Lepr Rev (1995) **66,** 89–95

Editorial

TRAINING IN LEPROSY: DOES THE CURRENT STRATEGY NEED REVISION?

The training of medical, paramedical and other health workers in leprosy started long before the advent of dapsone chemotherapy in the mid-1940s, much of it carried out by missions, nongovernment or voluntary agencies in institutions, hospitals or leprosaria, often situated in remote parts of leprosy-endemic countries. The availability of dapsone and the early promise of its effectiveness in arresting or curing the disease in individuals and reducing transmission stimulated the gradual development of leprosy control programmes by ministries of health and nongovernment agencies, the extent and effectiveness of which was heavily dependent on the numbers of staff who could be recruited and trained to carry out a range of essential duties, often under arduous conditions. The crucial importance of training became increasingly apparent from the late 1940s onwards and much effort and money was put into the setting up of regional, national and eventually international centres for this purpose. Literally thousands of health workers, including doctors, programme managers, supervisors, nurses, paramedical workers, laboratory technicians, physiotherapists, social workers and health educators were trained for a wide variety of activities covering all aspects of patient care. The 'control strategy' during this period was based on case detection (preferably early) and the administration of dapsone as monotherapy, often over long periods of time, and it was not until 1982, when the World Health Organization (WHO) published its recommendations for the treatment of all cases of leprosy with multiple drug therapy (MDT)[1] that it became obvious to all involved in leprosy training that radical changes were needed in curriculum content, the design of teaching modules and teaching methods. There was a need to orientate, train or re-train even larger numbers of people (including primary or peripheral health care workers in some situations), to avoid the further spread of dapsone resistance, whilst at the same time bringing the other benefits of MDT to as many patients as possible, without delay. Many of these changes were made expediently, backed by the distribution of a wide range of teaching and learning materials from WHO, ministries of health and members of the International Federation of Anti-Leprosy Associations (ILEP) under the heading of Talmilep (Teaching and Learning Materials in Leprosy). Translations into French, Spanish and Portuguese were made and submitted to training centres in various parts of the world, many of them closely linked or supported by ILEP. A list of training centres and course content is given in the Appendix.

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During the 1980s, the annual reports from most international centres describe active training programmes with many applicants, based on courses which appear to have been both popular through the years and appropriate to the needs of individual applicants, ministries of health, nongovernment agencies and leprosy control programmes in the countries served by any given centre. Criticisms were, however, raised on matters which included: 1, the relevance of the curriculum to the 'real life' conditions which students would encounter on return to their countries of origin; 2, the cost-effectiveness of maintaining such institutions, often of considerable size and expensive in terms of salaries and overheads; and 3, the difficulties of recruiting people with the necessary ability and commitment to the field of training. These criticisms should, however, not conceal the fact that many centres were active, well subscribed and successful in achieving what they considered to be their most important objectives at that time.

By the early 1990s it was fast becoming apparent that the success of control programme strategy based on early case detection/diagnosis and the use of MDT for both paucibacillary and multibacillary cases was so remarkable that further changes would have to be made, not only in operational procedures and programme planning but also in training. Furthermore, the massive reductions in estimated and recorded prevalence rates consequent upon the increasingly wide implementation of MDT, together with the development of an elimination strategy by WHO (based on a figure of less than 1 case per 10,000 of the population), were leading, perhaps inevitably, to the general perception of leprosy in many quarters as a disease no longer calling for serious concern. In a recent editorial in this Journal,[2] Feenstra has drawn attention to the possibility that this may undermine fund-raising and the need for persistent and sustained effort, well into the next century, in order to achieve a realistic level of 'elimination' at national and subnational level, combined with good standards of disability prevention and management.

These developments have not escaped the attention of boards of management and training directors, who have also taken note of the fact that some of their courses are now undersubscribed, for reasons which are so far unclear. Are some courses now seen to be irrelevant? Is the quality of teaching unsatisfactory? Are some centres now short of suitable cases for teaching? Have the referring agencies already concluded that money available for training would be better spent on staff working with other diseases? In seeking the answers to these questions, it also has to be recognized that an increasing amount of teaching, training and orientation is now carried out locally and at low cost, at district, regional or state level, using workshops or short courses, attended by large numbers of health workers.

In view of the remarkable differences between leprosy-endemic countries with regard to (a) the stage of development of their control programmes, and (b) the extent of MDT implementation,[3,4] it is difficult to comment on the world situation in general terms, but there are some important lessons to be learned from the situation in India, which may be relevant elsewhere. From the early days of the National Leprosy Control (later to be changed to Eradication) Programme, the Government placed great emphasis on the establishment and use of training centres in various parts of the country. There are no fewer than 49 centres in India of which 14 are run by voluntary organizations. Between 1955 and 1991 a total of 21,200 paramedical workers and over 5,500 medical officers had been trained.[5] Impressive though these figures may seem, they have to be assessed against the very large number of people working in the NLEP at any given time, whilst also taking into account a list of adverse comments on the activities and achievements of

these centres in successive reports from *Independent Evaluations* of the National Leprosy Eradication Programme. The report of the most recent (1991)[6] drew attention to deficiencies in the recruitment and training of medical officers, nonmedical supervisors, laboratory technicians, physiotherapists and health educators. Capacity utilization was described as extremely poor—and inexplicable in view of substantial numbers of workers found, during the Evaluation, to be untrained in each category. The uptake for medical officers was astonishingly low at 16·7% and site visits to various parts of India confirmed that many medical officers in the NLEP had received no training in leprosy at all. They were frequently unable to recollect any useful input of teaching on the subject during their undergraduate days in medical colleges—a reminder of the view recently expressed by two highly experienced Indian leprologists in a *Letter to the Editor* of this Journal[7] concerning the neglected and untapped potential of medical students, many of whom apparently receive little or no information or teaching on the subject during their course of training. The unsatisfactory situation with regard to training in India is now complicated by the fact that training or orientation is frequently organized at district level (without the involvement of government training centres) and is encountering problems with regard to the needs of (a) specialized (vertical) NLEP staff, who have a vastly reduced workload following MDT implementation; and (b) general (horizontal) multipurpose workers at primary health care level who are reluctant to cooperate because they know full well that NLEP staff have received financial incentives for work in leprosy. India has a vertical programme, but if integration is eventually to be introduced and succeed, there is clearly a need to re-examine the training priorities, paying careful attention to the attitudes of peripheral health care workers.

With regard to the future of the training of professionals in leprosy in general, the participants of Workshop 7 at the 14th International Leprosy Congress in Orlando in 1993 listed 5 recommendations covering: 1, learning and education methods; 2, curricular priorities; 3, training of trainers; 4, production of training materials; and 5, selection of students. Under 2, the need to 'tailor' training courses to low or high MDT coverage was mentioned, including the possible need to shorten courses in some situations, and emphasis was given to 'hidden programme needs', such as patient education, communication skills, management and psychosocial aspects. As events move towards elimination, the need to develop appropriate strategies for integration was also stressed. The Report of this Workshop does not in any way suggest that existing training centres should be closed or reduced in number, rather that continued efforts should be made to '... strengthen and consolidate what has already been achieved'.

Looking at the situation now (early 1995), it seems apparent that the present activities and future contribution of training centres call for yet further analysis and assessment. Despite the inherent difficulties in making generalizations about a disease which still has significant numbers of cases in 79 different countries, ranging from India with 1 million cases, to a group of 40 other countries which are expected to reach their elimination target in the near future, provided that present levels of activity are maintained,[3] it is surely clear that our training strategy in leprosy is due (in some countries overdue) for revision. Combined services with tuberculosis, skin and/or venereal disease have of course already received considerable attention and been established in some countries, but most observers appear to view integration of leprosy into the general health services, using the primary or peripheral health care system with supervision at district level, as a more important option for the future. If this proves correct, as seems very likely, there will be a

need to train large numbers of health care workers and to provide them with appropriate teaching and learning material, including the use of local languages. Ideally, this training should be provided by the teaching staff of paramedical schools or those responsible for the training of primary health care workers, but it is exceptional to find teachers in these situations with even basic knowledge and experience of the subject and they are often poorly supplied (if at all) with information on the national programme, or suitable teaching and learning material, if necessary in their own language. Whether the trainee trainers come from the staff of established paramedical or primary health care schools, or from the ranks of the national leprosy or leprosy–TB programme is a matter for further discussion. Either source could be valuable in pursuing the main objective of achieving a reasonable level of knowledge and awareness in health staff in integrated programmes on a regular and systematic basis.

Some training directors have already proposed that the training of trainers should now become the most important and possibly the only institution-based training activity, arguing; 1, that it is an important matter, calling for urgent attention if the transition from vertical (specialized) to horizontal (general) services is to take place with reasonable safeguards for the level of training of general health staff, and 2, that almost all other courses, with the possible exception of those dealing with management skills for senior staff, are better conducted locally (in districts, states or regions) and not in institutions. It has also been suggested that the job description of expert teaching–training staff members should include site visits to the countries of origin of students on a regular and systematic basis, participation in 'decentralized' training activities in nearby countries, and active involvement in health systems research, including strategies for improved case detection, MDT implementation and the prevention of disability.

Despite the risks, many observers now believe that integration will ensure the widest possible coverage of patients for leprosy control and elimination. If this is so, we must surely revise our strategy for training without delay, if only to ensure that enough trainers are available for the very large numbers of health staff who will be involved. Although written in 1988, the advice of the WHO Expert Committee in their Sixth Report,[8] under the heading of 'Manpower Training' is still highly relevant: 'Experience has shown that considerable training and re-training are necessary to implement the relatively new approaches to leprosy control and patient care that have been recommended. In addition, successful integration of leprosy into the basic health services necessitates training for the staff in those services: even in endemic countries, few doctors or other health staff receive training in leprosy at medical school. Implementation of training on the required scale demands a systematic approach, an appropriate strategy and a thorough command of the technology of training itself on the part of those responsible.'

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Appendix

All Africa Leprosy and Rehabilitation Training Centre (ALERT), Ethiopia/Ethiopie. PO Box 165, Addis Ababa, Ethiopia

Prevention and management of disabilities, Leprosy and tuberculosis control, Information, Education and communication, Training of trainers, Essentials of leprosy for non-medical staff, Social rehabilitation, Tropical Dermatology, Essentials of leprosy for medical staff, The eye in leprosy, Supervision of a district leprosy control programme.

Centre for Educational Development in Health (CEDHA), Tanzania/Tanzanie PO Box 1162, Arusha, Tanzania

Tuberculosis control: Epidemiology, Intervention strategies, Operation of a national programme, Bacteriology.

OCCGE—Institut Marchoux, BP 251, Bamako, Mali

Diagnostic et traitement de la lèpre, Réhabilitation du lépreux, Techniques de laboratoire pour la lèpre, Organisation et gestion de la PCT, Techniques d'intervention pour les malades lépreux, Préparation du CES de Dermato-léprologie, Bacilloscopie de la lèpre dans les laboratoires de référence, La lèpre: clinique et PCT, Organisation et Gestion de la PCT, Laboratoire lèpre: Bacilloscopie, Formation à la Gestion des programmes de lèpre, Mission chirurgie-lèpre.

Institute 'Lauro de Souza Lima', Rod. Cte. João Ribeiro de Barros, Km 225/226, Bauru—SP, CEP 17100, Brazil

Hansenology, Prevention of disabilities, Rehabilitation.

Centre Inter-Etats d'Enseignement Supérieur de Santé Publique d'Afrique Centrale (CIESPAC). BP 14513, Brazzaville, République du Congo

Diplôme Professionel de Santé Publique (DPSP), Diplôme de Technicien Supérieur en Santé Publique, Certificat d'Etudes Spéciales de Santé Publique (CES).

Gillis W. Long National Hansen's Disease Centre. United States Public Health Service Hospital, 5445 Point Clair, Carville, LA 70721, USA

Medical seminar in hansen's disease, International seminar on hansen's disease, The, Carville hand seminar: anatomy, biomechanics, insensitivity, Care of the insensitive Foot: the Carville approach.

Leonard Wood Memorial Centre for Leprosy Research, PO Box 727, Cebu City, The Philippines

Clinical research, Epidemiological research, Advanced laboratory techniques.

Institut de Léprologie Appliquée de Dakar (ILAD), BP 11023, Dakar-CD, Sénégal

Cours de Réadaption: Module 1, Cours de Réadaption: Module 2, CES de Léprologie. Cours de cordonnerie pratique, Stages individuels.

Sanatorio de San Francisco de Borja, 03791 Fontilles (Alicante), Espagne

Formation en Léprologie.

Schieffelin Leprosy Research & Training Centre, SLR Sanatorium PO, Tamil Nadu, 632 106 Karigiri, South India

Medical officer's course, Non-medical supervisor's course, Physiotherapy technician's course, Laboratory technician's course, Smear technician's course, Paramedical worker's course, Shoe-maker's course, Diploma course in Prosthetic and Orthotic Engineering. Ophthalmic aspects in leprosy, Condensed courses in leprosy, Refresher course in skin smears, Eye care in leprosy, In-service training in: Medicine, Surgery, Surgical Rehabilitation, Pathology, Laboratory Technology, Ophthalmology, Epidemiology, and Leprosy control. Medical record keeping, Basics of physiotherapy in leprosy, Medical Students course, Psychosocial aspects in leprosy.

'Alfredo da Matta' Institute for Tropical Dermatology, Rua Codajas, No. 25—Cachoeirinha, Manaus CEP 69 065—130 AM Brazil

Leprosy control, Laboratory techniques/bacilloscopy, Leprosy control/Programme management, Medical registrarship in dermatology, Sexually dransmitted diseases (inc. AIDS), Sanitary dermatology, Surgical management: prevention and treatment of ulcers, and septic conditions, Reconstructive surgery (preventive and rehabilitative), Prevention of eye disability, Sanitary dermatology, Laboratory and STD, Out-patient department.

Centro Dermatológico Pascua, Dr. Vértiz 464, Esq. Av. Central, Delegación Cuahutémoc, CP 06780, Mexico City, D.F. Mexique

Spécialisation en dermatologie, léprologie et mycologie, Cours intensifs de dermatologie, léprologie et mycologie.

The Leprosy Mission—Purulia Leprosy Home and Hospital, PO Box 9, Purulia 723 101, West Bengal, India

Paramedical workers, Nursing and medical students, Physiotherapy technicians, Medical officers, Shoe technicians.

Philadelphia Leprosy Hospital, Salur 532 591, Vizianagram District, India

Medical officers, Paramedical workers, Laboratory technicians, MA social workers, Physiotherapy technicians, Medical students, MDT orientation for doctors, MDT orientation for government nonmedical supervisors, MDT orientation for paramedical workers, Orientation for nurses, Orientation in tuberculosis, Orientation for rural health workers, Communications skills and psychosocial aspects in leprosy, Prevention of disability.

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Experimental leprosy in monkeys. I. Sooty mangabey monkeys: transmission, susceptibility, clinical and pathological findings

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Summary A total of 31 sooty mangabey monkeys (SMM) (*Cercocebus torquatus atys*) inoculated by various routes with differing numbers of SMM-origin *Mycobacterium leprae* (ML) and 4 SMM inoculated with human-origin ML were observed for 4–12 years. SMM-origin ML was more pathogenic in SMM than human-origin ML. The spectrum of disease ranged from indeterminate to borderline and lepromatous in different animals. Some animals developed pure neural leprosy. Erythema nodosum leprosum (SNL) was also observed.

Combined intravenous/intracutaneous (IV/IC) routes of inoculation more effectively induced advancing, disseminated lepromatous forms of leprosy; IV or IC routes alone were less effective at comparable doses. Total IV/IC doses of SMM-origin ML equal to or greater than 5×10^8, with morphologic indices (MIs) ranging from 5 to 10%, produced advancing, disseminated LL leprosy in 92% of SMM. Lower IV/IC doses and inoculations by a single IV or IC route produced fewer leprosy infections and more spontaneous regressions. As a species, captive SMM are highly susceptible to experimental leprosy and provide an excellent model for the longitudinal study of leprosy.

Introduction

We previously reported detailed descriptions of naturally-acquired leprosy in 2 wild-caught, captive sooty mangabey monkeys (SMM).[1,2] The first, animal, A015, was diagnosed in 1979 and the second, G932, a former cagemate of A015, in 1986. The causative agent, identified unequivocally as *Mycobacterium leprae* (ML), was isolated

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Table 1. *M. leprae* exposure of miscellaneous SMM

Tabular No	Mangabey tattoo No	Source of inoculum	*M leprae*[1] inoculated (No $\times 10^{-8}$) (Route)				Dates		Clincal data[2]
			I.V.	I.C.	Other	Total	Inoculation	Disease	
1	A015[3]	Unknown	0	0	0	0	Unknown[3]	Unknown[3]	LL; RFM + Dap, 1/81
2	G932[4]	A015[4]	0	0	0	0	Unknown[4]	1976[4]	LL; RFM, 9/87
3	A022	SMM A015	12	15	0	27	3/80	2/81	Progressive LL; died 2/84
4	A023	SMM A015	12	15	0	27	3/80	2/81	LL; RFM, 2/84
5	A041	Human/armadillo	100	160	0	260	12/80	12/81	LL; Clfz, 11/88 + RFM, 1/89
6	A042	Human/armadillo	100	160	0	260	12/80	12/81	Regressive LL, neuritic deformities
7	D087	SMM A041	2·1	4·5	0	6·6	5/83	3/86	Neural leprosy
8	D089	SMM A042	2·1	4·5	0	6·6	5/83	None	Died 6/84
9	D088[5]	SMM A022	200	280	202	500	7/83	Unknown	Died 3/86 neural leprosy
10	D086[5]	SMM A022	0	0	0	0[5]	—[5]	None	—
11	D213	SMM A022	0	0	0·03[6]	0·03	9/83	None	—
12	D214	SMM A022	0	0	0·05[6]	0·05	9/83	None	—
13	F098	SMM D177	0·18	0·28	0	0·46	12/85	6/86	LL; regressive self-healed
14	F104	SMM D177	0·18	0·37	0	0·55	12/85	6/86	BL-LL; possible ENL, died 1/87
15	F100	SMM D177	0·92	1·4	0	2·3	12/85	6/86	LL; Clfz, 5/88 + RFM, 6/88
16	F102	SMM D177	0·92	1·8	0	2·7	12/85	6/86	LL; RFM, 12/88
17	G930	SMM F102	11·2	5·2	0	16·4	10/88	8/89	LL; 10/89; RFM, Clfz, Dap, 2/90
18	G931	SMM F102	11·2	5·2	0	16·4	10/88	11/91	LL, Died 11/92

[1] MIs from 5 to 10%.

[2] RMF, rifampicin; Clfz, clofazimine; Dap, dapsone.

[3] A015 contracted leprosy by natural, unknown means, and had transient followed by sustained lesions for an unknown number of years before documentation of leprosy by biopsy in 1979.

[4] G932 was housed for several years with A015 prior to 1979, and appears to have contracted leprosy from A015; leprosy was diagnosed in G932 in 1986 (Ref.[1]).

[5] D088 was inoculated by i.v. + i.c. + an intranasal route and remained housed together with its infant, D086.

[6] D213 and D214 were inoculated by exposure to aerosol-borne ML.

Table 2. Inoculation[1] of SMM with titrated *M. leprae* doses

Tabular No	Mangabey tatoo No	*M. leprae* inoculated (No $\times 10^{-8}$) (Route) i.v.	i.c.	Total	Disease onset (date)	Clinical data
19	D171	200	280	480	9.83	LL; RFM[2], 1986 regressive LL, neuropathy,
20	D172	200	280	480	9/83	CLFZ[2], RFM, 1988
21	D173	20	28·0	48	7/91	BL–LL neuropathy LL, neuropathy, RFM
22	D174	20	28·0	48	7/88	CLFZ, 7/88
23	D175	2	2·8	4.8	None	—
24	D176	2	2·8	4·8	9/83	LL, RFM, 6/86
25	D177	0·2	0.28	0·48	9/85	LLs, neuropathy, RFM, 1/84
26	D178	0·2	0·28	0·48	6/86	neuroedema, neuropathy

[1] Inoculated in July, 1983; ML inoculum from SMM A022 (see No 11, Table 1); MI, 10%.
[2] RFM, rifampin; Clfz, clofazimine.

Table 3. *M. leprae* inoculation[1] of SMM: dose and route study

Tabular No	Mangabey tatoo No	*M. leprae* inoculated (No $\times 10^{-8}$) (Route) i.v.	i.c.	Total	Disease onset (date)	Clinical data
27	E045	4.5	6.2	10·7	6/84	LL; disseminated; RFM[2] 11/85; healed
28	E042	4·5	5·9	10·4	None	—
29	E043	4·5	6·2	10·5	12/85	LL; disseminated; neuropathy involvement; RFM 5/87
30	E044	4·5	6·0	10·5	6/87	LL; disseminated; died 5/88 after RFM initiation
31	E038	0·04	6·0	6·0	12/85	Regressive/Progressive LL; neuritic deformities; MCLN[2], 1991
32	E039	0	6·0	6·0	6/84	Regressive LL; self-healed by 1/88
33	D215	0	6·0	6·0	None	—
34	E040	4·5	0·06	4·6	10/84	Disseminated/regressive; Clfz[2]; 3/88 + RMF, 5/88
35	E047	4·5	0·06	4·6	4/85	LL; disseminated; neuropathic deformities; died 1/88 after RFM initiation
36	E041	4·5	0	4·5	5/84	Scrotal lesions, regressed
37	E046	4·5	0	4·5	6/86	Disseminated BL–LL; neuropathic deformities; RFM, 5/87

[1] Inoculated in February 1984; ML inoculum from SMM A022 (see No 11, Table 1); MI, 3%.
[2] RFM, rifampin; Clfz, clofazimine; MCLN, minocycline.

from A015 and used to inoculate additional SMM; ML from human sources was also utilized to inoculate SMM.[3,4] These studies showed that SMM were susceptible to infection by ML from SMM or human sources. Starting in 1980, 31 SMM were inoculated with or exposed to ML originally isolated from SMM A015, and 4 SMM received human-origin ML. We summarize here our observations on these 35 experimentally- and the 2 naturally-infected SMM.

Materials and methods

Inoculations: in initial passage studies, nonulcerated lepromatous nodules were surgically harvested from A015; subsequently, subinoculated SMM were employed as a source of MI. Lepromata were obtained aseptically, minced and homogenized in cold phosphate-buffered saline using a Dounce homogenizer with a 40 ML mortar and Teflon pestle (Wheaton Scientific, Millville, NJ), passed through gauze and centrifiuged at 200× **G** for 5 min at 4°C. The acid-fast bacilli (AFB) in the supernatant were counted and morphologic indices (MI) determined by the method of Shepard & McCrae.[5] SMM were inoculated with ML suspensions, usually by combined intracutaneous (IC) and intravenous (IV) routes, using 2 IC sites per ear, the tip of the nose, an outer forearm, an outer calf and sometimes the periorbital regions. IV inoculations were made via the saphenous vein. In some experiments, titrated doses of ML were given by both routes, sometimes only a single route was utilized and, in a few instances, other routes of inoculation were used as described in the text.

Clinical observations: animals were observed daily and examined in detail 3–4 times per year or more, depending on the status of the animal, and the clinical aspects of the disease recorded. The Ridley–Jopling system was used to classify leprosy histopathologically.[6]

Results

Data describing 37 SMM, including the 2 natural cases, are presented in Tables 1–3. Each SMM in the Tables is identified by the tattoo number and/or a tubular number to facilitate locating the animals to which reference is made in the text. The tabular numbers have no significance other than to aid in the discussion, but are arranged in chronological order with regard to the time of inoculation, in so far as possible. In all, 22 (Nos 3, 4, 9, 13–22, 24–27, 29–31, 34 and 35) of 24 (92%) SMM given ML (MI = 5–10%) of SMM-origin by both IV and IC routes developed leprosy within 2 months to 7 years postinoculation (PI) (SMM numbers 5–8 received human/armadillo-origin ML directly or after passage in SMMs A041 or A042, and were not included in the calculation of results with the SMM-origin inocula). D175 (No 23, Table 2) and E042 (No 28, Table 3) are the exceptions, showing no signs of leprosy by 121 months and 114 months PI, respectively.

Aerosol inoculation failed to produce leprosy in 2 SMM (D213 and D214, Nos 11 and 12, Table 1) and a third SMM, D088 (No 9), given IV + IC + intranasal inocula (5×10^{10} total ML) initially developed necrotic lesions at IC inoculation sites followed by complete healing of visible cutaneous leprosy; following the death of D088 due to

unknown causes, only neural lesions, classified as BB–BL with ENL, were identified histopathologically.[7] An uninoculated infant, D086 (No 10), remained housed with its inoculated mother, D088, for 35 months PI without the baby developing leprosy. These latter SMM (Nos 9–12) were also not included in the susceptibility calculation.

A041 and A042 (Nos 5 and 6), (both SMM) were inoculated IV and IC with $2{\cdot}6 \times 10^{10}$ total human ML passaged in an armadillo, and developed LL leprosy (Table 1). Although local lesions at inoculation sites developed within 1 year in both recipients of human/armadillo ML, they were slow to develop disseminated leprosy, and both had multiple episodes of spontaneous regression even though they were inoculated with the extremely large dose of greater than 10^{10} ML. The dermal disease in A042 regressed virtually completely within 5 years PI. There were, however, neuritic deformities, including an unusual involvement of the trigeminal nerve paralysing the muscles of mastication. Approximately 7 years were required for A041 to develop LL leprosy as advanced and as disseminated as that seen by 12–18 months in most SMM inoculated with fewer SMM-origin ML (see Tables 1–3), and 2 SMM, D087 and D089 (Nos 7 and 8, Table 1), subinoculated with human-origin ML reisolated from A041 and A042, respectively, developed primary neuritic leprosy (D087) or remained asymptomatic 13 months PI when D089 died of unknown causes.

To examine the effect of dose, SMM D171–D178 (Nos 19–26) received titrated doses of SMM-origin ML by combined IV/IC routes (Table 2). All but D175 developed leprosy. The results from this group suggest that doses were effective down to almost 5×10^7 SMM-origin ML by the IV/IC route. This inoculum had an MI of 10%; therefore, the minimal effective solidly staining dose tested is near 5×10^6. From this dose study, a relationship was previously suggested between susceptibility to leprosy and anti-PGL-I and anti-LAM IgG and IgM serum antibody responses.[4,7,8] High levels of anti-PGL-I IgM antibodies correlated with a high susceptibility to multibacillary forms of leprosy and high anti-PGL-I IgG levels correlated with a resistance to multibacillary leprosy; high initial levels of anti-LAM IgG correlated with a higher probability of developing multibacillary leprosy.[4,7,8]

A second group of 11 SMM were also given titrated doses of SMM-origin ML for further evaluation of the findings regarding dose effects in SMM D171–D178; groups receiving only IV or only IC inoculation were also included in this study (Table 3). Relationships between serum antibody responses to PGL-1 and LAM and susceptibility to leprosy among these 11 SMM are reported in Part II of this study.[9]

Among these 11 SMM, there was a dose relationship overall (Table 3) in that 3 of 4 high-total-dose SMM (E045, No 27, E043, No 29 and E044, No 30) developed progressive LL leprosy compared to 1 (E047, No 35) of 7 that developed progressive LL leprosy from lower total doses. Considering all forms of persisting leprosy, 3 (E045, No 27; E043, No 29 and E044, No 30) of 4 high-dose, 1 (E038, No 31) of 3 intermediate-dose and 3 (E040, No 34; E047, No 35 and E046, No 37) of 4 low-dose recipients developed disease (Table 3). Lower-dose recipients had more regressive leprosy episodes and more disease nearer the borderline to borderline lepromatous (BB–BL) or subpolar lepromatous forms and more neural disease (Table 3). There was also a route effect in that, of the 7 SMM with persisting leprosy, 6 received ML by combined IV/IC routes. Only E046, No 37, developed persisting BL–LL leprosy with neuropathy after inoculation by a single (IV) route, and 2 SMM inoculated by only an IC route (E039, No 32 and D215, No 33) were leprosy resistant (Table 3).

In this study, 3 of 4 SMM (E045, E043 and E044) given a total of more than 1×10^9 ML by combined IV/IC routes developed advancing, disseminated LL leprosy within 4–40 months and ultimately required treatment (Table 3). These 3 SMM fell into a common grouping designated susceptible. The fourth of these SMM (E042) failed to develop disease, and was grouped together with other SMM (see below) designated resistant.

E045 (No 27, Table 3) had advanced LL leprosy at inoculation sites and at sites distant from inoculation (dissemination) by 17 months PI. E045 was highly susceptible to leprosy requiring chemotherapy at 21 months PI.

E043 (No 29, Table 3) developed LL leprosy at or near inoculation sites and disseminated sites including the scrotum, but was prone to extreme enlargement of peripheral nerves, especially the superifical peroneal, radial and ulnar with associated neuropathic deformities. E043 was designated susceptible.

In all, 1 (E047, 35) of 3 SMM (No 31, 34 and 35) inoculated with $4{\cdot}56–6{\cdot}04 \times 10^8$ total ML by combined IV/IC routes developed disseminated, advancing LL leprosy with neuritic deformities and died 48 months PI after the initiation of rifampicin (RFM) chemotherapy (Table 3). E047 (No 35, Table 3) was highly susceptible to disseminated LL leprosy and was grouped with the susceptible SMM.

Of the other 2 SMM (E038 and E040, Nos 31 and 34) receiving $4{\cdot}56–6{\cdot}04 \times 10^8$ ML by IV/IC routes, E038 became positive for AFB in nasal secretions by 10 months PI and developed progressive BB–BL leprosy at IC inoculation sites by 22 months PI followed by a period of spontaneous regression to the point of apparent inactivity (progressive/regressive leprosy). Leprosy re-emerged in E038 26 months PI, was shown to be borderline (BB) leprosy at 76 months PI and lesions again self-healed by 83 months PI. Lesions re-emerged 90 months PI as subpolar lepromatous leprosy (LL_s) with dissemination to uninoculated sites (progression) and neuritic deformities.

The history of disease in SMM E038 can be summarized as progressive/regressive/progressive/regressive/progressive. E038 suffered multiple neuropathic deformities, presumably as a result of the multiple episodes of self-healing. E038 was placed on minocycline (MCLN) monotherapy 7 years PI; therapeutic response was dramatic with diminishing numbers of solidly-staining AFB in the tissues and healing of all lesions within 4–6 weeks.

E040, the other recipient of $4{\cdot}56–6{\cdot}04 \times 10^8$ MI by combined IV/IC routes, developed indeterminate (Ind) leprosy within 8 months PI. By 26 months PI, ulcerated lesions were seen on uninoculated digits of the feet. These lesions were not biopsied. By 32 months PI, a dermal nerve in a lower leg was enlarged to 3 mm wide and dermal lesions appeared to heal. By 46 months PI, AFB-positive nasal smears were obtained, LL leprosy was observed at inoculation sites (No 34, Table 3) and dissemination was confirmed by lesions appearing on the uninoculated tail. This was followed by spontaneous regression of dermal lesions and the appearance of neuritic deformities. After 49 months, continued exacerbation of some lesions was noted, classifiable as subpolar lepromatous leprosy (LL_s) with extensive neuritic involvement which, by 51 months PI, became classifiable as primary neural LL_s leprosy requiring treatment to halt the progress of neuropathic deformities. At 50–51 months, some biopsies of E040 lesions showed Ind leprosy and biopsies from other lesions showed primary neural LL_s leprosy. E040 had widespread evidence of bone reabsorption and atrophy (several digits were reabsorbed and approximately 50% of the tail was removed due to bone absorption and self-mutilation).

