and that such a preparation was an antigen with a "built-in" adjuvant. Proteins secreted by mycobacteria were similarly presented on the surface.

(5) FRACTIONATION OF ANTIGENS FROM *M. LEPRAE*

Dr Closs reported on work done in Oslo to characterize the *M. leprae* that has been recovered and purified from infected armadillos, using both immunological and non-immunological methods.

(a) *Immunological methods*

Antisera against highly purified *M. leprae* (A10), have been prepared by Dr Draper in 5 rabbits. Contrary to what has been observed when rabbits have been immunized with similar preparations made from other mycobacteria, only a limited number of antibody specificities developed. The antibody response was studied, using crossed immunoelectrophoresis (CIE). The number of precipitin lines that could be detected increased to a maximum level of 6 to 7 lines after 4 immunizations, and did not increase further with prolonged immunization. This is in striking contrast to what is usually observed when making antisera in rabbits against extracts of other mycobacteria, with which it is possible to detect about 40 different antigens in CIE.

The results with *M. leprae* indicate that: (1) the purified *M. leprae* preparation contains less soluble antigens than other mycobacteria used until now, or (2) there may be additional material present which is not immunogenic in rabbits and which is therefore not detectable by their rabbit antisera.

To clarify which of these 2 possibilities is the one more likely to explain the findings in CIE, additional experiments were carried out.

(b) *Non-immunological methods*

Acrylamide gradient gel electrophoresis was performed with 2 different *M. leprae* preparations (A10 and AB14) as well as with sonicates of BCG, *M. smegmatis, M. lepraemurium,* and *M. phlei* made to contain similar amounts of protein as measured by the modified Folin (Lowry) method.

Whereas the extracts made from the 3 cultivable mycobacteria produced between 40 and 50 distinct bands, the A10 preparation produced only 3 very weak bands, and the AB14 preparation produced the same 3 bands but much stronger in addition to one weak band.

Conclusion

By both immunological and non-immunological methods, the extracts made from *M. leprae* purified from infected armadillo tissue apparently contained only about one-tenth of that normally found in extracts made from other mycobacteria.

Dr Closs also reported on work done to investigate the degree to which components specific for *M. leprae* are present in the extracts. This work was done mainly by incorporating antibodies against other mycobacteria in an intermediate gel in the CIE reference system. All the components could be sedimented with several or all of the antisera used, indicating that all the components are widely cross-reacting among mycobacterial species and even Nocardia. The work of Dr Goran Kronvall was briefly mentioned—it has shown that at least one of the components carry *M. leprae* specific determinants.

Dr Dawidowicz reported on work done in Caracas to characterize the components responsible for skin test reactivity. Two different preparations of *M. leprae* were made:

(a) Infected armadillo tissue was disrupted with a Sorvall Omnimixer and the number of acidfast bacilli in the homogenate adjusted to 1.6×10^8 per ml. This suspension was first autoclaved for 15 min and then centrifuged for 2 h at 50,000 rev/min. The supernatant was then filtered through a 0.45 μm millipore filter and used for fractionation studies.

(b) Preparations were also made according to the method described by Dr Draper. The purified bacilli were sonified for 15 min and the sonicate autoclaved.

Preparations (a) and (b) were then run through a Sephadex G-200 column and the various fractions tested for activity in the 48 h skin reaction using patients with tuberculoid leprosy as test subjects. Two active fractions were obtained from both preparations (a) and (b); one with molecular weight greater than 200,000 daltons and another with molecular weight between 8000 and 20,000 daltons. By far the greatest activity was found in the high molecular weight fraction.

Preparation (b) also contained a third peak of material absorbing at 280 nm. However, this material was not active in eliciting a skin reaction in tuberculoid patients.

(6) TAXONOMY

Three papers were read in the taxonomy section.

(a) The first (by J. L. Stanford) stressed the importance of cell-mediated immune processes as a tool for taxonomy. It was pointed out that states of responsiveness and unresponsiveness ("anergy") to skin-test reagents exist in each of the major mycobacterioses. There are 2 types of "anergy" expressed in leprosy. The non-specific type occurring commonly in borderline types of disease has no apparent taxonomic value, but following exclusion of this type, the remaining more specific type of "anergy" predominantly occurring in lepromatous disease has considerable intertaxonomic discriminating power.

Using the technique, *M. marinum, M. nonchromogenicum* and *M. vaccae* show the closest relationship to *M. leprae.* No further work has yet been done with *M. marinum.* Separation of rough from smooth mutants and preparation of separate skin-test reagents from them has made it possible to demonstrate a closer antigenic relationship between the rough strain reagents and LRAB 14 (*M. leprae*), in a recent study carried out in South India.

Preliminary results of tests carried out in guinea-pigs demonstrated the close relationship between *M. vaccae* and *M. leprae* and the systems used might be of potential value in developing a vaccine.

Finally, it was recorded that the organisms grown by Dr Delville were not mycobacteria, but contained typical corynemycolic acids and belonged to the genus *Corynebacterium.* Organisms grown by Professor Skinsnes* were examined by many techniques† and over 95% were found to be *M. marianum* (*scrofulaceum*). The remaining organisms examined under the electron microscope on the basis of size qualified as *M. leprae* but they appeared to be degenerated and no further information about their identity could be obtained. Requests for further material from Professor Skinsnes have not been granted.

(b) Dr Walter presented a hypothesis (Annex 6) suggesting that the use of whole organisms in a suspension similar to lepromin, prepared from various mycobacterial species might provide information of taxonomic value.

(c) Professor Talwar, using a system similar to that proposed by Dr Walter, reported on his study of 71 coded strains. Following selection of 5 of the coded strains by LTT and MIF tests on tuberculoid patients, both Mitsuda and Dharmendra-like reagents were prepared from all 5. These were tested simultaneously in small numbers of tuberculoid and lepromatous patients. All 5 showed a relationship with *M. leprae*-derived reagents, but the number of subjects tested has been insufficient for meaningful studies of correlations. It was agreed that after adequate numbers of persons in each group had been studied, the identity of the 5 strains would be determined and the code broken.

A system for assessment of pathogenicity was proposed, but discussion on it was temporarily postponed. It was recommended that the identity of the selected organisms should be confirmed by laboratories specializing in mycobacterial taxonomy.

It was agreed that Professor Talwar's studies were of the greatest interest and urged that strains should be exchanged between Professor Talwar and Dr Stanford in the near future.

(7) INDUCTION OF CMI TO *M. LEPRAE*

Dr Lefford referred to previous experience with BCG in oil, which had shown that after an early transient swelling at the site of injection, a further phase of swelling developed at 3 to 4 weeks, accompanied by delayed hypersensitivity and immunity to challenge. He had therefore tested doubling concentrations in Tween-saline or water-in-oil emulsions of leprosy bacilli acquired from Dr Rees. Doses from 4 to 1000 μg of bacilli were injected into mouse foot-pads.

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* Skinsnes, O. K., Matsuo, E., Chang, P. H. C. and Anderson, B. (1975). *In vitro* cultivation of leprosy bacilli on hyaluronic acid based medium. *Int. J. Leprosy* **43,** 193.

† Stanford, J. L., Bird, R., Carswell, J. W., Draper, P., Lowe, C., McDougall, C., McIntyre, G., Pattyn, S. R. and Rees, R. J. W. A study on Skinsnes' leprosy bacillus strain C318,: *Int. J. Leprosy* (in press).

The highest dose gave some initial swelling, which subsequently fell, and the others tended to give a very ill-defined peak at 4 to 6 weeks.

However, when foot-pad tested in the contralateral foot-pad it was found that animals given 16 μg of bacilli or more, showed delayed hypersensitivity to PPD, and resistance to i.v. challenge with 10^5 RIRV. The *M. leprae* organisms given in Tween-saline were as effective or better at inducing these effects than were those given in water-in-oil emulsion. Similarly *M. leprae* in saline was more effective at inducing non-specific resistance to *Listeria* than were either *M. leprae* water-in-oil, or heat-killed BCG.

M. leprae injected in mouse foot-pads in saline also induced delayed hypersentivity to an antigen preparation supplied by Dr Rees' laboratory when tested at 1 month. The optimal test dose was 5 μg.

Dr Shepard reported that both living and heated *M. leprae* injected intradermally into the flanks of mice, caused regional node enlargement, and protection against subsequent challenge with *M. leprae*. BCG was only active if given life. Eleven other organisms were ineffective. The lymph-node enlargement was seen mainly in the paracortical areas.

Mice were immunized with 10^7 *M. leprae* organisms (heat-killed) injected intradermally and foot-pad tests performed at 14 days in the other foot. The optimal eliciting antigen was found to be autoclaved *M. leprae* in PBS or Banks BSS with Tween.

In subsequent series of experiments, all mice were challenged with autoclaved antigen, and the immunizing preparation was varied. Autoclaved antigen also proved best for immunization. This property was unaffected by phenol, or by any of the purification steps in Dr Draper's technique.

Mickle-disintegrated organisms were less effective for immunization whether heated, or unheated. This was true of the whole preparation, and of both cytoplasmic and cell-wall fractions. However, such preparations were effective as eliciting antigens, cell walls being more potent than the cytoplasmic fraction.

Data from an experiment in which all responses were rather low, suggested that Dr Draper's purification steps tended to decrease the efficiency of the organisms as eliciting antigen.

During the discussion, Dr Lagrange suggested that the soluble cytoplasmic fraction might inhibit the induction of CMI by a mechanism analogous to "immuno-deviation".

Dr Shepard noted that lymph-node enlargement caused by killed *M. leprae* appeared to last for 1 year or perhaps for life, in mice. This is not so after killed BCG.

Professor Bloom reported studies in which guinea-pigs had been immunized by injections of 0.5 mg of *M. leprae* organisms supplied by Dr Draper. Sensitization, tested at 1 month was greater when the organisms were injected in aqueous suspension (Hanks BSS), than in suspension in oil (incomplete Freund's adjuvant, without emulsification). The response to 6 μg A14 was greater than to 6 μg PPD. Sensitization also occurred when the *M. leprae* was injected with BCG (10^7), but in these animals PPD reactions were greater than those to A14.

Sonicated organisms sensitized poorly, whether in Hanks or in oil. Organisms suspended in saline and emulsified in adjuvant 65 (containing peanut oil) provided the most effective sensitization of any oil vehicle yet tried.

Antigens prepared from normal armadillo tissues always elicited negative responses. Without *M. leprae,* BCG (10^7) sensitized to PPD, but the A14 response remained negative. Immunization with an *M. vaccae* strain (296R)* in Hanks provided by Dr Stanford, resulted in good positive responses to A14, although less strong than those induced with *M. leprae.*

Intradermal immunization was better than the foot-pad. The animals were retested at 18 weeks. Both diameter and induration were measured. Animals which had received organisms in Hanks gave good responses to A14 by both measurements, whereas, when oil had been used, the diameter of the reaction was large, but induration much less so. At 18 weeks responses in animals given *M. leprae* and BCG were as good or better than those in animals given *M. leprae* only, and animals inoculated with *M. leprae* in emulsion with adjuvant 65 showed larger indurated reactions than when tested at 1 month. When *M. leprae* in Hanks solution (0.1 mg, 0.3 mg and 1 mg) were injected into 4 or 8 intradermal sites, subsequent skin-testing showed no marked dose-response relationship.

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* This strain differs in a number of respects from those of this species now considered most closely related to *M. leprae.*

In Dr Rees' work, induction of skin-test positivity in guinea-pigs to a number of different batches of *M. leprae,* purified by Dr Draper from armadillo tissues, was used to study the reproducibility of the preparations, and of skin-test antigens prepared from them.

0.5 mg (dry weight) of organisms was injected either as single dose into the groin, or distributed equally in the 4 foot-pads, of guinea-pigs (400 to 300 g Hartley strains). The optimal testing dose of antigen was found to be 6.0 μg. This technique showed there is little variation between preparations.

There were, however, 2 points of disagreement with Professor Bloom's studies.

(1) Organisms in Freund's incomplete adjuvant were more effective than organisms in saline. It was felt that this may have been due to the fact that Dr Rees' organisms were suspended in saline and then emulsified in oil adjuvant while, except for the adjuvant 65 protocol, Professor Bloom's were suspended directly in oil.

(2) In Dr Rees' experiments, *M. leprae*-immunized animals showed some sensitization to PPD. It was felt that this also might be due to differences in physical properties of the adjuvants, or to different populations of environmental organisms in the animal houses.

MDP (Muramyl dipeptide) was nearly as effective an adjuvant (0.2 mg/animal saline with the *M. leprae*) as water-in-oil emulsion.

(8) INDUCTION OF RESISTANCE TO EXPERIMENTAL INFECTIONS OTHER THAN *M. LEPRAE*

Dr Rook presented a paper on the CMI response to a non-pathogenic mycobacterial species, *M. nonchromogenicum* (*Mn*) in mice. CMI was measured in terms of DTH, namely, the 24-h increase in foot-pad thickness following the injection of a cell sonicate of *Mn.* Following 10^8 Mn into the base of the tail, DTH reached a peak at day 11 and decayed rapidly thereafter. This early type of DTH, which was shown to be distinct from the Jones-Mote phenomenon, was evoked by all of 8 mycobacterial species known to be non-pathogenic for the mouse, but not by the pathogens *M. avium, M. ulcerans,* or *M. kansasii.* A recall of DTH could be achieved by re-inoculation of *Mn.* Under these circumstances, the ability to elicit DTH was sustained indefinitely. The hypothesis was advanced that the day 11 evanescent DTH represented the primary antimicrobial effector mechanism and that the induction of a sustained state of high-level DTH was inimical to the host, since it was responsible for the tissue damage and progressive disease characteristic of progressive tuberculosis and tuberculoid leprosy. Furthermore, it was postulated that the induction of transient hypersensitivity was the normal immunological response to a noxious agent which the host could control, and sustained DTH was due to a loss of this normal T-cell regulatory control mechanism induced by virulent parasites. In such cases the host succumbed to infection.

