

THE CHEMOTHERAPY OF LEPROSY TODAY AND TOMORROW

SECOND INTERNATIONAL LEPROSY COLLOQUIUM
held at the
FORSCHUNGSINSTITUT BORSTEL

October 15 and 16, 1974

Chairman: Dr S. G. Browne

Edited by

E. Freerksen, Borstel; S. G. Browne, London; J. H. Thumim, Borstel
with the Editorial Board of *Leprosy Review*

The Forschungsinstitut Borstel is indebted to the Deutsches Aussätzigen-Hilfswerk for having supported this International Leprosy Colloquium and for the printing of this volume

CONTENTS

Address of Welcome Professor E. Freerksen	1
Chairman's Introduction Dr S. G. Browne	3
The Second International Leprosy Colloquium, Borstel; Concept and Aims	
<i>Original Papers Presented at the Colloquium</i>	
1. Chemotherapeutic Trials in Leprosy, their Design and Assessment	
The Role of WHO in Antileprosy Drug Trials, by J. Walter, F. M. Nouisitou and H. Sansarricq	9
Chemotherapeutic Trials and their Assessments, by R. J. W. Rees	17
The Technique of Evaluating Anti-leprosy Medications at the Forschungsinstitut Borstel, by E. Freerksen	25
Pharmacological Aspects of the Chemotherapy of Leprosy, by G. A. Ellard	41
Assessment of Treatment Procedures by Means of Bacteriological and Histological Examinations, by M. Rosenfeld	53
Problems in the Design of Medium and Long-term Therapeutic Trials, by D. S. Ridley	59
Chemotherapeutic Trials in Patients with Non-Lepromatous Leprosy, by J. M. H. Pearson	63
2. Current Concerns in the Chemotherapy of Leprosy	
(a) Monotherapy	
Viability of <i>Myco. leprae</i> in the Skin and Bone Marrow of Patients with Lepromatous Leprosy While on Dapsone or Lamprene, by A. B. A. Karat	69
Effect of Mono Treatment and Combined Treatment on the Morphology of <i>Myco. leprae</i> in the Skin, by D. L. Leiker	73
Treatment of Leprosy with Clofazimine, Rifampicin and Bayrena, by J. Languillon	81
A Preliminary Report on a Therapeutic Trial with Acedapsone in Lepromatous Leprosy, by K. Ramanujam, C. G. S. Iyer and G. Ramu	85
Low Dose Dapsone Treatment in Lepromatous Leprosy, by A. B. A. Karat	89
A Report on a Controlled Clinical Trial with Conventional and One Third Conventional Dose of Dapsone Administered Orally Once a Week in Lepromatous Patients, by K. Ramanujam, C. G. S. Iyer and G. Ramu	93
Personal Experience with Clofazimine in the Treatment of Leprosy, by R. D. Azulay, N. C. da Silva, A. Zeo, M. de Jesus and C. B. Franca	99

Long-term Follow-up of Clofazimine (Lamprene) in the Management of Reactive Phases of Leprosy, by A. B. A. Karat	105
The Effect of Long-term Steroid Therapy on Patients Treated with Clofazimine (Lamprene), by L. M. Hogerzeil and N. Prabhudas	111
Open Trial with Clofazimine in the Management of Recurrent Lepra Reaction and of Sulphone Sensitive Cases: A Preliminary Report, by K. Ramanujam, C. G. S. Iyer and G. Ramu	117
Rifampicin: The Investigation of a Bactericidal Antileprosy Drug, by R. J. W. Rees	121
The Use of Rifampicin in the Treatment of Leprosy, by E. J. Saelens	125
A Controlled Clinical Trial of Continuous and Intermittent Rifampicin Therapy During an Initial Three Months Period in Lepromatous leprosy: Final Analysis, by S. R. Pattyn, M. T. Rollier, R. Rollier, E. J. Saelens and P. Dockx	129
Antibiotics in Leprosy, with Special Reference to Rifampicin, by D. V. A. Opromolla and C. J. S. Tonello	141
The Effect of a Single Dose of Rifampicin on the Infectivity of the Nasal Discharge in Leprosy (Preliminary Communication), by L. M. Hogerzeil and R. J. W. Rees	147
Results of Leprosy Control Project, Malawi, by B. D. Molesworth	149

2. Current Concerns in the Chemotherapy of Leprosy (b) Combined Therapy

Combined Therapy in Leprosy, by J. C. Gatti	155
Preliminary Experience with Combined Therapy using Rifampicin and Isoprodian (L73A), by E. Freerksen	161
Treatment of Leprosy with Rifampicin and Isoprodian (L73A), by J. Terencio de las Aguas	165
Clinical and Bacteriological Effects of Rifampicin in Combination with L73A in Leprosy: Observation for Six Months, by S. Innami, O. R. Leguizamón and A. E. Alvarenga	169
Treatment of Leprosy with Rifampicin and Isoprodian in 38 Patients at St. Thomas Hospital, Chetput, South India, by M. Aschhoff	173
Rifampicin and Isoprodian in Combination in the Treatment of Leprosy, by G. Depasquale	179
Preliminary Experience with Rifampicin and Isoprodian (L73A)—Combination in Lepromatous Leprosy, by M. Hamzah and A. Kosasih	181
Preliminary Experience with Rifampicin and Isoprodian in Combination in Leprosy Treatment, by H. N. Krenzien	189
Report of Combined Therapy in Leprosy with Rifampicin and Isoprodian—Conducted at the Bisidimo-Center, Ethiopia, by R. Rohde	199
Preliminary Report of a Drug Trial conducted at Leprosy Relief Rural Centre, Chettipatty, South India, by E. Vomstein	207

The Leprosy Eradication Programme of Malta, by G. Depasquale	215
Discussion	
Part I Criteria for the Assessment of Drug Activity	221
I.1 Clinical Criteria	221
I.2 Bacteriological Assessment of Drug Activity	226
I.3 Animal Models	231
Part II Current Concerns in Therapeutic Research	233
II.1 Persistent <i>Myco. leprae</i>	233
II.2 Drug Resistance	235
II.3 Combined Therapy	239
II.4 Transfer Factor	245
Part III Clinical Trials	247
III.1 Choice of Patients	247
III.2 Duration of Trials	249
III.3 Duration of Therapy	250
III.4 Criteria for Non-infectivity	254
III.5 Intermittent <i>versus</i> Continuous Therapy: Toxicity and Side Effects	255
Part IV Practical Problems of Chemotherapy in Leprosy	258
IV.1 Clinical and Laboratory Control in Field Projects	258
IV.2 Prevention	260
IV.3 Combined Leprosy and Tuberculosis Control	261
IV.4 Practicability	263
List of Participants	265
Index	269

ADDRESS OF WELCOME

by

PROFESSOR E. FREERKSEN

Forschungsinstitut Borstel, 2061 Borstel, West Germany

Ladies and Gentlemen

I should like to thank all of you very cordially for having accepted our invitation. All the colleagues we asked to participate in this colloquium are present except, however, for a few whom I shall have to mention separately, since I was asked to forward their kind regards to the assembly. Professor Convit of Caracas regrets that he is unable to attend this meeting, because he has to comply with a special government assignment. Dr Shepard and Dr Levy are unfortunately unable to take part because of an American-Japanese congress, the dates of which were chosen a long time ago. Dr Waters cannot come because of staffing difficulties at Sungei Buloh. All these colleagues asked me to give you their very best regards.

The colloquia held in Borstel usually mean two full days of hard work. Nevertheless we try to render these occasions as pleasant as possible so that you will remember them later with pleasure. In order to carry out successfully such a colloquium within a period of two days, we shall have to keep strictly to the fixed schedule.

May I also mention a few words concerning the technique of our colloquia here in Borstel. Although many of you have already attended them in the past, I should like to make a short comment regarding their actual meaning and intention. In large congresses a great number of orators usually address a large audience in order to pass on information. This is not the intention of our colloquium, which is supposed to be a "round table discussion" even if we are not sitting round a table. Only those colleagues are participating who are actively concerned with the problem of chemotherapy, who wish to inform each other about the results of their work, to stimulate and correct each other, and who would like to get evidence about what is to be done in the future. That is why we shall present papers giving information about our various activities on the first day. On the second we shall not discuss the papers, but the general topics outlined by the papers.

Each colloquium needs its chairman, and it gives me great pleasure to say that Dr Browne was so kind to take over this function for the present one. I admit that I would hardly have dared to call you together here without his encouragement and promised assistance. I wish to thank him very cordially today and hereby pass over to him this colloquium's chairmanship, and thereby a great deal of responsibility.

CHAIRMAN'S INTRODUCTION

DR S. G. BROWNE

The Second International Leprosy Colloquium, Borstel

CONCEPT AND AIMS

As Chairman of this Second International Colloquium to be held in the Institut at Borstel, I would add my word of welcome to those just expressed by Professor Freerksen, and to wish all the participants a strenuous and satisfying meeting. We have come together from the four corners of the earth, to pool our knowledge, to debate and discuss our findings, and to stimulate further research on the chemotherapy of leprosy. In the words of the invitation sent to you over the names of Professor Freerksen and myself, the aims of this Colloquium are: "to compare the results of the relatively large number of studies recently made, to evaluate these studies, and to make recommendations and suggestions for future work".

I would stress that this is no tourist excursion to Hamburg; we have come here with the object of working together in order to thrash out some of the problems confronting us in the treatment of patients suffering from leprosy.

It may not be out of place, at this juncture, to indicate briefly the concept behind this Colloquium and the aims of the organizers.

Time was when the various branches of leprosy research could be embraced within the bounds of a single Congress, and when the "general practitioners" in leprosy could at least understand the great bulk of new findings and recent advances in the different fields. Not only so, but those actively pursuing the growing points in any one field could have more than a nodding acquaintance with, if not an intimate knowledge of, the general trends of such research. Now, such international congresses as the quinquennial meetings of the International Leprosy Association, however valuable as a forum where immunopathologists and microbiologists rub shoulders with reconstructive surgeons and epidemiologists, and where chemotherapy is discussed alongside the ophthalmological complications of leprosy, such congresses tend to become unwieldy and fragmented. This is especially noticeable when the needs and wishes of the majority of field workers have to be set in stark juxtaposition with the interesting and significant researches into, say, the serum immunoglobulins and the microbiology of the *Mycobacteriaceae*.

Hence the idea that a colloquium should be convened to follow up and amplify one of the most important subjects dealt with at Bergen last year. Any one of several possible subjects might have been chosen for such a colloquium, and interesting discussions would doubtless have ensued. However, to the patient suffering from leprosy, the overriding concern is to obtain an effective treatment that will "cure" him of his leprosy and prevent the sequelae that he so much dreads. To this end, the moving spirits in the Borstel Institute have invited individuals whose special knowledge and activities are related to the chemotherapy of leprosy. The catchment area might have been much wider, for in the last resort—to adapt Terence—nothing that is of

interest to the treatment of leprosy can be alien to our purpose. But the delimitations have been set, and the participants chosen.

You will have observed from the draft programme the grouped subjects that will serve as the basis for our deliberations. I need hardly remind you that our time is inexorably determined by the clock and the calendar. Everything need not be said; in such a meeting, much may be taken for granted—you know it already, or you would not have been invited. I would request you to be brief and to the point. We desire succinct reports of germane recent work, and a submission of personal findings to the independent arbitrament of objective scientific standards. Now that we have some yardsticks to measure the success of therapy, let us use them. And let us derive from our discussions some necessary deductions from the principles and methods already applied with success—deductions that will point the way to greater and more lasting success as we sympathetically view the patient infected with this unique micro-organism.

Just as *Myc. leprae* is no respecter of persons, of official decrees or of barbed wire, so our discussions will transcend national boundaries and partisan considerations. Some countries are faced with an intractable leprosy problem, well-nigh insurmountable at present; others have a plethora of highly skilled scientific investigators and financial resources beyond the dreams of Midas. The "haves" have an inescapable moral obligation—one compounded of economic components and scientific challenge—towards the "have-nots", and to utilize all possible means to help rid the leprosy patient of his trouble and rid a third of the world's peoples of the threatening spectre of leprosy.

We have purposely left out of consideration many facets of leprosy—not that these latter are unimportant, but simply because they are outside the purview of this meeting. In particular, I would mention the problems raised nowadays by the epidemiological discussions on transmission and susceptibility, and of the role of genetics and immunology in the patterns and persistence of leprosy in the countries where the disease presents a great and, indeed, a growing problem. However, I need hardly remind you that this knowledge—and this ignorance—will form the unexpressed basis of much of our debate during the next two days.

At the back of our thinking, too, must always lie the vexed question of prevention—of primary prevention by means of some enhancement or stimulation of the natural defences of the body, or the initiation of such mechanisms by modification of lymphocytic activity. Such discussions are outside the immediate scope of our meeting; they deserve a full and frank examination in the light of the discordant results reported from different countries. But one aspect of our discussions here in Borstel will impinge upon this question of prevention—the secondary prevention of infection among susceptible contacts by reason of the variably rapid reduction in infectivity of the index case by means of effective mycobactericidal or mycobacteriostatic therapy. At present, this course appears to be the best and the most certain, but its application ideally depends on the existence of an efficient health care system that embraces everybody and is adequately financed and staffed, well-organized and well supervised. An integral part of this desirable goal is the question of comparable cost of the various drugs at present available and their most economical deployment in the leprosy

campaign. We hope tomorrow to touch upon this very practical aspect of leprosy control in poor developing countries faced with other and more urgent and more amenable problems.

Another vast area of concern will also be at the back of our minds though not perhaps fully or explicitly adumbrated, during these days. I refer to the "public relations" aspect of leprosy treatment. Whatever we say or recommend at this meeting, the social components of any leprosy treatment programme is in the last resort of overriding and determinative importance. Acceptability of treatment, regularity of attendance at clinics, perseverance till the bitter end, case-holding, disclosure of early suspicions of leprosy infection, good public relations between staff and patients and potential patients, persuasion and demonstration that treatment is not only available—but is effective, especially when leprosy is diagnosed early—these factors in the long run determine the success or failure of any anti-leprosy campaign. Although they are outside our immediate purview as we discuss the chemotherapy of leprosy, they must never be absent from our thinking, for without the co-operation of patients, the community and the political leaders, any scheme for the treatment and control of leprosy is foredoomed to failure. The "real" questions in the minds of the sufferers from leprosy are not concerned with the morphology of the organism, or the biochemical composition of its cell walls, or the acetylation of the sulphones—but simply "How can I be made better?" and "How can my children be protected against this disease, a disease that I have inherited, or merited, or contracted by the 'evil eye of an enemy'?"

A word about the organization of this Colloquium may not be amiss. In conformity with the Borstel tradition, though admittedly at the risk of some compression and mental surfeit, it has been decided to have most of the papers today, and most of the discussion tomorrow. This system will make demands on the ready co-operation of participants and on their patience. It is hoped that you will make notes as you listen, so that you will be able to raise points in the discussion tomorrow as the various aspects of the chemotherapy of leprosy under review are debated. Please respect the time limits set, and concentrate on personal findings relevant to the theme.

The individual papers and the groups of papers will not be open for immediate discussion. The aim of the organizers is rather that these should form the basis of our wide-ranging discussions tomorrow. We, as practical field workers and fairly widely read practitioners, accept the basis of experimental observations and the new knowledge derived therefrom; in this meeting, we go from that *datum*, that starting point.

Tomorrow, we hope to devote most of the time to discussions under the various headings of today's papers, and come to definite conclusions and recommendations that could be published. These would not only concern the criteria that should determine the methodology of investigation of therapy, and the pros and cons of mono- *versus* poly-therapy, and matters like the duration of therapy in the various forms of leprosy and the choice of drug, but may also point the way to research workers and synthetic biochemists to possible lines of advance in the future.

As you see, these proceedings are being taped. The papers will be published in *Leprosy Review*, with an edited résumé of our discussions. And then, it is hoped, a considered summary of conclusions and recommendations will round off not

only our two-day Colloquium, but also the published proceedings. Indebted as we all are to the Borstel Institute for bringing us here, we and leprosy workers generally will be further indebted to the Institute when the relevant issue of *Leprosy Review* is read and digested and put into practice—to the lasting good of the patient suffering from leprosy and to the lasting benefit of the leprosy campaign throughout the world.

To this end, ladies and gentlemen, colleagues in the struggle against leprosy in the laboratory as in the field, in the administrator's office as in the immunological investigation unit, I beg you now to address yourselves, and I wish you well in all your deliberations and discussions.

**ORIGINAL PAPERS PRESENTED
AT THE COLLOQUIUM**

1. Chemotherapeutic Trials in Leprosy,
their Design and Assessment

The Role of WHO in Antileprosy Drug Trials

J. WALTER* F. M. NOUSSITOU†

and

H. SANSARRICQ‡

*Division of Communicable Diseases, World Health Organization,
Geneva, Switzerland*

The qualities and limitations of the drugs used in the treatment of leprosy are briefly outlined.

The need for primary prevention tools as against present secondary prevention (chemotherapy) methods is stressed.

In the absence of effective primary prevention, the prospects of improving the present antileprosy chemotherapy are considered and the past and present WHO drug trials reviewed.

The need for further efforts and future participation by WHO in drug trials is discussed.

WHO's Fifth General Programme of Work (1971), covering the period 1973-1977 inclusive, refers to leprosy as a communicable disease of major public health importance. In Africa (exclusive North Africa), the Americas and Asia, governments of developing countries considered leprosy, among other diseases, as a public health problem in 1957-1960 and again in 1965-1968 (Cockburn and Assaad, 1973).

To reduce progressively the prevalence of the disease, its associated deformities, and the human suffering it causes, has been the immediate objective of WHO's involvement in leprosy. The long-term epidemiological objective is to achieve a progressive reduction of the disease incidence. The achievement of both objectives would obviously benefit enormously from effective tools for primary, as opposed to presently available, secondary prevention methods.

Table 1 shows a secondary prevention method, chemotherapy, as the main pillar at our disposal to gain control of the disease, and explains the priority given by WHO to collaborative and research promoting activities in this sector, involving laboratory and clinical drug trials, to be followed closely by epidemiological investigations aimed at achieving primary prevention. Full attention will be paid by WHO, as an international organization, to the need for strengthening this type of research in the leprosy endemic countries themselves.

So much for the justification of WHO's role in promoting study and research in the chemotherapy of leprosy. The first successful use of sulphones by Faget (1943) as effective antileprosy chemotherapy was the most dramatic event

* Medical Officer, Leprosy.

† WHO Consultant, Leprosy.

‡ Chief Medical Officer, Leprosy.

TABLE 1

	Means and Measures	Programme Feasibility	Objective
1. Primary Prevention	1.1 Improvement of socio-environmental and other epidemiological risk factors	Investigations on nature of such factors in progress. Output promising, against natural decline in 100-200 years	LEPROSY CONTROL Progressive reduction of <i>Myco. leprae</i> transmission
	1.2 Specific antileprosy vaccination	Investigation proposed on vaccine development	
2. Secondary Prevention	2.1 Segregation	Impractical	
	2.2 Chemoprophylaxis	Of very limited public health value. Long-term protective value doubtful	
	2.3 Chemotherapy	Available, economically feasible but slow. Improvement required. Expectations favourable. Drug trials in progress and extension proposed	

since the discovery of *Myco. leprae* by Hansen. The frequently heard criticism that dapsone has not had a significant impact on the world leprosy situation is as superficial and unfounded as blaming penicillin for not having controlled VD, or DDT for not having eradicated malaria.

From the public health point of view, although we are fully aware of the limitations of secondary prevention in controlling leprosy, it is a fact that dapsone does reduce initial bacterial positivity of regularly treated cases in about 50% of lepromatous cases within an average of five years and in over 90% of cases within ten years.

Table 2 illustrates this point, showing the findings of reputable authors.

Accordingly emphasis has to be placed on regularity of treatment. Among irregularly treated lepromatous cases, 40% as shown by Vellut (1969) remain bacteriologically positive even after ten years of dapsone therapy.

Therefore, where dapsone is regularly taken, we do have a reasonably effective tool against the disease. On the other hand, the increasing importance of dapsone resistance, a greater danger to existing control efforts than the slow-acting property of dapsone, has been demonstrated in laboratory animals and in man (Pettit and Rees, 1964; Pettit *et al.*, 1966; Adams and Waters, 1966; Shepard *et al.*, 1969, and others). The real extent of dapsone resistance, specifically in long-term control programmes, is not known and requires urgent investigations by all concerned including WHO, which could coordinate such studies.

It is only logical to look out and search for alternatives to dapsone, and the desirable properties that a drug (drugs) for the treatment of leprosy should possess are:

- (1) Effectivity in rapidly suppressing clinical and bacteriological activity in the large majority of cases;
- (2) Good tolerance, excluding serious side-effects and keeping drug induced reactions at a minimum;
- (3) Negligible or non-existent development of resistance by *Myco. leprae* in the course of treatment, thus ensuring long-term results and a low proportion of reactivations;
- (4) Simplicity of administration, especially if the drug is to be used in mass treatment.

In Table 3 we have listed, together with their main characteristics, four drugs currently in use, possessing to a significant degree the already mentioned properties as measured by clinical and bacteriological improvement of cases.

These drugs have been chosen as being the ones about which the most information is available. Other drugs such as isoniazid, thiosemicarbazone (TBI), streptomycin, long-acting sulphonamides, etc., have not been included because their use in field programmes has been rather limited, or they have to be used with exceptional caution.

We shall now briefly review the role of WHO vis-à-vis antileprosy drug trials in the past, present and future.

In the WHO Programme of Leprosy Research, the evaluation of anti-leprosy drugs has been carried out in the following centres:

- (1) Central Leprosy Teaching and Research Institute, Chingleput, India (from 1962 to the present);
- (2) Instituto Nacional de Dermatologia, Ministry of Health, Caracas, Venezuela (from 1960 to the present);
- (3) Institut Marchoux, Bamako, Republic of Mali (from 1960 to the present);
- (4) Sanatorio-Villaggio Isola Alessandra, Gelib Giuba, Somalia (from 1968 to the present);
- (5) Institut de Léprologie appliquée, Dakar, Sénégal, (from 1971 to the present);
- (6) Leprosy Service Research Unit, Uzuakoli, Eastern Nigeria (from 1960 to 1964);
- (7) Colonia Sanatorio San Francisco de Borja, Fontilles, Alicante, Spain (from 1965 to 1968);
- (8) Lucha Dermatologica, Buenos Aires, Argentina (from 1965 to 1967).

Drug trial centres collaborating with WHO have some difficulty in following the requirements of WHO-Controlled Clinical Trials (Doull, 1960), and the number of untreated lepromatous patients available at these centres usually has been inadequate. Often an independent appraisal before therapy, at intervals throughout the study, and at the end of the trial, could not be undertaken owing to insufficient funds. Without going into details of results obtained, drugs or drug regimens which have been investigated are:

- Different brands of repository dapsone;
- Diethyl-dithiol-isophthalate;*
- Methimazole or Tapazole, an antithyroid drug;
- Two different long-acting sulphonamides (Ro 4-4393 and Sultirene);
- Injectable DPT

* Ditophal, Etisul.

TABLE 2

Author ^a	Year	Country and area	Years of observation	Weekly Dapsone dosage in mg	Regularity of attendance	Number of bacteriol. positive (L/B) cases	Annual reduction of bacteriol. positivity												
							% of remaining positive cases												
							1	2	3	4	5	6	7	8	9	10			
Lechat, M. ¹	1961	Congo Yonda	9	800	“regular”	1254	100	56	37	27	21	14	9	6	3				
		Nigeria North			0.75% +	1187	65				18								
		Nigeria South			75% +	664						20							
		Thailand			50-74%	73							35						
		Khon Kaen			25-49%	27							66						
														92					
Patwary <i>et al.</i> ²	1963	Cameroun	5	?	0-24%	13													
Quagliato <i>et al.</i> ³	1970	Brazil Campinas	10	400 to 600	75% +	690	82	71	55		31				9	3			
					“irregular”	125	80	73	72		55			26	17				
Basto, P. and Barbosa, A. ⁴	1968	Portugal Tocha	10	600	?	155										8			
Vellut, C. ⁵	1969	India Tamil Nadu	10	400 to 600	75% +	595			80		32					5			
					“irregular”	705											40		

^a 1-5 Rearranged data.

TABLE 3

Antileprosy drug (nonproprietary name)	Chemical name	<i>Myc. leprae</i> resistance	Tolerance	Other undesirable effects	Cost
Dapsone	4,4'-diaminodiphenyl-sulphone	Yes, extent unknown probably not under 5 years of treatment	Fair to good	—	Low
Clofazimine	Rimino-phenazine compound 3-(<i>p</i> -chloroanilino)-10-(<i>p</i> -chlorophenyl)-2,10-dihydro-2-(isopropylimino) phenazine	?	Good	Skin pigmentation	Moderate
Rifampicin	Antibiotic 3-[[[C 4-methyl-1-piperaziny] imino] methyl] rifamycin SV	?	?	?	High
Thiambutosine	Diphenylthiourea 1-(<i>p</i> -butoxyphenyl)-3-(<i>p</i> -dimethylaminophenyl)-2-thiourea	Yes, frequent after 1-2 years treatment	Good	—	Moderate

Combination of drugs such as:

- (1) dapsone + streptomycin + INH;
- (2) dapsone + INH + PAS;
- (3) dapsone + INH + TBI;
- (4) dapsone + DPT;
- (5) dapsone + Ditophal.

Most of these trials were initiated and terminated between 1962 and 1966. Results of all these trials, with regard to bacterial reduction, were not superior to those obtained with dapsone when given as a single drug (Bechelli and Martinez Dominguez, 1966).

The WHO Expert Committee on Leprosy (1966) recommended dapsone administration to be the basic treatment for field programmes.