E038 and E040 fell into a common grouping designated susceptible with resistance to indicate that they developed persisting leprosy with periods of regression of symptoms followed by periods of continued progression, and/or initially developed indeterminate (Ind) (E040) or BB–BL leprosy (E038). E040 subsequently developed LL_s dermally and neurally and E038 subsequently developed BB, then BB–BL and, eventually LL_s leprosy. E040, therefore, appeared to be more susceptible (less resistant) than E038, based on clinical observations and on the BB classification, since BB-forms of leprosy have more cell-mediated immunity (CM) (and more resistance) against ML than LL-forms.[6]

Of 2 SMM given $4{\cdot}5 \times 10^8$ ML by the single IC route, E039 developed LL leprosy limited to inoculation sites within 4 months PI (Table 3), but these self-healed within 41 months PI and failed to reappear; the other (D215) failed to show symptoms of leprosy to date (118 months PI). E039 and D215 were grouped as resistant SMM.

Of 2 SMM (E041 and E046) given $4{\cdot}5 \times 10^8$ ML by IV route alone, E041 (No 36) developed, within 3 months, erythematous lesions at the base of and on the skin and foreskin of the penis and on and near the scrotum, indicative of disseminated leprosy. These spontaneously regressed without recurrence of any disease (grouped as resistant); E046 (No 37) developed disseminated, progressive/regressive BL–LL leprosy by 24 months PI with continued progression of symptoms by 30 months PI when a biopsy indicated BL leprosy (Table 3). E046 developed severe neuropathic deformities in addition to significant dermal manifestations and required chemotherapy by 39 months PI. E046 was grouped with the susceptible SMMs because of the BL–LL characteristics of the disease and because of the relatively rapid progression of disease.

To summarize the results of the dose/route study, E045 (No 27), E043 (No 29), E044 (No 30), E047 (No 35) and E046 (No 37) were classified as susceptible; E038 (No 31) and E040 (No 34) as marginally susceptible or susceptible with resistance; and E042 (No 28), E041 (No 36), D215 (No 33) and E039 (No 32) as resistant.

Discussion

Susceptibility to experimental leprosy varied among individual SMM inoculated on the same day with identical IV and IC doses of ML from a given batch of SMM-origin inoculum. Doses of SMM-origin ML of 1×10^9 or greater by combined IV/IC routes produced LL leprosy in 11 out of 12 recipients (A022, A023, G930, G931, D171, D172, D173, D174, E045, E043 and E044, Tables 1 and 2). The time of disease onset varied from 2 to 96 months among these 11 SMM. Of these 11 SMM, D172 had self-regressive LL leprosy although he was a high-dose recipient. D172 was ultimately treated with clofazimine (CLFZ) and RFM because of severe neuritic complications. The regressive nature of the LL leprosy in D172 suggests that he was a leprosy-resistant animal. It is tempting to speculate that such an animal might not have developed disease or might have developed leprosy closer to the TT end of the spectrum if he had been inoculated with a lower dose of ML. A 12th SMM that received 1×10^9 SMM-origin ML by combined IV/IC routes, SMM E042 (No 28, Table 2) has shown no signs of leprosy to date (110 months PI).

In 8 SMM receiving SMM-origin ML at lower doses of $2{\cdot}3–6 \times 10^8$ by IV/IC routes, no disease was produced in D175 (No 23) within 110 months PI; progressive LL leprosy

was observed in F100 (No 15), F102 (No 16), D176 (No 24), E046 (No 37) and E047 (No 35); progressive BB–BL or BL–LL forms with regressive episodes occurred in E038 (No 31) and E040 (No 34), respectively (Tables 1 and 2).

Doses of SMM-origin ML lower than 1×10^8 by combined IV/IC routes produced self-healing, regressive LL leprosy in F098 (No 13), BL–LL leprosy with ENL in F104 (No 14), LL_s with neuropathy in D177 (No 25) and gross nerve enlargement/neuropathy in D178 (No 26) (Table 1).

Among 4 SMM given $4{\cdot}5–6 \times 10^8$ SMM-origin ML by a single IV or IC route, only 1 animal (E046, No 37) developed progressive, disseminated BB–BL[6] leprosy (Table 2). The other 3 SMM (D215 (No 33), E039 (No 32) and E041 (No 36)) given $4{\cdot}5 \times 10^8$ ML by a single route either failed to develop or sustain progressive leprosy. In this experiment (Table 3), 6 out of 7 SMM given $4{\cdot}5–10{\cdot}7 \times 10^8$ ML by combined routes (including 3 (E038, E040 and E047) that received all but $4–6 \times 10^4$ ML by a single route) developed sustained, progressive leprosy compared to only 1 (E046) out of 4 with sustained disease after inoculation by a single route. Thus, either the IV or IC route alone appears to be less effective than the combined routes in inducing progressive LL leprosy at a given dose. Even when the vast majority of inocula is given by only 1 route together with 40,000–60,000 ML by the other route, this combined IV/IC regimen appears more effective than a single IV or IC route alone.

These findings suggest that the susceptibility of SMM to leprosy depends upon variable individual animal factors and is dependent on the dose and route of inoculation. The exact factors responsible for this variability are not known but may be partly genetic or immunologic in origin.

The pathogenicity of the ML from different sources appears to vary. SMM-origin ML is highly pathogenic for SMM, but human-origin ML passaged through an armadillo was much less effective in inducing progressive LL leprosy in 2 SMM even with large doses ($2{\cdot}6 \times 10^{10}$ ML) of inocula (A041, No 13 and A042, No 14, Table 1), and 2 additional SMM subinoculated with $6{\cdot}6 \times 10^8$ human-origin ML reisolated from SMM's A041 and A042 also developed disease more slowly or not at all (D087, No 7, and D089, No 8, Table 1). D089 died 13 months PI due to apparently unrelated causes with no signs of leprosy at necropsy; D087 developed AFB^+ nasal secretions 34 months PI with nerve enlargement by 79 months PI and a skin lesion classified as indeterminate leprosy 102 months PI. These findings suggest that human-origin ML are less pathogenic in SMMs than ML or SMM-origin. The reasons for this difference are not known. Possible strain differences of these ML were not investigated, but all microbiological and genetic parameters of these 2 strains investigated thus far appear similar.[2] These ML isolates were not compared to each other in control mouse footpad studies to distinguish between strain variation as opposed to ML adaptation to the host species; unfortunately, the isolates are no longer available for study.

SMM D088 (No 9) was inoculated by IV/IC routes with $4{\cdot}8 \times 10^{10}$ SMM-origin ML together with 2×10^9 by intranasal instillation (Table 1). No clinical disease was detected in D088 other than prominent regressive, necrotic lesions at all IC inoculation sites within weeks of inoculation. These later healed, but at death 35 months PI, there was widespread peripheral leprous neuritis, classified as pure neuritic leprosy in the BL–LL area of the spectrum.[1–7] Intraneural ENL was also present in D088.[1] An infant, D086 (No 10) housed together with its mother, D088, failed to show any signs of clinical leprosy, which may not be surprising since D088's disease was confined to the nerves.

The possibility that the intranasal instillation of ML was responsible for a skin sensitization (vaccination?) resulting in the enormous reactions at dermal inoculation sites of D088 is plausible in view of the fact that 2 other SMM, D213 (No 11) and D214 (No 12), that were inoculated only by an aerosol route (Table 1) have never developed clinical signs of leprosy and are strongly lepromin skin-test positive (B. Gormus, unpublished observations). Uninoculated normal SMM and those with advancing disseminated LL leprosy are usually lepromin-negative (manuscript in preparation). These intriguing suggestions require further investigation.

In conclusion, captive SMM are highly susceptible to leprosy and provide a useful model for the study of clinical leprosy. Much of the spectrum of leprosy was observed among the inoculated SMM, and many of the complications and sequelae observed in human leprosy patients were also manifest in these nonhuman primates. It is virtually impossible to study the natural history of leprosy early after infection in humans, but the SMM model permits such an approach. The SMM model also permits the measurement of baseline, preinfection (control) data in individual animals and the longitudinal monitoring of each parameter in each animal with time in relation to individual baseline values and in relation to the progress of the disease.

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Experimental leprosy in monkeys. II. Longitudinal serological observations in sooty mangabey monkeys

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Summary In this study, 11 SMM were grouped and inoculated with differing doses of SMM-origin *Mycobacterium leprae* (ML) between $4{\cdot}5 \times 10^8$ and 1×10^9 by either combined IV/IC routes or by IV or IC route alone. The combined route was the most effective in eliciting progressive, disseminated LL leprosy. In all, 6 of 7 SMM inoculated by the combined routes developed leprosy requiring treatment at some point. Only 1 of 4 inoculated by a single route developed persisting leprosy requiring chemotherapy. Either no disease or spontaneous regression of initial disease occurred in the other 3 animals inoculated by a single route. Doses in excess of 1×10^9 ML were more effective than lesser doses.

An association was observed between the development of IgG anti-PGL-I ELISA OD values and resistance to leprosy and between IgM anti-PGL-I and leprosy progression or susceptibility. Serum PGL-I antigen levels, determined by dot ELISA, paralleled disease severity longitudinally. High positive OD values of anti-LAM IgG prior to ML inoculation were observed in the majority of leprosy-susceptible SMM in contrast to negative levels in more resistant animals. Anti-LAM IgG OD values exceeded the positive cut-off point after inoculation in 5 of 11 SMM; 3 of these 5 had concurrent detectable serum levels of PGL-I antigen.

Introduction

We previously observed that longitudinal serologic data from sooty mangabey monkeys (SMM) (*Cercocebus torquatus atys*) experimentally inoculated with *Mycobacterium leprae* (ML) may provide indicators for susceptibility to leprosy.[1,2] In that study,

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Table 1 Inoculations and results

M. leprae inoculated ($\times 10^{-8}$) Animal	IV	IC	total	Disease description and characteristics	Degree of susceptibility
E045	4·5	6.2	10·7	LL, disseminated	susceptible
E042	4·5	5·9	10·4	no disease	resistant
E043	4·5	6·2	10·5	LL, disseminated	susceptible
E044	4·5	6·0	10·5	LL, disseminated	susceptible
E038	0·04	6·0	6·04	BB-BL, progressive	susceptible*
E039	0	6·0	6·0	LL, self-healed	resistant
D215	0	6·0	6·0	no disease	resistant
E040	4·5	0·06	4·56	LL_s, neural	susceptible*
E047	4·5	0·06	4·56	LL, disseminated	susceptible
E041	4·5	0	4·5	no disease	resistant
E046	4·5	0	4·5	BL-LL, progressive	susceptible

* SMM E038 and E040 each showed some degree of resistance, including repeated episodes of spontaneous regression, followed by later progression. In E038, leprosy in the BB-BL or BB region was observed; E040 initially developed BL-LL, but eventually developed LL_s, primarily involving the nerves, but at some few sites there were also indications of dermal disease. These 2 SMM were, therefore, designated as 'susceptible with resistance'.

SMM were inoculated by combined intravenous (IV) and intracutaneous (IC) routes with titrated doses of SMM-origin ML and studied longitudinally by ELISA for IgG and IgM antibody (Ab) levels to phenolic glycolipid-I (PGL-I) antigen (Ag) and lipoarabinomannan (LAM) Ag. The prior data suggested that the ratio of the levels of IgM : IgG anti-PGL-I determined by ELISA were elevated in animals that were susceptible to lepromatous (LL) leprosy. By contrast, the IgM : IgG anti-PGL-I ELISA ratios were low in SMM that were resistant to LL leprosy. A longitudinal shift from low to high ratios of IgM : IgG anti-PGL-I OD values predicted and/or coincided with advancement of disease to a LL form.[1] Similar relationships were subsequently observed in 2 chimpanzees with naturally-acquired BL–LL leprosy studied longitudinally.[3]

The prior data also suggested that high preinoculation ELISA levels of anti-LAM IgG correlated positively with susceptibility to LL leprosy when compared to SMM with low or negative anti-LAM IgG levels.[2] Positive anti-LAM IgM levels were observed only in SMM with advanced, disseminated LL leprosy.[2]

In the present study we inoculated additional SMM with differing doses of SMM-origin ML using combined IV/IC routes. In addition, some SMM were inoculated with similar doses of ML by IV or IC routes alone. Longitudinal sera were assayed by ELISA for anti-PGL-I and anti-LAM IgG and IgM levels and correlated with clinical leprosy findings. Also, PGL-I Ag levels in sera were determined in parallel longitudinally by dot-ELISA.[4,5] Relationships between ELISA-determined IgM and IgG Ab proportions, PGL-I Ag levels and disease progression were determined.

Materials and methods

Inoculations: Preparation of SMM-origin ML and the method of combined IV/IC inoculations are described in Part I of this study.[9] Briefly, IV inoculation was via the

saphenous vein and IC sites were: 2 sites on each ear margin, the tip of the nose, an outer forearm, an outer calf and sometimes the periorbital regions.

Animals were inoculated and clinical characteristics noted (Table 1). Based on the clinical observations, the animals were subdivided into 3 groupings describing their apparent degrees of susceptibility to leprosy (Table 1).

Animals were examined 3–4 times per year with some exceptions, as noted in the text, and the degree of advancement over time was staged as previously reported.[1] Briefly, the staging system is: −, no disease; ±, nonulcerated areas (< 2 mm) of abnormal pigmentation or/and infiltration at dermal inoculation sites; 1+, well stained AFB in nasal secretions or in a biopsy specimen or >2 mm lesions at multiple inoculation sites; 2+, AFB in nasal secretions and in lesions at inoculation sites; 3+, lesions at uninoculated sites; and 4+, ulceration or enlargement (>1 cm) of or increases in numbers or disseminated dermal leproma.[1] Regressive episodes are defined as periods during which the staging criteria diminished in severity over time. Histopathologic classifications, lepromatous (LL), borderline lepromatous (BL), borderline (BB), indeterminate (Ind) or neuritic, were according to the Ridley–Jopling system based on evaluations of H & E and Fite–Faraco-stained biopsy specimens.[6–8] Details of clinical outcome of leprosy are described in Part I of this study.[9]

Baseline sera were obtained prior to ML inoculations and at intervals after inoculation and were stored frozen for later ELISA evaluations of anti-PGL-I or anti-LAM Ab and for determination of PGL-I Ag levels by a dot-ELISA method.[4,5]

ELISA: The assays were performed as previously reported.[1–3] Natural ML PGL-I and *M. tuberculosis* LAM were used as Ags (specificity for A-PGL-I was verified using the synthetic glycoconjugate, bovine serum albumin-O-(3,6-di-O-methyl–beta-D-gluco-pyranosyl)-(1–4)-(1-deoxy-2,3-di-O-methyl-L-rhamnose) (NDO-BSA), instead of natural PGL-I in all animals; only the natural PGL-I data are reported). PGL-I, LAM and NDO-BSA were provided by Dr Patrick J. Brennan, Colorado State University School of Veterinary Medicine, Fort Colline, CO under NIH contract No 1-AI-52582.

Briefly, 96-well plates were coated with Ag, washed, blocked with BSA, washed again and reacted with a previously determined optimal dilution of monkey serum. After incubation and washing, the plates were coated with peroxidase-labeled anti-human IgG or IgM Fc fragment γ- or μ-chain-specific Ab diluted according to prior titrations, incubated, washed, reacted with o-phenylenediamine + H_2O_2, acidified and ODs determined at 490 nm on an ELISA reader.[1,2] Final ODs represent the difference in absorbance between wells containing Ag minus wells lacking Ag but containing all other components. Each reagent in the ELISA was carefully titrated in a checkerboard manner to determine dilutions that would give final OD values between 0·1 and 0·5 OD whenever possible to utilize the OD range most sensitive to small changes in OD so that small changes from sample to sample would have maximal meaning and would accurately reflect longitudinal changes. All sera were assayed together once in given experiments to permit accurate relative comparisons. The same batch of peroxidase antibody was used throughout. All experiments were repeated on at least 2 separate occasions examining all sera together in each assay. OD values obtained with these precautions were reproducible in a given sample from 1 assay to another to within ±0·05. The data presented represent results from a single occasion. The following values were determined for normal SMM (mean ± 1 SD, $n = 101$): anti-PGL-I IgG, 0·011 ± 0·016; anti-PGL-I IgM, 0·019 ± 0·027; anti-LAM IgG, 0·118 ± 0·103; and anti-LAM IgM, 0·026 ± 0·049. The

mean + 2 SD, taken as the cut-off points, were for IgG and IgM, respectively, 0·043 and 0·073 (anti-PGL-I) and 0·324 and 0·124 (anti-LAM).

Detection of PGL-I antigen in sera: PGL-I antigen detection procedures have been described in detail previously.[4,5] Briefly, for serum lipid extraction, 100 μl of serum was added to filter paper discs ($\frac{1}{2}''$ in diameter) and dried completely. Lipids were then extracted using 2–3 ml of $CHCl_3 : CH_3OH$ (2 : 1) solution and dried under N_2. Serum lipids were dissolved in $CHCl_3$ and applied to fluorosil packed in a pasteur pipette, 60–100 mesh (Sigma Chemical Co., St Louis, MO, USA) and eluted with $CHCl_3$, followed by 5% CH_3OH in $CHCl_3$. The lipid fraction eluted with 5% CH_3OH was saved and dried under N_2 and examined for the presence of PGL-I by a dot-ELISA method as previously reported.[4,5] The lipid fraction was dissolved in 100 μl of hexane and a 5 μl portion was applied to a tuffryn (polysulphone) membrane (HT-200) (Gelman Sciences Inc., Ann Arbor, MI, USA), followed by anti-PGL-I antibody. A high titre of rabbit anti-PGL-I antibody (a gift from Dr P. J. Brennan) was used for the primary antibody and peroxidase-conjugated goat anti-rabbit IgG (Cooper Biomedical Inc., Malvern, PA, USA) was used as the secondary antibody. For colour development, 4-chloro-1-naphthol (Biorad Laboratories, Richmond, CA, USA) was used and the results were read visually.

Results

The longitudinal ELISA anti-PGL-I and anti-LAM IgG and IgM data were plotted in parallel with the longitudinal PGL-I serum Ag level and the degree of clinical disease (Figures 1–11). The ± stage of disease is not indicated on the graphs, i.e. it shows as zero. The clinical progress of leprosy in these 11 SMM is described in detail in Part I of the Study.[9] In all, 3 of 4 SMM given approximately $10{\cdot}5 \times 10^8$ ML ('high' dose) by combined IV/IC routes (E045, E043 and E044—Figures 1, 3 and 4) developed progressive (i.e. advancing visible clinical symptoms), disseminating (i.e. lesions appearing at uninoculated sites) LL leprosy concurrently with elevated levels of serum PGL-I Ag and were designated as leprosy susceptible. The remaining SMM in this group, E042, developed no disease, no serum PGL-I Ag was detectable and was designated resistant (Figure 2). Ratios of anti-PGL-I IgM : IgG ELISA readings in E045, E043 and E044 were >1 during the period of advancing disease and high PGL-I Ag loads (Figures 1, 3–4).

The PGL-I IgM : IgG ratio became elevated in excess of 1 in all 11 SMM immediately PI and remained >1 for up to 5 months PI in some cases. As a result, the IgM : IgG ratio data during the first 5 months PI is not a reliable indicator of the future course of the disease. Thus, the IgM : IgG ratios over the first 5 months PI will not be considered.

Ratios of anti-PGL-I IgM : IgG were <1 and no detectable PGL-I Ag was present throughout the period of study in E042, a leprosy-resistant SMM that received a high ML dose by combined IV/IC routes (Figure 2). A similar pattern of the ratio of IgM : IgG A-PGL-I being <1 with no detectable PGL-I serum Ag was also observed in other leprosy-resistant SMMs that received lower doses of ML by a single route (E039 and D215, 6×10^8 ML by IC route only, Figures 6 and 7). Another leprosy-resistant SMM, E041 (Figure 10), had relatively low and variable levels of IgG- and IgM-A-PGL-1 Ab which sometimes exceeded the cut-off points. This low and fluctuating Ab level

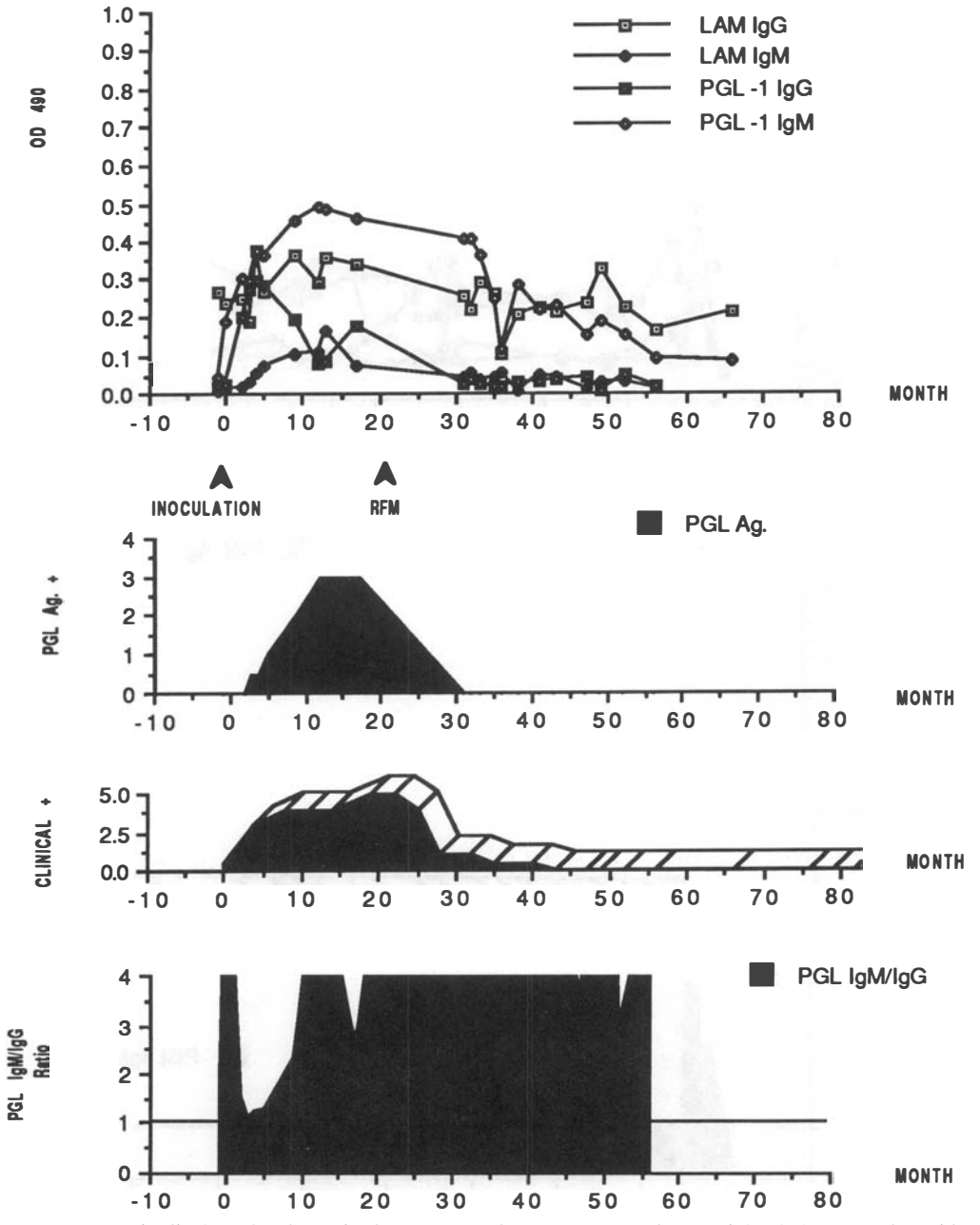

Figure 1. Longitudinal ELISA-determined A-PGL-I and A-LAM IgG and IgM Ab levels (top) together with serum PGL-I Ag levels (top middle), clinical staging of leprosy (bottom middle) and the ratio of ELISA-determined A-PGL-I IgM : IgG (bottom), leprosy-susceptible SMM E045, experimentally inoculated IV with $4{\cdot}5 \times 10^8$ and IC with approximately 6×10^8 ML.

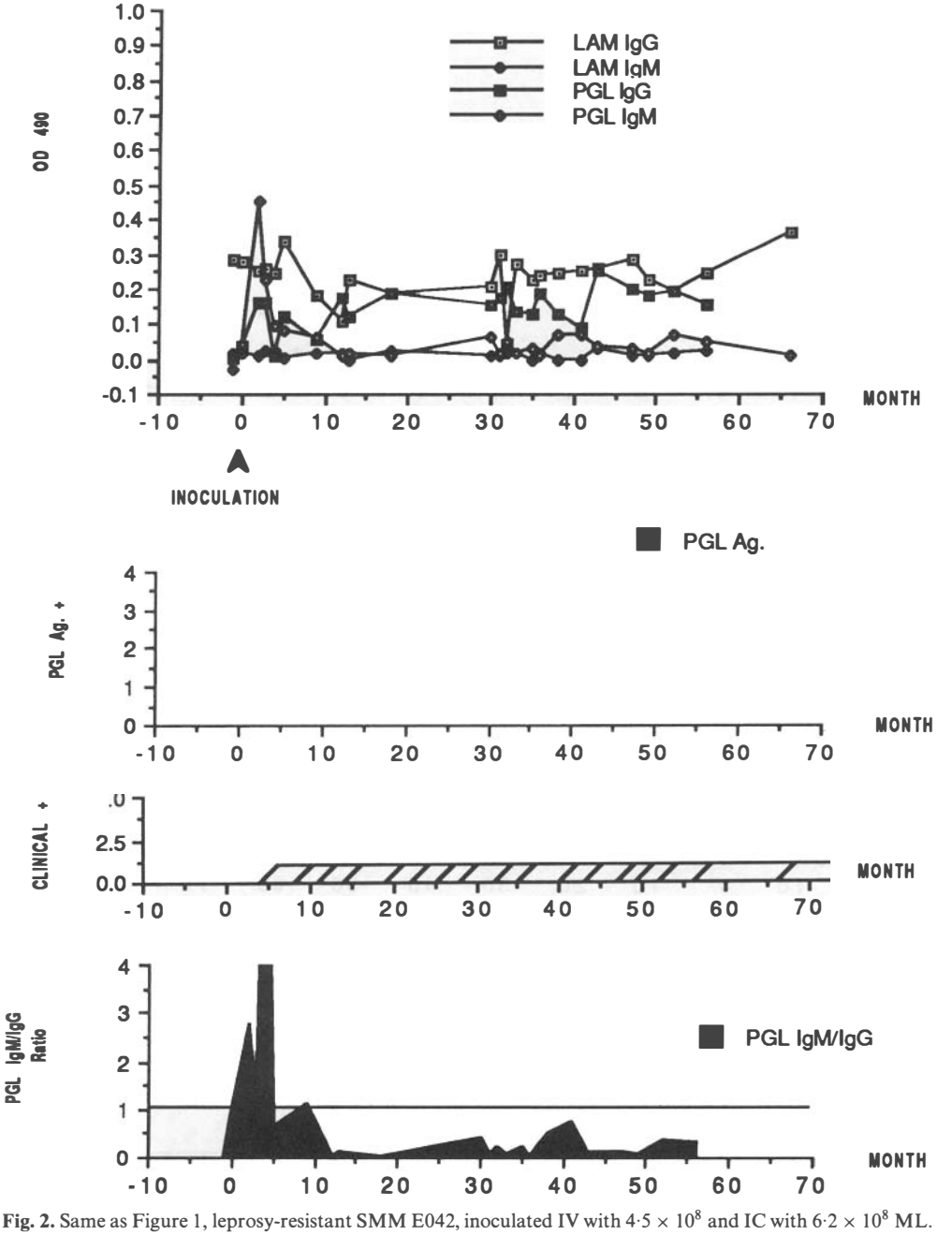

Fig. 2. Same as Figure 1, leprosy-resistant SMM E042, inoculated IV with $4{\cdot}5 \times 10^8$ and IC with $6{\cdot}2 \times 10^8$ ML.

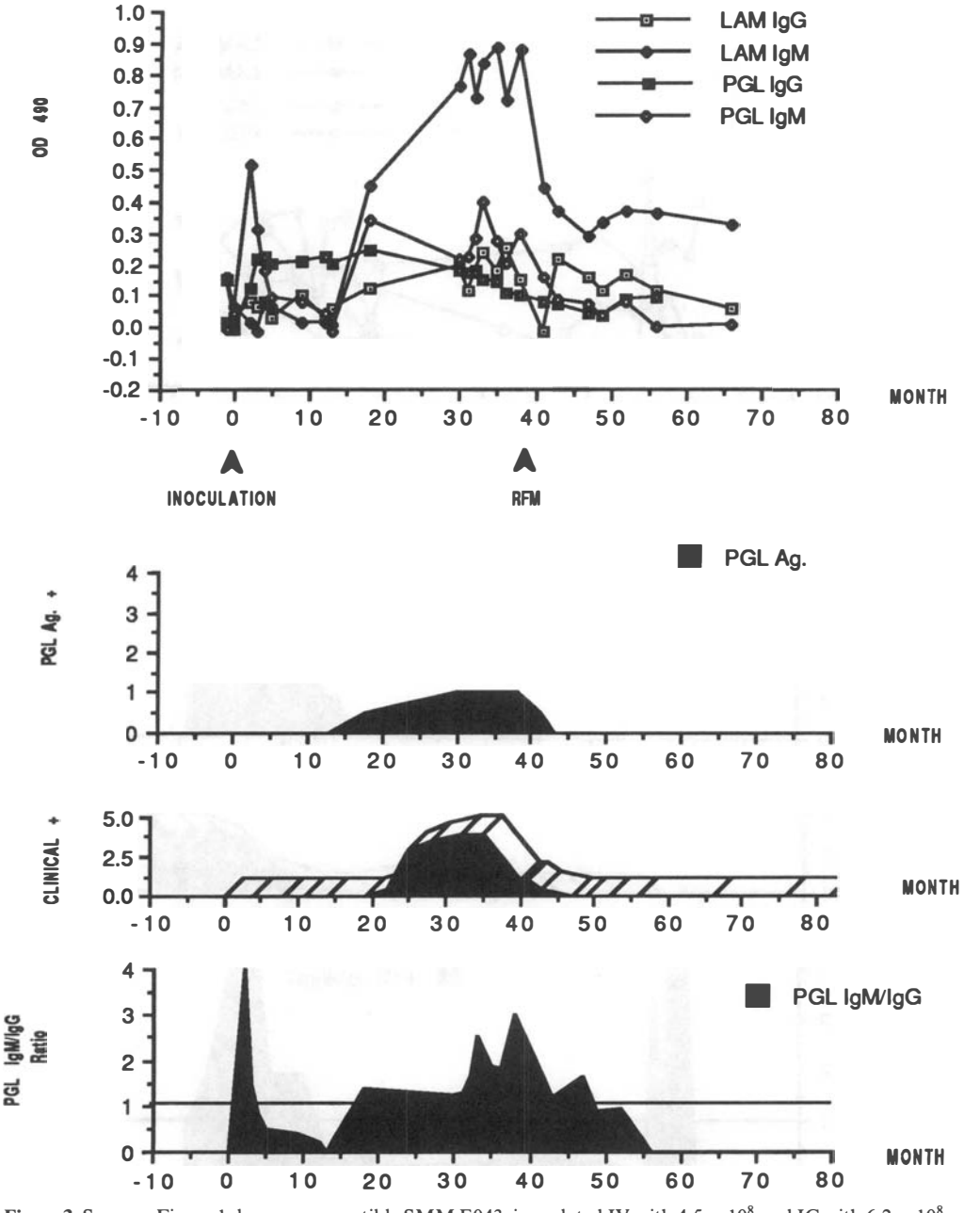

Figure 3. Same as Figure 1, leprosy-susceptible SMM E043, inoculated IV with $4{\cdot}5 \times 10^8$ and IC with $6{\cdot}2 \times 10^8$ ML.

