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Editorial

LEPROSY—EAST AND WEST OF SUEZ

The invited articles dealing with leprosy control that have appeared in the pages of the last two issues of *Leprosy Review* provide an interesting and, in many ways, salutary conspectus of typical situations. They emphasize the extremely wide range of factors that have to be considered in formulating and executing plans of campaign. It is not only that prevalence rates differ from one country to another, but that a whole series of factors—social, economic, geographical, financial, to mention a few—vary in importance and in their influence on the dimensions and the tractability of the leprosy problem. The attitudes both of the common people and of those who lead and govern, compounded as they are of historically conditioned and deep-seated beliefs, determine in large measure the degree of success or failure of any plan of action, however well conceived.

A medical factor that bursts forth repeatedly through these factual reports of the field application of control measures is the wide variation in the pattern of clinical leprosy. Individual lesions, and individual skin and nerve responses may, of course, be matched between one country and another, but the *ensemble*, the overall picture, of leprosy varies within wide limits. The low lepromatous/tuberculoid ratio and the low population densities in Africa may account for the confident optimism and relative satisfaction with present-day chemotherapy that characterize workers in that continent. Although it may be that in time regular, frequent and complete whole population surveys east of Suez would disclose more patients with indeterminate and tuberculoid leprosy than today's estimates suggest, the fact remains that, among diagnosed patients, there is a higher proportion of serious multibacillary (lepromatous and borderline), progressive leprosy in India and the East generally. (Incidentally, the numbers of self-reporting patients with severe deformities and mutilations and eye damage should alert public health authorities to the probability that the prevalence of leprosy may be much higher than they imagine.)

In the East, moreover, there is a higher proportion of patients with borderline types of leprosy who show clinical and immunological deterioration. Not only does leprosy appear to install itself widely in the body, but it progresses rapidly, causing early—even precocious—symmetrical polyneuritis, and early and severe eye damage. The skin lesions are succulent; sensory loss in the ulnar nerve distribution may be an early sign of impending rapid paralysis of the intrinsic muscles of the hand; facial palsy, unilateral or bilateral, is a common and not always a late sign. These intermediate varieties are unstable and unpredictable, with a distinct tendency towards the lepromatous. The proportion of patients with polar tuberculoid leprosy is lower to the east of Suez than to the west, and in the extreme east (e.g. Japan) well-defined hypochromic flat lesions, with or without papular borders, are uncommon. Associated with this fact is the occurrence, at the other extreme of the immunological spectrum, of rapidly progressing lepromatous disease, involving the entire skin and upper respiratory mucosa, with alopecia and early madarosis, and early widespread polyneuritis.

Reactional episodes, too, east of Suez tend to be more frequent, more severe and more prolonged. The rise in body temperature is higher and more sustained. Individual nodosal elements show a greater tendency to persist and to ulcerate; they may appear in greater numbers and in unusual situations (e.g. the pretibial skin). Eye damage occurs earlier, and more frequently, allergic iridocyclitis appearing in patients whose disease may have been classified as borderline. Arthralgia is more common, as is effusion into the joints, particularly the knees and elbows.

Histologically, these lesions of near-lepromatous leprosy are characterized by a highly bacilliferous granuloma, with scanty round cells and minimal focalization. The nerve fibrils show early damage, and are infiltrated with both

inflammatory cells and bacilli. Huge multinucleate globi containing 200 or more bacilli are not uncommon. The bacillary concentration in tissues removed from the region of the eyebrows and chin is marked. The response to treatment of the underlying disease, as well as that of the reactional episode, is more uncertain and in general slower.

These, then, are the broad clinical differences noted between leprosy as seen east and west of Suez. The bacilli inoculated into the mouse foot-pad, whatever their "country of origin", appear to multiply in similar fashion; in other words, no strain differences are apparent, to judge from this isolated criterion of capacity to multiply in the non-natural immunological and biochemical micro-environment of the mouse foot-pad. If the "seed" possesses no inherent significant modifying properties that would account for the epidemiologically important variations observed, the "soil" may eventually prove to be the changeable factor. Recent work on genetically-determined response patterns may provide the explanation.

Meanwhile, faced with the practical problems of leprosy control in these varying contexts, the field worker must apply existing knowledge in the best possible way for the sake of the present and future generations.

5th Technical Meeting of OCEAC, Yaounde, 4-7 March, 1970

OCEAC (Organization de Co-ordination pour la Lutte contre les Endémies en Afrique Centrale) is the co-ordinating body of the "Services des Grandes Endémies" in several countries, viz. the Federal Republic of the Cameroons, the Central African Republic (RCA), The Peoples' Republic of the Congo, Gabon, and Tchad.

Reports presented at the 5th Annual Meeting on the leprosy situation in 1969 for these countries, supplied the following data:

Countries	*Total cases*	*Prevalence per* 1000	*New cases,* 1969
Eastern Cameroon	5899	5.4	1160
Western Cameroon	49,660	11.6	3018
Congo	15,940	16.5	526
Gabon	9620	20.3	574
RCA	31,380	20.3	989
Tchad	35,617	11.4	1852

Trends in prevalence and case-detection from 1966 to 1969 in the 5 countries (except Western Cameroon) were as follows (per 1000 of the population):

	1966	1967	1968	1969
prevalence	17.2	15.7	14.0	12.9
incidence	0.90	0.87	0.75	0.70

From 1960 to 1969, a total of 98,166 leprosy patients were detected. During the same period 179,644 patients were removed from the register (discharged, deceased, etc.). From the beginning of leprosy control activities, 51,397 patients had been declared cured. Out of 148,116 patients registered on 31 December, 1969, 64,597 were either inactive and under surveillance, or discharged (43.6%). As emphasized by Dr. Labusquière, the general-secretary of OCEAC, it is worthy of note that countries that have concentrated on systematic out-patient treatment, such as RCA and Tchad, have a higher proportion of patients in whom the disease has become quiescent (77.0 and 63.6%, respectively) than countries, such as the Cameroons, where the main effort has been concentrated on leprosaria (43.6% of inactive cases in Western Cameroon).

The original scientific contributions presented at the meetings are to be published. Mention should be made of papers by General J. Languillon on the treatment of lepromatous leprosy by long-acting sulphonamides (Fanasil) and dapsone in low dosage, and the paper by Professor M. F. Lechat on epidemiometric models for the evaluation of leprosy control activities.

ELEP Medical Commission

The Medical Commission of ELEP (The European Federation of Anti-Leprosy Associations) met in Luxembourg on 21 March, 1970, under the chairmanship of Dr. L. P. Aujoulat. At the Annual General Assembly the following day, important reports from the Commission were presented on such matters of policy as: the pros and cons of the segregation of patients with lepromatous leprosy; the separation of children from parents suffering from leprosy; the principles of barrier nursing as applicable to leprosy patients in the wards of general hospitals. A document entitled *Guidelines and principles in the worldwide campaign against leprosy*, drawn up by the Medical Commission with a view to assisting both non-medical administrators in the evaluation of projects and doctors in the choice of priorities, was received with expressions of gratitude.

The following additional members were appointed to the Medical Commission: Professor P. G. Janssens (Belgium), Professor M. F. Lechat (Belgium), Dr. E. Montestruc (Martinique), and Dr. K. F. Schaller (Germany). Dr. Ernest Muir, the doyen of European leprologists, was accorded the high distinction of being elected *Membre d'Honneur* of ELEP.

The member-organizations agreed to continue their policy of devoting a certain proportion of their income to the fostering of research and the publication of the results of research in *The International Journal of Leprosy and Other Mycobacterial Diseases*.

The Leonard Wood Memorial was welcomed as an Associate member of ELEP.

The voluntary agencies play a considerable rôle in the campaign against leprosy. Through consultation, co-operation in joint projects, and the prevention of overlapping and duplication of effort, ELEP is in process of achieving its aims. The Medical Commission, by its advice on specific projects and its insistence on priorities in leprosy control, is helping to mould opinion and ensure that public interest is based on established scientific principles as well as on humanitarian considerations.

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The Use of B 663 (Clofazimine) in the Treatment of Chinese Leprosy Patients with Chronic Reaction

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This report confirms earlier impressions of the usefulness of B 663 in the treatment of chronic reaction in Chinese leprosy patients and gives the results of investigations made over a 2-year period. (This paper should be read with reference to Dr. Warren's previous paper in *Leprosy Review* (1968) Vol. 30, No. 2, p. 61.)

INTRODUCTION

The report of the interim findings at 6 months in a trial of the use of B 663 in the treatment of Chinese leprosy patients with chronic reaction (Warren, 1968) is completed by this supplementary report. The trial concerned 30 patients and details of their selection and of procedure are given in the original report.

RESULTS

The initial patient (MW, F/25) continued to make good progress on a maximum dose of 600 mg of B 663 (clofazimine) per week, which was later reduced slowly until she was reaction-free on 200 mg per week. She requested the withdrawal of B 663 after 21 months of treatment when her bacterial index (BI) was 1.5, and the resumption of treatment with DDS. This was agreed to, as she had been free of reaction for 6 months, and DDS was recommenced. On a dosage of DDS ranging from 25 mg to 50 mg per week, however, she gradually developed increasing amounts of erythema nodosum leprosum (ENL), and eventually in the sixth month after stopping B 663 she developed arthritis, neuritis, and many attacks of ulcerated ENL. She then requested that treatment with B 663 be resumed. Her skin coloured had faded considerably at this time. After about 6 weeks on B 663 at 600 mg per week she was again almost reaction free and well enough to return to work. She has continued taking B 663 for a further 12 months and her BI had fallen to 0.7. She has been totally free of reaction for 4 months on 300 mg of B 663 per week.

This experience warned us of the dangers of stopping B 663 in a patient with a relatively high BI, who previously had been reaction-prone even when not receiving any antileprotic drugs. A similar return of lepra reaction has been seen in a number of patients who stopped B 663 too early.

Group A

The 4 patients previously receiving prednisolone have not required further prednisolone.

Patient No. 1 (*F*/30) continued to require 1200 mg of B 663 weekly; any reduction in this dosage allowed reaction to return, but her BI has now fallen satisfactorily, if slowly, from 3.3 to 2.2 in 2 years and her general physical condition is much improved.

Patient No. 2 (*F*/46) continued to be reaction-free on 900 mg of B 663 per week, but a reduction to 600 mg per week was accompanied by a return of reaction, with ulceration, so the dose of B 663 was increased to 1200 mg per week and maintained there for 6 months, when she was definitely free of reaction. However, as her BI did not fall, she became very depressed and requested addition of IMI sulphetrone; this was granted in the twentieth month of B 663 treat-

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TABLE 1

Progress of Group B patients receiving B 663

Patient No.	*Sex, age in 1967*	*At commencement weight (lb.)*	*BI*	*At 12 months weight (lb.)*	*BI*	*At 2 years weight (lb.)*	*BI*	*Max. dose given per week (mg)*	*Estimated optimum dose per week (mg)*	*Remarks*
6	M/50	105	2.7	121	1.5	113	1.0	900	300	On 300 mg no reaction, but reaction recurred on 200 mg per week.
7	F/35	92	1.5	103	0.5	103	0.2	300	200	Reaction settled at once.
8	F/60	88	3.7	98	2.7	100	2.5	300	300	Good control of reaction.
9	F/43	105	2.7	113	1.3	Refused		600	400	Good control of reaction.
10	M/21	108	3.3	128	1.0	132	0.2	1200	600	ENL recurred as dose reduced.
11	M/27	109	2.0	118	1.0	116	0.5	1200	600	Reaction rapidly controlled, but returned when dose reduced.
12	M/35	106	3.5	106	2.5	113	2.2	600	500	Reaction rapidly controlled.
13	M/49	125	1.5	129	0.2	133 on DDS	Neg. 8 mths	600	400	Reaction rapidly controlled.
14	M/44	111	2.5	122	1.0	124	0.2	900	300	Rapidly controlled on 600 mg per week.
15	F/28	95	3.5	102	2.2	Refused		600	400	Good control.
16	F/55	108	1.2	113	0.2 Stopped	Discharged on DDS	neg.	600	300	Very good control.
17	M/49	130 Oedema	4.0	125	3.3	125	2.3	1200	400	Very good control.
18	M/53	130	3.7	144	2.2	144	1.3	900	700	Very good control.
19	M/31	118	2.5	120	2.2	118	2.0	1800	1200	Persistent ENL and neuritis till prednisolone self medication disclosed.
20	M/38	120	3.0	124	1.7	128	1.0	900	600	Very good control of reaction.
21	M/38	88	3.0	98	1.7	96	0.8	1200	900	Good control of reaction when on 900 mg, but reaction returned on lower dosage.

ment. The dosage of the latter has been reduced slowly, and she is now receiving 300 mg of B 663 weekly and 3 g weekly of sulphetrone by injection. She has had no reaction for the past 12 months, her BI is 0.8, and her general condition is excellent.

Patient No. 3 (*M*/35) required a maximum of 900 mg of B 663 weekly to control reaction. The dosage was then reduced, but after 8 weeks on 400 mg weekly he developed multiple small pustular reactional lesions on the hands and feet, so an increased dose of 600 mg of B 663 weekly was resumed. The fall in the BI has been slow but fairly consistent. This patient realizes that he is physically better and his general outlook has improved immensely.

Patient No. 4 (*F*/35) required 8 months for total weaning off prednisolone. During this time her BI hardly altered, but then fell dramatically over the next 12 months. Reduction of the dose of B 663 to 300 mg per week caused no problems. Her BI fell from 2.8 to 0.8 in 2 years and she is now fully active, after being a bed patient for over 2 years.

The general impression is that patients who have been receiving prednisolone require a higher dosage of B 663 for longer periods than patients with other forms of reaction. We now

TABLE 2
Progress of Group C patients receiving B 663

Patient No.	*Sex, age in 1967*	*At commencement weight (lb.)*	*BI*	*At 12 months weight (lb.)*	*BI*	*At 2 years weight (lb.)*	*BI*	*Max. dose given per week (mg)*	*Estimated optimum dose per week (mg)*	*Remarks*
22	M/41	114	2.5	122	1.5	119	1.3	1800	900	Reaction returned after a few weeks on 600 mg per week, but keeps well on 900 mg per week.
23	M/41	109	2.3	118	1.7	106	1.3	1200	600	Neuritis and reaction rapidly controlled on 600 mg—tried high dose as no BI fall.
24	M/33	106	2.3	110	1.3	112	0.8	900	900	Neuritis rapidly returned when reduced below 900 mg. Problem patient. Prednisolone self-medication eventually disclosed.
25	F/36	96	1.5	116 then stopped B 663	0.3	Now discharged		900	900	Neuritis settled quickly and no return on reduced dose.
26	M/40	105	2.0	104	1.5	106	1.0	1200	600	Required 1200 mg to stop neuritis and no reaction after that.
27	M/26	102	3.5	104	2.8	102	2.2	1200	1200	Neuritis returns after 900 mg for a few weeks, but very well on 1200 mg. Nerve function is improving.
28	M/37	108	4.2	117	2.8	126	1.8	1200	400	Occasional ENL and slight neuritis on 300 to 400 mg per week, but general attitudes have improved. He now works.

recommend that they receive 1200 to 1800 mg of B 663 weekly at the commencement. Reduction of the dose of B 663 is usually proceeded with slowly, and probably should not go lower than 600 mg weekly while there is any suggestion of reaction. It is observed that the BI frequently does not fall to any extent while the patient is still on prednisolone.

Group B

This group comprised 16 patients with chronic reaction, and their progress is summarized in Table 1.

An attempt was made to estimate the optimum dose of B 663 for each patient, that is, the minimum dose that prevented the return of reaction.

Two patients refused to continue taking B 663, giving the resulting skin discoloration as the reason. One of them (Patient No. 15) had shown a dramatic fall in the BI initially while on B 663, but refused to continue taking the drug because of this discoloration. She was therefore given DDS by mouth, the starting dosage being 50 mg weekly and gradually increasing. However, after 5 months, when receiving 100 mg of DDS weekly, she developed severe neuritis, especially of both median nerves at the wrist, the right being more severe than the left. She agreed to recommence B 663 at 600 mg per week while continuing the DDS, but later assented to stop DDS completely. A surgical decompression of the right median nerve was performed, with rapid relief of pain and re-

covery of function. She has agreed to remain on B 663 alone at present. A further 2 patients became negative and stopped B 663 treatment, but the others all completed 2 years' treatment and some are continuing for a third year. One patient (No. 19) was found to be medicating himself with prednisolone, but it is unlikely that the others in Group B did so.

Group C

This group consisted of 7 patients with neuritis as the main complication; all were controlled, but the average dose of B 663 was somewhat higher than in Group B. The neuritis was well controlled, but the level was often critical, and missing even 2 or 3 doses, each of 100 mg, in one week has precipitated neuritis in several of them. Their progress is summarized in Table 2.

In this group of patients nerve function was evaluated by a light-touch test, the areas of anaesthesia being entered on a chart, and also by voluntary-muscle tests to estimate the power of the muscles of the hands and feet. During the 2 years on B 663 a number of patients have shown improvement in muscle power. Increased sensory perception is not so obvious but has occurred in some patients.

Patient No. 24 developed an acute foot-drop on 10 October, 1967, that is 14 weeks after commencing treatment with B 663, but before the dose was increased to the level that was later found to be necessary to control his reaction and neuritis. By the end of the 2 years almost full muscle power had returned and improvement was still occurring. At the end of the 2 years this patient reported that he had been treating himself with prednisolone as an analgesic since before commencing B 663. His clinical condition and the response to sudden cessation of prednisolone do not support his story but it must be considered in examining his response to B 663.

Patient No. 25 had shown considerable weakness of the small hand muscles, increasing with each of many recurrent bouts of neuritis, before she commenced B 663. Within 9 months of starting on B 663 her voluntary-muscle tests had markedly improved and were virtually normal.

Patient No. 27 remained prone to neuritis even when on 900 mg of B 663 per week, and neuritis returned whenever he missed taking a few capsules. In June, 1969, he developed acute right median neuritis with gross enlargement and marked tenderness of the nerve, associated with muscle weakness and fibrillation. He had generalized neuritis at the time, and his dose of B 663 was increased again to 1200 mg weekly. A surgical decompression of the right median nerve was performed, and 3 months later he showed return of apparently normal power and sensation perception.

It would appear that neuritis will occur in some patients on B 663 even after many months of treatment, but at a suitably high dosage level neuritis does not occur and recovery of function may occur without further permanent neurological deficit.

Group D

Mr. G., aged 65, died after a coronary occlusion in the eighth month of B 663 treatment, but his general condition was much improved prior to his death.

Mr. K., aged 46, has continued to progress very well, his BI falling from 3.3 to 1.5 in 2 years. His diabetes is now completely controlled without drugs, and reduction of the dose of B 663 from 600 mg to 300 mg has been completed without trouble.

Group E

Relapsed patient (M/35) showed an initial good fall in his BI but this then became stationary and neuritis and reaction developed on a dosage of 900 mg weekly. In December, 1964, he had developed a right foot-drop, but this had gradually recovered until he had full power in the dorsiflexors of the foot in January, 1968. In April, 1969, 9 months after commencement of B 663, he developed an acute weakness of the dorsiflexors of the left foot. This was at a time when we were attempting to reduce his dosage of B 663 and he was receiving only 600 mg weekly. The dosage was therefore

TABLE 3
Response of patients changing from B 663 to dapsone

Patient No., sex and age	*Duration of B663 therapy*	*BI at change*	*Current dose of B 663 at date of change*	*Method of change*	*Commencing dose of DDS*	*Remarks*
M.W. (1) F/25	21 months, no reaction for 6 months	1.5	3/w	Change to	DDS 500 mg/w	Reaction slight within 3 weeks, but became severe. At 5 months she requested to restart B 663.
(2)	Further 13 months on B 663. No reactions for 3 months	0.7		Add DDS	25 mg/w	No reaction within 6 weeks. Increased DDS after 8 weeks.
2 F/46	15 months. No reaction for 6 months	1.3	12/w	Add IMI Sulph.	2 cc/w = 0.1 g Sulphetrone by injection	No reaction. IMI Sulphetrone increased to 6 cc weekly with B 663 at 3/w.
9 F/43	12 months. Had no reaction for 2-3 months	1.5	4/w	Sudden change to Refused more B 663	DDS 50 mg for 3 months then increased	Slight reaction only. Slow increase of DDS to 200 mg per week.
10 M/21	2 years	0.7	4/w	Add DDS	10-20 mg	ENL recurred within 3 weeks. Given B 663 alone again till BI 0.2.
11 M/27	2½ years	0.3	2/w	Add DDS	50 mg/w	No reaction for 4 weeks so stopped B 663.
14 M/44	2 years	0.3	3/w	Sudden	100 mg/w	No reaction.
15 F/29	9 months, refused more B 663 when no reaction for 3-4 months	1.2	5/w	Sudden change to	DDS 50 mg/w slowly increasing	Reaction returned at 100 mg (off B 663 under 6 months). Severe—see Case 15 details under Group B.
21 M/38	2 years	0.8	3/w	Sudden	50 mg/w	Reaction within 3 weeks. He requested to recommence B 663 alone.
	when restabilized		3/w	Add DDS	25 mg/w	Reaction in 2 weeks—so DDS stopped till BI lower.
22 M/41	18 months	1.5	18/w	Added IMI Sulph.	2 cc = 1 g/w	No reaction till B 663 dropped to 6/w then ENL recurred.
23 M/41	18 months	1.5	9/w	Add DDS	100 mg	No reaction—B 663 slowly reduced to 5/w. DDS increased to 150 mg/w then B 663 stopped.
31 M/45	13 months	2.7	12/w	Sudden change refused B 663	ASS ½ cc/w = 100 mg DDS	No real reaction for 3 months then recommenced ENL and neuritis with increasing severity.

increased and there has already been much recovery of muscle power, which is now nearly normal. He obviously required 1200 to 1500 mg of B 663 per week to remain free from reaction and neuritis, so the acute paresis occurred on a dosage that we now consider was too low for his needs.