Since 1966 other studies have been initiated and are, with the exception of the short-term thalidomide trial (Iyer *et al.*, 1971) still in progress. These are:

- Multicentre studies on conventional and low dapsone dosage schemes (four centres);
- Clofazimine and Aspirin or Thalidomide in lepra reaction (ENL), (three centres);
- Controlled acedapsone trial (3 centres);
- Dapsone chemoprophylaxis in children (two centres).

Future Orientation

Having stressed the need for the drug trials and reviewed past and ongoing activities, what is the most promising attitude for WHO to adopt in the immediate future, within its own limitations other than those obviously set by budgetary considerations, concerning laboratory, clinical and epidemiological trials of antileprotic drugs?

(a) The availability of a reliable and generally accepted test for determining under field conditions the viability of *Myc. leprae* in lesions. Previous research into the implications of the morphology of the bacillus, the mouse footpad technique, as well as the importance of the nose in the transmission of leprosy (Rees *et al.*, 1974) have paved the way for possible future developments in this field.

(b) The long periods of time required to achieve bacterial tissue clearance in lepromatous leprosy are common knowledge. The reasons for this slow removal of bacterial debris and a possible faster tissue clearance by increased immunoactivity need studies in animal models and in man.

(c) The search for new, safe and effective compounds, equally merits intensive research in infected animals and in patients.

(d) To explore further the advantages of combined drug therapy on the lines pioneered by Freerksen and colleagues (Freerksen and Rosenfeld, 1973), keeping in mind what has already been mentioned under desirable properties of antileprosy drugs.

(e) The ranking of established antileprosy chemotherapeutic agents in the order of their importance, evaluated from their safety point of view.

(f) The determination of drug resistance and its frequency in field control programmes is another urgent task, as well as practical measures to prevent the spread of dapsone resistant strains of *Myc. leprae*.

(g) Out-patient treatment of leprosy patients in preference to institutional care was for the first time recommended by WHO in 1953, and these recommendations were further extended to cover all forms of leprosy in 1966. In tuberculosis control, similar recommendations were made by WHO in 1959 and 1960 based on the results obtained in controlled studies in India, completed within one year. In contrast to the latter, in leprosy we still need a controlled comparison of institutional and domiciliary treatment. However, such studies would require follow-up periods of at least five years or more.

(h) Besides the search for new compounds which could be promising agents for safe, fast and effective chemotherapy, investigations in the field of immunotherapy should not be neglected. Attempts at immunotherapy have in the past chiefly consisted of the injection of peripheral leucocyte suspensions and leucocyte extracts, attempting to increase cell-mediated immunity in lepromatous leprosy. Areas for future research in the field of immunotherapy have been spelled out by the second WHO-convened meeting of immunologists in New Delhi (1973). In addition, the possibilities of increasing immuno-resistance by means of thymosin deserve appropriate investigations in animals and in man.

Constraints to our objectives which have to be taken into account are:

Ethical aspects: It is the responsibility of the institution and the principal investigator to safeguard the rights and welfare of human subjects involved in research supported in whole or in part by WHO, in accordance with the appropriate national code of ethics or legislation.

Regulatory requirements: It is the responsibility of the institution and the principal investigator to comply with national regulations pertaining to clinical studies of new drugs or devices.

Suitable Institutions for Drug Trials in Leprosy

In our opinion based on world-wide experience, the often expressed view on shortage of lepromatous patients for drug trials is only partially true. However, the number of well staffed and equipped institutions in countries which still have a relatively high incidence of lepromatous cases, needed for drug trials, is insufficient, whilst on the other hand several highly qualified investigators work in institutions and areas in which new lepromatous cases are becoming rare indeed.

Voluntary agencies supporting numerous institutions in nearly all leprosy endemic countries could expand their programmes and coordinate their relevant efforts with WHO. Thus more centres could participate in drug evaluation studies, the results of which would ultimately be of benefit to world-wide leprosy control efforts.

Several centres carrying out excellent research work in antileprosy drugs have not, so far, established any kind of link with WHO. It would be beneficial for private or national institutions involved in leprosy research, as well as for WHO, to develop without delay and with no implications of financial support or of any sort of commitment from the participants, a regular exchange of information about current investigations in leprosy therapy. It is felt that WHO with its various specialized units on drug evaluation and classification, pharmacology, cancer, immunology etc., including the WHO panel of experts, could probably serve as an objective forum.

Not confining ourselves to WHO activities in leprosy drug-research, a word

about the general allocation of resources to this field seems pertinent. To compensate for a diminishing interest on the part of the pharmaceutical industry in the search for new drugs against tropical diseases in general and leprosy in particular, an appeal is made for the pooling of resources to rationalize drug development. In a world with so many factors of financial instability at work, the mobilization of additional resources for drug development and trials is necessary to ensure further progress.

References

- Adams, A. R. D. and Waters, M. F. R. (1966). *Br. med. J.* 2, 872.
- Basto, P. and Barbosa, A. (1968). *Int. J. Lepr.* 36, 657 (Abstract of paper, Ninth International Leprosy Congress, 1968, London).
- Bechelli, L. M. and Martinez Dominguez, V. (1966). Drug trials in centres cooperating in the WHO programme of leprosy research. Unpublished WHO document *Lep. Int.* 2, 66.
- Cockburn, W. Chs. and Assaad, F. (1973). *Bull. Wld Hlth Org.* 49, 1-12.
- Doull, J. A. (1960). *Controlled clinical trials in leprosy*. Unpublished WHO document, MHO/PA/97.60.
- Faget, G. H. *et al.* (1943). *Publ. Hlth Rep., Wash.* 58, 1729-1741.
- Freerksen, E. and Rosenfeld, M. (1973). *Z. Tropenmed. Parasit.* 24, Spec. Nr 1, 17-25.
- Immunological Problems in Leprosy Research: 2 (1973). *Bull. Wld Hlth Org.* 48, 483-494. (Memorandum).
- Iyer, C. G. S. *et al.* (1971). *Bull. Wld Hlth Org.* 45, 719-732.
- Lechat, M. F. (1961). *Ann. Soc. belge Méd. trop.* 6, 509-521.
- Noussitou, F. M. (1974). (In preparation) Unpublished WHO document.
- Patwary, K. M., Martinez Dominguez, V. and Cress, K. M. (1963). *Int. J. Lepr.* 31, 584-586 (Abstract of paper, VIIIth International Congress of Leprology, 1963, Rio de Janeiro).
- Pettit, J. H. S. and Rees, R. J. W. (1964). *Lancet* 2, 673.
- Pettit, J. H. S., Rees, R. J. W. and Ridley, D. S. (1966). *Int. J. Lepr.* 34, 375.
- Quagliato, R., Bechelli, L. M. and Marques, R. M. (1970). *Int. J. Lepr.* 38, 250-263.
- Rees, R. J. W. *et al.* (1974). *Lepr. Rev.* 45, 112-120.
- Shepard, C. C., Levy, L. and Fasal, P. (1969). *Am. J. trop. Med. Hyg.* 18, 258.
- Tuberculosis Chemotherapy Centre, Madras (1959). *Bull. Wld Hlth Org.* 21, 51.
- Vellut, C. (1969). *Leprosy in India* 41, 276-281.
- World Health Organization (1971). *Fifth General Programme of Work Covering a Specific Period, 1973-1977 inclusive*. In: *WHO Official Records*, nr. 193, Annex 11, 65-81.
- WHO Expert Committee on Leprosy (1953). *Wld Hlth Org. techn. Rep. Ser.* 71.
- WHO Expert Committee on Leprosy (1966) *Wld Hlth Org. techn. Rep. Ser.* 319.
- WHO Expert Committee on Tuberculosis (1960) *Wld Hlth Org. techn. Rep. Ser.* 195.

Chemotherapeutic Trials and their Assessments

R. J. W. REES

*Laboratory for Leprosy and Mycobacterial Research
National Institute for Medical Research
Mill Hill, London NW7 1AA*

The well-established methods for the conduct and assessment of chemotherapeutic trials in leprosy have more recently been enhanced by the inclusion of the mouse footpad infection. Examples are provided of the use of this infection as a more sensitive method for the assessment of new drugs, their speed of action and the detection of persistently viable organisms and the emergence of drug-resistant bacilli. The importance of these results in relation to the value of short-term trials in the initial assessment of a new antileprosy drug and the necessity of very-long-term trials in the final assessment of a new drug or new drug regimen in the treatment of lepromatous leprosy are discussed.

In considering chemotherapeutic trials and their assessment in leprosy I will begin by quoting from a recent Editorial in the *Lancet* (1974): "The treatment of pulmonary tuberculosis is soundly based on the results of controlled clinical trials. Unfortunately it is not always effective, but if it fails the fault lies with the physician, the patient or the medical services. Failure is not due to inefficacy of the drugs or deficiencies of research. With other forms of tuberculosis the position is different. Few control trials have been done." This editorial incidentally referred to tuberculosis of the spine. However, my reason for quoting from this editorial is to compare and contrast the current situation in the chemotherapy of tuberculosis and leprosy. Historically dapsone was shown to be efficacious in the treatment of leprosy long before any antituberculosis treatment, streptomycin, was discovered and yet well defined and precise chemotherapeutic trial methods were evolved for tuberculosis long before they were applied to leprosy. On the other hand, because both infections were caused by a mycobacterium and both were chronic type infections, the well-defined methods for assessing trials in the treatment of leprosy followed the basic principles applied to chemotherapeutic trials in tuberculosis (Doull, 1960; Waters *et al* 1967). While all would admit in retrospect the need for incorporating well-defined criteria and basic methodology into trials concerned with the chemotherapy of leprosy and the acceptance that both infections were caused by a mycobacterium, the efficacy of therapy then available was entirely different. While it would be true to say that treatment of leprosy (by dapsone) was not always effective, unlike the chemotherapeutic agents for pulmonary tuberculosis, failure of dapsone therapy in leprosy could

not be said to be due to the fault of the physician, the patient or the medical services. Clearly, the difference could have arisen from deficiencies in dapsone, compared with antituberculosis drugs, or differences in the capacity of leprosy and tuberculosis patients to respond to chemotherapy.

Both differences are relevant and as such are fundamental to the design of chemotherapeutic trials in leprosy. Considering first the efficacy of dapsone against *Mycobacterium leprae*, current studies in the mouse indicate that it is a bacteriostatic drug, whereas the major antituberculosis drugs (streptomycin, isoniazid and rifampicin) are bactericidal drugs against *Mycobacterium tuberculosis*. On the basis of this important difference the antituberculosis drug would be expected to be more effective than would dapsone therapy for leprosy.

The second consideration is concerned with possible differences between leprosy and tuberculosis in the type of infection and the capacity of the patient to respond to chemotherapy. Here there are undoubtedly very great differences, not only between tuberculosis and leprosy but also among patients with leprosy. The appreciation of these differences are fundamental to the selection and basis of the conduct of chemotherapeutic trials in leprosy and the limit to which the methodology for chemotherapeutic trials in tuberculosis can be applied to leprosy. These differences are particularly pertinent when chemotherapeutic trial methods for pulmonary tuberculosis are directly applied to leprosy. Unfortunately, these fundamental differences have not always been appreciated by tuberculosis workers. The basic difference is that while acute pulmonary tuberculosis is a progressive and highly bacilliferous infection, leprosy can present a wide spectrum of disease within which only those patients with the lepromatous type of infection are highly bacilliferous and uniformly progressive. It is now well recognized that the majority of patients with leprosy have less acute infections, with fewer bacilli and where the clinical manifestations predominantly arise from a spontaneous capacity of the host to destroy bacilli. This capacity is greatly enhanced by chemotherapy, whereas the lepromatous patients are almost completely deficient of this capacity, even with chemotherapy. Therefore, in chemotherapeutic trials in leprosy only patients with lepromatous leprosy can be used to be comparable with trials in active pulmonary tuberculosis, although the immunological capacities of the patients will be greater in tuberculosis than in leprosy.

I have chosen to introduce the subject of chemotherapeutic trials and their assessments in leprosy as compared with such trials in tuberculosis because scientific methods for trials in leprosy came from experience gained in tuberculosis. However, once these general principles were applied, which undoubtedly were beneficial, it soon became apparent that there were major differences between the two infections and the type of chemotherapeutic drugs available, which would not be beneficial if strictly applied to leprosy.

In my paper I have followed the guidelines of Professor Freerksen in his opening remarks by assuming that the members of this Colloquium are fully conversant with the leprosy literature, and therefore this is not a review. I shall begin by underlining the general principles to be applied to chemotherapeutic trials and their assessment in lepromatous leprosy, pinpoint these features of leprosy and the drugs available compared with tuberculosis. I shall then present the broad results obtained from shorter and long-term chemotherapeutic trials in leprosy, particularly stressing the application and significance of the footpad infection in mice as more recently applied to these various trials. I will stress the

difficulties inherent in attempting to assess any new drugs, or drug regimens, as compared with dapsone for "curing" patients with lepromatous leprosy or assessing the emergence of drug resistance.

Standard Requirements for Leprosy Drug Trials

The requirements for trials in general and for leprosy in particular as proposed respectively by Doull (1960) and Waters *et al.* (1967), and which have withstood the test of time are summarized in Table 1. While all these requirements are

TABLE 1

Standard requirements for leprosy drug trials

-
- A. *Cases selected must be:*
- (1) Lepromatous (LL/LI) on Ridley-Jopling scale.
 - (2) Untreated, with a Morphological Index (MI) of 5 or more.
- B. *In control trials allocation to treatment groups must be randomized.*
- C. *Evaluation of treatment must be based on independent clinical, bacteriological and histological assessments.*
-

essential to produce reliable and reproducible results, to avoid bias in the assessments and provide comparability between different Centres, the correct selection of lepromatous patients is of overriding importance. There are two reasons for selecting only lepromatous patients, the first is basic to chemotherapy and the second relates to the very variable responses to therapy by non-lepromatous patients. Thus, by definition a chemotherapeutic trial is an assessment of an antibacterial agent, and within the spectrum of leprosy only lepromatous patients have an adequate *and* inevitably active and progressing bacteriological population on which to assess antibacterial drugs. Tuberculoid patients are excluded because they have too few bacteria and although patients with borderline (BB) or near-lepromatous (BL) leprosy may have relatively high bacterial populations, they are variable and they are killed and eliminated more rapidly and more variably with therapy than they are in lepromatous patients. All these bacteriological variabilities reflect variabilities in the capacity of the host against *Myco. leprae* and are not a measure of the efficacy of the antibacterial drug *per se*. It is for these two reasons that only lepromatous patients must be selected for trials concerned with assessing and comparing new antileprosy drugs and comparing them with dapsone. Now that it has been established that the spectrum of leprosy is essentially immunologically determined, the classification and selection of lepromatous patients (LL/LI) for chemotherapeutic trials should be based on the only currently reliable classification which takes into consideration immuno-pathological features (Ridley and Jopling, 1966; Ridley and Waters, 1969).

I have stressed these points, for although they are the basis of current concepts on the pathogenesis of leprosy, they are, unfortunately, still frequently ignored in chemotherapeutic studies.

Of the various assessments carried out in standard chemotherapeutic trials I will only comment on the bacteriological assessments because these are the only ones

directly concerned with antibacterial activity. Moreover, because *Myco. leprae* cannot be cultured *in vitro* indirect methods of assessing viability have had to be developed in place of routine bacteriological cultures, which are applied in chemotherapeutic trials concerned with all other bacterial infections. Thus the Morphological Index (MI) is the only substitute for indirectly determining viability of *Myco. leprae* in the routinely available skin scrape samples, which are also used for semi-quantitative assessments of the bacteriological load in the skin (Bacteriological Index, BI). Regarding the MI, based routinely on the morphology of 100 acid-fast bacilli, it is only of value for assessing and comparing the rate at which *Myco. leprae* are killed in the skin in the short initial period. This is because on standard dapsone therapy the MI falls to 0 by 6 months. Since trials must now be concerned with new drugs or drug combinations which are more rapidly killing than dapsone, the MI will be of no value after the first 6 months. At the same time it is essential to appreciate that a MI of 0 at 6 months, based on the assessment of only 100 acid-fast bacilli as against a possible total bacillary population in the patient of 10^{11} acid-fast bacilli, does not mean that there are no viable bacilli left—it in fact could mean that there are not more than 10^9 viable bacilli left. On the other hand, assessment of the BI can be continued for many years and in general the rate at which it diminishes, and if it continues to diminish at a steady rate of 1 log per annum, is good evidence that the drug under test is reducing the proportion of living *Myco. leprae* at a rate comparable to that obtained by dapsone. However, like the MI the BI has a finite value, and using the Ridley scale of 0-6, which is a logarithmic scale, then a BI of 0 represents less than 1000–100 acid-fast bacilli per gram of skin. Although the MI, as explained, is only a limited measure of viable organisms, and normally has no value after the first 6 months, it must still be assessed, since the reappearance of a positive MI and a rising MI, would indicate relapse, and as long as it could be certain that therapy had been taken, it would indicate the emergence of drug resistance.

Assessments of MI and BI can also be made on histological sections, and methods for these are well defined. Depending on the time spent on examining sections, these assessments can be made somewhat more sensitive than MIs and BIs based on smears; particularly the MI, since the assessment can be made on particular histological sites. This applies to dermal nerves and arrector pili muscle, sites in which morphologically intact bacilli are known to remain for long periods. A few morphologically intact bacilli in these sites are infinitely more sensitive than the examination of a skin scrape where the same bacilli would be overwhelmingly outnumbered by bacilli from the rest of the skin.

Although there is still no *in vitro* cultivation of *Myco. leprae*, since 1960 the mouse footpad infection has been available and more recently this technique has been applied to chemotherapeutic trials as a much more sensitive and direct method of assessing viable *Myco. leprae* than the MI, and the nearest to a routine culture. It is approximately 100 to 1000 times more sensitive than the MI. Moreover, the mouse footpad technique can not only be used to determine viable organisms from human tissues but also to determine their drug sensitivity. It is the application of the mouse footpad technique I will particularly draw upon in the rest of my paper, which will be concerned with short and longer termed chemotherapeutic trials, trials related to the problem of drug resistance and finally speculations on whether patients with lepromatous leprosy can be cured by chemotherapy alone and the need for trials on patients with non-lepromatous leprosy.

Short-term Pilot Trials

This type of trial was introduced in 1967 (Waters *et al.*) as the first type of trial to be used when testing a new antileprosy drug in man. Although the standard requirements were the same as those set out in Table 1, the key assessment is the MI and as this reaches 0 in 4.5-6 months with dapsone treatment, this was the period chosen for pilot trials to assess the relative efficacy of new drugs or drug combinations. All drugs used in the pilot trials must have first satisfied the pharmacological and drug safety regulations. The introduction of the pilot type trial preceded the use of the mouse footpad infection as a routine test for screening new antileprosy drugs. Therefore, at that time leprosy in man was being used to identify specific antileprosy activity. This is no longer justified. Now only new drugs that have been fully screened against *Myco. leprae* in the mouse footpad test, and shown to have activity comparable to dapsone, should be submitted to a pilot trial in man (see Committee on Experimental Chemotherapy, 1974).

Finally, and most importantly, the mouse footpad technique has now been added to the list of assessments in pilot trials. This technique is used to determine the rate at which *Myco. leprae* are killed. This is done by harvesting *Myco. leprae* from biopsies of skin at the beginning, during and end of the trial, and inoculating them into mice. This technique is a more accurate and sensitive method for determining the viability of *Myco. leprae* than is the MI. By the standard mouse footpad technique the skin of patients under standard dapsone therapy are cleared of viable (infectious) *Myco. leprae* within 3-4 months. By the same criteria rifampicin therapy clears bacilli from the skin within 3 weeks (Rees *et al.*, 1970). The rapid killing of *Myco. leprae* by rifampicin is consistent with it being a bactericidal drug, as compared with the bacteriostatic activity of dapsone. Moreover, although with rifampicin the MI falls more rapidly than with dapsone, the fall in the MI with rifampicin lags behind loss of viability of *Myco. leprae* as determined in the mouse. Thus the mouse technique is superior to the MI with a rapidly killing and bactericidal drug, such as rifampicin. The reason for the apparent discrepancy between these two tests is that the changes in the morphology of an organism take 7-10 days to become manifest.

Long-term Trials

In principle, the objectives of long-term trials are a logical sequence in determining the final efficacy of a drug or drug combination, using various regimens, to achieve cure. While for tuberculosis and other infectious diseases such long-term trials have a logical basis, because the infections can be cured, this has not been uniformly achieved in lepromatous leprosy using standard dapsone therapy. Therefore, as the primary objective of any chemotherapy has not been achieved in lepromatous leprosy, the primary objective must be to investigate new drugs in the hope of achieving cure. However, the special features of lepromatous leprosy, which have already been discussed in the earlier part of this paper, together with the failure of dapsone and its use only as monotherapy, have in themselves influenced the planning and objectives of long-term trials. Because of these special circumstances I will first pinpoint the problems as revealed from present knowledge using dapsone as monotherapy and the pattern of drug resistance, and recent results using rifampicin. In analysing the present situation I

shall heavily draw on pharmacological and bacteriological data obtained by using the mouse footpad infection.

I must first recapitulate that the chemotherapy of leprosy had been entirely based on monotherapy and nearly all the 30 years experience has been with dapsone or closely related derivatives. In lepromatous leprosy, for any semblance of cure, dapsone has had to be administered continuously for 5 years at least, frequently 10 years and now it is advised for life. Such prolonged therapy is unique, is impracticable since under no medical services and patient collaboration can such prolonged therapy be maintained. In the last 10 years, using the mouse footpad infection, it has been demonstrated that dapsone resistance can occur or that in spite of apparent continuous dapsone therapy for 10 years, a high proportion of such patients can be shown to harbour a few dapsone sensitive bacilli (Waters *et al.*, 1974). Regarding the emergence of dapsone resistance, the mouse footpad test has shown that by and large dapsone resistant infections take at least 6 years to evolve and can still evolve after 24 years dapsone therapy. The same studies have shown that dapsone is bacteriostatic. While from experience with the chemotherapy of tuberculosis, monotherapy would have been expected to have resulted in drug resistance similarly in leprosy, the prolonged time lag in leprosy is unique.

Two thiourea derivatives—thiacetazone and thiambutosine—have also been used to a limited extent in the therapy of leprosy, as monotherapy, and with both these drugs clinical relapses have been frequent after 2-3 years. Moreover, recently it has been established that these relapses are due to the emergence of resistant strains, as demonstrated in the mouse footpad infection. Therefore, the emergence of drug resistance to monotherapy by the thioureas has occurred much more rapidly than with dapsone, and within a period that is more consistent with the rate of emergence of drug resistance in tuberculosis.

Another antileprosy drug, clofazimine, has also been used as monotherapy for some 10 years, and to date there is no evidence of drug resistance.

Dapsone, the thioureas and clofazimine have all been shown in the mouse footpad infection to be bacteriostatic drugs.

Still more recently rifampicin has been used for about 5 years in the chemotherapy of leprosy, again largely as monotherapy, and to date no drug resistance has been reported. Rifampicin, on the other hand, differs from all the other antileprosy drugs in being bactericidal. However, as reported by us elsewhere in this Colloquium, where we have monitored in mice homogenates of skin and other tissues from patients treated continuously with rifampicin for up to 2 years, a significant proportion of such patients have been shown to still harbour some living *Mycobacterium leprae*.

On the basis of our experience with dapsone and all the data on other antileprosy drugs, we have now to decide the purpose for which future long-term trials should be undertaken and the general design and feasibility of such trials that are likely to improve the therapy of lepromatous leprosy. The primary reason for a long-term trial of a new drug that has proved efficacious in a pilot trial is to establish its continuing efficacy in controlling the infection as judged by clinical and bacteriological assessments. For leprosy, this would be a controlled trial comparing a group of patients on the new drug with a group on dapsone and the bacteriological assessment would be based on the rate of fall in the BI and the time taken for the BI to reach 0. This simple but logical approach will certainly identify new drugs less efficacious than dapsone, and identify new drugs giving

rise to drug resistance within 2-3 years, like thiambutosine and thiacetazone. On this basis, a long-term trial of 5 years would suffice. However, as we now know dapsone therapy alone is not necessarily a cure when maintained for 10 years or more because even when the BI is 0, dapsone sensitive viable organisms may persist and the patient relapse when treatment is stopped. Furthermore, dapsone treated patients can relapse with resistant organisms at any time after 6 years or more of continued dapsone therapy. In order to exclude this pattern of resistance for a new antileprosy drug, controlled long-term trials would have to be continued, with large groups of patients, for at least 10 years. It is on the basis of these two phenomena associated with dapsone therapy, and the fact that dapsone and all other antileprosy drugs have been administered as monotherapy, we need to reappraise the objectives for long-term trials. From the experience of chemotherapy in tuberculosis there is overwhelming evidence that all anti-tuberculosis drugs given as monotherapy universally result in drug resistance. Because monotherapy has so far been universally applied in leprosy and because dapsone is standard therapy, the most important long-term controlled trials which need to be undertaken in leprosy must be designed to establish whether a second drug given with dapsone significantly reduces the incidence of dapsone resistance. However, such a controlled trial would require at least 200 previously untreated lepromatous patients and would have to be continued for not less than 10 years. Unless a trial of this type is undertaken the role of combined therapy in leprosy will remain unanswered. Because of the danger of drug resistance there is a case for assuming without proof the efficacy of combined therapy because of the difficulties and delay in undertaking a trial. However, even if this principle was accepted, long-term trials would still be required to assess all new drugs which would then always have to be given in combination with, for example, dapsone or another known antileprosy drug. While resistance is one major reason for undertaking long-term trials, there is still the persist problem revealed from experience with dapsone, which also can only be investigated by long-term studies. Persisting viable bacilli and the need for prolonged therapy may well be associated and due to dapsone being a bacteriostatic drug. Therefore the discovery of rifampicin as the first bactericidal drug against *Myco. leprae* can now be used to test this hypothesis, and a number of trials are under way. However, preliminary results show that some viable bacilli persist still in patients treated daily with rifampicin for 2 years. Therefore rifampicin has not reduced the treatment time dramatically although it may well shorten the 10 years or more required for dapsone. Nevertheless viable organisms after 2 years treatment with a powerful bactericidal drug may indicate that chemotherapy alone will not cure lepromatous patients because of their diminished immunological competence. Further long-term trials alone will answer this important question. If the results then show that rifampicin is no more effective than dapsone, trials with combined immunotherapy will have to be investigated.