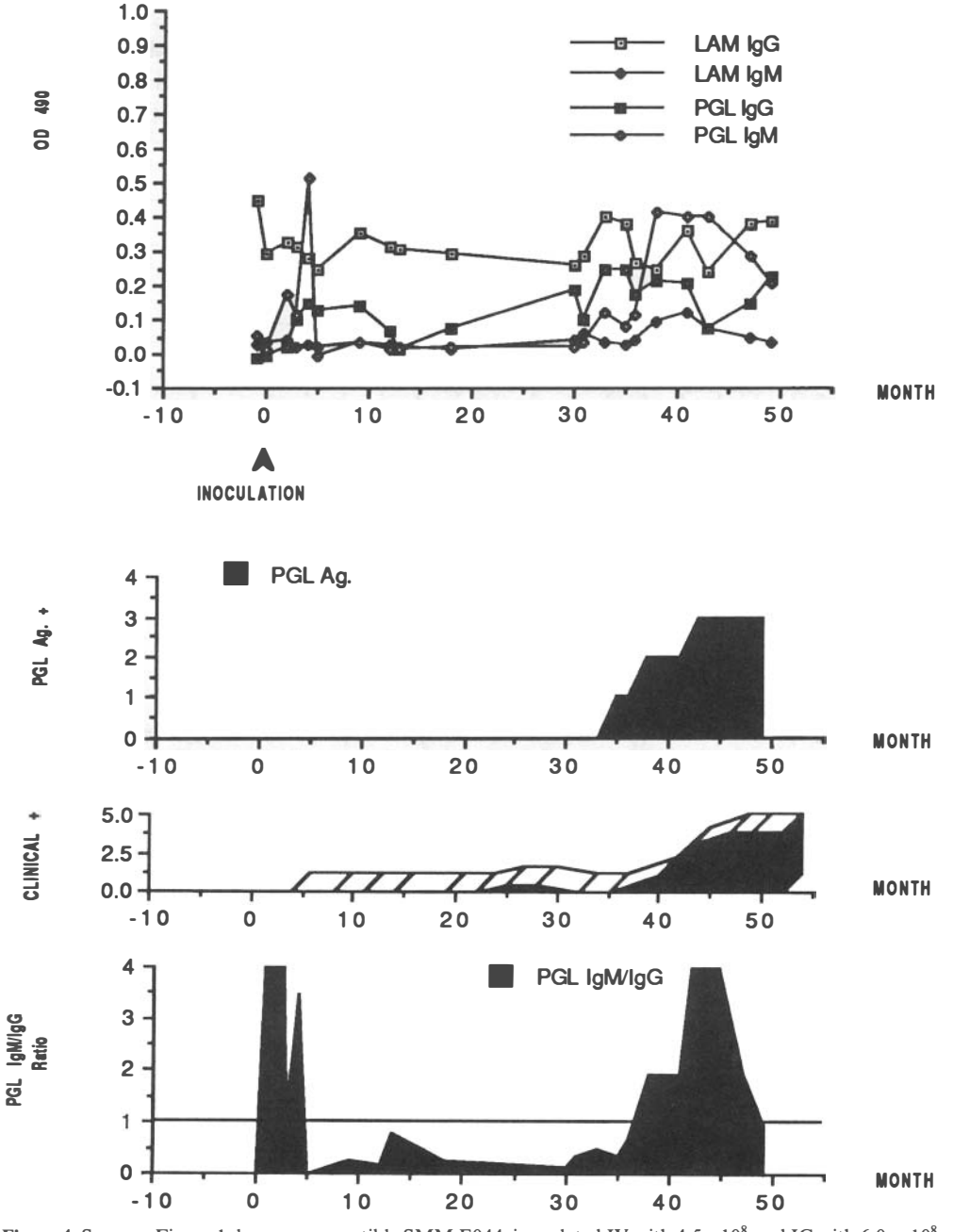

Figure 4. Same as Figure 1, leprosy-susceptible SMM E044, inoculated IV with $4{\cdot}5 \times 10^8$ and IC with $6{\cdot}0 \times 10^8$ ML.

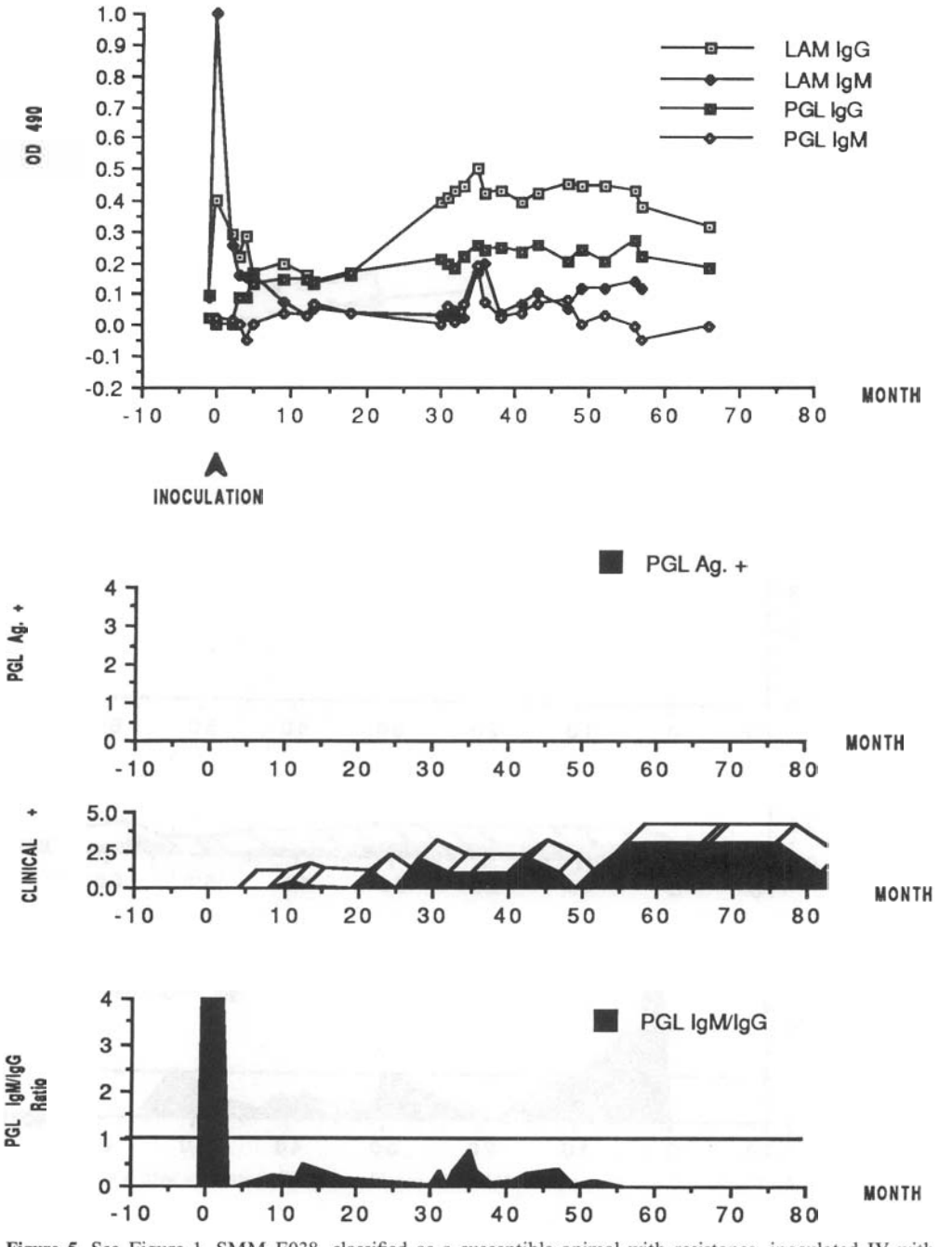

Figure 5. See Figure 1, SMM E038, classified as a susceptible animal with resistance, inoculated IV with $4{\cdot}0 \times 10^6$ and IC with 6×10^8 ML.

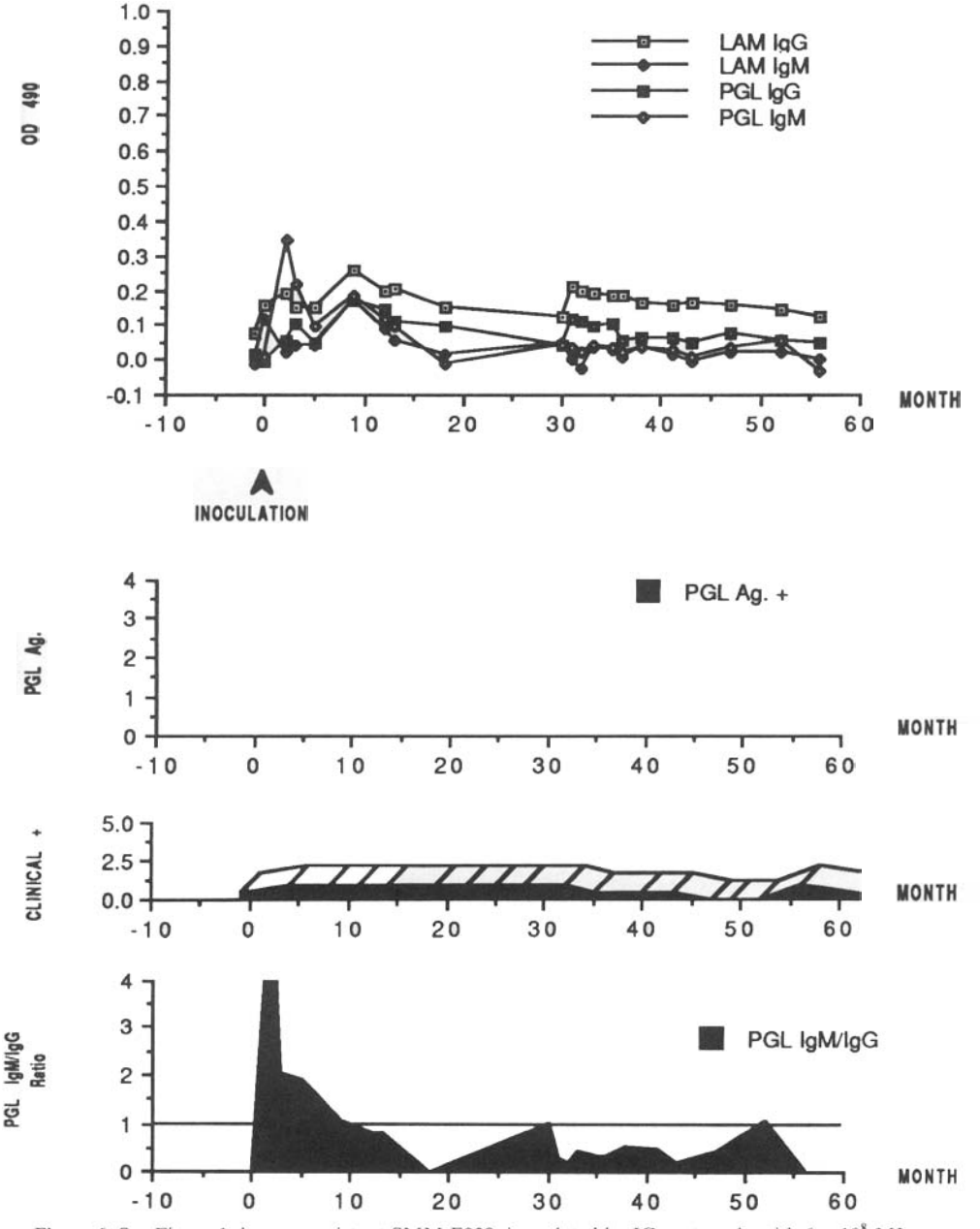

Figure 6. See Figure 1, leprosy-resistant SMM E039, inoculated by IC route only with 6×10^8 ML.

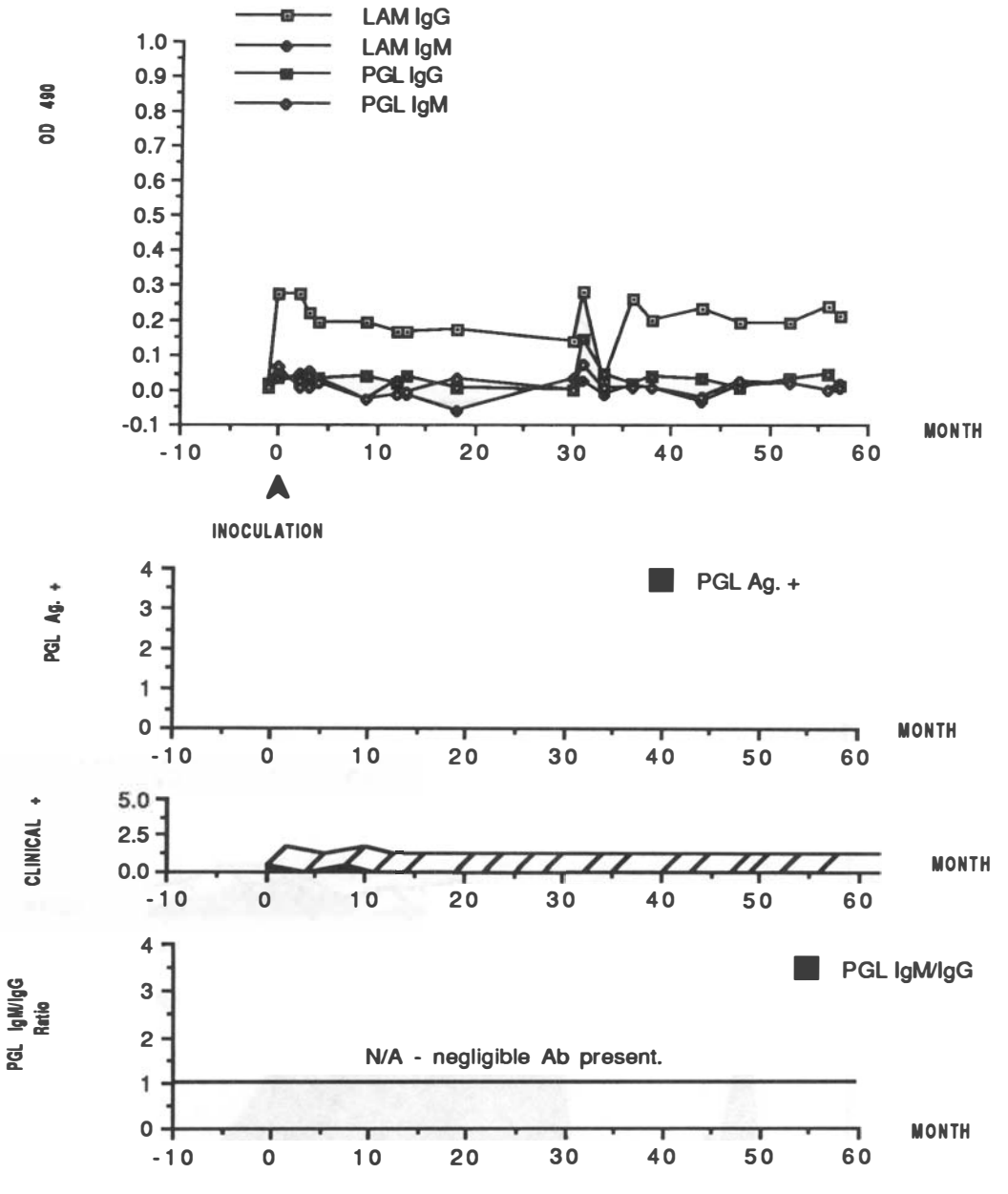

Figure 7. Same as Figure 6, leprosy-resistant SMM D215, inoculated by IC route only with $6{\cdot}0 \times 10^8$ ML.

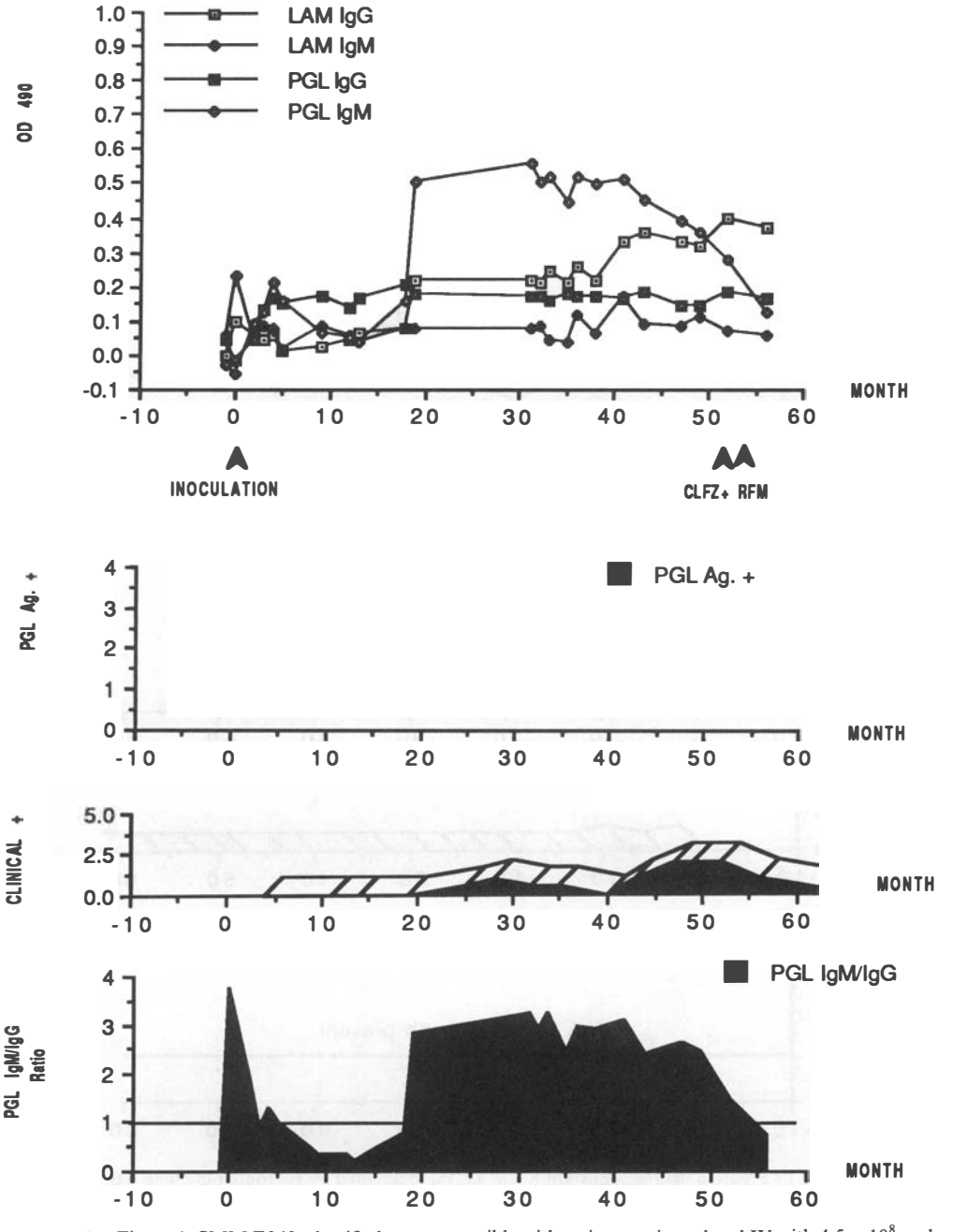

Figure 8. See Figure 1, SMM E040, classified as a susceptible with resistance, inoculated IV with $4{\cdot}5 \times 10^8$ and IC with 6×10^8 ML.

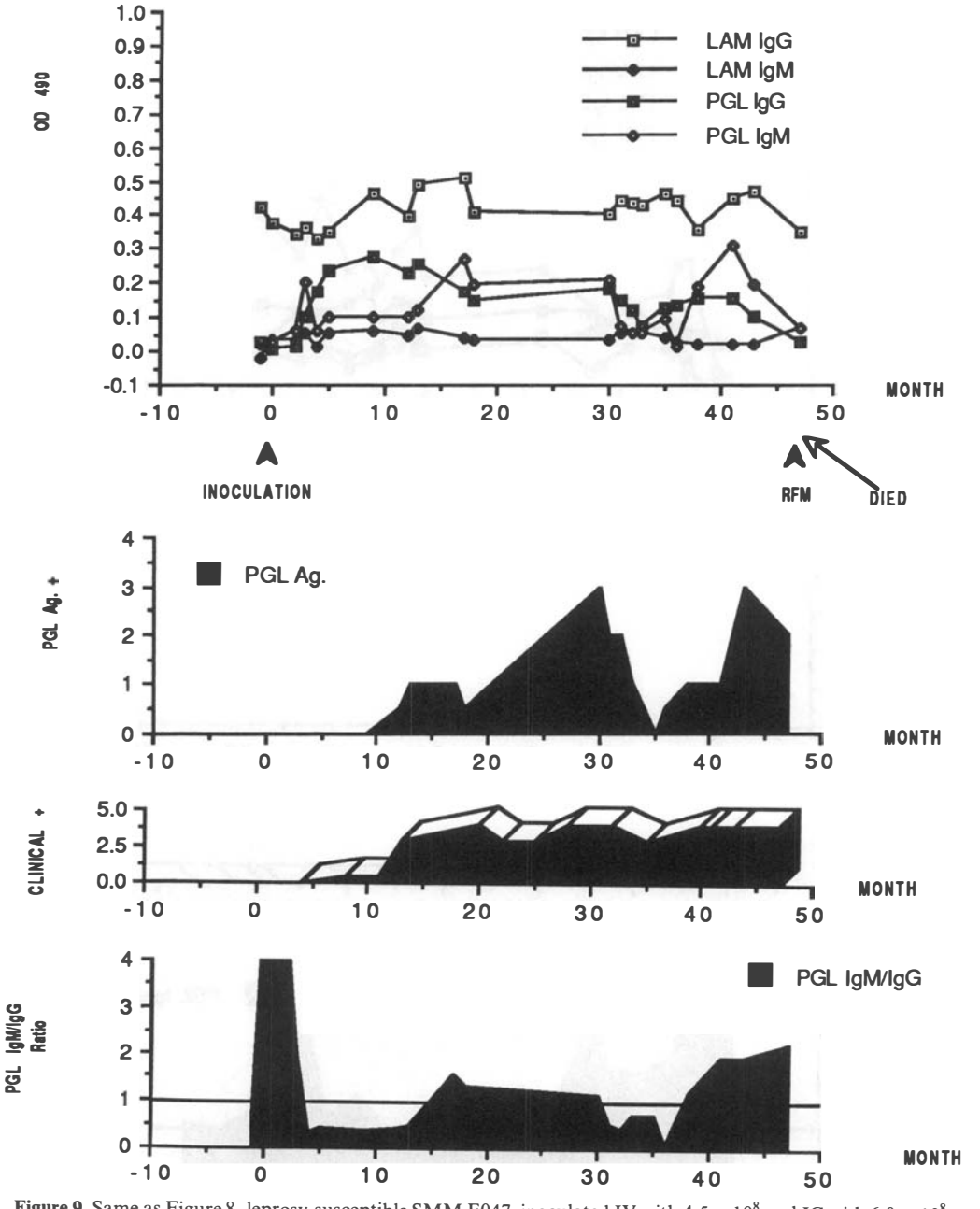

Figure 9. Same as Figure 8, leprosy-susceptible SMM E047, inoculated IV with $4{\cdot}5 \times 10^8$ and IC with $6{\cdot}0 \times 10^8$ ML.

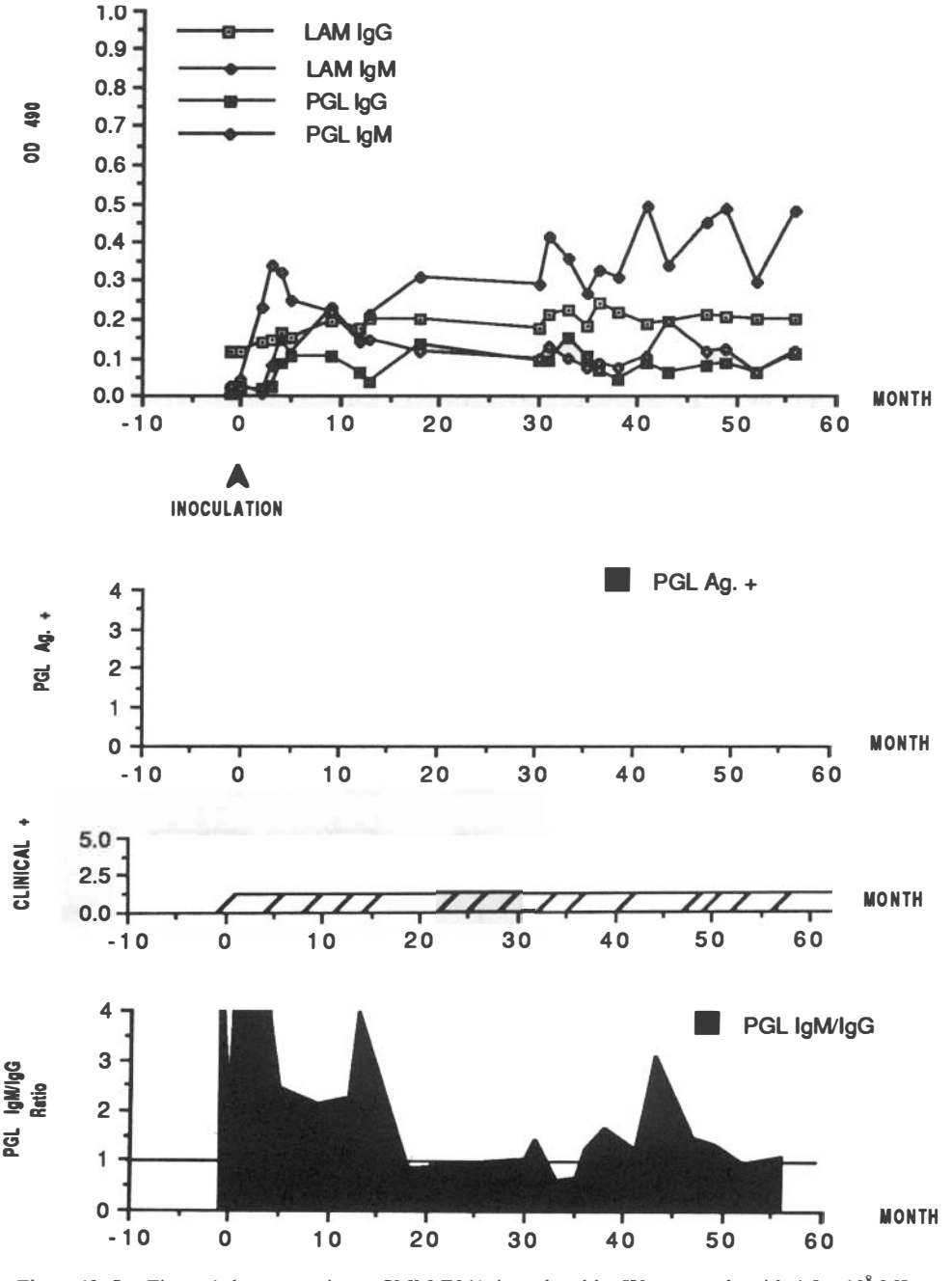

Figure 10. See Figure 1, leprosy resistant SMM E041, inoculated by IV route only with $4{\cdot}5 \times 10^8$ ML.

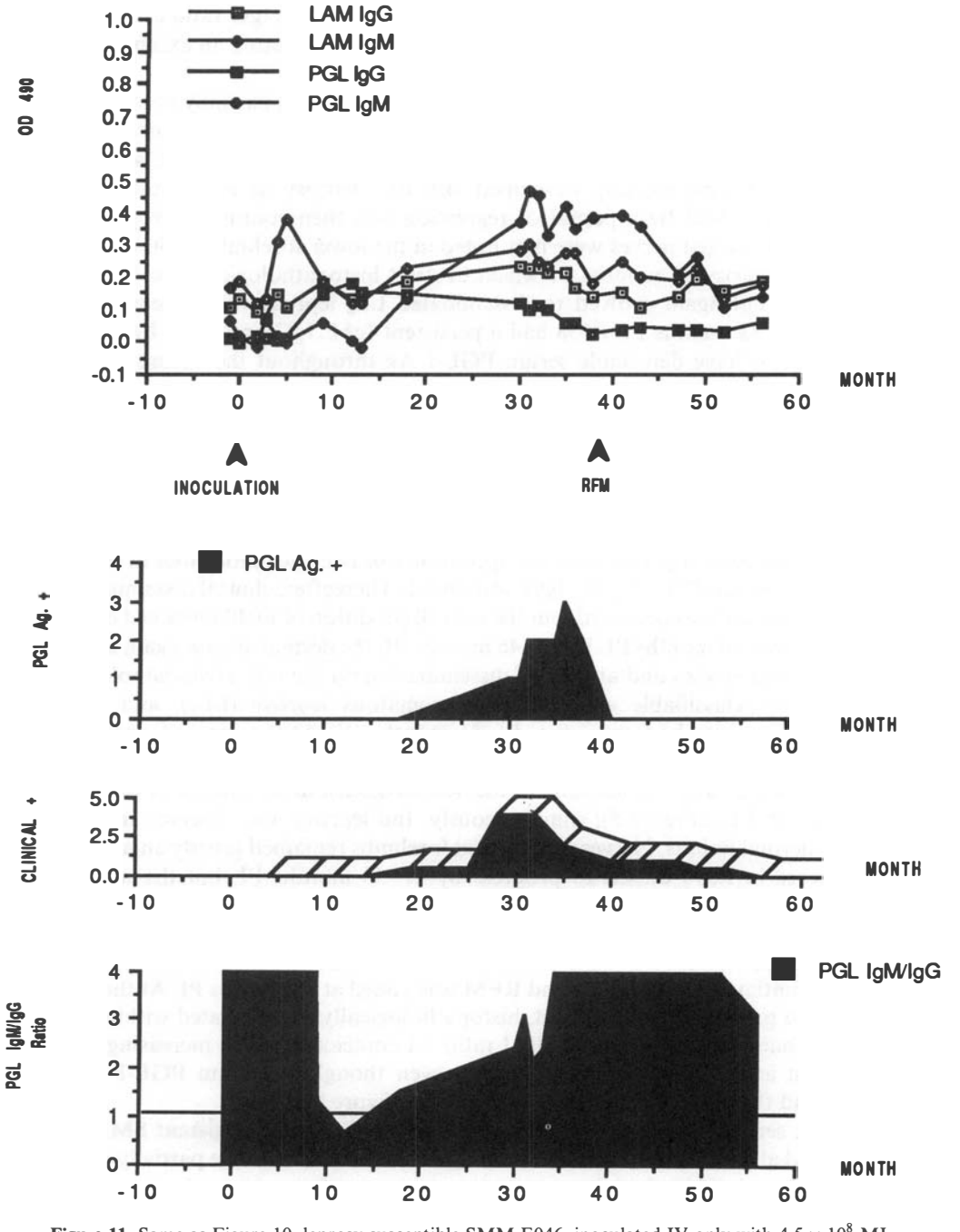

Figure 11. Same as Figure 10, leprosy-susceptible SMM E046, inoculated IV only with $4{\cdot}5 \times 10^8$ ML.

made the ratio calculation appear misleading in that the IgM : IgG ratio exceeded 1 at least once in E041 even though no disease was visible, representing an exception to the observations.