Drs Sansarric, Lagrange, Lefford and Godal participated in the discussion which followed. Lagrange, in particular, was dissatisfied with the evidence on which the main hypothesis was based. Lefford conceded that, while there was no direct relationship between DTH and antimicrobial immunity, the advantage to the host of sustained responses induced by mycobacteria was the generation of a population of memory cells which protected the host for a long period of time. This advantage might well be achieved at the cost of concomitant tissue damage.

Dr Lefford, using a strain of inbred mice (CB6) that was highly susceptible to *Mlm,* found that CMI to that parasite was nonetheless induced following the inoculation of 10^8 live *Mlm* (L-*Mlm*) into the hind foot-pad (HFP). A measure of the induction of CMI was the swelling of the inoculation site (HFP) which commenced at 3 weeks and stabilized at about 6 weeks. In T-cell depleted mice the onset of such swelling was delayed, but then eventually exceeded that of normal mice. A similar suppression of induction of HFP swelling was produced by concomitant i.v. infection with 10^7 to 10^9 *Mlm,* the degree of inhibition being proportional to the dose. The sequence of initial suppression of HFP swelling followed by enhancement of swelling could be produced by concomitant or prior challenge with 10^9 heat-killed (HK) *Mlm* i.v. Attempts were made to reverse the effects of i.v. antigen on the CMI response to *Mlm,* namely, splenectomy and pre-treatment with 10^7 live BCG i.v. Splenectomy was entirely without effect. BCG was unable to reverse the suppressive effect of 10^9 live *Mlnm* i.v., but when given 2 to 4 weeks prior to challenge, ameliorated the effect of 10^9 HK-*Mlm* i.v.

The author concluded that inappropriate methods of immunization were not without hazard, and this should be borne in mind with respect to vaccination against leprosy. There was

some comfort to be derived from the finding that BCG might be able to prevent some of these untoward effects.

In the discussion that followed, Dr Closs pointed out that the apparent enhancement of infection at the site of inoculation might be due to local retention of organisms and the total mouse load of bacilli might not be greater than that of mice that were not challenged intravenously.

Dr Lagrange presented preliminary data from an *Mlm* model system in which he attempted to influence the course of that infection with living BCG. For this purpose both susceptible (C3H) and resistant (C57/bl) mice were used.

The injection of 2×10^7 *Mlm* into the FP produced a progressive increase in FP thickness which eventually plateaued in 2 to 3 months. This response developed more rapidly in C57/B1 than in C3H mice and was shown to be dependent on T-lymphocytes since it did not develop in nu/nu mice. The difference between C57/B1 and C3H was unaffected by varying the size of the infectious inoculum, and was reflected by the recovery of larger numbers of *Mlm* from the popliteal lymph nodes of the latter strain.

Mice were pre-treated with 10^6 live BCG i.v. prior to FP infection with 2×10^7 *Mlm*. BCG treatment did not influence the tempo of FP swelling in C3H mice, but produced a more rapid onset of swelling in C57/Bl mice. The induction of FP swelling by live *Mlm* could be suppressed bu concomitant i.v. injection of either 2×10^8 live or HK-*Mlm* in both mouse strains. Deaths occurred sooner in C57/B1 mice infected i.v. than in C3H mice. Attempts to reverse the suppressive effects of systemic heat-killed *Mlm* with prior i.v. immunization of 10^7 living BCG failed.

The influence of immuno-modulating agents on the induction of immunity to *Mlm* was then examined in B6 x D2 F1 mice. Immunization with HK-*Mlm* either alone or in combination with living BCG and/or cyclophosphamide (CY) was followed by FP infection with live *Mlm*. Pre-immunization with BCG/CY/*Mlm* or BCG/*Mlm* resulted in a DTH response seen 24 h after injection of live *Mlm* which thereafter subsided. Subsequent chronic FP swelling was more rapid in all immunized groups than in controls.

The induction of DTH to *Mlm* was attempted using BCG, CY and CP (*C. parvum*) as modulating agents. Significant sensitivity was induced only by using *Mlm* with BCG or CP, the latter having the greater effect. C57/B1 mice developed greater sensitivity than C3H mice.

Dr Rees presented preliminary data on the induction of immunity to *Mlm* in C3H mice by a combination of living BCG and dead (^{60}Co-irradiated) *Mlm*. Counts of challenge with *Mlm* injected into the foot-pad were available for up to 18 weeks after infection. 10^7 live BCG alone and 10^5 live BCG + 0.001 mg killed *Mlm* appeared to be protective

In the following discussion, Dr Lefford thought the shape of the growth curves suggested that whereas 10^7 BCG alone was exerting a non-specific effect, BCG + *Mlm* appeared to induce a specific immune response. Dr Rees agreed.

(9) RESISTANCE TO EXPERIMENTAL INFECTION WITH *M. LEPRAE*

Dr Shepard presented extensive studies on the protection afforded by various vaccines against mouse foot-pad infection with *M. leprae* (*Ml*). The standard procedure was to inoculate either 10^7 organisms or the equivalent in terms of packed mycobacterial cells intradermally into the flank on day 28. Mice were infected with 5.0×10^3 *Ml* on day 0. The size of the lingual lymph node (draining the immunization site) was monitored at 28-day intervals. When the counts of *Ml* in the FP of controls exceeded 10^6, counts were made from the FP of vaccinated mice. These counts were repeated 90 days later.

The effective vaccines were living BCG (Pasteur/Trudeau and Rosenthal) and dead *Ml*. Other vaccines that had little or no effect included *M. vaccae* (3 strains), *M. nonchromogenicum* (3 strains), live H37a (both IP and intradermal), *Myco. RNA* (Youmans) derived from H37a, *M. phlei, M. smegmatis, M. diernhoferi* and heat-killed BCG. There was a close association between inguinal LN enlargement and protection.

A number of variables affecting the efficacy of *Ml* vaccines was studied. Freshly prepared and frozen-preserved live *Ml* and ^{60}Co-irradiated *Mlm* derived from armadillos were all effective immunogens. However, their efficiency was increased by heating for 30 min at 60° or 80° or autoclaving for 15 min. By contrast, the immunizing efficiency of living BCG was almost entirely lost by heat-killing. Initially it was thought that freeze-thawed *Ml* was also more immunogenic than live *Ml* but this was not confirmed. The influence of the suspending medium was also investigated. Various combinations of PHS/Tween Hanks BSS with or without 10%

BSA were compared. It appeared that there might be a small advantage to using Hanks/Tween. Testing of live *Ml* at different stages of purification revealed no loss of immunogenicity.

In the discussion, Dr Lefford suggested that before the non-*Ml* vaccines were finally discarded as ineffective, much larger inocula should be tried, e.g. 1 to 4 mg dry weight equivalent. Dr Rook indicated that optimal induction of DTH in mice, by a single subcutaneous injection of *M. nonchromogenicum* or *M. vaccae* may require 10^9 organisms, but 10^7 will give a significant response. Alternatively, powerful sustained responses can be induced by a second injection into the same site at 4 weeks. It also emerged that heating *Ml* vaccines resulted in bacterial clumping which might be a factor in immunogenicity.

(10) EPIDEMIOLOGICAL SKIN-TEST STUDIES

The first 2 reports concerned the results obtained under Protocol 5/75 (comparative testing in non-endemic areas). The purpose had been to compare different antigenic preparations from *M. leprae* by skin-testing in non-endemic areas to determine whether there is a correlation with tuberculin sensitivity. More than 60 subjects were to be included in each study. The antigens to be compared were (a) LRA6, a material prepared in Dr Rees' laboratory by disrupting *M. leprae* that had been purified from armadillo livers by Draper's method; (b) LCA, the high-speed centrifugal supernatant from an autoclaved lepromin prepared from armadillo liver; (c) a control preparation from normal armadillo liver, and (d) PPD (RT23, 2 TU).

Mrs Pinardi reported the results she and Dr Convit had obtained. They had carried out the skin-tests in Santiago, Chile. Many of the subjects had been vaccinated with BCG. They found a low percentage (approximately 10%) of positive reaction at 72 h with LRA6 and LCA in healthy adults and tuberculosis patients, and only 0.2% in healthy children. The control armadillo material gave no positive reaction. The PPD gave 92% positive in tuberculosis patients, 68% in healthy adults, and 22% in healthy children. There was suggestive correlation between the reactions from *M. leprae* and those from *M. tuberculosis.*

Dr Rees reported results in the United Kingdom on Oxford students. Most of the students had received BCG vaccine at age 13 to 15. LRA6 had given 8% positive; LCA 8% positive armadillo control only, 61 positive and PPD 38% positive. Most of those reacting to *M. leprae* antigens were positive to PPD, whereas most of those not reacting to *M. leprae* antigens were negative to PPD (Annex 7).

Thus in both studies there was suggestive correlation between the reactions from *M. leprae* and those from *M. tuberculosis,* but many of the positive reactions to *M. leprae* could not be explained as cross-reactions caused by infection with *M. tuberculosis.* However, it should be noted also that there was a 40% (2/5) discrepancy in individuals reacting to both LCA and LRA6.

Mrs Pinardi also described experiments carried out with lepromin from human sources. In one approach, an attempt was made to determine whether the response to a high dose of lepromin (600×10^6 AFB/ml) could be used for determining the need to continue treatment of LL patients who after years of therapy had remained skin-negative. The lepromin site was biopsied 30 days later and showed either absence or persistence of AFB in a macrophage granuloma. If AFB persisted chemotherapy was continued.

She described another study using a "lepromin" test containing one part of BCG vaccine mixed with 9 parts of lepromin (160×10^6 AFB/ml) before injection. In lepromatous patients who were tuberculin positive, a local reaction occurred in which the AFB (including *M. leprae*) were destroyed. *M. leprae* at other sites were not destroyed. In the discussion it was pointed out that the results indicate: (a) local activation of macrophages as a result of interaction between sensitized lymphocytes and BCG, and (b) a lack of immunosuppression by *M. leprae* on the response to BCG.

Dr Stanford than reported the results of his skin-test studies in Burma. Antigen A6, the soluble product after disintegration of *M. leprae* purified by the Draper method, was used as a skin-test antigen in normal controls, leprosy patients, their close contacts, and tuberculosis patients. The incidence of positives was approximately as follows: 20% of controls, 20% of indeterminate, 40% of tuberculoid, 2% of lepromatous patients, and 10% of tuberculosis patients. In close contacts the figure was 8% of females and 38% of males. In other groups the males showed positive rates that were equal to or only slightly in excess of those in females.

Further examination was made of the results in close contacts. In BCG vaccinated, the male: female ratio was 43%:0%, compared to 35%:10% in BCG unvaccinated. In patients with "general anergy" (negativity to 4 other mycobacterial antigens), the ratio was 6%:28% in

vaccinated and 13%:14% in unvaccinated. In patients with "specific anergy" (negativity to *M. leprae*-related antigens) the ratio was 38%:44% and 37%:79% in vaccinated and unvaccinated groups respectively.

The rate of skin-test reactivity to the antigens from 4 selected cultivable mycobacteria was compared in Burma and Uganda. In Burma, BCG vaccine had given much less protection against leprosy than it had in Uganda. The reaction rate was about the same with *M. leprae*-related antigens (those from *M. vaccae* and *M. nonchromogenicum*), but it was much higher in Burma with certain *M. leprae*-unrelated antigens (*M. marianum* and *M. kansasii*) 79% *versus* 3.5% for marianin and 60% *versus* 0% for kansasin. In persons in Burma the incidence of positivity to marianin and kansasin rose from 20 to 30% at age 6 to 60 to 80% at age 15 or more. The results suggested that positivity to marianin inhibited the effect of BCG vaccination in increasing reactivity to the *M. leprae* and related antigens.* Experiments in mice were carried out in England to see if infection by *M. marianum* would inhibit the immune response to BCG. The mice were given *M. vaccae* or *M. marianum* by mouth in the drinking water, and injected with BCG into the foot-pad. Acquisition of tuberculin reactivity was decreased in both orally infected groups, as compared to the group receiving BCG only, especially at a time 11 days after BCG injection. The experiment is continuing.

Specificity and epidemiological significance of the trichloracetic acid precipitated *M. leprae* (armadillo derived) protein prepared by Dr Kirchheimer (Carville) will be studied in India.

(11) IMMLEP *M. LEPRAE* BANK REPORT

Dr Rees submitted a detailed report of the IMMLEP Bank of armadillo-derived *M. leprae* tissues, purified bacteria and antigens held at, and distributed from, London (see Tables 1 and 2). It was gratifying that there was currently in the Bank approximately 4.3 kg of infected tissues as compared with 1.0 kg at the time of the last SWG, December 1975. The tissues received were from 17 armadillos (Carville, 8; GSRI, 4 and London, 5). Allowing for gross fat included with the lymph nodes and skin nodules, the average yield of infected tissues was approximately 210 g per animal. Of the 17 armadillos received since December 1975, 5 (London) had been infected with *M. leprae* from leprosy patients, and the remainder with bacilli passaged in armadillos.

(12) SUPPLY OF *M. LEPRAE*

(a) *Establishment of* M. leprae-*infected armadillos in a non-armadillo area*

The successful establishment of *M. leprae*-infected armadillos in the United Kingdom (housed at the Microbiological Research Establishment, Porton) was presented by Dr Rees (Annex 8). Twenty armadillos were supplied, already laboratory adpated, by Dr Storrs, GSRI, and they were shipped, by air, 5 to a cage, without loss, However, 2 were slightly injured, and one of these subsequently died. No injuries occurred in a recent consignment of 20 armadillos from Florida, caged individually. Dr Rees concluded from his experience and results that it is feasible to establish *M. leprae* infected armadillos in non-armadillo areas of the world. In particular his study showed that a large intravenous dose resulted in a high proportion (11/16) of heavily infected animals surviving 12 to 24 months. The results suggested that the turnover of infected armadillos could be increased by killing-off animals surviving for 2 years.