References

- Committee Report on Advances in Experimental Chemotherapy (1974). 10th Internat. Leprosy Congr. 1973. *Lepr. Rev.* 45, 48.
- Doull, J. A. (1960). Controlled clinical trials in leprosy. W.H.O. Geneva. Document MHO/PA/97.60.
- Editorial (1974). Tuberculosis of the spine. *Lancet*, i, 137.
- Rees, R. J. W., Pearson, J. M. H. and Waters, M. F. R. (1970). Experimental and clinical studies on rifampicin in the treatment of leprosy. *Br. med. J.* 1, 89.

- Ridley, D. S. and Jopling, W. H.(1966). Classification of leprosy according to immunity. A five-group system. *Int. J. Lepr.* **34**, 255.
- Ridley, D. S. and Waters, M. F. R. (1969). Significance of variations within the lepromatous group. *Lepr. Rev.* **40**, 143.
- Waters, M. F. R., Rees, R. J. W., McDougall, A. C. and Weddell, A. G. M. (1974). Ten years of dapsone in lepromatous leprosy: Clinical, bacteriological and histological assessment and the finding of viable leprosy bacilli. *Lepr. Rev.* **45**, 288.
- Waters, M. F. R., Rees, R. J. W. and Sutherland, I. (1967). Chemotherapeutic trials in leprosy. 5. A study of methods used in controlled chemotherapeutic trials in lepromatous leprosy. *Int. J. Lepr.* **35**, 311.

The Technique of Evaluating Anti-leprosy Medications at the Forschungsinstitut Borstel

E. FREERKSEN

Forschungsinstitut Borstel, 2061 Borstel, West Germany

I should like to demonstrate only a few results selected from a great number of experiments, and explain several principles which finally made us prefer a certain form of chemotherapy. Mr Alvarenga, Mrs Aschoff and Messrs Depasquale, Hamzah, Krenzien and Rohde will each read a paper about their practical results tomorrow.

(1) Leprosy is an infectious disease. Just about everywhere in the world the same method is principally applied to find new medications against such diseases and to determine their value: natural or synthetic substances are looked for and found, are modified and become derivatives. When substances have proved to be effective in *in vitro* experiments, and with research animals, one tries to find out about their clinical effectiveness (Fig. 1(a)).

This is true for all infectious diseases, and in principle also for leprosy. But leprosy research involves the tremendous difficulty that the bacteria cannot be cultivated, and experiments therefore cannot be carried out in the usual manner. That is why we had to look for mycobacterial strains replacing *Myc. leprae* in *in vitro* and animal experiments (Fig. 1(b)).

We use various strains *in vitro* (*Myc. marinum*, *Myc. avium*, *Myc. ulcerans*, *Myc. lepraemurium* for instance, but also *Myc. tuberculosis*) in order to find out up to what extent they may be influenced by antimycobacterial substances. As far as animal experiments are concerned, the mouse footpad test introduced by Shepard and Rees surely is the most important aid we have in experimental leprosy research. This, however, should not keep us off looking for different methods. It was Eleanor Storrs who introduced armadillos in leprosy research, and there is no doubt today that *Myc. leprae* multiply in such animals. In Borstel we started using hedgehogs in animal trials. However, since the trials I should like to demonstrate today are not based upon the hedgehog as experimental animal, I shall not go into details with regard to these experiments.

(2) The experiments I shall talk about today were mainly carried out with *Myc. marinum* (substituting *Myc. leprae*) and mice. After intravenous infection *Myc. marinum* causes processes in mice affecting mainly tails, pads, ears, and the mucous membranes of mouth and nose (Fig. 2 α). In these experiments also appear the typical nodules which could be called "marinomas" instead of "lepromas" (Fig. 2 β). But marinomas and lepromas can hardly be distinguished; they also ulcerate, and they can easily be cured (Fig. 2 γ (a), (b), (c), (d)). The tails

regain their smooth appearance, but there may remain scars such as in human beings. Parts of the body which are already destroyed do of course not regenerate.

Histological examinations reveal formations which are typical for leprosy such

ISOLATION	<i>In vitro</i>	Serum	Clinical Therapeutic Assessment therapeutic efficiency compatibility side-effects duration of therapy dosage	Clinical Efficiency	General
	<i>In vivo</i> (experimental animal)				
SYNTHESIS		Activity		Comparisons	Medical
DERIVATIVES	Experiments serum-activity therapeutic efficiency toxicity (inclusive adaptation) biologic profile	(man)	in research clinics	in various clinics	Application

(a) Finding, synthesis, assessment of antimicrobial substances

ISOLATION	<i>In vitro</i> Substitutes for <i>Myc. leprae</i> : <i>Myc. marinum</i> <i>Myc. avium</i> <i>Myc. ulcerans</i> <i>Myc. lepraemurium</i>	Serum	Clinical Therapeutic Assessment therapeutic efficiency compatibility side-effects duration of therapy	Clinical Therapeutic Efficiency	General
	<i>In vivo</i> footpad (mice) armadillo hedgehog				
SYNTHESIS		Activity		Comparisons	Medical
DERIVATIVES	Experiments serum-activity therapeutic effect toxicity (inclusive adaptation) biologic profile	(man)	in research clinics	in various clinics	Application

(b) Finding, synthesis, assessment of anti-leprosy substances

Fig. 1.

as the rarefaction of muscles, the replacement by fibroid infiltrates and encircling of nerves by fibrous tissue (Fig. 3(a), (b)).

(3) Of course we know that this model does not represent a case of leprosy produced in animals, but rather a mycobacteriosis similar to leprosy offering the great advantage that *Myc. marinum* is easily cultivable and virulent in mice. With the help of this method we found a number of substances which Shepard and Rees also considered to be the most effective in the mouse footpad test:

Rifampicin (RAMP)
 clofazimine (B663)
 Isoniazid (INH)

Thioisonicotinic-acid-amides:
 Ethionamide(Prothionamide (ETH/PTH)
 Sulphones (DDS)
 Long-acting-sulphonamides (LS)
 Trimethoprim-sulphonamide preparations (TSP)
 Ethambutol (EMB)
 Streptomycin (Sm)
 Kanamycin (Km)

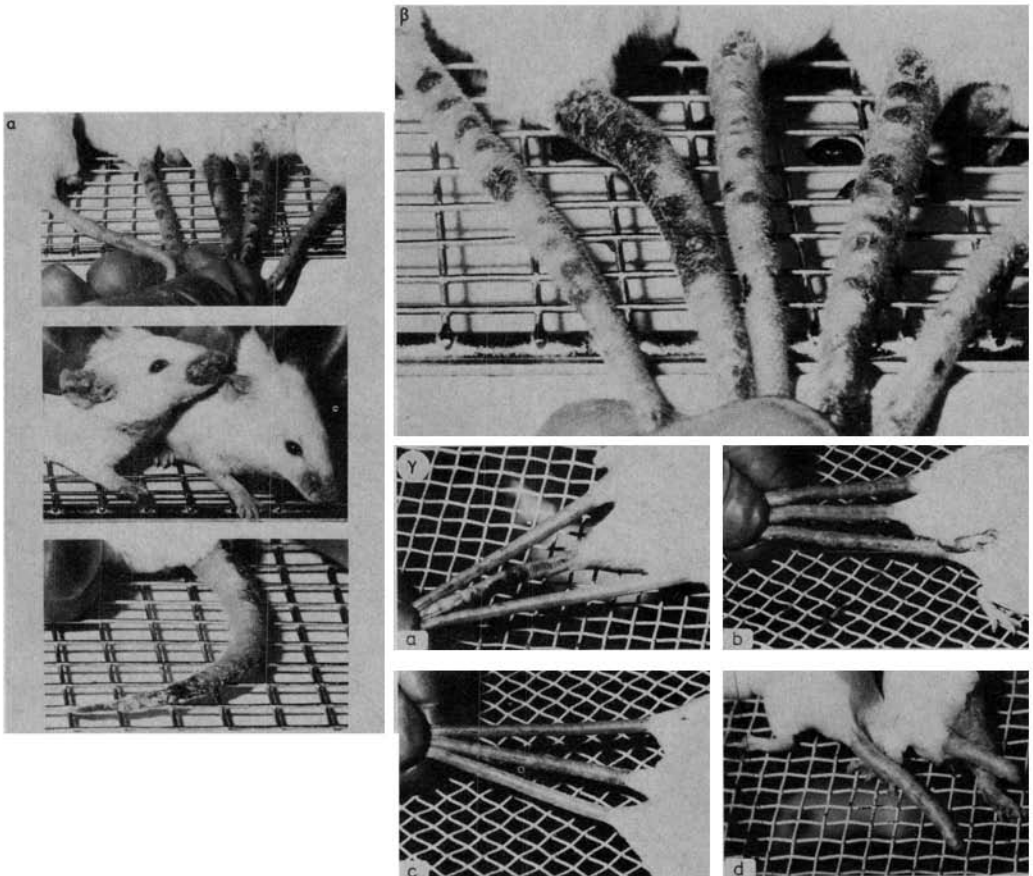


Fig. 2.

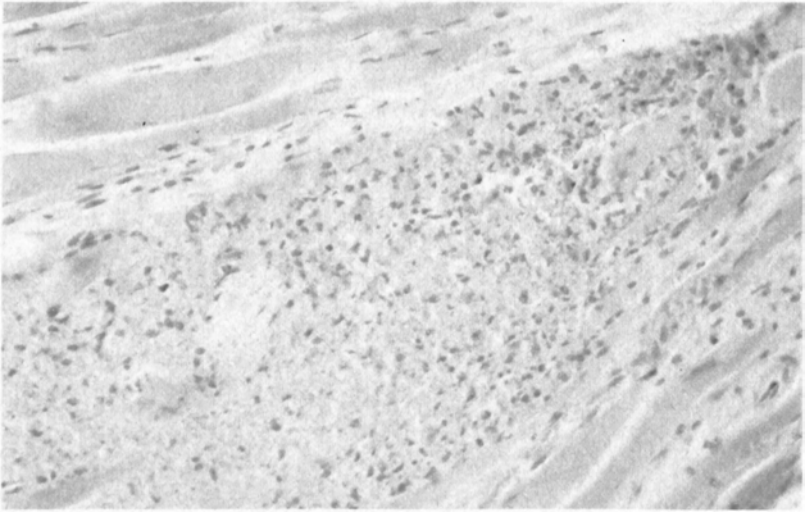


Fig. 3a.

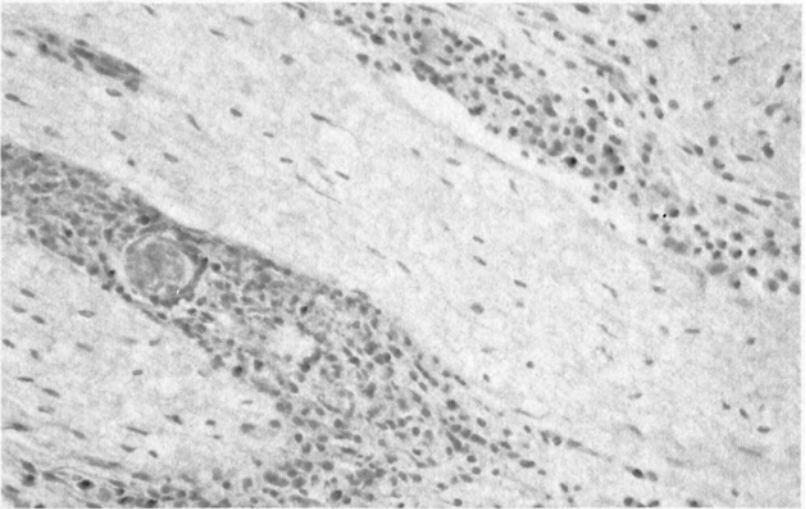


Fig. 3b.

(4) Figure 4 contains the data of a simple survival test carried out with this method (mouse-marinum). You notice the extraordinary efficacy of rifampicin depending on the dosage, which is typical for this medicament. The three substances of the sulphone and sulphonamide group do not show any particular differences. Long-acting sulphonamides, dapsons and Trimethoprim-sulphonamide combinations have practically the same effect in these trials if used in different concentrations. From this point of view dapsons is the most effective of all. Only 50 mg of dapsons are necessary to induce the same effect as 100 mg of any other sulphonamide and sulphonamide-preparation. Combined therapy is often more effective than monotherapy. A few animal experiments carried out as

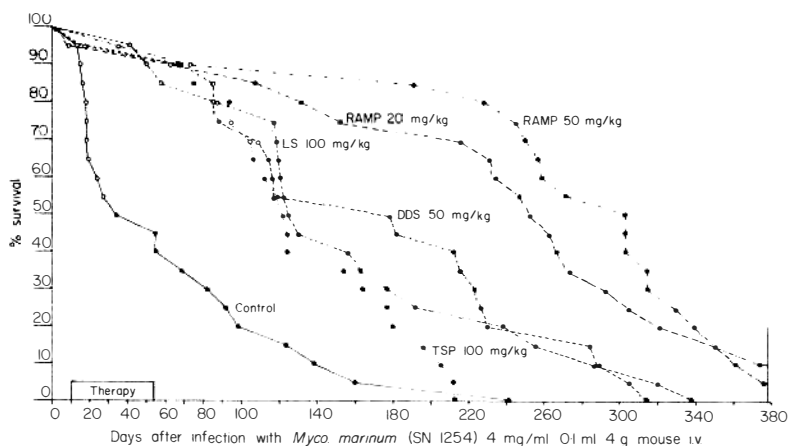


Fig. 4.

survival tests demonstrate this. Rifampicin can for instance be combined with Lamprone (B663) or ethionamide (Fig. 5(a), (b)). You notice once again that the combination is undoubtedly more effective than the single substance. But this is not always the case, not even if the substances used on their own prove to have a good effect (Fig. 5(c)).

A comparative test (Fig. 6) with *Myco. tuberculosis* (Middelburg) selected from a series of experiments demonstrates once again the great efficacy of combined treatment. Ten mg of rifampicin induce an effect which resembles that one obtained by combining isoniazid, prothionamide and dapsone (used as a fixed combination called Isoprodian and produced by Saarstickstoff-Fatol) although none of these substances used on their own in the dosage of the above mentioned combination has not even approximately the same effect as the combination. The activity of this combination can be considerably increased if rifampicin is added. A large number of experiments which cannot all be demonstrated here finally enabled us to give preference to a certain number of substances (Fig. 7). This choice was also based upon the aim that the substances to be applied in leprosy treatment should be as little toxic as possible and suitable for oral administration.

(5) Toxicity does not only depend on the chemical structure of the substance, but also on the administered dose as well as the duration of treatment. There do not exist many tests to demonstrate this. I have therefore chosen one which is not quite so common which, however, confirms very clearly my above statement:

For this sort of trial we preferably use hens, since there exist breeds today trained to lay one egg every day. These eggs are counted, and thus quantitative results can easily be obtained. Within a very short time rifampicin is capable of reducing the ovaries of these hens to such an extent that the animals are no longer able to produce eggs. At this stage of the experiment one could come to the false conclusion that rifampicin is an extremely dangerous substance. Many toxic phenomena are, however, nothing else but symptoms of adaptation. Here you can

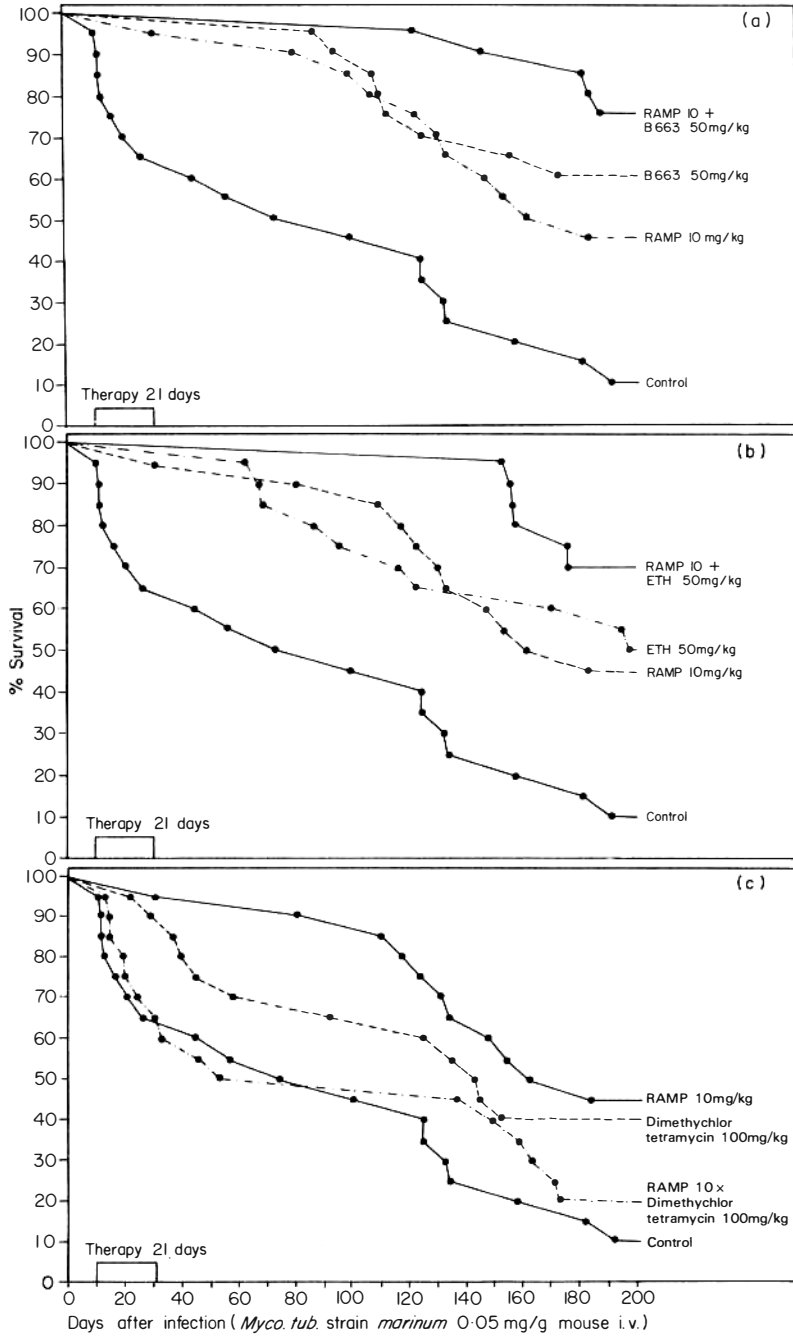


Fig. 5.

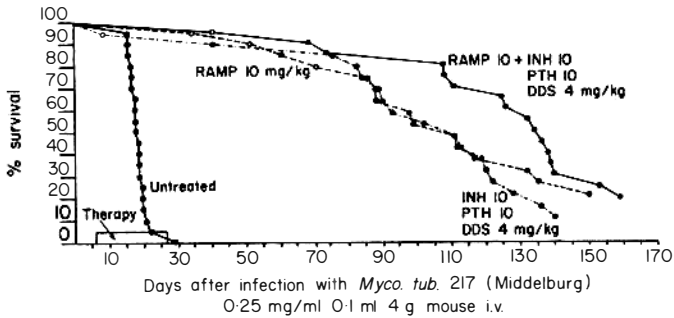


Fig. 6.

Rifampicin—Combinations for Antimicrobial Chemotherapy

**Rifampicin
(RAMP)**

- + Isoniazid (INH)
- + Sulphone (DDS)
- + Long-acting sulphonamides (LS)
- + Trimethoprim-sulfonamide-preparations (TSP)
- + Ethionamide (ETH)
- + Prothionamide (PTH)

Combined therapy preferred at present:
RAMP + Isoprodian (INH, DDS, PTH)

Fig. 7.

see a chart (Fig. 8) in which each cross represents one laid egg. Rifampicin administered at a dose of 10 mg/kg does not induce the above phenomenon, whereas 100 mg do, but only for a short time. During further administration of rifampicin the normal situation is restored. This ability of an organism to adapt itself to the toxic effect of certain substances is characteristic for many substances and is not always sufficiently taken into consideration. 500 mg of rifampicin stop the production of eggs completely, which shows that the capacity of adaptation is restricted. I therefore think very accurate tests also referring to this phenomenon of adaptation are necessary before declaring a substance as being toxic. The occasional increase of transaminases under administration of rifampicin and the anaemia-inducing effect of dapsone which is now and then encountered probably are such phenomena of adaptation. But here again the problem of dosage should not be neglected.

(6) A problem regarding *in vitro* experiments is characterized by the terms

bactericidal effect and *bacteriostatic effect*

the inexact definition of which often leads to misunderstanding. Rifampicin for example is considered to have a bactericidal effect, a property which was also

1 mg/ml <i>Myc. tub.</i> H ₃₇ Rv in saline		Subcultures (0.1 of 10 ⁶) on Löwenstein-Jensen egg-medium after washing twice								
Time of contact	Drug γ /ml	1	2	3	4	5	6	7	8 weeks	
6 days	INH	0								
		50								
		10								
		2								
	SM	0								
		50								
		10								
		2								
	EMB	0								
		50								
		10								
		2								
RAMP	0									
	50									
	10									
	2									
13 days	INH	0								
		50								
		10								
		2								
	SM	0								
		50								
		10								
		2								
	EMB	0								
		50								
		10								
		2								
RAMP	0									
	50									
	10									
	2									
20 days	INH	0								
		50								
		10								
		2								
	SM	0								
		50								
		10								
		2								
	EMB	0								
		50								
		10								
		2								
RAMP	0									
	50									
	10									
	2									

Fig. 9.

bactericidal substances only manifests itself when sufficient doses act for a long period of time. Under therapeutical conditions bactericidal substances prove to have only a bacteriostatic effect. This means that a potential bactericidal *substance* is far from being a bactericidal *medicament*. This difference must be emphasized in order to avoid false interpretation and methods of application.

Figure 10(a) and (b) show an experiment where combinations are used. Under the conditions chosen in the experiment of Fig. 10(a), neither rifampicin nor isoniazid, streptomycin, ethionamide or ethambutol are able to exert a total bactericidal effect *in vitro* if they are used as single substances. Similar negative results are obtained by combining ethionamide, ethambutol or streptomycin. The subcultures show a very heavy growth. A bactericidal effect is approached (single colonies which are countable instead of strong growth in the culture) if RAMP is used on its own, and even more if RAMP is combined with Sm or EMB.

A complete bactericidal effect is neither obtained by RAMP alone nor by RAMP + Sm and RAMP + EMB, but rather by RAMP + ETH and RAMP + INH used as double combinations. All triple combinations used in this work and containing rifampicin therefore produce a bactericidal effect as long as INH or ETH are included. A bactericidal action without these two partners can only be achieved by using the combination RAMP + Sm + EMB.

OI mg/ml H ₃₇ Rv in γ/ml drugs					(a) Subcultures (OI of 10 ³) on Löwenstein-Jensen egg-medium							(b) Subcultures (OI of 10 ³) on Löwenstein-Jensen egg-medium						
RAMP	INH	SM	ETH	EMB	2	3	4	5	6	7	8	2	3	4	5	6	7	8
1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
3	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
4	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
5	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
6	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
7	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
8	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
9	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
11	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
12	4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
13	4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
14	4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
15	4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
16	4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
17	4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
18	4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
19	4	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
20	4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
21	4	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
22	4	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
23	4	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
24	4	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
25	4	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
26	4	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

Medium: Lockemann
Time of contact 14 days
(after washing twice)

Medium: Lockemann + 4% bovine serum
Time of contact 14 days
(after washing twice)

Fig. 10.

However, this result is not simply transferable to therapeutic conditions. Already a slight approach to *in vivo* conditions results in a reduction of the anti-bacterial effect. This is demonstrated in the experiment of Fig. 10(b) which was modified only by the addition of 4% of bovine serum to the primary culture medium.

Very good results are approached by using the following substances:

1. RAMP used on its own
2. RAMP + INH
RAMP + ETH
RAMP + EMB
RAMP + Sm } used in double combinations
3. RAMP + INH + EMB
RAMP + INH + ETH
RAMP + INH + Sm
RAMP + Sm + EMB
RAMP + Sm + ETH
RAMP + ETH + EMB } used in triple combinations

In this investigation only the following combinations exert a total bactericidal effect

RAMP + INH + ETH

and

RAMP + INH + EMB + Sm

In the case of reduced sensibility it could be useful to administer quadruple combinations:

RAMP + INH + ETH + EMB
RAMP + Sm + ETH + EMB

It is thus a matter of fact that a bactericidal action can be induced *in vitro* by a potentially bactericidal substance if the latter is administered simultaneously with highly active bacteriostatics.

This example chosen from the tuberculosis field applies of course also to leprosy, but here the conditions appear to be less favourable, because the sensibility of *Myco. leprae* against those substances and combinations is probably less significant than that of *Myco. tuberculosis*. Nevertheless it can be considered as a matter of fact that well chosen RAMP combinations are more effective than RAMP on its own and that RAMP is more active than any antimycobacterial substance we have known in the past.