SMM E038 (Figure 5, Table 1) was a progressive/regressive, partially resistant SMM designated susceptible with resistance (it had multiple episodes of spontaneous regression followed by further progression). E038 was inoculated with 6×10^8 IC and 4×10^6 IV ML (Table 1) and initially developed BB–BL[9] leprosy at inoculation sites by 22 months PI followed by a period of regression and then continued progression at 26 months PI. Enlarged nerves were first noted in the lower forelimbs at 30 months PI. E038 had LL leprosy 55 months PI which evolved histopathologically to BB leprosy 76 months PI, but again evolved to disseminated LL_s leprosy with extensive neural involvement by 83 months PI. E038 had a persistent IgM : IgG anti-PGL-I Ab ratio of <1 and failed to have detectable serum PGL-I Ag throughout the course of disease (Figure 5).

E040 (Figure 8), a second partially leprosy-resistant animal ('susceptible with resistance', see Table 1), showed an IgM : IgG anti-PGL-I Ab ratio $\ll$ during the early stages (10–18 months PI) prior to the progression of Ind dermal lesions at inoculation sites (Figure 8). After 20 months of incubation, skin lesions, with Ind leprosy classification, remained at inoculation sites. During the ensuing 10–12 months, the disease progressed together with the appearance of neuritic deformities in E040 and an increase in the anti-PGL-I IgM : IgG ratio to >1. Thereafter, clinical dissemination to the uninoculated tail was observed, but the overall condition of E040 remained definable as regressing until 40 months PI. By 40–46 months PI, the dermal disease again activated at some inoculation sites and at sites of dissemination on the tail. Histopathologically, the disease was classifiable as subpolar lepromatous leprosy (LL_s), and extreme neurologic deformities had appeared. By 51 months PI, AFB remained prevalent in the nasal secretions of E040 and dermal lesions remained at inoculation sites and on the tail. Histopathologically, the majority of the dermal disease at 51 months PI was located in the nerves as LL_s (Figure 8); simultaneously, Ind leprosy was observed in biopsies from other dermal lesions. Nerves in the distal forelimbs remained grossly enlarged. The dermal disease in E040 ceased to progress by 47–53 months PI, but the neurologic disease became severe, presumably causing the SMM to self-mutilate, necessitating treatment. During this static phase in dermal disease, the anti-PGL-I IgM : IgG ELISA ratio began to spontaneously fall to nearly 1, and continued to fall after clofazimine (CLFZ) was initiated at 51 months and RFM was added at 53 months PI. At the time of treatment, the preponderance of AFB, histopathologically, were located within dermal waves. E040 had a IgM : IgG anti-PGL-I ratio >1 coincidental with increasing leprosy dissemination and evolution to LL_s leprosy even though no serum PGL-I Ag was detectable and the disease stage never exceeded 2 (Figure 8).

Similarly, serum PGL-I Ag was absent in the other partially resistant SMM E038 (Figure 5) and all 4 of the resistant SMMs (Figures 2, 6, 7 and 10). The partially resistant SMMs, E038 and E040, had in common a strong tendency towards severe neural involvement and no detectable serum PGL-I Ag.

SMM E047 (Figure 9) received the same low dose of ML by the same route as E040 ($4{\cdot}5 \times 10^8$ IV and 4×10^6 IC), but followed a 'susceptible' course of disease similar to the high-dose SMMs E045, E043 and E044. In SMM E047, the ratio of anti-PGL-I IgM : IgG ELISA values was <1 in the early months PI until the disease began to

progress rapidly with the appearance of PGL-I Ag in the serum when the ratio began to exceed 1. At about 35 months PI, there was a temporary natural regression of clinical symptoms, a disappearance of PGL-I Ag from the serum and a simultaneous drop in the IgM : IgG ratio to < 1. Thereafter the clinical symptoms again began to progress, together with a reappearance of PGL-I Ag in the serum and an increase in the anti-PGL-I IgM : IgG ratio to >1 (Figure 9).

SMM E046 (Figure 11) received $4{\cdot}5 \times 10^8$ ML by only an IV route, developed LL leprosy, and followed a path similar to the other susceptible animals (E045, E044, E043 and E047). E041 (Figure 10), which received the same dose of $4{\cdot}5 \times 10^8$ ML by an IV only route (see above), was categorized as resistant (Table 1). E046 developed continuously progressive BL–LL leprosy by 24 months PI, together with continuously increasing serum PGL-I Ag levels and anti-PGL-I IgM : IgG ratio, both peaking at approximately 30–36 months PI. Thereafter, the dermal disease spontaneously regressed in E046, beginning at about 34 months PI, coincident with significant neural leprosy symptoms. The IgM and IgG anti-PGL-I Ab ratio and the PGL-I serum Ag level remained essentially constant, however, until RFM chemotherapy was initiated at 39 months PI. Chemotherapy resulted in falling IgM and IgG anti-PGL-I ELISA values (the ratio remained constant) and eventual curing of dermal leprosy.

From the foregoing results, 5 of 11 SMM (E045, E044, E043, E046 and E047) that were previously categorized as susceptible, based on clinical observations, were all found to have serologic indications in agreement with this designation, namely elevated proportions of anti-PGL-I IgM : IgG ELISA values and detectable PGL-I Ag levels in the circulation reflecting a high ML load,[1] and 4 additional SMM (D215, E039, E041 and E042) previously categorized clinically as resistant were found to lack detectable serum PGL-I Ag and often had very low or insignificant absolute levels of Ab. Where anti-PGL-I Ab levels were significant in those 4 resistant SMM, the IgM : IgG anti-PGL-I ratios remained nearly 1 or < 1 throughout.

The 2 SMM, E038 and E044, which had been categorized as being susceptible with resistance had more moderate dermal indications of leprosy than the susceptible SMMs (E038, no greater than 3+; E040, no greater than 2+), 1 or more episodes of pronounced spontaneous regression, more gradual onset of disease symptoms, severe neural involvement and they lacked detectable serum PGI = I Ag. The IgM : IgG anti-PGL-I Ab ratio remained < 1 in E038 for the duration of this study. E038 initially developed BB–BL leprosy, evolved after regressive episodes to BB and, ultimately, to LL_s. The < 1 anti-PGL-I IgM : IgG ratio is consistent with the immunologic resistance (more cell-mediated immunity (CMI) against ML) implied by the classification[6] closer to BB for most of the period of study in E038. In E040, which initially developed BL–LL leprosy ultimately evolving to predominantly neural LL_s leprosy (implying less CMI than E038), however, after 18 months PI the proportion of IgM : IgG became and remained $\gg 1$ until after chemotherapy initiation even though dermal disease severity never exceeded the 2+ stage (Figure 8). E040 represents an exception to our usual observations in that it was the only SMM with minimal dermal leprosy (albeit BL–LL or LL_s disease), a tendency towards resistance and predominantly neural LL_s leprosy, no detectable serum PGL-I Ag and, yet, it displayed a very large IgM : IgG anti-PGL-I ELISA Ab ratio for the majority of the study. Nevertheless, the high proportion of IgM : IgG anti-PGL-I is consistent with the disease classification near the LL end of the spectrum. E038 appeared clinically more resistant than E040 and the anti-PGL-I IgM : IgG proportion was consistent with that interpretation.

In all animals where PGL-I Ag was detectable, the peak(s) of Ag concentration coincided with peaks of clinical exacerbation of disease and periods during which the proportion of IgM anti-PGL-I Ab values increased to > 1 relative to IgG anti-PGL-I Ab values; SMM with detectable serum PGL-I Ag levels greater than 1+ had 3+ to 4+ levels of disease severity (Figures 1, 3, 4, 9 and 11).

Anti-LAM IgG levels were elevated near or above the mean + 2 SD cut-off point of 0·324 in the susceptible SMMs E045, E044 and E047 prior to inoculation, but were negligible in the susceptible SMMs E043 and E046 (Figures 1, 3, 4, 9 and 11). Among the 4 high-dose combined IV/IC route recipients, anti-LAM IgG Ab fluctuated with time but peaked together with serum Ag load in E045 and E044 as well as the low dose susceptible SMM E047 (Figures 1, 4 and 9).

Anti-LAM IgG was below the cut-off point prior to inoculation in the leprosy-resistant SMM_s E039, D215, E041 and E042 (Figures 2, 6, 7 and 10) and the 2 SMMs showing regressive episodes followed by continued progression and neuritic complications, i.e. the 'susceptible with resistance' animals E038 and E040 (Figures 5 and 8). The anti-LAM IgG level remained below the positive level throughout the study in the resistant SMMs E039, D215 and E041 but rose above the positive level in E038 and E040, the SMMs designated as 'susceptible with resistance', concurrently with LL leprosy appearance.

Anti-LAM IgM rose to a sustained peak considerably in excess of the cut-off point in the susceptible animals E043 and E046 in unison with peak clinical symptoms and PGL-I Ag loads (Figures 3 and 11) and in resistant SMM E041 (Figure 10); anti-LAM IgM levels exceeded the cut-off point only transiently or not at all in other susceptible (E046 and E047, Figures 9 and 11), susceptible with resistance (E038 and E040; Figures 5 and 8) and resistant (E039, E042 and D215; Figures 2, 6 and 7) SMM. Anti-LAM IgM levels peaked just above the cut-off points coincidently with peak PGL-I Ag levels in susceptible SMMs E045 and E044.

Elevated Ab levels and PGL-I Ag levels fell within 4–11 months after treatment, except for anti-LAM IgG levels which, once elevated, generally remained elevated throughout the period of study (Figures 3, 8, 9 and 11).

Discussion

The results extend and are in basic agreement with our prior observations in other groups of monkeys and in chimpanzees.[1–3] First, susceptibility to experimental leprosy was variable from animal to animal, including different SMMs inoculated with identical doses of ML via the same route(s). In all, 3 of 4 SMMs given the highest dose (approximately $10{\cdot}5 \times 10^8$ organisms) by combined IV/IC routes developed progressive, disseminated LL leprosy, whereas the 4th animal (E042) failed to develop clinically recognizable leprosy, as described in Part I.[9] An SMM (E038) given 6×10^8 ML + 4×10^6 IV ML and another (E040) given 6×10^6 IC + $4{\cdot}5 \times 10^8$ IC developed leprosy with regressive episodes ultimately culminating as LL_s leprosy, whereas another SMM (E047) given 6×10^6 IC + $4{\cdot}5 \times 10^8$ IV ML developed progressive, disseminated LL leprosy.[9] Of 2 SMM given 6×10^8 ML by only the IC route, 1 (D215) failed to develop disease and the other (E039) developed spontaneously regressive LL leprosy which self-healed.[9] Of 2 animals receiving $4{\cdot}5 \times 10^8$ ML by IV route only, 1 (E041) failed

to develop progressive disease and the other (E046) developed progressive BL–LL leprosy which required chemotherapy by 46 months PI.[9]

The described differences between individual SMM in clinical manifestations of experimental leprosy during early stages PI, a time in which it is not feasible to study leprosy in humans, clearly indicate that individuals differ from each other initially in the likelihood of developing leprosy after exposure to a given number of ML. Moreover, a given inoculum by a given route or routes can induce different classifications of disease in different SMMs. Based on these results, it is conceivable that a given individual may be resistant to clinical leprosy at a given ML dose level but may be susceptible at a higher ML dose.

The reasons for the observed individual differences in leprosy susceptibility are unknown but are almost certainly multifaceted and could include genetic differences, prior exposure to other mycobacteria and the presence of other unknown infectious agents.

As previously suggested, IgM anti-PGL-I ELISA OD values lower than IgG anti-PGL-I OD values were usually observed in animals that were resistant to LL leprosy (E042, E039 and D215) and/or during periods of resistance in SMM with spontaneously regressive episodes (E047) or prior to advancement/dissemination in SMM that developed LL leprosy more slowly (E044). Conversely, IgM anti-PGL-I OD values were higher than IgG A-PGL-I OD values in susceptible animals that rapidly developed LL forms of leprosy (E045 and E043) and/or during periods of dissemination and advancement in animals with LL leprosy (E043, E044, E046, E047 and E040). Thus, in leprosy-resistant animals and/or animals undergoing periods of spontaneous regression, the proportion of ELISA-determined IgM : IgG anti-PGL-I Ab OD values is generally < 1, whereas the IgM : IgG anti-PGL-I proportion is generally > 1 in leprosy-susceptible SMMs and/or during periods of advancement/dissemination of multibacillary leprosy. E040 is consistent with these observations in that the proportion of anti-PGL-I IgM exceeded the IgG throughout the course of leprosy (BL–LL) onset, progression, dissemination to the tail, regression and further progression to sustained, neural LL_s leprosy (Figure 5). Clinically, E040 initially appeared more like a susceptible animal in accord with the IgM : IgG ratio, since it developed BL–LL leprosy at inoculation sites and AFB could be found in nasal mucous (dissemination). E040 manifested resistant indications, however, such as regressive episodes, disease severity or stage no greater than level 2 +, no PGL-I Ag detectable in the serum and, ultimately, neural LL_s leprosy with some Ind leprosy lesions remaining simultaneously at dermal inoculation sites. This combination of observations clearly shows E040 to be an unusual susceptible case. E047, which received the same doses as E040 by the same combined IV/IC routes, was clearly a susceptible SMM.

Essentially all ML-inoculated SMMs had an initial ELISA spike of IgM A-PGL-I higher than IgG A-PGL-I within the first 6 months PI. The IgM : IgG Ab ratios later changed depending on whether regression or advancement of disease occurred. Thus, the ELISA results obtained in the first 5–6 months PI can be misleading and do not necessarily follow the generalizations. For this reason the ELISA data spanning approximately the first 6 months PI is not considered in this report. Aside from this initial spike, which soon subsided, SMMs that were resistant to leprosy or that developed early lesions at inoculation sites followed by spontaneous healing (E039, E041, D215 and E042) maintained anti-PGL-I IgM : IgG ratios < 1 or had very low

levels of Abs, often below the cut-off points, in which case the significance of the ratio is diminished and/or misleading.

In all cases of LL leprosy in which high levels of PGL-I Ag were found in sera, the ratio of ELISA-determined OD values of IgM : IgG anti-PGL-I was > 1. We have previously reported that advancing/disseminating LL leprosy in SMM coincides with a longitudinally-decreasing ratio of T-helper : T-suppressor cells in peripheral blood and with decreasing responses to the mitogens PHA, Con A and PWM,[7] and we have recently confirmed that observation in additional SMMs (B. Gormus *et al.*, manuscript in preparation). It, therefore, appears likely that variations in A-PGL-I Ab isotype levels directly or indirectly reflect changes taking place in lymphocyte subset regulation or involvement in cellular immunity during stages of progression or spontaneous regression of leprosy after ML infection.

As before, an association was observed between leprosy-susceptibility vs resistance and the initial IgG anti-LAM level,[2] and 3 of 4 SMMs with the greatest susceptibility to LL leprosy (E045, E044 and E047) had preinoculation anti-LAM IgG ELISA levels near or above the mean + 2 SD cut-off level of 0·32; 2 LL-leprosy-susceptible SMMs (E043 and E046) had an initial anti-LAM IgG level near zero; 5 of 6 of the more resistant SMMs (E038, E039, D215, E040 and E041) had anti-LAM IgG ELISA levels $\ll 0{\cdot}32$; and the remaining more resistant animal, E042, had an anti-LAM IgG level of 0·28, near but below the cut-off point. Thus, high ELISA-determined OD values for IgG antibody to the mycobacterial common, ubiquitous LAM Ag is associated with increased susceptibility to LL leprosy, in agreement with our prior results.[1] The mechanism of the increased susceptibility to multibacillary leprosy in the presence of high anti-LAM antibody levels is not known, but may be related to prior exposure to 'environmental' or to pathogenic mycobacteria, possibly by way of cross-reacting antigens or epitopes among mycobacteria.

Anti-LAM IgG appears to be the last of the 4 Abs studied longitudinally to diminish after treatment. As previously observed by Cho *et al.*,[5] PGL-I Ag disappears from serum within months post-treatment in LL leprosy accompanied by a decline in anti-PGL-I IgG and IgM towards baseline values.

Anti-LAM IgM was only transiently elevated above the 0·124 cut-off point in SMM E038 which was LL-susceptible, but which exhibited periods of resistance evidenced by spontaneous regression, and in SMM E039 and E040 which were relatively LL-leprosy resistant. Anti-LAM IgM was persistently elevated in E041, a leprosy-resistant animal which lacked serum PGL-1 Ag and in 3 LL leprosy susceptible SMMs, E045, E043 and E046, each of which had detectable serum PGL-1. Ag. Thus, 3 (E045, E043 and E046) of the 4 with persistent positive anti-LAM IgG ELISA levels each had detectable PGL-I Ag. These observations suggest that anti-LAM IgM appears and persists in the presence of high ML loads reflected by high serum PGL-I Ag levels. The exception, E041, had transient lesions on and near the scrotum, an uninoculated site, indicating that dissemination had occurred even though a high ML load was not present as reflected by elevated serum PGL-I Ag levels detected by dot-ELISA.

The observations confirm that longitudinal serum PGL-I Ag levels appear to correlate with higher ML loads and can be used to monitor the effectiveness of treatment.[5] Also, it could be predicted from our observations that longitudinal monitoring of IgG and IgM A-PGL-I Ab OD values by ELISA would be of importance in detecting leprosy contacts with pre- or subclinical leprosy.[1–3] Contacts with

persistently elevated anti-PGL-I IgM would be predicted to be highly at risk and those with persistently positive anti-PGL-I IgG OD values would be considered at a lesser risk of developing LL leprosy. The persistent longitudinal existence of positive ELISA OD values of anti-LAM IgG and/or IgM together with persisting or increasing positive anti-PGL-I IgM (and/or IgG) values would constitute the highest risk of incubating subclinical leprosy. Increasing IgM anti-PGL-I ELISA-OD values together with diminishing IgG anti-PGL-I OD values is an indication of an especially bad prognosis.[1,3]

Acknowledgments

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Classification of leprosy cases under field conditions in Bangladesh. I. Usefulness of skin-smear examinations

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Summary In 2 non-governmental organization projects in Bangladesh 244 new leprosy patients were classified in the field according to clinical criteria. Skin smears were taken at 4 standardized sites and at the most active peripheral lesion, where a biopsy was also taken.

Comparison of the clinical field classification with the results of the skin smears and biopsies gives a sensitivity of 92·1% for the clinical criteria, but a specificity of only 41·3%. The skin-smear results, on the other hand, have a sensitivity of 88·4% and a specificity of 98·1%.

Thus, skin smears may contribute considerably to the operational classification of leprosy patients under field conditions.

Quality control of the peripheral laboratory is essential. Appropriate site selection for the smear taking will also contribute to increased performance. Analysis of the skin-smear results suggests that the policy of taking smears at standardized sites should be abandoned in favour of the earlobes and active peripheral lesions.

Introduction

According to WHO recommendations,[1] the operational classification of leprosy cases in paucibacillary (PB) and multibacillary (MB) patients should be based on the bacteriological index, whereby the presence of acid-fast bacilli (AFB) at any single site is the criterion used for classification as MB. However, the validity of skin smear results has often been questioned,[2–4] and many leprosy control programmes base their operational

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classification on clinical criteria.[3] These criteria differ from programme to programme, and their rationale is not always clear. The validity of the clinical criteria used in leprosy control programmes in Ethiopia[5] and Nepal[6] has been studied. The present study looks at the results of 2 programmes in Bangladesh: the Danish–Bangladesh Leprosy Mission project in Nilphamari and the Damien Foundation project in Jalchatra.

In the first part of the analysis, the usefulness of skin smears and their potential contribution to the classification of patients under field conditions is examined.

Materials and methods

From 1 March to 31 July 1993 all new cases diagnosed in Nilphamari (NIL) and Jalchatra (JAL) leprosy control projects were enrolled in the study. After a detailed clinical examination, the leprosy control assistant (LCA) drew a body chart, indicating skin lesions, skin infiltration, enlarged nerves, anesthesia and deformities. The results of sensory testing, voluntary muscle testing (VMT) and WHO disability grading were entered on the patient record by a physiotechnician, who also verified the nerve palpation.

Skin smears were taken at 4 standard sites (JAL: left earlobe, right forehead, left cheek, right elbow; NIL: right earlobe, left forehead, chin, left buttock (in males) or left thigh (in females), and at the biopsy site. In JAL, smears were taken by the LCA, in NIL by the laboratory technician. Smears were stained according to the Ziehl–Neelsen hot method, using sulphuric acid (20%) for the decoloration. The skin smears were read by the laboratory technician, and the bacteriological index (BI) according to the Ridley–Jopling scale was determined.

A punch biopsy of 5-mm diameter was taken by the physician at the most active area of the most peripheral active lesion, excluding the face. The biopsy was fixed in formalin 10% and sent to the leprosy laboratory of the Institute of Tropical Medicine, Antwerp, Belgium, where sections were stained using the Trichrome–Fite–Faracco technique.

The physician classified the patient clinically according to the Ridley–Jopling classification, and prescribed the MDT treatment regimen in function of the operational classification. The following criteria were used in the projects in order to arrive at the operational classification:

if > = 10 lesions: MB;
if < = 3 lesions: PB;
if 4 to 9 lesions:
  if > = 2 enlarged nerves: MB;
  if < = 1 enlarged nerve: PB;
whereby lesion = either skin lesion or enlarged nerve.

(If, afterwards, the skin-smear result of a patient classified as PB turns out to be positive, this patient is changed to MB.)

For the purpose of the present study, the operational classification was compared to the bacteriological classification based on biopsy and skin-smear results.

A patient is bacteriologically classified as MB if the biopsy result is either LL or BL or BB *or* if the BI of the biopsy is positive *or* if the BI of the skin smear is positive at any

single site. A patient is bacteriologically classified as PB if the biopsy result is either BT or TT or I *and* if the BI of the biopsy is negative *and* if the BI of the skin smears is negative.

Results

Between 1 March, and 31 July, 1993, a total of 244 leprosy patients were diagnosed in NIL and JAL. They were classified in 6 groups (Table 1). In all, 1 patient refused the biopsy, and the biopsies of 3 patients were impossible to cut or stain properly; 2 patients, treated as PB, had negative skin smears, and are included in group 6; 1 patient, treated as MB, also had negative skin smears, and is included in group 5; 1 patient, treated as MB, had positive skin smears and is included in group 1. Positive skin smears were found in 79 patients.

Standard skin-smear sites in NIL and JAL are not identical, but are sufficiently similar to allow the combination of the results of both projects. The BI values obtained at the 4 standard sites and at the biopsy site could vary considerably in the same patient. The difference (in BI units) between the highest and the lowest value was 0 in 7 patients and 1 in 29 patients (together constituting 45·6% of the smear positive patients), but it was 2 in 16 patients, 3 in 18 patients, 4 in 8 patients, and 5 in 1 patient, giving a mean variation (in BI units) between the highest and the lowest value of 1·92.

The bacterial yield of the various skin-smear sites is given in Table 2. Results for the

Table 1. Operational and bacteriological classification of the leprosy patients

		Operational classification[1]	
		MB	PB
Group	Bacteriological classification[2]		
1. Confirmed MB	MB	82	
2. Confirmed PB	PB		50
3. False PB	MB		7
4. Unconfirmed MB	PB	73	
5. Unconfirmed leprosy treated as MB	Unconfirmed	18	
6. Unconfirmed leprosy treated as PB	Unconfirmed		14
Total		173	71
		244	

[1] If > = 10 lesions: MB. If < = 3 lesions: PB. If 4 to 9 lesions: MB if > = 2 enlarged nerves; PB if < = 1 enlarged nerve (whereby lesion = either skin lesion or enlarged nerve).

[2] MB: either the biopsy result is LL or BL or BB, or the BI of the biopsy is positive, or the BI of the skin smear is positive at any 1 site.

PB: the biopsy result is BT or TT or I, and the BI of the biopsy is negative, and the BI of the skin smear is negative.

Unconfirmed: no evidence of leprosy found in the biopsy and all skin smears negative.

Table 2. Bacteriological yield of the various skin smear-sites in the skin-smear positive leprosy patients (total of 79 patients)

Skin-smear site	Earlobe (right or left	Forehead	Face (cheek or chin)	Limb (elbow, buttock or thigh)	Biopsy site	Earlobe + biopsy site taken together
Sum of the BI* values of all patients, at each of the sites	239	208	207	211	251	Not applicable
Mean BI, at each of the sites	3·0	2·6	2·6	2·7	3·2	3·1
frequency of highest scores:						
number of patients[1]	47	27	24	25	42	66
% of patients[2]	60%	35%	31%	32%	54%	84%

*BI, bacteriological index.
[1] Number of patients in whom a particular site presented the highest BI value (either as sole highest site, or as 1 of several sites with the highest BI value).
[2] Percentage of patients in whom a particular site presented the highest BI value.

earlobe plus the biopsy site taken together are also given. The BI found in the biopsy is compared to the BI found in the skin smear at the biopsy site in Table 3. A patient without a biopsy and a patient who was not smeared at this site are not included in this

Table 3. Difference in bacterial yield between biopsy and skin smear at the biopsy site. (Total of 87 patients: 1 patient without a biopsy result and 1 patient without a skin-smear result are not included)

Group	Difference (in BI units) between the BI in the biopsy (reference BI) and the BI in the skin smear taken at the biopsy site	Number of patients
Biopsy: BI positive	0	31
Skin smear: BI positive	−1	20
	+1	6
	−2	4
	+2	2
	−3	1
		Total: 64
Biopsy: BI positive	0	0
Skin smear: BI negative	−1	6
	−2	3
	−3	1
		Total: 10
Biopsy: BI negative	0	2
Skin smear: BI positive	+1	7
	+2	1
	+3	1
	+4	1
	+5	1
		Total: 13

Table 4. Bacteriological characteristics of MB patients with AFB in the biopsy present solely in the dermal nerves

Operational classification[1]	BI* in nerves	BI in skin smear (highest score)	Histopathological image	Number
MB	1+	0	I	1
		0	BT	4
	2+	0	BT	3
		1+	BT	3
		2+	BL	1
		4+	BT	1
	3+	0	BT	1
		3+	BT	3
PB	1+	0	BT	1
		1+	I	1
		2+	I	1

[1] See legend of Table 1 for definition of the operational classification categories.
* BI, bacteriological index.

comparison. Twenty patients presented a positive BI in the biopsy, but with the AFB present solely in the dermal nerve sections—10 of these patients had negative skin smears. The characteristics of these patients are summarized in Table 4.

There were 13 patients who had a positive skin-smear result while presenting a BT anatomopathological image with a negative BI in the biopsy.

Discussion

From a strictly bacteriological point of view, only those cases with an anatomopathological image of LL, BL or BB, or with a positive BI in the biopsy, or with a positive BI at any 1 skin-smear site, should be classified as MB.

Applying these criteria to the patients in Table 1, there are 89 MB cases in the study group. Of these, 82 were correctly identified in the field (a sensitivity of 92·1%). However, an additional 91 cases were also diagnosed as MB leprosy, thus bringing down the specificity to 41·3%. If only the cases confirmed as leprosy by the biopsy (groups 1–4) are taken into consideration, the sensitivity remains the same (92·1%) and the specificity is almost identical (50/123 = 40·7%).

If classification were based on the skin-smear results, 79 MB cases out of 89 would have been correctly identified (a sensitivity of 88·8%). Since all other cases were skin-smear negative, the specificity is 100%. The 10 MB cases which were missed all belong to the BT group with bacilli present solely in the dermal nerves—6 of these (see Table 4) presented a BI of 1+. Since the original cut-off point for MB classification[7] was a BI of 2+, it can be argued that these 6 cases would have been correctly treated if they had received a PB regimen. Of the remaining 4, 3 had a BI of 2+ in the nerves, and 1 of 3+. As *Mycobacterium leprae* is a nerve pathogen, the nerves could well be the primary site of multiplication. Thus, patients with a negative skin-smear result but many bacilli in the nerve should be considered as true MB which cannot be detected by smear

taking only. The incidence of such cases in the present study is 4/244, or 1·6%. Treatment of these patients with a PB regimen may result in an MB relapse. However, the chance of selecting drug-resistant bacilli after regular PB treatment would be exceedingly small.

The question that should be asked is whether the skin-smear negative patients were truly negative. Quality control of the performance of the laboratory technicians, done independently from the present study, had revealed that no positive slides (BI > =2) were missed, and that BI readings did not differ more than 1 unit from the control reading in 95% of the cases. This suggests that the smear reading results obtained in a well-functioning peripheral laboratory where regular quality control is performed, can be reliable. This has also been observed in other studies:[8] the peripheral laboratory results had a positive predictive value of 96·6% (253/262) and a negative predictive value of 82·2% (106/128), with 10 out of the 22 false negatives having a BI of 1+ at the reference laboratory.

Thus, it is safe to assume that all positive readings are truly positive, and if any errors are made, they will be made to the advantage of the patient. Nevertheless, it could be argued that the 13 cases with a positive skin smear but a negative BI in the BT biopsy constitute false positives. But closer analysis reveals that in 10 out of those 13 patients, a positive BI was found in at least 4 out of 5 skin-smear sites, making a reading error unlikely. Of the 3 remaining patients, 2 had a BI = 1+ at 2 sites, and 1 had a BI = 1+ at 1 site. If these 3 patients would be considered false positive, the sensitivity of the skin-smear examination would be 88·4% (76/86) and the specificity 98·1% (155/158).

These results are remarkably similar to a study of 204 patients in Senegal[9] who were classified according to BI and histopathological result. Out of 85 patients histopathologically classified as MB, 80 were correctly identified by the skin-smear examination (a sensitivity of 94%), while 6 smear positive patients were not confirmed by the biopsy (a specificity of 113/119 = 95%).

In a study in Nepal,[6] a computer simulation based on observations in 54 patients showed that 24 out of 30 patients classified as MB according to biopsy result were correctly identified by the skin-smear examination (sensitivity 80%) while 4 smear-positive patients had a PB biopsy result (specificity 19/23 = 83%). The lower performance in Nepal, as suggested by the authors, may be due to problems with the quality of smear examination.

It is always possible that bacilli in the skin smear are missed due to uneven distribution, especially in the case of a BI of 1+: when examining 100 microscopic fields, only 2·5% of the smear area is covered.[8] Bacilli in the biopsy may be missed because the biopsy is taken at the wrong spot or because the bacilli are concentrated in 1 specific area but the biopsy slices do not include that area, especially in the case of low density bacillary load.[10] In this connection, it is particularly interesting to compare the BI found in the biopsy with the BI found in the skin smear at the biopsy site (see Table 3). In 72 out of 87 patients (82·7%), the difference does not exceed 1 unit. In 9 patients (10·3%), the BI in the biopsy is 2 or 3 units higher than the BI in the skin smear at the biopsy site, but in 5 of these patients the bacilli in the biopsy were present only in the nerves. In 6 patients (6·9%), the BI is 2 or more units higher in the skin smear at the biopsy site than in the biopsy, while in 4 of these patients the biopsy actually has a negative BI. It has to be pointed out that in each of these 4 cases the BI is at least 2+ at each of the 5 smear sites. If we exclude clerical errors, of which we find no evidence, we

can only conclude that the discrepancy is due to an unfortunate selection of the biopsy site.