Dr Kirchheimer, from his much more extensive experience, reported a similar significant increase in the proportion of infected animals by using large intravenous doses of *M. leprae.*

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* The original hypothesis that the presence of identified leprosy-related species was synergistic with administration of BCG in Uganda and that these organisms were not present in Burma has had to be modified in the light of the results obtained. In view of the evidence that sensitization to the leprosy-related species was almost the same in the 2 countries, an alternative explanation of the fall off in efficiency of BCG against leprosy in Burma was sought. Data was presented indicating that the high level of marianin sensitivity soon acquired with age in Burma might prevent the development of DTH to leprosy and related organisms following vaccination with BCG.

TABLE 1

IMMLEP bank (NIMR: London) of armadillo-derived M. leprae *tissues, purified bacteria and antigen stocks received and distributed in period December 1975-31 January 1977*

tissue bank

Source	Tissues received (g)* Liver	Spleen	Lymph node	Skin	Tissues issued (g)* Liver	Lymph node	Skin	User
Carried forward from 1975					50	–	–	Abe
Carville	375	–	89	–	–	15	–	Convit
GSRI	326	53	85	162	–	17	157	David
Total	701	53	174	162	40	65	–	Rees
					–	169	–	IMMLEP†
Received December 1975–January 1977					90	266	157	
Carville	992	138	200	162				
GSRI	658	84	91	60				
London	800	73	154	286				
Total	2450	295	445	508				
Grand total	3151	348	619	670				

Total in hand 31 January 1977				
Liver	3061	Liver	67	from GSRI dead animals
Spleen	348	Spleen	19	
Lymph node	353	Lymph node	17	
Skin	513	Skin	20	
	4275		123	

*All tissues from killed animals.

†Used for preparing purified bacteria and antigen at NIMR for IMMLEP.

TABLE 2

Purified bacteria and antigen bank

Issued December 1975-31 January 1977 (mg) Purified bacteria	Antigen	User	In hand 31 January 1977 (mg) Purified bacteria	Antigen	Comment
100	1.2	Bloom	909	–	Several batches
160	0.56	Harboe	–	26.8	Several batches
250	1.22	Lefford	–	33.6	Batch LRA6
10	–	Nakayama			
10	–	Ozawa			
50	–	Pervukhin			
–	1.0	Rees			
–	1.0	IMMLEP Protocol 5/75			
580	4.98				

(b) *On the possibility of using a radio-immunoassay in the monitoring of* M. leprae *infection in armadillos*

Dr Closs reported on a study of antibodies against a "common" mycobacterial antigen (*M. leprae* antigen No. 7) in armadillos infected with *M. leprae*. Using a radio-immunoassay technique, higher levels of antibodies were found in animals which at autopsy were found to have established a disseminated *M. leprae* infection, as compared with normal animals. Animals

which had been inoculated but which at autopsy showed no signs of *M. leprae* infection did not have antibody levels differing significantly from those of normal animals.

The method offers the possibility of being able to screen and identify armadillos showing evidence of having encountered infections with mycobacteria. This would be a most important advance in ensuring a "mycobacterial-free" colony of animals for inoculating with *M. leprae*.

(c) *Attempts to increase the supply of* M. leprae

The Chairman of the IMMLEP Steering Committee (Dr Godal), prefaced his report by thanking in particular Dr Kirchheimer for all the infected armadillos he had supplied for the IMMLEP programme at its initiation, when supplies were very short, and also Dr Rees for donating 5 of his infected armadillos to IMMLEP.

Although approaches to several centres where armadillos are found failed to secure new supply centres of infected animals, only one, at the Institute Pasteur de la Guyane française (Dr Baranton), seemed likely to be able to help. However, Dr Godal pointed out that the situation had greatly improved during the past year since it had been established that intravenous inoculation significantly increased the proportion of positive animals (up to 70%) and reduced the time taken to become heavily infected. Therefore, he estimated that the presently established IMMLEP supply centres, together with 8 infected armadillos promised from the US-Japan Leprosy Panel, would provide some 10 kg of infected tissues in 1977.

The Steering Committee had proposed 3 additions to Protocol 1/75 (supply of *M. leprae* for IMMLEP programme):

(i) regular medical examination of all personnel in contact with armadillos;
(ii) rigorous precautions against escape of armadillos from infected area;
(iii) detailed records to be kept of all inoculated armadillos and the records to be available for inspection by WHO.

These additions were unanimously agreed by the SWG, and are incorporated in a new Protocol 1/77 which now supersedes Protocol 1/75.

(13) IMMUNE COMPLEXES

Dr Lambert reported on immune complexes in leprosy sera. With the C_{1q} binding test, increased levels of immune complexes are detected in a high proportion of leprosy patients, especially lepromatous patients, but this test did not distinguish between patients with erythema nodosum leprosum (ENL) and patients without ENL.

On the other hand, increased levels of C3 split products (C3d) have been found only in ENL patients. It is likely that this reflects complement activation in extravascular spaces possibly related to local formation of immune complexes.

A variety of methods is used for detection of immune complexes of which 18 were included in a comparative study organized by WHO. Methods showing promising results in leprosy include the conglutinin binding test, the platelet agglutination test, neutrophil inhibition test and radioactive C_{1q} binding test. For further methodological details see Annex 9.

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The Treatment of Leprosy Today and Tomorrow: The LEPRA Consultation on Chemotherapy

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Several disturbing factors have recently appeared in the world of leprosy—so disturbing are they, in fact, that the whole strategy of leprosy treatment and leprosy control must be critically reviewed and revised as a matter of urgency. Any one of these factors would distort predictions ostensibly based on accumulated experience or on data fed into an epidemiometric model programmed for situations fast becoming out of date. Together, they pose such problems for governments and voluntary agencies that the sooner the nature and dimensions of the crisis are realized, and steps taken to meet it, the better for all concerned. To repeat the obvious, these factors are: the emergence of dapsone-resistant leprosy bacilli wherever they have been looked for, the persistence of viable organisms, dapsone-sensitive, despite ordinarily adequate treatment, reduced patient compliance, as evidenced by serious irregularity in following prescribed treatment; in short, a leprosy problem whose size and gravity have not apparently been significantly changed by the vast expenditure and the vast efforts of the past few decades.

These considerations were uppermost in the minds of an international and heterogeneous group of leprosy workers invited by LEPRA to thrash out the implications of these factors and make practical recommendations to guide field workers in the treatment of leprosy sufferers and fund raisers as they orientate themselves and their constituencies to the changing outlook. The Medical Commission of ILEP, for long conscious of the need to help guide the thinking of organizers who are raising annually about 15 millions of US dollars for "leprosy", was well represented, with Belgian, German, Dutch, French and British members from diverse voluntary organizations, and others came from the Medical Advisory Board of LEPRA, the World Health Organization, and The Leprosy Mission. Three of the participants had been members of the 5th Expert Committee on Leprosy of the WHO, whose report had emphasized the seriousness of the present situation. The group met in London on 16 August.

As the vigorous discussions proceeded, under the able chairmanship of Dr R. J. W. Rees, Chairman of LEPRA's Medical Advisory Board, a consensus began to emerge, which may be taken to indicate the distillation of informed medical opinion viewing the whole problem objectively and dispassionately.

The basic facts are, generally, known and admitted. The implications of dapsone-resistance will in the future undoubtedly pose novel problems similar to

those encountered before the arrival of the sulphones on the therapeutic scene. While the extent of the problem may not at present appear to be equally grave in all countries, and may indeed continue to be minimal in those few areas of low lepromatous/tuberculoid ratio and satisfactory whole population detection and treatment coverage, the global outlook is far from reassuring.

So far, secondary dapsone-resistant bacilli have been demonstrated only in lepromatous and near-lepromatous leprosy, and in view of the relatively small numbers of bacilli present in tuberculoid leprosy—and also apparently adequate degrees of cell-mediated immunity—there would seem to be a negligible risk of resistance appearing in patients suffering from this form of leprosy. Since among the dark-skinned African, about nine-tenths of those with diagnosable leprosy are suffering from non-lepromatous forms of the disease, the problem of dapsone-resistance should be seen in its proper global perspective. The situation is, of course, potentially more serious in Asia and South America.

When the group got down to the real business of its meeting, which was "to prepare guidelines for the application of therapeutic regimens and individual drugs to be used in large scale field programmes", it became abundantly evident that, by whatever route this central problem was approached, the way seemed to be blocked by barriers of ignorance or finance or prejudice.

Some of the barriers of ignorance could—and should—be removed quite speedily. For example, the practicability and long-term effectiveness of a single dose of say, 1200 mg, of rifampicin at the beginning of treatment, to be followed by dapsone; or a definite pronouncement on the "reactogenic propensity" of high doses of dapsone in patients with borderline leprosy who are liable to suffer down-grading neuropathies; or the short-term efficacy of the combination thiacetazone-dapsone, and its acceptability in different countries. The answers to these, and similar, questions are to be sought in centres where good clinical and laboratory standards are maintained and accurate records kept. Certain other investigations were considered to be urgently necessary, such as the true extent and worldwide prevalence of dapsone-resistant disease, and its correlation with various treatment regimens.

The financial barriers were mostly an expression of the greater expenditure required in all parts of a serious leprosy treatment/control programme: for alternative and additional drugs, like rifampicin and clofazimine and such anti-inflammatory agents as the corticosteroids (and perhaps thalidomide); for better laboratory cover in field work and institutions (and this would include microscopes and stains, and better-trained laboratory technicians); for upgrading of auxiliary and supervisory staff, and in-service training of all grades, with special emphasis on the recognition and management of patients whose relapse—or whose primary disease—is probably due to dapsone-resistant organisms. In addition to the few existing centres where mouse foot-pad inoculation facilities are available for the confirmation of clinically suspected drug resistance, or the detection of primary resistance in newly-diagnosed patients, the group considered that the dimensions of the problem of drug resistance were such as to justify a recommendation that more centres for experimental monitoring of suspected instances should be created in selected countries faced with the actual or potential risk on a large scale.

The social barriers may be less easily appreciated by armchair scientists, and less easily quantifiable or categorized, but in the long run they may prove to be just as important as the mouse foot-pad or the armadillo. The group had to admit

that patient compliance, in the sense of continuing regular treatment for a long time in the case of multibacillary leprosy, was dangerously—even abysmally—low in many leprosy programmes. Not only would this predispose to the emergence of dapsone resistance on an unmanageable scale, but it would also tend to nullify any attempt to introduce multi-drug regimens. Another very practical socially-orientated (as well as medically important) problem concerns the prescription of an additional (and, of course, more expensive) drug to standard dapsone: should this regimen be advised for all patients with multibacillary disease, newly diagnosed, or should it rather be given to those patients who have already been receiving monotherapy for some years, some of whom may be in the incubating stage of dapsone-resistance? In either case, the social repercussions may be serious, and the long-term medical consequences unforeseeably grave.

If these social barriers appear formidable when seen by workers in the field, those faced by fund-raisers and publicists in the voluntary agencies are likely to prove just as insurmountable, but in different ways. The new situation arising (because particularly of drug resistance) must entail a re-examination of conventional appeals. The group considered that voluntary bodies and governments should take advantage of the growing interest in leprosy to upgrade the training of all field staff, to finance postgraduate study of research workers, to train laboratory technologists (particularly in accurate assessment of bacteriological and morphological indices, and in mouse footpad procedures), to encourage the strengthening of health services generally, from which the leprosy programmes should benefit.

Coming down to the practical problems of therapy in the light of the implications of the 5th Expert Committee Report, the group emphasized the following points:

(1) A good therapeutic regimen for the individual is also good in the long term for the community. Thus, dapsone with the addition of either rifampicin or clofazimine, given to patients with multibacillary leprosy, will lead to clinical and bacteriological improvement, and postpone indefinitely the risk of the emergence of dapsone-resistant bacilli—which would be bad for the patient and bad for the community.

(2) While in theory, combined regimens should henceforth be advocated for patients suffering from any kind of leprosy—since in tomorrow's world many of those with non-lepromatous disease will necessarily be infected with dapsone-resistant organisms—in practice this counsel of perfection is probably unnecessary, and would be financially and socially unacceptable.

(3) For the time being, it would be advisable in most situations to proceed with extreme caution with new plans for the integration of leprosy programmes into the general health services. Leprosy requires rather specialized knowledge not readily available to or assimilable by the average multipurpose health auxiliary. Notwithstanding the continuing danger of the perpetuation of stigma if the leprosy programme is kept separate from the other parts of the general health services, the group considered that the clinical recognition of drug-resistant relapse, as well as the diagnosis and management of leprosy, required an intensification rather than a dilution of leprosy control programmes.

The only practicable departure the group would admit from this general pronouncement would be that the combination of leprosy control and

tuberculosis control in a joint programme may be explored in certain situations.

(4) Although dapsone enjoys a well-deserved reputation for relative freedom from undesirable side-effects, the group recommended that clinicians should maintain good and standardized records of all side-effects they encounter, with particular attention to allergic phenomena, skin rashes, anaemia, hypermanic activity (including insomnia and suicidal tendencies), nephrotoxicity, etc. Since rifampicin and clofazimine will probably be used on a much larger scale than heretofore, clinicians and auxiliaries should be on the look-out for signs of toxicity caused by these drugs, and keep notes. In particular, auxiliaries should be taught what to watch for, how to recognize these side-effects, and how to treat them.