A further 30 patients have been treated with B 663, some of them for reaction, with similar results, but usually with more rapid control due to the experience gained in this trial. This group of patients included a number with relapsed lepromatous leprosy who are apparently resistant to dapsone and/or to thiambutosine; it also included patients with borderline and atypical lepromatous leprosy.

TABLE 4

Serial haemoglobin and erythrocyte sedimentation rates for the whole group

Patient No.		*Haemoglobin (g%)*					*Erythrocyte sedimentation rates (mm/1st hour)*				
		Initial Value	*At 3 months*	*At 6 months*	*At 12 months*	*At 2 years*	*Initial Value*	*At 3 months*	*At 6 months*	*At 12 months*	*At 2 years*
1	F/30	10.2	10.2	9.9	10.2	10.5	80	68	45	65	50
2	F/46	10.5	10.2	11.4	12.0	11.4	72	52	27	28	45
3	M/35	10.2	11.4	10.7	11.4	12.8	72	45	52	70	60
4	F/35	10.7	9.2	10.2	11.4	12.3	73	102	22	36	40
6	M/50	11.4	9.5	11.0	11.7	9.9	110	80	50	55	75
7	F/35	8.8	11.0	12.4	12.1	12.0	109	63	34	68	
8	F/60	10.2	10.2	11.0	11.4	10.2	65	90	60	67	75
9	F/43	12.4	11.4	10.7	11.4	11.1	52	55	47	52	
10	M/21	10.2	9.9	10.5	12.0	13.7	108	60	55	43	37
11	M/27	11.0	11.4	11.0	12.1	13.1	105	73	65	40	5
12	M/35	11.4	11.7	10.2	11.4	12.3	48	36	76	30	31
13	M/49	12.8	11.4	11.7	12.4	13.4	81	45	35	32	
14	M/44	12.4	13.1	10.7	12.1	12.6	80	47	45	45	45
15	F/28	12.1	13.9	12.4	11.7	11.4	23	20	28	26	15
16	F/55	12.1	11.7	11.4	12.0		45	27	30	10	
17	M/49	9.9	9.9	11.0	11.7	13.4	82	40	38	15	8
18	M/53	11.4	11.0	11.0	12.1	14.3	120	65	33	30	12
19	M/31	10.2	10.2	10.2	11.4	12.3	108	110	78	76	25
20	M/38	10.2	11.0	10.5	11.7	13.6	106	113	70	56	61
21	M/38	8.8	9.9	11.7	12.4	14.0	70	23	20	33	15
22	M/41	9.9	9.9	9.9	11.0	12.3	94	58	37	52	48
23	M/41	11.7	11.4	10.2	11.4	12.0	92	72	84	52	18
24	M/33	9.9	9.9	9.9	10.2	10.8	74	75	70	35	34
25	F/36	10.7	9.5	10.5	11.4	11.7	108	53	20	38	
26	M/40	12.1	14.0	11.7	12.0	14.3	10	15	25	28	5
27	M/26	11.0	11.0	11.0	11.0	11.4	81	72	56	54	62
28	M/37	11.7	8.8	9.9	10.5	10.8	44	72	42	47	45
29	M/46	10.5	13.1	11.7	11.4	12.0	88	44	45	47	20
30	M/35	12.1	11.7	11.0	11.7	11.1	5	7	36	20	33

Normal values: male 13.5 to 18 g %; female 11.5 to 16.5 g %; male 0 to 15 mm/hour; female 0 to 20 mm/hour.

SIDE EFFECTS

Apart from the skin pigmentation no undesirable effects have been seen. Two female patients refused B 663 after 12 months' treatment because of skin discoloration, and several patients have refused to start taking the drug for the same reason.

DOSAGE LEVEL

We would now recommend for Chinese leprosy patients with reaction, the following dosage schedules:

(1) B 663 at 1200 mg weekly initially for patients with marked neuritis;
(2) B 663 at 1200 to 1800 mg weekly for patients dependent on prednisolone; and
(3) B 663 at 600 to 900 mg weekly for other forms of reaction.

If control of the reaction is not achieved within 6 weeks the dosage should be increased. The dose that controls reaction should be maintained for 3 months before any reduction is attempted, or, in the case of patients dependent on prednisolone, until the patient has been weaned from the latter for 3 months. The level of dosage does not appear to affect the rate of fall of the BI provided reaction is controlled.

CESSATION OF B 663 TREATMENT

Two patients in this trial requested the stopping of B 663 treatment while the BI was still high. Each of these patients developed increasing amounts of reaction until finally they asked for the resumption of B 663.

After this experience it was decided to vary the routine of change from B 663 to dapsone,

TABLE 5

Changes in blood protein levels of patients on B 663

Patient No.	*Serum Protein*					*A/G ratio*				
	Initial Value	*At 3 months*	*At 6 months*	*At 9 months*	*At 12 months*	*Initial Value*	*At 3 months*	*At 6 months*	*At 9 months*	*At 12 months*
1	6.7	7.0	6.8	7.4	6.2	2.1/4.6	2.9/4.1	4.5/2.3	3.6/3.8	3.0/3.2
2	7.9	6.1	6.4	7.2	6.7	4.3/3.6	3.5/2.6	4.5/1.9	5.3/1.9	4.3/3.4
3	7.9	6.9	7.2	7.9	5.4	2.8/5.1	3.2/3.7	4.5/2.7	4.1/3.8	3.3/2.1
4	8.1	6.7	7.4	8.1	7.4	3.3/4.8	2.5/4.2	4.1/3.3	4.6/3.5	3.8/3.6
6	7.8	7.6	6.7	8.0	7.0	2.5/5.3	3.4/4.2	4.0/2.7	4.1/3.9	3.3/3.2
7	8.2	7.6	7.4	8.0	7.6	3.3/4.9	3.5/4.1	4.9/2.5	4.3/3.7	4.3/3.3
8	7.8	7.1	6.6	8.8	7.1	3.0/4.8	3.1/4.0	4.2/2.4	4.1/4.7	3.6/3.5
9	7.8	7.1	7.0	7.1	7.0	3.2/4.6	3.5/3.6	4.0/3.0	4.2/2.9	4.0/3.0
10	6.8	7.3	7.1	8.0	7.2	1.5/5.3	3.0/4.3	4.0/3.1	3.1/4.9	3.4/3.8
11	7.1	8.0	7.4	7.8	7.2	1.6/5.5	3.5/4.5	4.5/2.9	3.8/4.0	3.7/3.4
12	6.8	7.0	6.5	7.4	7.8	3.0/3.8	3.6/3.4	4.2/2.3	4.1/3.3	4.6/3.2
13	7.0	7.2	6.1	8.2	8.0	2.6/4.4	4.0/3.2	4.0/2.1	5.1/3.1	3.9/4.1
14	7.6	7.5	7.5	8.3	7.7	2.4/5.2	3.6/3.9	4.6/2.9	3.5/4.8	4.3/3.4
15	7.6	7.5	6.3	7.8	7.6	3.2/4.4	3.6/3.9	4.2/2.1	4.3/3.5	4.1/3.1
16	6.7	6.7	7.0	7.3	7.0	2.7/4.0	3.5/3.2	4.5/2.5	4.1/3.2	4.3/2.7
17	5.9	6.8	7.0	7.9	7.2	1.3/4.6	3.3/3.5	4.0/3.0	4.7/3.2	4.3/2.9
18	8.2	6.6	8.1	5.7	6.95	2.3/5.9	2.6/4.0	4.1/4.0	2.7/3.0	3.8/3.15
19	7.7	7.5	6.9	7.7	6.6	2.4/5.3	3.4/4.1	3.9/3.0	3.9/3.8	3.6/3.0
20	6.9	7.7	6.8	7.7	7.3	2.6/4.3	3.6/4.1	3.6/3.2	3.8/3.9	3.9/3.4
21	6.9	6.3	5.5	6.3	6.1	2.9/4.0	3.7/2.6	3.5/2.0	4.2/2.1	4.3/1.7
22	6.6	6.3	5.9	6.7	6.4	2.8/3.8	3.2/3.1	3.5/2.4	3.2/3.5	3.1/3.3
23	7.7	6.7	6.7	7.7	6.7	2.7/5.0	3.3/3.4	3.9/2.8	4.0/3.7	3.5/3.2
24	6.5	6.2	5.9	4.2	5.5	3.0/3.5	3.6/2.6	4.1/1.8	2.4/1.8	3.2/2.3
25	7.9	7.4	7.4	8.0	7.7	2.7/5.2	3.3/4.1	4.7/2.7	3.8/4.2	3.5/4.2
26	6.3	5.5	5.6	6.8	4.7	3.2/3.1	3.2/2.3	3.7/1.9	3.8/3.0	2.8/1.9
27	6.6	7.0	7.3	7.8	6.6	2.0/4.6	3.1/3.9	4.9/2.4	3.6/4.2	3.2/3.4
28	6.6	6.1	6.7	6.4	6.1	2.4/4.2	3.1/3.0	4.1/2.6	3.7/2.7	2.9/3.2
29	7.3	6.0	6.1	6.3		2.9/4.4	3.5/2.5	3.6/2.5	4.0/2.3	
30	7.4	6.3	6.4	6.6	6.4	3.5/3.9	3.5/2.8	3.9/2.5	3.8/2.8	3.7/2.7

Normal value: 6.5 to 7.9 g %; albumin 4.2 to 5.2 g %; globulin 1.5 to 3.0 g %.

but as far as possible to continue with B 663 until the BI was under 0.5 (or at least under 1.0) and the patient had not had reaction for at least 6 months.

The routines adopted were:

(1) Sudden cessation of B 663 therapy and commencement of low dose dapsone; or

(2) Reduction of B 663 dosage to 200—300 mg weekly, and then addition of a low dose of dapsone, while maintaining the B 663 until the dapsone was increased to 100 mg weekly.

Table 3 summarizes the results of these treatment schedules. One patient who had been reaction-free for 6 months on 300 mg of B 663 per week was allowed to change over to dapsone when his BI was 0.2. Within 2 weeks, however, he had a recurrence of ENL and recommenced B 663 with resulting control of the reaction after 4 weeks.

Two patients whose BI was 0 when the B 663 was suddenly stopped had no trouble when changing from B 663 to DDS. Several other patients with a higher BI also had no recurrence of reaction associated with a sudden change from B 663 to DDS.

It was observed that it is very difficult to foresee how a particular patient will react, and whether a change from B 663 to DDS can be effected without a return of reaction. It is obviously desirable to have the patient completely free from reaction for some months on 200 to 300 mg of B 663 per week before trying to recommence DDS. We now usually give both drugs together for several months before stopping the B 663 completely.

LABORATORY INVESTIGATIONS

A series of laboratory and biochemical investigations were performed every 3 months for these 30 patients.

Table 4 summarizes the changes in the haemoglobin level and in the erythrocyte sedimentation rate (ESR). It will be observed that patients with anaemia at the start of B 663 treatment tended to show rising haemoglobin levels. The ESR was high in some patients at the beginning of B 663 therapy and tended to fall, though in many patients it did not reach normality (0 to 15 mm for males and 0 to 20 mm for females in the first hour) in the 2 years under observation.

Table 5 summarizes the changes in the serum protein levels and the albumin/globulin (A/G) ratio for the first 12 months of the trial. Unfortunately it was not possible to continue these estimations. It can be seen that there is definite reversal of the A/G ratio in many of the patients at the commencement of B 663 treatment but that this ratio had usually returned to near normal within 12 months.

DISCUSSION

The advent of B 663 has changed the whole outlook for our Chinese leprosy patients with reaction. Even the problem of the discoloration of the skin is usually outweighed by the obvious improvement of so many patients taking B 663, and also the fact that patients now know other patients in whom the colour has faded on cessation of the drug. The treated patients are also able to continue working and have spent much less time in hospital, so reducing the nursing care previously needed by many of them for long periods.

Over the years, in patients with borderline leprosy who develop acute paralysis we have come to expect a high degree of recovery of muscle power without the use of B 663. But those in the present series who have demonstrated returning function are patients with lepromatous and atypical lepromatous leprosy in whom we would not previously have expected a return of function. A longer study will be needed to ascertain how much permanent recovery has occurred or if increasing weakness occurs again when B 663 is stopped. This happened in one patient (No. 15) and recovery occurred again on resumption of B 663.

The laboratory findings support the impression that the patients generally show improved health after a period on B 663.

The use of dapsone together with B 663 did not have any obvious effect on the rate of fall of the BI, but did in a number of patients precipitate lepra reaction, which however settled again either on increased dosage of B 663 or on withdrawal of dapsone. In these cases the dapsone was added to the treatment only of a patient already stabilized on B 663, and who had not had reaction for some months. The dose of B 663 was not changed when the dapsone was started.

CONCLUSIONS

The rapid fall in the BI observed in the first 6 months was not maintained for the 2 years, but it is obvious that the fall in BI was on the average at least equal to that expected in similar but uncomplicated cases. In most patients the BI fall far exceeded that for the same patient in the previous 2 years.

The control of reaction was complete, and by adjusting the dose of B 663 other anti-reaction measures could be discontinued. The optimum dose of B 663 varies with the type of leprosy and with the severity of the reaction, and must be adjusted for each individual.

Patients showing an increasing nerve deficit before commencing B 663 showed some degree of, or complete, recovery of function of the affected nerve. There were some cases of new neuropathies developing in the first few months of treatment with B 663, but no nerve lesion that developed after 6 months on B 663 resulted in permanent marked loss of muscle power. The dose of B 663 can be adjusted so that neuritis does not occur even in patients who were previously neuritis-prone.

SUMMARY

Over a period of 2 years B 663 has successfully controlled chronic lepra reaction in its various forms in Chinese patients. At the same time it has obviously acted therapeutically, assisting in the elimination of the disease.

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Clinical Evaluation of Lamprene (Geigy) A Preliminary Report*

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The brief case histories here reported of 18 patients with leprosy, in come cases of long standing, show that treatment with clofazimine (B 663, Lamprene) brought about, in all but one case, improvement which ranged from good to remarkable. It is suggested that the drug may be particularly useful in treating patients intolerant of DDS.

INTRODUCTION

Favourable reports of the action of Lamprene (clofazimine) in leprosy encouraged us to carry out an uncontrolled trial at the above hospital.

PATIENTS

The series consisted of 20 patients in the following groups who were given Lamprene between June and September, 1967: (1) 7 new patients who had not previously received any antileprotic drugs; (2) 4 patients who had been in hospital for 2 years or more and whose progress had been greatly retarded by persistent erythema nodosum leprosum (ENL); and (3) 9 patients who had relapsed on one or more occasions and whose condition was deteriorating despite treatment. The types of leprosy in these groups are shown in Table 1.

TABLE 1

Type of disease	*Group* 1	*Group* 2	*Group* 3	*Totals*
Lepromatous	2	3	4	9
Dimorphous	4	1	5	10
Tuberculoid	1	–	–	1
Total	7	4	9	20

Of the 20 patients, 12 were males and 8 females, the majority being Fijian (9) and Indian (6). The youngest was a 19 year old Fijian male, and the oldest an Indian female aged 61.

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PROCEDURE

The usual taking of the case history was followed by routine blood tests, including haemoglobin estimation, blood red and white cell and differential counts, blood grouping, and examination for filaria. Serum protein estimation, but not electrophoresis, was done in 15 of the patients. Biopsies were performed, not less than 4 smears being taken from each patient. The Bacterial Index (B.I.) (Ridley, 1967) was checked regularly. Urine and stools were checked, and intestinal parasitoses treated before starting Lamprene therapy. Photographic records were taken before, during, and after the 12-month trial period. All patients were weighed initially and again at follow-up examination. Lamprene was given in a dosage of 700 mg per week, that is 1×100 mg capsule daily for 5 days and 2 capsules on the sixth day; none was given on Sundays. Patients were examined as regularly as possible—during the first 6 months every one or 2 weeks—for clinical evaluation of lesions. Only 2 patients were unable to complete the trial: one because of bilateral tuberculous pleural effusions, and the other because he developed pneumonia; the other 18 patients completed the 12-month preliminary trial, 6 in Group 1, 3 in Group 2, and 9 in Group 3.

CASE REPORTS

Group 1

T.M. 4104, male, Fiji-Solomon Islander, aged 28, single, admitted to hospital 4 weeks before

the trial started with a history of peripheral neuritis in both feet, progressive fatigue, puffiness of the face and ears, and oedema of the hands and feet. A diagnosis of lepromatous leprosy was made. During the first few months of treatment with Lamprene his condition failed to show any marked improvement, but during the sixth month his skin began to return to normal. Oedema then subsided slowly and he started to become active, improving steadily during the second 6 months of treatment when he was able to work in the hospital grounds. No ENL was experienced.

B.D. 4105, female, Indian, aged 61 years, admitted with dimorphous leprosy. At the end of the third month of Lamprene therapy there was definite improvement in the lesions, which gradually shrivelled during the fourth month. She continued to improve thereafter, without ENL reaction, and gained 9 lb. (4.1 kg) in weight.

Tara 4058, female, Indian, aged 19 years, admitted with nodular lepromatous leprosy. Again the initial response was slow, but after the first 3 months of treatment the discrete nodules over her back began to recede, followed after 6 months by those on the arms and face. During the last 2 months of the trial her clinical appearance improved remarkably (see Fig. 1, a, b). No ENL reaction occurred during the 12-month trial period and the patient gained 12 lb. (5.4 kg) in weight. Because this patient's skin is normally very dark, the colour change seen in patients treated with Lamprene was barely noticeable.

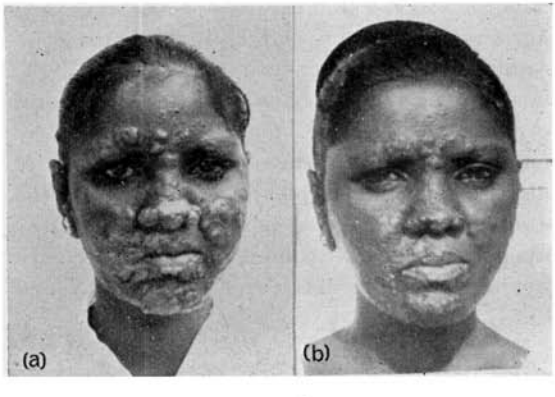

FIG. 1
Tara, 4058. 19-year-old Indian girl of Group 1 type. (a) Before Lamprene treatment; (b) after treatment with Lamprene.

T.T. 4108, male, Banaban, aged 21 years, was admitted suffering from pulmonary tuberculosis and dimorphous, lepromin-negative leprosy. He continued to receive anti-tuberculosis chemotherapy as well as Lamprene throughout the trial. Both lung condition and leprosy improved satisfactorily, the skin over his lesions beginning to shrivel from the eighth week of treatment and the infiltration receding rapidly. His grip strength improved from 10 lb (4.5 kg) (left) and 20 lb (9 kg) (right) to 50 and 60 lb (22.7 and 27.2 kg) respectively, and body weight from 128 to 152 lb (58 to 69 kg).

R.D. 4112, male, Indian, 52-year-old cane farmer, admitted with lepromin-positive tuberculoid leprosy (the only tuberculoid patient in this trial). Lesions were concentrated on the extremities and torso, and he had a right foot drop. Only 7 months after starting treatment with Lamprene no skin lesions could be seen, though the foot drop was still just noticeable.