In all, 73 (80·2%) of the 91 patients with a negative skin smear classified in the field as MB presented a PB anatomopathological image. The remaining 18 showed no histological evidence of leprosy. Among the 64 smear-negative patients operationally classified as PB, 14 showed no signs of leprosy in the biopsy. All of these 32 unconfirmed cases presented clinical signs suggesting leprosy: anaesthetic skin lesions (24 patients), enlarged nerves (7 patients), grade 2 disability of both feet (1 patient). Again, the lack of histological evidence of leprosy may be due to an inappropriate selection of the biopsy site. It raises the question of reliability of diagnosis, but this falls outside the scope of the present article.[11] Whether the smear-negative cases without histological leprosy evidence are true leprosy cases has no direct bearing on the main issues under discussion: the false-negative cases and the MB overclassification. The 32 unconfirmed leprosy cases are discussed in more detail in the accompanying article.[12]

Both in NIL and JAL, smears are taken at standard sites, and the average BI is entered on the patient record. However, it was found that there can be considerable variation between the BIs at various sites. As a result, the average BI will often not reflect the bacillary status of the patient accurately.

This is mainly due to the policy of taking skin smears at standardized sites. Table 2 clearly shows that 3 out of 4 standard sites yield considerably less bacilli than the earlobe or the biopsy site. The earlobe and the biopsy site present the highest mean BI, and most often yield the highest BI in a patient. In fact, in 66 of the 79 smear-positive patients (84%), either the earlobe or the biopsy site, or both, yielded the highest BI. Indeed, many leprosy researchers recommend a minimum of either 2 earlobes and 1 active site or 1 earlobe and 2 active sites for smear taking.

If, for the group of patients in the present study, skin smears had only been taken at the earlobe and the biopsy site, 3 out of the 79 smear positive cases (3·8%) would have been missed: 1 patient with a BI = 1+ in the cheek only, and 2 patients with a BI = 1+ in the forehead only. On the other hand, if the smears had been limited to the standard sites, excluding the biopsy site, this would also have resulted in 3 missed cases: 2 with BI = 1+ at the biopsy site, and 1 with BI = 5+ at the biopsy site. This last patient had a biopsy result BL, BI = 4+, illustrating the importance of good site selection.

Conclusion

In spite of the low esteem in which skin-smear results are held in many programmes, the bacteriological performance in NIL and JAL is quite acceptable. In this context, the importance of quality control of the laboratory performance cannot be overstressed.

Relying solely on skin-smear results, 11·2% of MB cases (10 of 89) would have been missed. But more than 50% of the cases missed have a BI of 1+ in the dermal nerves only, and would probably respond satisfactorily to PB treatment. The operational classification strategy in the field missed 7·9% of the MB cases. But the price for this increased sensitivity is a specificity of only 41·3%. In order to treat 3 additional MB cases, 91 'false' MB's have to be treated as well. This MB overclassification puts a serious managerial and financial burden on the leprosy programme.

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Classification of leprosy cases under field conditions in Bangladesh. II. Reliability of clinical criteria

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Summary In 2 non-governmental organization projects 244 new leprosy patients in Bangladesh were classified in the field according to clinical criteria i.e. number of skin lesions and number of enlarged nerves.

Comparison of these classification results with the results of skin smears and biopsies yielded a sensitivity (for detection of a MB case) of 92·1%, but the 'unconfirmed MB rate' amounted to 52·6%.

In order to improve the reliability of the operational classification, several additional clinical criteria were investigated. It was found that neither the presence of anaesthesia in the skin lesions nor the presence of grade 2 disabilities or peripheral anaesthesia or voluntary muscle testing (VMT) impairment contributed to an improved classification. Counting the number of body areas showing signs of leprosy, which had proven very useful in other programmes, did not result in a more reliable classification in the 2 projects in Bangladesh.

The presence of clinical signs of lepromatous leprosy, more specifically nodules or diffuse infiltration, could be a useful addition to the classification criteria. If the sensitivity must remain higher than 90%, the lowest 'unconfirmed MB rate' obtainable in Bangladesh, using clinical criteria only, is 46·4%, for a sensitivity of 91·0%. However, the inclusion of skin-smear results in the classification criteria could improve the sensitivity to 96·6% and lower the 'unconfirmed MB rate' to 40·3%. A reduction in MB overclassification will result in more efficient and more cost-effective leprosy control programmes.

Introduction

Many leprosy programmes rely on clinical criteria in order to classify the patients into paucibacillary (PB) and multibacillary (MB) groups. A first part of the present study[1]

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looked at the usefulness of skin-smear results in 2 programmes in Bangladesh: the Danish–Bangladesh Leprosy Mission Project in Nilphamari, and the Damien Foundation project in Jalchatra. The second part of the analysis looks into the following questions:

1 How reliable are the clinical criteria presently used?
2 Is it possible to identify additional criteria to make the clinical classification more accurate?
3 Is it possible to define a classification strategy which will keep MB overclassification to a minimum, without missing any MB case?

Materials and methods

These are described in detail in the first part of the study.[1] A summary is given below.

From 1 March, to 31 July, 1993, all new cases (totalling 244) diagnosed in Nilphamari and Jalchatra leprosy control projects were enrolled in the study. The following data were recorded: skin lesions, skin infiltration, enlarged nerves, sensitivity of skin lesions (using a 0·5 gram nylon monofilament), deformities, results of sensory testing of hands (using a 1 gram nylon mono-filament) and feet (using a ballpoint pen), voluntary muscle testing of hands, feet and eyes, and WHO disability grading.

Skin smears were taken at 4 standard sites (which included 1 earlobe) and at the most active area of the most peripheral active lesion, excluding the face. The latter was also the site of a punch biopsy of 5-mm diameter. MDT treatment was prescribed in the field in function of the operational classification:

if > = 10 lesions: MB;
if < = 3 lesions: PB;
if 4 to 9 lesions:
  if > = 2 enlarged nerves: MB;
  if < = 1 enlarged nerve: PB;
whereby lesion = either skin lesion or enlarged nerve.

The present study compares this operational classification with the 'bacteriological' classification based on biopsy and skin-smear results: a patient is bacteriologically classified as MB if the biopsy result is either LL or BL or BB or if the BI of the biopsy is positive or if the BI of the skin smear is positive at any single site. A patient is bacteriologically classified as PB if the biopsy result is either BT or TT or I and if the BI of the biopsy is negative and if the BI of the skin smears is negative.

Results

Out of the 244 patients diagnosed in Nilphamari (NIL) and Jalchatra (JAL), 173 (70·9%) were classified in the field as MB and 71 as PB, and 82 of the MB cases (47·4%) were bacteriologically confirmed while 7 of the PB cases (9·9%) were bacteriologically MB (see Table 1).

Clinical signs of lepromatous leprosy (diffuse infiltration, nodules, madarosis, nose

Table 1. Operational and bacteriological classification of the leprosy patients

Bacteriological classification	Operational classification[4] MB	PB	Total
Bacteriologically confirmed MB[1]	82	7	89
Confirmed PB cases without bacteriologically confirmed MB evidence[2]	73	50	123
Bacteriologically negative, no anatomopathological signs of leprosy[3]	18	14	32
Total	173	71	244

[1] Biopsy result is LL or BL or BB, or BT or I with a positive BI in either the biopsy or the skin smear or both.
[2] Biopsy result is BT or TT or I, with a negative BI both in the biopsy and the skin smear.
[3] No evidence of leprosy found in the biopsy, and all skin smears negative. But clinical evidence of leprosy present in all patients (anaesthetic skin lesions with or without enlarged nerves: 24; enlarged nerves without anaesthetic skin lesions: 7; grade 2 disability of both feet: 1).
[4] If > = 10 lesions: MB; if < = 3 lesions: PB; if 4 to 9 lesions: MB if > = 2 enlarged nerves; PB if < = 1 enlarged nerve (whereby lesion = either skin lesion or enlarged nerve).

collapse and gynaecomastia) were found in 34 patients. Their characteristics are summarized in Table 2.

The overall number of skin lesions in each patient is given in Table 3. Because of the striking difference between the MB patients with lepromatous lesions and those without lepromatous lesions, these 2 groups are mentioned separately.

The number of body areas where a skin lesion is present were also counted, body areas being the head, the left arm, the right arm, the front of the trunk, the back of the trunk, the left leg and the right leg. It was observed that at least 3 body areas were involved in 100% of patients presenting 6 or more lesions, and in 72% of patients presenting 4 or 5 lesions.

Table 2. Presence of clinical signs of lepromatous leprosy in relation to bacteriological and operational classification of leprosy patients

Bacteriological classification: Anatomo-pathological image	BI (in biopsy or skin smear)	Operational classification[2]	Signs of lepromatous leprosy: Diffuse infiltration	Nodules	Madarosis	Nose collapse	Total
LL	+	MB	11	(6*)	(3†)	(1†)	11
BL	+	MB	17	3 (+6*)	(2†)	(1†)	20
BT	+	MB	2				2
Unknown[1]	+	MB	1				1
Total			31	3 (+12*)	(5†)	(2†)	34

* Patients also presenting diffuse infiltration; † patients also presenting either diffuse infiltration or nodules.
[1] BI in skin smear = 5+.
[2] See Table 1, note 4.

Table 3. Number of skin lesions in leprosy patients, in relation to bacteriological classification

Bacteriological classification	Number of skin lesions									
	0–3	4–5	6–9	10–14	15–19	20–49	50+	Mean	Median	Range
Bacteriologically confirmed MB[1] with lepromatous lesions	22	3	1	2	1	0	5	10	2	0–99+
Bacteriologically confirmed MB[1] without lepromatous lesions	7	3	6	5	5	20	9	30	22	1–99+
Confirmed PB cases without bacteriologically confirmed MB evidence[2]	54	21	16	13	8	11	0	8	4	1–45
Bacteriologically negative, no anatomopathological signs of leprosy[3]	17	4	3	4	1	2	1	10	3	1–99+

[1] See table 1, note 1.
[2] See table 1, note 2.
[3] See table 1, note 3.

Anaesthesia of skin lesions was observed in 187 patients. The presence of anaesthesia in function of the bacteriological classification is given in Table 4.

Enlarged nerves were found in 219 patients. The number of enlarged nerves for each patient is given in Table 5.

The number of extremities (the head being counted as an extremity) presenting enlarged nerves was counted for each patient. In 100% of patients presenting 5 or more enlarged nerves, at least 3 extremities were involved. In patients presenting 4 enlarged nerves, 65% showed an involvement of at least 3 extremities, and 35% of 2 extremities. In patients presenting 3 enlarged nerves, 50% showed an involvement of 3 extremities, 33% of 2 extremities and 17% of 1 extremity. Only 43% of patients presenting 2 enlarged nerves showed involvement of a single extremity.

Apart from the presence of enlarged nerves, nerve involvement due to leprosy may manifest itself peripherally through corneal anaesthesia, glove or stocking anaesthesia, impaired VMT results for the muscles of the face, the hands and the feet, and the presence of grade 2 disabilities. Grade 2 disability was present in 27 patients (11·1%). Peripheral anaesthesia or VMT impairment or both were found in all 27 patients with grade 2 disability and in an additional 105 patients. In 112 of the patients (45·9%) there was neither peripheral anaesthesia, or VMT impairment, or grade 2 disability. Of these, 19% were confirmed MB.

Among the patients with single limb involvement, the confirmed MB amounted to 23%, and to 66% among patients with involvement of 2 or more limbs.

The number of body areas showing signs of leprosy, either skin lesions or enlarged nerves or nerve function impairment, is given in Table 6.

Table 4. Anaesthesia of skin lesions of leprosy patients in relation to bacteriological classification

Anatomopathological image	BI (in biopsy or skin smear)	Total number of patients	Patients with anaesthetic lesions	
			Number	(%)
LL	+	13	3	23
BL or BB or unknown[1]	+	44	19	43
BT or I	+	32	22	73
Total for bacteriologically confirmed MB		89	44	49
BT	–	111	107	96
TT or I	–	12	12	100
Total for confirmed PB cases without MB evidence		123	119	97
No evidence of leprosy or unknown[2]	–	32	24	75
Grand total		244	187	77

[1] Includes 1 patient with skin smear BI = 5+.
[2] Includes 3 patients with BI = 0.

Discussion

Many leprosy control programmes, afraid to miss an MB case, have established classification criteria resulting in the MB classification of a large number of bacteriologically negative patients. It could be argued that a certain overclassification may be accepted, since the reliability of skin-smear results in field programmes is often questioned.[2–4] However, classification criteria should be aimed at correctly classifying a maximum number of MB cases (this is the 'sensitivity' of the criteria), while limiting the

Table 5. Number of enlarged nerves in leprosy patients in relation to bacteriological classification

Anatomopathological image	BI (in biopsy or skin smear)	Total number of patients	Number of enlarged nerves					
			0	1	2	3	4	5
LL	+	13				1		12
BL or BB or unknown[1]	+	44	1	1	1		5	36
BT or I+	+	32	3	1	3	3	3	19
Total for bacteriologically confirmed MB		89	4	2	4	4	8	67
BT	–	111	13	28	16	10	11	33
TT or I	–	12	3	1	1	1	2	4
Total for confirmed PB cases without MB evidence		123	16	29	17	11	13	37
No evidence of leprosy or unknown[2]	–	32	5	6	7	9	2	3

[1] 1 patient with skin smear BI = 5+.
[2] 3 patients with BI = 0.

Table 6. Number of body areas (head, left arm, right arm, front of trunk, back of trunk, left leg, right leg) presenting signs of leprosy: either skin lesions and/or enlarged nerves and/or nerve function impairment (anaesthesia, VMT impairment, grade 2 disability), in leprosy patients in relation to bacteriological classification

	Number of body areas involved			
Bacteriological classification	1	2	3	4+
Bacteriologically confirmed MB[1]	9	6	13	61
Confirmed leprosy without bacteriologically confirmed MB evidence[2]	41	19	15	48
Bacteriologically negative, no anatomopathological signs of leprosy[3]	10	8	14	0

[1] See Table 1, note 1.
[2] See Table 1, note 2.
[3] See Table 1, note 3.

number of cases classified as MB without bacteriological evidence (the 'false positives' among those classified as MB). The percentage of cases classified as MB without bacteriological evidence among all cases classified as MB, can be called the 'unconfirmed MB rate', and corresponds to: 1− predictive value MB.

Before analysing the findings of the present study, the question should be asked: are all patients included in the study truly leprosy cases? In 32 patients, the biopsy and the skin smears were negative. However, 24 of these (see Table 4) presented with anaesthetic skin lesions (a cardinal sign of leprosy) with or without enlarged nerves, while 7 of the remaining 8 presented suspect but sensitive skin lesions with enlarged nerves (also a cardinal sign of leprosy), and the 1 remaining patient presented grade 2 disabilities on both feet. Most leprologists would agree that the presence of anaesthetic skin lesions and the presence of enlarged nerves are clear clinical signs of leprosy in a leprosy endemic area, even if the biopsy shows no evidence of leprosy. Thus the diagnosis of leprosy could be justified in at least 31 of these 32 patients. Nevertheless, the presence of anaesthesia should be considered a doubtful criterion at best, in view of the fact that Table 4 shows that 77% of all patients present anaesthetic lesions, including 23% of LL patients and 40% of BL patients. The interpretation of sensory testing, however well done, is influenced by too many factors to remain strictly objective. In this particular group of patients, it seems as if the expectations of the examiners have biased the sensory testing results. The interpretation of nerve enlargement is equally subject to inter- and intra-observer variation. The presence of grade 2 disability without any other sign of leprosy in a patient could suggest several other diagnoses (for instance ideopathic peripheral neuropathy).

Thus, we cannot say with certainty that all 244 cases are truly leprosy patients. However, since it is equally impossible to say with certainty that they do not have leprosy, all patients will be included in the analysis.

Of the 244 patients in the study, 89 are bacteriologically classified as MB, and 155 as non-MB (see Table 1). The application of the criteria of the operational classification resulted in correctly identifying 82 of 89 MB cases, a 'sensitivity' of 92·1%. For 91 of 173

patients there was no bacteriological evidence of MB leprosy, an 'unconfirmed MB rate' of 52·6%.

Analysis of the individual patient records reveals that the classification criteria were not always applied rigorously, e.g. a patient with only 2 lesions classified as MB, or a patient with 2 enlarged nerves classified as PB. But this does not significantly alter the results: strict application of the criteria would still correctly classify 82 MB cases ('sensitivity': 92·1%) while 101 patients would be classified as MB without bacteriological evidence ('unconfirmed MB rate': 55·2%).

The goal of the operational classification is to miss as few MB cases as possible. Short of treating all patients as MB, the highest 'sensitivity' obtainable, using the number of skin lesions and the number of enlarged nerves as classification criteria, would be 96·6%, if all patients presenting 6 or more skin lesions or 2 or more enlarged nerves would be treated as MB. But 3 out of 89 MB cases would still be missed, and there would be 105 'false positives'—an 'unconfirmed MB rate' of 55·0%.

Since the 'unconfirmed MB rate' is very high, investigations should determine if any additional clinical criteria could be helpful in increasing the reliability of the operational classification. A study in Ethiopia[5] shows that a combination of 5 or 6 clinical criteria produces the most reliable results. It is unfortunate that the Ethiopian study does not start its analysis with the criteria 'number of skin lesions' and 'number of enlarged nerves', which would have made comparison with the present study easier. In addition, no systematic biopsy taking was done in Ethiopia: as a result, the reference MB classification had to be based on a combination of skin-smear results and clinical criteria. But it is exactly these clinical criteria which are under investigation. Thus the sensitivity, specificity and predictive values of that study cannot be compared to the present study. A score chart used in Papua New Guinea[6] rates 8 clinical criteria from 1 to 3, a total score of $>=$ 12 resulting in an MB classification. The reliability of this approach is not analysed.

A study in Nepal[7] discussed the reliability of a system based on affected body areas, while at the same time using a computer simulation to study various other methods of PB/MB classification.

In the present study, various additional clinical criteria were added to the baseline criteria (number of skin lesions and number of enlarged nerves) in order to examine whether a more reliable classification could be obtained. As already pointed out, anaesthesia of skin lesions (see Table 4) was present in 187 patients spread out across the whole spectrum of the bacteriological classification. Although anaesthesia was observed in almost all PB patients, it was also present in 49% of the MB patients, including 23% of the LL patients. The suspected examiner bias has already been discussed above. In this particular study, the presence of anaesthesia does not contribute to a more correct classification of the patients.

The number of body areas involved is not helpful either. Most patients have at least 3 areas involved the moment they present 4 or more skin lesions, and when 2 or more nerves are enlarged, this usually involves at least 2 limbs, while almost 50% of the patients (including 19% of the MB patients) do not present any peripheral neurological impairment.

If all the patients who were presenting at least 2 body areas with leprosy signs (see Table 6) were considered MB, this would result in a 'sensitivity' of 89·9% and an 'unconfirmed MB rate' of 56·5%. If the presence of at least 2 enlarged nerves were

included as an MB criterion, the 'sensitivity' would increase to 93·3%, but the 'unconfirmed MB rate' would be even higher, at 57·8%.

If the MB criterion were presence of 3 body areas affected by leprosy, the 'sensitivity' would be 83·1%, and the 'unconfirmed MB rate' would be 51·0% . This is in marked contrast with the study in Nepal,[7] where the criterion of 3 affected body areas (in patients who had a biopsy) resulted in a 'sensitivity' of 93% and an 'unconfirmed MB rate' of 33%. If the criterion of 2 affected body areas were used, the 'sensitivity' was pushed up to 100%, while the 'unconfirmed MB rate' was 36%. The reason for this marked difference is to be found in the higher number of MB patients in Bangladesh with only 1 or 2 affected body areas. In Bangladesh, 9 of 89 MB patients (10%) show involvement of a single body area, and 15 of 89 (16·9%) of 1 or 2 areas. In Nepal, these figures are 0 of 31, and 2 of 31 (6·5%), respectively.

Most likely, this is due to earlier case detection in Bangladesh, as illustrated by the proportion of WHO grade 2 disabilities among newly-detected cases: 11·1% in Bangladesh against 22% in Nepal. This would suggest that the body area criterion would be more useful in advanced cases.

The presence of clinical signs of lepromatous leprosy is a very sensitive and specific indicator of MB leprosy (see Table 2). All 34 patients with lepromatous signs are MB cases. The presence of diffuse infiltration in 2 histological BT patients, although they presented a positive BI, may be doubted. This could be a manifestation of examiner bias. However, all observations made by the field worker were checked by the medical officer. Although the presence of concomitant diseases presenting with similar clinical signs was not explicitly excluded, no evidence of any such disease was found in the biopsies, and all patients presenting clinical signs of lepromatous leprosy had a positive BI. Thus, the attribution of these signs to leprosy seems justified.

The presence in a BL patient of madarosis (2 patients) or nose collapse (1 patient) would suggest we are dealing with LL patients rather than BL patients.

Since no patient presented with gynaecomastia, and the 2 patients with nose collapse and the 5 patients with madarosis also presented diffuse infiltration or nodules or both, the presence of diffuse infiltration or nodules should be a useful addition to the clinical criteria of the operational classification. The addition of the criterion of lepromatous signs to those outlined under materials and methods would increase the 'sensitivity' to 94·4%, but the 'unconfirmed MB rate' would still be 54·8%. If the MB criteria were the presence of either lepromatous signs, or of 10 or more skin lesions, or of 3 or more enlarged nerves, the 'sensitivity' would be 93·3%, and the 'unconfirmed MB rate' 49·4%. If the last criterion was made more restricted (presence of 3 or more enlarged nerves, if also 3–9 skin lesions are present) the 'sensitivity' would be 91·0% and the 'unconfirmed MB rate' 46·4%.

A lower 'unconfirmed MB rate' could not be obtained without lowering the 'sensitivity' below 90%.

This discussion suggests that an operational classification based on clinical criteria will inevitably result in a very high overclassification of MB cases.

The first part of this study[1] shows that reliable skin-smear examinations may contribute to the reliability of the classification. Based on skin-smear results alone, 88·8% of the MB cases are correctly identified without overclassifying a single case. Of those MB cases missed, 60% had a BI of 1+ in the dermal nerves only. If these cases were to be considered PB, the 'sensitivity' of the skin-smear criterion would be 94·7%.

Table 7. Sensitivity (defined as: proportion of patients presenting either a biopsy result of LL or BL or BB or a positive BI in either the biopsy or the skin smear, correctly identified as MB) and false MB rate (defined as: proportion of patients without histological MB evidence and with negative skin smears, identified as MB) for various sets of classification criteria

Classification criteria for MB	Sensitivity (%)	False MB rate (%)
Either > = 10 lesions (skin or nerve) or 4–9 lesions (skin or nerve) with > = 2 enlarged nerves	92·1	52·6
Either > = 6 skin lesions or > = 2 enlarged nerves	96·6	55·0
Either presence of lepromatous signs or > = 10 skin lesions or > = 3 enlarged nerves	93·3	49·4
Either presence of lepromatous signs or > = 10 skin lesions or 3–9 skin lesions plus > = 3 enlarged nerves	91·0	46·4
> = 2 body areas affected	89·9	56·5
Either > = 2 body areas affected or > = 2 enlarged nerves	93·3	57·8
Skin smear positive	88·8	0
Either skin smear positive or > = 20 skin lesions or > = 4 enlarged nerves	96·6	40·3

If various combinations of skin-smear examinations and clinical criteria with different cut-off points are looked into, the most reliable result would be the following: if the criteria for MB classification are either a positive skin smear, or 20 or more skin lesions, or 4 or more enlarged nerves, the 'sensitivity' is 96·6%, while the 'unconfirmed MB rate' is 40·3%.

These figures are valid if skin smears are taken at the 4 standard sites (see Materials and Methods) and at the most active peripheral site. If skin smears are taken only at the earlobe and the most active peripheral site, the 'sensitivity' becomes 95·5% and the 'unconfirmed MB rate' 40·6%.

For easy reference, Table 7 summarizes the 'sensitivities' and 'false MB rates' obtained by using the most representative of the various sets of criteria discussed in this article.

Conclusion

Each patient classified as MB without proper justification will require a treatment regimen which is 14 times more expensive than the PB regimen, while he will at the same time require 4 times as many monthly medical contacts. Thus MB overclassification will have considerable consequences in terms of drug budget and workload of the field workers.

To illustrate this with an example: a programme has to treat 1000 patients, 400 of whom are bacteriologically confirmed MB cases. The choice is between strategy Y with a

'sensitivity' of 95% (380 MB cases found) and a 'unconfirmed MB rate' of 52%, and strategy Z with a 'sensitivity' of 90% (360 MB cases found) and an 'unconfirmed MB rate' of 41%. Strategy Y will be almost US$7300 more expensive for the drug cost alone, while it will also require 3276 monthly medical contacts in excess of strategy Z. The programme planner has to decide whether this extra cost is justified by 20 additional MB cases which would be found by strategy Y.

The present analysis suggests that the inclusion of the skin-smear results would considerably improve the reliability of the classification strategy. In many programmes, skin smears are taken, but their results are not used optimally, if used at all, often because the validity of these results is doubted. Such programmes would profit tremendously from an upgrading of the quality of their laboratory facilities. Refresher courses for the laboratory technician and regular quality control of smear taking and smear reading would result, for a limited cost, in improved reliability of the smear results. This would permit the inclusion of these smear results in the classification criteria, which would lead to more MB cases being correctly classified and less unconfirmed MB cases being treated as MB, thus resulting in a more cost-effective programme. However, in programmes without laboratory facilities, the introduction of skin-smear examination may not be cost-effective in view of the cost of hiring and training qualified personnel, of installing the laboratory and of setting up a system to assure the continued quality of its performance.

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The efficacy of podiatric orthoses as an adjunct to the treatment of plantar ulceration in leprosy

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Summary This study examines the outcome of a mangement approach to plantar ulceration secondary to leprotic neuropathy. Locally-available resources were used to produce podiatric orthoses which were supplied to an experimental group. The effects on healing time and quality of healing were compared with a control group. Both groups were ambulant (the programme sought not to interfere with socioeconomic independence). Using standard nonparametric methods of analysis, it was demonstrated that the effects on healing rate, attributed to the experimental intervention, were highly significant. Over a 7-month period, 57% of the experimental group ulcers healed, while only 12·5% of the control group ulcers healed. The experimental intervention also demonstrated a positive effect on the quality of ulcer healing. This effect was not reflected in the control group.

Introduction

Disability prevention, as an issue, is gaining status as awareness of the potential for leprosy eradication as a health care problem becomes increasingly plausible. This study developed as a need was perceived to improve the current approach to the treatment of simple ulcers whilst observing the resource limitations of an institution in a developing country was recognized.

The therapeutic rationale supporting the intervention of mechanical therapy for the neuropathic foot was based on findings reported in the literature. Other investigators have sought to explain the action of orthotic devices, or footwear modifications, by examining the effects of intervention on the distribution of pressure or on the redirection of the centre of force.[1–11] These investigators have validated principles of deflection, cushioning, increased weight-bearing area or alteration of the rearfoot alignment with the supporting surface.

Recognizing the significance of mechanical factors as agents of destruction threatening the neuropathic foot created a challenge that has been vigorously pursued

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since the late 1950s.[1,12–15] The concern to develop conservative treatment of plantar ulceration arose from the recognition that ulceration was an initiating factor precipitating the apparent vortex of destruction, all too commonly culminating in amputation.[16]

Extensive groundwork has been conducted to demonstrate desirable design features, and approaches to treatment that would address pathomechanical characteristics of ulceration. Plaster of Paris casting and rest have demonstrated efficacy.[17–18] However, the effectiveness of the approach is less satisfactory as recurrence is common, and repeated or prolonged treatment has undesirable social and medical consequences.

Many of the early footwear innovations were laudable. It is broadly agreed that a rigid-soled shoe with a carefully placed rocker effectively reduces focal pressure (generally accepted to be an aetiological factor effecting ulceration). The beneficial effects are explained by the principle that a rigid-soled shoe pivoting on a carefully placed rockerbar will cause loading to be redistributed over a larger area of the foot.[1] A consequence is that the loading time for greater areas of the foot in contact with the rigid shoe will be increased thereby decreasing focal concentrations of force. This assumption is not necessarily correct as the effect of mixed variables requires consideration, e.g. the functional adaptations of the structure of the foot as a kinematic response effected by peculiarities of gait.

Brand[19] has expressed reserve in his opinion of orthotic intervention for neuropathic feet. His concern was that improperly placed devices may increase focal pressures and exacerbate ulceration. Whilst recognizing this hazard, the results of this study illustrate that orthotic intervention can significantly reduce the moribidity of ulceration. Although regression of ulceration in a minority of cases may be attributed to damage by devices it would appear that a significant majority benefited by the intervention. It is accepted that the significance of the findings demonstrated in this investigation may be an indication of professional expertise and may therefore be limited in their application among the wider population. The training of leprosy workers and the assessment of their ability to prescribe and manufacture devices may demonstrate the wider potential benefit of this form of intervention.

Method

SAMPLE SELECTION

A sample of 71 subjects was drawn from outpatients and employees at the Dr Bandorawalla Leprosy Hospital, Kondhawa, Pune, India. All subjects presented with sequelae of leprosy including, anaesthesia and plantar ulceration. All were suitable for prescription of an individual orthosis from a wide range of podiatric orthoses.

The criteria for subject inclusion excluded bedrest patients, patients being treated with plastercasting, patients presenting with acute osteomyelitis or patients for whom specialized orthopaedic footwear had been prescribed. The selection criteria for both experimental and control groups were identical. There was no selection bias. The supply of orthoses depended on the mutual availability of subjects, the interpreter and the researcher.

We fitted 37 subjects with orthoses and allocated them to the experimental group; 34 were not offered orthoses and these were allocated to the control group. By March,

5 subjects had dropped out of the experimental group and a further subject was excluded due to intervention with plastercast treatment. These exclusions reduced the number of subjects to 31, reducing the number of ulcerated feet for analysis to 35 and the number of ulcers to 40 (4 feet presented with multiple ulcers). In the control group, 3 subjects had dropped out, reducing the number of subjects to 31, the number of ulcerated feet for analysis to 35 and the number of ulcers to 39 (4 feet presented with multiple ulcers).

METHODS OF ASSESSMENT AND EVALUATION

All subjects were assessed for sensory loss and deformity during the initial visit. For this study the patients' response to pain and vibration was tested using the techniques described by Bickerstaff & Spillane.[20] A 128 Hz tuning fork was used to test vibration and the pinprick test was applied to test for pain response. Findings relating to sensory loss and observations of deformity were recorded diagrammatically on foot maps as described by Watson.[21]

The assessment of ulceration followed standardized criteria established by Wall[22] who described general features of ulceration that indicated stages of degeneration, chronicity or resolution.

After recording the number of lesions, the size of individual ulcers was measured. Measurements were recorded at increments of 0·25 cm. Size was recorded as:

The greatest distance between 2 points on the edge, longitudinally.
The greatest distance between 2 points on the edge, horizontally.

The area of ulceration was then calculated using the formula:

$$(\text{Horizontal length} + \text{Longitudinal length}) \times 0{\cdot}785^{23,24}$$

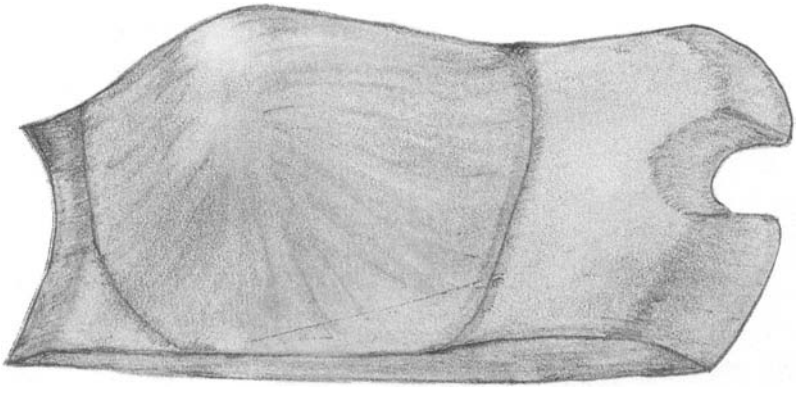
Ulceration was further described by categorical rating of edge and surface morphology.