(7) Figure 11 shows an example for the importance of right dosage:

- (a) The action of rifampicin at a dose of 50 mg/kg cannot be improved by adding 5 mg/kg or 10 mg or 20 mg of ethambutol. The differences are not significant. This could lead to the conclusion that the activity of rifampicin cannot be improved by combination with ethambutol. This, however, would be a false interpretation.
- (b) If a very small dose of rifampicin (2 mg/kg) is combined with 5, 10, and 20 mg/kg of ethambutol, the effect of rifampicin even decreases. The choice of the wrong dose might (a) prevent the combination effect or (b) decrease the activity. When combining substances one should consider that the administration of too low doses is as dangerous as the choice of wrong proportions.
- (c) If 10 mg/kg of rifampicin are combined with 5, 10, or 20 mg/kg of ethambutol, we can notice a combination effect, an increased activity due to the administration of higher doses of ethambutol. Not all doses are suitable for combinations.

(8) Another serious problem: Can we transfer the data obtained *in vitro* or by animal experiment to our clinical work? I wish to emphasize here that this cannot and must not be done! Mice differ from guinea-pigs. Guinea-pigs differ from rabbits, and rabbits differ from humans. Each macro-organism behaves in its own way.

One needs as connecting link (Fig. 1) the determination of the serum activity in healthy persons or in patients, i.e. in human beings. *In vitro* experiments and animal experiments reveal whether a substance is effective or not and whether it induces any action in macro-organisms. But the data we require for the treatment of human beings can only be obtained by using material from human beings.

A few typical examples concerning the determination of human serum activity follow. Figure 12 shows the activity of several substances administered in monotherapy in doses applicable to human beings and used against *Myco. marinum*. Figure 13 demonstrates a determination of the serum activity of combinations. In this case the results obtained against *Myco. marinum* are juxtaposed against those obtained against *Myco. tuberculosis*. If rifampicin is combined with isoniazid, the effectiveness of rifampicin slightly decreases. By combining rifampicin with prothionamide the activity is remarkably improved. A better result is obtained if rifampicin is combined with INH and PTH. The best result is obtained by RAMP + INH + PTH + DDS. We combine rifampicin with isoniazid, with sulphones or sulphonamides or even sulphonamide combinations, with ethionamide or prothionamide depending always on the tolerance and special condition of the patient.

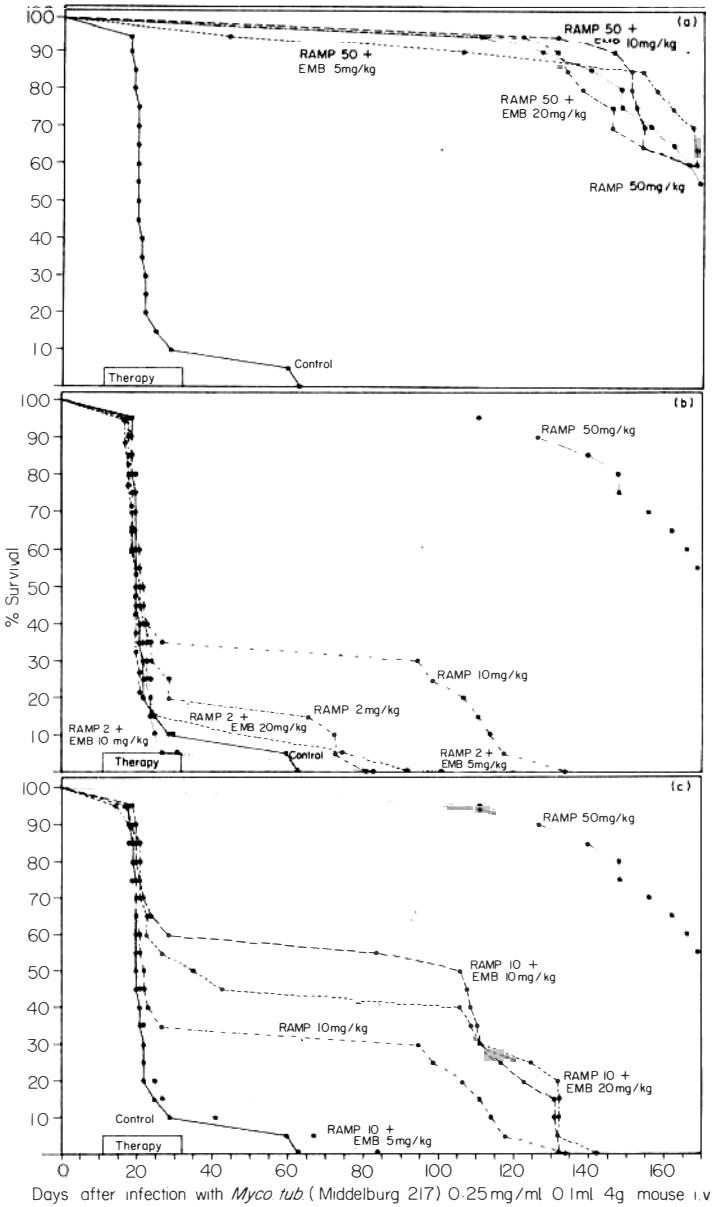


Fig. 11.

(9) To decide the question whether the above mentioned increase of the antibacterial activity of special combinations can be explained as pharmacokinetic effects or is caused by combined activities against the germ, Havel has carried out *in vitro* experiments which will be published elsewhere in detail. They offer the

<i>Myc. marinum</i> SN 1254	h	(a)							(b)						
		2	3	4	5	6	7	2	3	4	5	6	7		
Rifampicin 1 x 600mg (60 kg)	0	#	#	#	#	#	#	#	#	#	#	#	#		
	1	#	#	#	#	#	#	#	#	#	#	#	#		
	3	-	-	-	+	+	+	-	-	-	+	+	+		
	5	-	-	+	+	+	+	-	-	+	+	+	+		
	7	-	-	+	+	+	+	-	-	+	+	+	+		
	9	-	+	+	+	+	+	-	+	+	+	+	+		
	24	-	+	+	+	+	+	-	+	+	+	+	+		
Sulfamethoxyipyrazine 1st day 800mg : 200mg daily (74 kg)	0	#	#	#	#	#	#	#	#	#	#	#	#		
	1	+	+	+	+	+	+	+	+	+	+	+	+		
	3	+	+	+	+	+	+	+	+	+	+	+	+		
	5	+	+	+	+	+	+	+	+	+	+	+	+		
	7	+	+	+	+	+	+	+	+	+	+	+	+		
	9	+	+	+	+	+	+	+	+	+	+	+	+		
	24	+	+	+	+	+	+	+	+	+	+	+	+		
Prothionamide (Ethionamide) 250mg (52 kg)	0	#	#	#	#	#	#	#	#	#	#	#	#		
	1	#	#	#	#	#	#	#	#	#	#	#	#		
	3	#	#	+	+	+	+	#	#	#	#	#	#		
	5	#	#	+	+	+	+	#	#	#	#	#	#		
	7	#	#	+	+	+	+	#	#	#	#	#	#		
	9	#	#	+	+	+	+	#	#	#	#	#	#		
	24	#	#	+	+	+	+	#	#	#	#	#	#		
Bactrim 2 x 960mg 8 ⁰⁰ h 18 ⁰⁰ h (80 kg)	0	#	#	#	#	#	#	#	#	#	#	#	#		
	1	-	-	-	-	+	+	-	-	-	+	+	+		
	3	-	-	-	-	+	+	-	-	-	+	+	+		
	5	-	-	-	-	+	+	-	-	-	+	+	+		
	7	-	-	-	-	+	+	-	-	-	+	+	+		
	9	-	+	+	+	+	+	-	+	+	+	+	+		
	24	-	+	+	+	+	+	-	+	+	+	+	+		

Fig. 12.

Combinations partners	h	<i>Myc. marinum</i> SN 1254														<i>Myc. tuberculosis</i> H ₃₇ Rv													
		6 day							18 day							11 day							18 day						
RAMP 10mg/kg	0	[Detailed grid of symbols for RAMP 10mg/kg]																											
Schu	0	[Detailed grid of symbols for Schu]																											
RAMP 10mg/kg PTH 5mg/kg	0	[Detailed grid of symbols for RAMP 10mg/kg + PTH 5mg/kg]																											
Schr	0	[Detailed grid of symbols for Schr]																											
RAMP 10mg/kg INH 5mg/kg	0	[Detailed grid of symbols for RAMP 10mg/kg + INH 5mg/kg]																											
Ho	0	[Detailed grid of symbols for Ho]																											
RAMP 10mg/kg PTH 5mg/kg INH 5mg/kg	0	[Detailed grid of symbols for RAMP 10mg/kg + PTH 5mg/kg + INH 5mg/kg]																											
Mo	0	[Detailed grid of symbols for Mo]																											
RAMP 10mg/kg PTH 5mg/kg INH 5mg/kg DDS 2mg/kg	0	[Detailed grid of symbols for RAMP 10mg/kg + PTH 5mg/kg + INH 5mg/kg + DDS 2mg/kg]																											

Fig. 13.

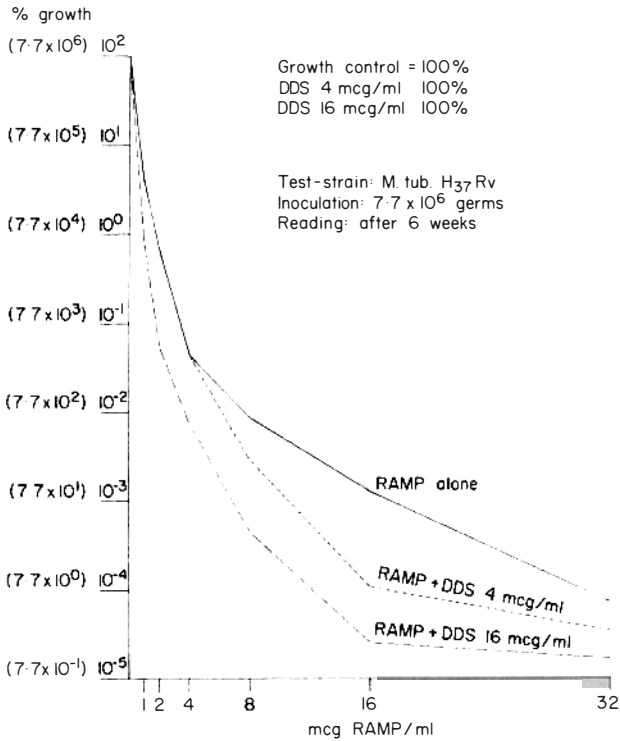


Fig. 14

advantage that each pharmacokinetic influence can be eliminated. Out of the great number of investigations I should like to present only one example (Fig. 14) where DDS alone at a dose of 4 and 16 mg revealed no antibacterial effect and where the activity of rifampicin can be increased in the presence of dapsone. This effect of increase by dapsone is dose-dependent. This phenomenon can principally be seen also at remarkably lower doses of dapsone, e.c. when administered simultaneously with rifampicin and isoniazid.

(10) May I say here a few words referring to the clinical trial as such. I think that the time has come to set an end to finding effective therapeutics by means of trials lasting for years. If systems such as the determination of serum activity are integrated correctly into the total experimental system, we can predict the efficacy of a treatment which then only remains to be confirmed by the clinical results.

(11) We assume that the diseases induced by mycobacteria are comparable in spite of clinical differences, simply through the similarity of the disease-causing microbes. Chemotherapy is a causative therapy and is, as such, always directed against the pathogenic organism. This treatment is comparatively more effective against *Myco. tuberculosis* (Fig. 13) than against *Myco. marinum* (substituting *Myco. leprae*), but nevertheless proves to be more successful than the application

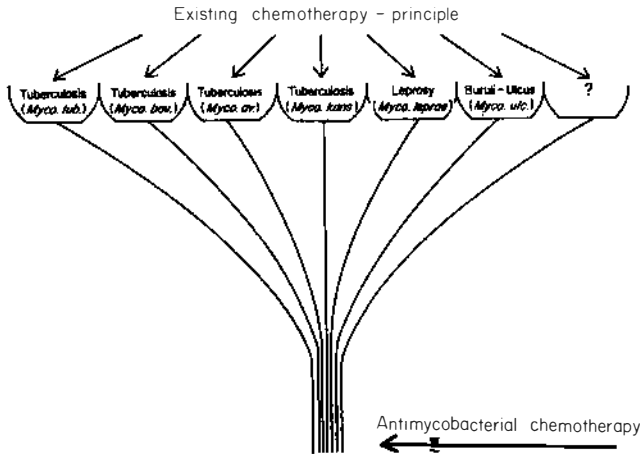


Fig. 15.

of all substances and combinations we have known up to now. We may therefore well apply this therapy with similar success against leprosy as well as tuberculosis. Our intention is to render leprosy treatment as effective, as short and at the same time as non-toxic as possible. We aim at making leprosy treatment an ambulatory treatment and try to accomplish that such a therapy will be effective not only against tuberculosis, but also against all diseases induced by mycobacteria. Figure 15 is supposed to show this in diagram. In other words: our objective is to find a universally effective antimycobacterial therapy.

Pharmacological Aspects of the Chemotherapy of Leprosy

G. A. ELLARD

MRC Unit for Laboratory Studies of Tuberculosis, Royal Postgraduate Medical School,
Ducane Road, London W12 0HS

Pharmacological and bacteriological aspects of the treatment of lepromatous leprosy with dapsone, rifampicin, clofazimine, acedapsona, long-acting sulphonamides, thiacetazone, thiambutosine and other diphenyl thioureas are considered, and the problem of preventing lepromatous patients ultimately relapsing with drug-resistant strains of *Myco. leprae* is discussed.

The chemical structures of the most important antileprosy drugs are shown in Fig. 1, together with their minimal inhibitory concentrations (MICs) against *Myco. leprae* as determined using the mouse footpad model. The part of each molecule that appears essential for antileprosy activity is shown in heavier type. Dapsone (DDS) is by far the most active antileprosy drug known, with an MIC against *Myco. leprae* of only about 0.003 $\mu\text{g/ml}$ (Ellard *et al.*, 1971; Ozawa *et al.*, 1971; Peters *et al.*, 1972). Although other sulphonamides such as sulphadimethoxine and sulphadoxine are also active, their antileprosy activity is only about a 10,000th of that of DDS (Ellard *et al.*, 1970). Acedapsona or diacetyl-DDS (DADDS) is almost certainly devoid of intrinsic antileprosy activity, but is active *in vivo* because it is deacetylated by the body to DDS (Glazko *et al.*, 1968; Ozawa *et al.*, 1971; Russell *et al.*, 1973). Rifampicin is a semisynthetic antibiotic whose synthetic side-chain is not essential for antimycobacterial activity, but conveys important pharmacological properties on the drug. Its MIC against *Myco. leprae* (Holmes and Hilson, 1972) is similar to that against *Myco. tuberculosis*. Although the minimal effective doses of thiambutosine, thiocarlide and thiacetazone required to prevent the multiplication of *Myco. leprae* in the mouse have been determined recently (Personal communication, M. J. Colston), their MICs against *Myco. leprae* have still to be established. The MIC of clofazimine against *Myco. leprae* cannot be determined because of its uneven tissue distribution (Banerjee *et al.*, 1974; Levy, 1974). Although it is highly probable that other sulphonamides will be found with significant antileprosy activity, it is very unlikely that another member of this group of compounds will be found with activity comparable to that of DDS. There is however no reason why other diphenyl thioureas with greater antileprosy activity than either thiambutosine or thiocarlide might not be found, or a more potent thiosemicarbazide than thiacetazone.

For an antileprosy drug to be effective in man, well-tolerated doses must produce tissue concentrations that at least temporarily exceed its MIC against *Myco. leprae*. The administration of each successive dose to a patient results in some viable drug-sensitive leprosy bacilli being killed and in others ceasing to

multiply. The relative importance of these two effects depends on whether the drug is primarily bactericidal or bacteriostatic. Rifampicin is primarily a bactericidal drug, but all the other antileprosy drugs appear to be basically bacteriostatic. The chief reasons for therapeutic failure when bacteriostatic drugs are used are probably irregular dosage, which results in drug concentrations falling below their MIC against *Myco. leprae* for an appreciable length of time and so enables a significant number of leprosy bacilli to multiply between doses, and relapse caused by the appearance of drug-resistant *Myco. leprae*. Hence one might anticipate that the relative efficacy of different bacteriostatic drugs in the treatment of human leprosy is related both to the duration in which concentrations greater than the MIC are maintained after giving well-tolerated doses of the drugs, and to the ratios of peak drug concentrations to the MIC. The attainment of high peak drug concentrations would however be much less important if combined treatment were being employed to minimize the likelihood of ultimate relapse with drug-resistant leprosy.

Experimental studies have demonstrated the excellent tissue penetration of DDS and rifampicin (Francis, 1953; Shepard and Chang, 1964; Keberle *et al.*, 1968; Murray *et al.*, 1974; Weddell *et al.*, 1975) and it is therefore reasonable to assume that tissue concentrations of most antileprosy drugs probably parallel their serum levels. Approximate estimates of the ratio of the peak serum concentrations to their MICs against *Myco. leprae* and the durations of coverage achieved with well-tolerated doses of the most widely used antileprosy drugs are summarized in Table 1. Dapsone, the 2 long-acting sulphonamides, rifampicin and

TABLE 1
Absorption, peak concentrations and durations of coverage achieved with well-tolerated doses of antileprosy drugs

Drug	Dose (mg)	Percentage dose absorbed	Ratio peak serum concentration to MIC against <i>Myco. leprae</i>	Duration serum concentrations greater than MIC (days)
Dapsone	50	>90	300	10
Sulphadimethoxine	1500	>90	7	4
Sulphadoxine	1500	>90	4	14
Acedapsone	225	100	16	200
<i>Rifampicin</i> ^a	600	>90	30	1
Clofazimine	300	<50	—	—
Thiambutosine	1500	10	—	?<2
Thiocarlide	2000	2	—	?<2
Thiacetazone	150	>90	—	?<2

^a Primarily a bactericidal drug; all other drugs basically bacteriostatic.

thiacetazone are all well absorbed (Keberle *et al.*, 1968; Israeli *et al.*, 1973; Ellard *et al.*, 1974). Clofazimine, thiambutosine and thiocarlide are much less water-soluble than the other drugs and are poorly absorbed in man. The extent of the absorption of clofazimine in man is very difficult to determine (Banerjee *et al.*, 1974), but there is conclusive evidence concerning the poor absorption of the diphenyl thioureas thiambutosine and thiocarlide (Ellard and Naylor, 1961; Emerson and Nicholson, 1965).

When considered from these points of view, the antileprosy activity of dapsone clearly surpasses that of all the other bacteriostatic drugs. Thus giving a single

dose of 50 mg DDS results in peak serum concentrations of approximately 300 times its MIC against *Myco. leprae* and coverage for about 10 days. By contrast much less adequate levels of antileprosy activity are attainable with the long-acting sulphonamides sulphadimethoxine and sulphadoxine and there is therefore no justification for continuing to use these drugs for the treatment of leprosy. The use of other sulphonamides would also appear unwarranted, at least until their MICs against *Myco. leprae* have been definitively established using the mouse footpad system. Acedapsone (DADDS) is without doubt the long-acting preparation of choice since a single intramuscular injection of 225 mg gives peak DDS plasma concentrations about 16 times the MIC against *Myco. leprae* and concentrations of greater than the MIC are maintained for about 200 days. Because the MICs of clofazimine, thiambutosine, thiocarlide and thiacetazone against *Myco. leprae* are not known, similar calculations are not possible for these drugs. However, from what is known of the pharmacology of the last 3 drugs in man, it is probable that bacteriostatic concentrations of these drugs are only maintained for between 1 and 2 days after giving single doses. By contrast it is possible that active concentrations of clofazimine, which is accumulated in a most remarkable way by the reticulo-endothelial system, may only be achieved after several weeks of treatment, although they may then be maintained for several weeks after stopping dosage at the end of a lengthy period of treatment.

The results of treating lepromatous patients with single drugs (monotherapy) for periods of up to 5 years will now be considered. It must be emphasized that the bacteriological assumptions on which Figs 2-5 are based are necessarily at the

Drug	Structure	M.I.C. against <i>Myco. leprae</i> ($\mu\text{g/ml}$)
Dapsone		0.003
Acedapsone	$\text{CH}_3\text{CO NH-C}_6\text{H}_4\text{-SO}_2\text{-C}_6\text{H}_4\text{-NHCOCH}_3$	Inactive converted to DDS
Sulphadimethoxine		20
Sulphadoxine		35
Rifampicin		0.3
Clofazimine		-
Thiambutosine	$(\text{CH}_3)_2\text{N-C}_6\text{H}_4\text{-NHCSNH-C}_6\text{H}_4\text{-OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	-
Thiocarlide	$(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{O-C}_6\text{H}_4\text{-NHCSNH-C}_6\text{H}_4\text{-OCH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$	-
Thiacetazone	$\text{CH}_3\text{CONH-C}_6\text{H}_4\text{-CH=NNHCSNH}_2$	-

Fig. 1. Structure and minimal inhibitory concentrations of antileprosy drugs.

best only reasonable guesses, since there is at present no data available to enable one to predict reliably either the total numbers of dead or viable leprosy bacilli, or the numbers or proportions of naturally drug-resistant mutants of *Myco. leprae* that would be likely to be present in a leprosy patient prior to treatment, or the actual degrees of resistance of such mutants.

When lepromatous patients are treated with daily doses of thiambutosine, thiocarlide, other diphenyl thioureas, or thiacetazone, an initial favourable response is seen which is similar to that encountered when DDS is given. However after 2-4 years treatment relapses occur due to the appearance of drug-resistant *Myco. leprae* (Lowe, 1954; Davey, 1960; Quyen *et al.*, 1960; Rees, 1967*a,b*; Garrod and Ellard, 1968). Possible changes in the total body population of *Myco. leprae* in a lepromatous patient treated with one of these drugs are outlined in Fig. 2. In the bacteriological model used to draw up the figure it has been

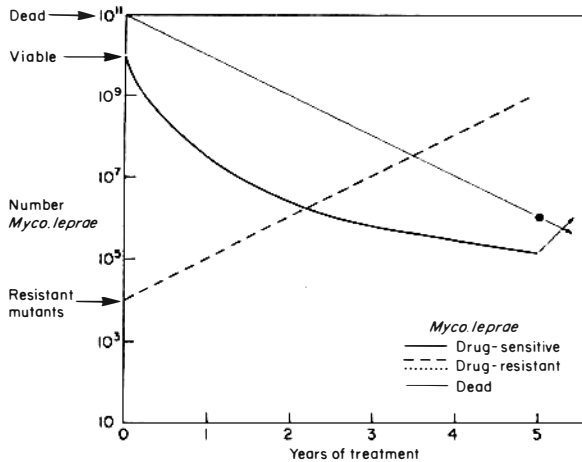


Fig. 2. Possible changes in numbers of *Myco. leprae* in a lepromatous patient treated with thiambutosine, thiocarlide or thiacetazone.

assumed that prior to treatment such a patient might harbour a population of the order of 10^{10} viable leprosy bacilli, of which 10^4 (1 in 10^6) might be naturally resistant to these drugs, as well as some 10^{11} dead *Myco. leprae*. Daily treatment with thiambutosine, thiocarlide or thiacetazone would not be expected to kill a significant proportion of viable leprosy bacilli as these drugs are primarily bacteriostatic, but should prevent the further growth of most of the drug-sensitive leprosy bacilli. The number of viable *Myco. leprae* would then be expected to fall slowly as a result of killing by the very limited cell-mediated immune response manifested against *Myco. leprae*. The drug-resistant mutants would however continue to multiply until both bacteriological and clinical relapse became apparent.

The results that might be anticipated when such a lepromatous patient is treated with 225 mg DADDS intramuscularly every 2½ months or with 50 mg oral DDS daily are illustrated in Fig. 3. The results expected with low dosage DDS treatment or by giving DDS derivatives such as sulphtrone or promin would be intermediate between those shown for DADDS and DDS. Treatment with

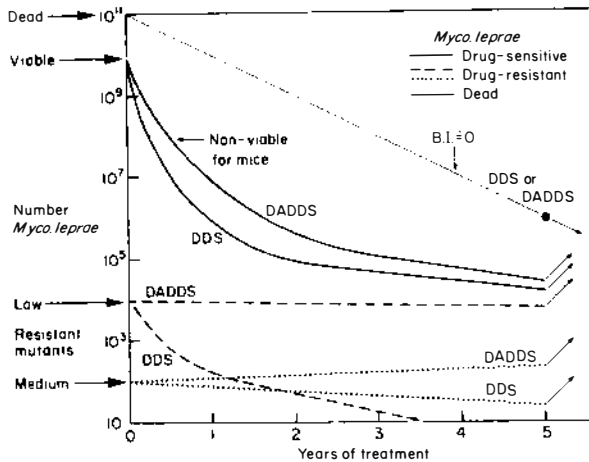


Fig. 3. Possible changes in numbers of *Myco. leprae* in a lepromatous patient treated with DDS or DADDS.

DADDS results in the numbers of viable *Myco. leprae* falling about a hundred-fold in about 6 months (3-9 months), since at this point inocula are no longer infective for mice (Shepard *et al.*, 1972). The same workers showed that when patients are treated with DDS the numbers of viable *Myco. leprae* fall more rapidly, inocula usually becoming non-infectious for mice within about 3 months treatment. These findings suggest that the continuous presence of DDS concentrations vastly in excess of its MIC against *Myco. leprae* results in DDS being partially bactericidal. Such bactericidal activity would only be expected to be displayed against a small proportion of actively growing bacilli (Then and Angehern, 1973), and against the great majority of leprosy bacilli all concentrations of DDS would probably be primarily bacteriostatic. Giving either DADDS or DDS should prevent the growth of all drug-sensitive leprosy bacilli and after the first few months of treatment the rate of elimination of *Myco. leprae* might well be similar whichever drug was given and depend principally on the extent of the cell-mediated immune response of the patient to *Myco. leprae*.