(5) Clofazimine would probably be the commonest drug to be used, after dapsone. At a dose of one 100 mg capsule every other day, the incidence of unacceptable degrees of skin darkening is much reduced, and intestinal disturbances are unknown. The disadvantages inherent in a treatment to be taken at less frequent intervals than daily suggest that a 50 mg capsule would be highly desirable.

(6) Since there exists a very widespread experience that dapsone given daily in doses of 100 mg may apparently precipitate serious reversal reaction in a small but important proportion of patients with borderline leprosy (the proportion possibly varying from country to country), any implementation of this regimen should ensure that facilities for immediate recognition and adequate treatment of this eventuality are readily available to all patients at risk.

(7) While in some quarters "voluntary and temporary admission to hospital" is being advocated for certain categories of newly-diagnosed patients (for full assessment, stabilization on drugs, administration under medical supervision of an expensive drug like rifampicin), the group did not agree that more hospital beds would be required for the more intensive therapy advised for patients with multibacillary disease. Just as with tuberculosis, outpatient treatment with admittedly more toxic drugs than dapsone, has a considerable history and a reasonably small risk of untoward drug-related complications.

The group considered that many of its deliberations had perhaps emphasized the obvious, but that knowledge of the obvious had not yet filtered down to many workers in clinical charge of leprosy control programmes. While some of the recent research findings and deductions might seem far removed from the individual leprosy patient in some remote village in a distant land, yet he should be the first to benefit from the new knowledge: the treatment he receives should not only arrest his disease but should save him from the risk of relapse.

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Obituary

ALEXANDER DEWAR DUFF, MB, ChB
1897–1977

The recent death of Dr Duff should not go unnoticed by *Leprosy Review*, for without his timely help during a critical period the continued publication of this journal would have been in jeopardy. After the sudden passing of Dr Ross Innes in 1968, the Executive Committee of LEPRA requested its Medical Secretary to assume the duties of Chairman of the Editorial Board of *Leprosy Review*. This task would have been impossibly difficult without the expert subeditorial assistance of Dr Duff.

Alexander Dewar Duff was born on 7 May 1897. He qualified in medicine from Aberdeen in 1927, and thought to become a general practitioner. Because of a bad stammer, he soon gave up this idea and pursued an early linguistic bent, and studied in Lausanne and Vienna. During the Second World War, he put to good use his excellent knowledge of French and German, translating medical and scientific texts, and devising, translating and applying tests for staff selection of the Free French forces.

"Sandy" Duff really came into his own in the years following the war, when he was appointed Assistant Editor of the *British Medical Bulletin* and then held a similar position in regard to the *Abstracts of World Medicine*. When ordinary mortals would have welcomed a real retirement, "Sandy" Duff responded with youthful zest to the invitation to undertake the unspectacular but highly important duties of subeditor of *Leprosy Review*. For 5 years he carried out these tasks. Of his careful attention to detail, his literary flair, his editorial competence, and his rapid grasp of the essential concepts and vocabulary of the science of leprosy, I cannot speak too highly.

He was there when he was needed, and we are grateful.

S. G. BROWNE

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Leprosy and the Community

LEPRA REPORT 1977

The 53rd Annual Report of Lepra, The British Leprosy Relief Association, covers the year 1976 and continues the story of dedicated service to the cause of the eradication of leprosy which has characterized Lepra from the beginning. The Report gives the main guidelines of policy pursued by Lepra and for which support is encouraged as:

Leprosy research and the dissemination of information.
Prevention and cure of leprosy, particularly in children.
The training, provision and support of indigenous medical staff workers.
Assistance to Governments, WHO and other organizations in support of effective leprosy work.
Integrated control schemes providing domiciliary treatment.

In March 1976 Lepra became a full member of The International Federation of Anti-Leprosy Associations (ILEP), and is participating in the policy making and programme of this most important Organization.

The control work undertaken by Lepra tends to be concentrated in certain areas, notably, Malawi, where Lepra is the co-ordinator for all leprosy work; Sierra Leone, with grants in aid to control projects in Zambia, India and Uganda.

The involvement of Lepra in leprosy research is important, with grants for individual projects at several centres, in addition to that undertaken at Oxford by Lepra's Clinical Consultant, Dr A. C. McDougall.

The encouragement of work among children has always been important to Lepra. In 1976 The Children's Fund brought help to 30,470 children with leprosy, 26,149 of them in India. The encouragement of training for leprosy workers at all levels is also basic Lepra policy, and this has actively been pursued.

Support for Lepra from within the United Kingdom has greatly increased in recent years, and in 1976, for the first time total income exceeded £500,000. Substantial aid was given to anti-leprosy work in 18 countries; £208,000 was spent on leprosy control projects, £58,000 on treating children, nearly £22,000 on research, and £5300 on training personnel.

Leprosy Review is not the least of Lepra's responsibilities, and it is fitting on behalf of the Editorial Board to express our gratitude to the Director, Executive Committee and Medical Advisory Board for so much support and encouragement.

T. F. DAVEY

ANNUAL REPORT OF THE LEPROSY MISSION FOR 1976

The Annual Report of The Leprosy Mission for 1976, entitled, "To Seek and to Save", is presented very attractively and breaks new ground. To quote from the Introduction, "The Singapore Conference in 1976 emphasised that the only hope for overcoming the scourge of leprosy is conscientious, thorough, and wide ranging outreach. We must go deeper into the community; we must go more often; we must go more intensively; and we must keep on going back. Only in this way can those who are in danger—particularly the children—be saved from misery and deformity." In accordance with this the first half of the Report concentrates on the least spectacular aspects of leprosy work, the seeking for, and caring of leprosy sufferers in their home environment, and under the general heading "Partners in the Search", has sections on the paramedical worker, the mobile team, the rural clinic, the educator, the hospital back-up, and the imponderables, all very well illustrated.

The second section of the Report consists of brief Regional Reports, devoted to Africa, Southern Asia, Asia East and South-East, illustrated by maps and showing the depth and wide range of the Mission's concerns. The Leprosy Mission is now very much an international organisation, and a section on the International General Council includes references to the Singapore Conference and to ILEP, of which The Leprosy Mission was a foundation member. The concluding section on Finance is presented clearly and in an interesting way. 1976 was an outstandingly successful year, the income of The Leprosy Mission rising by 43% to a total of £1,725,798. "The international nature of the Mission is demonstrated by the fact that 20 different countries are now making significant regular contributions, and this year no one country gave more than 20% of the total income". This is a remarkable fact, especially when it is recalled that American Leprosy Missions Inc. is an independent organisation. The Leprosy Mission stands for sacrificial work and sacrificial giving, especially directed to those in greatest need. As the Introduction to the Report puts it, "Christian mission in all its forms must therefore always be a search, a reaching out to where neglected suffering humanity is to be found."

T. F. DAVEY

GANDHI MEMORIAL LEPROSY FOUNDATION

The Gandhi Memorial Leprosy Foundation has completed 25 years of work, and the occasion of its silver jubilee cannot be allowed to pass without an expression of appreciation for the outstanding contribution of the Foundation to leprosy control in India. In the depth of its concern for patients and the dedication of its staff the Foundation has continued to express the spirit of Gandhiji in an exemplary manner. None of the hundreds who were present at the All India Silver Jubilee Congress at Sevagram in 1973 will forget the courtesy and spirit of fellowship which pervaded the gathering. The Foundation has taken a leading role in leprosy education, and its training courses and rural control units have been a great help to many. We offer our congratulations and best wishes for the years ahead.

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News and Notes

30TH WORLD HEALTH ASSEMBLY, APRIL 1977

The Address by Dr H. Mahler, Director-General of the World Health Organization to the 30th World Health Assembly, included the following:

"A year ago, when I last addressed this assembly, I advocated a social revolution in community health. I did so because of my conviction that health policy should be determined by social goals, whereas all too often it is dictated by disease technology, applied without sufficient thought to its social purpose and consequences. . . .

". . . . The attainment of health is not only an individual human aspiration; it is also a social goal that in turn complements other social and economic goals. We must therefore choose health technology in the light of its ability to help attain these goals. We must constantly look for better ways of applying existing and new health knowledge for the benefit of all the world's populations and not merely for a privileged few. A more just distribution of health resources within and among countries is a social imperative for this last quarter of the 20th century."

MEXICO CITY—CONGRESS ILEP INTEREST

At the 17th Working Session of ILEP (the International Federation of Anti-Leprosy Associations), held in Amsterdam in June 1977, the Member-Organizations expressed their continuing interest in the forthcoming 11th International Leprosy Congress, to be held in Mexico City, 13 to 18 November 1978. They were particularly concerned that the social aspects of leprosy should receive adequate emphasis at the Congress, and welcomed the renewed interest in problems being faced by field workers.

As in previous Congresses, these voluntary agencies will sponsor the attendance of as many participants as possible from countries of the Third World, not confining their help to doctors and others actually working in one or other of the programmes sponsored in whole or in part by a Member-Organization of ILEP. The hope was expressed that certain international agencies might make matching grants and that governments also might be persuaded to make generous financial contributions towards the overheads of such a Congress.

The preliminary announcement should be available shortly. The Local Secretary is Dr A Saúl (XI Congreso Internacional de la Lepra, Centro Dermatológico Pascua, Dr Vértiz 464, Mexico 7 DF, Mexico).

Leprologists and others wishing to take advantage of the limited number of bursaries that may be available, and who are not being sponsored by a

Member-Organization of ILEP or other body, are invited to write in the first instance to: Dr S. G. Browne (The Leprosy Study Centre, 57a Wimpole Street, London W1M 7DF), giving full particulars in support of their application. As already intimated, the number of proffered papers that will be accepted for reading at the Congress will be small.

1981 INTERNATIONAL YEAR FOR DISABLED PERSONS

At an Interagency Consultation on Rehabilitation of the Disabled, held in Paris on 11 and 12 July 1977, discussions were held between representatives of The United Nations, the World Health Organization, UNESCO, the International Labour Office, and 3 members of the Executive Committee of the Council of World Organizations Interested in the Handicapped. The International Leprosy Association is represented on this Committee through its Secretary-Treasurer.

The most important subject studied, as far as leprosy is concerned, was the decision of The United Nations to make 1981 the "International Year for Disabled Persons". Non-governmental agencies will be organizing regional Congresses, a special stamp will probably be issued, and a world programme outlining suggested activities in the field of rehabilitation will be published.

This preliminary announcement is given so that workers in leprosy may be alerted in time to enable them to ensure that the needs of the disabled victims of leprosy are not forgotten in the preparations for the special year. Their co-operation will be enlisted in the compilation of brochures dealing with technical assistance and resources available. There are plans afoot for an international rally of disabled persons to be held in Geneva in March 1981.

BASIC KNOWLEDGE ABOUT LEPROSY

The West African Secretariat of ILEP have produced a booklet entitled, "*Basic Knowledge about Leprosy,* to assist leprosy patients, and thus helping the control of this disease. This guide for non-medical personnel, is aimed at patients and members of the general public who are able to read basic English. It is well illustrated with photographs and diagrams and presents the facts of leprosy clearly. The booklet is orientated towards Africa, where it should serve a useful purpose. It is obtainable from The West African Leprosy Secretariat, P.O. Box 673, Freetown, Sierra Leone (West Africa).

LEPROSY IN MEDIEVAL ENGLAND

The Gazette of the Institute of Medical Laboratory Science, Vol. 21, No. 6 of June 1977 includes an interesting article by J. H. Bayliss on Leprosy in Medieval England. The author quotes contemporary sources which suggest that leprosy attained importance in the British Isles before the time of the Crusades. A map of England shows the location of the numerous "leper homes", 190 of which have been recorded. Their distribution closely follows the population density pattern of the period. A histogram illustrates that the foundation of such homes reached a peak during the latter half of the 12th century, fading to insignificance by the 15th, and follows quite strikingly the incidence pattern that would be expected in a leprosy epidemic.

Where prevalence is concerned, the cases of Exeter and Oxford are quoted. In

1163 a leper house was built at Exeter to accomodate 13 infected people, at a time when the population of the city was estimated at 1,438. A similar house at Oxford held 12 leprosy sufferers when the estimated population of Oxford was 1,411, suggesting at least the possibility in these areas of a leprosy prevalence of around 1%. The city of London made regulations regarding begging by leprosy sufferers in 1346, 1348, 1367, 1372 and 1375, and the very frequency of these suggests both the significance of the leprosy problem and some degree of humanity in relation to it, a less rigorous repression than applied on the continent of Europe. A discussion on the decline of leprosy leads to the conclusion that after 200 years the development of resistance in much of the population was important. There is a useful bibliography.

DAMIEN-DUTTON AWARD TO DR AND MRS (DR) BRAND

It is a pleasure to congratulate Paul and Margaret Brand on the joint award to them of the Damien-Dutton Award for 1977. Their service to leprosy sufferers in the sphere of orthopaedics, rehabilitation and ophthalmology is known throughout the world, and millions of patients are indebted to them. The Award has never been more richly deserved.

THE VICTOR HEISER AWARDS FOR RESEARCH IN LEPROSY

These awards are funded by a bequest from Dr Victor Heiser, a well-known doctor with a world-wide experience in public health medicine and a life-long interest in leprosy and leprosy research. The primary purpose of the awards is to foster training in basic biomedical research in fields related to leprosy and to encourage national and international cooperation and research exchange in the scientific investigation of this disease.

The following awards are available:

1. POSTDOCTORAL RESEARCH FELLOWSHIPS

Candidates should have the Ph.D. or M.D. degree and be at the beginning or early stage of postdoctoral training in a field of basic biomedical science directly related to leprosy. Applications will be accepted either from individuals directly, or from heads of laboratories active in leprosy research, for authorization to appoint a fellow. Up to two years of support will be provided at stipend levels between $10,000 and $14,000 per annum.