SUPPLY OF ORTHOSES

The devices issued incorporated features aimed at addressing both palliative and functional demands (Figure 1). Prescription was based on observations of gait and examination of foot structure. The choice of materials used was determined by local supply. Devices were fabricated from microcellular rubber to accommodate the requirements of individual subjects. The supply of elasticated removable devices was limited to subjects demonstrating an uncompromised vascular supply and sufficient manual dexterity. All other devices were adhered to subject's footwear.

The subject's choice of footwear was respected, however, and if damaged it was either replaced or repaired. All changes to, or of, footwear over the experimental period were recorded. The use of gauze swabs secured by tape or minimal bandage was domonstrated to experimental group subjects. Where ulcers did not present with excessive exudate experimental group subjects were encouraged to dress ulcers with zinc tape. This approach has been shown to demonstrate an effect not significantly different from gauze bandage.[25] Control group subjects continued to dress ulcers with gauze bandage.

Filler Pad Incorporating Valgus Dome And Cut Away For Pressure Deflection



Filler Pad Incorporating Valgus Dome With Forefoot Modification And Cut Away For Pressure Deflection

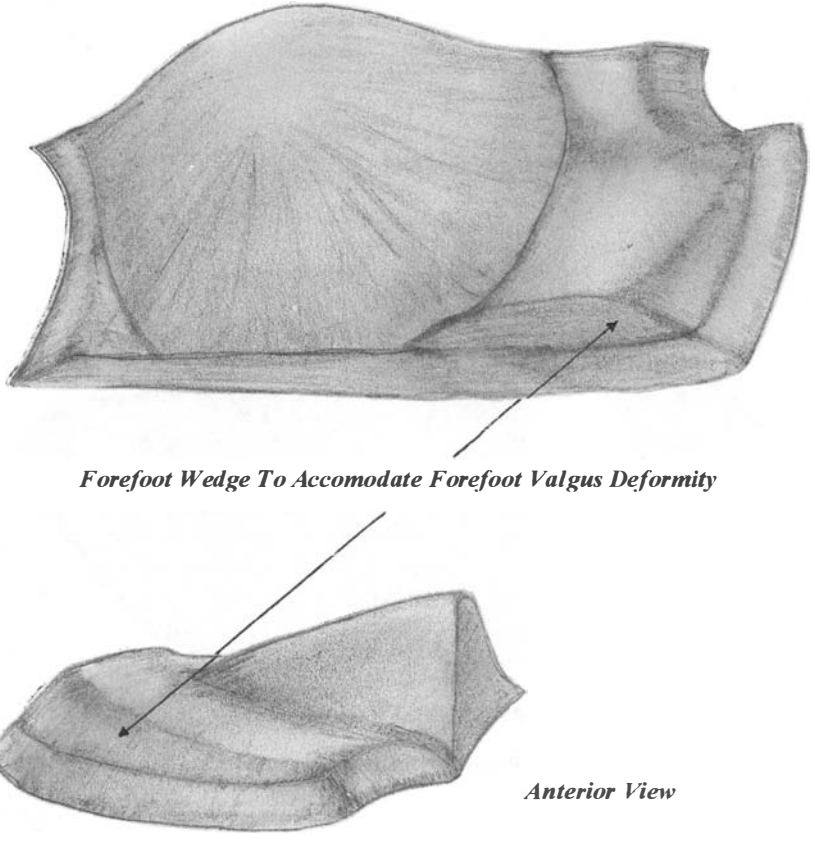
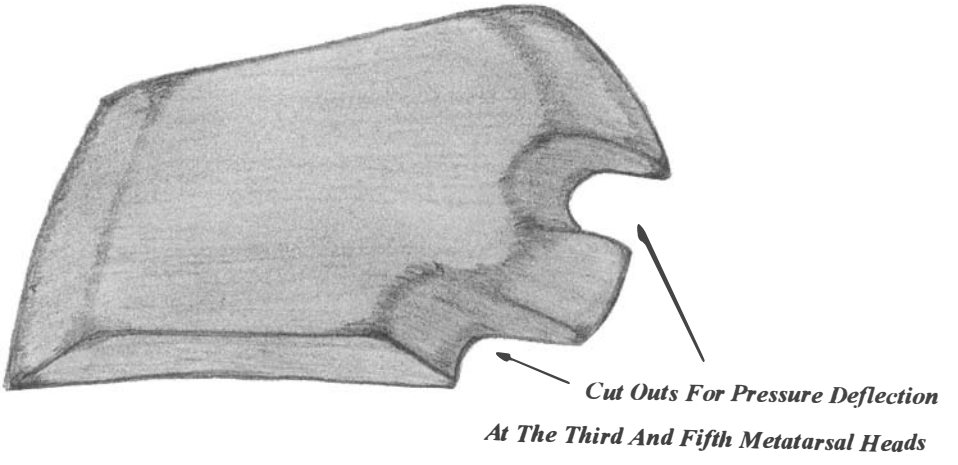


Figure 1. Orthoses supplied to the experimental group, July–August 1994.

Plantar Metatarsal Pad



Removable Plantar Metatarsal Pad

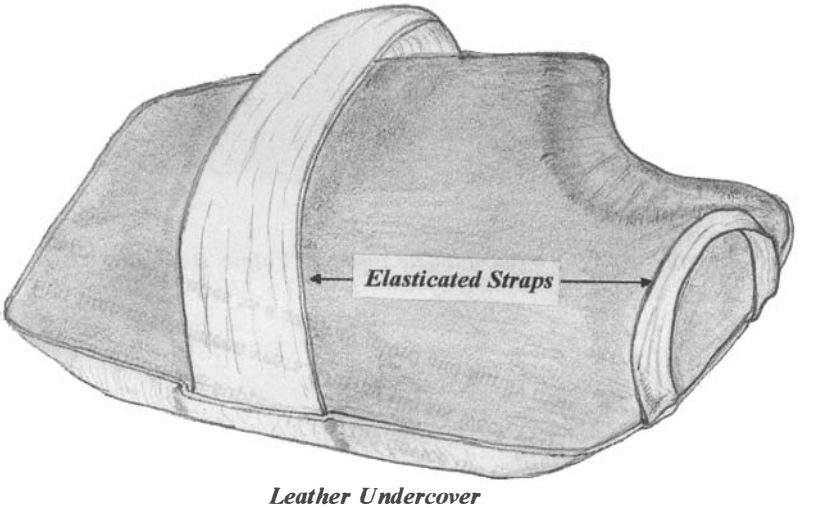
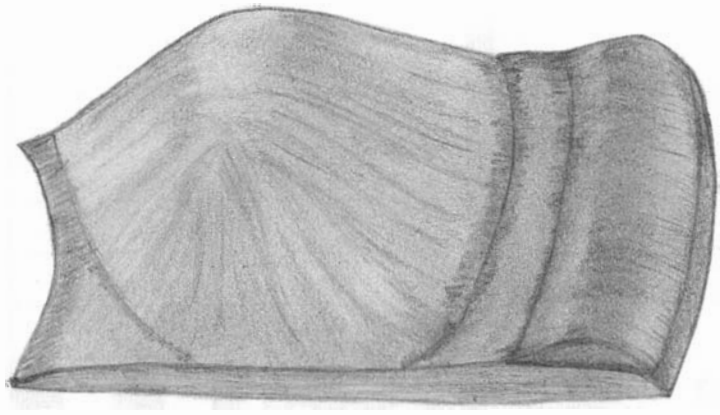
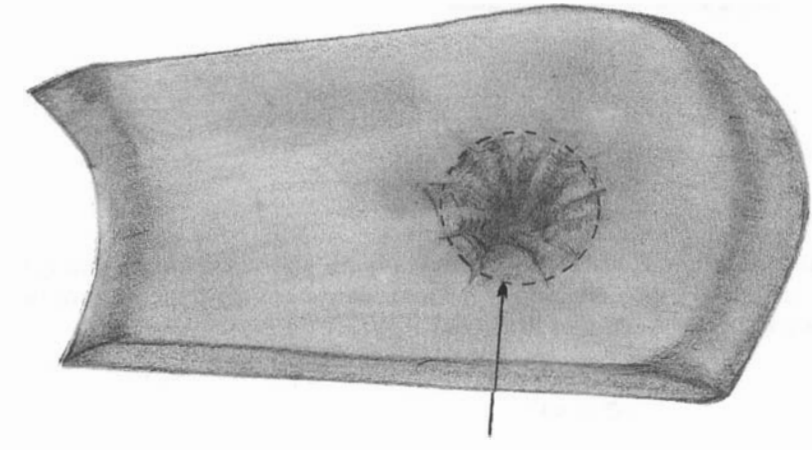


Figure 1. (Continued).

Filler Pad Incorporating Valgus Dome And Anterior Rocker Bar



Filler Pad Incorporating A Window



Cavity Excavated Beneath Device

Lateral View

Figure 1. (Continued).

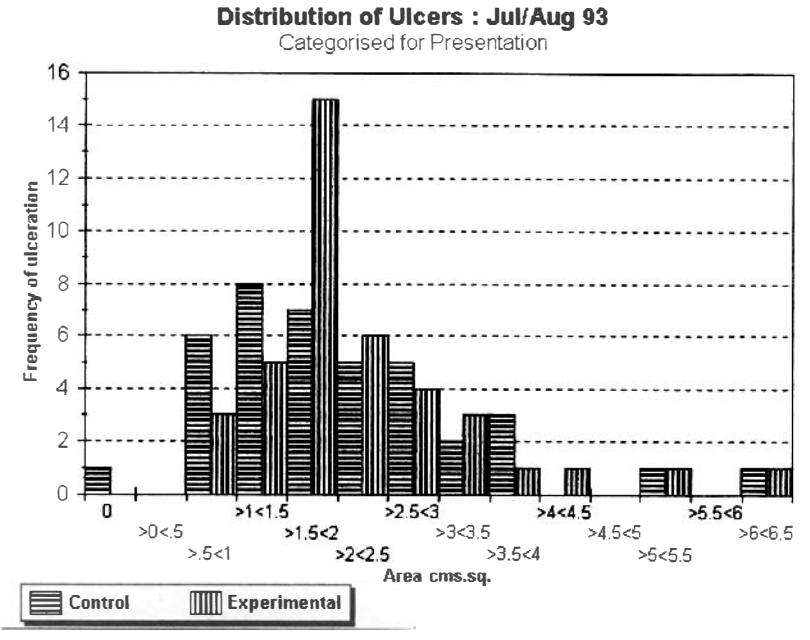


Figure 2.

BASELINE DATA

Ulcer size

The Mann–Whitney *U*-test was used to compare ulceration dimensions (expressed as area of ulceration) between experimental and control groups at the onset of the trial. The data represented here excludes drop outs:

$$n1 = 39,$$
$$n2 = 40,$$
$$\mathrm{U} = 758,$$
$$\text{'U'} = 782{\cdot}5, 95\%\mathrm{CI} = -0{\cdot}39 \text{ to } 0{\cdot}39, \text{ NS.}$$

(See Figure 2 and Tables 1 and 2.)

Table 1. Comparison of edge morphology

Type	Undermined	Indurated	Shelved	Total
Experimental	20	15	5	40
Control	25	11	3	39
Total	45	26	8	79
χ^2	0·43/NS	0·39/NS	0·36/NS	

Table 2. Comparison of surface morphology

Type	Slough	Granulation	Perforating	Total
Experimental	9	20	11	40
Control	13	21	4	39
Total	22	41	15	79
χ^2	0·83/NS	0·06/NS	$0{\cdot}2{\cdot}8/p = 0{\cdot}08$	

Morphology of ulceration

The Fisher–Irwin exact test was used to compare the edges and surfaces between both groups. The findings demonstrate that there was no significant difference between groups.

Results

ULCER SIZE

Data relating to the March 1994 assessment of the control group were compared with those of the experimental group during the same period.

The experimental group data displayed that of 40 ulcers 23 (57.5%) had healed. The

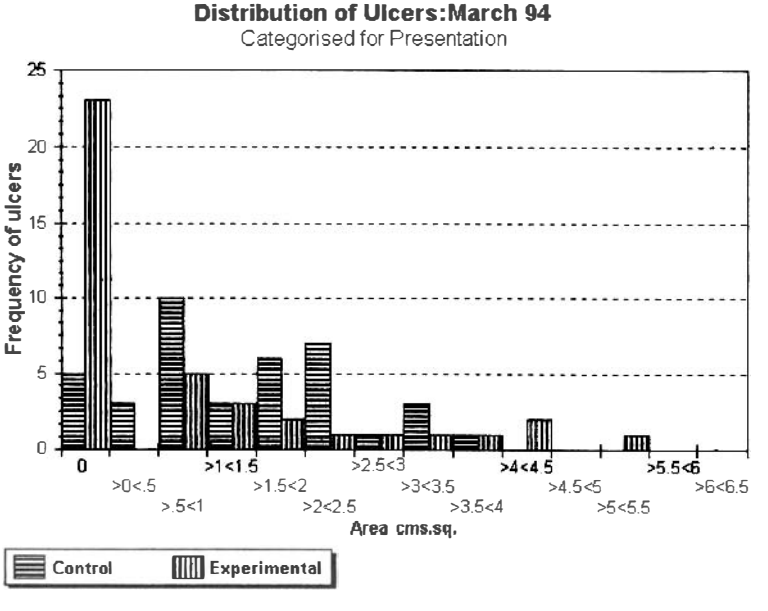


Figure 3.

control group data displayed that of 39 ulcers 5 (12.5%) had healed. Comparison of data representing the ulcer area in March 1994

Control Group	$n = 39$	
Experimental Group	$n = 40$	
Mann–Whitney *U*-Test		
U = 1089 'U' = 451.5	95% CI 0.2 to 1.18	$p = 0.0009$

(See Figure 3.)

UNRESOLVED ULCERS

Comparison of data representing the area of unresolved ulcers in March 1994.
Control Group $n = 34$;
Experimental Group $n = 16$.
Mann–Whitney *U*-test
U = 337·5, 'U' = 96, 95% CI = 0·02 to 1·18, NS.

Analysis

The results demonstrate that a highly significant reduction in the mean area of ulceration was demonstrated between both groups in March. This reduction is explained by the 5-fold number of healed ulcers in the experimental group when compared with the control group. However, the unhealed ulcers in the experimental group were not significantly different in size from the unhealed ulcers in the control group.

CHARACTERISTICS OF ULCERATION

A hypothesis suggesting that positive changes in ulcer morphology were concurrent with changes in the area of ulceration was tested. χ^2 was used to demonstrate whether the trend in mean scores between the area of ulceration at each assessment and groups categorized as regressive, static and progressive were significantly different.

Observations relating to undermined edges were grouped with observations relating to perforating and hypergranulating surfaces and were categorized as regressive.

Observations relating to indurated edges were grouped with observations relating to sloughing ulcers and were categorized as static.

Observations relating to shelved edges were grouped with observations relating to granulation and were categorized as progressive. (See Tables 3 and 4.)

EXPERIMENTAL GROUP

Area and progressive:

$$\chi^2 \text{ for trend in mean scores} = 5{\cdot}91, \text{ df } 1, p = 0{\cdot}01.$$

Area and static

$$\chi^2 \text{ for trend in mean scores} = 0{\cdot}28, \text{ df } 1, \text{NS}.$$

Area and regressive

$$\chi^2 \text{ for trend in mean scores} = 2{\cdot}35, \text{ df l, NS.}$$

Table 3. Experimental group: changes in ulcer characteristics relative to area*

Group	July	September	December	March
Regressive	32	7	12	6
Static	35	16	18	10
Progressive	13	37	16	18
Total area of all observations	83·76	51·52	33·72	37·07

* The increase in area from December to March (experimental group) was not significant. $n1 = 23$, $n2 = 17$ Mann–Whitney U-test, U = 253·5, 'U' = 86·5, 95% CI = 0 to 1·56, NS.

Table 4. Control group: changes in ulcer characteristics relative to area

Group	July	September	December	March
Regressive	28	19	17	18
Static	24	24	28	25
Progressive	24	23	23	25
Total area of all observations	80·12	68·73	63·04	54·4

Analysis

As the experimental group area of ulceration decreased at consecutive assessments, the increase in the number of observations relating to progressive characteristics was significant. Conversely the comparative trends in mean scores relating to area and regressive or static characteristics were not significant. This finding suggests that these characteristics decreased as the area of ulceration decreased.

Difference in trend of mean scores relating to positive characteristics presented by the control group were not significant.

These results suggest that the intervention may have imposed a stabilizing effect on ulcers in the experimental group creating conditions in which the healing process was enhanced.

Confounding Variables

Care was taken to examine the potential effects of other independent variables to confound the results. The effects of deformity, sites of ulcertion and occupation were examined and found not to have demonstrated a significant effect on the results.

Different types of orthotic device were examined and found not to have favoured sub groups within the Experimental group.

Discussion

The results presented indicate that after a 6-month period subjects in the experimental group were more likely to present with healed ulcers (52·5% healed) than subjects in the control group (12·5% healed).

Favourable alterations in the morphology of ulceration, concurrent with a reduction in area was a feature of experimental group ulcers. The trend was not reflected in the control group where a reduction in ulcer area was not accompanied by changes characteristic of a sound healing process. On this basis, a statement suggesting that orthotic intervention enhances the quality of healing is supported. The major implications of this finding are 2-fold. Primarily, orthotic treatment reduces the time required to heal an ulcer (when compared with gauze dressing treatment). Furthermore, by attenuating or reducing the effects of irritation during healing the opposition to the homeostatic response to ulceration is reduced.

SCAR TISSUE

During the maturation or remodelling phase of tissue repair there is a decline in concentration of fibroblasts. A complex reorientation activity organizes random collagen fibres into a system of optimally oriented fibres. The eventual result is the consolidation of scar tissue, which displays a maximum strength of 20% less than that exhibited by intact skin.[26,27]

The rapid process of synthesis and lysis of collagen in the early stages of healing is reversed during maturation such that the rate of lysis exceeds that of synthesis. The nature of biochemical bonding is also alerted. This results in the establishment of stronger molecular structures and links between collagen fibrils and ground substance. It is fundamental therefore to promote rapid healing to discourage the excessive linkage of collagen and ground substance. The weaker bonding of collagen in developing scar allows for limited stretch as a response to stress. With maturation scar tissue does become less resilient. However, recurrent trauma during the maturation phase leads to increasing deposits of more dense and toughened mature scar organized into progressively less resilient tissue. Brand[19] has discussed the problem of scarring as a response to recurrent trauma. He has related the common recurrence of ulceration to the cumulative degeneration of skin into scar tissue.

The application of plastercasts have proven efficacious in the rapid healing of neuropathic ulceration.[16] Anecdotal evidence suggests that ulcers may heal within a period of 3 weeks. Birke *et al.*[17] recorded that patients treated with walking casts presented with ulcers that healed in 37·7 days. However, the recurrence of ulceration following this procedure is common, particularly where predisposing mechanical factors have not been addressed subsequent to treatment. A more subtle problem may be the effect of immobilization on the healing response.

The realignment of collagen fibres is thought to be a response to pressure. When pressure is applied collagen releases 'piezoelectric substances.'[26] It is postulated that

these stress generated voltages are responsible for the realignment and general maintenance of collagen. This provides an important perspective to wound healing as it suggests that the strength of healed skin is determined by biomechanical stresses acting on healing time. The fragility of healing resulting from immobility may be reduced by permitting careful movement of healing tissue. It is not suggested here that orthotic intervention of the type under review is particularly subtle. However, it may be that by permitting the subject to be fully ambulant whilst controlling traumatic mechanical factors, the maturation phase of the healing process may also be enhanced.

LIMITATIONS OF THE STUDY

It was aimed to establish a research protocol that did not compromise the demand for academic integrity whilst demonstrating direct relevance within the existing infrastructure of an Indian leprosy hospital. An implication is that the generalizability of the study should be such that similar leprosy hospitals would be able to relate to it. However, the investigators accept that the elevation of ethical issues and external validity as priorities contributed to the difficulty of controlling potentially confounding variables.

It is accepted that the significance of the findings demonstrated in this investigation may be an indication of professional expertise and could therefore be limited in their application among the wider population. The training of leprosy workers and the assessment of their ability to prescribe and manufacture devices may demonstrate the wider potential benefit of this form of intervention.

SOCIOECONOMIC IMPLICATIONS OF THE STUDY

It has been demonstrated that expensive footwear or footwear meeting with low patient acceptability is not a prerequisite to successful treatment. This is a fundamental implication of this study where the population under review is from a low socioeconomic group and resources are limited. Furthermore, subjects were all ambulant, they were not expected to curtail any normal activity and were not further stigmatized as all the devices were discrete. The significance of this was that no loss of earnings was experienced during the period under review and no alterations to lifestyle were imposed. It is suggested that for these reasons compliance was readily embraced. Enthusiasm for the intervention was apparent and may have been a factor contributing to the generally successful outcome.

Conclusion

The apparent efficacy of podiatric orthoses as an adjunct to the treatment of ulceration may be greeted with restrained enthusiasm. Unless the treatment can be maintained and developed within the social and cultural parameters affecting leprosy sufferers and workers, the effectiveness of podiatric orthotic intervention remains speculative.

This project shall continue to assess the long-term effects of orthoses as a treatment and as a prophylactic measure in the prevention of recurrence of ulceration. By adopting a broader sociomedical perspective it may be determined whether this approach is an acceptable and realistic management option.

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Estimating the size of the leprosy problem: the Bangladesh experience

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Summary Assessing the size of the leprosy problem in a country is an important but difficult issue for the purpose of programme planning. Different methods have been proposed but often estimates have proved to be very different from reality. We have attempted to address this issue in Bangladesh, a country where official estimates are more than 5 times greater than the registered number of leprosy cases.

A combination of methods, including surveys, data from leprosy control programmes and local knowledge based on the Delphi technique have been combined to construct an estimate of the total number of cases in Bangladesh. This figure (173,196) is only 10% greater than the official estimate (136,000). It will be possible over the next few years to see how close this figure is to reality through data obtained from the National Leprosy Control Programme which is now rapidly developing to cover the whole country.

Introduction

Accurate estimation of the size of the leprosy problem is a global as well as national issue. In the past estimates have been shown to be highly inaccurate, particularly when random sampling methods have been used. This has been due to the clustered pattern of the distribution of leprosy as well as to the operational problems of defining a case for survey purposes. We have attempted to combine a number of different methods to produce an estimate for Bangladesh, an approach which may be applicable to other countries.

According to the WHO report for 1994, the estimated number of leprosy patients in Bangladesh is 136,000.[1] This makes Bangladesh third on the list of leprosy endemic countries of the world, after India and Brazil. The leprosy problem is taken seriously and in November 1993 a national project was introduced by the government of Bangladesh for 'Further Development of TB and Leprosy Control Services'. The aim is to strengthen TB and leprosy control services in an integrated programme and, as far as leprosy is concerned, make MDT available in all districts of the country by 1995.[2] Although leprosy control activities, both by government and nongovernmental organizations

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(NGOs), have been going on for many years in some parts of the country, there are hardly any studies available on the extent of the leprosy problem. It is therefore important for planning purposes for this new leprosy control initiative to produce an accurate estimate of the size of the problem.

In a review article from 1945 entitled 'Leprosy in Bengal',[3] it is mentioned that leprosy was most common in the western area (now West Bengal in India) with prevalence rates of 10–30 per 1000, followed by the central and northern districts with a prevalence rate of 5–9 per 1000. The lowest rates (less than 5 per 1000) were indicated to be found in the low lying delta districts of south-east Bengal (the present Bangladesh). In 1965 the prevalence rate in East Pakistan (now Bangladesh) was put at 1·3 per 1000, with a total number of estimated cases of 150,000.[2] In a report of the World Bank of 1990, a prevalence rate of 2·5 was postulated, amounting to 275,000 leprosy cases.[4] This figure was largely based on known prevalence rates in the neighbouring countries and not on specific studies within the country. The currently quoted figure of 136,000 is essentially based on the original figure of 1965, minus the number of cases reported to have completed Multidrug therapy (MDT).

From experience it is known that leprosy is highly endemic in the north-western area of Bangladesh (the Rajshahi Division). This paper reports on surveys conducted in 1993 in 4 districts of the Rajshahi Division, combined with expert opinion from the other divisions of Bangladesh. The objective was to establish more accurately the size of the leprosy problem in order to implement adequate control activities. On the basis of these figures an estimation is made of the prevalence of leprosy in Bangladesh.

Methods

Surveys were conducted in Panchagar, Thakurgaon, Nilphamari and (part of) the Rangpur districts in the north of the Rajshahi Division of Bangladesh. The total population in this area is 4·2 million (1991 census) and the area size 5655 km^2. In these districts a leprosy control programme has been conducted by the Danish–Bangladesh Leprosy Mission (DBLM) since 1978. MDT was introduced in 1984 and extended to all 4 districts by 1990.

In 1993 numerous small surveys were done within the project area. The objectives of these surveys were both to generate more accurate statistics and as a case-finding activity. The surveys were carried out in small localities which were chosen for various reasons, including a location near clinics and requests from community leaders. The surveys entailed mapping, enumeration, health education programmes, checking and rechecking, using standard forms.

All suspect cases were examined by experienced senior paramedical workers or medical officers for confirmation of the diagnosis. The WHO definition of a case was used, namely 'cases needing treatment'.[5] Skin smears were carried out on cases that subsequently presented to a clinic. Dubious cases were observed for 3 months, examined monthly and subsequently discharged or registered as a true case. During the surveys, leprosy was classified on the spot on clinical grounds according to the Ridley–Jopling scale and by MB/PB classification, where MB include LL and BL cases only, because skin smears were only taken at a later stage.

Definitions used:

New case prevalence rate: New cases detected at the time of the survey per 1000 population.
Active case prevalence rate: New cases and cases already under MDT treatment per 1000 population (= prevalence rate).
Total case prevalence rate: Includes all living cases released from treatment, new, and under treatment per 1000 population.

The *active case prevalence rate* is used in this paper to establish the size of the leprosy problem, in accordance with WHO advice from the Expert Committee.[5]

To obtain a best estimate for Bangladesh as a whole, the abovementioned method was combined with data and information from relevant sources elsewhere in the country, in particular the leprosy NGO programmes. This method has been referred to as the Delphi technique. It has been described as an excellent method of obtaining and refining group judgment based on the premise that a group of experts is better than a single expert when exact knowledge is not available.[6,7]

Results

In 1993, a total of 5096 new patients in Bangladesh started treatment in programmes conducted by leprosy NGOs in various parts of the country (Table 1, Figure 1). This represents nearly 75% of all patients newly detected in Bangladesh during that year, the remaining 25% detected by government health services. Of all new patients, 3307 (65%) were from the Rajshahi Division, mainly from the northern part. Because leprosy NGO control programmes have consistently maintained accurate records and data for many years, their experience and information is important when assessing the leprosy problem in their areas of operation. From that experience it is known that in the southern districts

Table 1. Data from the leprosy NGO programmes in Bangladesh (source: ILEP B forms 1993)

Name project	Division	Population control area	On MDT	New patients 1993	On surveillance or care
DBLM	Rajshahi	4,200,000	2910	1965	6743
RDRS	Rajshahi	2,556,000	1371	458	1790
DLC	Rajshahi	2,288,811	1743	621	2664
DLC	Rajshahi	3,359,716	689	203	527
SLCP	Rajshahi	165,659	60	60	0
SA	Dhaka	133,395	178	74	318
TLCP	Dhaka	7,817,128	311	96	489
MLCP	Dhaka	5,000,000	309	208	759
NLCP	Dhaka	1,671,320	114	34	190
SA	Khulna	33,000	39	33	4
DLC	Khulna	663,340	619	412	763
HEED	Chittagong	1,975,211	760	537	1669
CLCP	Chittagong	7,200,000	1355	395	288
Total		37,063,580	10,458	5096	16,204

Figure 1. Map of Bangladesh. The vertical shaded area is the Rajshahi Division. The horizontal shaded area in the Rajshahi Division indicates the districts where surveys were carried out.

Table 2. Summary of survey results in 4 northern districts of the Rajshahi division of Bangladesh

DMP proportion	Nilphamari	Rangpur	Thakurgaon	Panchagar	Total
Population					
Enumerated	7158	11602	36766	7600	63126
Examined	6766	10373	33450	7283	57882
% examined	94·7%	89·4%	91·0%	95·8%	91·7%
New case prevalence rate	2·7	7·2	2·3	5·9	3·7
M:F ratio	3·2	1·9	1·4	0·7	1·5
Child proportion	0·0%	16·0%	3·9%	37·2%	14·5%
MB proportion	50·0%	26·7%	32·6%	25·6%	30·4%
Active case prevalence rate	4·7	11·1	3·7	7·8	5·7
M:F ratio	4·0	2·1	1·5	0·8	1·7
Child proportion	0·0%	13·9%	4·1%	28·1	11·3
MB proportion	56·4%	42·6%	47·8%	42·15%	45·8%
Total case prevalence rate	8·3	18·5	10·13	12·1	11·7
M:F ratio	2·8	1·8	1·6	0·8	1·6
Child proportion	5·4%	14·8%	4·4%	22·7%	9·8%
MB proportion	55·3%	43·8%	33·7%	36·3%	38·7%

of the Rajshahi Division the problem is less acute than in the northern districts, although occasional surveys have indicated (active case) prevalence rates of 2 per 1000.[8]

Figure 1 shows the districts in which the surveys were conducted. A total of 47 surveys are included in this report; 8 in Panchagar, 27 in Thakurgaon, 3 in Nilphamari and 9 in the Rangpur district. The total population enumerated was 63,126, the number of people actually examined 57,882 (or 91·7%). The average size of the surveys was 1232 (range: 237–3898). Table 2 summarizes the findings of the surveys. The living case prevalence rate for all areas together was 11·7 per 1000. The new case prevalence rate was 3·7 per 1000 and the active-case prevalence rate 5·7 per 1000. The overall male : female ratio is 1·7. The overall proportion of children is 9·8% and the proportion of MB cases 38·7%.

The active-case prevalence rate figure of 5·7 per 1000 undoubtedly reflects the size of the leprosy problem better than the total case prevalence rate (11·7 per 1000), especially in areas where leprosy control activities has been going on for some time and patients have completed treatment. From Table 2 it can be seen that the Rangpur district has both a high living case prevalence rate (18·5 per 1000) and active case prevalence rate (11·1 per 1000). This reflects the particular social situation in that district which has large crowded communities of immigrants from Bihar in India. Also leprosy control activities there have only recently been started.