Mutants with varying degrees of resistance to DDS have been isolated from patients after prolonged treatment with DDS or other sulphonides (Rees, 1967a; Pearson *et al.*, 1968; Shepard *et al.*, 1969a). In the extremely simplistic model used as a basis for Fig. 3 it was assumed that prior to treatment there were 10^4 viable leprosy bacilli (1 in 10^6) resistant to 10 times the normal MIC of DDS against sensitive bacilli and 100 bacilli (1 in 10^8) resistant to 100 times this value. Treatment with high dosage DDS might still be expected to result in the killing significant numbers of actively-growing low-resistant mutants and to result in their elimination within 3-4 years. By contrast DADDS treatment would be purely bacteriostatic since it would result in DDS levels only slightly above the MICs of the mutants. Furthermore such DDS concentrations would be incapable of preventing the growth of mutants with medium resistance whereas their growth would still be prevented by high dosage DDS treatment.

The changes in bacterial populations of sensitive and drug-resistant *Myco. leprae* illustrated in Fig. 3 have been drawn up to take account of the length of

persistence of DDS-sensitive bacilli during treatment with high dosage DDS (Waters *et al.*, 1974), the long periods before drug-resistance becomes apparent (Meade *et al.*, 1973), the higher incidence of resistance and earlier occurrence of resistance after treatment with low dose DDS regimens, and the tendency of resistance encountered with such regimens to be of a lower level than when high dosage DDS treatment is employed (Meade *et al.*, 1973; Personal communication J. M. H. Pearson and R. J. W. Rees). Alternative bacteriological models could however also explain such findings. Thus it is possible that there may be initially only mutants with low degrees of DDS resistance and that mutants with higher degrees of resistance only arise as the result of a series of further mutations.

Whichever model one considers, one would expect continued treatment to result in the gradual selection of DDS-resistant mutants, regular treatment with high dosage DDS to be the most successful form of monotherapy, and irregular treatment with low dosage DDS to be most likely to lead to relapse occurring with the appearance of DDS-resistant *Myc. leprae*.

The fall in numbers of viable bacilli obtained during treatment with clofazimine is intermediate between the results obtained with DADDS and DDS. The fact that clofazimine-resistant strains of *Myc. leprae* have not yet been isolated suggests that the frequency of initially resistant mutants is probably less than that encountered with thiambutosine or thiacetazone. The possibility that long term treatment with clofazimine alone will also result in patients relapsing with drug-resistant *Myc. leprae* must however always be borne in mind.

The results that might be anticipated when a lepromatous patient is treated with 600 mg rifampicin a day are illustrated in Fig. 4. Several studies have shown

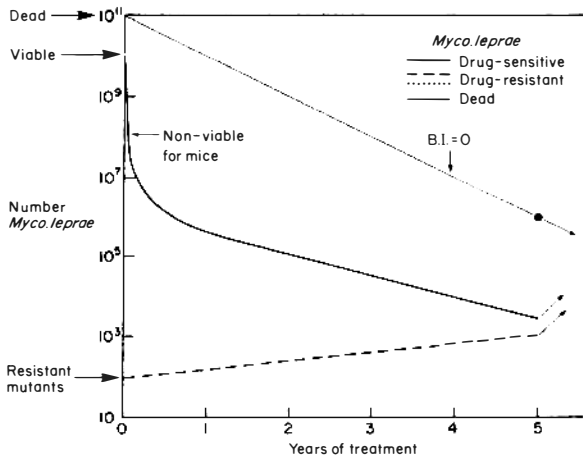


Fig. 4. Possible changes in numbers of *Myc. leprae* in a lepromatous patient treated with rifampicin.

that such treatment results in inocula no longer being infective for mice after as little as a week's treatment, indicating that in this period over 99% of the viable leprosy have been killed by the drug (Rees *et al.*, 1970; Shepard *et al.*, 1972b, 1974). Rifampicin's powerful bactericidal activity against *Myc. leprae* parallels that against *Myc. tuberculosis*. The persistence of viable rifampicin-sensitive

leprosy bacilli for periods of up to 2 years despite continued daily treatment with rifampicin indicates that a proportion of the bacterial population remain insensitive to its action (Personal communication, R. J. W. Rees and M. F. R. Waters). Again these results parallel findings with *Mycobacterium tuberculosis* where *in vitro* studies have shown rifampicin has very little bactericidal activity against non-growing organisms (Dickinson *et al.*, 1972; Awaness *et al.*, 1975). Although no case has yet been reported of a patient relapsing with rifampicin-resistant *Mycobacterium leprae*, experience in the treatment of tuberculosis suggests that the possibility of this occurring should not be dismissed.

In the past, the most widely employed form of treatment has been monotherapy with DDS or other sulphones. The most important limitations of such treatment are the great length of time required to eliminate all viable *Mycobacterium leprae* from lepromatous patients (Waters *et al.*, 1974) and the ultimate relapse of a significant proportion of patients with DDS-resistant *Mycobacterium leprae* (Meade *et al.*, 1973). The most probable causes of relapse appear to be the use of regimens giving relatively lower levels of DDS in the body and interruptions to treatment. The ideal regimen should be fully effective in all types of leprosy patients, should not result in lepromatous patients relapsing with drug-resistant *Mycobacterium leprae*, should be economical, should be free from adverse side-effects, and should be administratively convenient to supervise. Experience in the chemotherapy of tuberculosis indicates that relapse with drug-resistant organisms can be avoided by using combined chemotherapy. The most effective two-drug regimen that one can envisage at present for the treatment of leprosy patients would be to give DDS (50 mg) plus rifampicin (600 mg) each day throughout treatment. The cost of rifampicin however obviously makes such a regimen impracticable for most countries. Long-term treatment with DDS plus clofazimine would probably be unacceptable to many patients because of skin discoloration. From an economic point of view, the most feasible two-drug regimen would probably be DDS (50 mg) plus thiacetazone (150 mg) daily. Unfortunately the adverse side-effects encountered with thiacetazone are such that one could not recommend its long-term use in several areas of the world (Miller *et al.*, 1970).

Practical chemotherapy is necessarily a compromise between efficacy, cost and convenience of administration. The treatment scheme outlined in Fig. 5 represents my attempt to arrive at such a compromise. It employs as its mainstay 2 years supervised daily treatment with high dosage DDS, since DDS is still the most effective economical antileprosy drug available. In the case of lepromatous patients it is suggested that this treatment should be supplemented by the addition of 600 mg rifampicin each day during the first week. Increasing the duration of this rifampicin supplement might well reduce the ultimate chances of subsequent relapse with DDS-resistant *Mycobacterium leprae* occurring, but it would probably be better to treat a given number of lepromatous patients with a week's rifampicin rather than half the number with a fortnight's supplement. It is then suggested that after the first 2 years, treatment should be based on injections of DADDs every 3 months since this is the most reliable method of ensuring that DDS concentrations greater than the MIC against *Mycobacterium leprae* are continuously maintained in patients.

Using the same bacteriological model as that employed in drawing up the previous figures, the results obtained with such a treatment scheme might resemble those illustrated in Fig. 5. The first week's treatment under full supervision with 50 mg DDS and 600 mg rifampicin each day should reduce the

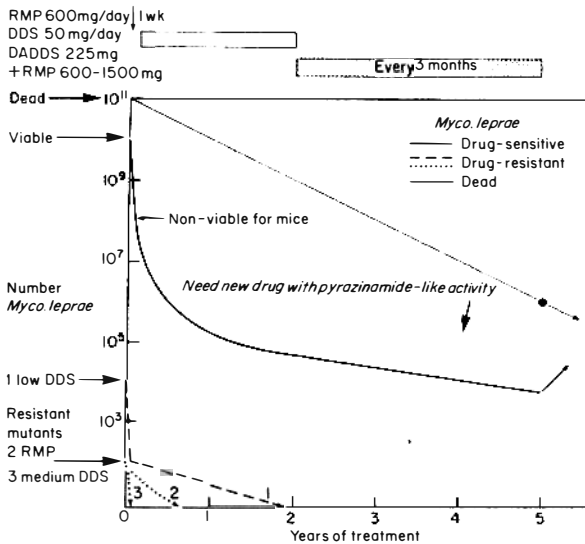


Fig. 5. Possible changes in numbers of *Myco. leprae* in a lepromatous patient treated with the suggested treatment schedule.

number of viable leprosy bacilli to less than 1% of their original total and effectively render the patient non-infectious. It should also reduce the number of mutants with low degrees of DDS resistance to a hundredth of their original number, and almost entirely eliminate rarer mutants with higher degrees of DDS resistance. During the subsequent 2 years of supervised high dosage DDS treatment one would hope that the remaining mutants of low degrees of DDS resistance and any rifampicin resistant mutants would be eliminated. During this period in-patients might receive 50 mg DDS daily and out-patients 300 mg DDS once a week. At the end of this period treatment with injections of 225 mg DADDS every 3 months should be sufficient to prevent the growth of the remaining viable *Myco. leprae*, all of which ought to be fully sensitive to DDS.

In situations where supervision of treatment is impossible to organize, chemotherapy might be based on 3 monthly injections of DADDS, supplemented by supervised dosage with 1500 mg rifampicin once every 3 months as suggested by Shepard and his colleagues (Shepard *et al.*, 1971; Shepard *et al.*, 1972*b*; Levy *et al.*, 1973), and by giving out at the same time 3 months supply of 50 mg DDS tablets for daily self-administration. Such a schedule should also help to minimize relapses caused by the emergence of DDS-resistant *Myco. leprae* even if many of the patients failed to take their oral DDS doses regularly (Ellard, *et al.*, 1974).

As has been emphasized previously, the lack of reliable data concerning the number of naturally drug-resistant *Myco. leprae* that might be anticipated in a lepromatous patient prior to treatment, precludes a proper discussion of the relative merits of different methods of treating patients in such a way as to minimize the likelihood of their ultimately relapsing with drug-resistant *Myco. leprae*. As a consequence the results of the treatment scheme illustrated in Fig. 5 are speculative. Thus it could be that the principal factor influencing the emergence of DDS resistance is not the number of DDS-resistant mutants present

at the start of treatment, but rather the extent of multiplication occurring during treatment either because of gross irregularity of drug ingestion or because some multiplication of DDS-sensitive bacilli may be able to occur despite regular DDS treatment. The best method of preventing patients relapsing through the emergence of DDS-resistant strains of *Myco. leprae* depends on which mechanism is the most important. If, as has been assumed, the number of DDS-resistant mutants present at the start of treatment is the most important factor, then the addition of rifampicin at the start of treatment is likely to be the best supplement to use. If irregularity in drug taking is more important, one should concentrate on improving methods of supervising drug dosage. If however the most important cause of resistance were the ability of a significant proportion of DDS-sensitive leprosy bacilli to multiply despite regular treatment with DDS, one would recommend prolonged treatment with 2 drugs if this were at all possible.

Unfortunately, despite the great advances in recent years in experimental leprosy, the possibility of obtaining the bacteriological data necessary to put such treatment on a sound basis in the foreseeable future is still remote. Therefore the only possible prospective approach to the problem of preventing patients relapsing with DDS-resistant leprosy is to compare the results of different treatment schemes by means of controlled clinical trials. For example if one wanted to evaluate the sort of treatment scheme outlined in Fig. 5, one might compare the results of a treatment scheme without an initial rifampicin supplement, with the same treatment scheme supplemented by either a week or a month of rifampicin treatment. Because of the many years before DDS-resistance becomes apparent and the hundreds of patients that would have to be treated to obtain a statistically significant conclusion, the whole idea of trying to make such a comparison may seem to be utterly daunting. However, as studies in the chemotherapy of tuberculosis have shown, the scope of the controlled clinical trial can be very extensive (Fox, 1971). Thus in a situation where rigid control of treatment of patients over any length of time was completely impractical, one might arrange for all lepromatous patients commencing treatment in an area to be allocated at random to the treatment scheme currently being employed and to the same treatment scheme supplemented in ways that were practical for the area in question. The supplement might consist of the addition of a week's rifampicin at the start of treatment or alternatively of 3 monthly injections of DADDs (with or without large single doses of rifampicin) given over many years. The organisational problems of such an approach are of course formidable for hundreds of patients would need to be studied and their therapeutic response followed for 10-20 years and *Myco. leprae* would have to be isolated from all patients who appeared to be relapsing and tested in the mouse footpad to establish whether they were DDS-resistant or not (Pettit *et al.*, 1966). Nevertheless, unless such comparisons are made in trials carried out with sufficient numbers of patients, the possibility of finding out whether the emergence of DDS-resistance can be prevented would seem remote.

It must be emphasized that all the approaches discussed so far would not be expected to shorten significantly the period required to cure lepromatous patients since it is apparent that neither DDS nor rifampicin are capable of killing near-dormant organisms with any speed. Among antituberculosis drugs, pyrazinamide appears to possess an almost unique ability in killing semi-dormant bacilli (Fox and Mitchison, 1975). Regrettably the evidence at present available

suggests that doses of pyrazinamide that are well tolerated in man are inactive against *Myc. leprae* (Shepard and Chang, 1964; unpublished results G. A. Ellard and M. J. Colston). Whether an analogue of pyrazinamide might be found with significant activity against *Myc. leprae* remains to be established. If such a compound could be found that was also well tolerated in man, it could conceivably lead to the possibility of curing lepromatous leprosy in a shorter time.

Acknowledgement

I should like to thank Prof. D. A. Mitchison and Dr R. J. W. Rees for their advice.

References

- Awaness, A. M., Dickinson, J. M. and Mitchison, D. A. (1975). Bactericidal activity of rifampicin and isoniazid against tubercle bacilli. *In press*.
- Banerjee, D. K., Ellard, G. A., Gammon, P. T. and Waters, M. F. R. (1974). Some observations on the pharmacology of clofazimine (B 663). *Am. J. trop. Med. Hyg.* **23**, 1110.
- Davey, T. F. (1960). Some recent chemotherapeutic work in leprosy. *Trans. R. Soc. trop. Med. Hyg.* **54**, 199.
- Dickinson, J. M., Jackett, P. S. and Mitchison, D. A. (1972). The effect of pulsed exposures of rifampicin on the uptake of uridine-¹⁴C by *Mycobacterium tuberculosis*. *Am. Rev. resp. Dis.* **105**, 519.
- Ellard, G. A., Gammon, P. T. and Harris, J. (1974). The application of urine tests to monitor the regularity of dapsone self-administration. *Lepr. Rev.* **45**, 224.
- Ellard, G. A., Gammon, P. T. and Rees, R. J. W. (1970). The minimal inhibitory concentrations of sulphadimethoxine and sulphadoxine against *Mycobacterium leprae*. *Lepr. Rev.* **41**, 223.
- Ellard, G. A., Gammon, P. T., Rees, R. J. W. and Waters, M. F. R. (1971). Studies on the determination of the minimal inhibitory concentration of 4,4'-diamino-diphenylsulphone (Dapsone, DDS) against *Mycobacterium leprae*. *Lepr. Rev.* **42**, 101.
- Ellard, G. A. and Naylor, R. F. (1961). The absorption, metabolism and excretion of 1-(p-dimethylaminophenyl)-3-(p-butoxyphenyl)-2-thiourea in man. A study using ³⁵S-labelled drug. *Lepr. Rev.* **32**, 249.
- Emerson, P. A. and Nicholson, J. P. (1965). The absorption of 4,4'-diisoamyloxythiocarbonyl (Isoxyl) using radioactive material (S.35 tagged). *Trans 24th Res. Conf. Pulm. Dis.* p. 44. Washington: Veterans Administration Armed Forces.
- Fox, W. (1971). The scope of the controlled clinical trial, illustrated by studies of pulmonary tuberculosis. *Bull. Wld Hlth Org.* **45**, 559.
- Fox, W. and Mitchison, D. A. (1975). Short course chemotherapy for pulmonary tuberculosis. *Am. Rev. resp. Dis.* **111**, 325.
- Francis, J. (1953). The distribution of sulphone in the tissues of various animals. *J. Comp. Path.* **63**, 1.
- Garrod, J. M. B. and Ellard, G. A. (1968). Appearance of resistance during prolonged treatment of leprosy with thiambutosine. *Lepr. Rev.* **39**, 113.
- Glazko, A. J., Dill, W. A., Montalbo, R. G. and Holmes, E. L. (1968). A new analytical procedure for dapsone. Application to blood-level and urinary-excretion studies in normal men. *Am. J. trop. Med. Hyg.* **17**, 465.
- Holmes, I. B. and Hilsen, G. R. F. (1972). The effect of rifampicin and dapsone on experimental *Mycobacterium leprae* infections; minimum inhibitory concentrations and bactericidal action. *J. med. Microbiol.* **5**, 251.
- Israeli, Z. H., Cucinell, S. A., Vaught, J., Davis, E., Lesser, J. M. and Dayton, P. G. (1973). Studies of the metabolism of Dapsone in man and experimental animals: Formation of N-hydroxy metabolites. *J. Pharmac. exp. Ther.* **187**, 138.
- Keberle, H., Schmid, K. and Meyer-Brunot, H. G. (1968). The metabolic fate of Rimactane in the animal and in man. *A symposium on Rimactane, Ciba.* p. 20.
- Levy, L. (1974). Pharmacologic studies of clofazimine. *Am. J. trop. Med. Hyg.* **23**, 1097.
- Levy, L., Shepard, C. C. and Fasal, P. (1973). Death of *Myc. leprae* following treatment of leprosy patients with 1500 mg rifampicin in a single dose. *Paper read at Tenth International Leprosy Congress, Bergen. 17.8.73. Abstract Int. J. Lepr.* **41**, 490.

- Lowe, J. (1954). The chemotherapy of leprosy. Late results of treatment with sulphone and with thiosemicarbazone. *Lancet* ii, 1065.
- Meade, T. W., Pearson, J. M. H., Rees, R. J. W. and North, W. R. S. (1973). The epidemiology of sulphone resistant leprosy. *Paper read at Tenth International Leprosy Congress, Bergen, 17.8.73. Abstract Int. J. Lepr.* **41**, 684.
- Miller, A. B., Nunn, A. J., Robinson, D. K., Ferguson, G. C., Fox, W. and Tall, R. (1970). A second international co-operative investigation into thioacetazone side-effects. *Bull. Wld Hlth Org.* **43.**, 107.
- Murray, J. F. Jr., Gordon, G. R. and Peters, J. H. (1974). Tissue levels of dapsone and monoacetyl-dapsone in Lewis rats receiving dietary dapsone. *Proc. West Pharmac. Soc.* **17**, 150.
- Ozawa, T., Shepard, C. C. and Karat, A. B. A. (1971). Application of spectrophotofluorometric procedures to some problems in *Mycobacterium leprae* infections in mice and man treated with dapsone (DDS), diacetyl-DDS (DADDS), and di-formyl-DDS (DFD). *Am. J. trop. Med. Hyg.* **20**, 274.
- Pearson, J. M. H., Pettit, J. H. and Rees, R. J. W. (1968). Studies on sulfone resistance in leprosy. 3. A case of "partial" resistance. *Int. J. Lepr.* **36**, 171.
- Peters, J. H., Gordon, G. R., Murray, J. F. Jr., Fieldsteel, A. H. and Levy, L. (1972). Minimal inhibitory concentration of dapsone for *M. leprae* in rats. *Int. J. Lepr.* **40**, 467.
- Pettit, J. H. S., Rees, R. J. W. and Ridley, D. S. (1966). Studies of sulfone resistance in leprosy. 1. Detection of cases. *Int. J. Lepr.* **34**, 375.
- Quyen, L. K., Buu-Hoi, N. P. and Xuong, N. D. (1960). Résultats d'un traitement antilépreux pilote par le 4,4'-diethoxycarbanilide dans un hôpital du Sud Vietnam. *Bull. Acad. natn. Méd.* **144**, 535.
- Rees, R. J. W. (1967a). Drug resistance of *Mycobacterium leprae* particularly to DDS. *Int. J. Lepr.* **35**, 625.
- Rees, R. J. W. (1967b). A preliminary review of the experimental evaluation of drugs for the treatment of leprosy. *Trans. R. Soc. trop. Med. Hyg.* **61**, 581.
- Rees, R. J. W., Pearson, J. M. H. and Waters, M. F. R. (1970). Experimental and clinical studies on rifampicin in the treatment of leprosy. *Br. med. J.* **i**, 89.
- Russell, D. A., Peters, J. H., Vincin, D. R., Scott, G. C. and Shepard, C. C. (1973). Clinical assessment at 5 years in the acedapsone (DADDS) trial in the Karimui, New Guinea. Correlation with plasma sulphone levels. *Paper read at Tenth International Leprosy Congress, Bergen, 13.8.73. Abstract Int. J. Lepr.* **41**, 486.
- Shepard, C. C. and Chang, Y. T. (1964). Activity of antituberculosis drugs against *Mycobacterium leprae*. Studies with experimental infection in mouse footpads. *Int. J. Lepr.* **32**, 260.
- Shepard, C. C., Levy, L. and Fasal, P. (1969). The sensitivity to dapsone (DDS) of *Mycobacterium leprae* from patients with and without previous treatment. *Am. J. trop. Med. Hyg.* **18**, 258.
- Shepard, C. C., Levy, L. and Fasal, P. (1972a). The death rate of *Mycobacterium leprae* during treatment of lepromatous leprosy with acedapsone (DADDS). *Am. J. trop. Med. Hyg.* **21**, 440.
- Shepard, C. C., Levy, L. and Fasal, P. (1972b). Rapid bactericidal effect of rifampicin on *Mycobacterium leprae*. *Am. J. trop. Med. Hyg.* **21**, 446.
- Shepard, C. C., Levy, L. and Fasal, P. (1974). Further experience with the rapid bactericidal effect of rifampicin on *Mycobacterium leprae*. *Am. J. trop. Med. Hyg.* **23**, 1120.
- Shepard, C. C., Walker, L. L., Van Lingham, R. M. and Redus, M. (1971). Kinetic testing of drugs against *Mycobacterium leprae* in mice. Activity of cephaloridine, rifampicin, streptovaricin, vadrine, and viomycin. *Am. J. trop. Med. Hyg.* **20**, 616.
- Then, R. and Angehern, P. (1975). Sulphonamide-induced 'Thymineless Death' in *Escherichia coli*. *J. Gen. Microbiol.* **76**, 255.
- Waters, M. F. R., Rees, R. J. W., McDougall, A. C. and Weddell, A. G. M. (1974). Ten years of dapsone in lepromatous leprosy: Clinical, bacteriological and histological assessment and the finding of viable leprosy bacilli. *Lepr. Rev.* **45**, 288.
- Weddell, A. G. M., Ellard, G. A., McDougall, A. C., Allen, B. W., Gammon, P. T., King, R. C. and Rees, R. J. W. (1975). The penetration of dapsone, rifampicin, isoniazid and pyrazinamide into peripheral nerves. *In press*.

Assessment of Treatment Procedures by Means of Bacteriological and Histological Examinations

M. ROSENFELD

Forschungsinstitut Borstel, 2061 Borstel, West Germany

The decisive criterion for assessing the value of a therapy directed towards a high antibacterial effect, must be its action on the bacteria. We use biopsies taken at monthly intervals as random sample of the patient's bacterial status. Bacillary counting is made by simultaneous examinations. As it is our aim to obtain reduction of the number of bacteria to zero, any detectable acid-fast material, whether solid, granulated bacilli or bacterial residues, is classified as "positive".

- (1) The best way of determining the quantitative decrease in the number of bacteria during therapy is by counting. We therefore apply the technique after Rees, modified by Krenzien, i.e. mycobacterial counting in the tissue homogenate of formalin-fixed biopsies. The material is stained with carbol fuchsin by heating three times. We differentiate with 4% sulphuric acid for exactly 1 minute and counterstain with malachite green. The lower measuring limit of this method is approximately 10^2 organisms/mg biopsy when the homogenate is not further diluted, and counting is performed according to the aforementioned method.
- (2) A further basis for assessing the therapeutic value is the examination of frozen sections. The sections are prepared from the same biopsy, the other part of which has been homogenized for counting. Cold staining of the section with carbol fuchsin after Pattyn reveals the best results. We differentiate with 0.1% hydrochloric alcohol or with 2-4% sulphuric acid and counterstain with malachite green or methylene blue. This technique allows an exact examination of the entire section with regard to the number of bacteria in nerves, muscles, vessels, etc. and the diagnosis of the histopathological situation. We consider this method as the most important for the decision "negative" or "positive".
- (3) Smears are collected together with the biopsies. In accordance with the Havel technique, blotting paper with carbol fuchsin is placed on the smear and heated only once; differentiation with 0.1% hydrochloric alcohol. This is a very careful technique to harvest a high number of bacteria.

The results obtained by means of these 3 methods are compared with one another for control and final evaluation. As we know from our experimental work with different mycobacteria in different macroorganisms that dead bacteria are also able to cause lengthy granulomatous processes after injection into the tissue and that the bacilli themselves can stay acid-fast, even solidly acid-fast, over a

longer period (granulation is a reactional stage of living mycobacteria), the decrease of mycobacterial mass per mg/biopsy is an important indication to the value and efficacy of a therapeutic measure. The elimination of dead material is therefore included in this criterion for the assessment of a treatment.

This method appears to be satisfactory as far as practical work is concerned. We must, however, bear in mind that mycobacteria not only vary tremendously in shape and structure, but that they are even able to lose their acid-fastness under suitable conditions and nonetheless can multiply and become acid-fast again.

We are certainly aware of the fact that the described method represents no optimal solution. But it quite reliably indicates the trend, despite occasional discrepancies between the results of the different techniques. The examples in the tables may verify this opinion.

Tables 1-3 follow on pages 55-58.