A.L. 4114, 19-year-old male Fijian with very active dimorphous, pre-lepromatous leprosy; lepromin negative. After 3 weeks his condition deteriorated, with lesions becoming more active and oedema of the limbs and ears. Prednisolone, 10 mg daily, was added to the Lamprene therapy in the sixth week to control a febrile exacerbation. Although he had lost 8 lb (3.6 kg) in weight, his general condition improved and steroid dosage could be reduced and then finally withdrawn by the tenth week. (Doubling of the dose of Lamprene was considered but was not found necessary.) Two weeks later the patient was so much better that he could resume normal activity, including bicycle riding. After 5 months of Lamprene therapy his lesions had subsided remarkably (though heavily pigmented, they left no tissue-paper appearance), weight was increasing, and there was no further oedema. After an initial decline in weight from

136 lb to 128 lb (61.7 to 58 kg), his weight was up to 141 lb (64 kg) at the end of the trial.

Group 2

A.N. 3883, a 32-year-old Fijian female, was first admitted in 1961 suffering from lepromatous leprosy with an average B.I. of 6+. After 9 months' DDS therapy she developed bronchial asthma, followed by nodular reactions only partially controlled by steroids. Treatment with over 50 mg of DDS weekly then gave rise to ENL reactions. Thiambutosine was tried but proved unsatisfactory, and the patient continued to have periodic ENL reactions, with constant neuritic pains necessitating prolonged steroid therapy. After 9 days of Lamprene treatment her neuritic pain disappeared and, apart from one brief recurrence, there has been no further neuritic pain or ENL reaction; 11 months after starting treatment with Lamprene, steroid therapy was tapered off. The B.I. showed a dramatic response (see Table 2), and she gained 11 lb (5 kg) in weight.

L.C. 3938, Fijian female, aged 25 years, was admitted with lepromatous leprosy in 1962, with a B.I. of 6.0+. On a dosage of 200 mg DDS weekly she started developing neuritic pains and ENL reactions after 5 months. These were partially controlled by steroids, a reduction of the dosage of DDS to 10 mg weekly, and then by 9 months on thiambutosine. After 5½ years of treatment her B.I. had fallen to 3.75, but she was still having neuritic pains and ENL reactions. Five days after the start of treatment with Lamprene she developed another nodular reaction, but this completely subsided within 12 days. Since then there have been no further reactions, and her lesions have steadily improved.

J.N. 3964, male, part Chinese, aged 37 years, was admitted in 1963 with lepromin-positive dimorphous leprosy. The patient's ears were thickened, nodulated and generally puffy and his face slightly puffy with minimal madarosis. The nasal septum was collapsed and ulcerated and there were scars on the upper lip. Both auricular nerves were enlarged, and the ulnar, peroneal and popliteal nerves palpable and tender. Deep indurations were present in both upper and lower extremities accompanied by glove/stocking anaesthesia. The dosage of DDS reached 100 mg twice weekly before reactions and albuminuria interrupted his progress. Parenteral DDS therapy was tried during quiescent periods, with or without steroids, but

TABLE 2

Patient		*Sex*	*Type*	*Bacterial Index* *Before Lamprene*	*After 6 months*	*After 12 months*	*Clinical improvement*
TM	4104	M	L2	4.6	5.6	4.0	Marked
BD	4105	F	D—L/T	4.0	3.3	3.3	Considerable
Tara	4058	F	LL	4.6	5.6	4.0	Very marked
TT	4108	M	D—T/L	2.6	2.3	2.0	Marked. Lesions shrivelling
RD	4112	M	T	2.6	1.6	1.3	Macules less at 16 days. All lesions gone at 7 months
AL	4114	M	D—L/T	4.2	3.5	2.75	Remarkable—no ENL
AN	3883	F	L2	4.0	3.5	3.0	Marked
LC	3938	F	L3	3.75	3.25	2.0	Excellent
JN	3964	M	D Pre-L	4.5	3.5	2.5	Excellent
PV	4014	M	LL	4.5	4.0	3.5	Good
SN	4075	M	LL	4.5	4.75	4.5	Slow
PK	3950	M	D Pre-L	3.5	3.0	3.0	Remarkable. Sensations regained. Foot-drop disappeared
EF	4051	F	D Pre-L	3.0	3.5	3.6	Weight loss—no ENL
WM	4084	F	D Pre-T	4.0	3.75	3.5	Good
SB	4030	F	LL	4.4	4.0	3.8	Good. Dramatic bacterial response
MPR	3983	F	D Pre-L	3.5	3.2	—	Good—no ENL
PS	4110	M	LL	4.0	4.25	5.0	Marked
SR	3969	M	D Pre-L	5.5	4.8	—	Good

it was a continuous battle. However, 24 days after Lamprene treatment was begun the patient recovered from his last ENL reaction, and he has been steadily improving since. After the fifth month of treatment he was able to referee a football match, and during the sixth month he played volleyball with other patients. After 10 months on Lamprene his grip-strength had increased from 20 to 100 lb (9 to 45 kg) (right) and from 15 to 80 lb (6.8 to 36 kg) (left). Anaesthesia was slowly receding over the back of his legs and forearms.

Group 3

P.V. 4014, male Fijian 40 years of age, was first admitted in 1945 with lepromatous leprosy, treated with chaulmoogra oil, and discharged in 1961 on a dose of 200 mg of DDS weekly. He abandoned treatment 2 years later and was then without drugs for 2 years. Thereafter he relapsed and was re-admitted to Makogai in 1964 with lepromatous disease. After restarting DDS therapy he remained on an even keel for 6 months before developing skin irritation on a dosage of 400 mg of DDS weekly. Reduction of the dose to 300 mg weekly and antihistaminic drugs had no effect. A further reduction to 12.5 mg of DDS intramuscularly per week was made, but anaphylaxis continued, the patient becoming weaker and depressed, so that the drug had to be stopped completely. Streptomycin, 1 g daily, proved beneficial, but 5 months later he was given Lamprene instead, and since then there has been steady improvement. Irritation subsided, appetite improved, nerve pains cleared, he became physically active, and weight increased from 180 to 193 lb (81.6 to 87.5 kg).

S.N. 4075, male Fijian aged 31 years, was discharged from Tamavua Tuberculosis Hospital in March 1950 and admitted to Makogai Hospital 14 days later with lepromatous leprosy. After successful DDS therapy he was discharged in 1959. At first he continued to take 200 mg of DDS per week at home, but for some 18 to 20 months before his re-admission in 1966 with diffuse lepromatous leprosy he had taken none. Despite a low dosage of DDS when treatment restarted, he developed reactions requiring long periods in hospital and prolonged steroid therapy. Even when DDS was replaced by streptomycin, frequent ENL episodes persisted and the B.I. rose from 4.0 to 4.5. The clinical response to Lamprene was slow and less dramatic than in the other patients, but during the first 5 months of treatment he suffered only 2 bouts of mild ENL reaction, after the second of which he was weaned off steroids. Three more mild attacks of ENL during the following 7 months were controlled by short courses of steroids.

P.K. 3950, male Fijian aged 57, first admitted to Makogai in 1941 with lepromatous leprosy, had responded to amithiazone, but was allergic (manifested by exfoliative dermatitis) to this and several other drugs, and had a history of ENL. As a result, his B.I. (up from 3.0 to 3.5) and clinical condition had deteriorated. After 2 months of treatment with Lamprene his lesions were clearly receding; the nodules were flattening, and it was clear that Lamprene was the right drug for the long-standing and resistant disease in this patient. During the thirteenth week some nodules became almost as flat as normal skin, but most striking of all was the disappearance during the sixth month of an earlier right foot drop.

E.F. 4051, female Rotuman aged 59 years, was first admitted in 1937 with neural disease, was re-admitted in 1945 with lepromatous leprosy for which she was treated with DDS, and discharged in 1958. The patient confessed to being very irregular in taking her pills at home. She relapsed again and was admitted a third time with dimorphous leprosy. The second relapse was ushered in by severe irritation all over her body which seems to have been an anaphylactic reaction to a single large dose of DDS. On her third admission, the B.I. was only 0.75. Standard doses of DDS were tried, but her B.I. went up to 3.0 and the patient was then given Lamprene. She tolerated this drug well and her lesions cleared, but the B.I. is still rising. This phenomenon is still not fully understood, but it may be related to increasing

bacterial *density* in a shrinking granuloma. Probably because of polyuria, profuse sweating and her great activity, this patient has lost 23 lb (10.4 kg) in weight in 12 months.

W.M. 4084, female Fijian aged 38 years, was first admitted in 1945 with lepromatous leprosy and treated with chaulmoogra oil until 1958. The patient relapsed in 1962 but responded well to standard doses of DDS. She relapsed again less than 2 years later, however, and the disease was classified as dimorphous. She could not tolerate even small doses of DDS and had repeated reactions, for which steroids were given. Her B.I. on this third admission was 2.0, but it had increased to 4.0 by the time Lamprene was started. Thereafter her clinical response was slow but steady. She had 2 more reactions towards the end of the sixth month of the trial but was finally weaned off steroids in the eighth month.

S.B. 4030, a 51 year old Indian woman, was first admitted with lepromatous leprosy in 1941. Treated at first with chaulmoogra oil and later with DDS, she was finally discharged in 1963. She failed however to continue treatment at home and ultimately relapsed. On her second admission in 1965 she was again treated with DDS, but her condition became progressively worse, with leprides appearing on the trunk and numerous nodules over the buttocks. DDS was discontinued and thiacetazone tried, but this caused depression and was ultimately replaced by Lamprene. The initial clinical response to the latter was good, with increased appetite and general well-being but her condition later appeared to be stationary for some months. However, during the second half of the trial period the response became more evident and the lesions receded markedly.

M.P.R. (*T*) 3983, a female Samoan aged 30 years, had spent the 10 years 1946-56 in Makogai with lepromatous leprosy. Some 2 years after discharge irregularity in taking her drug had resulted in relapse of the leprosy, now of dimorphous type, and she suffered from episodes of ENL on restarting treatment in 1964 so that the dosage had to be reduced and steroids given in addition. Thiambutosine was also given, but had to be discontinued because of severe depression. Clinical improvement was noted from the very first week of starting treatment with Lamprene. No ENL recurred and steroids could be withdrawn 2 months later. The patient was physically active and gaining weight.

P.S. 4110, an Indian male 46 years old, was first admitted to Makogai in December 1948 with lepromatous leprosy and discharged in 1962. After irregularity in taking DDS the patient relapsed, was re-admitted to hospital in August 1967, and put on treatment with Lamprene 5 days later. After 3 months' chemotherapy his nodules receded markedly, with tissue-paper formation of the overlying skin. No ENL reaction was encountered throughout the period of trial, and the patient gained 12 lb (5.4 kg) in weight, though the B.I. is still rising. Closer observation is being carried out in this patient to evaluate why the B.I. is rising, although once again reduction of swelling may be the explanation.

S.R. 3969, male Indian aged 43 years, was originally admitted to Makogai in 1943 with lepromatous leprosy. Treated with chaulmoogra oil and later with DDS, he was discharged in 1955 but later relapsed as a result of defaulting on DDS treatment and was re-admitted to Makogai in October 1963. On re-admission he showed the 2 characteristic polar types of leprosy. Treatment with DDS was reinstituted with slowly increasing doses, but 2 years later, on a dosage of 800 mg weekly, he began to have nodular reactions and neuritic pains. Dosage was reduced to 20 mg per week and DDS finally discontinued in 1967, steroids being given periodically to control reactions. Before starting Lamprene the B.I. had reached 5.5 and he required constant nursing in bed. During 11 months of observation this patient had only 2 mild attacks of ENL (4 and 16 weeks after starting Lamprene). Steroids were ultimately withdrawn after 6 months. Lesions on the arms, legs, body and face are receding well and the patient is now doing strenuous

road maintenance work. His B.I. (see Table 2) declined to 4.8 after 6 months of treatment with Lamprene.

SUMMARY AND CONCLUSION

Of 18 patients suffering from all types of leprosy who have been treated with Lamprene for 12 months, 6 had received no previous treatment, while the remaining 12 had proved either intolerant or resistant to other forms of therapy. One patient responded poorly, but all the others improved during Lamprene therapy, the response being dramatic in several cases (see Table 2).

This trial confirms that Lamprene is the most exciting new drug to be introduced into the treatment of leprosy since the advent of DDS. It is not a "miracle drug"—the fact that no patient's disease was arrested after 12 months of continuous therapy proves that—but it is a most effective aid to treatment. For patients with ENL or those unable to tolerate DDS, Lamprene is undoubtedly an excellent substitute. It may, indeed, save their lives. However, it is as yet uncertain whether Lamprene will prove the better long-term drug in patients who can take DDS.

No resistance to Lamprene appeared in the 12-month period, but further trials are required to ascertain whether resistance will develop at a later date. Studies are also needed to determine whether patients who suffer from ENL during treatment with DDS can safely revert to that drug after a period of Lamprene therapy and subsidence of the acute reaction. It would also be interesting to know whether DDS and Lamprene have a synergistic effect, that is, whether patients receiving both drugs do better than those treated with either drug by itself.

ACKNOWLEDGEMENTS

My thanks are due to Messrs. Geigy Pharmaceuticals S.A. for supplies of Lamprene, and to Dr. Th. Ahrens of Geigy, Basle, for his assistance, advice and interest throughout the trial.

I am also indebted to Dr. C. H. Gurd, Director of Medical Services, Fiji, for permission to publish; to Dr. D. W. Beckett, Assistant Director of Medical Services, for the summary and conclusion, and to the nursing Sisters for their encouragement and help.

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Treatment of Leprosy with a Phenazine Derivative (B 663 or G 30 320)—Clofazimine*

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A report of good results obtained in 35 leprosy patients treated with B 663 (clofazimine)

The phenazine compound known as B 663 or G 30 320 (clofazimine) is a rimino compound obtained by progressive manipulation of a molecule of aniline aposafranine. It can be administered orally and if given in large doses is deposited in the principal organs and especially in the reticulo-endothelial cells. Like many other anti-leprosy drugs, it was first tried out in the treatment of tuberculosis. The Therapy Committee of the Eighth International Leprosy Congress at its meeting in Rio de Janeiro in 1963 advised a continuation of the trials started a short time previously, after noting its beneficial effects in the treatment of leprosy patients.

Browne and Hogerzeil (1962*a*) reported the results in 16 patients with lepromatous leprosy and concluded that B 663 had a beneficial clinical and bacteriological effect; this effect was enhanced by later adding DDS or, in some cases, ditophal. Browne (1966*b*) also drew attention to the anti-inflammatory effect of B 663 as seen in 10 patients with reactions controllable by steroids; he was able to eliminate steroid treatment gradually, by replacing it with B 663. This author also noted a suppressive effect on the lepra reaction in 26 lepromatous cases. Together with Hogerzeil (1962*b*) he described 5 cases in which after 12 months of B 663 administration a bacteriological resistance apparently developed but disappeared again as treatment was continued.

Pettit and Rees (1966) described 3 cases of DDS resistance which, when treated with B 663 for one year, showed clinical, bacteriological and histological improvement. They also noted the intense red coloration of the skin and the blue-black pigmentation of lepromatous lesions which had already been described by Browne (1966*a*). These authors, together with Ridley, Pettit *et al.* (1964), gave B 663 for 5 months to lepromatous patients previously untreated and obtained results comparable to those obtained with sulphone treatment.

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PERSONAL OBSERVATIONS

Number of patients, clinical type, dose and duration of treatment

The present study was carried out on 35 selected leprosy patients, of whom 30 had lepromatous leprosy, 5 with reactions, 3 were tuberculoid cases without skin lesions but with residual nerve involvement, one dimorphous case, and one indeterminate case. Of these 35, 10 of the lepromatous patients and the patient with indeterminate disease were previously untreated. Out of the remaining 20 lepromatous cases which had been treated previously (with sulphones or thiambutosine or long-acting sulphonamides) 5 had undergone intense reactions of erythema-nodosum type whatever the drug used. The other 15 and the dimorphic case had all shown resistance to these drugs.

Following the modern practice of using low doses of sulphones in treating leprosy, which results in equal effectiveness with a lower incidence of reactions, we gave 25 of the patients 100 mg of B 663 by mouth daily, the other 5 lepromatous cases acting as a control group

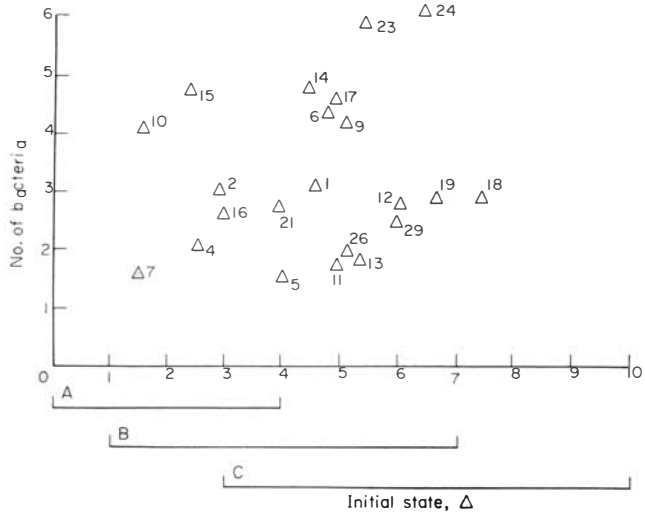

FIG. 1

Bacteriology. Morphological Index: A, typical agroupic bacteria (1); typical aislic bacteria (2-4); B, fragmented bacteria (1-7); C, granular bacteria (3-10).

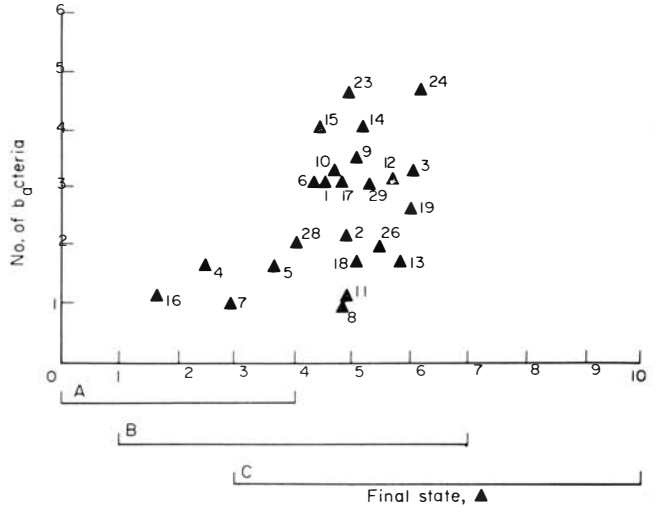

FIG. 2

Bacteriology. Morphological Index: A, typical agroupic bacteria (1); typical aislic bacteria (2-4); B, fragmented bacteria (1-7); C, granular bacteria (3-10).

on 300 mg daily. The 3 patients with tuberculoid leprosy, residual neural damage, and lepromatous reactions were also given 300 mg a day. The drug was administered for between 4 and 13 months. Of the 30 lepromatous patients, 2 have almost completed one year of treatment and 22 a period of 6 months.

RESULTS

Subjectively the patients were all content with the results of treatment and in general were not particularly disturbed by the red coloration of the skin. The objective clinical findings were as follows:

(a) The general condition of the patients remained unchanged, with no variation in body weight or appetite.

(b) In all cases, after one month of treatment the skin lesions showed less infiltration together with flattening, and this was very evident towards the sixth month. The lepromatous lesions mostly became frankly atrophic, with folds upon the surface and usually taking on a blue-black colour upon a skin which appeared xerodermic especially in the distal areas of the limbs. In 2 patients the skin became obviously ichthyotic; in the patient with an indeterminate condition the lesions disappeared completely by the sixth month.

(c) In the 3 tuberculoid patients with residual nerve damage and in 4 lepromatous patients who also had intense neuritis, the lesions improved after the second week of administration of B 663; the lightning pains disappeared, as also did the aching in the elbow and the sensations of formication and paraesthesia.

(d) In one patient with lepromatous leprosy and obvious lesions of the rhino-pharynx and larynx it was observed that after 6 months the nose became less congested, there was obvious healing in the pharynx and larynx, and the epiglottis was less infiltrated and more mobile.