On the basis of the experience of leprosy control activities of NGOs working in various other parts of the country, together with the results of the surveys reported above, it is possible to estimate the size of the leprosy problem in Bangladesh. This estimation is based on the assumption that the active case prevalence rate is 5 : 1000 in the 8 northern districts of the Rajshahi division, 2 : 1000 in the 8 southern districts of the Rajshahi division and an average of 1 : 1000 in the rest of the country. This is

Table 3. Estimation of active case prevalence rates in the Rajshahi division and other divisions of Bangladesh

Area	Population	Prevalence rate	No. of patients
Northern 8 Rajshahi districts	12,199,000	5:1000	60,995
Southern 8 Rajshahi districts	14,496,000	2:1000	28,992
Other divisions of Bangladesh	83,209,000	1:1000	83,209
Total	109,904,000	1.6:1000	173,196

summarized in Table 3. It is noted that prevalence rates are higher in the districts along the eastern border (the Chittagong Division), compared with the central and coastal districts. According to this calculation, the estimated total number of leprosy patients in Bangladesh is 173,196. This is slightly higher than the official figure of 136,000. Of these, 89,987 (52%) are in the Rajshahi Division. At present, there are approximately 20,000 leprosy patients registered with both government and NGO services in Bangladesh. About 10,000 have completed MDT, and the cumulative MDT coverage percentage for Bangladesh is currently 88·90.[1] If the official WHO figure and our own calculation of the estimated total number of patients are in the right order, it is possible that there are still approximately 150,000 patients who require treatment.

Discussion

It is very difficult to make a reliable estimate of the prevalence of leprosy in a given area or country.[9] Total population examination is both extremely expensive and unnecessary. Sample surveys, the standard method for obtaining information about disease prevalence, need to be large because of the uneven distribution of leprosy. A number of simple methods have been recommended: extrapolation from registered cases, rapid community surveys, extrapolation from child prevalence rates and the Delphi technique (expert opinion). The approach described in this paper combines some of these methods, gaining from the data and local experience of well-established leprosy programmes in various key areas of the country, together with data from surveys conducted in the high endemic districts of the northern Rajshahi Division. The estimated number of leprosy patients using the above methodology (173,196) is only 10% greater than the official estimate. It will be possible in the next few years to see how close this figure is to reality through data from the national leprosy control programme which is now rapidly developing to cover the country.

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A method for texture discrimination in the sole of the foot. A preliminary communication

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Summary A new method for testing sensibility in the sole of the foot is described. In this method the ability to distinguish different surfaces while walking is assessed. This dynamic, functional and more objective test is recommended as an additional tool to evaluate sensibility in the sole of the foot.

Introduction

The assessment of nerve function is of the utmost importance in evaluating the extent of nerve damage and the result of therapy. To evaluate progress (or lack of progress) during therapy, an objective assessment is of greater value. Such an assessment also needs to be functional, as that would reflect the functional neural status from the patient's point of view. As most of the available methods are designed for assessment of the hand, there is a need for a similar method for the assessment of the sole of the foot. Hence, this simple, dynamic, functional, and more objective test has been devised.

Materials and Methods

We constructed 3 wooden trays ($10' \times 2' \times 6''$ each), containing either pebbles, sand, or microcellular rubber, filled to the height of $4''$ and fixed, so that the materials did not become displaced in the tray. The trays were covered with identical thin, smooth cloth and provided with wooden platforms on 1 side, which was at the same level as the sand pebbles or rubber in the tray (Figure 1).

Patients were blindfolded[4] and led to walk with 1 foot on 1 of the trays and the opposite foot on the adjacent platform (Figure 2). In this way they were led to walk on all 3 surfaces, 3 times each in a random fashion, and the patient's observations were recorded. Texture discrimination was taken as positive only when they sequentially identified the surfaces on all 3 occasions. The test was repeated for the opposite foot.

Before any clinical application, 20 of our staff members with normal sensibility were tested and all of them were able to identify the surfaces correctly.

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Figure 1. The 3 wooden trays containing pebbles, sand and microcellular rubber, with platforms in between.

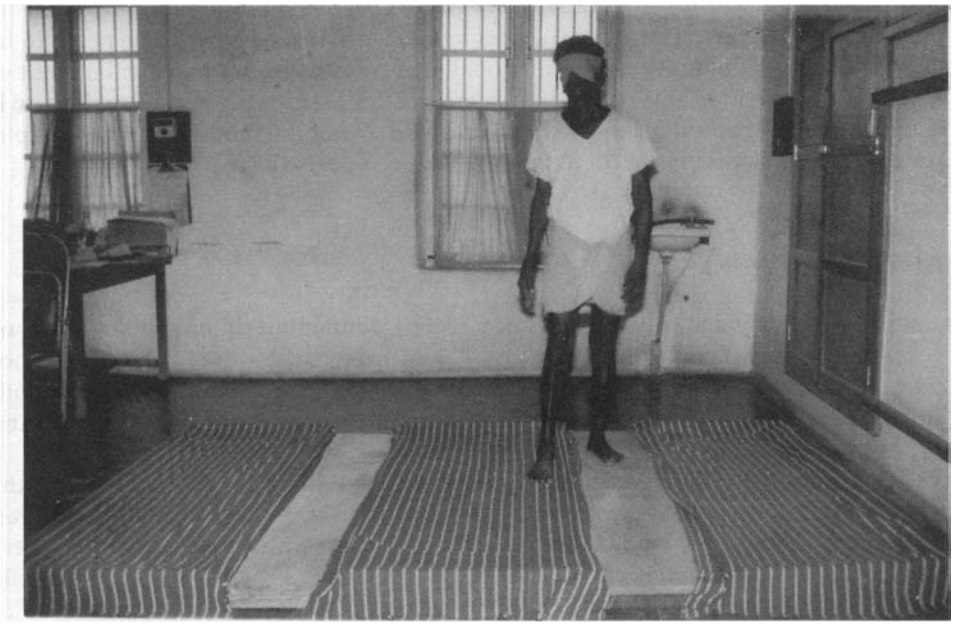

Figure 2. A blindfolded patient walks with 1 foot on a tray and the other on a platform trying to identify the material under foot.

In addition to other sensory tests, this has been performed at our centre since April 1992 for leprosy patients with posterior tibial neuritis, symptoms of sensory and/or motor involvement of posterior tibial nerve and plantar ulcers. The treatment given to them varied between nonsteroidal anti-inflammatory drugs, corticosteroids, posterior tibial nerve decompression and nerve muscle graft. The test was repeated during follow-up of the 4 therapeutic regimens. The results reported here refer to the pre-operative findings for patients who underwent decompression or muscle graft operations. The category 'other' includes those treated with corticosteroids and nonsteroidal anti-inflammatory drugs.

Results

Table 1. Texture test for foot

	No. of feet tested	Findings					
		Positive			Negative		
		Peb	S	Rub	Peb	S	Rub
Controls	40	40	40	40	–	–	–
Patients		Preoperative and pretherapy findings					
1 Posterior tibial nerve muscle graft	9	0	0	0	9	9	9
2 Posterior tibial nerve decompression	85	74	53	11	11	32	74
3 Others	29	26	18	2	3	11	27

Peb, pebbles; S, sand; Rub, MCR.

Discussion

Sensory testing is a sensitive method in the follow-up of nerve involvement; as a prognostic test, it is also shown to be of use in early mild neuritis.[3]

Each sensory modality tested and recorded separately is an unreliable indicator of useful sensory function. Sensory discrimination and stereognostic sense are the true elements of useful sensory function.[5]

According to Moberg, most of the tests described were of academic nature and inadequate to determine whether the person could use their extremity with safety.[1]

Patients do not think in terms of sensory modalities. What is of immediate concern to them is whether or not the affected part has a protective sensation,[6] because this is the major factor in ulcer formation.[2]

What is required is a simple test that can be conveniently and easily performed and a routine assessment for sensory function that is practicable, reproducible, clinically acceptable[5] and mimics normal conditions and sensory perception.

The test described in this paper involves texture discrimination and object identification. Texture discrimination is the ability to appreciate differences in the texture of the combined fabric and surfaces by the sensation aroused when the object and the skin are in contact with each other.

The test objects we used are materials with which our patients are familiar. Being an agricultural area, most of our patients are bare-footed and walk on stones, mud, clay and sand.

This test differs from the conventional test in that the stimulus is not applied at any single point and is not aimed at testing a single sensory modality.

Another important difference is that the patients are asked to walk during the test. Movement is an essential component of discriminating textures and identifying objects.

Conclusion

This dynamic, inexpensive and functional test is considered as a significant and practical contribution to testing sensibility of the sole of the foot and is recommended as an additional method to evaluate the extent of the posterior tibial nerve involvement and the results of treatment.

As the threshold of the stimulus in this test is very high, it does not obviate the use of other methods with stimuli of lower threshold, particularly when seeking early signs of sensory impairment.

Being a test with high threshold stimulus, it is of definite use in selecting patients with no residual sensory (and motor) function for nerve muscle graft and for comparable controls for randomized study. In other patients who undergo nerve decompression and are given antireaction drugs to induce recovery of sensory function, this test is expected to be of use in prognostic evaluation and this aspect is under investigation.

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SPECIAL ARTICLE

Achieving multidrug therapy for all leprosy patients—ILEP Medical Bulletin*

The ILEP goal of multidrug therapy (MDT) for all leprosy patients before the year 2000 was accepted in 1990. This goal is fully consistent with, if not even more ambitious than the WHO goal of the elimination of leprosy as a public health problem, adopted by the World Health Assembly in 1991.

In order to review the progress towards the ILEP goal and to ensure that this goal will be achieved, the ILEP Medical Commission organized a survey in which 228 leprosy projects participated. The outcome of the survey confirmed the belief that many leprosy programmes have difficulties in achieving effective MDT implementation, i.e., full MDT coverage and adequate MDT completion rates.

The following issues were considered as crucial:

— Not all cases are on MDT, WHY?
— Many cases, who were submitted to MDT, do not complete their treatment, WHY?
— How should the problems causing inadequate MDT coverage and/or inadequate MDT completion be solved?

The major findings and recommendations related to the above issues were published in an ILEP Medical Bulletin, reprinted below. This Medical Bulletin was produced by a Temporary Expert Group of the ILEP Medical Commission and endorsed by the Medical Commission in December 1994. At an Interface Meeting with ILEP Member Associations in December 1994, ILEP Members expressed their commitment to achieving the 1995 interim target outlined in the text.

The Medical Commission gratefully acknowledges the assistance of ILEP Members and the contribution of the 228 leprosy projects who took part in the survey in order to identify the current constraints on and solutions to MDT implementation.

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1 INTRODUCTION

The ILEP Medical Bulletin No. 1 of September 1990 stated the Medical Commission's view that Multidrug Therapy (MDT) should be given to all leprosy patients in need of chemotherapy.[1] Because of the danger of drug resistance there is no justification to treat patients with any monotherapy.

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Many programmes have already achieved effective MDT implementation, that is all their patients registered for chemotherapy are being treated with MDT (100% MDT coverage) and the proportion of patients successfully completing their treatment within the specified time period is adequate (more than 75%). However, several programmes are experiencing difficulty in achieving 100% MDT coverage and high treatment completion rates.

It is important to understand the reasons why some programmes find this difficult and at the same time learn how other programmes have succeeded. For this purpose, the ILEP Medical Commission organized in 1994 a questionnaire survey of 228 field projects in Africa, Asia, Latin America and Europe with a total of 239,574 leprosy patients registered for chemotherapy. The survey covered about 40% of the projects and patients supported by ILEP Members. The recommendations in this Medical Bulletin are based on the results of this survey and an analysis of the ILEP B forms (the project annual report) for the year 1993. The focus is on the major issues and the frequently reported obstacles to achieving MDT for all leprosy patients.

Although this Bulletin is primarily aimed at programmes which have difficulties in achieving full MDT coverage and high treatment completion rates, the recommendations may also be useful for programmes with full MDT coverage wishing to increase the cost-effectiveness of their operation. Implementation of the recommendations will assist the attainment of the ILEP goal of 'MDT for all leprosy cases by the year 2000' as well as the WHO goal of 'Elimination of leprosy as a public health problem by the year 2000'.

2 MAJOR FINDINGS

— At the end of 1993, 1 in 3 of the patients registered for treatment in programmes assisted by ILEP Members were not receiving MDT (worldwide almost 1 in 2 of the patients registered for treatment were not on MDT).
— More than 22% of the programmes still prescribe dapsone monotherapy to some of their new patients, although this treatment has been considered obsolete for more than a decade.
— More than 10% of the new patients detected are not started on MDT.
— 1 in 4 projects report that less than 75% of the patients who started MDT completed their prescribed course of MDT within the required period.

3 RECOMMENDATIONS FOR ACHIEVING FULL MDT COVERAGE AND ADEQUATE COMPLETION OF TREATMENT

Too many opportunities to implement MDT are being missed. The major obstacles to effective MDT implementation can be categorized into **patient management obstacles** and **programme management obstacles**.

3.1 PATIENT MANAGEMENT OBSTACLES

(a) Inappropriate prerequisites and contra-indications for MDT

Problem:

Many programmes still apply inappropriate prerequisites be fulfilled before patients can be started on MDT. Inappropriate contra-indications for MDT are still widely used.

Example:

Several programmes report that they exclude from MDT persons who are elderly, who have TB, who are pregnant, who live far away (e.g. more than 10 km), who cannot come to the clinic every month, who have no fixed address, who have mental disorders, hypertension, etc.

Recommendation 1

MDT must be given to all leprosy patients except in the rare case of severe liver disease or serious drug hypersensitivity.

(b) Delay between diagnosis and the start of MDT

Problem:

Often there is a delay between the diagnosis and the start of MDT. During this delay, patients receive only dapsone monotherapy or no treatment at all.

Example:

Patients have first to prove that they collect their treatment regularly before they 'qualify' for MDT; the results of skin smears or biopsies are to be known before MDT can be started (even if the diagnosis was confirmed on clinical grounds); staff have to check the residence address of the patient, etc.

Recommendation 2

All patients should be started on MDT at the time of diagnosis.

(c) Inadequate review of patients registered for dapsone monotherapy

Problem:

Many projects have not yet started or completed the screening/updating of their old treatment register.

Example:

Some projects have many patients on register for dapsone monotherapy who have not reported for several years or who are already cured and are not in need of treatment any more. These patients are included in the calculation of MDT coverage resulting in an unrealistic low figure.

Recommendation 3

All projects which still have patients registered for dapsone monotherapy should as soon as possible review all these patients and decide whether they should be either released from treatment or be started on MDT. All patients eligible for anti-leprosy chemotherapy should be submitted to MDT at the time of screening.

(d) Inflexible system of drug delivery

Problem:

Several programmes do not provide more than a 1-month supply of drugs, even when a patient has a valid reason to justify this.

Example:
Patients who cannot come every month to the leprosy clinic because of long absences (e.g. patients living far away, those in areas inaccessible during the rainy season, patients who cannot afford to lose their wages during the harvest season, women, sailors, etc.) or occasionally (e.g. marriage, childbirth, funeral, pilgrimage etc.).

Recommendation 4

Patients should receive their monthly pulse dose under the supervision of health staff. Where this is not possible, treatment should be supervised by a reliable person, e.g. community leader or family member. In circumstances where supervision of drug intake is impossible, patients who cannot attend every month should be given a supply of drugs for several months.

(e) Unnecessary continuation of treatment

Problem:
Several programmes still continue Multibacillary (MB) MDT until the skin smears are negative and Paucibacillary (PB) MDT until skin lesions have become inactive. This may result in low reported treatment completion rates.

Example:
MB patients who have already completed 24 monthly doses but were kept on MDT and default before the skin smear is negative are in these programmes considered as 'treatment not completed'.

Recommendation 5

Fixed duration MDT for MB leprosy, that is treatment with 24 monthly doses within 36 months has been recommended by the ILEP Medical Commission[1] and by WHO[2] and should be implemented in all leprosy control programmes. For PB leprosy fixed duration of treatment, i.e. treatment with 6 monthly doses within 9 months has always been the recognized standard and should be adhered to.

(f) Inadequate patient education

Problem:
Many programmes report inadequate patient education as a major factor responsible for low treatment completion rates.

Example:
Patients stop taking treatment because of improvement of the lesions or because of drug side effects or leprosy reactions and nerve function complications.

Recommendation 6

Leprosy control programmes must give a high priority to patient education. All levels of staff should be adequately trained in patient education and appropriate patient education materials should be used.

(g) Inadequate patient care

Problem:
Inadequate patient care does not only result in the occurrence of disability which could have been prevented but contributes to low treatment completion.

Example:
Patients who during MDT develop disabilities because of inadequate reaction treatment, lose confidence in the programme and may default from MDT.

Recommendation 7

Adequate patient care, including early detection and treatment of nerve function impairment and the prevention of worsening of existing disabilities, should be an integral part of all leprosy control programmes.

(h) Inadequate procedures regarding absentees

Problem:
Many projects do not implement adequate absentee retrieval procedures.

Example:
Several projects, especially those which are hospital based, do not implement any activity for the retrieval of absentees (e.g. letters, messengers, messages via other patients, village health workers or village heads, home visits, etc.).

Recommendation 8

All programmes must have a standardized absentee retrieval procedure appropriate to local conditions. Projects which do not have staff for retrieval activities should closely collaborate with existing control programmes. As a rule all patients should be referred to the treatment delivery point nearest to their residence.

3.2 PROGRAMME MANAGEMENT OBSTACLES

(a) Inadequate management capacity

Problem:
Most programmes with low MDT coverage have inadequate organization and management capacity as an important cause for deficient MDT implementation.

Example:
Several national, regional and/or district programme managers have difficulty in planning the expansion of MDT coverage. Some are unable to identify weaknesses in their programme through routine monitoring and many do not know how to identify solutions for difficult or unusual situations.

Recommendation 9

Programme managers from the national, regional and district levels should receive training in relevant aspects of routine programme management.

The application of the WHO and ILEP management training modules should be expanded.[4,5] Where appropriate, training in specific problem solving management (health systems research) should be undertaken.

(b) Lack of standardized operational guidelines

Problem:
Many programmes do not have uniform, standardized operational guidelines for health workers giving guidance on patient management and operational procedures.

Example
Lack of guidelines leads to confusion and uncertainty among field workers resulting in a low-quality programme.

Recommendation 10

All leprosy control programmes should have well-defined, practical, operational guidelines in the form of a national leprosy control manual.

Programmes which do not have such a manual should make use of the ILEP publication *Guidelines for writing a health workers manual for leprosy control.*[3]

(c) Inadequate recording and reporting system

Problem:
Many programmes are unable to report treatment completion rates.

Example:
Programme managers who cannot monitor treatment completion rates are not aware of the quality of MDT implementation in their programmes.

Recommendation 11

Effective MDT implementation involves not only full MDT coverage but also adequate MDT completion. Therefore, the assessment of treatment completion rates should be included in the routine monitoring of the programme performance.

Problem:
Many programmes keep absentees too long on the treatment register.

Example:
Patients are kept on the register who have not reported for more than 5 or even 10 years.

Recommendation 12

All patients who have not reported for treatment for more than 2 years and who have been subjected to absentee retrieval action should be deleted from the treatment register.

(d) Insufficient facilities and/or trained staff

Problem:
Many programmes with low MDT coverage report a lack of health facilities (clinic buildings, in-patient facilities, laboratory, vehicles) and/or staff, whilst they do not involve the general health services facilities or staff.

Example:
A peripheral leprosy worker stationed near a general health centre cannot regularly visit an isolated village with many patients and has therefore kept the patients in that village on dapsone monotherapy. He could have involved the general health centre whose staff are visiting the village at least once a month in order to supervise the village health workers of this village. Some programmes who do involve these workers only allow them to supply patients with dapsone monotherapy.

Recommendation 13

Leprosy control programmes should involve the general health services facilities and staff for the implementation of MDT wherever possible. Where peripheral staff are

insufficiently trained for the diagnosis and treatment of leprosy and its complications, this should be urgently corrected.

(e) Inadequate supply of MDT drugs

Problem:

Some programmes experience an insufficient supply or interrupted stocks of MDT drugs.

Example:

Due to inadequate planning, failure of communication, delays in transport, or no budget allocated for the transport of drugs, patients do not get their MDT when they report for treatment. This results in reduced credibility of the programme and consequently reduced treatment completion and can lead to a reduction in self-reporting by new patients.

Recommendation 14

Programme managers should secure a regular uninterrupted drug supply. MDT drugs should be ordered in advance, including the maintenance of an adequate buffer stock. Programme managers should continuously monitor drug stocks at the periphery. Needs should be promptly communicated to suppliers.

(f) Lack of infrastructure or security problems

Problem:

Some programmes fail to implement MDT in very isolated, difficult to reach areas without any health services infrastructure or in areas with security problems.

Example:

Even where MDT has been successfully implemented for a number of years, some projects reach a situation where the remaining patients are located in difficult areas. This results in a reporting of lower MDT coverage rates. Although in general this is not a constraint at the initial stages of starting MDT, it will become relatively more important in the future, not only at the programme level but at the global level.

Recommendation 15

Creative solutions should be developed for these special situations. In general, the solution should be specifically developed for the unique local situation.

4 CONCLUSIONS

The ILEP goal of MDT for all by the year 2000 aims to bring MDT to **all** leprosy cases.

At present, far too many leprosy patients do not yet benefit from MDT. This concerns mainly patients in areas with inadequately organized and/or managed leprosy control programmes or patients living in geographically difficult access areas or areas exposed to civil insecurity.

With the application of the above recommendations, it should be feasible to achieve the ILEP goal.

The following intermediate target will assist in securing the goal:

With the exception of those areas, which have a complete lack of infrastructure or suffer from civil insecurity:

By the end of 1995, all cases registered in the projects currently supported by ILEP Members should be on MDT.

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Obituary

DICK L. LEIKER, MD, PhD
1919–1995

During the night of 11 January 1995 Dick Leiker passed away at the age of 75 years. In command, as usual, he decided that treatment of the complications of his vascular disease should be discontinued.

Dick was born on 28 November 1919 in Buitenpost, The Netherlands. He graduated from the medical faculty of Groningen University in 1948. From 1949 to 1958 he worked as a government physician, responsible for leprosy control in the former Netherlands New Guinea. On departure from New Guinea he suffered a most tragic catastrophe: the plane crashed and he lost his wife and their four children. All his scientific data, so meticulously collected and researched during the previous years, were lost in the same crash. Dick never flew again.

After a long period of recovery he specialized as a dermatologist from 1958 to 1961 at the Erasmus University Hospital in Rotterdam. Then he served as a leprosy consultant in Northern Nigeria till he joined the Royal Tropical Institute (KIT) in Amsterdam in 1965. He was also part-time consultant leprologist at the dermatological clinics of the University of Amsterdam (from 1968) and the Erasmus University of Rotterdam (from 1970). He retired from the KIT in 1982, but remained active as a medical adviser to The Netherlands Leprosy Relief Association (NSL) and as a visiting professor in tropical dermatology and leprosy at the University of Genoa, Italy. He was a member of several committees including the WHO Expert Advisory Panel and the Medical Commission of the International Federation of Anti-Leprosy Association (ILEP). He was a contributing editor to the *International Journal of Leprosy*.

Dick Leiker was a man of vision. He was a gifted teacher and had a strong interest in research. He contributed to the development and introduction of multidrug therapy. He published about 100 scientific articles covering virtually all aspects of leprology, including immunology, histopathology, epidemiology and public health. He contributed to several books as an author or editor. Because of his scientific merits, the University of Amsterdam awarded him an honorary doctorate in 1981 and he became a Knight of the Order of Orange Nassau. He received the Albert Schweitzer Prize, the Eykman Medal, the Mendes da Costa Medal and the NSL Award. He was an honorary member of the International Leprosy Association (ILA).

With the death of Dick Leiker, The Netherlands leprosy community have lost their nestor. He stood at the basis of the leprosy activities of the Royal Tropical Institute and was the co-founder of NSL. With his enthusiasm and dedication, sometimes close to

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obsession, he motivated many young Dutch doctors to join the fight against leprosy. Numerous doctors out of Leiker's 'stables' have served in leprosy control programmes in developing countries, and several of them have made a lasting professional career in anti-leprosy work.

It was a privilege to have Dick as our teacher. Even after his retirement he remained our profoundly respected mentor.

We express our deep sympathy to his wife, who lovingly cared for him, devoting all of her strength during the long and arduous period before he passed away. We extend our sincere condolences to her and Dick's children.

WILLIAM FABER
PAUL KLATSER
PIETER FEENSTRA
BEN NAAFS

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Letters to the Editor

CONCOMITANT OCCURRENCE OF LEPROSY AND TUBERCULOSIS: LEPROSY VACCINE, A MYTH OR REALITY?

Sir,

S, a 40-year-old man, presented complaining of nasal blockage, crusting and loss of sensation over the hands and feet for $2\frac{1}{2}$ years. He had apparently been well 3 years before when he had a problem of a blocked nose with crust formation in the anterior nares. This was initially neglected, but he was alarmed when he noticed streaks of blood in the nasal discharge. Subsequently he noticed that the sensation in his hands and feet had diminished, and he often inadvertently burned his finger tips when holding hot objects. His attention was drawn to an ulcer over the sole of his right foot by the foul smell emanating from it. Meanwhile, his wife noticed a change of appearance in his face, which had become oily and coarse, with loss of eyebrows. He sought advice in a hospital where he was put on treatment with monthly doses of rifampicin (600 mg) and clofazimine (50 mg) and dapsone (100 mg). He was, however, irregular in taking his medicines. A few weeks before reporting for treatment he developed fever, malaise, an evening rise of temperature and a productive cough. He revealed that he had had similar symptoms 5–6 years before which had been diagnosed and confirmed as pulmonary tuberculosis. He had been adequately treated with short-course intensive therapy with rifampicin (600 mg) isoniazid (300 mg) and streptomycin (1 g daily) for 3 months after which streptomycin was discontinued, and treatment continued with rifampicin and isoniazid for a further 6 months to complete a 9-month course. His response to treatment was favourable and he was pronounced cured and the treatment was discontinued. He remained symptom-free until he once again had a recurrence. The symptoms and signs were indicative of activation of pulmonary tuberculosis.

Examination revealed that he was febrile, with a temperature of 100°F. The vital and general physical examination was unrewarding. Respiratory examination was marked by a few diffuse fine bilateral crepitations. Cutaneous examination was marked by hypopigmented shiny macules with ill-defined margins merging imperceptibly into the surrounding skin. There were innumerable lesions that were extensively distributed over his extremities and trunk. Facial examination demonstrated atrophic wrinkled skin, atrophic earlobes, a depressed bridge of the nose and a lateral loss of one-third of the eyebrows. Nasal examination was indicative of haemorrhagic crusting resulting in an oooze and crust formation. Other mucosae were normal. The sensation of temperature, touch and pain were impaired over the palms and soles. The greater auricular, radial, ulnar, common peroneal and anterior and posterior tibial nerves were thickened. A trophic ulcer was present over the base of the great toe on the right side. The laboratory investigations were marked by haemoglobin 11·5 gm/dl, total leukocyte count 6800 cu/mm, differential leukocyte count polymorphs 50, lymphocytes 34, eosinophils 16, erythrocyte sedimentation rate (Westergren) 134 mm/1st hour. Liver and kidney function tests were within normal limits. A Mantoux test was non-reactive. Sputum for acid-fast bacilli was negative. The results of sputum culture on Lowenstein–Jensen median did not yield any growth after 5 weeks. The enzyme-linked immunosorbent assay (ELISA) for IgG to *Mycobacterium tuberculosis* was 162/ml (suspect positive 161–199). The immunoglobulin/profile assay revealed raised levels of antibodies, IgM 74·83 g/l (0·5–2 g/l), IgA

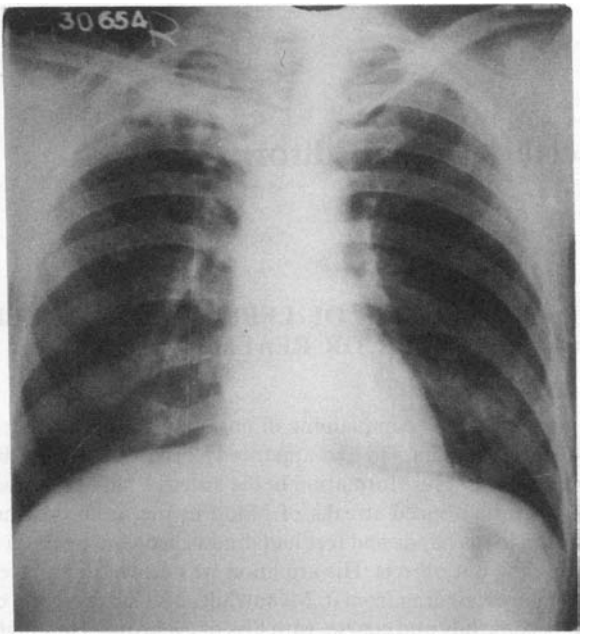

Figure 1.

5·73 g/l (0·6–2), and IgG 737·7 g/l (8–16 g/l). An X-Ray of the chest was marked by intense infiltration of lung parenchyma, reflecting in the form of soft opacities in the right upper zone, suggestive of pulmonary tuberculosis (Figure 1). The trachea was central, and the heart was normal in size. The bony cage was within normal limits. Histopathological examination of a tissue section revealed nonspecific dermal inflammatory infiltrate indicating resolving granuloma.

Leprosy, a chronic infective disease, has shown a steady decline across the globe[1] apparently because of an overall amelioration of the socioeconomic status, improved health care delivery systems, the advent of multidrug therapy (MDT) and its compliance.[2] However, with the advent of the acquired immunodeficiency syndrome (AIDS), a resurrection of mycobacterial diseases, including leprosy, has been observed. A similar trend has been noticed in systemic tuberculosis that has once again been recorded in places where it had been eradicated. The compromised cellular immunity probably reactivates the dormant bacilli that had become quiescent following adequate chemotherapy.

The interaction between leprosy and tuberculosis is rather intriguing. Initial reports suggest that leprosy encouraged the development of tuberculosis. It could be speculated that both mycobacterial diseases probably shared a common genetic predisposition.[3] Besides the low socioeconomic factors that conferred higher susceptibility to both diseases, it was observed that BCG vaccination of mice inhibited subsequent multiplication of *M. leprae* in footpads.[4] This initiated the exploration of crossimmunity between both diseases and the possibility of a mycobacterial vaccine offering protection from leprosy.[5–8] In the ensueing years, BCG emerged as a candidate that was used in trials for the immunoprophylaxis and immunotherapy of leprosy. However, many studies[9,10] on the protective efficiency of BCG vaccine have provided equivocal results. The initial euphoria has been further offset by an interesting revelation that delayed type hypertensitivity (DTH) and protective cellular immunity are directed to separate mycobacterial antigens and DTH may be augmented by MDT, repeated lepromin testing, cytokines *per se* and

antigenic challenges that induce cytokine activation. These have cast a doubt on the potential of mycobacterial vaccines to achieve immunological upgrading.[11,12] The coexistence of leprosy and tuberculosis[13,14] once again compels us to explore this myth.

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INOCULATION OF THE *MYCOBACTERIUM LEPRAE* INTO THE HAMSTER CHEEK POUCH

Sir,

The lack of *in vitro* techniques for the cultivation of *Mycobacterium leprae* and the fact that *M. leprae* multiply and produce disease in a limited number of species represents an important barrier to progress in leprosy research. Mycobacterial inoculation into the footpad of immunologically intact mice remains the basic tool for assessing the effectiveness or otherwise of drugs against the bacilli. Unfortunately, this animal model has limitations because of the long duration of the experiments due to the very slow rate of growth of *M. leprae*. Immunodeficient animals are less often used in experimental leprosy due to the high cost of the animals and difficulties in their maintenance; furthermore, mortality is high before dissemination of the disease.[1]

We therefore decided to study the behaviour of viable *M. leprae* inoculated into hamster's

cheek pouches. This structure is an invagination of oral mucosa, where the lack of lymphatic drainage cuts the afferent arm of immune response.[2] In addition, we compared the histological aspects of lesions induced by viable *M. leprae* inoculated into the pouch and into the footpad, an area rich in lymphatics.