TABLE 1

A case after 2 years of treatment in the status to be discussed as "negative". Patient is not yet classified as "negative". Twenty years of pre-treatment with dapsone

Malta	30		B. J.		40		SB009	
	Serial No.		Name		Age		Pat. No.	
Date	Skin-smear		Biopsy			Histology		
	^a Ma	^b Bo	HBI	HMI	Dil.	Bact.	Remarks	Therapy
1972								
July 21	+					++		
August								
Sept. 2/30		++	5.20×10^5	16/100	1 : 2	+++		
		++	1.09×10^6	10/100	1 : 2	+++		
Oct. 28	++	++	5.58×10^4	0/28	1 : 2			
Nov.	++	+++						
Dec. 9	+	+	6.78×10^4	0/67	1 : 2			
1973								
Jan. 8	++	+++	1.48×10^3	0/20	1 : 2	++		
Feb. 3	++	+++	1.34×10^4	0/4	1 : 2	+++		
March 3/31	+		1.54×10^4	0/8	1 : 2			
	+		1.87×10^4	0/13	∅			
April 29			5.27×10^3	0/11	∅			
May 26	+	+	1.28×10^5	1/93	∅	+++		
June 23	-		2.60×10^4	1/40	∅			
July 21	-					++		
August 18	-		9.68×10^2	1/12	∅ ^d	+		
Sept. 15	+sc		2.96×10^3	1/40	∅ ^d	++		
Oct. 13	++	++	1.08×10^5	4/38	1 : 2	+++		
Nov. 10	+	+	1.67×10^3	0/16	∅ ^d	+++		
Dec. 15	+	+	3.10×10^2	0/3	∅ ^d	++		
1974								
Jan. 12	+sc		4.04×10^4	0/25	∅	++		
Feb. 9		+	2.45×10^2	0/2	∅ ^d	++		
March 9	-	+	1.61×10^4	0/20	∅			
April 6	-	(+)	7.40×10^1	1/1	∅ ^d	((+))		
May 4	-					((+))		
June 1	-		3.05×10^2	0/1	∅ ^d	+		
July 1/27	-/-		∅	∅	∅ ^d	∅		
August 24	-	+	∅	∅	∅ ^d	∅		
Sept. 21			2.16×10^2	0/1	∅ ^d	((+))		

RAMP
COMB.

a Malta
b Borstel
sc scanty

TABLE 2

A case that will require even longer than 2 years. Fourteen years of pre-treatment

Date	Skin-smear		Biopsy			Histology		Therapy
	^a Ma	^b Bo	HBI	HMI	Dil.	Bact.	Remarks	
1972								} RAMP COMB.
July						(+)		
August 4		++			1 : 2	+++		
Sept. 1/29	++		2.82×10^5	0/67	1 : 2			
	+++		3.28×10^4	0/12	1 : 2			
Oct.								
Nov. 3/21		+++	3.09×10^5	1/104	1 : 2	++		
			5.48×10^3	0/25	\emptyset^d			
Dec. 19	+	++	1.12×10^5	0/75	1 : 2			
1973								
Jan. 16	++	(+)	3.59×10^3	0/5	1 : 2	+		
Feb.								
March 1			7.13×10^3	0/4	1 : 2			
April 3	+		2.94×10^3	0/3	\emptyset			
May 2/30	--		5.32×10^2	0/1	\emptyset			
	+	((+))	2.52×10^4	0/19	1 : 2	+		
June 6	+		1.00×10^4	0/18	\emptyset			
July	+	(+)						
August	+sc							
Sept. 18	+		4.68×10^4	0/20	1 : 2	+++		
Oct. 30	+		3.05×10^3	0/21	\emptyset^d	++		
Nov. 27	+		5.48×10^3	0/25	\emptyset^d			
Dec.								
1974								
Jan. 8	+		9.38×10^2	0/9	\emptyset^d			
Feb. 5	--	\emptyset	2.08×10^2	0/3	\emptyset^d	(+)		
March 5	+	+	1.51×10^4	0/70	\emptyset^d	((+))		
April 19	--							
May 14	--		1.91×10^3	1/3	\emptyset^d	\emptyset		
June 11	+		\emptyset	\emptyset	\emptyset^d	((+))		
July 9	--		6.79×10^2	0/5	\emptyset^d	(+)		
August 6	+sc	(+)	4.17×10^3	0/12	\emptyset^d	(+)		
Sept. 3	--		9.62×10^2	0/3	\emptyset^d	((+))		

^a Malta
^b Borstel
 sc scanty

TABLE 3

A case without pre-treatment, reaching the status to be discussed as "negative" already after 1 year

Date	Skin-smear		Biopsy			Histology		Therapy
	^a Ma	^b Bo	HBI	HMI	Dil.	Bact.	Remarks	
	Malta		Serial No.	P. C. Name	37 Age	28117 Pat. No.		
1973								
July								} RAMP COMB.
August								
Sept.	+++							
Oct. 15	+		1.12×10^5	1/44	∅	+		
Nov. 12	++	++				+		
Dec. 10	+		3.48×10^4	5/44	∅	+		
1974								
Jan. 7	+		1.50×10^4	4/30	∅ ^d	+		
Feb. 4	-		∅	∅	∅ ^d	+		
March 4	+	++	1.58×10^5	3/77	1 : 2	+++		
April 1/29	+sc/-	(+)	2.03×10^3	0/20	∅ ^d	((+))		
			2.05×10^3	3/20	∅ ^d	((+))		
May 27	-		4.87×10^2	0/3	∅ ^d	((+))		
June 24	--		2.12×10^2	0/2	∅ ^d	((+))		
July 22	--		5.21×10^2	0/2	∅ ^d	((+))		
August 19	+	((+))	∅	∅	∅ ^d	((+))		
Sept. 16	--		5×10^1	0/1	∅ ^d	((+))		

a Malta

b Borstel

sc scanty

TABLE 4

A typical case with a lower number of bacteria. The reduction of the number of bacteria to zero is reached much more rapidly

Date	Skin-smear		Biopsy			Histology		
	Ma	Bo	HBI	HMI	Dil.	Bact.	Remarks	Therapy
1972								
July								
August								
Sept.								
Oct.								
Nov.								
Dec.								
1973								
Jan.								
Feb.								
March								
April								
May								
June								
July								
August 6		+	5.29×10^3	5/44	\emptyset^d	++	} RAMP	
Sept. 24		(+)	1.42×10^2	0/1	\emptyset^d			
Oct.								
Nov. 6			\emptyset	\emptyset	\emptyset^d	+		
Dec. 16			\emptyset	\emptyset	\emptyset^d	\emptyset		
1974								
Jan. 15			\emptyset	\emptyset	\emptyset^d	\emptyset		
Feb.								
March 19		\emptyset	\emptyset	\emptyset	\emptyset^d	\emptyset		
April								
May								
June								

Problems in the Design of Medium and Long-term Therapeutic Trials

D. S. RIDLEY

Hospital for Tropical Diseases, London NW1 OPE

The killing of *Myc. leprae in vivo* and its subsequent lysis are separate functions, both of which are governed by immunity. The first is also effectively achieved by chemotherapy, but it has not been shown that any of the known drugs has any effect on lysis. Any such effect is greatly outweighed by that of immunity even in lepromatous patients.

Medium and long-term drug trials in leprosy should be concerned with the general progress of the patient and the detection of relapse. It is doubtful whether there are any drugs that warrant the type of trial which is based on an assessment of bacterial lysis. Such trials are complex, time consuming and the resources available are limited. If there is any regimen that justifies such a trial present opportunities should not be wasted. In such trials the initial MI need not be a limiting factor.

I am afraid that some of the remarks I am going to make are rather obvious, even if they have not been voiced to-day already, and they will therefore be all the better for being brief. The object in bringing them up is that they raise questions which need an answer.

I refer to the problem of medium and long-term trials, that is those of more than six months duration; or rather, any trial that is designed to do more than study the effect of a drug on bacterial viability. The study of bacterial morphology combined in some cases with the more sensitive test of animal inoculation does actually test the performance of a drug in all that it can be expected to do, namely its bacteriostatic or its killing potential. This applies both to the initial effect of the drug, and also to that other acid test of its efficacy, prevention of relapse after prolonged dosage.

From the patient's point of view this leaves unresolved the important question of the lysis of bacilli, on which also hangs susceptibility to reactions. Both the killing of bacilli and their lysis are functions of immunity, though the mechanisms of the two actions are probably independent of each other. At the lepromatous end of the spectrum immunity is slight and its killing potential, if any, is greatly outweighed by drug action. But as regards lysis of bacilli it has not so far been possible to demonstrate any drug effect; and if there were any it would be heavily outweighed by the lysis due to immunity, which even in lepromatous patients is by no means negligible. Of course if one takes a drug such as rifampicin which kills bacilli perhaps two months sooner than dapsone, the rifampicin group may have the advantage over the other as regards reduction of bacilli at the end of a six

month trial, but after a year or two the two months advantage will be imperceptible and of no account.

However, the curing of the patient is a very important matter that must somehow be assessed, and so supposing it is decided to index the fall in the number of bacilli, let us look at the "natural" background against which the effect of a therapeutic agent must be viewed. By this I mean the rate of fall on existing drug therapy, which it is assumed has no effect on bacterial numbers. The figures in the table refer to the fall in the logarithmic biopsy index, which for brevity is here called Histological Index (HI), during a period of six months treatment. It seems clear that the only group which would offer a good chance for the detection of a drug effect would be the polar LL group (LLp) in which the effect of immunity is low and it is uncomplicated by reversal reactions. In the subpolar lepromatous group (LLs or LI: it avoids confusion if this and the LLp groups are both regarded as subdivisions of LL) there are about 7.5% of reversal reactions in the first six months, about 10% in the first year and more in the second year. When a reversal reaction occurs, which may not be recognized as such clinically, the fall in the HI is increased in a variable manner to about six times on average that of a polar LL patient. The effect on the BI would be similar. With the BL group the high incidence of reversal reactions and their rather unpredictable outcome would probably make any increase in the fall in the HI due to drug action very difficult to detect. Ideally, therefore, polar LL patients should be selected for this type of trial, but as they are too few in number one uses in practice a mixture of the two forms of LL, excluding BL.

TABLE 1

Percentage fall in histological index after six months treatment in 61 patients, and percentage of patients with reversal reactions

% Fall HI	LLp	LLs	BL
All cases	5.5	14	23
Cases with no reaction	5.5	12	14
Cases with reversal reaction	—	32	42
% Patients with reaction	0	7.5	33

If a new drug were unexpectedly found to have a strong effect on the rate of elimination of dead bacilli, it would of course be easy to demonstrate this. A marginal effect could only be proved by using a very large number of patients, especially if the trial were only to last six months. Unfortunately large numbers are not available, and the high drop out rate would appear to exclude the possibility of long term trials at most centres. A year seems to be the most that can usefully be envisaged. Attempts to overcome the deficiency of long stay patients by undertaking multicentre trials have so far proved disappointing in their outcome. In the recent multicentre trial of low-dose clofazimine versus dapsone, organized by Ciba-Geigy, which extended over a five year period and involved at some time or other 19 centres, only 71 suitable biopsies (35 pairs) were received at six months, and fewer thereafter. This trial produces some positive results which will be published elsewhere by Dr Th. Ahrens and colleagues. But it did not encourage the belief that the multicentre approach is an easy answer to the problems posed by this sort of trial.

My conclusions are that it is not profitable at present to attempt to measure the rate of elimination of bacilli from skin over a long period, at least at most centres, and that such a measure should not be used as a test of performance of the drugs at present available. Long-term trials should be used mainly for studies of clinical acceptability, general progress, the incidence of reactions and, in the late stage, of relapse. However, from this negative conclusion there are two positive corollaries.

(1) It is important to consider whether there are any therapeutic regimens which are worthy of a long term trial including the accurate assessment of bacterial indices. The resources throughout the world that are suitable and available for this purpose are very limited, and in view of the length of time required for such trials opportunities ought not to be wasted. Would it be useful for recommendations to be made for the guidance of any who wished to use them? Such recommendations might cover regimens considered worthy of test, if any, and possibly the protocol for a trial. In my view biopsies at stated intervals are an essential feature of such trials, for accurate classification and as the most reliable means of assessing bacterial numbers. The biopsy must extend down to the subcutis, and for the HI to be useful the granuloma in the initial biopsy must cover at least a quarter of the dermis in the section.

(2) As the bacteriostatic or bactericidal action of drugs appears to be altogether separate from the mechanism of their lysis and resorption, there is no point in stipulating a certain level of MI for trials concerned with the rate of lysis, although patients ought not to have received much treatment. It is the stipulation of a certain MI that is the cause of the exclusion of many otherwise suitable cases. The two sorts of trial ought to be regarded as separate.

Immunological Agents

The situation as regards the therapeutic testing of immunological agents such as lymphocytes and transfer factor is quite different from that of testing drugs. It would be hoped that immunological agents would not only increase the rate of bacterial lysis, but would also bring about an upgrading of immunity within the spectrum. Reactions therefore would be something to look for, instead of being a complicating factor. From this point of view the subpolar LL group would be perhaps the most useful, since patients in this group show some potential for upgrading; and at the same time the incidence of upgrading reactions on ordinary drugs is sufficiently low to make any significant increase due to an immunological agent readily detectable.

Chemotherapeutic Trials in Patients with Non-Lepromatous Leprosy

JOHN M. H. PEARSON

*Medical Research Council Leprosy Project,
All-Africa Leprosy and Rehabilitation Training Centre (ALERT)
Addis Ababa, Ethiopia*

The only way to determine whether a leprosy patient is cured is to discontinue anti-leprosy treatment and continue follow up to see if his disease recurs. Trials of this type are required in non-lepromatous leprosy: their aim should be to determine, in different types of leprosy, the minimum period of treatment required to give an acceptable relapse rate. Such trials may also serve to identify promising new drugs or drug combinations for the treatment of lepromatous leprosy, for a regime which shortens the time required to cure lepromatous leprosy may be expected to reduce the relapse rate in non-lepromatous cases.

For the past 15 years or so it has been largely assumed that drug trials should be carried out only on patients suffering from lepromatous leprosy (Waters *et al.*, 1967). The purpose of this paper is to re-examine this axiom, and suggest that for certain purposes it is essential to undertake drug trials in non-lepromatous leprosy.

At the most basic level, the following information is required about any drug for use against leprosy:

(1) Does it kill *Mycobacterium leprae*?

This information should be obtained primarily from experimental infections in the mouse footpad. Short term (about 6 months) pilot trials, assessing chiefly the bacillary kill, will confirm the footpad findings (Rees, 1971). For such trials patients with lepromatous leprosy are required.

(2) What are the complications during treatment?

In the case of leprosy, this means primarily the reactions: how frequent, how severe, what relationship to drug dosage, and what is the comparison with a "Standard" regime. The reactions in leprosy vary very greatly in type and severity according to the classification of the disease (Ridley, 1969); therefore such trials must include patients suffering from all types of leprosy. These studies should continue for as long as patients are liable to develop reactions—probably about five years on average, though less in tuberculoid cases, and longer in lepromatous. Such trials will also serve to evaluate drug toxicity.

(3) Does the drug cure leprosy, and if so how long does it take?

The only way to see if a patient is cured is to stop treatment and see if the patient relapses. Such trials clearly require patients with all types of leprosy, and their duration will depend on the classification. The aim will be to determine, in each type of leprosy, the shortest period of treatment which will bring about an acceptable relapse rate.

When these three requirements are set against our knowledge of drug therapy in non-lepromatous leprosy, it is clear that much work remains to be done. There is little information on the relationship of particular drugs or dosages on the incidence, severity or duration of reactions; and no systematic study has been made of the relapse rates following various periods of treatment in different types of leprosy. It appears, then, that in non-lepromatous leprosy (i.e. for at least three-quarters of leprosy patients) we do not know what drug to use, in what dosage, or for how long. After a quarter of a century of experience with dapsone, this is unsatisfactory.

Drug trials in non-lepromatous leprosy are therefore urgently required, to give accurate information on optimal practical drug regimes. There is, however, a further application for such trials, namely, to use non-lepromatous leprosy as a model to study the therapy of lepromatous leprosy. This application can be clearly seen when applied to the problem of "persisting" bacilli.

Probably the most serious problem of therapy in lepromatous leprosy is the time that is required to cure a patient. Even after many years of treatment with adequate doses of dapsone or other drugs, patients are liable to relapse when treatment is stopped. In such cases, bacilli must have survived anti-leprosy treatment; these bacilli are usually drug sensitive, for relapse cases normally respond *satisfactorily* to treatment with the original drug. It is the prolonged survival of these persisting bacilli which makes it necessary to continue dapsone treatment in lepromatous leprosy for decades rather than years. Any drug or drug combination which shortens the time required to cure leprosy must do so by virtue of an action on these persisters.

Persisting bacilli can be demonstrated in peripheral nerve, and smooth and striated muscle, in patients with lepromatous leprosy, as well as in skin (Waters and Rees, in preparation). These sites are probably not the only ones. However, the numbers are on the edge of detectability even with the most sensitive techniques available, and it is most unlikely that it will be possible to isolate "persisters" from patients under treatment for non-lepromatous leprosy: there will be too few bacilli. Nevertheless, the fact that there is a significant relapse rate in borderline and tuberculoid leprosy even after 2 years of effective chemotherapy (long enough to cure most cases of pulmonary tuberculosis) indicates that persisters are to be found even in these types of leprosy.

Direct study of persisters in lepromatous leprosy is difficult and in non-lepromatous leprosy probably impossible; but in all types of leprosy they can be studied indirectly, for if a patient relapses after a course of treatment, viable bacilli must have persisted. A few such cases will, no doubt, be due to reinfection; but the majority will be recurrences of the original infection. However, studies of this type in lepromatous leprosy would require a time scale of 2 decades (10 years at least of treatment, 10 years of follow up) and it is clearly desirable that the benefits of a new drug or drug combination should be demonstrated more rapidly than this.

It is likely that this could be achieved if non-lepromatous leprosy were used as a model for lepromatous. Persisting bacilli, with consequent relapse, are to be found in all types of disease, and it seems unlikely that the greater degree of cell mediated immunity to be found at the tuberculoid end of the spectrum will affect the results of a comparative trial of standard versus new therapy. Subpolar tuberculoid patients would probably prove most suitable for such a trial. The relapse rate after about 2 years of standard treatment might well be in the order of 10%, and the majority of these relapses would occur in the first 2 years after stopping treatment. Any drug which acted on persisters (and so had a chance of reducing the time required to cure lepromatous leprosy) would significantly reduce the relapse rate in these non-lepromatous cases.

There is, of course, no certainty that a drug or drug combination which reduced the relapse rate in tuberculoid cases would do so in lepromatous leprosy. But it is hard to conceive that a regime which failed to alter the relapse rate in tuberculoid cases would have any effect in lepromatous leprosy, in which cell mediated immunity is virtually absent. The attraction of this type of study is that it suggests a rational means of determining, in a reasonable period, whether any new therapy is likely to shorten the time required to cure lepromatous leprosy. The method deserves trial.

References

- Rees. (1971). The impact of experimental leprosy in the mouse on leprosy research. *Int J. Lepr.* **39**, 201-215.
- Ridley. (1969). Reactions in leprosy. *Lepr. Rev.* **40**, 77-81.
- Waters, Rees and Sutherland. (1967). Chemotherapeutic trials in leprosy. 5. A study of methods used in clinical trials in lepromatous leprosy. *Int. J. Lepr.* **35**, 311-335.

2. Current Concerns in the Chemotherapy of Leprosy (A) Monotherapy

Viability of *Myco. leprae* in the Skin and Bone Marrow of Patients with Lepromatous Leprosy While on Dapsone or Lamprene

A. B. A. KARAT

St. Catherine's Hospital, Birkenhead, U.K.

The pattern of killing of *Myco. leprae* in the skin and bone marrow of untreated lepromatous leprosy patients was studied after initiation of specific treatment with dapsone 100 mg daily (5 patients) as compared with clofazimine 100 mg daily (5 patients). It was found that while both clofazimine and dapsone appear to be equally effective in killing *Myco. leprae* in the skin, bacilli remained viable in the bone marrow long after they ceased to be viable in the skin, in 4 patients (2 on dapsone and 2 on clofazimine) after 720 days. The implications of this in relation to relapse/recrudescence are discussed, and the usefulness of the mouse model in providing information of value to the clinician is emphasized.

Introduction

It has been fairly widely accepted that *Myco. leprae* multiply better in the cooler parts of the body. The persistence of *Myco. leprae* in the reticulo-endothelial system (e.g. liver and bone marrow) after their disappearance from the skin casts some doubts on this hypothesis (Karat, 1966; Karat *et al.*, 1971). It was further demonstrated that *Myco. leprae* in the liver and bone marrow were not effete organisms but viable and able to multiply in the footpads of mice.

A prospective study was therefore undertaken to determine the pattern of killing of *Myco. leprae* in the skin and bone marrow of untreated lepromatous leprosy patients after initiation of specific treatment with dapsone 100 mg daily and compare it with patients on Lamprene 100 mg daily.

Materials and Methods

Consecutive patients with untreated lepromatous leprosy and B.I. more than 3+ (Ridley, 1964) were randomly allocated to 2 therapy groups:

- I To receive 100 mg dapsone daily orally
- II To receive 100 mg Lamprene daily orally.

Skin biopsy and bone marrow aspiration were obtained on day "0" and every 90 days thereafter for two years. The skin biopsy and bone marrow aspirate were homogenized in the usual way to obtain *Myco. leprae* in suspension and 5000 *Myco. leprae* were inoculated into the hind footpads of thymectomized C.B.A.

mice. These mice were harvested at regular intervals and harvest counts of *Myco. leprae* were obtained.

Of the 15 patients who entered the study 5 dropped out and results presented here in relation to the remaining 10 patients (5 on dapsone and 5 on Lamprene).

Results

Dapsone treated patients

The viability of *Myco. leprae* in the skin and bone marrow aspirate of dapsone treated patients is shown in Table 1.

TABLE 1
*Viability of Myco. leprae in skin and bone marrow
of dapsone treated patients*

No. of days	I		II		III		IV		V	
	S ^a	BM ^b	S	BM	S	BM	S	BM	S	BM
0	+	+	+	+	+	+	+	+	+	+
90	-	+	+	+	+	+	+	+	-	+
180	-	+	-	+	+	+	-	+	-	+
270	-	-	-	+	-	+	-	+	-	+
360	-	-	-	+	-	+	-	+	-	+
450	-	-	-	-	-	+	-	+	-	+
540	-	-	-	-	-	+	-	+	-	+
630	-	-	-	-	-	+	-	-	-	+
720	-	-	-	-	-	+	-	-	-	+

^a S = skin.

^b BM = bone marrow.

Between 90 and 270 days (3 to 9 months) *Myco. leprae* in the skin were non-viable in the footpads of mice. The *Myco. leprae* from bone marrow remained viable in 2 cases at the end of 2 years; in one they were non-viable at 9 months, in another at 15 months and in the third at 21 months.

Lamprene treated patients

The viability of *Myco. leprae* in the skin and bone marrow aspirate of Lamprene treated patients is shown in Table 2.

Myco. leprae in the skin became non-viable in 180 to 360 days (6 to 12 months) and those in the bone marrow aspirate in 3 cases at 360, 450 and 540 days (12, 15 and 18 months) respectively. In 2 cases they remained viable at the end of 2 years.

Comments

Both Lamprene and dapsone appear to be equally effective in killing *Myco. leprae* in the skin of lepromatous leprosy patients when administered orally in a

TABLE 2
*Viability of Myco. leprae in skin and bone marrow
of Lamprene treated patients*

No. of days	I		II		III		IV		V	
	S	BM	S	BM	S	BM	S	BM	S	BM
0	+	+	+	+	+	+	+	+	+	+
90	+	+	+	+	+	+	+	+	+	+
180	-	+	-	+	+	+	+	+	-	+
270	-	+	-	+	+	+	-	+	-	+
360	-	+	-	+	-	+	-	-	-	+
450	-	-	-	+	-	+	-	-	-	+
540	-	-	-	-	-	+	-	-	-	+
630	-	-	-	-	-	+	-	-	-	+
720	-	-	-	-	-	+	-	-	-	+

dose of 100 mg daily. The leprosy bacilli in the skin of lepromatous leprosy patients appear to be very sensitive to orally administered dapsone and Lamprene.

By contrast *Myco. leprae* in human bone marrow appear to be relatively refractory to orally administered dapsone and Lamprene, remaining viable in the bone marrow long after they have ceased to be viable in the skin. This could be either due to the inaccessibility of *Myco. leprae* in the bone marrow to the action of these drugs or because the drugs do not attain the required lethal level of concentration in the bone marrow. The latter is not the case as far as dapsone is concerned since the blood level of dapsone and the level of dapsone in the bone marrow aspirate were comparable in these patients. On the other hand it is conceivable that the environment of the bone marrow may be more conducive for the multiplication of *Myco. leprae* despite the known higher temperature of the bone marrow in man.

If in fact *Myco. leprae* not only persist in the bone marrow longer than in the skin but also remain viable in the bone marrow longer than in the skin, this has far-reaching therapeutic and clinical significance. These "persisters" among *Myco. leprae* in man could explain the rather high rate of relapse/recrudescence of leprosy among bacillated types of leprosy patients following premature cessation of specific therapy. Thus prolonged uninterrupted specific therapy becomes mandatory in bacillated types of leprosy in order to reduce the possibility of relapse/recrudescence of leprosy. The problem of persisters also raises a query as to the merits of monotherapy and polytherapy of leprosy with 2 or more drugs given simultaneously. Further longitudinal studies along these lines are indicated.

Once again the footpads of mice have provided very valuable information regarding the behaviour of *Myco. leprae* in man, which enables the clinician to make rational therapeutic decisions.