Bacteriologically, within a month there was a fall in the bacillary count in most cases, with an increase in granulation in the bacilli. Fig. 1 shows a high bacillary index at the beginning

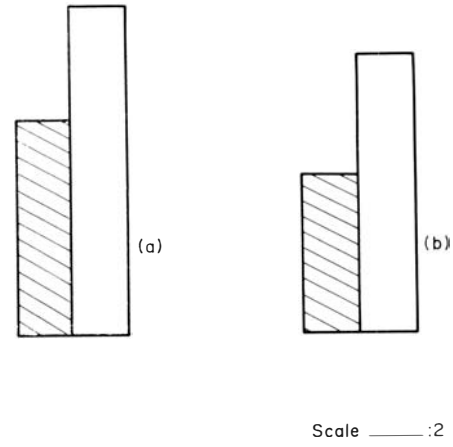

FIG. 3

Bacteriology—absolute values. (a) Initial, (b) final. The bacteriological index is shown shaded and the morphological index open.

of treatment with most of the bacilli lying within the range of morphologically normal grouped and isolated bacilli. Fig. 2 on the other hand, which represents a stage after treatment, shows that the bacillary index has fallen and the morphological index has stabilized within the middle range. Fig. 3 summarizes the findings in Figs 1 and 2 and demonstrates a significant change in the number of bacilli and a fall in the morphological index, with 3 negative cases. In the 2 lepromatous patients treated for one year no bacterial resistance has developed.

Histologically, the biopsy specimens taken during the early months of treatment showed favourable changes, consisting in a diminution in Virchow cells, and the appearance of fibroblasts in lepromatous cases with accentuation of tuberculoid structures; in the dimorphic case there was a diminution in lepromatous structures. Although there were changes in the number and morphology of bacilli, this was not so evident as the cellular change. Where the histological change was not very obvious, the patient had usually been treated previously with other drugs which had produced an improved and more or less stable histological and bacillary picture.

There were no significant changes in the lepromin reaction.

Tolerance, complementary studies

Tolerance of B 663 was good in all cases. The one notable secondary effect due to the drug was a red pigmentation of the whole skin, especially in exposed sites, which appeared after 15 days and was more obvious in those given 300 mg daily. After 4 or 5 weeks of treatment, it was found that the skin had become xerodermic and in 2 cases frankly ichthyotic.

No significant changes during treatment were detected at any of the 3-monthly laboratory examinations which included liver function tests and serum electrophoresis.

B 663 coloured the urine a yellowish-red and after 3 or 4 days of treatment there was a level of 0.005 to 0.015 mg of the drug per 100 ml of urine. No trace of the drug was detected in the cerebrospinal fluid. These studies were carried out on 13 patients receiving 100 mg of B 663 daily.

Reactions

None of the patients given 100 mg of clofazimine daily underwent a reaction, and on this dosage one steroid-dependent patient lost his dependency on steroids.

Out of 5 lepromatous patients given 300 mg of clofazimine daily, 4 had had an erythema nodosum reaction and one of these showed a typical Lucio phenomenon; reactions subsided in all cases with thalidomide administration. When treatment was resumed with 100 mg daily, the reactions did not reappear.

Comments

In spite of the short period of study and the small number of patients involved, which does not permit of a definite statement, we can say with certainty that B 663 has a clinical effect comparable with that of the sulphones and indeed acts even more rapidly. During the period of observation there was histological and bacteriological improvement, and a definite effect on nasal and laryngeal lesions and on specific neuritis was also observed.

The finding that patients in whom a leprosy reaction had been overcome did not have further reactions when the drug was resumed in the lower dosage of 100 mg, endorsed our view that B 663 should be used in small doses, since these will produce as good a therapeutic effect with a lesser incidence of reactions. Another argument in favour of this lower dosage is that patients who are attending as out-patients will have less skin pigmentation.

SUMMARY

Thirty-five leprosy patients with various clinical forms of the disease were treated with B 663 (clofazimine) for 4 to 13 months. An excellent clinical result was obtained, together with both histological and bacteriological improvement, on a dosage of 100 mg a day. Reactions were absent on this dose and the drug was tolerated perfectly.

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Lepr. Rev. (1970) **41**, 93-99

The Growth of *Mycobacterium leprae* in the Foot Pads of Swiss White Mice (Rockefeller Strain) Without Constant Thermoregulation*†

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One of the greatest advances in the study of leprosy during the last 10 years has been the development of a method of cultivation of *Mycobacterium leprae* in the laboratory in the foot pads of mice. It has been stressed that constant thermoregulatory devices are essential to obtain optimum growth of this organism when inoculated into the foot pads of mice (Shepard and McRae, 1965; Shepard and Habas, 1967). The high cost of providing optimum thermoregulatory devices, application of proper techniques of experimentation, and the non-availability of a steady supply of suitable mice appeared to be the main handicaps in the initiation of such studies, and this may partly be the reason why similar success has not so far been reported in India by workers making use of Shepard's technique.

Even though there is only a limited multiplication of *Myco. leprae* in the foot pads of mice, it would seem a major handicap not to have the means to grow the bacillus with a view to employing this technique in the study of leprosy, its epidemiology, and the development of newer methods of treatment of patients with leprosy. Experiments in the cultivation of *Myco. leprae* in the foot pads of Swiss white mice (Rockefeller strain) have been in progress for the last 2 years at the Schieffelin Leprosy Research Sanatorium, Karigiri. The laboratory housing the mice here did not have air-conditioning because of financial considerations.

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The present communication therefore constitutes the first report of a continuing study wherein we present data to demonstrate that with fairly careful regulation of techniques, reasonably reproducible results of cultivation of *Myco. leprae* can be obtained even with restricted facilities. The findings in 39 experiments, in which inoculum obtained from untreated patients with lepromatous leprosy was used, are reported in this paper.

MATERIAL

Skin biopsy specimens from the patients were obtained and processed. The morphological index of the inoculum (determined according to Shepard's technique (Shepard, 1962*b*)) in each of the 39 experiments is as shown in Table 1.

TABLE 1
Morphological index of inoculum

Morphological Index, %	*Total*
1 and below	15
1.1—3	11
3.1—5	6
5.1—7	3
7.1—9	3
9.1—11	—
11.1 and over	1
Total	39

The experiments were carried out throughout the year, 15 being set up during the 4 months July to October, 14 during November to February, and 10 during March to June. The seasonal variations in laboratory temperature during these periods were as shown in Table 2.

TABLE 2
Seasonal variations in laboratory temperature, in °C

Temperature	*July to October*, 1967			*November to February*, 1967-8			*March to June*, 1968		
	8 *a.m.*	12 *noon*	4 *p.m.*	8 *a.m.*	12 *noon*	4 *p.m.*	8 *a.m.*	12 *noon*	4 *p.m.*
Maximum	31	35	36	33	30	32	31	34	36
Minimum	23	25	25	19	21	20	25	27	28
Average	27.0	30.0	30.5	26.0	25.5	26.0	27.7	30.9	32.3

Regulation of temperature was not possible except by providing ordinary ceiling fans in the laboratory housing the animals. Owing to an acute scarcity of the desired strain of mice, we had to use a relatively small number of animals during the initial phases of the experiment. Later, we were able to obtain sufficient mice so that at least 10 animals were used for each of the later experiments. However, it was felt worthwhile to use both hind foot pads instead of one foot pad only, in order to increase the number of footpads harvested without adding more animals.

METHOD

The technique for inoculation of the foot pads was that described by Shepard (1960*a*, *b*; 1962*a*) and later by Rees (1964). In 37 of the 39 experiments here reported, the inoculum contained 4.0 to 6.0×10^3 *Myco. leprae* per foot pad. In a few randomly chosen cases one of the inoculated hind foot pads was subjected to histological examination to provide additional confirmation of the presence of acid-fast bacilli in the tissues.

The time of harvesting was deliberately arranged a little later than that recommended by Shepard *et al.* (1965*b*; 1967) in view of their observation that a rise in environmental temperature delays the rate of multiplication of *Myco. leprae* and also their finding that there was no significant multiplication of the organism during the first 3 months after inoculation. The time of harvesting was also delayed by 30 to 60 days when the number of animals used in an experiment was relatively small. In any experiment thus far, the minimum number of harvests made 150 days after inoculation was 2. Harvest homogenates were cultured using media suitable for the growth of *Myco. tuberculosis*, to ensure that the acid-fast bacilli that were seen were not cultivable by the conventional methods. In the later experiments the harvested bacilli were passaged.

We have also prepared lepromin from mouse-foot-pad homogenates and standardized it to contain 1.0×10^8 bacilli per ml, similar to the lepromin from human material prepared in our laboratory for the Mitsuda lepromin test.

RESULTS

Proportion of "takes"

In the 39 experiments carried out so far, 280 animals have been harvested after the 150th day from the time of inoculation of the foot pad. Of these, 177 or 63.2% have shown at least a 10-fold increase—a significant take. The proportion of "significant" takes in the animals in each experiment is shown in Table 3.

TABLE 3
The number of experiments showing significant growth (at least 10-fold increase) of *Myco. leprae* based on harvests made after 150 days

Percentage of animals showing 10-fold increases or more in each experiment	*No. of animals harvested per experiment 150 days after inoculation*		
	2–4	5 *and above*	*Total*
Nil	1	–	1
0.1—10.0	–	–	–
10.1—20.0	–	1	1
20.1—30.0	1	2	3
30.1—40.0	–	3	3
40.1—50.0	2	2	4
50.1—60.0	–	2	2
60.1—70.0	–	4	4
70.1—80.0	2	7	9
80.1—90.0	–	6	6
90.1—100.0	4	2	6
Total	10	29	39

Total number of animals harvested	280
Number of animals showing at least 10-fold increase	177
Percentage	63.2

The "maximum-fold" increases observed to date in each experiment are shown in Table 4.

TABLE 4

Maximum-fold increase obtained to date in each experiment

Fold increase	*No. of experiments*
Nil	–
1—9	1
10—24	–
25—49	6
50—74	5
75—99	3
100—249	11
250—449	7
450—749	5
750—999	1
Total	39

Since all the animals inoculated in these 39 experiments have not yet been harvested, these results are to be considered preliminary, indicating the lower limit of success obtained in our experiments. Out of 39 experiments 38 have shown increases of 10-fold or more and the findings from these 38 experiments were used for estimations of incubation period (i.e., time between inoculation and harvest) and generation time. It must be stated that since harvests have not been arranged to show the earliest positive evidence of bacterial multiplication, the estimated generation time should be considered as tentative.

The proportion of "takes" in the animals and the maximum increases have not shown any significant seasonal variations. The maximum-

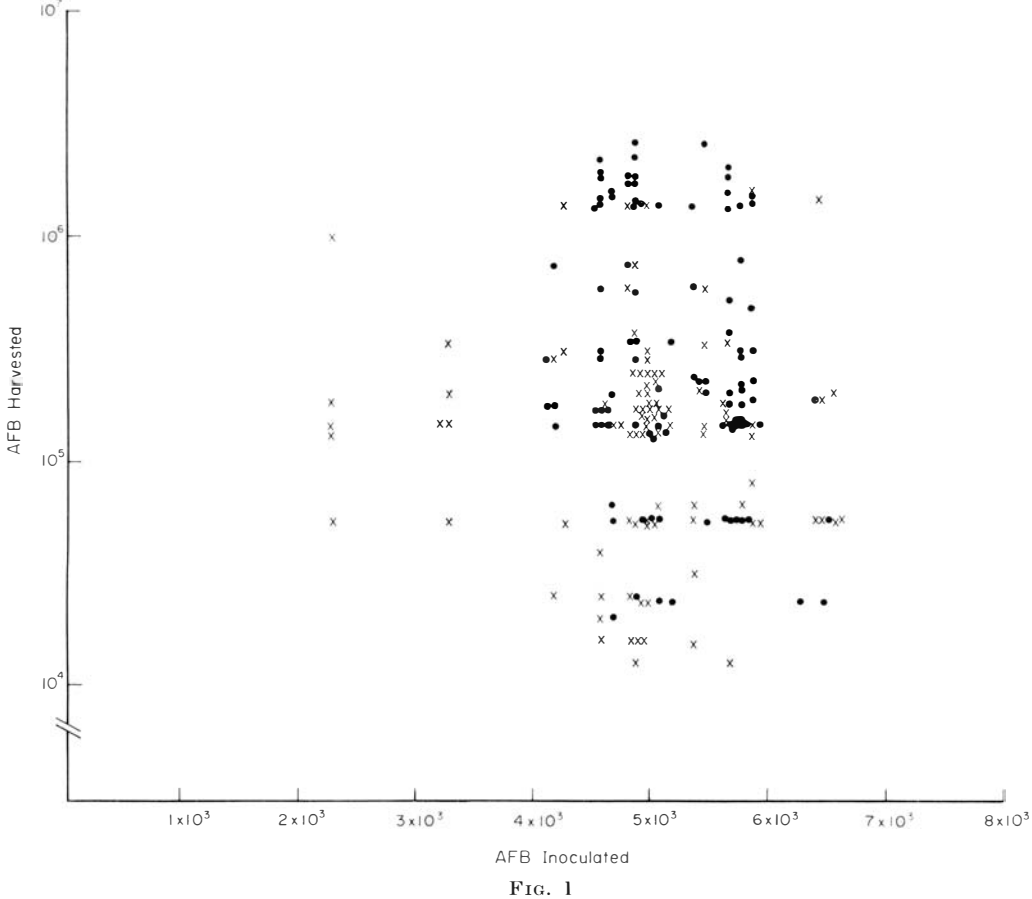

FIG. 1

To show the relationship between the number of acid-fast bacilli (AFB) inoculated and the number harvested. ●, Time taken > 300 days; ×, time taken < 300 days.

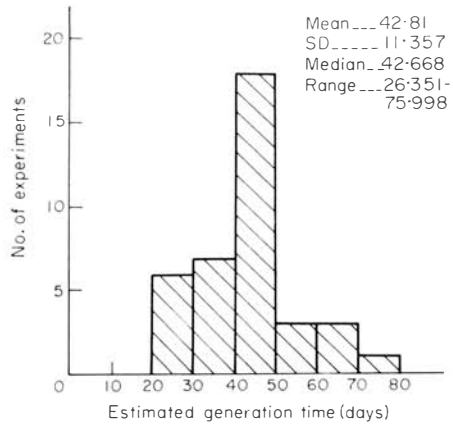

FIG. 2
Frequency distribution of estimated generation time (days).

fold increases seen so far in the experiment in relation to the morphological index in the inoculum are shown in Table 5.

TABLE 5

Maximum-fold increase in relation to Morphological Index (M.I.) in the inoculum

M.I.	*Maximum fold increase*	1—9	10—99	100—999	*Total*
1 and below		–	11	4	15
1.1—5		–	2	15	17
5.1 and over		1	1	5	7
Total no. of experiments		1	14	24	39

It is interesting to note that good harvests have been obtained in experiments in which the inoculum had less than 1% solid organisms. Since harvests were in general delayed for varying lengths of time, it could have happened that all the harvests were collected in the "plateau phase" after the end of the logarithmic phase of the growth curve. Whether the time required to reach the end of the logarithmic phase is greater with inocula containing a small number of solids can only be determined after further carefully planned timing of harvests.

Incubation period (time between inoculation and harvest)

The variations noted, based on the animals harvested and found to show a specified fold-increase at the time of harvest, are shown in Table 6.

TABLE 6

Number of days taken for the acid-fast bacilli inoculated to show the designated fold increase in the harvested animals

Fold increase	*No. of animals*	*Incubation period (days)* *Mean*	*SD*	*Range*	*Median*
10—24	43	289.5	95.2	162—496	268
25—49	45	325.2	117.6	155—582	306
50—74	23	324.1	128.5	155—535	304
75—99	12	315.0	93.6	151—529	311
100—249	29	353.8	103.6	187—582	367
250—499	16	344.3	87.5	242—538	327
500—749	8	393.8	32.3	337—439	393
750—999	1	399.0	–	–	399

The number of acid-fast bacilli harvested in relation to the number inoculated and the number of days to harvest is shown graphically in Fig. 1.

Generation time

Generation time has been calculated by means of the formula supplied by C. C. Shepard (personal communication). It is as follows:

$$\text{Estimated generation time} = \frac{\text{No. of days between inoculation of a group and harvesting from this group}}{\text{Log}_2 \dfrac{\text{No. of organisms harvested}}{\text{No. of organisms inoculated}}}$$

Example:

Inoculated 4.6×10^3 AFB on 20 October, 1967.

Harvested 2.57×10^6 AFB on 19 September, 1968.

No. of days between inoculation and harvest = 337.

$$\text{Log}_2 \frac{2.57 \times 10^6}{4.6 \times 10^3} = 9.13$$

$$\text{Estimated generation time} = \frac{337}{9.13} = 36.9 \text{ days.}$$

The maximum harvest count obtained for the first time in each experiment was used to determine the generation time. The computed generation time varied between 26.4 and 76 days, the mean and standard deviations being 42.8 and 11.4 respectively (Fig. 2).

In a few experiments, half the biopsy material was sent to Dr. Shepard's laboratory for cultivation of *Myco. leprae*. The estimations according to Dr. Shepard's experiments are compared with those obtained in our experiments in Table 7.

It is encouraging to note the close similarity of the estimations based on the growth of *Myco. leprae* in the 2 laboratories. In 3 instances the differences in harvests seem to have resulted from the fact that one of the laboratories carried out the harvest during the logarithmic phase, and thus obtained a harvest well below the plateau value.

In Table 8 the estimated generation time in days according to the month of inoculation into the footpads is shown.

TABLE 8

Estimated generation time (days) according to month during which inoculation was performed

Month	*July—Oct.*	*Nov.—Feb.*	*Mar.—June*
No. of experiments	15	13	10
Mean	46.5	39.3	41.9
S.D.	13.3	9.8	8.0
Range	26.4—76.0	26.4—63.6	29.7—54.7
Median	43.4	36.6	43.1

Again no significant seasonal fluctuations occurred. This would suggest that the seasonal variations of temperature at Karigiri appear to have had no significant influence on the generation time of *Myco. leprae*.

Histology

In the few sections of the foot pads we have studied so far, the results are very encouraging in that one is able to demonstrate acid-fast bacilli in the foot-pad muscles, as well as in the connective tissue and nerve between the muscle bundles (Fig. 3).

Viability of lepra bacilli harvested from mouse foot pad and immunological identification

Passage of *Myco. leprae* obtained from foot-pad harvests has given consistently positive results similar to those in the original experiments.

TABLE 7

Comparison of generation time obtained by Shepard and Karat in experiments set up simultaneously with the same biopsy specimen

	Shepard's results (U.S.A.)				*Karat's results (Karigiri)*			
	A.F.B.		*Time from*	*Generation*	*A.F.B.*		*Time from*	*Generation*
S. No.	*Inoculated*	*Harvested*	*inoculation to harvest (days)*	*time (estimated)*	*Inoculated*	*Harvested*	*inoculation to harvest (days)*	*time (estimated)*
1	5.0×10^3	2.99×10^5	182	30.9	5.72×10^3	2.4×10^5	203	37.7
2	5.0×10^3	3.91×10^5	176	28.0	6.5×10^3	1.4×10^6	262	33.8
3	5.0×10^3	7.51×10^5	287	39.7	4.72×10^3	1.46×10^5	192	38.8
4	5.0×10^3	1.41×10^5	159	33.2	4.95×10^3	8.5×10^5	277	37.3
5	5.0×10^3	4.19×10^5	131	36.2	5.66×10^3	2.2×10^5	289	54.7
6	5.0×10^3	$< 2.7 \times 10^4$	220	> 90.5	4.3×10^3	1.3×10^6	245	29.7

FIG. 3
Photomicrograph of mouse foot-pad 342 days after inoculation to show acid-fast bacilli. Harvest of the opposite foot yielded 1.02×10^6 bacilli.

The lepromin readings at 21 days in 4 volunteer subjects is shown in Table 9.

TABLE 9
Comparability of Lepromin readings at 21 days in 4 volunteers

S. No.	*Subject*	*Reading (mm)*	
		Human Lepromin	*Mouse Lepromin*
1	Male—lepromatous leprosy, resolved	Negative	Negative
2	Female—healthy	9	6
3	Male—healthy	5	7
4	Male—healthy	8	9

They show that the lepromin reaction to human and mouse lepromin are comparable. The detailed findings in relation to passage experiments and lepromin tests will be described in a further communication.

COMMENTS

The purpose of this paper is not to describe new techniques but to confirm that the existing techniques yield reproducible results, and to indicate that even with restricted facilities it is possible to obtain satisfactory multiplication of *Myco. leprae* in the foot pads of mice. It is interesting to note that significant multiplication of the organism in the foot pads was obtained with inoculum containing less than 1% solid organisms (according to Shepard's technique) in some of the experiments, suggesting that multiplication of the bacilli in the foot pads is a sensitive index of viability of these organisms.

In these experiments the precise incubation period, meaning the time from inoculation to first positive harvest and/or first positive histological section, has not been determined.