2. VISITING RESEARCH AWARDS

Applicants should be established investigators in leprosy who wish to carry out a specific project at a distant institution. Per diem and travel support will be provided for up to six months of collaborative research with an appropriate laboratory or clinical facility. Preference will be given to proposals that plan field/clinical experience with leprosy.

3. RESEARCH GRANTS

A few, small research grants may be awarded to support proposals which are both of high scientific calibre and clearly related to leprosy if funds remain available after the review of applications in the above two categories. These grants will be

awarded to laboratories involved in leprosy research—especially those providing training opportunities in this field. The grants will not exceed $10,000, they will not be awarded for clinical trials, and they may not be used for salaries of personnel. Use of the grants for institutional overhead is limited to 10% of the total awarded.

The deadline for receipt of all applications is February 1, 1978.

Decisions of the Scientific Advisory Committee will be announced by May 1, 1978 and all awards must be activated by December 31, 1978.
Further information and instructions for making application may be requested from Ms. Caroline R. Stanwood, Director, Heiser Fellowship Program for Research in Leprosy, 1230 York Avenue, New York, New York 10021, U.S.A.

SCHIEFFELIN LEPROSY RESEARCH & TRAINING CENTRE, KARIGIRI SOUTH INDIA, SCHEDULE OF COURSES FOR THE YEAR (TRAINING) 1978

Courses	Qualifications	Duration	Date
I. For doctors			
(a) Condensed course for doctors	MBBS, or equivalent from any recognised University	1 week	Jan. 16-21
(b) Medical students' course	Undergraduates	1 week	*Apr. September*
(c) Medical officers' training course	Medical personnel engaged in leprosy work	6 weeks	Jan. 30-15 Mar Jul. 17-26 Aug
(d) Ophthalmic aspects in Lep.	Qualified Medical personnel (to follow Jan. condensed course)	1 week	Jan. 23-28
II. For non-medical personnel			
(a) Non-medical supervisors' course	Fully qualified Para-medical Workers with a minimum of 5 years experience—PUCs, graduates preferred	4 months	June 5th
(b) Orientation Course in Leprosy (personnel not requiring a Government recognized certificate)	For paramedical personnel (nurses, physios, O.T., & Administrators) (1 week Doctors course & 3 weeks in service training)	1 month	Jan. 16- Sep. (Med. Stu.)
(c) Paramedical Workers'	PUCs, graduates preferred	6 months	April 3rd Oct. 2nd
(d) Medical Record-keepers'	2 months inservice by previous arrangement—SSLC with proficiency in typing & good English	2 months	April October

(e) Physiotherapy Technicians'	SSLC passed	9 months	June 14
(f) Social workers', & Medical Administrators	Any other category wishing an orientation are invited to correspond for a period of in service training	1 month	
III. Inservice training			
(a) Inservice training in Medicine, Surgery, Pathology, Control & Lab. technology	For qualified personnel— on previous arrangement	9 months	
(b) Prosthetic Technicians	SSLC passed, PUC preferred	18 months	July 4th
(c) Shoe-makers' Course	V standard with knowledge in English preferred	by prev. arrangement. 6 months	
(d) Smear Technicians'	SSLC passed	3 months by prev. arrangement.	

Note. These Courses are recognized both by the Government of Tamil Nadu and the Government of India. Candidates will be awarded a Government recognized certificate.

All courses for Non-medical personnel are open only for sponsored candidates. Private candidates will not be accepted for any of them.

Food and accommodation will be provided either in the Guest House in the case of Medical and Overseas personnel or in the Hostel for non-medical personnel. Family accommodation *wili not* be provided unless previously arranged, subject to availability.

Application forms will not be considered, if they are not accompanied by a Postal Order for Rs. 10/— towards registration fee in the case of doctors.

*These courses will be conducted only on request either from the Government or other Voluntary Agencies.

For prescribed forms and other details, please contact the Training Officer, SLRT Post Karigiri, via Katpadi, N. Arcot, Tamil Nadu, S. India.

Lepr. Rev. (1977) **48**, 295–300

Letters to the Editor

On the Mode of Transmission of *Mycobacterium leprae*

I was most interested to read Dr Leiker's article on this important subject (*Leprosy Review* **48** Number 1, March 1977, 9–16) and its publication prompts me to ask if you could find space for me to record a request concerning nipple biopsies in untreated lepromatous patients who are actively lactating?

It is perhaps a printing or typing error, but on page 10 of the above article, Dr Leiker refers to the presence of large numbers of bacilli in the milk glands of lactating lepromatous mothers, but in fact the article, as correctly referenced at the top of p. 10, referred to a *non*-lactating patient.

This route of transmission is obviously difficult to investigate, particularly as regards entry of bacilli into the susceptible child. However the exit of bacilli from the lactating breast and nipple is worth further study, as it has proved to be with the nose, and the purpose of this letter is to record my interest in receiving such biopsies from any leprologist who may have the opportunity to obtain them.

I fully realise that it would be unethical to attempt such a biopsy in an actively lactating mother with a living child. If however, there is a neonatal death, or for some other reason, breast feeding is to be stopped, I would be grateful for the opportunity to study the histopathology of tissues from this site. Formol-Zenker, with subsequent transfer to 70% alcohol, as described in previous articles in the *Leprosy Review,* would be the ideal fixative.

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The Hypothesis of Skin to Skin Transmission

May I be allowed to make some comments on Dr Leiker's paper entitled: "On the mode of transmission of *M. leprae*" (*Leprosy Review* (1977) **48**, 9–16). In the paragraph headed: "Transmission via the skin", he says:

> ". . . the number of bacilli reaching the surface of the skin is . . . . sufficiently high for the transmission of *M. leprae*".

I do not know if Dr Leiker has actually attempted to *count* the number of bacilli reaching the surface of the skin, as I reported so doing, in the paper (Pedley, 1970*b*) to which he refers. My purpose in making a prolonged search of the skin surface of lepromatous patients was primarily to challenge the age-old hypothesis accepted by generations of leprosy workers. The hypothesis was this: that *M. leprae* emerged on to the surface of the skin in "great", "large",

"enormous", "innumerable" numbers (to quote some of the adjectives used in the literature). From the above quotation, Dr Leiker appears to have much the same idea. His reasons for it are given as follows:

(1) The probability that what looks like intact skin is "seldom unbroken, minor scratches . . . usually being present."
(2) The presence of *M. leprae* found in the epidermis at various levels.
(3) The presence of *M. leprae* in sweat-ducts.

When I reported my search, in the paper to which Dr Leiker refers, I, too, was aware of these possible sites of discharge of *M. leprae*; also of another which Dr Leiker does not mention, namely hair-follicles. Using a method which I called the Composite Skin Contact Smear (CSCS) method (Pedley, 1970*a*), in which every field searched was actually 10 fields, I examined ONE MILLION consecutive microscopic fields of very infiltrated and highly bacilliferous intact (to the naked eye) skin of 28 untreated advanced lepromatous cases. This search was a long and tedious one. It took 70 h of microscope work—spread over a period of 14 months. I would emphasize that in order to insure a uniform standard of technique and work on which I could rely, the preparation, staining, and examination of the slides was done entirely by myself. I claim that by the CSCS method, a scientific attempt was made to collect bacilli from the orifices of COUNTLESS sweat-gland ducts, hair-follicle openings, and MINOR SKIN ABRASIONS (not easily visible to the naked eye). In this extensive search I found only 52 acid-fast bacilli. As the presence of these 52 AFB was associated with nose-blows, heavily infected with *M. leprae,* and were found on skin READILY ACCESSIBLE TO THE FINGERS, I concluded that, in all likelihood, they had been transferred from the nose to the skin. That so few bacilli were found, appeared to me to be clear evidence that *M. leprae* are seldom, if ever, discharged from (what appears to be) intact skin.

In another part of his paper, Dr Leiker writes: "Pedley (1970) has shown that the number of bacilli present on the surface of the skin of highly bacilliferous patients is *relatively low* as compared with the large numbers of bacilli released by the nasal mucosa" (underlining—J.C.P's). This is *not* so. Actually what I did show was this: the number of bacilli reaching the surface of the skin of highly bacilliferous patients is practically NIL as compared with the large numbers discharged from the nose.

Thus, I am unable to agree with Dr Leiker when he says: "The transmission of *M. leprae* via the skin remains a definite possibility". My findings lead me to believe that the transmission of leprosy by skin to skin contact is unlikely to occur.

I would also like to comment on Dr Leiker's concluding remark to his paper, which reads:

> "Until such time . . . . that conclusive evidence is found that leprosy can be spread by droplet infection from one person to another . . . . great caution is needed in publicizing this hypothesis".

I submit, however, that the following findings do provide strong evidence for this hypothesis:

(1) Millions of bacilli can be discharged even in ONE nose-blow of an untreated advanced lepromatous case.
(2) *M. leprae* can remain viable for days outside the human body (Davey and Rees, 1974).

(3) The presence of *M. leprae* in *multitudes* of droplets discharged by advanced untreated lepromatous patients was observed by Schaffer (1898), and confirmed (in sneezing) and photomicrographed by Pedley and Geater (1976).

In my view, these findings do make the conclusion stated negatively in the Summary of Dr Leiker's paper: ". . . that droplet infection via the respiratory tract is not a common mode of transmission", a highly debatable point. Nevertheless, I am still of the opinion that: ". . . the present trend of abandoning segregation and other restrictive measures against leprosy patients should not be reversed".

J. C. PEDLEY

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References

Pedley, J. C. (1970*a*). Composite skin contact smears: a method of demonstrating the non-emergence of *M. leprae* from intact lepromatous skin. *Lepr. Rev.* **41**, 31–43.

Pedley, J. C. (1970*b*). Summary of the results of a search of the skin surface for *M. leprae*. *Lepr. Rev.* **41**, 167.

Davey, T. F. and Rees, R. J. W. (1974). The nasal discharge in leprosy: clinical and bacteriological aspects. *Lepr. Rev.* **45**, 121.

Schaffer (1898). On the spread of leprosy bacilli from the upper parts of the respiratory tract. *Arch. Derm. Syph. XLIV,* 159. Reprints in English available from the Leprosy Study Centre, London. Also extensive quotations given in the next reference:

Pedley, J. C. and Geater, J. G. (1976). Does droplet infection play a role in the transmission of leprosy? *Lepr. Rev.* **47**, 97.

Clofazamine From Broken Bottles

I have been interested to read the reports of gastro-intestinal side-effects of clofazamine. In my experience this is a real problem, but also rare. It is interesting to note also, that symptoms may be intermittent even on a constant dose of the drug.

I have wondered how much these symptoms can be related to the ingestion of capsules from broken bottles. Sometimes the jars are broken in transit, the glass becomes powdered and firmly adherent to the capsules, hardly sparing 1 in 1000. I am grateful to Dr M. F. R. Waters who has described to me a method of cleaning the capsules by washing them in spirit, and then cleaning each individually with a spirit soaked swab. Unfortunately this is a very time consuming process demanding the ultimate in patience and good eyesight to do the job properly.

I am concerned that some centres are probably using the capsules from broken bottles without taking proper care to see they are properly cleaned of glass pieces. In these circumstances the risk of serious gastro-intestinal side-effects are significantly increased. I would appeal to all leprosy workers to be very careful in the use of capsules from broken bottles, and to the drug company and agencies

supplying clofazamine to please pack the capsules in unbreakable containers and thus eliminate this risk.

P. M. TAYLOR

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References

Jopling, W. H. (1976). *Lepr. Rev.* **47**, 1.
Warren, A. G. (1976). *Lepr. Rev.* **47**, 343.

Evidence for the Occurrence of Tissue Inhibitors of *o*-Diphenoloxidase in *Mycobacterium leprae* Obtained From Infected Armadillos

We routinely test *Mycobacterium leprae* separated from armadillo tissues for *o*-diphenoloxidase, using D-dopa as substrate. The bacilli convert D-dopa to pigment; and when the bacterial preparations are heated. the activity is lost, indicating that dopa oxidation by the organisms is an enzymatic process. Except for *Mycobacterium leprae* (obtained from different sources), no other mycobacteria have so far been found to possess this metabolic property. Of course, it is well-known that dopa undergoes auto-oxidation under alkaline pH, and that metal ions stimulate the conversion of dopa to pigment. However, this is not the same as the enzymatic oxidation of the substrate by *o*-diphenoloxidase.

Recently, some preparations of *Mycobacterium leprae* from armadillo tissues showed extremely low levels of the enzyme or no activity at all. We diluted the bacterial suspensions and compared the oxidation of dopa by the concentrated and the diluted preparations. All the diluted samples oxidized dopa, and surprisingly, these samples had higher activity than the concentrated suspensions. This observation suggests that the *Mycobacterium leprae* preparations contain inhibitors of *o*-diphenoloxidase, derived from the armadillo tissues.

The bacilli were separated from the infected tissues by differential and density-gradient centrifugation in solutions of sucrose and KC1. For routine testing of *o*-diphenoloxidase, these preparations are used without further purification, because mammalian tyrosinase does not act on D-dopa. (Greater purification is achieved by treating the bacterial suspensions with trypsin, NaOH, acetone and ether.) In the experiments reported here, the bacilli were incubated with D-dopa at pH 6.8 for 60 min. The reaction mixture was centrifuged at 25 000 g for 30 min and the spectrum of the supernatant fraction was determined. After centrifugation, the bacterial residue also was examined. A good proportion of the pigment formed from dopa sediments with the bacteria.

If the reaction is positive, the sediment of the sample containing bacilli and dopa would be black; bacilli alone or heated bacilli plus dopa would show little colour development. When the bacterial preparations have low enzyme activity, the spectrum of the supernatant fraction reveals no well-defined peak, since sufficient amounts of quinones do not accumulate in the reaction mixture. In the data presented in Table 1, absorbance values for 400 nm or 480 nm are given, as an indication of the amount of pigment contained in the supernatant fraction.