Acknowledgements

This work was sponsored by Radda Barnen, Stockholm and Ciba-Geigy, Basle. I am grateful to Mr Rajan Albert for technical assistance and all the junior doctors who have worked in my department and assisted me in obtaining specimens from the patients and in the continuing care of these patients.

References

- Ridley, D. S. (1964). Leprosy in Theory and Practice 2nd ed. (Eds. R. G. Cochrane and T. F. Davey) p. 620. Bristol: John Wright & Sons Ltd.
- Karat, A. B. A., Job, C. K., Rao, P. S. S. (1971). *Brit. med. J.* 1, 307.
- Karat, A. B. A. (1966). *Int. J. Lepr.* 34, 415.

Effect of Mono Treatment and Combined Treatment on the Morphology of *Myco. leprae* in the Skin

D. L. LEIKER

Royal Tropical Institute, Amsterdam

A study is made of the effect of clofazimine, of rifampicin, of a combination of rifampicin with isoniazid and sulphamethoxy-pyrazinamide and of a combination of rifampicin with tri-methoprim-sulphonamide and prothionamide, on the morphology of *Myco. leprae* in foamy cells, in arrectores pilorum muscles, in blood vessel walls, and in nerves in the skin of patients with lepromatous leprosy. The method of assessment was by blind examination of serial biopsies, taken each time from the same lesion.

At the onset of the trial the percentage of granular bacilli was, on the average, 14.3% lower in blood vessel walls, 8.3% lower in arrector pilorum muscle and 8.1% lower in nerves, than it was in foamy cell infiltrates. Occasionally higher percentages of granular bacilli were found in muscle or nerve, and this was related to previous treatment.

After 1-2 months of treatment, with all drug regimens, the percentages of granular bacilli increased markedly, not only in the foamy cell infiltrates, but also proportionally in smooth muscle and nerve.

After 1-2 years of treatment in most patients all or nearly all bacilli had become granular, with no significant differences between the percentages in foamy cell infiltrates, smooth muscle and nerve.

The effect of clofazimine was slower than of the other drug regimens.

No significant difference was found between the group of patients treated with rifampicin and those treated with a combination of rifampicin with other drugs. The finding of 99% granular bacilli in several patients treated for 1-2 years indicates that none of the drug regimens had produced complete clearance of viable bacilli. Even if only 1% of the non granular bacilli is viable, in a lepromatous patient with a load of bacilli of 10^{10} , a granularity index of 99% means that 10^6 viable bacilli are still present.

The method used is not regarded as sufficiently sensitive for excluding the possibility that even in patients with counts of 100% granular bacilli complete clearance of viable bacilli has been achieved. The rapid and good response of bacilli in muscle and nerve in the skin to all drug regimens suggests that these sites are not the only or the most important sites of therapy-resistant bacilli. Other sites, e.g. large peripheral nerves, bone marrow and internal organs should be investigated. One patient treated with the combination supposed to have the highest bacteriocidal activity (rifampicin-*cusaprim*-*ethionamide*), absconded after 4 months of treatment and relapsed after a period of 2 years without treatment, indicating that not all viable bacilli were eliminated. In this patient in a biopsy of an old lesion large numbers of bacilli were present, but all bacilli were granular, whereas in the new relapse lesions a high percentage of non-granular bacilli was found. This suggests that the relapse was not due to survival of bacilli in old skin lesions, but to therapy resistant bacilli at other sites.

Introduction

The presence of *Myc. leprae* in the smooth muscle of blood-vessels was first reported by Nishiura (1960) and the presence of *Myc. leprae* in arrectores pilorum muscles was reported by Neves (1961). Harman (1968) found that *Myc. leprae* in smooth muscles may stain less irregularly than the bacilli in the surrounding infiltrate. Leiker (1969) had found in skin biopsies morphologically intact bacilli in smooth muscle in treated lepromatous patients long after all bacilli in smears had become granular, occasionally even after smears had become bacteriologically negative. It was thought that these bacilli might be the origin of relapses.

It was also noticed that the bacilli located within smooth muscle cells do not elicit a reticulo-endothelial cellular response, in contrast with the interstitial myositis seen in some lepromatous patients. The absence of a lymphocytic reaction suggests immunological incompetence. It is possible that the bacilli are only very feebly metabolically active and that therefore drugs which normally interfere with metabolic processes do not effect the "dormant" bacilli (Leiker, 1971). In a previous article (Leiker *et al.*, 1973) the effect of rifampicin and a combination of rifampicin with other drugs on the Bacterial Index (BI) was compared. No significant difference was found. The BI decreased by about 1+ per year with both regimens. In the present study of 4 groups of patients with different drug regimens a comparison is made of the morphology of *Myc. leprae* in foamy cell infiltrates, smooth muscle tissue of arrectores pilorum muscles and blood-vessel walls, and in nerve twigs in the skin.

Material

Group I consisted of 6 lepromatous patients treated with clofazimine, to begin with 100 mg daily, in some patients followed by 100 mg every second day.

Group II consisted of 7 lepromatous patients treated with 600 mg rifampicin daily.

Group III consisted of 7 lepromatous patients treated with 600 mg rifampicin, 400 mg isoniazid and 200 mg sulfamethoxyprazine daily (triple I).

Group IV consisted of 4 lepromatous patients treated with 600 mg rifampicin, 1000 mg trimethoprim-sulfonamide (eusaprim) and 250 mg ethionamide or prothionamide daily (triple II). Freerksen had found that in mouse experiments with *Myc. marinum* these combinations of drugs were more active than the single drugs alone. All patients were highly bacilliferous lepromatous patients with BI 6+ and with at least 20% non-granular bacilli at the onset of the trial.

Method

In each patient serial biopsies were taken each time from the same skin lesion. The Granularity Index (GI) was calculated by one investigator. All readings were made blindly.

Because it is less difficult to distinguish between granular and fragmented bacilli than between completely solidly stained and slightly fragmented bacilli, the percentage of granular bacilli (GI), instead of the percentage of solid bacilli (MI) was recorded.

Results

In some biopsies no arrectores pilorum muscle was present and in others no bacilli were found in the muscle. In sections from biopsies taken at the onset of the trial of the 12 patients, however, bacilli were present in arrectores pilorum muscle, blood-vessel wall and nerve, in addition to bacilli in foamy cell infiltrates. In half of these patients the GI in the first 3 tissues was on the average 25% lower as compared with the foamy cell infiltrates. In 2 other patients on the average 14% less granular bacilli were seen in blood-vessel wall and nerve, but 11% more granular bacilli in arrectores pilorum muscle. In 1 other patient 14% less granular bacilli were found in blood-vessel wall, but 31% more granular bacilli in arrectores pilorum muscle and nerves. In the remaining 3 patients the granularity index was on the average 9% lower in the infiltrates as compared with the other tissues. In all 12 patients the average GI was 14.3% lower in blood-vessel wall, 8.3% lower in arrectores pilorum muscle, and 8.1% lower in nerve, as compared with foamy cell infiltrates. These figures confirmed that in general higher percentages of non granular bacilli are found in smooth muscle and nerves but also that there are exceptions, probably related to previous treatment.

In the group of patients treated with Lamprene (Table 1), after 3–6 months of treatment the GI in all patients had significantly increased. The increase in GI was seen in the foamy cells as well as in smooth muscle and nerve tissue. Three out of 6 patients, however, failed to reach a high GI; not only in muscle and nerve, but also in foamy cells.

After 1–2 years of treatment in nearly all patients the GI had reached 100% or nearly 100%. In only 1 patient (no. 3) a significant number of non granular bacilli was found in blood-vessel wall after 2 years of treatment.

In the group of patients treated with rifampicin (Table 2), after 3 months of treatment all patients but 1 showed a high granularity index in foamy cells as well as in the other tissues. In 1 patient presenting low GI's the treatment had been temporarily interrupted. The effect of rifampicin on the morphology of *Mycobacterium leprae* was more rapid than that of clofazimine, as expected. After 12–24 months of treatment in nearly all patients the GI reached 100% or nearly 100%, in foamy cells as well as in smooth muscle and nerves.

In the group of patients treated with triple combination I (Table 3), after 3 months of treatment 2 out of 7 patients, and after 9 months of treatment 1 out of 7 patients still showed a relatively low GI. After 1–2 years of treatment in all patients the GI had become 100% or nearly 100%, in foamy cells and in smooth muscle and nerves. No significant difference was found between this group and the group of patients treated with rifampicin alone.

In the group of patients treated with triple combination II (Table 4), after 3 months of treatment in all patients the GI had reached 100% or nearly 100%. There is no significant difference with the group of patients treated with rifampicin alone.

One patient of group 4, after a period of 4 months of treatment, absconded and was seen again after a period of nearly 2 years without treatment, with a clinical and bacteriological relapse.

In this patient, male, 46, lepromatous leprosy with a Mitsuda reaction of 0 mm, treatment was started in 1962 with 600 mg DDS weekly for 1 year, followed by 400 mg DDS weekly for 4 years, 600 mg DDS for 2 years and 400 mg DDS weekly for 1 year. The BI decreased from 6+ in 1962, to <1+ in 1968 and in

1969 no bacilli were found in a biopsy specimen. In 1971 a clinical and bacteriological relapse was seen, thought to be due to sulphone resistance. This was confirmed by mouse footpad tests.

Treatment was resumed with 600 mg rifampicin daily combined with 1 g eusaprim and 500 mg ethionamide daily. After 2 months of treatment the GI had increased from 47% to 98% and after 4 months of treatment to 99%. Thereafter the patient absconded and no treatment was taken. Two years later, after relapse of the disease, 2 biopsy specimens were taken, 1 from an old lesion and 1 from a new lesion. In the first specimen a high BI was found, but all bacilli were granular. In the second specimen a high BI was found as well, but a high percentage of the bacilli were non granular.

Discussion

The results obtained after 12–24 months of treatment show that all drug regimens are not only active on bacilli in foamy cells, but also on bacilli in smooth muscle and nerves. Apparently most bacilli in these tissues are less “dormant” than it has been assumed.

Apart from a slight delay in increase in GI's in smooth muscle and nerve, as compared with foamy cells, the morphological changes are correlated. After 1–2 years with all drug regimens in nearly all patients and at all sites investigated the GI had reached 100% or nearly 100%. In all groups however, a few patients showed a GI of slightly less than 100%. If in a lepromatous patient with a bacterial load of 10^{10} bacilli, the granularity index is 99%, and if only 1% of the non-granular bacilli are viable, it means there are still 10^6 viable bacilli present.

The relapse seen in a patient treated with triple combination II shows that a short course certainly is not sufficient for eliminating all viable bacilli. The fact that after 1–2 years of treatment with rifampicin or with the combination of rifampicin with other drugs in some patients still 1–2% non-granular bacilli were found, indicates that even after 1–2 years viable bacilli may still be present.

The method of assessment, apart from being very time consuming, is not regarded as sufficiently sensitive for accurate evaluation of the sterilizing effect of drugs. Even if in all sections of a biopsy specimen, in foamy cell infiltrates, smooth muscle and nerves 100% granularity of the bacilli is found, the presence of persistent viable bacilli at other sites is not excluded.

The rapid increase in the percentage of granular bacilli in smooth muscle and nerves in the skin seen after treatment with all drugs and drug combinations, and the absence of non granular bacilli in a biopsy specimen of an old highly bacilliferous lesion in the patient who relapsed, suggest that the skin may not be the most important site where therapy resistant bacilli survive. Other sites, e.g. large peripheral nerves, bone marrow may be equally if not more important and deserve further investigations.

References

- Harman, D. J. (1968). *Mycobacterium leprae* in muscle, *Lepr. Rev.* **39**, 197.
Leiker, D. L. (1969). The problem of concealed bacilli in treated leprosy patients. *Scientif. Conf. on Mycobacterial and Related Diseases, Dar es Salaam*.
Leiker, D. L. (1971). Chemotherapy of leprosy, *Int. J. Lepr.* **39-2**, 462.
Leiker, D. L., Verhagen, A. R. (1973). Assessment of the bacteriological effect of combined treatment with rifadin, sulfamethoxypyrazine and isoniazide in lepromatous leprosy, *Z. Tropenmed. Parasit.* **24**, 32.

- Neves, R. G. (1961). O *mycobacterium leprae* no musculo erector do pélo, *Bol. Serv. Nac. Lepr.* **20**, 17.
- Nishiura, M., Sirsat, S. M., Khanolkar, V. R. (1960). Electron microscopic study of leprosy lesion, *Lepr. India* 32-90.

Treatment of Leprosy with Clofazimine, Rifampicin and Bayrena

J. LANGUILLON

Institut de Léprologie, Dakar, Senegal

In Africa, 8% of leprosy patients have the lepromatous form, and 85% have the tuberculoid form of the disease. Treating these patients with dapsone needs several years to produce good results, treatment with acedapsone is still in the experimental stage, and rifampicin is too expensive. There are two drugs remaining; clofazimine, which is the treatment of choice for those with lepromatous leprosy, and sulphanilamides, treatment for the tuberculoid form of leprosy and for acute inflammation of the peripheral nerves.

Since 1968 we have used some drugs that have shown activity against *Myc. leprae*: clofazimine, rifampicin and Sulphamethoxypyrimidine.

Clofazimine

Clofazimine (B663, Lamprene) seems to us the most interesting antileprosy drug because it is active in three ways: Specific; Anti-inflammatory; Efficacy of action on *Myc. leprae* that are resistant to dapsone or sulphonamide.

Specific activity

We have experience of clofazimine given daily or weekly. For daily treatment we used 100 mg for adults. We have already treated 70 patients suffering from the lepromatous form of leprosy, and after 1, 2 or more years of treatment we have always obtained good results, which were presented by English speaking leprologists at the London Conference in 1968. That is to say:

- Identical activity with that obtained with dapsone (Disulone) at a dosage of 100 mg daily, both from the clinical and bacteriological point of view;
- Rarity of lepromatous reactions;
- Perfect tolerance among African patients.

Mass treatment is the rule in Africa, where thousands of leprosy patients are scattered over vast territories.

In a double blind trial, we have compared the activities of clofazimine and dapsone given once weekly to 2 groups of adult leprosy patients previously treated or untreated. The first group received a weekly dose of 600 mg

clofazimine, the second group a weekly dose of 600 mg dapsons. After 24 months of regular treatment, the results were as follows.

Clinical improvement has been obtained in all cases, and the Amelioration Index of 2.23 in the dapsons group and 2.20 in the clofazimine group permits the conclusion that the clinical improvement is comparable in both groups.

Similar comparison of the Bacteriological Index before and after treatment has shown a bacteriological reduction of 60% with dapsons and 70% with clofazimine. The bacteriological results are thus slightly superior with clofazimine.

Of particular interest is the fact that ENL appeared only among 2 patients treated with clofazimine. The reactions have been single and benign. Severe and repeated reactions occurred in 8 patients treated with dapsons. Tolerance of the drug was good. Liver and kidney function, as well as blood and skin condition, did not deteriorate. There are no problems with African patients concerning the red pigmentation caused by clofazimine.

As a specific treatment for the lepromatous type of leprosy, clofazimine has similar activity to dapsons in both clinical and bacteriological improvement, while clofazimine induces fewer reactions.

Anti-reactional activity

For many years we treated systematically all reactional patients with clofazimine; most had lepromatous leprosy and presented with severe reaction or repeated reactions. The dosage given of 300 mg daily to 600 mg daily has varied according to the seriousness of the signs. General and cutaneous signs disappeared between 15 and 30 days, but we continued treatment until C-reactive protein became negative, generally between 30 and 60 days. We then progressively decreased the dosage of clofazimine to 100 mg a day. With this specific and anti-inflammatory therapy, 98% of our 41 cases have improved without developing further reactions.

Activity of clofazimine on Myco. leprae resistant to dapsons and other drugs

Up till now we have treated 15 patients with lepromatous leprosy who presented with very slow clinical improvement or even aggravation and increase of the Morphological Index above 30% in the nasal mucus and skin. Mouse footpad tests are not available to us, but we consider the above mentioned aspects as signs of resistance. Of these 15 patients 12 received dapsons and 3 Sulphorthomidine. After having stopped the specific treatment, all patients received clofazimine in a dosage of 300 mg a day for 6 months, which gave us a good clinical and bacteriological response. After a period of 3 months with 200 mg clofazimine daily we reduced the dosage to 100 mg per day without recommencing specific treatment. After 1 year of treatment good clinical improvement was obtained, a fall of the Morphological Index to 2 or 3%, and a reduction of 50% in the Bacteriological Index.

In conclusion, clofazimine has the same degree of activity as dapsons, and because of its anti-inflammatory action it is the treatment of choice in patients with lepromatous leprosy in reaction. Patients who are resistant to dapsons or other drugs respond very well to treatment with clofazimine. In Africa where the follow up of patients is difficult, clofazimine should be used in the treatment of lepromatous leprosy.

Rifampicin

According to the work of Rees *et al.*, Leiker and Dormer, and others, we have tried rifampicin on several patients. We have already reported results obtained after treatment for 1 year in 22 patients with lepromatous leprosy. One group of 6 patients received 900 mg a day; the second group of 12 patients received 600 mg a day; the third group of 6 patients received 300 mg a day. The best results were obtained with a daily dose of 900 mg; from the clinical point of view, decrease or disappearance of lepromata, decrease in generalized infiltration, cessation of epistaxis, improvement of rhinitis and laryngitis in 2 cases. Treatment with a daily dosage of 600 mg has given slightly inferior results, the amelioration rate being 2.3 as against 2.8.

From the bacteriological point of view the assessment of the Morphological Index has been done monthly for 8 months, and shows a rapid fall with 900 mg and 600 mg rifampicin daily to 0% within 4 to 5 months. The same result was obtained with dapsone treatment within 6 months. Improvement in the Bacteriological Index has been greater with 900 mg (1.35) than with 600 mg (1.25). With a daily dosage of 300 mg, the Bacteriological Index showed less good results.

Reaction occurred in all 3 groups; but tolerance was good and no side-effects occurred. The daily dose of rifampicin was kept at 600 mg and 900 mg because of the high cost of the drug. This drug should be reserved for special cases, and such patients who have both leprosy and tuberculosis.

Following the work done in Zaire by Belgian phthisiologists and by Pattyn, we have treated patients with lepromatous leprosy with a weekly dose of 30 mg/kilo body weight for 5 months. Thereafter we continued with 225 mg acedapsone every 75 days by injection. Our experiments are continuing, but we can already affirm that a weekly dose of 30 mg/kilo body weight of rifampicin gives the same bacteriological response as a daily dosage of 900 mg.

Sulphamethoxypyrimidine

Since 1958, we have used long-acting sulphonamides in patients with tuberculoid leprosy and neuritic lesions, giving first a weekly dose of 1.5 g of Sulphorthomidine and then 750 mg sulphamethoxypyridazine (Lederkyn) every 2 days. We have reported good results between 1959 and 1972. Now we have under experiment a new sulphanilamide, Sulphamethoxypyrimidine, the formula of which is 2-sulphamide-5-methoxypyrimidine. We administer 750 mg every 2 days to adult patients. Tolerance has been good, for the blood status as well as the skin condition. Out of 35 patients, 20 have received this drug for 1 year, their classification being as follows:

Tuberculoid leprosy	7
Interpolar (borderline)	4
Lepromatous	9

In 1 patient with tuberculoid leprosy, skin lesions have disappeared, while the other 6 cases have much improved. Out of 3 patients who had claw hands, 2 are totally cured, and the third has improved considerably. This sulpha drug has thus a quick and excellent effect in the therapy of allergic tuberculoid forms and neuritic lesions. The 4 patients with interpolar leprosy showed good clinical

improvement and the Bacteriological Index fell to zero. One of them, classified histologically BT, showed a positive Mitsuda reaction. The 9 patients with lepromatous leprosy showed clinical improvement, decrease of lepromata and reduction in the infiltration of diffuse lepromatosis. Four of them have a negative nasal mucus; ENL appeared in 2 of them.

Sulphamethoxypyrimidine gives the same results as were obtained with other long-acting sulphonamides, namely:

Similar activity to that of dapsone in lepromatous and interpolar types of leprosy;

Lowered tendency to reactions;

Perfect tolerance, particularly with regard to the skin.

A Preliminary Report on a Therapeutic Trial with Acedapsone in Lepromatous Leprosy*

K. RAMANUJAM, C. G. S. IYER AND G. RAMU

*Central Leprosy Institute,
P.O. Tirumani, Chingleput 603001, S. India*

Fifty cases of lepromatous leprosy were included in a double blind trial to assess the therapeutic value of DADDS in lepromatous leprosy using DDS as the control drug. During the period of 19 months the study has been in progress, 28 cases were lost to the study owing to patients going away on voluntary discharge, etc. In the 22 cases who continued to participate in the study over a period of 15-19 months, the findings indicate that the drug is effective and well tolerated.

Subjects for the Study

Young male adults suffering from moderate to well advanced uncomplicated active lepromatous leprosy confirmed histopathologically and immunologically constituted subjects for the study. Although it was originally intended that only those cases with Morphological Index of at least 4% and above should be included in the study, this criterion had to be relaxed because of the non-availability of such subjects.

Size and Duration

A total of 50 cases were included in the study. They were allocated to one or other of the 2 groups, the Trial Group and Control Group, by randomization. The duration of the trial was initially fixed for two years, its further continuance being determined by the observations made during this period.

Methods

The Trial Group received DADDS in a dose of 225 mg by the intramuscular route once in 75 days, and placebo tablets every day. The Control Group received

* This investigation received financial support from the WHO.

placebo injection once in 75 days, and tablets of DDS orally every day in strict relation to body weight, starting with a small dose, stepping up gradually and reaching the maximum dose of 10 mg/kg body weight/week over a period of 22 weeks as per the schedule given by the WHO.

Investigations

Initially the patients were given a complete physical examination to exclude serious intercurrent disease. Subsequently investigations including recording of leprosy status of the patient, bacteriological examination, haemogram, liver function tests, urinalysis and stools examination, skin biopsy for histopathological examination, lepromin test using lepromin supplied by the WHO Regional Reference Centre, clinical photography, and recording of body weight, were carried out.

During the follow-up, clinical charting of the cases, bacteriological examination, liver function tests, haemogram, urinalysis and stools examination were repeated every 3 months. Body weight was recorded every month. Skin biopsy was repeated once a year or earlier if found necessary. Clinical photography was repeated as and when indicated. Sulphone level in the blood and urinary excretory pattern of the drug were carried out prior to the injection of the drug, 4 days, 6 days, 25 days, and 50 days following the injection of DADDS using the fluorimetric method of Glazko *et al.*

The Study Proper

The investigation commenced on 1 February, 1973 with 19 cases and during the intake phase, lasting 5 months, 31 more cases were added to the study bringing the total to 50, 25 in the Trial Group and 25 in the Control Group. During the course of 19 months the investigation has been in progress, 28 cases were lost to the study due to various reasons. As on 31 August, 1974 there are 22 cases participating in the investigation. Fifteen of these cases are on DADDS and 7 receive DDS orally.

The 15 subjects in the Trial Group have received 6 to 8 injections of 225 mg of the drug intramuscularly each time at an interval of 75 days and placebo tablets orally every day. Cases in the Control group numbering 7, have been on continuous DDS therapy by the oral route and have received 6 to 8 injections of placebo intramuscularly once in 75 days.

Findings

(i) All the cases, both on DADDS and DDS have recorded progressive clinical improvement, (ii) only 1 case receiving DADDS has shown improvement bacteriologically, (iii) regarding the occurrence of complications 2 cases in the Trial Group developed severe lepra reaction, one of which has become recurrent and another pustular. A third case manifested painful arthritis of the knees and 3 had 1-2 attacks of lepra reaction. In the control group, 3 cases developed recurrent attacks of lepra reaction and 2 others lepra reaction twice, (iv) DADDS is well-tolerated, though causing some pain at the injection site for 24 to 48 h following the injection, and (v) laboratory investigations revealed normal values throughout in all the cases.

In conclusion it may be said that the present findings indicate that DADDS is well tolerated, and appears to be effective. Further, though there are no indications so far regarding the development of drug resistance with this treatment, this probability should be borne in mind.

Low Dose Dapsone Therapy in Lepromatous Leprosy

A. B. A. KARAT

St. Catherine's Hospital, Birkenhead, England

Under the conditions of this study, dapsone in doses of 5 mg and 10 mg daily when administered to patients with lepromatous leprosy is an ineffective therapy in terms of killing and elimination of *Myco. leprae* from human skin and bone marrow. A real danger of facilitating the emergence of resistant bacilli exists. Therefore, until there is more evidence from long term therapeutic trials of low dose dapsone in bacillated types of leprosy, conventional dosage of dapsone is recommended.

Clinicians treating lepromatous leprosy patients before and after the introduction of sulphones as specific therapy have gained the impression that both the incidence and severity of erythema nodosum leprosum reactions in leprosy have greatly increased. There have been reports of the beneficial effects of low dose DDS in reducing the incidence of these reactions in lepromatous leprosy. The apparently effective inhibition of multiplication of *Myco. leprae* in the footpads of mice by extremely low concentrations of dapsone in the diet (of the order of 0.0001 g%) (Shepard *et al.*, 1966) had tended to breed an undue sense of optimism and confidence in the efficacy of homeopathic doses in man. This optimism was further compounded by extrapolation of reported changes in Morphological Index of *Myco. leprae* in skin smears to death of *Myco. leprae*.

A study was initiated to elucidate the precise relationship between dose of dapsone and incidence of reactions, as well as the period of viability of *Myco. leprae* in skin and bone marrow of lepromatous leprosy patients on low and high dose of dapsone.

Material and Methods

Thirty consecutive untreated lepromatous leprosy patients were randomly allocated to three therapy groups:

- (1) dapsone 5 mg daily;
- (2) dapsone 10 mg daily;
- (3) dapsone 100 mg daily.