Using the available data regarding the time from inoculation to harvest, a tentative figure for generation time has been computed, which is found to be on an average longer than those reported by Shepard and by Rees. The longer generation times thus observed may be in part, or wholly, related to the fact that the majority of the harvests were probably carried out in the plateau phase rather than the logarithmic phase of the growth curve. Further, while the lack of thermoregulation in the animal laboratory may not be adequate to suppress the multiplication of *Myco. leprae* in the foot pad it could have conceivably delayed the rate of multiplication. Studies are under progress to elucidate these points.

CONCLUSION

A preliminary report of the successful adoption of Shepard's technique for obtaining multiplication of *Myco. leprae* in the foot pads of mice in Karigiri, India, is presented.

The lack of thermoregulatory devices and the seasonal and diurnal fluctuations of temperature in the animal laboratory did not materially affect the "take" rate. The histological sections have confirmed the findings of "foot-pad" harvests.

SUMMARY

The great difficulty experienced until recently in attempts to cultivate the leprosy bacillus in the laboratory has been a serious obstacle to progress in the treatment of leprosy. In this paper the author demonstrates that such cultivation is possible even without the strict regulation of temperature hitherto considered essential.

ACKNOWLEDGEMENTS

I owe a great deal to Dr. O. W. Hasselblad of the American Leprosy Missions, Inc., for making it possible for me to embark on these experiments by giving me financial support and continued encouragement.

I must also acknowledge the training facilities that were made available to me by Dr. Charles C. Shepard, and to my technologist, Mrs. Hilary Harmer, by Dr. R. J. W. Rees. Both Dr. Shepard and Dr. Rees have given advice and guidance throughout the period of this study.

It is with pleasure I thank Mrs. Hilary Harmer and Mr. Japes Fowler for the very excellent quality of technical assistance that they have given throughout these studies. I would also like to express my deep appreciation of the statistical assistance received from Mr. P. S. S. Sundar Rao, Chief of the Biostatistics Department, Christian Medical College and Hospital, Vellore. To my secretarial staff, Mr. M. S. Balasubramanian and Miss K. Saroja, I am grateful for all the help rendered.

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Lepr. Rev. (1970) **41**, 100-102

A Foot Drop Spring*

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INTRODUCTION

Active splints have long been accepted as a basic therapeutic measure for the prevention of deformity due to paralysis and in the treatment of paresis. However, in leprosy their use has frequently been neglected. The fitting of an active splint to the hand is difficult, compared with the ease of fitting an efficient active splint that will provide a functional support to allow normal walking in a foot with paralysis of the anterior and or lateral leg muscles (foot drop). Many types of splint have been devised over the years and have proved effective, but some may not be acceptable for the treatment of large groups of persons in poor financial conditions.

The requirements of an efficient active splint for foot drop are that it should be: (1) effective, (2) comfortable, (3) adaptable for making with local materials by patients themselves, (4) cheap, (5) easy to apply, even with deformed hands, and (6) that it can be used with socially acceptable clothes and shoes and can conform to local customs. Over the years the staff at Hay Ling Chau have evolved a foot drop spring that we consider fulfils these conditions in Hong Kong.

DESCRIPTION

A simple cuff is made to encircle the leg immediately below the knee and to fasten in front of the leg. Attached to this by 2 arms is a "Y" piece, to the lower end of which is fastened a metal spring which is hooked on to the shoe; the degree of lift required is adjusted by the length of the "Y" piece, which is provided with a number of holes for use with a pair of buckles on the upper cuff, thus providing a choice of length.

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MATERIAL

(a) Any locally available material can be used. Leather is readily usable, but webbing, canvas, or any similar strong material is equally satisfactory.

(b) The upper cuff, if made of leather, is padded with sponge rubber to assist grip on the leg and reduce localized pressure. A cuff made of other material may not need padding.

(c) Buckles are used for fastening, but eyelets and laces could be used, or "Velcro Magic tape" for patients with bad hands, or "Gripper" fasteners or other patent fastenings as available.

(d) Metal springs are reliable and wear well, but strong elastic may be used or strips of heavy rubber from the inner tubes of lorry tyres will provide adequate stretch.

(e) A dressmaker's hook stitched to the shoe (or sock) will provide the point of attachment, or the spring can be hooked through shoe laces or on to a loop or ring stitched to the shoe.

In countries where shoes are usually removed at the door and left outside, it is possible to attach the spring to firm socks, or to provide a cuff to go round the forefoot at the level of the metatarsal-phalangeal joint so that the spring can be worn in the house. As the paralysed foot is usually associated with an anaesthetic sole it is best to advise these patients to wear some type of footwear at all times so as to prevent trauma.

PATTERN

The Hay Ling Chau design is as follows:

(1) A leather cuff with a sponge-rubber inner lining and furnished with a tongue and a strap to pass through the buckle in front of the leg carries 2 further buckles, one on each lateral aspect, angled forward to provide attachment

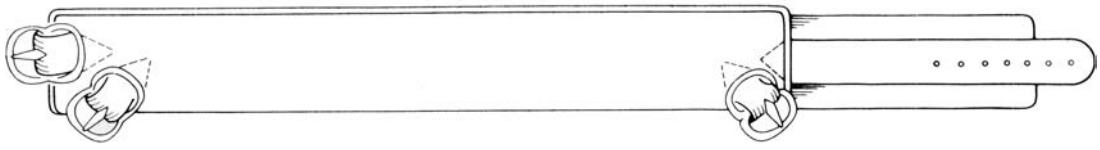

FIG. 1
Upper leg cuff showing tongue lining and placement of buckles.

for the "Y" piece (see Figs 1 and 3). *Note:* All buckles should be on the front of the leg to prevent them damaging the anaesthetic skin of the popliteal fossa when patients sit or squat. The cuff must, of course, be tight enough to hold up above the calf. Cuffs may be pre-made, but should allow for different calf sizes (lengths of 10 and 12 in. (25 and 30 cm) are commonest for adults in Hong Kong).

(2) In acute paralysis, where the lateral popliteal nerve is tender, it may not be possible to tighten this type of cuff adequately without causing pain in the nerve; also, in patients with marked wasting of the calf there will not be enough muscle bulk to hold up this cuff. In such case a double cuff is desirable. The upper cuff can be fastened firmly while the lower cuff is left looser. The latter is essential as it provides the correct site for the pull of the spring. If the spring is attached above the knee its tension will be lost when the knee is flexed; hence to be effective the spring must be attached below the knee. The side bars joining the 2 cuffs should be directly mid-lateral to prevent rubbing during movement of the knee (Fig. 3).

(3) The "Y" piece is also lined with leather for strength and has 4 to 6 punch holes on each upper end to allow adjustment of the length; it has also a metal bracket at the lower end for attachment of the spring (Fig. 2).

(4) The spring is about 5 in. (12.5 cm) in length, 6 or 7 mm in diam. and the 5 in. length should stretch to 6 or 7 in. (15 to 17 cm) when strong pull is applied. Weak springs will rapidly be distorted by the power of the gastrocnemius and soleus muscles. The lower end of the spring is easily bent out to form a ring for use on the hook, or to pass through a ring or lace on the shoe.

(5) The hook on the shoe should be situated over the head of the fourth metatarsal to provide adequate lateral lift in a full foot drop. This site may need to be adjusted if there is paresis in order to obtain a suitable balance and prevent inversion or eversion of the foot. The shoe need not be an expensive or orthopaedic one, provided it fits well and firmly so that it will not be pulled off by the spring (i.e. has a heel counter); it should also have a good sole to protect the anaesthetic foot that usually accompanies foot drop. The final appearance of a completed spring with double upper cuff is shown in Fig. 3. *Note:* For night use a cuff to encircle the foot at the level of the metatarsal-phalangeal joint can be made to attach to the spring and so minimize the chances of contracted Achilles tendon.

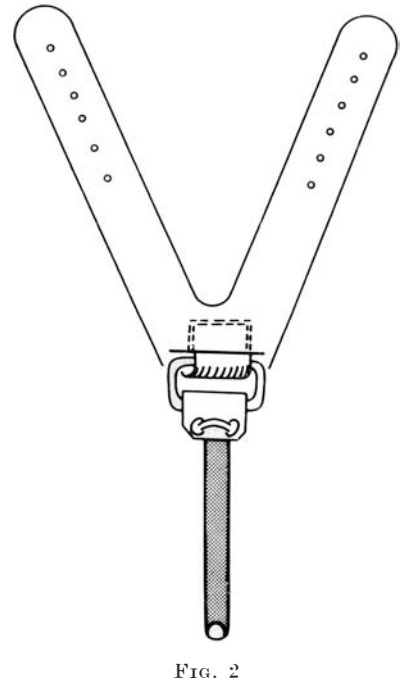

FIG. 2
The "Y" section showing metal attachment and spring.

FIG. 3
Complete spring with double upper cuff, showing shoe attachment.

These springs can easily be adjusted to ensure adequate lift of the foot to prevent a flapping gait during walking. Many patients appreciate the relative comfort of walking with one of these springs after years of "flapping feet".

SUMMARY

A description is given of a simple form of foot drop spring that is cheap and easy to make and has proved effective in controlling the paralyzed foot and preventing further deformity.

ACKNOWLEDGEMENTS

The design of this spring has gradually evolved over many years of co-operation by staff and patients. We merely present the version we are using today to help others to help themselves. Our thanks go to Miss K. Collett for the illustrations and to the Hong Kong Government physiotherapists for their encouragement and assistance in improving the design.

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Dry Bones Come Alive*

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On 9 December, 1969, at the Medical Historical Museum attached to the University of Copenhagen, Dr. Johs G. Andersen successfully defended his doctoral thesis entitled *Studies in the Mediæval Diagnosis of Leprosy in Denmark*† before a packed auditorium. He was interrogated for upwards of 3 hours by Professor V. Møller-Christensen, Professor of the History of Medicine in the University of Copenhagen; Dr. Jorg Balsler Jorgensen; Dr. D. L. Weiss, Professor of Pathology in the University of Kentucky; Dr. Egill Suorason; Dr. Otto Kœfœd Petersen; and Dr. S. G. Browne, Secretary-Treasurer of the International Leprosy Association; and others.

Dr. Andersen's researches embody in effect part of the continuing studies of the material originally excavated by Professor Møller-Christensen in the burial ground attached to the mediaeval monastery at Næstved in Denmark, studies that have already given to the world such important publications as *Bone Changes in Leprosy*, *Ten Lepers from Næstved in Denmark*, and numerous articles by Møller-Christensen in learned journals; and *Spondylosis Cervicalis: a Pathological and Archaeological Study*, by Philip Sager. A dental colleague, Danielsen, is known to be making a study of the dentition, the microscopic appearances of the teeth, and the changes present in the tooth-bearing bones of the skulls retrieved from the same burial-ground.

These fascinating glimpses into the past may shed unexpected light on the clinical and epidemiological problems of today, as well as provide indications concerning the spread of leprosy in the Middle Ages, the dimensions of the endemic, the clinical identification of the disease at the time, and the persistence over hundreds of years of recognizable patterns of specific bony changes attributable to leprosy. It was through these early studies that the erosion of the nasal spine and of the alveolar process of the maxilla was first recognized. Since then, of course, these specific stigmata of leprosy have been identified by numerous radioscopic and clinical studies in the living; microscopic investigations of cartilage and bone have incriminated direct infection of these tissues by *Mycobacterium leprae* and secondary invaders.

Dr. Andersen's thesis summarizes his first-hand investigation of many of the historical references to leprosy that have been cited uncritically by numerous authors subsequent to their first—often tentative and equivocal—publication. Herein lies the most obvious and most valuable contribution of Andersen to the continuing debate on the origin and spread of leprosy. The issue has been, and still is, repeatedly confused by vocabulary, and by the vagueness and imprecision of descriptive terms used in a pre-scientific age.

However, certain conclusions appear to be clear-cut and reasonably well based. Despite numerous claims to the contrary, the Chons' swellings referred to in the Ebers papyrus (c. 1552-1350 B.C.) are not considered to be indicative of leprosy, but rather perhaps of gas gangrene. The references to "leprosy" in the Authorized and subsequent versions of Old Testament scriptures (Hebrew *tsara'ath*) emphasize ritual defilement associated with a scaly condition of human skin, cloth, and leather goods and the walls of houses. There is no osteological, archaeological, or literary evidence that would incriminate infection with *Myco. leprae* in any of the instances of *tsara'ath* recorded in the Old Testament.

Andersen makes great play with the fact that true leprosy was unknown to even such a careful observer and precise chronicler as

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†*Studies in the Mediæval Diagnosis of Leprosy in Denmark. An Osteo-archaeological, Historical and Clinical Study*, by Johs G. Andersen. Copenhagen: Costers Bogtrykkeri, 1969. Also, published as supplement 9, *Danish Medical Bulletin* (1969) **16**.

Hippocrates. Had the disease that had been known and accurately described in India for at least 300 years been present in Europe, Hippocrates would certainly have recognized, described and recorded it. His "*lepra*" was probably a summer prurigo. Andersen then links these 2 facts, first that leprosy was known in India, and second that the disease made a sudden (and well-documented) appearance in the Mediterranean littoral around 300 B.C. He suggests that the troops of Alexander the Great, returning from the Indian campaign in 327-6 B.C. must have brought back leprosy with them. Certain it is that thereafter the occurrence and spread of leprosy may be traced with certainty and in some detail throughout Europe. In those early records the salient clinical features of low-resistant leprosy are recognizably described, as well as the pathognomonic signs in the skin and peripheral nerves. These 2 groups of observations are held to differentiate this new disease from any previously known morbid condition.

Meanwhile, there is some evidence that true leprosy may have existed at this time in Egypt, perhaps introduced there from Central Africa by Nubian slaves. Pompey's troops, returning from Egypt in 62 B.C., almost certainly took leprosy with them into Italy. Thenceforward, leprosy spread in the wake of soldiers, merchants, and later, priests and crusaders.

Since leprosy is known to have existed in the first century of our era in the countries bordering the Mediterranean, some of the New Testament instances of *lepra* may have referred to true leprosy. In this case, the lay Greek term was used, and not the medical term for leprosy, which was *elephantiasis Graecorum*.

Andersen reminds us that the earliest skeletal remains showing indubitable signs of leprosy date from the fifth century of our era, and are in Coptic mummies from the Upper Nile. Even though the victims of leprosy in ancient times might have passed their days and ended their lives far from the haunts of men, the absence of osteological evidence of leprosy from those distant epochs is, to say the least, passing strange.

In Denmark, low-resistant leprosy appears to have been accurately diagnosed by the laity, to judge from the Næstved bones. In mediaeval England, however, the word "leprosy" had a very broad connotation, embracing any chronic skin disease and (by extension) dirt, beggary, and even venery; it was also used for the blight of growing crops and mildew of stored grain. Hospices originally founded for the relief of "lepers" may never have housed any person suffering from true leprosy as at present defined.

In a succession of interesting chapters, Andersen brings us right up to date, as he clothes the dry bones rescued from the oblivion of the Danish mediæval churchyard with the flesh and blood of the living patients he examined and recorded in the Mission Hospital in Purulia, West Bengal, and elsewhere. The specific maxillo-facial bony changes are seen clinically and visualized radioscopically; the non-specific but extremely characteristic absorption of the phalanges and the mid-tarsal bones, the ossification of the interosseous membrane, the typical clawing of hands and feet, the evidence of long-standing secondary infection of the exposed bones of the extremities —are all documented from the mediæval burial-ground and the modern leprosarium.

One striking feature of the Næstved study is the predominance of low-resistant leprosy in the bony remains. The skeletons themselves provide no answer to the questions whether high-resistant leprosy was unknown, or not recognized as leprosy, or not regarded as needing either compassionate care or segregation. Literary and palaeo-archaeological studies elsewhere may provide answers to these questions.

Dr. Andersen has, by his painstaking studies and critical review of historical documents, placed the world of leprosy in his debt. The quotations from classical authors alone, and his critical interpretation of long-available translated material that has been either too precise or too vague, will make his thesis an indispensable source-book for any medical historian who in the future thinks of writing on the history of leprosy.

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Griseofulvin in Leprosy

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A controlled trial of Griseofulvin showed that the drug had no apparent beneficial effect in patients with lepromatous leprosy.

INTRODUCTION

The present study of the action of Griseofulvin in leprosy was undertaken because previous trials must for various reasons be adjudged unsatisfactory; moreover, they produced conflicting results.

MATERIALS AND METHODS

Selection of patients

All 120 patients included in the trial were suffering from lepromatous or borderline-lepromatous leprosy and were in-patients at the McKean Leprosy Hospital, Chieng Mai. The 60 patients given Griseofulvin were paired as closely as possible with 60 control patients on the basis of age, sex, duration of disease, tendency to erythema nodosum leprosum (ENL), clinical activity of the leprosy, bacterial index, and type of treatment received.

Bacterial status

All the patients had a bacterial index (BI) of at least 1.25 at the beginning of the study, and in 16 of them it ranged from 1.25 to 2.50; initially all the patients had had a BI of 3.0 or higher except 3 in whom it was between 2.25 and 2.50.

Age

All the patients but one were over 12 years of age.

Supervision

Regular clinical examinations and charting of lesions were under the personal supervision of the author. The trial was double-blind.

Dose of Griseofulvin

Griseofulvin was given in a dosage of 2× 0.5 g tablets daily (fine particle) for 3 months, and then 3 similar tablets daily thereafter. Two patients who could not tolerate the higher dose continued taking only 2 tablets daily.

Duration of trial

This was actually $8\frac{1}{2}$ months. The original protocol had provided for the trial to last 12 months, but the interim results at $8\frac{1}{2}$ months indicated that prolongation of the trial after this time would not be justified.

Anti-leprosy drugs

These were taken without interruption at the same dose as that before starting the trial with Griseofulvin. Dapsone was the usual drug, taken in a dosage of 100 mg 3 times weekly. Other drugs being administered, such as sulphetrone (by injection), thiacetazone, thiambutosine, or isoniazid (with or without streptomycin) were continued. The 60 control patients received a placebo of identical appearance and taste.

This report is based on the findings in the 93 patients who remained in McKean Hospital throughout the period of the study, that is, 43 taking Griseofulvin and 50 taking the placebo.

RESULTS

No significant differences could be detected between the patients taking the trial drug and those taking the placebo under any of the following heads: bacterial index, granularity index, development of erythema nodosum leprosum, or clinical activity of the disease.

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DISCUSSION

In this study, Griseofulvin was given for a longer time and at a higher dose than in any previous study. The number of patients taking the drug was equal to the combined totals of those in trials previously reported. The present study was double-blind and carefully controlled, whereas only one previous report included controls—and that was a small series of 6. It is noteworthy that the addition of Griseofulvin to standard therapy had no effect in accelerating either the rate of disappearance of morphologically normal *Mycobacterium leprae* or the reduction in the bacterial index.

CLINICAL FINDINGS

No evidence of improvement in the general clinical condition of any patient attributable to Griseofulvin was noted. In regard to erythema nodosum leprosum, 32 patients had none at any time during the period of the trial. No significant differences were seen in patients taking Griseofulvin compared with those in the control group.

On the other hand, the patients' own assessments of their subjective improvement during the period of the trial indicated that those in the control group reported a greater degree of improvement than those taking Griseofulvin.

SUMMARY

A double-blind trial of Griseofulvin as an adjunct to the standard treatment of 43 patients with lepromatous leprosy (compared with 50 similar patients receiving a placebo) provided no evidence that the addition of Griseofulvin accelerated bacillary destruction or bacillary clearance, or resulted in more rapid clinical improvement than was to be expected.

ACKNOWLEDGEMENTS

I wish to express appreciation of the help afforded by Messrs. Glaxo Ltd. in making available adequate supplies of both Griseofulvin and placebo tablets, and by Dr. E. S. Snell (Medical Director) and Mrs. P. S. Keen. I also wish to thank Dr. S. G. Browne, O.B.E., Director of the Leprosy Study Centre, London, for his interest and advice.

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"Mobile" Leprosy Control in the Eastern Province of Zambia. Parts I and II*

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I. Planning and Operation of Treatment Circuits

INTRODUCTION

The LEPRA Control Project in Malawi started in 1965, and the present scheme in the Eastern Province of Zambia, which is a co-operative one between the Health Department of the Republic of Zambia and the British Leprosy Relief Association (LEPRA), is based very largely on the example and experience of the parent project in Malawi. There is similarity in the terrain chosen in the 2 countries, but the volume and distribution of the respective populations differ greatly. Both campaigns, however, were launched with the same idea—namely, to bring early and regular treatment to as many patients as possible, with reasonable regard to the costs involved, and to include a control system at least 75% effective.