TABLE 1
Comparison of o-diphenoloxidase in concentrated and diluted suspensions of Mycobacterium leprae *from armadillos*

Experiment number	Concentrated suspension		Dilute suspension	
	Colour of sediment	Absorbance of supernatant	Colour of sediment	Absorbance of supernatant
1	Light black	0.022	Deep black	0.036
2	Light black	0.035	Deep black	0.045
3	Brown	0.008	Black	0.025
4	Brown	0	Black	0.022
5	Light black	0.022	Deep black	0.035

The readings for the different samples vary, because the concentration of inhibitory material present in them would not be the same.

The undiluted bacterial suspension contained over 10^{10} bacilli/ml. These were diluted 5 times or 10 times. If the preparations had no inhibitory substances, readings for the concentrated samples would have been 5 to 10 times higher than those for the diluted suspensions. The presence of higher amounts of inhibitory material in the concentrated preparations appears to be responsible for the lower activity shown by them. When the bacterial suspensions are too dilute, very little colour development would be observed, because of the insufficient number of organisms to oxidize the substrate. Another significant finding was regarding samples 3 and 4; one would have concluded that they contained no dopa oxidase activity, if the diluted samples were not tested. In purified preparations of *Mycobacterium leprae* from human sources, such marked inhibition of *o*-diphenol-oxidase has not been detected.

At the time of sacrificing the animals (from which the bacterial suspensions used in the study were derived), they were subjected to cardiac exsanguination under anaesthesia. Further studies on the tissue inhibitors of *o*-diphenoloxidase of *Mycobacterium leprae* are in progress.

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Lepr. Rev. (1977) **48**, 301–303

Book Reviews

Emotional Care of the Facially Burned and Disfigured, by N. R. Bernstein, 1976. Published by Little, Brown & Co., Boston, U.S.A. 24 pp. Price in the U.K. £7.50.

This book is a sensitive and detailed study of the emotional effects of burns of the face written by an experienced psychiatrist at one of the leading burns treatment centres in the U.S.A. The traumatic effects of facial disfigurement on the sufferer, the community and those concerned with the care of patients are all explored. Detailed case histories are included, illustrating the different ways patients react to their disfigurement and different approaches to the problems of treatment. Concluding chapters are concerned with psychiatric care and rehabilitation, and the importance of a sustained integrated approach which combines understanding and sympathy with positive encouragement in adjusting to life in the community.

All this is of the highest relevance to workers in leprosy, for whom facial disfigurement is so much a matter of everyday experience that it is easy to forget how intense is the psychological trauma it creates in many of our patients. For all concerned with the treatment of sufferers from leprosy this book will be read with interest and profit.

T. F. DAVEY

The Challenge of Leprosy, by T. N. Jagadisan, (1977). Published by Kasturba Kushta Nivaran Nilayam, Malavanthangal P.O., via Kandachipuram, S.O. South Arcot District, PIN:605 701, S. India. 60 pp.

This book is a selection of articles and papers coming from the pen of Professor Jagadisan, and compiled at the suggestion of his friends. Anyone who knows T. N. Jagadisan, the story of his life and his great service to the cause of sufferers from leprosy will read this book with pleasure and affection for its author, who in a very personal concluding chapter tells of his own experience of leprosy and how he came to take up leprosy work.

This selection of his writings typifies the vision and deep compassion of the author. "An approach to rural leprosy work"; "A world within a world", "Rehabilitation of the physically handicapped with reference to leprosy"; "Physical and emotional problems in restoration of leprosy patients": in all these and other chapters he speaks with the authority of personal experience and with great felicity of language, qualities which give exceptional beauty to his study of Father Damien. His Presidential Address to the 12th All India Leprosy Workers' Conference is another example, not only or literary mastery but of that elevation of spirit which the experience of deep suffering has brought to a very remarkable man.

T. F. DAVEY

The Mycobacteria, by C. Ratledge. 1977. Shildon: Meadowfield Press Ltd. Pp. 130. £3.20 (paper-back).

Dr Ratledge has provided a series of cross-referenced critical reviews of various aspects of the mycobacteria, concentrating especially on work reported since 1960. The chapters discuss the diseases caused by mycobacteria and their immunology, taxonomy, structure and ultra-structure, metabolism, lipids, nucleic acids and genetics, and antimicrobial drugs. Though there

is some unevenness in the depth with which these subjects are treated, reflecting the particular interests of the author (and also of the reviewer), the whole is rather successful.

There are some disappointments. The chapter on metabolism is scanty, and contains no hint of the idea that fast- and slow-growing mycobacteria may have important metabolic differences. There are some curious statements about chemotherapy; it is implied that clofazimine is a more effective antileprosy drug than dapsone, and that it is applied direct to the skin of the patient; it is unlikely that cycloserine directly prevents the development of resistance to other anti-tuberculosis drugs. Considering the detailed treatment of the various modes of DNA transfer that occur in bacteria (few of which have been convincingly demonstrated in mycobacteria) it is surprising that the idea that drug-resistance arises by selection, rather than by any action of the drug to modify the bacterium, is not explained more clearly.

The treatment of the lipids is well done. The author has attempted to avoid the classical categories—waxes A, B, C and so on—and has instead classified mycobacterial lipids according to their structure. Taxonomy is well summarised, and structure interestingly dealt with (though it seems unlikely that many electron microscopists would now accept Imeda's structure of the mycobacterial wall).

The author seems not to have been too kindly treated by the publishers. The object of photographic typesetting from typescript is presumably rapid production—for this one has to put up with untidy right margins and unattractive typefaces. Yet production of the book has been so delayed that Dr Ratledge has been obliged to add a chapter on recent progress (since 1973). In some cases the recent work negates large sections of the original chapters, which the author should have had the opportunity to rewrite. This has, for example, made a considerable muddle of his own interesting and important work on iron-transport. One may only speculate on the purpose of the eccentric system of page-numbering.

The real mystery remains—for whom is this book intended? The preface lists a variety of potential readers, but the treatment seems too elaborate for students or clinicians not especially interested in mycobacterial diseases, but too superficial for a specialist in any of the fields covered. It would form a useful introduction to the field for research workers or clinicians proposing to involve themselves with mycobacteria, and is cheap enough for most to afford. They would be well advised not to believe all the reported information about the genus, which sometimes seems as much supported by ingenuity as by data.

P. DRAPER

The Pathogenesis of Infectious Disease. Cedric Mims. Academic Press. 1977. xii + 242 pp. £3.40 (paperbound).

The first question raised by this new addition to Monographs for Students of Medicine is why it was not written before. The answer, presumably, is that few people have made themselves as well versed as Professor Mims over such a broad field on the whole subject of infection—inflammation—immune response—pathogenesis of disease. The point of the book is that this vast topic is dealt with as a whole, in general terms. Diseases are used not as chapter headings but as examples to illustrate the stratagems evolved by invading organisms and their hosts to counter each others' defences at each stage of the sequence from contagion to recovery. Every type of micro-organism is dealt with, including a number that are primarily of veterinary importance. The author is particularly strong on viruses, but he gives many useful insights too into bacteria, fungi and protozoa, and the diseases caused by them. Obviously the subject is not dealt with in depth and the book is not intended to supplant conventional text-books. It is a synthesis of knowledge and ideas, and to pick holes in it would be to miss the point. There are holes, but the big ones are those due to deficiencies of present knowledge.

Aspects that will be of particular interest to leprologists will be mechanisms of entry of organisms to the body by different routes and methods of dissemination, the process of phagocytosis and digestion, the advantages and limitations of the intra-cellular and extra-cellular habitats, the pathogenesis of diseases other than leprosy in which the causative organism resides in neural tissue, and the addendum on vaccines.

The book is lucidly written and helpfully illustrated in a style that will be readily comprehended by students (if necessary with the aid of the glossary provided). Although, perhaps, students will be the chief beneficiaries there must be few specialists, teachers or research workers in this complicated field who will not enjoy, and gain from reading, such a comprehensive though fairly brief survey of the subject. It is a splendid concept, successfully executed. The book is moderately priced and highly recommended.

D. S. RIDLEY

Lepr. Rev. (1977) 48, 304–314

Abstracts

1. MICROBIOLOGY

94. KATO. L. & ISHAQUE, M. **A simplified hyaluronic acid based culture medium for mycobacteria isolated from human lepromata.** *Int. J. Lepr.,* 1976, v. 44, No. 4, 431– 434.

"Acid-fast bacilli multiplied in liquid culture media containing hyaluronic acid when inoculated with mycobacteria from a lepromatous leprosy nodule. The culture was readily subcultured at 10 day intervals in the homologue media, but failed to grow in the Dubos, Middlebrook and Lowenstein media. These findings confirm the results of Skinsnes *et al.* (1975). Identification of this culture is not yet available, however it gives positive immunofluorescence with authentic anti-*M. leprae* serum. The obtained culture also grows as a chromogenic culture at 34°C on a simple medium prepared from trypsin digested human umbilical cord, yeast extract powder and glycerol. This medium can be sterilized in an autoclave, but filter sterilized sheep, bovine or horse serum must be added aseptically as an esential ingredient. The medium does not differ considerably from the hyaluronic acid medium proposed by Skinses *et al.,* but it is easier to prepare, it is inexpensive and permits a logarithmic growth within 7 days of the so far unidentified culture isolated from leprotic nodules."

95. LEVY, L. & MERIGAN, T. C. **Inhibition of multiplication of *Mycobacterium leprae* by polyinosinic-polycytidylic acid.** *Antimicrob. Agents Chemother.,* 1977, v. 11, No. 1, 122-125.

"Contrary to the results of an earlier study in which polyinosinic-poly-cytidylic acid [poly(I:C)] administered intraperitoneally to mice had no effect on multiplication of *Mycobacterium leprae* in the mouse footpad, the local administration of poly(I:C) every 12 h for 15 doses during logarithmic multiplication was found both to inhibit bacterial multiplication and to produce high tissue levels of interferon (IF). Local administration of poly(I) alone inhibited multiplication of *M. leprae* to almost as great a degree without at the same time producing a measurable IF titer in the footpad tissues. Mouse IF and 'mock' IF both inhibited bacterial multiplication to the same degree, but administration of only the former resulted in a measurable IF titer. Polyadenylic-polyuridylic acid administered locally neither inhibited multiplication nor induced IF; fetal calf serum, administered in the same concentration as found in the preparations of IF and mock IF, was modestly inhibitory, without inducing IF. Thus, the local administration of poly(I:C) appears to have inhibited multiplication of *M. leprae* independently of IF induction."

96. MUROHASHI, T. & YOSHIDA, K. **[Drug sensitivity test of *M. leprae* using liquid media.]** *Lepro,* 1976, v. 45, No. 1, 1-8. [In Japanese.]

The English summary appended to the paper is as follows:–

"Drug sensitivity was examined using semi-synthetic liquid media on two strains of *M. leprae* isolated from nodules of L-type leprosy patients. The results revealed that L-Jul-74-1 strain was senstitive to both DDS and Rifampicin, and L-Feb-75 strain was sensitive to all of DDS, Rifampicin and Isoniazid. According to the information of the leprosaria, to which the host patients of these strains belong, the administration of DDS to the former case and Rifampicin

to the latter, respectively, resulted in the rapid and remarkable improvement of clinical symptoms, in good agreement with the above mentioned test results. It was revealed, further, that the drug sensitivity of *M. leprae* could be determined by this *in vitro* test method as early as about 3 months' incubation at 37° C. Drug sensitivity test using liquid culture media will facilitate the selection of adequate drugs to be administered to the concerned leprosy patients."

97. MATSUO, Y, & OTSUNOMIYA, S. **Attempts at cultivation of *Mycobacterium leprae* in cell cultures.** *Jap. J. Microbiol.*, 1976, v. 20, No. 5, 471-473.

Mycobacterium leprae failed to multiply in a mouse cell culture system which had proved successful for the cultivation of *M. lepraemurium.* However, in 2 out of 14 experiments, *M. leprae* was proved by subsequent mouse inoculation to have survived for 54 and 70 days. Technical details are given of the culture system, which is based on footpad cells.

D. S. Ridley

98. BALAKRISHNAN, S. & DESIKAN, K. V. **Blood and tissue levels of diamino diphenyl sulphone (DDS) in experimental mice.** *Indian J. Med. Res.*, 1977, v. 65, No. 2, 201-205.

"Blood and tissue levels of diamino diphenyl sulphone (DDS) in 24 experimental mice receiving diets containing 0.01% DDS, were estimated. An average concentration of 1.2 μg/ml of DDS was found in the blood. The concentration of DDS in the liver was about twice that in blood. In the spleen, the level of DDS was slightly higher than in blood but the muscles contained much less. The drug was detectable in the nerves at a concentration almost equal to that in the blood. The clinical implications of these findings in the treatment of leprosy are discussed."

99. LEVY, L. **The activity of a thiadiazole on *Mycobacterium leprae.*** *Proc. Soc. Exp. Biol. Med.*, 1976, v. 153, No. 1, 34-36.

"A new broad-spectrum antimicrobial, 2-amino-5-(1-methyl-5-nitro-2-imi-dazolyl)-1, 3, 4-thiadiazole, reported inactive against *Mycobacterium tuberculosis,* inhibited multiplication of *M. leprae* in the mouse footpad when administered orally to the mice. The dose-response curve was very steep: 0.2 g% of the drug exhibited considerable activity, whereas 0.05 g% was only modestly active in one experiment and inactive in another. This drug appears to be one of the few that is bactericidal for *M. leprae.*"

100. HASTINGS, R. C., RICHARD, V., JR, CHRISTY, S. A. & MORALES, M. J. **Activity of ascorbic acid in inhibiting the multiplication of *M. leprae* in the mouse foot pad.** *Int. J. Lepr.*, 1976, v. 44, No. 4, 427-430.