Suspensions of viable *M. leprae* were prepared from lepromatous nodules, as described by Shepard.[3] Their mycobacterial identification was done by inoculation of the bacteria into culture medium (Loewenstein–Jensen) and into the footpads of balb/c mice.[3]

Male hamsters (*Mesocricetus auratus*), 2 months old, were divided into 2 groups: in group 1, 34 animals were inoculated, under anaesthesia (sodium nenbutal, 40 mg/kg) into the submucosa of the everted pouch with 0·1 ml bacilliary suspension containing 5×10^8 viable bacilli/ml. In group 2, 18 animals were inoculated into the footpad with the same dose of bacilli. A minimum of 3 hamsters were killed by ethyl ether inhalation 30, 60, 120 and 150 days postinoculation (pi). Postmortem samples of inoculated pouch tissue and inoculated footpads were taken, formol fixed, embedded in paraffin, cut and stained using hematoxin & eosin and Fite-Faraco.

No gross alterations were observed in the footpads of group 2 animals. Histologically, in 5 out of 8 hamsters studied 30 days pi, the mycobacteriua evoked focal epithelioid granulomas, with giant cells, lymphocytes and very few, if any, bacilli. No macroscopic or histological alterations were observed in the footpads of animals killed 30 days pi.

In 34 hamsters inoculated into the cheek pouch, 7 showed nodules 3–5 mm in diameter, and these were removed for histological study. From animals which did not present gross alterations, 3 randomly selected fragments of cheek pouch tissue were taken.

Histological alterations were observed in 16 out of 34 of the pouch-inoculated hamsters; it is possible that the absence of lesions in the remaining animals was related to the lack of gross alterations and the fragments submitted to histology did not represent the inoculation site. In order to check this possibility, further experiments are being done by tattooing with Indian ink 1 cm above and 1 cm below the inoculation site.

In the pouch that showed lesions, the reactions were represented by accumulations of large grossly vacolated macrophages containing numerous bacilli, without any epithelioid transformation. This pattern persisted up to 150 days pi and was similar to that observed in anergic forms of the human disease.

The ability of *M. leprae* to evoke epithelioid granulomas in the footpad, but not in the cheek pouch, an immunoprivileged site, confirms that, in leprosy, the epithelioid granulomas are directly related to the development of immune response to *M. leprae*.[1]

Moreover, since *M. leprae* grows readily in the pouch, this model may represent a better alternative for the study of new antileprosy drugs and drug resistance.

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A CASE OF RELAPSED BORDERLINE-LEPROMATOUS (BL) LEPROSY FOLOWING 27 MONTHS OF MULTIPLE DRUG THERAPY, BHUTAN

Sir,

In July 1984 at Yebilaptsa a 30-year-old male patient was diagnosed with clinical findings typical of borderline-lepromatous (BL) leprosy. The bacteriological index (BI) of skin smears was 3, with a morphological index (MI) of 0·5. He was treated with multiple drug therapy (MDT) (dapsone, clofazimine and rifampicin) according to the WHO recommendations for multibacillary leprosy, and he completed 27 months treatment without default. He was released from treatment in October 1986, when skin smears had been negative at monthly intervals on 3 occasions. His clinical state and skin smears remained negative on annual surveillance.

In early January 1993, more than 6 years after release from treatment, he presented complaining of tingling and pain in the right arm, both legs, and the left side of his face. The right radial, both ulnar, and both popliteal nerves were mildly tender on palpation. There was no new anaesthesia or muscle weakness. No skin lesions were found on any part of the body, despite repeated examination. Skin smears from all sites were negative.

There was discussion as to whether, more than 6 years after release from treatment, he was having a very late reversal (upgrading type I) reaction, relapse without any skin involvement, or was malingering to avoid heavy labour. He was started on Prednisolone 40 mg daily for possible reaction and sent to the national referral centre at Gidakom for consultation and nerve biopsy. A skin biopsy was taken, the site being arbitrarily chosen, since no skin lesions were detectable at this time, from a previously affected site, and a nerve biopsy was taken from the terminal branch of the right radial nerve, at the wrist. Dr Sebastian Lucas (University College and Middlesex Hospital Medical School, University Street, London WC1E 6JJ) reported the skin biopsy as showing 'slight perineural inflammation (in dermal nerves), but no acid-fast bacilli' and the nerve biopsy as 'active borderline-lepromatous (BL) leprosy neuritis, with BI 4, many solid-staining forms'. The patient was therefore re-started on MDT in July 1993 and has continued treatment without any neurological complications or reaction. He does continue to have mild nerve tenderness and tingling pain, especially when doing heavy work.

Particularly (taking into account) the bacteriological findings in the nerve biopsy, we consider that our revised diagnosis of relapse is correct. The heavy involvement of nerve and the complete absence of skin lesions under these circumstances is clearly of interest. Furthermore, had this patient reported in another part of Bhutan, or in a different country, and failed to reveal his previous history, it is possible that he would have been diagnosed as having 'purely neuritic' leprosy.

DAVID E. REIMER

Yebilaptsa Hospital,
Tingtingbhi PO,
Shemgang, Bhutan

STEEN M. ANDERSEN

Gidakom Hospital,
The Leprosy Mission,
Khasadrapchu PO,
Thimphu, Bhutan

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Teaching Materials and Services

Schieffelin Training Calendar, 1995

Most of the courses listed below are run every year. For those courses that have already been run this year, please write to the address given at the end for the 1996 dates.

Course	Qualifications	Duration	Commencing date
I *Courses recognized by the Government of India*			
1 Medical Officers' Course	Medical personnel engaged in leprosy work	6 weeks	January 30–March 11 July 24–September 2
2 Non-Medical Supervisors' Course	Qualified Paramedical workers with a minimum of 5 year's experience	2 months	January 9–March 11
3 Physiotherapy Technicians' Course	+2 passed or PUC (with science subjects)	12 months	June 26
4 Laboratory Technicians' Course	+2 passed Science graduates preferred	12 months	June 26
5 Smear Technicians' Course	+2 passed (with science subjects)	3 months	January 16–April 15 June 4–September 2 September 18–December 16
6 Paramedical Workers' Course	+2 passed Graduates preferred (with science subjects)	4 months	August 16–December 16
7 Shoe-makers' Course	V Standard with knowledge of English preferred	6 months	January 2–June 24
8 Diploma Course in Prosthetic & Orthotic Engineering	+2 passed Graduates preferred (with science subjects)	30 months	June 26
9 Ophthalmic Aspects in Leprosy	Qualified medical personnel	1 week	March 13–18
II *Other courses offered by the institution*			
1 Condensed Course in Leprosy	Nonmedical personnel	1 week	March 27–April 1
	Medical personnel	1 week	November 6–November 11
2 Refresher Course in Skin Smears	Trained laboratory technicians	2 weeks	April 17–April 29 September 4–September 16

Course	Qualifications	Duration	Commencing date
III *In-service training*			
a Inservice training in Medicine, Surgery Surgical Rehabilitation, Pathology, Laboratory Technology, Ophthalmology and Epidemiology and Leprosy Control	For qualified medical personel/health professionals	3 months	By arrangement
b Medical Record Keepers	+2 passed with proficiency in typing and good English	2 months	By arrangement
c Basics of Physiotherapy in leprosy	Bachelor in Physiotherapy	1 week	By arrangement
d Medical Students' Course	Clinical Medical Students	1 week	By arrangement
e Psychosocial aspects in leprosy	Non-Medical Personnel	1 week	By arrangement
f Eye care in leprosy	Paramedical Workers	1 week	By arrangement

Mailing address: Director/Head, Branch of Training/Training Officer, S.L.R. and T. Centre Karigiri, 632 106, N.A.A. District, Tamil Nadu, South India

Telephone: (0416) 21522; Telegram: 'Lepsearch' Vellore-7, Fax: 91-416-26759

Training in tropical disease; regional networks of TDR

The UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) invites junior researchers in Latin America, South-East Asia and the Pacific region to apply for grants enabling them to acquire graduate (M.Sc. or Ph.D.) or post-doctoral training in field or laboratory research on malaria, schistosomiasis, lymphatic filariasis, onchocerciasis, Chagas' disease, leishmaniasis or leprosy. Grant recipients will receive multidisciplinary training at 2 or more centres participating in each of the following regional TDR networks:

For Latin America, information is available from:

- Hooman Momen, Ph.D., Department of Biochemistry and Molecular Biology, Instituto Oswaldo Cruz, Rio de Janeiro, Brazil [fax: 55-21/590.34.95; e-mail: momen@brlncc.bitnet].
- Nancy G. Saravia, Ph.D., Fundación CIDEIM, A.A. 5390, Cali, Colombia [fax: 57-23/672.989; e-mail: cideim@ujccol.bitnet].
- Ulises Lopez, D.Sc., Institute of Biophysics, Universidade Federal de Rio, Rio de Janeiro, Brazil [fax: 55-21/265.1903].
- Daniel G. Colley, Ph.D., Division of Parasitic Diseases, Centers for Disease Prevention and Control (CDC), Atlanta, Georgia [fax: 1-404/488.7794].

For South-East Asia:

- Department of Medical Research, 5, Ziwaka Road, Yangon, Myanmar.
- Centre for Health Economics, Faculty of Economics, Chulalongkorn University, Bangkok 10330, Thailand.
- Malaria Research Unit, Department of Parasitology, Faculty of Medicine, University of Colombo, Kynsey Road, Colombo 8, Sri Lanka.

For the Philippines:

Dr Wilfred U. Tiu, College of Public Health, University of the Philippines, Manila, P.O. Box EA-460 Ermita, Manila, Philippines [tel: 63-2/596.808; fax: 63-2/521.1394].

Extracted from *TDR News*, No. 44 March 1994. TDR Communications, WHO, 1211 Geneva 27, Switzerland.

Tropical Medicine Resource, The Wellcome Trust, UK

The Tropical Medicine Resource is a comprehensive computer-based visual archive comprising many thousands of images illustrating current tropical health problems, including:

- social and economic factors;
- epidemiology;
- aetiological agents and vectors;
- clinical effects and diagnostic techniques;
- prevention and control.

Currently the most comprehensive tropical medicine image collection in the world, this unique archive has evolved from the Wellcome Museum of Tropical Medicine transparency collection. It has been greatly enhanced and updated by the contribution of pictures from individuals with specialist knowledge of tropical medicine, from academic institutes and the picture libraries of organizations such as the World Health Organization, Geneva and the Centers of Disease Control, Atlanta.

Each of the images can be located using a text-specific computer search based on a thorough description of the image. The 'Search Program' insert card provides more information.

Further information: The Secretary, The Topical Medicine Resource, The Wellcome Trust, 183 Euston Road, London NW1 2BE, UK. Fax: 0171 611 8735.

Ophthalmic Epidemiology—a new journal

A new international journal entitled *Ophthalmic Epidemiology* has been established to provide an outlet for articles of interest to workers in the field. It is concerned with the publication of solid scientific articles that cover the broad scope of ophthalmic research in the fields of epidemiology, public health and prevention of blindness. The journal's editorial board is very interested in reviewing manuscripts related to scientific endeavours of IAPB members, in an effort to disseminate this knowledge to the ophthalmic community. Authors are invited to write directly to: James P. Ganley, MD, DrPH, Dept. of Ophthalmology, Louisiana State University, Medical Center—Shreveport, PO Box 33932, Shreveport, LA 71130-3932, USA. Fax +318 674 6000.

CBM/LEPRA Ophthalmic Course, Karigiri, India, 1995

The 10th annual 5-day ophthalmic teaching module was held at the Schieffelin Leprosy Research and Training Centre, Karigiri, 13–18 March 1995. The course, which was again sponsored jointly by the Christoffel Blindenmission and LEPRA, was designed to give instruction to leprologists on the detection, prevention and management of the ocular complications of leprosy by means of a series of lectures and videos, clinical and surgical demonstrations and field trips.

Teaching included presentations on basic anatomy, physiology and pathology of the eye with special emphasis on leprosy: in addition there were lectures on the clinical signs and management of lagophthalmos, corneal ulcers, intra-ocular inflammation and infiltrative lesions, together with

discussions on 'high risk eyes', ocular manifestations of relapsed disease, rehabilitation and the global aspects of blindness in leprosy.

The course, which was attended by 13 participants working in India and Nepal, was run by Dr Margaret Brand of The Leprosy Mission and Mr Timothy ffytche from St Thomas's Hospital, London, together with Dr Ebenezer Daniel, Dr Mary Jacob, Dr Shirley Chacko and Dr Prem Kumar of Karigiri.

The Director and staff of Karigiri and The Leprosy Mission are to be congratulated on their continued support for this important and popular contribution to teaching.

Partners. A magazine for paramedical workers (The Leprosy Mission International)

A recent issue of *Partners*, Number 28, includes a most valuable section entitled 'Leprosy—The Great Imitator', which deals with conditions which may imitiate indeterminate leprosy, tuberculoid leprosy and neural leprosy, written by Dr S. Arunthathi, Schieffelin Leprosy Research and Training Centre, Karigiri, South India. The accompanying colour plates are of high quality and should be of great value in establishing the correct diagnosis of leprosy, especially in the early stages of the disease.

Partners—printed and dispatched on behalf of The Leprosy Mission International. Editor—Christine Smith. Address—TLMI, 80 Windmill Road, Brentford, Middlesex TW8 0QH, UK.

For India, Nepal, Sri Lanka and Burma, the address is The Leprosy Mission Health Education Centre, Naini Leprosy Hospital, PO Naini, Allahabad District, UP 211 008, India.

A Bengali edition is available from Dr S. Chaudhury, Grecaltes Training Centre, 23 Market Street, Calcutta, 700 087, India.

A French edition, *Associés*, is also available—write to: La Mission Evangélique Contre la Lèpre, chemin de Réchoz, 1027 Lonay/VD, Switzerland.

Translation is also available in Chinese. For more information please contact the editor.

WHO publications on epidemiology and disabilities

Manual of Epidemiology for District Health Management, edited by J. P. Vaughan and R. H. Morrow. 1989, vii + 198 pages [E, F]. ISBN 92 4 154404 X. Sw.fr. 35.–/US $31.50. In developing countries: Sw.fr. 24.50. Order no. 1150335

A simple, practical, step-by-step guide to the use of epidemiology as a tool for improving the management of health services. Addressed to general health workers, the book uses clear definitions, analogies, examples, checklists, sample forms and calculations, and abundant illustrations to demystify the methods of epidemiology and show how they can work in concrete situations. Particular emphasis is placed on the simple knowledge and skills needed to collect and then use epidemiological data to monitor health problems commonly found in developing countries.

The book shows how a 4-phase epidemiological approach, involving descriptive, analytical, intervention, and evaluation epidemiology, can supply virtually all the information needed to pinpoint health problems, design targeted interventions, and define reliable indicators for monitoring progress. Other chapters offer guidance in the collection of demographic data, the conduct of routine health surveillance, the use of epidemiology to control an epidemic, and the design of special surveys to collect additional information.

The second half of the book concentrates on the analysis, presentation, and use of results. Topics covered include the use of record forms and coding, methods of data processing and analysis, and the presentation of health information in tables, figures, graphs, diagrams, charts, and maps. The final chapter, which constitutes the core of the manual, shows how the knowledge and skills previously described can be used to formulate plans for the management and monitoring of district health services.

Basic Epidemiology, R. Beaglehole, R. Bonita and T. Kjellström. 1993, viii + 174 pages [E, F*; S* PAHO]. ISBN 92 4 154446 5. Sw.fr. 18.–/US $16.20. In developing countries: Sw.fr. 12.60. Order no. 1150395

A textbook providing a basic introduction to the principles, methods, and applications of epidemiology in medicine and public health. Intended for use in a formal training course, the book aims to prepare students for an approach to health care that is increasingly concerned with preventive medicine and the most efficient use of resources. To this end, the authors use numerous examples from the scientific literature to show how the tools of epidemiology can be applied to the prevention of disease, the promotion of health, and the formulation of rational policies. Particular attention is given to the use of epidemiological research to detect associations between modifiable environmental factors and specific diseases.

The book has 11 chapters. The first 2 chapters describe the history and scope of epidemiology, highlight some of its major triumphs, and discuss various approaches to the measurement of disease. The 3rd chapter, devoted to the different types of epidemiological study, describes the applications, advantages, and limitations of the major types of observational and experimental studies, emphasizing the many possibilities for errors in epidemiological measurement. Chapter 4 gives a brief account of some basic statistical concepts and techniques. Chapters 5 and 6 describe the epidemiological approach to causation and explain when and how epidemiology can be used in preventive medicine, including the design of screening programmes. A chapter on communicable disease epidemiology describes the detailed and systematic epidemiological work needed to investigate an epidemic, identify its cause, and determine the best means to control it.

Other chapters explain the application of epidemiological principles and methods to the practice of clinical medicine, and discuss the special features of environmental and occupational epidemiology, including techniques for risk assessment.

Training in the Community for People with Disabilities, by E. Helander, P. Mendis, G. Nelson and A. Goerdt. 1989, 684 pages, 2,160 illustrations [Ar, C*, E, F, S from PAHO]. ISBN 92 4 154401 5. Sw.fr. 80.–/US $72.00. In developing countries: Sw.fr. 56.–Order no. 1150330

Provides the information, advice, and step-by-step instructions needed to teach people with disabilities how to develop their many abilities. Citing compelling reasons for an approach to rehabilitation that puts the community's talents and resources to work, the manual is itself an embodiment of a community-based approach, adopting a format, style and content that speak to community needs.

Every feature of the manual, from scales for rating progress to instructions for producing walking aids, is the outcome of more than a decade of efforts to give the millions of people with disabilities living in developing countries an effective modern technology for improving their daily lives. Emphasis is placed on rehabilitation procedures that will help people perform such activities as eating, dressing, communicating, moving around, playing, going to school, and taking part in work and social activities.

At the heart of the manual's information and instructions is a 'consensus technology' that combines the indigenous solutions worked out by the people themselves with the technologies accepted by experts in rehabilitation.

The manual, which runs some 700 pages and features over 2000 illustrations, consists of 4 training guides and 30 training packages. The 4 guides communicate basic facts and advice important for the community worker (local supervisor) responsible for the community rehabilitation programme, the people with disabilities, the community rehabilitation committee, and local schoolteachers. Points repeatedly emphasized include the importance of community participation and self-reliance, the use of an evaluation system to monitor results, and the need to refer rehabilitation problems that cannot be handled at the local level.

The training packages, which constitute the core of the manual, present material for 7 types of

disability: seeing difficulty, hearing and speaking difficulty, moving difficulty, feeling difficulty, strange behaviour, fits, and learning difficulty. In all, 6 packages deal with activities, such as play (early stimulation), schooling, and household functions, relevant to children or adults with any type of disability. Whether involving training to express needs and functions or the simple message that a person's life can be happy despite a disability, each package communicates practical, tested information that has proven its capacity to reach people with disabilities and improve their lives.

To facilitate translation and adaptation, great care has been taken to simplify the language. The vocabulary has been restricted to about 1800 words and sentences have been kept short and simple. Throughout, the abundant use of line drawings reinforces the simple, step-by-step instructions that can help people with disabilities help themselves to a better life.

Prevention of Disabilities in Patients with Leprosy, A Practical Guide, H. Srinivasan. 1993, viii + 140 pages [E, F*, S*]. ISBN 92 4 154456 2. Sw.fr. 29.–/US $26.10. In developing countries: Sw.fr. 20.30. Order no. 1150401.

A practical guide to the many simple things that can be done—by health workers and patients alike—to prevent the development of disabilities in patients with leprosy. Addressed to peripheral health personnel, the manual concentrates on the various conditions leading to disability and deformity that can be arrested if action is taken at an early stage. To this end, readers are given extensive practical information on the signs to look for, the questions to ask, and the tests to perform in order to recognize these conditions at the earliest possible stage and take appropriate action. Preventive measures described consist of simple treatments, devices, exercises, and behavioural changes that are easy and inexpensive as well as highly effective. Details range from step-by-step instructions for preparing a finger splint from rubber or plastic tubing, through simple tests for determining when leg muscles are weakened, to illustrated exercises that patients can perform at home. Throughout the book, numerous tables, charts, checklists, and some 100 illustrations are used to help readers absorb information and acquire the full range of necessary skills.

The book has 8 chapters. Background information is provided in the first 3, which discuss the impairments caused by leprosy, explain nerve trunk involvement and its consequences, and set out a framework for disability prevention which categorizes patients according to level of risk and maps out the precise actions to be taken by health workers and patients.

The core of the manual consists of chapters focused on the specific actions needed to prevent disability and deformity in patients with insensitive hands and feet and to preserve nerve function. Although prevention is stressed, measures that can limit or correct deformities are also covered. Each richly illustrated chapter provides detailed information on the assessment of patients, the recognition of normal and abnormal conditions, the assignment of risk status, and the principles and specifics of management. Highly didactic, these chapters also alert readers to common errors and pitfalls, and specify the precise do's and don'ts of effective management. Readers learn how to do such things as dress injuries correctly, construct simple protective devices, recognize cases requiring the most urgent attention, and know when patients should be referred. Readers also receive advice on how to teach patients to perform exercises, care for themselves, be alert to certain symptoms, and report them promptly. Methods of eye care are not included in the book in view of the number of excellent guides covering this subject.

In view of the crucial role of the patient and the need for proper motivation and support, the book concludes with chapters offering practical advice on the instruction and training of patients, the monitoring of their performance in disability prevention, and the provision of adequate material and moral support.

All the above are available from: WHO Publications, Distribution & Sales, 1211 Geneva 27, Switzerland.

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News and Notes

Robert Cochrane Fund for leprosy

The Fund, in memory of the great leprologist Robert Cochrane, is administered by the Royal Society of Tropical Medicine and Hygiene. It is to be used to finance up to 3 travel Fellowships each year, to a maximum value of £1000 each.

The Fund will support travel for:

leprosy workers, who need to obtain practical training in field work or in research; and
experienced leprologists in order to provide practical training in a developing country.

There is no restriction on the country of origin or destination, providing the above requirements are fulfilled.

Application forms are available from the Society and completed forms must be received by the Society at least 6 months ahead of the proposed visit. All applications must be sponsored by a suitable representative of the applicant's employer or study centre, and agreed by the host organization. A 2-page report on the travel/study should be submitted to the Society within 1 month of the recipient's return.

Apply: Robert Cochrane Fund for Leprosy, Royal Society of Tropical Medicine, Manson House, 26 Portland Place, London W1N 4EY, United Kingdom. Tel: 0171 580 2127; Fax: 0171 436 1389.

Bicycle trailer/handcart; *Intermediate Technology*, UK

The Newsletter of *Intermediate Technology*, Spring/Summer 1993, carries information and an illustration of a cycle trailer/handcart, which is relatively easy to construct and can be towed behind a bicycle or pushed/pulled as a handcart. The cycle trailer was first introduced to Sri Lanka by IT in 1989 when 2 models were imported from India. A demonstration project was begun by IT Sri Lanka in 1990, together with VINIVIDA, a small NGO based in the Puttalam district, in northwestern Sri Lanka.

Initially, 4 manufacturers were trained by IT Transport to make the cycle trailer in Puttalam. There are now 15 cycle trailer users in the Puttalam District. A small revolving credit-fund has helped people buy the trailers.

The trailer can be constructed in a workshop which has the basic metalwork facilities of cutting, welding and drilling. Good welding skills are needed to make the joints strong enough to stand up to the fairly severe shock loading which will be experienced by the trailer when being used on rough roads. Reasonably accurate cutting, bending and setting up of parts is needed if a good quality trailer is to be built.

For further details, including diagram and dimensions, apply to Mr R. Dennis, Design & Development Engineer, IT Transport Ltd, Consultants in Transport and Rural Development, The Old Power Station, Ardington, Nr Wantage, Oxfordshire OX12 8QJ, UK. Fax: 01235 832186.

VIIth International Congress of Dermatology, New Delhi, India, February/March, 1994

Over 1,000 delegates attended this Congress, from South-East Asia and many other parts of the world. It was remarkable for the wide range of dermatological and other conditions covered in formal papers, discussions and 'state of the art' lectures. In view of the current WHO predictions with regard to the likely increase in the incidence of HIV infection and AIDS in South-East Asia in the near future, many papers dealt with the complex relationships between skin disease, venereology, tuberculosis, leishmaniasis and leprosy. The meeting was also memorable for the number of sessions and the time allocated to various aspects of leprosy, which included a round table discussion on the role of dermatologists in the elimination of leprosy and its subsequent management when leprosy prevalence is low. The chairman for this meeting was Dr S. K. Noordeen of the Leprosy Unit, WHO, Geneva. Short papers were presented on (1) the role of dermatologists in leprosy elimination (Dr Clovis Lombardi, Pan American Health Organization, Caracas, Venezuela), (2) the current status and organization of dermatology and its capacity to contribute to a programme 'sine lepra' (Professor T. J. Ryan, Oxford, UK), (3) the inclusion of leprosy with dermatology in curricula at all health levels (Dr A. Colin McDougall, Oxford, UK) and (4) the re-training of leprosy officers (Dr Henning Grossmann, Moshi, Tanzania). A total of 416 papers are listed, with summaries in a book of *Abstracts*, a copy of which is obtainable on application to Glaxo Pharmaceutical Division, Glaxo India Ltd, Dr Annie Besant Road, Worli, Bombay 400025, India (who sponsored its production).

Evaluation of the SIDA-supported leprosy control projects in India

In the late 1970s, The Swedish International Development Authority first established links with the National Leprosy Control (later Eradication) Programme in India, and in 1981 embarked on a programme of support for case-finding, implementation of multiple drug therapy (MDT) and disability management, beginning in the district of Wardha in Maharashtra. This was soon extended to Purulia (West Bengal), North Arcot (Tamil Nadu), Ganjam (Orissa) and Srikakulam (Andhra Pradesh). Other high-endemic districts were gradually added, bringing the total to 19 by 1993. During this period, MDT has been given to a total of 837,519 cases, with a remarkably low relapse rate (to date) in both pauci- and multi-bacillary cases. SIDA recently appointed an evaluation team under the leadership of Dr Malcolm Peat, Associate Dean (Rehabilitation), Faculty of Medicine, Queen's University, Kingston, Ontario, Canada, supported by Dr Lillemor Brolin (Stockholm, Sweden), Dr Ranaswamy Ganapati (Bombay, India), Dr A. Colin McDougall (Oxford, UK), Dr Chandrakant R. Revankar (Bombay, India) and Ms Jean Watson (Brentford, UK). The team carried out site visits to a number of SIDA-supported districts in India and held discussions with Dr B. N. Mittal (Directorate General of Health Services, New Delhi), representatives of WHO, UNICEF, DANIDA, The Leprosy Mission and a number of State Leprosy Officers. Their findings, which probably represent one of the most detailed analyses of leprosy control in these 19 districts so far attempted, have now been submitted to SIDA in Stockholm. Subject to agreement by SIDA, it is hoped to present some of the more important conclusions and recommendations for publication in the near future.

Low cost disability management

The 125th Gandhi Jayanti provided the opportune time for the birth of an imaginative and much needed project 'Low Cost Disability Management' in Bombay.

Mr R. Narasimhan Chief Guest and Senior Superintendent, Vocational Rehabilitation Centre (VRC) for the Handicapped, Bombay, inaugurated the 'Low Cost Disability Management' project

in Bombay on the 125th anniversary of the birth of Mahatma Gandhi at the BLP office and said that services to leprosy patients should be integrated with those offered to any other handicapped, as is practised in VRC.

Low Cost Disability Management (LCDM) is a partnership project jointly managed by the Bombay Leprosy Project (BLP) and the Indian Leprosy Foundation (ILEF). BLP will look after the medical component while ILEF will take care of social and financial components.

LCDM is a frontier project with futuristic vision. It aims at prevention, care and management of disabilities arising out of leprosy and to provide a scientific model for national adoption.

Dr R. Ganapati, Director of BLP, said that BLP had had 20 yeas of experience in leprosy work. It has to its credit several disability management programmes. The techniques, like prefabricated splints, grip aids for hand deformities as well as POP for foot deformities, had been field tested by BLP extensively in the Prakasam and Kurnool districts of A.P. with resounding success.

Professor A. R. K. Pillai, President, Indian Leprosy Foundation, said that Gandhi Jayanti offered an excellent opportunity to emulate the ideals for which Gandhi lived and died. On the 125th anniversary of the birth of Mahatma Gandhi, Low Cost Disability Management is launched as a joint pilot project and this will cover Bharat Nagar Slum in East Bandra and Kalyan Block in Thane District initially. About 500 disabled persons will benefit directly from these 2 projects.

Mr S. Kingsley, Physiotherapy Technician, welcomed the gathering and Dr C. R. Revankar, Director, proposed a vote of thanks.

International Leprosy Meeting for Missionaries and Auxiliary Staff, 8–21 October 1995; Paramedical staff 12–18 November 1995

For further details of the above meetings, both of which cover a wide range of topics, write to: Dr Jose Terencio de las Aguas, Santorio San Fco. de Boja, 03791 Fontilles, Spain.

Addenda—'Relapse following various types of multidrug therapy in multibacillary leprosy'. M. F. R. Waters

Please add the following to the above paper published in *Lepr Rev* (1995) **66**: 1–9:

On page 6, paragraph 2, line 2 it states (concerning the THELEP Karigiri MDT Field Study)

'After a 7–8 year follow-up, relapses did not exceed 3 in number.'

This figure was based on statements made at the 2nd Wurzbürg Symposium, 1992, where the Karigiri and Polambakkan studies were presented together and known cases of relapse were not separated by trial site. Dr P. S. S. Sundar Rao, Director, and Dr Kumar Jesudasan, Epidemiologist, Schieffelin Leprosy Research and Training Centre, Karigiri, have now informed me that to date, in fact, no relapses have occurred. They write, 'Of the original Cohort of 1067 MB patients included in the trial, 562 were put on A Regimen [the THELEP regimen of rifampicin 600 mg and clofazimine 600 mg on 2 consecutive days every 4 weeks, plus dapsone 100 mg daily unsupervised plus asodapsone by injection every 8 weeks], and 505 were put on B [WHO] regimen; 980 patients completed their treatment and were released from treatment. The total duration of follow-up of 7123 per years yielded *no* relapses.'

Dr P. Feenstra's State-of-the-Art Lecture, reference 22, has now been published, *Int J Lepr*, 1994; **61:** 599–608.

Instructions to Authors

Papers submitted for publication in *Leprosy Review* should be sent to the Editor, Professor J. L. Turk, LEPRA, Fairfax House, Causton Road, Colchester CO1 1PU, England. The name(s) of the author(s) and the place where the work was done should be clearly indicated below the title of the paper. Degrees and diplomas are not to be included.

It is understood that the paper is offered to *Leprosy Review* alone, that it will be subject to editorial revision, and that its copyright becomes the property of LEPRA. Manuscripts should be typewritten, in double spacing, on one side of A4 (297 × 210 mm) paper, with wide margins (4 cm all round). Contributors must send three complete copies of the text, tables and figures. On a separate sheet give the title, short title, name and postal address of the author, together with the name of the institution where the work was done. Abbreviations of titles of journals should follow the list of journals indexed in *Index Medicus*. References to books should include the editor(s), publisher and place of publication. Once manuscripts have been accepted a copy on disk that matches the hard copies exactly would be very much appreciated.

Units and Abbreviations. The Journal recognizes the adoption of the Système International d'Unitès (SI Units) proposed in *Units, Symbols and Abbreviations* (1972) published by the Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. Abbreviations should only be used for unwieldy names, and only when they occur frequently.

Proofs are submitted to authors for immediate return by air.

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