In Malawi the control area is only about one-sixth that of Zambia's Eastern Province, but it contains an estimated population 5 times as great. In Zambia the scattered nature of the population was an important factor in the decision to change from dapsone tablets to 4-weekly depôt injections—a decision which also gave the leprosy teams more time for village case-finding, examination of school-children, periodic review of registered cases, and the accurate presentation of statistical information.

POPULATION AND TERRAIN

In the Eastern Province of Zambia the total population is approximately half a million, with a density varying from 90 persons per square mile (35 per sq. km) in the 3 "urban" areas, to 4 per square mile in the widely-spaced enclaves of the Western boundary of the Province in the Luangwa River valley. Villages are generally small, consisting of about 100 persons, with distinct groupings at intervals of 3 to 40 miles. Few of them are on the 2 main transport arteries. Apart from the Luangwa River, which floods considerably between January and April and which does not approach the main population areas, most steams are dry from June to December. Hills mostly present as isolated sharp elevations from the huge plateau and form no hindrance to the movement of vehicles, though many unbridged watercourses become impassable to both vehicle and patient during the rainy season.

INSTALLATION OF CIRCUITS

For this a map of scale 1 : 250,000 was used, and with available information on population density and village groupings, tentative points were plotted before the ground was covered. Various revisions soon became necessary as the roads, rivers and bridges were checked in detail. Rural health centres, which formerly dispensed treatment to limited numbers of patients within walking distance, remained focal points in the network. In the more thickly populated areas a practical average distance between treatment points was found to be 12 km (7½ miles). Where possible, these points were located at schools, local courts, grinding mills, or village stores, and it was found advantageous to distribute simple time-tables of the unit's 4-weekly calls to each point on the circuit. More

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comprehensive time-tables were posted at each rural health centre included in a specific treatment run, and these showed the entire day's schedule for a year. Medical personnel in charge of these centres are thereby able to advise their former leprosy patients, or potential new patients, at which point they can most conveniently obtain advice.

All circuits were initially launched on fortnightly tablet treatment, the first week's dose being taken with water under direct supervision, the second dose being given to the patient in a container to be taken at home. There was an expected interchange and movement of patients from one treatment point to another as the network expanded. An overall 75% attendance rate has been maintained throughout the first year.

Each team consists of 3 persons: a medical assistant with experience in the diagnosis, treatment, and assessment of leprosy, an auxiliary for clerical work and the preparation and handling of equipment, and a driver. Overnight stays by members of the teams are necessary when the work is mainly in areas far distant from the main base.

LOGISTICAL DETAIL

In an attempt to bring early and regular treatment to as many patients as possible in a scheme of this kind, constant thought must be given to the level of effectiveness, both clinically and economically. In the drama of contacting a few cases of tuberculoid leprosy in a remote area, one can too easily fall below the "level of effectiveness at which a campaign continues to represent a good use of resources". (WHO, 1966.)

The success of the operation depends on many factors, such as: (1) the number of patients per treatment-mile; (2) the daily distance to be covered before the first patient is treated; (3) the number of new cases discovered per month or per year; (4) the quality of drivers and rate of deterioration of vehicles; (5) the regularity of attendance of registered patients; (6) the ratio of total number of cases under

FIG. 1

Interior view of vehicle modifications for injection purposes. Glass (not disposable) syringes are normally used. Adequate room is needed inside the cabinet for full opening of the drum lids. (The upper 2 drums are not normally carried, and were photographed for demonstration purposes only.)

treatment in the new project to the numbers and salaries of the staff involved; (7) whether or not it is necessary to finance and staff a base hospital for the small percentage of leprosy patients needing admission; and (8) the "turnover" of cases introduced to treatment and those released from control.

In work of this type the final step of release from control should be taken slowly and carefully, with very close regard to the possibility of a mistake in clinical assessment and also to the fact that many leprosy patients feel rejected and disappointed if told not to come back again. Our policy throughout has been to release them and to certify this, but to make it very clear that they are always welcome to return to see us at any time.

The processing may thus be outlined:

(1) Contact and village case-finding
(2) School examinations.
(3) Transfers from leprosaria.
(4) Transfer from rural health centres.
(5) Voluntary presentations to mobile unit.

→ Mobile out-patient treatment or review.

↓

Clinical and bacteriological review of registered cases.

↓

Release from control.

Of the 3 units proposed for adequate provincial control, 2 were functioning fully on a 28-day treatment regime by injection at the end of the first year. Each 4-weekly period *per unit* works out as follows, based on a 5-day working week. In fact the central office is also open on Saturdays for administration, documentation of the current week's work, and briefing for the next week:

Approximate control cover	6000 sq. miles (15,500 sq. km)
Treatment days	10
Treatment miles	800 (1290 km)
Overall mileage for treatment purposes	1000 (1610 km) (depending on overnight accommodation)
Established treatment points	80
Average no. of patients per treatment point	7

Thus 10 days are allocated for administration at base, vehicle maintenance, preparation of equipment, health education, planning and carrying out of village and school examinations, and clinical assessment of patients under treatment.

SUGGESTED PROCEDURE FOR VILLAGE EXAMINATIONS

Two factors may ruin attempts to examine the whole-body surface of villagers, namely complete lack of understanding of what the exercise is about, and lack of reasonable privacy. House-to-house examinations might in some ways be more effective, but in this area it is very unlikely that the time and organization involved would be justified, and good lighting is always a problem. Section II of this paper includes a description of the canvas screen which we have used in setting up a central examination point either in a village or at some treatment point already known and familiar to many people in the area.

At least one advance visit, with full explanation in the local dialect is absolutely essential. As a matter of courtesy the local chief, rural council, and schoolmaster are always informed of our plan. Also of value has been the advance distribution, through the local chief and in the local dialect, of (1) simply-phrased letters to the village headmen and their

people explaining the reason for the visit, how the newly-found patient may receive treatment, and placing great emphasis on out-patient management; and (2) posters outlining the main signs and symptoms of leprosy; across these are written the date and time of the proposed visit. If the first distribution of this information can coincide with a short speech and introduction of the examiners, this is again a great advantage and may help to reassure the timid potential patient.

Figure 2 shows only one screen in use, but it is an easy matter to erect another compartment adjacent to this one and to use it for undressing and dressing if the number of patients is large. A record of all persons examined is made, by age-group and sex.

The year's work has shown that the value of these examinations in case-finding is not impressive, but on the other hand as a means of promoting public confidence and interest their value is considerable, and certainly greater than that of exhortations in press or radio. It is thought that these examinations, conducted in an informal and friendly way, coupled with the acceptance and handling of leprosy cases at village level, may bring forward even more voluntary presentations as the work proceeds.

CASE NOTES AND CARDS

In a tough plastic cover, each patient carries an out-patient card bearing his coding, dosage, and treatment and review dates. A final section is printed on this card for the stage of release from control. The patient's main case-note carries a registration coding compiled from: (1) the area of the day's run; (2) the day on which the run is made; (3) the number of the treatment point for that day; (4) the classification and sex of the patient; (5) the patient's serial number in the register for that day. Thus CN/TUE/6/NLM/23 signifies that the patient is in Chipata North, on Tuesdays, at treatment point 6, is classed as non-lepromatous, male, and number 23 in the register.

Each register is sectioned by classification and sex. For the purposes of field work, all cases are divided into lepromatous and non-lepromatous,

FIG. 2

Canvas examination screen erected and secured to a tree. There is more than enough room inside it for the examiner and one patient; the vehicle's back door is fixed widely open and access to the interior is easy.

and for immediate recognition of the lepromatous case all data on records and registers are in *red*, those for non-lepromatous cases in *black*.

On initial registration an additional coding system may easily be devised to indicate: (1) the completely untreated case starting on low dosage; (2) the previously treated case from a rural health centre; or (3) the case recently transferred from a leprosarium.

CENTRAL CONTROL REGISTRY AND OFFICE

This office was established in the Provincial centre at an early stage. A suitable shelved storage capacity of at least 125 cubic metres is also essential for a scheme of this size involving 3 vehicles and teams. In order to locate and register every known case of leprosy in the Province, all medical records, leprosy registers and drugs were initially withdrawn from rural health centres and other treatment points; these are now filed in the Central Registry. Monthly statistical information both for LEPRA and the Government being issued from this office. The clarification and improvements resulting from this central control are described in the paper by McDougall and Drake (see p. 115).

II. Landrover Modification for Dapsone Injections and Clinical Examination

MODIFICATIONS AND EQUIPMENT FOR INJECTION

For this purpose 3 factors are essential: (1) maximum standard of sterility of equipment in all conditions; (2) rigidity of the equipment on rough roads; and (3) privacy for the patient receiving an intramuscular injection.

For 8 months of the year the air in this Province is heavily dust-laden. Against this constant enemy, equipment must be hermetically sealed, lids must fit perfectly, drums must be carefully anchored on their base, and everything must be as far off the floor as is practicable. Figures 1, 3, 4, 5 and 6 show the basic arrangement.

If the spare wheel *must* be carried within the vehicle, it should be completely covered with lined canvas, and both wheel and canvas must be periodically washed with soap and water. The 3 sterile drums within the metal cabinet are 23 cm in diameter, sit firmly in a wooden base, and can be fully opened within the cabinet. The lid of the cabinet is lowered to form a work-table for the medical assistant; "formica" surfacing of the lid would be an advantage. Used syringes are stowed in a plastic box; syringe-holding forceps and dressing forceps are immersed in an antiseptic solution in a covered plastic container.

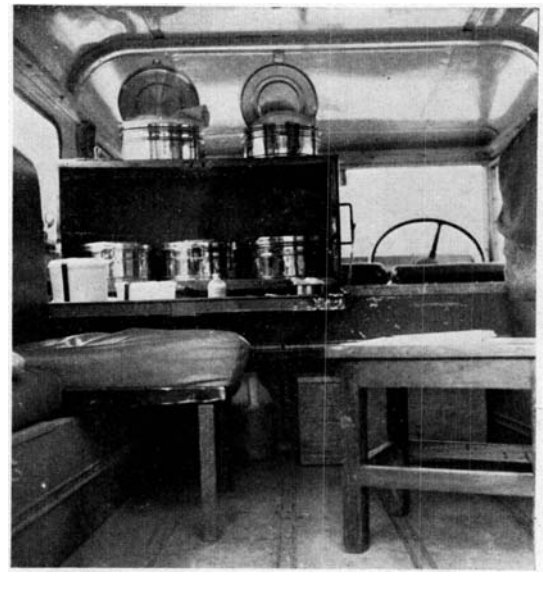

FIG. 3

Interior view of vehicle modifications for injection purposes. Adequate room is needed inside the cabinet for full opening of the drum lids. (The upper 2 drums are not normally carried and were photographed for demonstration purposes only.)

The 3 sterile drums contain respectively: (1) 30×5-ml syringes in sterilizing envelopes, and needles, at least 5 per syringe, in one envelope plainly marked; (2) cleansing swabs; and (3) a 23-cm kidney-dish to receive the syringe in use. This should suffice for a minimum of 125 injections, with a change of syringe after 5 or 6 consecutive injections at the same treatment point.

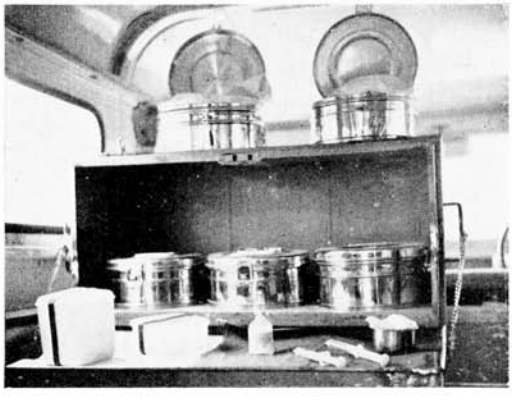

FIG. 4

Interior modifications for injection purposes; the cabinet, with lid lowered to form a working surface. Glass (not disposable) syringes are normally used. Adequate room is needed inside the cabinet for full opening of the drum lids. (The upper 2 drums are not normally carried and were photographed for demonstration purposes only.)

The depôt sulphone used is "Sulfone UCB" (Brussels) and contains 250 mg per ml, made up with sodium carboxymethyl-cellulose, sodium ethyl-mercuri-thiosalicylate and glycerin. Filler needles of a larger gauge are advised as the solution may be turgid. Thorough cleansing of the rubber sealing is even more important than usual. Four-weekly injections are given intramuscularly into alternate buttocks, the patient sitting on a small stool with his back to the injector and in complete privacy within the vehicle. Sitting is considered an added advantage, since in this position "it is quite impossible to strike the sciatic nerve" (Cochrane, 1964).

Once patients are familiar with the routine after their initial attendance, the time per injection can be reduced to a very few minutes. The auxiliary helper keeps a close watch on the register, supervises the stream of patients, and advises the injector on any recorded change in treatment. The date of the team's next visit is explained to the patients verbally and also recorded for each patient.

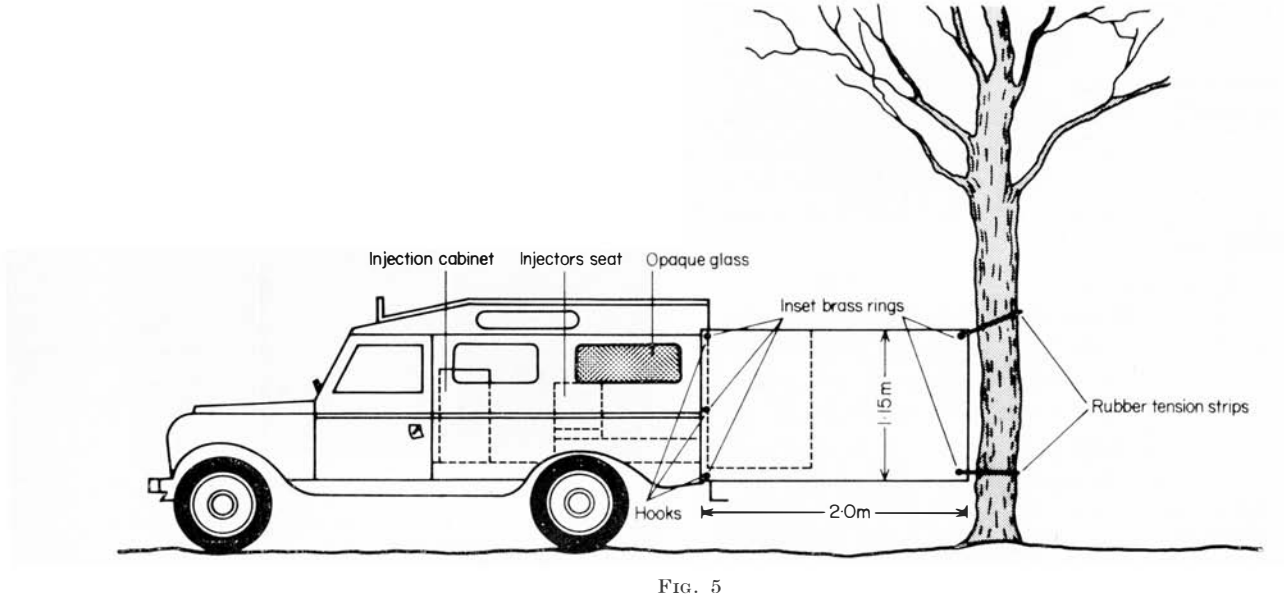

FIG. 5

Side-view diagram of the injection vehicle with canvas screen for clinical examinations erected and secured to a tree.

PORTABLE SCREEN FOR CLINICAL EXAMINATIONS

Since treatment is only an adjunct to control, the review (re-assessment) of cases (clinically and bacteriologically) is carried out at treatment points with the aid of a portable canvas screen (Fig. 2). These reviews should be carried out by the medical assistant who has dispensed treatment to the patient over the previous 6 or 9 months, and time for them should be allowed in the 28-day time-table of work. The screen is also of value in village and school examinations. The canvas is of medium thick quality, measures approximately 4 by 1.15 metres, and has 2.5 cm brass rings at all corners and at appropriate intervals along its edges. Strips of old motor-car inner-tube are useful for attaching the screen to trees. Bacteriological examinations can be carried out within the privacy of the vehicle, as can also clinical examination of the lower part of the body if the patient feels the privacy of the screen is not enough.

When the examination is being carried out the contacts of infectious patients should, ideally, be seen at the same time, and very much greater emphasis on this method of case-finding is now being given in the Eastern Province.

The current cost of this screen in Zambia is about £11 (11 pounds sterling), but this is considered unreasonably high; elsewhere it might be purchased for about half this price.

DISCUSSION

Some practical details of this first year of work in the Eastern Province of Zambia are presented (at what may seem a very early stage) because the methods used appear, so far, to be both successful and economical. Discussions are now in progress on extending the work into another province (Luapula), and it may be that the modifications described here could have application in other countries where leprosy prevalence and the terrain are similar.

Vehicle modification as demonstrated in the accompanying figures is already under revision for the use of a third team. However, with the available local resources only, it is difficult to produce the standard of equipment needed for work of this kind. Inside the vehicle, the exact disposition of the equipment in inches and centimetres is important, as is also the sealing of all containers and the provision of efficient devices for opening and closing them dozens of times during a hot and tiring day's work.

To those who believe that out-patient treatment with tablets has its limitations, and with the possibility of DADDS becoming available in the future, safe and efficient techniques for "mobile" injection therapy under rural conditions may become more important. It is hoped that this paper may lead to the development of a perfected built-in assembly based on the prototype described.

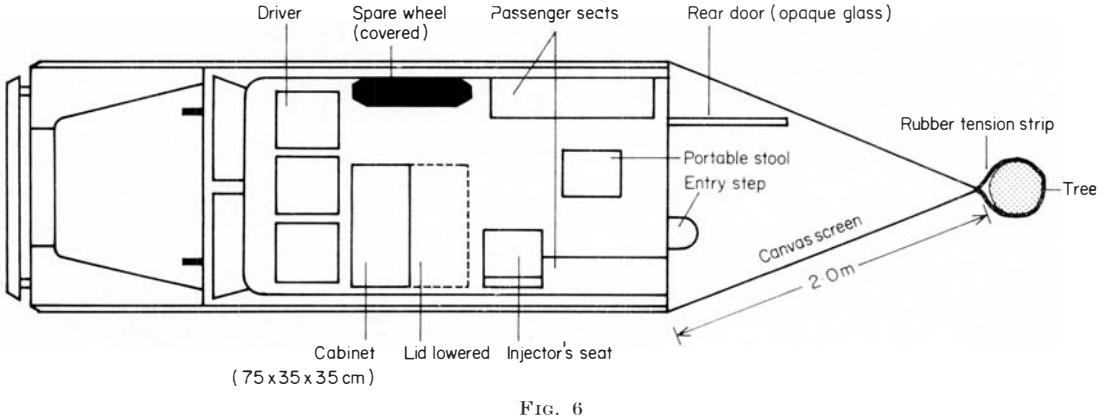

FIG. 6

Plan of the injection vehicle, showing clinical examination screen in place, and position of interior equipment.

SUMMARY

A procedure for the installation in Landrovers on mobile treatment circuits is described, with reference to population density, terrain, patient yield, attendance rates, and the best economic use of time and personnel.

This scheme in the Eastern Province of Zambia is a joint, co-operative one between the Zambian Department of Health and the British Leprosy Relief Association in London. As the first year of work has developed, modifications to the Landrovers have been necessary for the giving of injections inside the vehicle; these are described in some detail, as is also the use of a canvas screen for carrying out clinical examinations in reasonable privacy.

There is a need for a strong, practical built-in unit for giving drugs by injection, bearing in mind the rural circumstances described. If DADDS comes into general use, this need could be even more important. The hope is expressed that the prototype used in this scheme may lead to the production of a perfected, built-in unit for "mobile" injection purposes.

ACKNOWLEDGEMENTS

I would like to thank the Permanent Secretary, Department of Health, Lusaka, and the British Leprosy Relief Association, London, for permission to publish this article.

I wish to record that the organization and methods now in practice in the scheme in Zambia have developed from previous experience with the inauguration of the LEPRA Control Scheme in Southern Malawi, 1965-7. Indeed, the whole idea of this modification for mobile control in Zambia derives directly from LEPRA's work in Malawi.

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"Mobile" Leprosy Control in the Eastern Province of Zambia. Part III*

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Impressions of the First Year of a Joint Campaign by the Zambian Department of Health and the British Leprosy Relief Association (LEPRA)

INTRODUCTION

In 1967 a leprologist from the World Health Organization (WHO) visited Zambia and undertook a comprehensive tour of over 9000 miles in order to examine and assess the leprosy services generally, and advise on future development. While acknowledging excellent work in some parts of the country, his report (Papinutto, 1968) rightly drew attention to an over-dependence and emphasis on no fewer than 27 leprosaria, and to a general weakness in out-patient services.