"Ascorbic acid was fed to mice in concentrations of 0.05%, 0.15%, and 0.45% w/w in the diet. Six months after inoculation of *M. leprae* into the foot pads, there were significantly fewer acid-fast bacilli harvested from animals receiving 0.15% and 0.45% w/w ascorbic acid than from control mice. On the other hand, *M. leprae* did multiply in mice fed ascorbic acid while no multiplication at all was observed in animals fed dapsone, clofazimine or rifampin. No toxic effects of ascorbic acid were noted in these mice."

101. SHEPARD, C. C., YOUMANS, A. Y. & YOUMANS, G. P. **Lack of protection afforded by ribonucleic acid preparations from *Mycobacterium tuberculosis* against *Mycobacterium leprae* infections in mice.** *Infection & Immunity,* 1977, v. 15, No. 3, 733-736.

"Mycobacterial ribonucleic acid preparations from H37Ra, an attenuated strain of *Myco-*

bacterium tuberculosis, provide their usual marked protection against *M. tuberculosis* challenge; however, they provided no protection against *Mycobacterium leprae* challenge. Suspensions of intact H37Ra were not effective against *M. leprae.* Suspensions of BCG gave their usual distinct protection against *M. leprae* challenge."

2. BIOCHEMISTRY, PATHOLOGY, IMMUNOLOGY

102. REA, T. H., LEVAN, N. E. & TERASAKI, P. I. **Histocompatibility antigens in patients with leprosy.** *J. Infect. Dis.,* 1976, v. 134, No. 6, 615-618.

"The frequencies of distribution of 25 histocompatibility antigens were determined in 92 Mexican patients with leprosy and compared with those in 315 Mexicans who did not have the disease. No statistically significant differences were found between the patients and the controls in regard to histocompatibility antigens, and subgroups with a significant difference could not be identified by division of the patients according to the density of *Mycobacterium leprae* or the presence or absence of cell-mediated immunity directed against antigens of *M. leprae*."

103. PARMASWARAN, M., GIRDHAR, B. K., DEO, M. G., KANDHARI, K. C. & BHUTANI, L. K. **Macrophage function in leprosy.** *Int. J. Lepr.,* 1976, v. 44, No. 3, 340-345.

"The macrophage function in patients with leprosy was assessed by estimating histochemically the acid phosphatase activity in skin biopsies and by assessment of phagocytic and lytic capability of *in vitro* cultured macrophages derived from peripheral blood monocytes, challenged with live *M. leprae.*

"Acid phosphatase was demonstrated in skin biopsies of different groups of leprosy patients classified according to the Ridley and Jopling scale. The degree of acid phosphatase positivity was correlated with clinical spectrum, Bacterial and Morphologic Indices and treatment status.

"Peripheral blood monocytes from patients with leprosy, either tuberculoid or lepromatous, were cultured in monolayers and challenged with *M. leprae.* The phagocytosis and lysis of mycobacteria by macrophages was observed at different time intervals from the 1st to the 28th day. The morphology of the macrophages in different types of leprosy was also studied.

"The results suggest that macrophages from patients with either tuberculoid or lepromatous leprosy are not be themselves capable of lysing live *M. leprae.*

"Live *M. leprae* injected into the foot pad of Wistar strain of rats evoked similar responses on the tenth day, in normal and protein deficient animals."

104. ANDERS, E. M., MCADAM, K. P. W. J. & ANDERS, R. F. **Cell-mediated immunity in amyloidosis secondary to lepromatous leprosy.** *Clin. Exp. Immunol.,* 1977, v. 27, No. 1, 111-117.

"Cell-mediated immunity in lepromatous leprosy patients with and without amyloidosis has been studied. Amyloidosis occurred mostly in patients with a history of recurrent erythema nodosum leprosum (ENL) reactions. For this reason, 2 control groups of leprosy patients were included, one having a history of recurrent ENL and the other little or no ENL. The lack of responsiveness to lepromin *in vivo* and *in vitro,* characteristic of lepromatous leprosy, was not altered by the presence of amyloidosis or a history of ENL. No significant difference between the patient groups was observed in the response to PPD *in vitro,* but skin reactivity to PPD was significantly lower in the patients with amyloidosis than in those without amyloidosis. In contrast, the PHA responses of patients with amyloidosis were significantly higher than those of control patients without a history of ENL, but not significantly different from those of control patients with a history of recurrent ENL.

"Lepromatous leprosy patients who develop amyloidosis thus appear to belong to a group, susceptible to repeated attacks of ENL, whose PHA responses are higher than those of other lepromatous leprosy patients. The lower skin reactivity to PPD observed in the amyloid group may reflect a general impairment in delayed cutaneous hypersensitivity."

105. THOMAS, M., JOB, C. K. & KURIAN, P. V. **Susceptibility to leprosy and serum atypical pseudocholinesterase.** *Int. J. Lepr.,* 1976, v. 44, No. 3, 315-318.

"The pseudocholinesterase levels and the nature of the enzyme as shown by the dibucaine number (D.N.) were estimated in 720 controls and 420 lepromatous leprosy patients, and 301 tuberculoid leprosy patients. There was no statistical difference in the esterase levels between leprosy patients and normal controls. But the distribution of D.N. was significantly different in the leprosy patients compared to the normal population studied. The D.N. below 40 indicates the samples with the atypical pseudocholinesterase–the presence of which is genetically determined. The distribution of samples with D.N. below 40 was significantly higher in the lepromatous leprosy patients compared to the normal population or tuberculoid leprosy patients. It is proposed that since there is a greater incidence of the atypical enzyme in lepromatous leprosy cases, the presence of this enzyme or the deficiency of the typical enzyme may make a person more susceptible to leprosy."

106. DATE, A., THOMAS, A., MATHAI, R. & JOHNY, K. V. **Glomerular pathology in leprosy. An electron microscopic study.** *Am. J. Trop. Med. Hyg.,* 1977, v. 26, No. 2, 266-272.

"Electron microscopic examination of renal biopsies from 19 patients with leprosy who had edema, proteinuria, or hematuria showed a proliferative glomerulonephritis in 12, amyloidosis in 2, and no lesion in 5. The proliferative glomerulonephritis was of different patterns: diffuse with or without exudation, focal, or mesangial. Subendothelial and/or subepithelial deposits were seen in 5 biopsies. Of the patients with glomerulonephritis, 3 had a reduced total serum complement level, 5 had erythema nodosum leprosum, 5 had evidence of recent streptococcal infection, and 2 had microfilariae in the peripheral blood. The significance of these findings is discussed."

107. KAUR, S., WAHI, P. L., CHAKRAVARTI, R. N., SODHI, J. S., VADHWA, M. B. & KHERA, A. S. **Peripheral vascular deficit in leprosy.** *Int. J. Lepr.,* 1976, v. 44, No. 3, 332-339.

Trophic changes in leprosy have always been attributed to nerve degeneration. This paper reports on studies of their vascular component, including clinical nutritional changes, histopathological changes and, in particular, brachial arteriography, in 35 patients, and posterior tibial arteriography in 1 patient. Arteriographic abnormalities, including occlusion, narrowing, tortuosity, dilatation, post stenotic dilatation, irregularity and incomplete filling of the lumen with radio-opaque material, were seen in more than 2 vessels in 50% of the arteriograms in wrist and palm; digital arteries showed abnormality in more than 75% of patients. The ulnar artery was more frequently involved (74%) than the radial (50%). Superficial and deep palmar arches were equally affected. There was no predilection for one form of leprosy to show arterial changes more than others. This careful study clearly demonstrates the frequency of vascular changes in the extremities in leprosy and, in the opinion of the authors, these must play an important role in causing mutilations and deformities.

T. F. Davey

108. CARAYON, A., LANGUILLON, J. & GIRAUDEAU, P. Névrites réactionnelles micro-angiopathiques dans la lèpre borderline. **[Micro-vascular lesions in peripheral nerves appearing in the course of acute reaction in borderline leprosy.]** *Méd. Afr. Noire,* 1976, v. 23, No. 11, 681-690.

The authors review the pathology of damage to the peripheral nerves that appears during reactional episodes in patients suffering from borderline leprosy and suggest that much of the damage is due to lesions in the blood vessels (vasa nervorum) surrounding the nerve trunks and penetrating intraneurally. They thus consider that the lesions are on a par with auto-immune phenomena, as in Guillain Barré's neuropathy, periarteritis nodosa and rheumatoid arthritis.

The commonest history of these cases is for an initial downgrading reaction to be followed—usually after a period of anti-leprosy treatment—by a reversal reaction. The localization of the lesions in the nerve trunks is usually distant from the classical sites of predilection and may affect nerves that are less frequently damaged in leprosy, for example, the radial, the median (in its lower path) and the internal popliteal. The enlarged nerve is usually soft on palpation, the consistency being due to the presence of localized oedema.

Clinical suspicion of the occurrence of this type of neuropathy is based on the unusual localization, the late appearance of the lesions, an association with pre-existing nerve lesions of classical type, the insidious and painless progression of the nerve damage, and the presence of submaximal electrophysiological changes, notwithstanding the degree of motor and sensory deficit. Because no branches leave the nerve trunk at the sites affected, the extent of the functional destruction may long remain unsuspected.

The result of the lepromin test and the histopathological picture are consistent with the hypothesis of a microvasculitis affecting the media of the small vessels. Complement and immunoglobulin are deposited in these situations, together with immune complexes.

The authors favour limited surgical intervention for precise indications, with operative endoneurolysis in selected cases to relieve pressure on nerve fibres and to accelerate nerve conduction velocity. They even suggest removal of a segment of irreversibly damaged nerve in order to remove a local source of antigenic material. They recommend long-acting sulphonamides with adequate doses of corticosteroids to control the acute manifestations.

In their view, high doses of anti-leprotics (dapsone or sulphonamides) may safely be given to patients who have no sign of nerve damage, but where there are indications of pre-existing damage, then drugs may precipitate a serious exacerbation.

S. G. Browne

109. NAIK, S. S., TANKSALE, K. G. & GANAPATI, R. **Study of urinary nitrogenous constituents in reactions of leprosy.** *India. J. Med. Res.,* 1977, v. 65, No. 2, 193-200.

"Nitrogen intake through vegetarian diet was studied in uncomplicated hospitalised leprosy patients and patients in different stages of reactions. The protein intake in hospitalised leprosy patients was more than in an average Indian diet. It was reduced in reaction cases of leprosy in accordance with the severity of the episode. Total nitrogen excreted through 24 h urine was studied in leprosy patients along with urinary nitrogenous constituents, such as urea, uric acid, creatinine, creatine, α-amino acid nitrogen, hydroxyproline. These urinary constituents were found to increase in accordance with the severity of reaction. The excretion of α-amino acid nitrogen and hydroxyproline in urine was significantly increased in reaction of leprosy. It is suggested that these parameters along with hydroxyproline: creatinine ratio can be used to assess the severity, subsidence and onset of reaction in leprosy. Impairment in functions of kidney and adrenal cortex was observed during reactions of leprosy. The causes for the increased excretion of the nitrogenous constituents in reaction of leprosy have been discussed."

110. CARNUS, H., LANGUILLON, J. & BAQUILLON, G. Etude de la sensibilité comparée à la tuberculine chez des lépreux lépromateux et tuberculoïdes, dans la région de Dakar (données préliminaires—février 1976.) **[A study of comparative tuberculin sensitivity in patients with lepromatous or tuberculoid leprosy in the Dakar area.]** *Bull. Soc. Méd. Afr. Noire Lang. Fr.*, 1976, v. 21, No. 3, 376-382. English summary (6 lines).

Having noted the considerable discrepancies in published work on the matter, the authors investigated tuberculin sensitivity (0.1 ml of tuberculin RT23, administered by intradermal injection), in 3 groups of patients with leprosy: 109 in-patients, 141 out-patients, and 162 inmates of a rural leprosy village. They compared the results among patients with either lepromatous or tuberculoid leprosy and a group of 176 healthy people from the outskirts of Dakar.

The study revealed no marked depression of tuberculin sensitivity, either among those with lepromatous leprosy or among those with the tuberculoid form. There were, however, suggestions of definite differences between the groups of patients with lepromatous leprosy, depending on the place where they were living. This observation calls for further study.

S. G. Browne.

111. SKINSNES, O. K. & HIGA, L. H. **The role of protein malnutrition in the pathogenesis of ulcerative "Lazarine" leprosy.** *Int. J. Lepr.*, 1976, v. 44, No. 3, 3346-358.

The systematic study of an experimental model, using Wiersung rats infected with *Mycobacterium lepraemurium,* leads the authors to suggest that Lazarine leprosy may result from enhanced lepromatous infection occurring as a result of protein malnutrition. The pathogenic mechanisms appears to be impairment of cellular immunity, probably enhanced by concomitant impairment of humoral antibody immunity, with lowered resistance to secondary infection. The tendency to ulceration is also the likely result of protein malnutrition.

T. F. Davey

3. CLINICAL

112. MCDOUGALL, A. C. & SALTER, D. C. **Thermography of the nose and ear in relation to the skin lesions of lepromatous leprosy, tuberculosis, leishmaniasis, and lupus pernio.** *J. Invest. Derm.*, 1977, v. 68, No. 1, 16-22.

"The nasal and aural temperature patterns of 100 normal subjects have been investigated by infrared thermography, paying particular attention to possible errors of instrumentation and technique which may arise in such areas of complex morphology.

"Although by no means invariable, the pattern of thermograms confirms that certain areas which are relatively cool are often affected in lepromatous leprosy, tuberculosis, leishmaniasis, and lupus pernio. In lepromatous leprosy, low temperature appears to govern the localization of disease in most parts of the body, and the possible reasons for this are discussed. Thermography may have a place in the investigation of other skin diseases in which the distribution of lesions on the body surface is unexplained."