By good fortune, the neighbouring country of Malawi had already established, through the British Leprosy Relief Association (LEPRA) in London, its own Leprosy Control Scheme (see Molesworth, 1969). One of us (CM) was able to visit this area in late 1967 with a view to deciding if the scheme could be modified for use in Zambia, either as a demonstration or pilot project or as a practical and economic method of leprosy control. Its introduction into Zambia has proved possible. The present paper describes the first year of operation, with emphasis on the improvement in attendance rates and the remarkable clarification of facts and statistics which has resulted.

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CHOICE OF PROJECT AREA

Zambia covers over 290,586 sq. miles (over 780,000 sq. km) and has a total population of just under 4 million. Apart from the Luapula Valley in the north, few areas have a regular "mobile" visiting system for out-patient control and supervision, and any one of the 8 provinces could have been chosen with benefit to some of the 15,000 leprosy out-patients already registered in this country.

However, the Eastern Province was chosen for a number of reasons, of which the chief were: (1) an excellent tarred road was nearing completion and ran the whole length of the Province; (2) there was no petrol rationing in the Eastern Province at that time; (3) there was no overall Government control of leprosy and no developed out-patient supervision; (4) there was an excellent Mission leprosarium near the Provincial centre, with trained staff and a visiting surgeon highly skilled in reconstructive surgery; and (5) it was though likely that "routine" statistical reports and notifications from this area did not accurately reveal the true leprosy control situation.

ORGANIZATION AND METHODS

In June, 1968, LEPRA provided the services of an experienced leprosy control officer (A.H.D.), who had the great advantage of

having helped with the initial planning of treatment circuits in the LEPRA Project in Malawi. His posting to Zambia was accepted on the understanding that this country would provide: (a) Zambian medical assistants prepared to learn and eventually take over the major part of the work; and (b) petrol for and maintenance of all vehicles supplied by LEPRA.

The Eastern Province covers 26,682 sq. miles (68,000 sq. km), of which Chipata has 7114, Petauke 7333, and Lundazi 12,235. A full examination was made of the 2 most southerly districts, Chipata and Petauke, in order to determine as far as was possible the village density, quality of roads, and the numbers of leprosy patients already recorded at fixed treatment centres.

The planning and organization of treatment circuits at this stage is of fundamental importance to the success or failure of the project, and a separate paper in this issue (Drake, 1970) gives details of this (see p. 107). Briefly, the Landrovers with their teams are based on either the Provincial centre or one of the district centres and make frequent, regular and closely-timed circuits of the whole area under control. The scheme started with leprosy patients already registered at fixed Government or Mission centres. They were systematically transferred to treatment points which were either in their village or very much nearer to it than the previous treatment centre. At the same time, new patients presenting spontaneously, or being referred, were registered and started on treatment.

Towards the end of 1968, 2 Landrovers were already at work on treatment runs and 664 patients had been transferred to "mobile" control. By August, 1969, 3 Landrovers were in full operation and 1093 patints were registered, with attendance rates of nearly 85% coming for treatment and 77% for patients under review only—higher figures than had ever been known before in this or other Zambian provinces.

PERSONNEL

Before this scheme was envisaged, 9 Zambian medical assistants were sent to the All-Africa Leprosy and Rehabilitation Training Centre in Addis Ababa for an intensive course in rural area supervision of leprosy. All successfully completed the course and returned to Zambia to take up positions of responsibility. Two were assigned to this project, and have very largely taken over control of their respective areas. Each Landrover carries a junior grade of worker (Tuberculosis/Leprosy Preventive Assistant) to help with records and handling of patients.

For the third district another medical assistant with good local experience of leprosy has joined the scheme, and this probably completes the present staff needs—a remarkably small and economic group for the care of well over 1000 patients in such an area.

STATISTICS

Table 1 shows the situation before patients were allocated to our mobile treatment circuits. (These figures were finally brought together towards the end of 1968.) Those for district No. 3 (Lundazi) were collected on a small number of visits and are given with considerable "benefit of the doubt"; the real attendance rates are almost certainly not as good as those expressed in this table.

TABLE 1

Total number of patients and attendances in Eastern Province prior to transfer to mobile treatment circuits, as at December, 1968. ("Regular" attendance is taken to mean attendance on 75% or more of possible occasions, and "out of control" to mean absent (or lost sight of) for 2 years or more.)

District	*No. of fixed centres treating leprosy*	*Total leprosy cases originally registered*	*No. attending regularly*	%	*No. attending irregularly*	%	*No. not attending at all ("out of control")*	%
(1) Chipata	22	806	339	42	467	58	236	29
(2) Petauke	15	239	100	42	139	58	84	35
(3) Lundazi	17	212	123	58	89	42	66	31

Table 2 shows the latest position as clarified by the joint scheme, approximately one year after inauguration, that is as at August, 1969. The higher total presented to us at the outset (1257 as in Table 1) is due to the fact that we are still unable to trace over 200 names. However, many of these patients are believed to be dead or to have left the country, or the figures may represent double (or even treble) entries for one patient.

TABLE 2

Figures as at August, 1969, approximately one year after the beginning of the joint GRZ-LEPRA scheme, showing numbers and percentages of patients on treatment or review, and attendance rates.

Total no. of patients registered on GRZ-LEPRA Mobile circuits — 1093
Of these

	No.	%
On active treatment	960	88
On review only	133	12
Combined total of patients attending regularly	951	87
Therefore, total not attending regularly	142	13

TREATMENT

Treatment was started with dapsone tablets, using both 100 and 25 mg strengths. The maximum dose for any adult was 200 mg weekly, and this has now become standard practice throughout Zambia.

In the early stages of the scheme we contacted every patient once every 2 weeks. A dose was given with a drink of water, under direct supervision, and the following week's dose was handed to the patient in a plastic container, with careful instructions. This produced excellent contact with the people, gained their confidence, and resulted in attendance rates which were remarkably high.

However, it was felt that the second week's dose might not be taken by the patient, or taken at the wrong time. Commercially prepared reagent strips containing the usual para-dimethylaminobenzaldehyde solution were tried out on several hundred leprosy patients in other provinces who were taking dapsone under direct supervision as in-patients. The strips were found to be of no value whatever; the stated colour change did not occur with the dapsone dosage being used, or was so slight that it could not be clearly distinguished from the original light yellow of the paper. This failure, and the appearance of "deputies" sent to collect dapsone on behalf of a patient, especially if they were children, acted as a warning.

In early 1969 it was decided to make plans for the conversion of a Landrover for the giving of dapsone intramuscularly. This received further impetus from the preliminary reports of the use of DADDS, a development which it was thought might have important applications in Zambia and elsewhere. There is in fact no clear evidence that dapsone is sold or otherwise misused in Zambia, but this possibility, together with wrong dosage by the patient, wrong timing and malabsorption of the drug are ruled out by use of the intramuscular route. It does raise some difficulties, however, and these are discussed in the accompanying paper by Mr. Drake, in which the practical details of Landrover modification for giving drugs by injection are described.

CLOSURE OF LEPROSARIA

In 1968, one of the 3 Mission leprosaria in the Province was closed down. This was made possible by a number of factors, these including a great improvement in staffing and accommodation at what is now the remaining leprosarium for the Province, together with a very active programme against ulceration, with reconstructive surgery for selected cases. However, another very important factor was the out-patient service provided by GRZ-LEPRA for patients whose nearest treatment point would otherwise have been too far from their village.

In mid-1969 a second leprosarium was closed, and in this case the decisive factor was undoubtedly the provision by us of satisfactory out-patient treatment or supervision. Apart from the psychological trauma and disruption

of family life and wage-earning which admission to a leprosarium involves, it is known to cost 10 times as much as out-patient treatment. Even in this short period, the saving to Mission and Government must already have been significant.

The remaining leprosarium in the Province is now increasingly orientated towards the admission of the "problem" case, together with offering vocational guidance, education in anaesthetic problems, reconstructive surgery, teaching, and the provision of suitable footwear. Three years ago, this leprosarium had over 160 patients with ulcer problems, whereas today there are only 16 such cases; it is in fact becoming difficult to find typical perforating ulcers for teaching purposes.

CASE-FINDING

The WHO (1966) estimate for leprosy prevalence in Zambia was between 1 and 4.9 per 1000 of the population, and the likely figure for the Eastern Province is certainly not greater than this. Indeed, on the evidence so far, the prevalence in this area must be classed as low, and accordingly even more emphasis will now be given to the examination of contacts of infectious cases as the most likely productive group for case-finding. During the year, large numbers of schoolchildren and villagers have been examined; the figures for these, together with the numbers of confirmed cases presenting voluntarily at treatment points, are shown in Table 3.

In the year ending December, 1967, the Province notified 137 new cases of leprosy. In the first, somewhat tentative, year of the present scheme 190 cases have been notified, of whom no fewer than 148 of the patients presented themselves voluntarily at treatment points for diagnosis and advice.

TABLE 3

Case-finding, GRZ-LEPRA, August, 1968, to August, 1969, in schoolchildren, villagers, and patients presenting voluntarily.

Group examined	*No.*	*Leprosy cases found*	%
Schoolchildren	9431	21	0.2
Village examinations	3716	**21**	**0.6**
Patients presenting voluntarily	About 225	148	—

HEALTH EDUCATION

Thousands of posters in the local dialect explaining the main signs of leprosy have been distributed, mainly to schools. The 16-mm colour and sound film by LEPRA entitled *Out-patients not Outcasts* has been shown to thousands of schoolchildren, accompanied by a talk and discussion by a leprosy officer.

A short booklet, explaining in very simple terms the main facts about leprosy, has been written in the local dialect for the Adult Literacy Campaign, and 15,000 copies have been distributed in this Province through the Department of Community Development. Though unassessed as yet, this channel of communication and health education in leprosy could prove of lasting value, for the booklet has been accepted as standard reading material for adult literacy classes in Zambia, and is being printed in all the other main Zambian dialects.

RE-ASSESSMENT OF REGISTERED CASES

Only one of the 3 leprosaria in this Province had a programme of recall and re-assessment, and this was the one which now remains. For the purposes of re-assessment, journeys from the village to the leprosarium and back of nearly 400 miles (640 km) were not unusual. In 1967 alone, 77 patients travelled some 13,860 miles (22,000 km) for this purpose. In contrast, by the end of 1969 it is expected that GRZ-LEPRA will have reviewed and re-assessed about 1000 patients near their homes or in their villages at various points on the mobile treatment circuits. Comparison shows that at least twice the number of patients can be reviewed in this way at one-quarter of the cost in a given 12-month period.

Bacteriological examination, as elsewhere in rural areas of leprosy control in Zambia, has never been a strong point in this Province. However, the vast majority of all patients so far registered have at some time or other had

slit-skin smears taken at a leprosarium, and a trained member of the team is now doing this working during treatment circuits and reviews. WHO standards for clinical and bacteriological "inactivity" are being followed.

DISCUSSION

To people working in equatorial Africa and other hyperendemic areas, the figures presented in this paper will seem absurdly small. It is our belief, however, that big figures are not important in this context, and that what matters is the method of approach and whether or not it works.

These first-year impressions are presented because the results so far seem both practical and economic. In addition, the modifications used for a comparatively sparsely populated area could prove of importance if DADDS comes into general use. It is conceivable that the most effective and economical way of ensuring that antileprosy treatment is taken "early, regularly and for long enough" might be the injection of a correct dose of very long-acting dapsone into each patient intramuscularly. For in an area of the kind here described, with difficult roads and a hazardous wet season, there are serious limitations to the frequent supervision of oral treatment.

Mobile leprosy control is certainly not a new idea. Zambia has copied this scheme from the work of LEPRA in Malawi (to whom very full acknowledgement is due) and it is possible that they in turn had in mind the remarkable service in Ghana (Gold Coast) from 1955 to 1966. In the early years of this Ghana scheme, following a welcome delivery of 14 Landrovers from UNICEF, about 36 000 patients were receiving satisfactory out-patient treatment with dapsone (McElvie, personal communication). Jarison (1968) has drawn attention to the use of mobile teams in equatorial Africa and Madagascar in bringing treatment to 150,000 leprosy patients "who had hitherto not been included in any census or been under medical supervision of any kind—for fear of being shut up in leprosy hospitals".

Preliminary discussions are already well-advanced for expansion of the present pattern of work into another province of Zambia. Meanwhile in the Eastern Province serious thought is being given to the complete integration of the work into the general health services before the end of the third year of operation. Before the end of the second year it should be possible to reach a decision about the size of the leprosy problem generally and the likely prevalence of the disease, based on known registered cases, examination of contacts, and school and village examinations.

The absence of any initial investigation into individual and community attitudes to leprosy is in retrospect considered to have been a basic error. Little is known of this aspect of leprosy work in Zambia, and an enquiry lasting 6 to 12 months by an experienced officer would not only have made the pathway easier for this control scheme, but would also have given valuable information in the matter of case-finding. Even at this stage, however, an application has been made for a health educationalist to undertake this work and also to examine the next province under consideration. The third year of "handing back" leprosy control to the general services may well be the most difficult, but could be greatly helped by basic information on attitudes to leprosy combined with a health-education programme aimed at the general public, schools, political organizations, and the medical staff who will be re-involved with this work.

At the outset of this scheme it was not known how LEPRA might best contribute to leprosy control in the area chosen. The Association has of course provided not only 3 Landrovers, but also the services and salary of an experienced leprosy control officer. Apart from these considerable gifts the scheme, after one year of operation, appears to contribute mainly as follows: (1) a clear demonstration of how the work should be done; (2) a great improvement in facts, figures, statistics, reports; (3) a great saving in money, as compared with the conventional leprosarium approach; (4) the pro-

duction of high attendance rates due to close and repeated contact with the patients; and (5) a medium of great potential value for health education.

Finally, the experience gained with the modification of Landrovers for giving intramuscular injection and for "mobile" re-assessments may prove to have useful application elsewhere.

SUMMARY

The first year of a leprosy control project in the Eastern Province of Zambia is described.

This project is a co-operative one between the Department of Health in Zambia and the British Leprosy Relief Association in London, and is modelled on the latter's LEPRA Control Project in Malawi.

One year after the start of the joint project, 2 out of 3 leprosaria in the Province have been closed, attendance rates have improved very greatly, and remarkable changes in statistical information have been revealed.

Experience has been gained in the practical details of Landrover modification for intramuscular injection of dapsone, and it is thought that this might have wider application if DADDS lives up to its present expectations.

As the second year of the work proceeds, plans are being made to extend the work into another Province (Luapula). Meanwhile, careful thought is being given to 2 aspects of the work: (a) an estimate of the leprosy prevalence in the Province and a further definition of the overall size of the leprosy problem; and (b) the total re-integration of leprosy control into the general medical services before the end of the third year of operation.

ACKNOWLEDGEMENTS

We are indebted to the Permanent Secretary of the Department of Health, Lusaka, and to the British Leprosy Relief Association, London, for permission to publish this article.

We wish to record that the present scheme in Zambia is based almost entirely on the parent LEPRA Control Project in Malawi, at present under the direction of Dr. B. D. Molesworth.

Lastly, we thank Mr. Lloyd Stone, Mr. Alexander Kamanga, and Mr. Akabana Mulundumina for their enthusiastic co-operation in the work described.

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Lepr. Rev. (1970) **41**, 121-125

Leprosy in Burma

TIN SHWE

Medical Team Leader, Yame Thin District, Burma Leprosy Campaign

A brief history of the spread of leprosy into Burma is outlined and the present prevalence of the disease is discussed. In addition, a short epidemiology of the disease, the Leprosy Control Project in Burma, and the present role of leprosy colonies and institutions in Burma are presented.

SPREAD OF LEPROSY

No definite records exist regarding the origin and spread of leprosy in Burma, although there are indications that the disease may have been imported from India and China. During the past 900 years the Chinese have invaded Burma more than once and many Chinese remained in Burma. More recently, merchants from India have visited Burma for purposes of trade. Both Chinese and Indians live generally in the larger towns of Burma. Hence, leprosy has been more prevalent near the old Burmese capital towns.

After the first Anglo-Burmese war (1826) British traders established themselves in the coast areas and began exporting rice to the West. After the second Anglo-Burmese war (1852) and the opening of the Suez Canal (1868) there was a great increase in the amount of rice exported, and this crop depended for its cultivation on an influx of people from upper to lower Burma. Many Indians also came to Burma and their numbers doubtless included some with leprosy. Thus leprosy, which had hitherto been localized to the larger towns, began to spread into the villages.

The second large migration of Burmese took place during the Second World War (1941-45). This time the direction of movement was from lower Burma to upper Burma.

The third migration occurred immediately after the war, because of the unsettled state of the outlying areas; the movement was therefore from rural to urban areas, in other words from areas relatively free of leprosy to areas where leprosy was already present. These successive migrations have had their influence on the spread of leprosy in the country (Dr. Kyaw Lwin, personal communication).

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PREVALENCE

The earliest records of leprosy as derived from census reports indicate that the prevalence of the disease in lower Burma in 1867-72 was 1.16 per 1000, in 1881 it was 0.69, and in 1891, 0.63 per 1000. According to the 1931 census there were 11,000 cases of leprosy in the whole country.

Leprosy surveys carried out between 1932 and 1941 in 9 districts of Burma, indicated an average prevalence of 17.4 per 1000 of the population (Dharmendra, 1953).

In 1951, Dr. Dharmendra (WHO consultant) estimated the prevalence of leprosy over the whole of Burma to be about 5 per 1000, or about 100,000 cases for the whole country. In 1953, a WHO survey team (WHO, 1957) estimated the leprosy prevalence in hyperendemic areas in Shwe Bo and Myin Gyan districts in Central Burma, as 25 per 1000 (equivalent to 591,600 in a population of 23,664,000)—but this was an overestimate.

The Burma Leprosy Campaign, begun in 1952, registered an increasing number of patients, and in 1969, the total number registered was 209,706. The Campaign had now covered most of Burma. The probable prevalence of leprosy throughout the country is in the region of 10 per 1000, or 250,000 cases in all. (Estimate

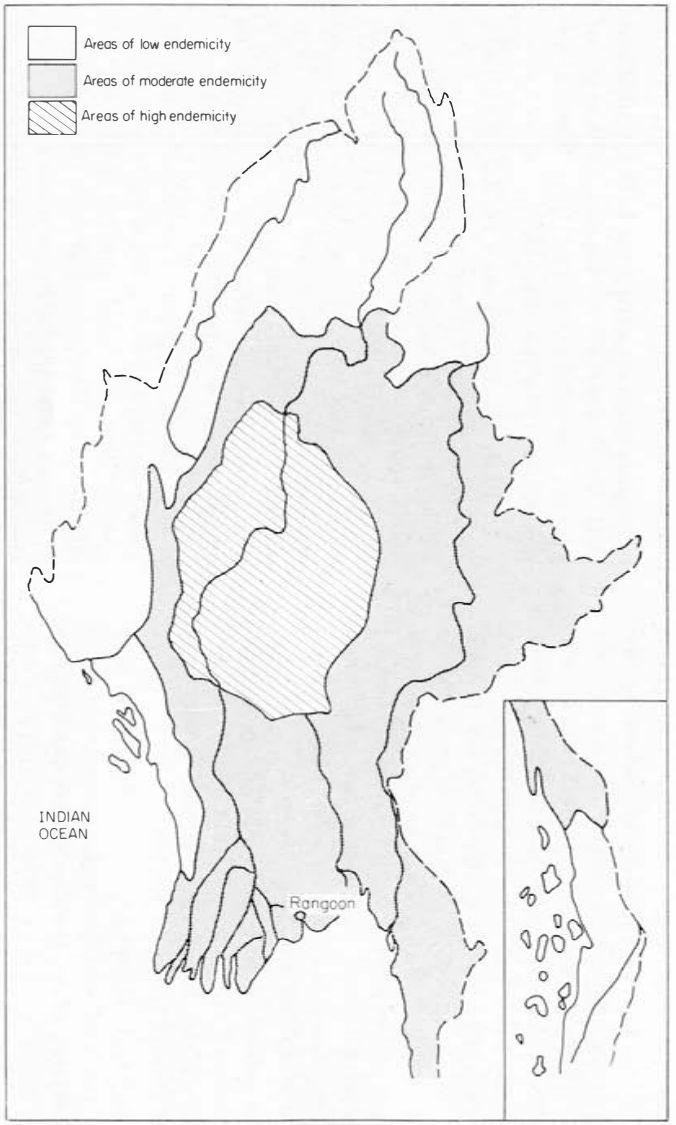

FIG. 1
Distribution of leprosy in Burma.

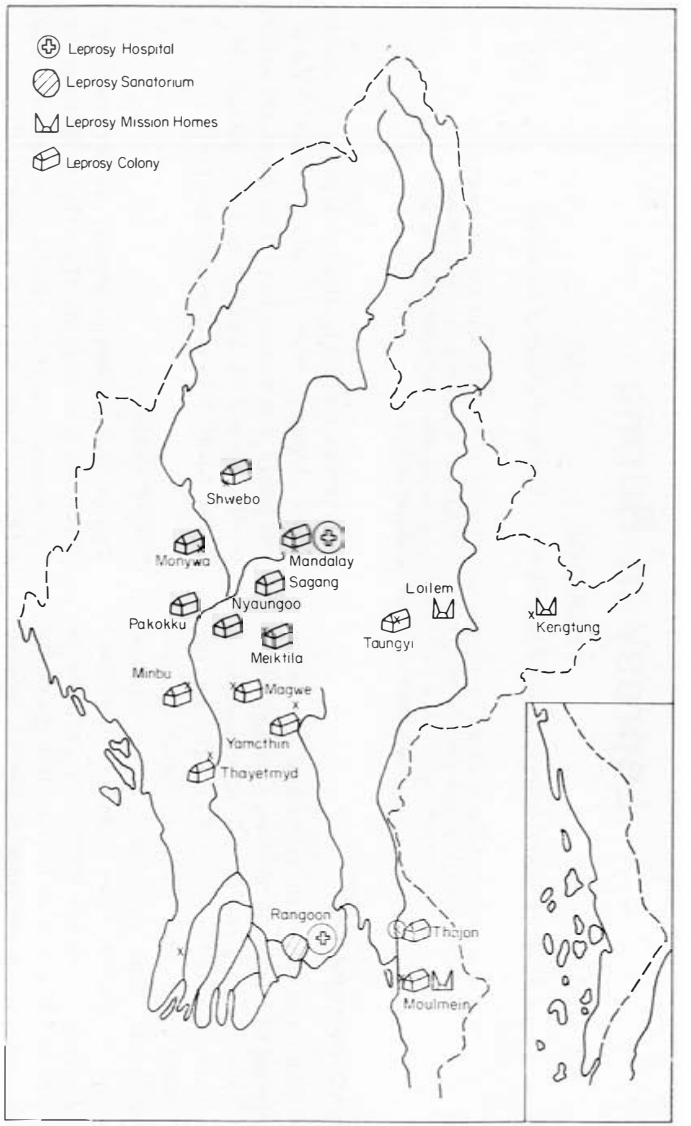

FIG. 2
Leprosy hospitals, homes and colonies in Burma.

of the Directorate of Health Services, Union of Burma.) These figures from Burma are indeed high when compared with neighbouring countries such as Ceylon (1963) 0.97 per 1000, Pakistan (1963) 2.23, China Mainland (1960) 3.42, India (1962) 5.56, Thailand (1963) 6.94, and Nepal (1962) 7.8 per 1000.

DISTRIBUTION

No part of the country is free from the disease, but its distribution is not uniform. The dry zone of Central Burma with an annual rainfall of below 4in. (10cm) has the highest prevalence rate (up to 40 to 50 per 1000). The coastal areas (Arakan Division, the lower part of Tenesseram Division) and the Chin Special Division (the hilly area bordering on India) have low rates, less than 5 per 1000. The remaining areas (Shan States, Irrawaddy Division, and areas outside the dry zone) have moderate rates.

The proportion of patients with lepromatous leprosy is approximately 25% in Burma, a figure comparable with that found in other Mongolian races, but distinctly higher than that in India (20%) or Africa (6 to 10%).

FREQUENCY OF DISABILITIES

There is a high incidence of disability among leprosy patients in Burma, with rates of 44.66 and 52.72% in the Shwe Bo and Myin Gyan Districts respectively, compared with a rate of 23.4% in Northern Nigeria. The figure for Burma, however, may be related both to the type of leprosy and the size of the untreated backlog of leprosy sufferers.

LEPROSY CONTROL PROJECT OF BURMA

Before World War II there was only one leprosy officer in the Department of Health and he was responsible for the leprosy campaign in the whole of the country. After the war, in 1951, assistance from the United Nations was forthcoming. Dr. Dharmendra visited Burma as consultant for the WHO, and as a result, the Burmese Government made plans to begin leprosy control, which was inaugurated the following year with the help of WHO.

In 1952-3 The Central Leprosy Institute (known as the "Special Skin Clinic") was established in Rangoon near Rangoon General Hospital, and at once instituted courses of training for medical and paramedical workers. In 1953 a Government Leprosy Sanatorium with accommodation for 450 patients was inaugurated at Htauk Kyant. In 1957-8, with the co-operation of WHO and UNICEF, an intensive programme for the control of leprosy was drawn up and implemented initially in pilot areas in the states of Shwe Bo, Myin Gyan, and Shan. On the basis of the experience gained in these pilot areas, the programme for leprosy control has been expanded to other hyperendemic areas. Apart from the actual treatment of leprosy patients, sources of contagion are traced. In the Magwe pilot area, the team leader (who is a medical officer) has charge of 18,000 patients; he is assisted by 3 inspectors, one assistant inspector, and 51 junior leprosy workers, and has at his disposal 4 jeeps, 5 motor cycles, and 48 bicycles.

From 1956 onwards, UNICEF has helped the leprosy campaign with equipment and transport. In 1964-5 the following 3 organizations assisted the Burma Leprosy Control Programme by contributing $150,000 (U.S.) through WHO to pay for additional staff over a period of 5 years, namely: (1) International Committee for Assistance to Leprosy of the Order of Malta, (2) Committee of Emmaus Suisse (Switzerland), and (3) Deutsches Hilfswerk (Germany). A 5-year programme (1963-8) was drawn up for leprosy control throughout the country.

In July, 1966, the Burmese Government established 2 leprosy hospitals (after nationalizing leprosy asylums in Rangoon and Mandalay) to serve as the main centres of the campaign.

The leprosy control work in Burma, which has now been expanded to 34 project areas covering almost the whole of Burma, is under the Assistant Director of Health Services, Rangoon. The main objects of these field units are to discover new cases of leprosy and to provide regular treatment for all registered patients either through leprosy clinics or by house-to-house visits.

By March, 1968, 181,524 leprosy patients had been registered, of whom 172,616 (or 76% of the then estimated total number of patients in Burma) were under regular treatment; 85% of them are in the rural areas, where the bulk of the population lives (see Fig. 1).

LEPROSY COLONIES AND INSTITUTIONS IN BURMA

Before World War II

After the annexation of Burma by the British Government in 1885 the missionaries also came along with the new government officials. The Roman Catholic Mission established 4 large asylums for leprosy patients and the Mission to Lepers (International and Interdenominational) established a further 3. In 1930 the Government appointed one special leprosy officer for Burma. He was sent for training under Dr. Ernest Muir at the Calcutta School of Hygiene and Tropical Medicine. In those days "isolation of infected lepers" was the only measure advocated to all leprosy workers to check the spread of the disease. On his return from Calcutta the leprosy officer organized the establishment of leprosy colonies in various districts of Burma. In order to establish these colonies the Burma branch of the then British Empire Leprosy Relief Association (now LEPRA) gave a cash grant of Rs 500 initially and subsequently an offer of one rupee per head per month. This kind of financial help stimulated the formation in many localities of District Leprosy Relief Associations and led eventually to the establishment of leprosy colonies in 9 districts.

After World War II

After the war 6 large leprosy colonies belonging to the missionaries were re-established as soon as possible. The Baptist Mission modernized their colonies to form 2 leprosy homes and hospitals. Similarly the voluntary associations had also re-established 17 smaller colonies for leprosy patients. The Government also established a leprosy sanatorium near Rangoon (see Fig. 2).

In 1963 the total number of patients living in leprosy colonies from all over Burma was 3681, which constitute only 1.5% of all the known patients in the country. Keeping this small percentage of leprosy patients in colonies will have no significant effect on the control of leprosy and at the same time it is a big burden on the Government. Moreover, many of the patients in these colonies later lost contact with their families and friends and became permanent dependants of the colonies, thus creating further social and other rehabilitation problems.

Realizing the innate difficulties and drawbacks the Government therefore decided to limit the admission of new patients into these colonies from the year 1963. On 22 July the Government nationalized the leprosy asylums at Rangoon and Mandalay and established 2 leprosy hospitals, which are now serving as research and training centres for the Burma Leprosy Campaign.

ACKNOWLEDGEMENTS

I express my gratitude to Dr. U Kyaw Lwin, Assistant Director (Leprosy), Directorate of Health Services, Burma, under whose guidance this paper was prepared.

I also wish to express my thanks to the following, with whose help all the data used in this paper were obtained: Dr. U Khin Mg Gyi, M.S. Leprosy Hospital, Mandalay; Dr. U Hla Toe, Regional Leprosy Officer, Rangoon; Dr. U Pe Khin, M.S. Leprosy Hospital, Rangoon; Dr. W. Edwards, M.S. Leprosy Home and Hospital, Moulmein; Dr. U Saing of Htauk Kyant Leprosy Institute; and Mr. Saw Thar Phwe of the Directorate of Health Services.

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Lepr. Rev. (1970) **41**, 126-128

Abstracts

The following abstract is reprinted, with permission, from *Trop. Dis. Bull.*, 1970, **67**, 1:

1. **Thalidomide in the treatment of lepra reactions,** by P. La Rosa and A. Casciano. *Minerva Derm.*, 1968, **43**, 166. English summary.

The authors from Messina treated 15 patients suffering from leprosy by thalidomide. Six patients had the lepromatous form, 7 the intermediate form, and 2 the tuberculoid form. The dose of thalidomide used was 300 mg/day, 2 tablets of 50 mg being given every 8 hours for a period which depended on the regression (or not) of the lepra reactions, but was usually from a few days to a week. No other drugs were given during the thalidomide treatment. When there was repression of the lepra reactions the dose was reduced progressively to 50 mg/day and continued for up to 30 days, but in the cases where there was no repression of the lepra reactions after 8 days, the thalidomide treatment was suspended.

The results were: lepromatous form, 6 patients treated, 3 excellent, 1 moderate, 2 failures; intermediate form, 7 patients treated, 3 excellent, 2 moderate, 2 failures; tuberculoid form, 2 patients treated, both showed moderate improvement. The effects of the drug were usually seen after 24 hours and became more evident in the days following. Side-effects noted were asthenia, loss of appetite, and somnolence but these lessened with the improvement in the clinical condition and ceased with the reduction in dosage. No changes caused by the drug were seen after the usual laboratory tests on blood, liver function or urine. The authors state that although only a few patients were treated and the results favourable in only about 50% the drug would appear at present to be the treatment of election in lepra reactions.

W. K. Dunscombe.

The following 4 abstracts are reprinted, with permission, from *Trop. Dis. Bull.*, 1970, **67**, 2:

2. **Immunologic reactivity in patients with leprosy,** by J. N. Sheagren, J. B. Block, J. R. Trautmanand S. M. Wolfe. *Ann. Intern. Med.* 1969, **70**, 295.

Alterations in some aspects of immunologic reactivity in a group of (38) patients with leprosy were found primarily in patients with the lepromatous form of the disease (32). Such patients had impaired lymphocyte transformation to streptolysin O antigen. The ability to form circulating antibodies was preserved. Levels of IgG and IgA immunoglobulins were increased in lepromatous disease while IgM levels were normal in all groups. The concentration of serum complement was normal in all patients with uncomplicating disease but was elevated in those lepromatous patients suffering erythema nodosum leprosum (ENL) reactions or amyloidosis. Reticuloendothelial system phagocytic function was increased in patients with lepromatous leprosy and especially in those with ENL reactions.

3. **Secondary amyloidosis in leprosy,** by J. C. Sachdex, D. Puri and S. Bansal. *Lepr. India*, 1969, **41**, 73.

Three cases of amyloidosis secondary to lepromatous leprosy have been reported. Two patients developed nephrotic syndrome and the third renal failure due to amyloid deposits in kidney. The definite diagnosis of renal amyloidosis was established by positive renal biopsy. Although amyloidosis has been regarded as rare in lepromatous patients in India, yet we should be on the look-out for this complication. The efforts may prove rewarding in an occasional patient.

4. **Hyperreflexia and spastic paralysis among New Caledonian leprosy patients,** by J. A. Brody, Y. Yase, G. Chemier and Y. Philippe. *Am. J. Trop. Med. Hyg.*, 1969, **18**, 132.

The authors confirm the findings of Desmoulins and Zeldine (*Trop. Dis. Bull.*, 1969, **66**, abstract 213), who reported spastic paralysis of upper neurone type confined to patients with leprosy in New Caledonia who had been treated with sulphones. Complete neurological investigations of patients with leprosy with suggestive symptoms revealed 18 suffering from frank spasticity, mainly of the lower limbs. Further enquiry among the remaining in-patients with leprosy disclosed that 10 out of 41 Melanesians examined (out of a total of 99), and 5 out of 10 Europeans examined (out of 48) had pathologically hyperactive reflexes in the upper extremities. (It is noteworthy that the prevalence rates of leprosy are said to be approximately equal in the Melanesian and the European population.) No case of spasticity was discovered among 23 patients with tuberculosis, and none has been reported from the largest hospital complex in New Caledonia.

The authors compared this syndrome with cases of spasticity reported among malnourished populations and war prisoners, and consider that it appears to be more closely related to nutritional and toxic syndromes than to motor-neurone disease reported from other Pacific areas (or to a condition induced by a virus with a very long silent period). It has not been recorded from countries where treatment of leprosy with sulphones has been widespread for years.

(Perhaps a key sentence in this paper is the following: "The major industry on the island is nickel-mining; almost the entire population is engaged in some work related to this industry." It is not impossible that dapsone may potentiate or accelerate the known neurotoxic properties of nickel.)

S. G. Browne.

5. **Histoid leprosy,** by R. E. MANSFIELD. *Arch. Path.*, 1969, **87**, 580.

This is an account of 5 new cases of histoid leprosy. Points of interest are that all of the patients had a history of leprosy of at least 20 years duration, and that 4 of the 5 had become resistant to the drug with which they were being treated; bacilli were abundant and the lesions were rapidly growing.

The pathology of histoid lesions has already been fully described by Wade (*Trop. Dis. Bull.*, 1964, **61**, 673). The object of the present communication is to draw the attention of general pathologists to the differential diagnosis of histoid leprosy and of dermatofibroma and similar skin tumours, which may also be found in patients with leprosy.

D. S. Ridley.

The following 4 abstracts are reprinted, with permission, from *Trop. Dis. Bull.*, 1970, **67**, 3:

6. **Pharmacodynamic effects of the diformyl derivative of diaminodiphenyl sulfone (DDS),** by D. M. AVIADO, G. MARROQUIN and S. R. SHORE. *Int. J. Lepr.*, 1968, **36**, 432.

The antimalarial activity of the diformyl derivative (DFD) of dapsone (DDS) is presumably not due to conversion of the drug *in vivo* to the parent substance, because it is more active, and the experiments reported in this paper were aimed at confirming that the drug is not changed *in vivo* and at characterizing its pharmacological action.

The intravenous LD50 of DFD in the anaesthetized cat was 255-350 mg/kg which compares with 55-180 mg/kg for DDS. In the anaesthetized dog, infused intramuscularly at the rate of 1 mg/kg/minute, it caused hypotension and increased pulmonary resistance.

The blood levels after oral administration of DFD and DDS to rabbits gave similar blood levels and as urinary excretion studies did not reveal any evidence of DFD being excreted more slowly than DDS, the high antimalarial activity of DFD reported earlier (*Trop. Dis. Bull.*, 1968, **65**, abstract 493) cannot be explained by differences in rates of excretion. In immature rats, 10 mg DDS per kg caused 19% goitrogenic effect, as measured by increase in thyroids, whereas 100 mg DFD per kg had no similar effect. In rabbits there was no evidence of abnormal forms of haemoglobin being produced.

The authors suggest that, if DFD can be shown to have activity in mouse infections with *Mycobacterium leprae*, it should be tried in human infections.

S. R. M. Bushby.

7. **Chemotherapeutic trials in leprosy. 6. Pilot study of the riminophenazine derivative B 663 in low dosage (100 mg twice weekly) in the treatment of lepromatous leprosy,** by M. F. R. WATERS. *Int. J. Lepr.*, 1968, **36**, 391.

Clofazimine (B 663, Geigy) was given at a dose of 100 mg twice weekly to 8 light-skinned patients with lepromatous leprosy, previously untreated. The Morphological Index fell from an average of 30 to 0.5% in 4½ months, and the clinical and histological improvement was similar to that of patients taking clofazimine at a dose of 300 mg daily, or dapsone in standard doses. Skin pigmentation developed more slowly and was less intense than in the case of patients taking higher doses of clofazimine, and no diarrhoea occurred.

The author discusses the difficulties of blind assessment of patients taking a drug that produces changes in skin colour.

(For Part 5, see *Trop. Dis. Bull.*, 1968, **65**, abstract 925.)

S. G. Browne.

8. **Isolation of a strain of *Mycobacterium lepraemurium* from normal laboratory mice,** by S. R. PATTYN and G. VERDOLAEGE-VAN LOO. *Ann. Soc. Belg. Méd. Trop.*, 1969, **49**, 465.

"Isolation of a strain of *Mycobacterium lepraemurium* from 'normal' laboratory white mice is related.

Its implication on foot pad passage work with *Myco. leprae* is discussed."

9. **Biochemical and ultrastructural study of the relationship between lysosomal enzyme activities and chemotherapy,** by F. KANETSUNA and T. IMAEDA. *Int. J. Lepr.*, 1968, **36**, 417.

This paper describes the morphological and biochemical effects of dapsone (DDS), glucosulphone (Promin) and streptomycin on lysosomal activities in mice infected with *Mycobacterium lepraemurium*. Studies by other workers have shown that chemotherapy with dapsone elicits the formation of the opaque droplets around leprosy bacilli in the human disease, and because these droplets contain acid phosphatase they were named lysosomal substance. As this substance is not seen around bacilli in murine leprosy, the authors consider that these lesions could be useful for confirming whether or not chemotherapy provokes the formation of opaque droplets in human lepra cells.

In 2 experiments, mice were infected with *Myco. lepraemurium*; in the first, some of the animals were treated with sodium glucosulphone, and in the second, groups were treated with sodium glucosulphone, dapsone or streptomycin. In both experiments, uninfected mice were also treated with the drugs. At the end of periods of treatment of 3 and 6 weeks, the livers, spleens and mesenteric lepromas were removed from the mice of the first experiment and the lepromas and serum were removed after 6 and 19 weeks' treatment from the mice of the second experiment. The β-glucuronidase, acid phosphatase and cathepsin contents of the organs were estimated, and lysosomes and the lepromas were examined by the ultrastructural-cytochemical techniques of Ericsson and Trump (*Lab. Invest.*, 1964, **13**, 1427).

The results indicate that the enzymes are enhanced in the organs of the infected mice, irrespective of whether or not the organs contain bacilli; the serum levels were also raised, suggesting that the enzymes are released from the tissues. There was no evidence that the hydrolases accumulated in the lysosomes as opaque droplets, although there was evidence of major amounts dispersed throughout the cytoplasm. Streptomycin provoked increases of hydrolase activity without increasing the opaque droplets in lepra cells or bacteria-free histiocytes. Dapsone, on the other hand, not only increased the hydrolase activity in the lesions, but also enhanced the formation of the acid-phosphatase active droplets; sodium glucosulphone had less effect.

On the basis of these findings, the authors consider that anti-leprosy drugs, especially dapsone and streptomycin, not only have anti-mycobacterial activity, but also elicit lysosomal hydrolase activities that may indirectly inhibit bacterial metabolism.

S. R. M. Bushby.

Letter to the Editor

The report of Dr. Crawford in *Leprosy Review* of July, 1969 (**40**, 159), about the reduction of leprosy prevalence in Northern Nigeria from 43/1000 in 1952-5 to 1.6/1000 in 1967-8 is extremely interesting and highly significant. If his findings are correct, this is the greatest argument for widespread DDS prophylaxis yet submitted.

As part of that widespread use of DDS in Northern Nigeria during that period, I must admit that my colleagues and I resisted the idea of such "promiscuous" use of a dangerous drug. The cost of DDS on the black market was then 6d. per tablet (a workman's wage was then 10d.). The Government's policy of providing DDS free to all requiring or suspected of requiring anti-leprosy therapy completely knocked the bottom out of the black market. Dr. Crawford's study would indicate that it would also knock prevalence of leprosy down rapidly.

The evidence for, and support of, DDS prophylaxis are increasing.

M. L. Brubaker

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