113. SEHGAL, V. N., AGGARWAL, D. P. & SEHGAL, N. **Ocular leprosy.** *Indian J. Med. Res.*, 1976, v. 64, No. 11, 1600-1606.

"Four hundred and thirty leprosy patients were studied for ocular involvement of which 229 were of tuberculoid, 69 of lepromatous, 69 of borderline, 63 of neuritic and 3 patients of

reaction of which 2 were lepromatous and 1 borderline leprosy. Ocular lesions were seen in 106 patients comprising 43 (18.7%) tuberculoid, 30 (43.4%) lepromatous, 15 (21.7%) each borderline and neuritic and 3 (4.2%) of reactions. Majority of patients with affliction of the eyes were in the age group of 20 to 59 years. The commonest clinical signs in different types of leprosy were madarosis and infiltration of the eyebrows and eyelids and were seen frequently in lepromatous leprosy. Conjunctivitis, episcleral nodules, interstitial keratitis, pannus, punctate keratitis and corneal opacities were also seen, but their occurrence was infrequent. The affection of the posterior segment of the eye was uncommon. The demonstration of *Mycobacterium leprae* in conjunctival scrapings and/or fluid in patients of lepromatous leprosy was of interest as it supports the earlier reports of direct invasion of ocular tissues in this type of leprosy."

114. MCDOUGALL, A. C. & ARCHIBALD, G. C. **Lepromatous leprosy presenting with swelling of the legs.** *Br. Med. J.,* 1977, Jan. 1, 23-24.

This is a report from Oxford of an adult Pakistani male who sought medical advice because of oedema of both legs and was found, on examination, to have skin lesions of erythema nodosum leprosum (ENL). There was a past history of nasal blockage and epistaxis. Large numbers of leprosy bacilli were found in skin and nasal mucosa, and biopsies were diagnostic of lepromatous leprosy in reaction. The aetiology of oedema in leprosy is discussed.

[The important lesson to be learnt from this paper is that skin lesions of lepromatous leperosy can be preceded, often for years, by nasal symptoms and by oedema of the legs.]

W. H. Jopling

115. PAPY, J. J., LANGUILLON, J., PAPY-TEMIME, M. & COURNIL, C. Les multinévrites hanséniennes. Signes électrophysiologiques, infracliniques et diagnostic. **[Leprous polyneuritis: electrophysiological signs of subclinical and diagnostic importance.]** *Méd. Afr. Noire,* 1976, v. 23, No. 11, 693-696.

The great rarity of specific alterations in nerve trunks pathognomonic of leprosy induced the authors to search for a series of indications that would together make the diagnosis of leprosy most likely in patients in whom skin lesions were absent or equivocal. They selected patients with only a single nerve apparently damaged and proceeded to investigate the other main peripheral nerve trunks. In these 59 patients, they determined the following 3 values: qualitative electrodiagnosis, electromyogram and measurement of the motor conduction velocity.

They found that the motor conduction velocity was the most sensitive indication of nerve damage in the absence of any clinical evidence of such damage. They insist that examination of a length of nerve (e.g., the median) should be done segment by segment since examination of the whole nerve may not disclose considerable local damage. They adduce some evidence that the initial site of damage may be in the vicinity of the fibro-osseous tunnels along the course of the nerve. It is regretted that no investigative apparatus exists for the precise measurement of sensory loss; in leprosy, such loss generally precedes gross motor deficit.

As a matter of practical advice, the authors suggest that, when a patient presents with evidence of ulnar nerve damage in the absence of unequivocal indication of the cause, the nerve conduction velocity of the contralateral ulnar nerve and other nerve trunks should be investigated.

S. G. Browne

4. THERAPY

116. FIELDSTEEL, A. H. & LEVY, L. **Dapsone chemotherapy of *Mycobacterium leprae* infection of the neonatally thymectomized Lewis rat.** *Am. J. Trop. Med. Hyg.*, 1976, v. 25, No. 6, 854-859.

"In order to learn whether the neonatally thymectomized Lewis rat (NTLR) infected with *Mycobacterium leprae* could serve as a model for chemotherapeutic studies in a situation resembling that found in human lepromatous leprosy, NTLR inoculated with *M. leprae* either locally or intravenously 9 to 16 months earlier were treated for from 1.5 to 8.5 months with dapsone (4,4′-diaminodiphenylsulfone, DDS) incorporated in the rat chow in the concentration providing the minimal inhibitory concentration of the drug for *M. leprae* and in the 100-fold larger concentration. NTLR were killed at intervals; the *M. leprae* were counted and passed to mice. Treatment with the smaller dosage of dapsone neither killed *M. leprae* nor reduced the number of organisms in the bacterial populations, whereas treatment with the larger dosage both killed *M. leprae* and reduced their numbers. The rate at which the organisms were killed (i.e., rendered noninfective for mice) was much the same as that in patients treated with dapsone in comparable dosage. The dead organisms were removed from the rat tissues at a faster rate than encountered in patients. The NTLR may indeed be suitable for chemotherapeutic studies relevant to man. In addition, the more rapid disappearance of dead *M. leprae* from the rat tissues may facilitate the study of treatment regimens designed to eradicate persisting viable organisms."

117. HASTINGS, R. C., JACOBSON, R. R. & TRAUTMAN, J. R. **Long-term clinical toxicity studies with clofazimine (B663) in leprosy.** *Int. J. Lepr.*, 1976, v. 44, No. 3, 287-293.

"Fifty-one leprosy patients receiving long term clofazimine, have undergone systematic clinical laboratory testing in a search for any toxicity secondary to the drug. In approximately 220 patient-years of observation and in analyzing approximately 40,000 test results, no statistically significant changes in the direction of abnormality have been observed in SGOT, thymol turbidity, serum globulins, uric acid, alkaline phosphatase, white blood cell count or differential, hematocrit, hemoglobin, BUN, serum creatinine, serum cholesterol, serum albumin, serum potassium, serum calcium, stool for occult blood, routine urinalysis, or reticulocyte count. Statistically significant changes toward abnormallity were found in fasting blood sugar and total serum bilirubin. These statistically significant changes in the direction of abnormality were of small magnitude, were not associated with related clinical signs or symptoms, and do not seem to be of major clinical significance. Despite the accumulation of relatively massive amounts of the drug in various tissues, clofazimine appears remarkably free of serious or life-threatening toxicity clinically. Although the skin and gastrointestinal side effects of clofazimine limit its usefulness, on the evidence to date, its advantages outweigh its disadvantages in those leprosy patients for whom it is indicated."

118. JACOBSON, R. R. & HASTINGS, R. C. **Rifampin-resistant leprosy.** [Correspondence.] *Lancet,* 1976, Dec. 11, 1304-1305.

This letter to the editor reports on a patient with sulphone-resistant lepromatous leprosy who experienced clinical and bacteriological relapse while on rifampicin monotherapy, the first case of rifampicin-resistant leprosy confirmed by mouse footpad studies. The spectre of multiple drug-resistant leprosy bacilli suggests the importance of multiple drug therapy as routine.

T. F. Davey

119. COURBIL, L., J., MERRIEN, Y. & CARAYON, A. Réactivation proximale des muscles intrinsèques des doigts les paralysies cubitales de la lèpre. **[Proximal reactivation of the intrinsic muscles of the fingers in cases of cubital paralysis of leprosy.]** *Bull. Soc. Méd. Afr. Noire Lang. Fr.,* 1976, v. 21, No. 4, 425-428.

"In cases of cubital paralysis of leprosy, the authors describe a technique for the reactivation of the intrinsic muscles, at the level of the palm of the hand, by sectioning the large palmar muscle at the wrist and its extension by four narrow strips of fascia lata.

"Concerning 12 cases, they analyse the technical problems posed by this operation and its results."

120. DIGOUTTE, J. P., ROCHE, J. C., BRULE, M. & GAILHBAUD, M. Traitement des lèpres lépromateuses par le B.C.G. itératif à dose croissante. **[Treatment of lepromatous leprosy with repeated increasing doses of BCG.]** *Bordeaux Méd.,* 1977, v. 10, No. 11, 703-706.

The English summary appended to the paper is as follows:—

"Following Ruscher's research on the treatment of leprous leprosy by B.C.G. injected with increasing and repeated doses, a similar experiment was carried out on a group of 21 patients considered as being leprous.

"The treatment with B.C.G. was always associated with a specific chemotherapy, comprised first of all of a daily absorption of 'Rifampicine,' followed by a treatment with 'Disulone' and with 'Lamprene'. Each patient received the B.C.G. injections every fortnight over a period varying from 15 to 18 months.

"Tolerance to the treatment was good. At most, a few necrotic lesions were observed at the point of injection, which rapidly disappeared.

"The clinical results are good, as out of our 21 patients, only 1 did not show any marked improvement, 14 were blanched, and 6 present only a few bacillae that are greatly altered. On the immunological plane, based solely on the interpretation of the Mitsuda, only 5 reactions proved to be positive.

"On the other hand, the histological results carry a more varied interpretation, as even after the colour-change of a Mitsuda, 3 out of 5 patients maintained an interpolar aspect of their lesions upon the final biopsy.

"We have recently given patients with an indeterminate negative Mitsuda form the benefit of this therapy with encouraging results."

[See *Trop. Dis. Bull.,* 1974, v. 71, abstr. 2277.]

121. LOUVET, M., SAINT-ANDRÉ, P. & GIRAUDEAU, P. Traitement médical des maux perforants plantaires lépreux. (A propos de 34 observations.) **[Medical treatment of perforating ulcers of the foot in leprosy.]** *Méd. Trop.,* 1976, v. 36, No. 5, 429-433. English summary (7 lines).

Following a short clinical description of neuropathic plantar ulceration, all too commonly seen as a late complication of tuberculoid leprosy, the authors briefly refer to the aetiological factors (nervous, vascular and traumatic) and the appropriate treatment (neurolysis, periarterial sympathectomy and protection, respectively).

They then summarize the results obtained in an uncontrolled series of 34 patients suffering from plantar ulcers. In addition to bed rest, local treatment, and plaster of Paris immobilization, they considered that the administration by injection of extract of *Centella asiatica* (Madécassol) accounted for the good results obtained—healing of three-quarters of the ulcers in an average of 45 days. [This conclusion is not supported by the evidence given.]

[See also *Trop. Dis. Bull.,* 1960, v. 57, 252.]

S. G. Browne

5. EPIDEMIOLOGY AND CONTROL

122. KOTICHA, K. K. & NAIR, P. R. R. **Antileprosy measures in Bombay, India: an analysis of 10 years' work.** *Bull. Wld. Hlth Org.,* 1976, v. 54, No. 1, 67-77.

This is a valuable addition to the series of papers which reflect the vigorous campaign against leprosy being waged in a city where the problems are immense. Imaginative educational activities in leprosy are given great importance and are believed to be responsible for the fact that the majority of patients with early leprosy attend clinics on their own initiative. Case detection by screening schoolchildren for leprosy is useful and inexpensive, and it is intended to extend this to industry. Case holding is an even higher priority. Trials have confirmed the effectiveness of chemoprophylaxis with dapsone for contacts of infectious index cases in crowded households. Useful recommendations are made regarding urban leprosy control measures.

T. F. Davey

123. VERMA, O. P. **Some epidemiological features of leprosy in a rural area in Hooghly district.** *Lepr. India,* 1976, v. 48, No. 4, 371-381.

An intensive leprosy survey of 5 contiguous villages in the Hooghly District of West Bengal is reported, in an area where the prevalence of leprosy was thought to be negligible. Coverage was 92.8% (males 91.2%, females 94.8%). A leprosy prevalence rate of 4.5 per thousand out of 3314 people surveyed was obtained; over 60% of cases were in children of school age and 75% of cases had developed in the 2 years preceding the survey. Only 1 lepromatous case was found and the distribution of cases led to the conclusion that contact investigation on its own cannot suffice to bring to light either total cases or total people susceptible.

T. F. Davey

124. SEHGAL, V. N., REGE, V. L. & KHARANGATE, V. N. **Epidemiological and clinical pattern of leprosy in Goa.** *Lepr. India,* 1976, v. 48, No. 4, 382-390.

"A review of 1,053 patients of leprosy revealed its prevalence in the hospital population as 2.4 per thousand. The commonly affected age group was 20-39 in both sexes; males predominating females in 1.8:1. The sequence of frequency of clinical types of leprosy was tuberculoid, borderline, neuritic and lepromatous. Mostly the patients reported in the course of 2 years of awareness of the disease. The clinical features were classical and type specific."

125. BELDA, W. Aspectos epidemiológicos da hanseníase no Estado de São Paulo, em 1974. **[Epidemiological aspects of leprosy in the State of S. Paulo, Brazil, in 1974.]** *Hanseno gia Int.,* 1976, v. 1, No. 1, 11-24. English summary.

The 1907 cases of leprosy registered during the year 1974 are analyzed according to regional distribution within the state, the locality in which the patient was living when the disease began and various socio-economic factors. Although São Paulo is one of the main foci of the disease within Brazil, the problem has attracted little administrative interest in the past and the treatment remains protracted.

Ann Grant

6. SOCIOLOGY AND REHABILITATION

126. MEHTA, J. M. **Occupational therapy in leprosy.** *Int. J. Lepr.*, 1976, v. 44, No. 3, 359-365.

"This paper presents a broad discursive assessment of the philosophy and practices of occupational therapy as related to leprosy. It stresses the role of society, self-care by the patient, integration, vocational training, rehabilitation and the amotivational syndrome, and presents some illustrative original innovations. In conclusion some new approaches are suggested."

Thanks are due to the Director, Bureau of Hygiene and Tropical Medicine for permission to reprint Abstracts from *Tropical Diseases Bulletin* May, June and July 1977.

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