Skin smears were taken from 8 standard sites by slit-skin method once a month and Morphological Index (Shepard and McRae, 1965) and Bacterial Index (Ridley, 1964) were determined. Skin biopsy and bone marrow aspiration were obtained immediately prior to initiation of treatment and once in 3 months during the first year and once in 6 months for 2 subsequent years. *Myco. leprae* homogenates from these specimens were injected into hind footpads of thymectomized CBA mice which were harvested at regular intervals and harvest

counts obtained. Clinical records included specific reference to occurrence of ENL, painful neutritis, iritis or any other intercurrent complication. The reactions were treated with 4 week course of 15 to 30 mg of prednisolone.

Of the 30 patients only 15 patients—5 in each group—completed the study and the data regarding these patients is presented here.

Results

Morphological Index

In the majority of cases the MI was between 3 and 10% at initiation of treatment and came down to below 1% in 12 to 24 weeks in all the groups. There was no significant difference in rate of fall of MI between the low and the high dose group.

Bacterial Index

(a) *100 mg dapsone*. There was a fairly uniform fall in BI at the rate of 1+ per year. Three of the 5 patients were skin smear negative at the end of 3 years. However, in 4 of the 5 patients bone marrow aspirates continued to be positive for *Myc. leprae*.

(b) *10 mg dapsone*. In 1 patient the BI fell at the same rate as that seen in patients in 100 mg dapsone. In 2 patients there was no significant change in BI and in 2 patients there was a gradual rise in BI throughout the period of therapy despite the MI remaining persistently below the 0.1% in these cases.

TABLE 1
Dapsone 10 mg daily

Changes in BI over 3 years		
Steady fall 1	No change 2	Gradual rise 2

(c) *5 mg dapsone*. There was a steady fall in BI in 1 patient, no change in 1 patient and a gradual rise in 3 patients.

TABLE 2
Dapsone 5 mg daily

Changes in BI over 3 years		
Steady fall 1	No change 1	Gradual rise 3

ENL

Two patients in each of the 3 therapy groups developed ENL and there was no clinically recognizable difference between the 3 groups.

Bacilli in the bone marrow

Except for 1 patient on 100 mg dapsone whose skin smear also had become negative at 2 years, in all the other patients AFB was demonstrable in bone marrow aspirates throughout the period of study.

Viability of Myco. leprae in skin and bone marrow while on therapy

(a) *100 mg dapsone daily.* In all patients, *Myco. leprae* from skin biopsy homogenates were non-viable in footpads of mice between 6 and 12 months of treatment with dapsone 100 mg daily. In 2 the *Myco. leprae* from bone marrow became non-viable at 24 months, in 1 at 30 months, in 1 at 36 months; while in 1 it was viable at the end of 36 months.

TABLE 3

Viability of Myco. leprae in skin and bone marrow of patients treated with dapsone 100 mg daily

Time	Site	I		II		III		IV		V	
		S	BM	S	BM	S	BM	S	BM	S	BM
0		+	+	+	+	+	+	+	+	+	+
3 months		+	+	+	+	+	+	+	+	+	+
6 months		-	+	+	+	-	+	+	+	+	+
9 months		-	+	+	+	-	+	-	+	+	+
12 months		-	+	-	+	-	+	-	+	-	+
18 months		-	+	-	+	-	+	-	+	-	+
24 months		-	-	-	+	-	-	-	+	-	+
30 months		-	-	-	+	-	-	-	-	-	+
36 months		-	-	-	-	-	-	-	-	-	+

(b) *10 mg dapsone daily.* In 1 patient the bacilli from the skin became non-viable at 18 months and in another at 36 months while in the rest of the 3 patients the bacilli were still viable at 36 months. However, in all the patients the bacilli from the bone marrow remained viable at 36 months.

TABLE 4

Viability of Myco. leprae in skin and bone marrow of patients treated with dapsone 10 mg daily

Time	Site	I		II		III		IV		V	
		S	BM	S	BM	S	BM	S	BM	S	BM
0		+	+	+	+	+	+	+	+	+	+
3 months		+	+	+	+	+	+	+	+	+	+
6 months		+	+	+	+	+	+	+	+	+	+
9 months		+	+	+	+	+	+	+	+	+	+
12 months		+	+	+	+	+	+	+	+	+	+
18 months		-	+	+	+	+	+	+	+	+	+
24 months		-	+	+	+	+	+	+	+	+	+
30 months		-	+	+	+	+	+	+	+	+	+
36 months		-	+	+	+	+	+	-	+	+	+

(c) *5 mg dapsone daily*. In 1 patient the bacilli from the skin became non-viable at 18 months and in another at 36 months. In none of the patients the bacilli from the bone marrow attained non-viability at the end of 36 months (Table 5).

TABLE 5
*Viability of Myco. leprae in skin and bone marrow
of patients treated with dapsone 5 mg daily*

Time	Site	I		II		III		IV		V	
		S	BM	S	BM	S	BM	S	BM	S	BM
0		+	+	+	+	+	+	+	+	+	+
3 months		+	+	+	+	+	+	+	+	+	+
6 months		+	+	+	+	+	+	+	+	+	+
9 months		+	+	+	+	+	+	+	+	-	+
12 months		+	+	+	+	+	+	+	+	-	+
18 months		+	+	+	+	+	+	+	+	-	+
24 months		+	+	+	+	-	+	+	+	-	+
30 months		+	+	+	+	-	+	+	+	-	-
36 months		+	+	+	+	-	+	+	+	-	-

Comments

(1) There is no evidence to show that ENL reactions can be reduced by reduction of dosage of dapsone. The occurrence of reactions in lepromatous leprosy seems to follow an "all or none" law as far as dapsone is concerned.

(2) Morphological Index, under the conditions of these experiments, appears to be an unreliable measure of viability of *Myco. leprae*.

(3) Dapsone when administered orally in dosage of 100 mg daily, renders the *Myco. leprae* in human skin non-viable in 6 to 12 months. However, a significant lag period exists between killing of *Myco. leprae* in skin and in bone marrow, the latter being viable for 12 to 24 months after the bacilli in the skin are dead.

(4) Dapsone when administered in daily doses of 5 mg and 10 mg over a 3 year period is far less effective in both killing and eliminating *Myco. leprae* from skin and bone marrow.

Acknowledgement

It is a pleasure to acknowledge the support for this study from Radda Barnen, Stockholm. I am grateful to Mr Rajan Albert and Mr S. Kumar for technical assistance.

References

- Ridley, D. S. (1964). *Leprosy in Theory and Practice* 2nd ed. (Eds R. G. Cochrane and T. F. Davey), p. 620. Bristol: John Wright & Sons Ltd.
 Shepard, C. C. and McRae, D. H. (1965). *J. Bact.* **89**, 365.
 Shepard, C. C., McRae, D. H. and Hebas, J. A. (1966). *Proc. Soc. exp. Biol. Med.* **122**, 893.

A Report on a Controlled Clinical Trial with Conventional and One Third Conventional Dose of Dapsone Administered Orally Once a Week in Lepromatous Patients*

K. RAMANUJAM, C. G. S. IYER AND G. RAMU

*Central Leprosy Institute,
P.O. Tirumani, Chingleput 603001, S. India*

Therapeutic investigation with dapsone administered orally in the conventional (10 mg/kg of body weight/week—Group A), and one third of the conventional dose (3.33 mg/kg of body weight/week—Group B), as a single dose once a week to lepromatous cases, using double-blind procedures over a period of 130 to 265 weeks was concluded in September, 1973. The findings of the study showed (1) DDS administered as a single dose once a week was therapeutically effective. (2) One third the conventional dose was as effective (perhaps better) as the conventional dose. (3) Lepra reaction occurred in both the groups but tended to be more severe in Group A and (4) Insomnia was a frequent and sometimes a disturbing side-effect in this regimen of therapy.

Objectives

(i) To compare the results of DDS therapy in lepromatous leprosy using the conventional dose (10 mg of DDS/kg body weight/week) and one third of this amount (3.3 mg/kg body weight/week) administered orally as a single dose once a week. (ii) To determine the relationship between blood levels of the drug and the clinical and bacteriological results.

To the above 2 main objectives the following were added: (i) The study of the incidence of complications/side-effects in the 2 groups. (ii) The trend in the blood sulphone level in respect of the dose of the drug and the duration of treatment and (iii) The study of the effect of this regimen of treatment on the renal, hepatic and haemopoietic systems.

* This investigation received financial support from the WHO.

Method

This trial was conducted using double-blind procedures.

The subjects

Active male lepromatous cases in reasonably good general health and without complicating diseases, preferably untreated or who had received specific anti-leprosy treatment for 6 months or less, constituted the subjects for the study.

Dosage schedule

One group—Group A, was given the conventional dose of DDS *viz.* 10 mg/kg body weight/week, this being reached by stages over a period of 22 weeks according to a previously worked out schedule. The other group, Group B, was given a maximum dose which was one third of the conventional dose *viz.* 3.33 mg/kg body weight/week, this being built up gradually over a period of 6 weeks. These doses were prescribed each month in strict relation to body weight.

Allocation to the 2 groups

Patients were allocated to Group A or Group B according to the table of random allocation provided by the WHO.

Administration of the drug

The appropriate dose of DDS was administered to each case every Monday, packed in gelatin capsules. On the rest of the 6 days in the week, the patients received capsules identical in appearance and number containing an innocuous substance like calcium lactate or sodi. bicarb.

Investigations, initial and follow-up

These comprised (i) Diagrammatic representation of the clinical status of the patient, repeated once a quarter without reference to the previous recording. (ii) Bacteriological examination, involving taking of 6 skin smears and evaluated with reference to bacterial density—Bacteriological Index, and morphology of organisms—Morphological Index, repeated every 3 months. (iii) Laboratory investigations comprising of haemogram, urinalysis, stools examination and liver function tests performed at the time of entry of the subjects into the study and repeated thereafter every 3 months in order to keep a watch on the haemopoietic, urinary and hepatic systems. (iv) Estimation of blood level of sulphone, as far as possible, every month. (v) Skin biopsy from a representative skin lesion before entry into the study and thereafter once a year preferably from the same lesion. (vi) Lepromin test with the antigen supplied by the WHO (160 million/mm³) at the time of entry into the study and repeated at the termination of the study.

Assessment of results

The progress of cases under treatment was gauged by periodical assessment of these cases, clinical and bacteriological, once in 3 months. In addition, the

incidence of complications and side-effects were also recorded and taken into account during assessment of progress of cases.

The study proper

The study was commenced on 2 September, 1968. Between September, 1968 and March, 1969, 40 cases were admitted into the study. The investigation was originally planned for 2 years and should have terminated by September, 1970. However, in view of the small number of cases participating in the study towards the end of the 2 year period, and the importance of the investigation, the investigation was continued for 3 more years after adding 15 new subjects to the study. Over the 5 year period of the investigation 34 cases were lost to the study, only 21 cases continuing treatment up to September 1973. Ten of these were receiving DDS in the conventional dose (Group A) and 11, a third of the conventional dose (Group B) once a week.

Findings of the Study

Clinical progress

All the cases registered progressive clinical improvement including those who had become subjects of recurrent reactive episodes. One case in Group B, after initial improvement, showed clinical and bacteriological deterioration with a rise in the Morphological Index. He was suspected to be developing sulphone-resistance and hence changed to Group A. His further deterioration was stemmed. Other unusual developments observed during the follow-up were: One case in Group A improved progressively under treatment but developed 2 fresh nodules after 170 weeks' treatment and got progressively worse. One case in Group B, developed a fresh nodule 222 weeks after commencement of treatment, after registering progressive improvement. No further nodules appeared. A third case in Group A, developed 1 fresh nodule after registering appreciable improvement during 235 weeks' regular treatment. Further nodules did not appear.

Bacteriological progress

All the 21 cases registered a progressive fall in the Morphological Index to a level of less than 1%. One case however in Group B, showed a tendency for an increase in the MI after an initial fall to less than 1%. This coincided with the clinical deterioration observed in the case.

The fall in the BI was progressive except in 2 cases—1 case on one third of the conventional dose who became a subject of recurrent pustular lepra reaction and another receiving the conventional dose. The latter registered initial progressive improvement but later showed progressive bacteriological deterioration for no apparent reason.

A case in Group A, a subject of recurrent pustular lepra reaction and steroid dependent, and another case in Group B with recurrent lepra reaction showed considerable clinical and bacteriological improvement in spite of recurrent reactive episodes. No case became bacteriologically "negative".

Occurrence of complications

Lepra reaction of varying grades of severity and frequency occurred in both the groups. It was difficult to predict or anticipate the onset of reactive states. The factor or factors provoking the reactive state were not identifiable either, except in one instance—a case in Group B, who developed the first attack of lepra reaction and glycosuria following severe local reaction to Vole bacillus antigen. The glycosuria reappeared with each bout of lepra reaction. Although the incidence of the reactive state was more in Group B, it tended to be more severe in Group A.

Side-effects

Insomnia was observed to be one of the undesirable and disturbing side-effects which arose in many of the cases in the early part of the investigation. This occurred in both the groups but was more frequent and perhaps more intense in the cases in Group A. In 1 patient in Group B, the persistent insomnia led to an explosive mental episode when the patient became aggressive and assaulted other patients in the Sanatorium.

Findings of the laboratory investigation

Laboratory investigations such as haemogram, urinalysis and liver function tests carried out on these cases every three months did not reveal any abnormal findings attributable to this regimen of therapy. In all but 2 instances, levels of sulphone in blood tended to be commensurate with the dose of DDS administered orally.

Acceptance of the therapy by patients

It may be stated that this method of treatment was acceptable to the patients except in instances where insomnia became persistent.

Results

Assessment done on these groups of cases at the end of 3–5 years showed: (i) None of the cases became “Negative”. Cases receiving the smaller dose had done better than those receiving the conventional dose, 9 out of 11 of them having “Much Improved”, (ii) The average uptake of DDS was definitely more in Group B than Group A, (iii) The incidence of reactive episodes was more in the group getting the smaller dose, 8 out of 11 cases having manifested moderate to severe reactions as against 5 out of 10 cases in Group A. However, recurrent reactive episodes were more in Group A than Group B.

Conclusion

(i) DDS is therapeutically effective when administered orally as a single dose once a week. (ii) One third of the conventional dose is as effective as the conventional dose, perhaps better. However, there is the possibility of this small dose proving ineffective in an occasional case. (iii) Complications like lepra reaction occurred in both the groups although the severity appeared to be more in Group A. (iv) Insomnia of varying grades of severity and duration was the

predominant undesirable side-effect of this regimen of therapy. (v) Adverse effects attributable to this regimen of treatment were not observed on the haemopoietic, renal or hepatic systems. (vi) Once a week regimen is generally acceptable to the patient except in instances where insomnia proved irksome.

Personal Experience with Clofazimine in the Treatment of Leprosy

R. D. AZULAY

*Av. Atlantica 3130, Apt. 701, Copacabana,
Rio de Janeiro, Brazil,*

and

N. C. DA SILVA, A. ZEO, M. DE JESUS AND C. B. FRANCA

*Institute of Leprology and Hospital of the Curupaity Colony,
Rio de Janeiro, Brazil*

The authors present the results obtained with 20 patients in an advanced stage of longstanding lepromatous leprosy, 15 of whom had sulphone resistant bacilli.

- (1) Clofazimine has definite activity in leprosy and in patients with sulphone resistant bacilli.
- (2) Activity is shown by resolution of the lesions and disappearance of bacilli.
- (3) Clofazimine does not precipitate leprosy reaction as is seen in patients taking dapsone.
- (4) Side-effects are negligible and do not interfere with treatment.

Introduction

Since Barry *et al.* (1957) showed that a phenazine compound named B-663 had anti-tuberculous activity, several reports were presented showing that the drug also had definite activity in leprosy. Browne and Hogerzeil (1962) published the first results of the treatment of 16 cases of lepromatous and borderline leprosy patients with B-663. Later on Browne (1965) confirmed those results and, in addition, suggested that the drug had anti-inflammatory action in that the frequency of lepra reaction was considerably lower than with dapsone treatment. Many other papers have since appeared, confirming these results.

Our Experience

We treated 20 patients with advanced lepromatous leprosy who presented the characteristics detailed in Tables 1 and 2.

The group consisted of adults, predominantly male, all Brazilian except for one Portuguese, who had had leprosy for periods ranging from 1 to 28 years, for one Portuguese having had leprosy for more than 10 years. Fifteen out of the 20 patients had been treated before as may be seen from Tables 3 and 4.

Fifteen patients had been treated previously with a sulphone, either alone or associated with other drugs. Judging from the duration of therapy, (over 5 years in 14 patients) and from the failure of treatment, we may probably deduce that these patients harboured sulphone resistant organisms.

TABLE 1

*All patients were in-patients of the Curupaity Hospital,
grouped as follows*

	No. of cases
Sex	
Male	16
Female	4
Colour	
White	12
Black	3
Nationality	
Brazilian	19
Portuguese	1
Age	
15-19	2
20-29	1
30-39	10
40-49	4
50-59	2
60-69	1

TABLE 2

Duration of illness	No. of cases
0- 4 years	3
5- 9 years	1
10-14 years	3
15-19 years	5
20-24 years	6
25-30 years	2

TABLE 3

Previous therapy

Duration in years	No. of cases
0- 4	1
5- 9	2
10-14	1
15-19	5
20-25	5
25-30	1

TABLE 4
Previous therapy

Drugs	No. of cases
Sulphone	3
Sulphone plus thiambutosine	6
Sulphone plus thiambutosine plus thiacetazone	2
Sulphone plus isonicotinyl Hydrazide (INH)	1
Sulphone plus thiambutosine plus INH	2
Sulphone plus Tebessal	1

TABLE 5
Therapeutical results of clofazimine on 20 patients suffering from advanced lepromatous leprosy (L3)

Duration of treatment	Previous treatment	Regression of cutaneous lesions				Total
		Complete	Marked	Discrete	None	
1 year	Yes	0	2	1	0	3
	No	1	2	1	0	4
2 years	Yes	1	9	2	0	12
	No	0	0	1	0	1
Total		2	13	5	0	20

Urine analysis, blood levels of glucose and nitrogen, blood counts and bacteriological examination of nasal mucosa, skin and ear-lobe, as well as biopsy were performed both before and during treatment.

Present Treatment

The patients were treated with clofazimine for 5 years; during the first months of treatment, the daily dose was 200 mg, which was then reduced to 100 mg daily.

Results

Clinical

Tables 5 and 6 show the results of the treatment on the skin lesions.

Bacteriological

Table 7 shows the results after 2 and 5 years of treatment.

TABLE 6

Therapeutical results of clofazimine in 20 patients suffering from advanced lepromatous leprosy (L3)

Duration of treatment	Previous treatment	Regression of cutaneous lesions		
		Complete	Marked	Total
5 years	Yes	15	0	15
	No	3	2	5
Total		18	2	20

TABLE 7

Overall results of bacterioscopic tests on 20 patients treated with clofazimine

Treatment	Results of bacterioscopic tests			
	Positive		Negative	
	2 years	5 years	2 years	5 years
Before	20	20	0	0
After	10	0	10	20

Histopathological

Histopathological examination were performed before, during, and after 2 years of treatment, i.e. 3 per patient. The results of the 5 year study are not yet available. Some histopathological findings seen after 2 years of treatment should be emphasized.

- (1) Reduction of the leprotic infiltration.
- (2) Considerably reduced bacillary count.
- (3) Granular and fragmented forms were more numerous than solid staining forms of the bacillus.
- (4) The Virchow cells disappeared. These cells increased in size, and showed marked lipid intra-cytoplasmic degeneration; they became practically free from bacilli.
- (5) Of 12 patients who were histologically lepromatous before therapy, 8 became regressive.
- (6) In some patients we found brownish pigmentation in both dermis and epidermis.

Lepra reaction

We tried to observe the action of the drug in relation to lepra reaction. This is shown in Table 8.

There is no doubt that clofazimine has a definite action on lepra reaction.

TABLE 8
Effect of clofazimine on leprotic reaction

Frequency	Before treatment	After treatment	
		2 years	5 years
Very frequent	3 cases	0	0
Frequent	3 cases	1 case	0
Rarely	5 cases	1 case	0
None	9 cases	18 cases	20

Side-effects

The following were observed: reddish pigmentation, dark pigmentation, ichthyosis like lesions of the skin and some dyspeptic symptoms. The dark pigmentation which was more intense in the first years of treatment improved with the resolution of the lesions.

References

- Barry, V. C., Belton, J. G., Conalty, M. L., Dennemy, J. M., Edward, D. W., O'Sullivan, J. F., Twomey, D. and Winder, F. (1957). A few series of phenazines (rimino-compounds) with high anti-tuberculous activity. *Nature (Lond.)* **179**, 1012-1015.
- Browne, S. G. and Hogerzeil, L. M. (1962). B-633 in the treatment of leprosy. Preliminary report of a pilot trial. *Lepr. Rev.* **33**, 182-184.
- Browne, S. G. (1965). Treatment of leprosy with B-663. Appraisal of the pilot trial after three years. *Lepr. Rev.* **36**, 13-15.

Long-term Follow-up of Clofazimine (Lamprene) in the Management of Reactive Phases of Leprosy

A. B. A. KARAT

St. Catherine's Hospital, Birkenhead, England

Observations in 120 leprosy patients with reaction treated with Lamprene for periods ranging from 3 months to 5 years are presented. Lamprene was found to be an effective therapy for ENL, acute neuritis, eye complications associated with reaction, epistaxis, haemoptysis and nasal discharge due to leprous rhinitis. No adverse effects were noticed in 3 women who were on continuous treatment with Lamprene immediately prior to their becoming pregnant, throughout pregnancy and puerperium. Except for hyperpigmentation of the child, no other deleterious effect on the foetus was noted. Two patients developed "granulomatous enteritis" while on Lamprene. Bacterial clearance as judged by fall in BI was comparable to that seen in patients on dapsone 100 mg daily.

After 6 months of continuous treatment, no recurrence of ENL was seen in any of the patients. There was significant improvement in motor and sensory functions in patients with acute neuritis in all types of leprosy.

A large number of short-term studies since the original reports of the efficacy of Lamprene in lepromatous leprosy have confirmed both specific bacteriostatic effect on *Myc. leprae* as well as an anti-inflammatory effect in suppressing clinical manifestations of reactive phases in leprosy (Browne and Hogerzeil (1962a, 1962b; Browne 1965; Hastings and Trautman 1968; Karat *et al.*, 1970; 1971). We have had the opportunity to treat 120 leprosy patients with complicating reactive phase over a 5 year period of whom 50 patients were followed up for 5 years. This paper summarizes our findings.

Material and Method

Two hundred and forty leprosy patients with 1 or more complications of reactive phases of leprosy were treated with Lamprene over a 5 year period and entered a controlled clinical trial. All of them had a detailed clinical examination, bacteriological and histological assessments, detailed assessment of neurological and ophthalmic functions. One hundred and twenty of these patients were on Lamprene 100 mg t.d.s. for 12 weeks followed by a maintenance dose of Lamprene 100 mg daily. The other 120 patients were on dapsone 50 mg daily along with Prednisolone 10 mg t.d.s. for 12 weeks and thereafter a maintenance therapy of dapsone 50 mg daily. In this paper only the patients on Lamprene are described.

Findings

The distribution of patients according to classification of leprosy and complication(s) of reaction is shown in Table 1.

TABLE 1
Distribution of patients according to classification of leprosy and complication of reaction

Complication \ Classification	TT	BT	BL	LL	Total
	Acute neuritis	6	10	30	34
ENL (Grade III/IV)	—	—	24	60	84
Iritis/Iridocyclitis/Scleritis	—	—	6	10	16
Epistaxis/stuffy nose	—	—	10	20	30
Hoarseness of voice	—	—	—	10	10

Erythema nodosum leprosum (ENL)

Only patients who had 3 or more episodes of severe ENL were included in the study. Of the 84 patients in this category, in 80 patients (95%), the ENL was controlled in 4 to 8 weeks. The remaining 4 patients while showing clinical improvement continued to have manifestations of less severe ENL and needed additional therapy in the form of Prednisolone 5 mg t.d.s. for 4 to 12 weeks to adequately control the reaction.

Recurrence of milder ENL while on maintenance therapy with Lamprene 100 mg daily was noted in 8 (10%) of the 80 patients in whom the reaction had come under control on Lamprene 300 mg daily for 12 weeks. No recurrence of ENL was noted after 6 months in any of the patients, 50 of whom were followed up for 5 years.

All the patients showed a weight gain of 5 to 10 kg during the follow-up period.

There was significant rise in haemoglobin and haematocrit values while on Lamprene without supplementation with haematinics. The reversal of albumin-globulin ratio in the serum tended to correct itself with rising albumin and falling globulin. The sedimentation rate also showed a significant reduction.

Acute neuritis

(a) *Tuberculoid Leprosy*. Six patients with acute mononeuritis of less than a week's duration were studied. There was complete relief of pain in 4 weeks in all the patients. Motor and sensory recovery was first noted between 2 to 4 weeks from commencement of treatment and continued to improve for 12 months. No significant improvement was noticed after 12 months during follow-up period which ranged from 6 months to 4 years. In none of the patients was a recurrence of neuritis seen after 12 months of treatment. In 2 patients there was no change.

Neurological status of TT patients on Lamprene (6 patients)

No. of patients	Symptoms and signs	Pain relief	Motor recovery		Sensory recovery		No change in neurological function
			Partial	Complete	Partial	Complete	
	6		3	1	3	1	2

(b) *Borderline/Tuberculoid (BT) Leprosy (10 patients)*. The response in this group was similar to TT.

No. of patients	Symptoms and signs	Pain relief	Motor recovery		Sensory recovery		No change in neurological function
			Partial	Complete	Partial	Complete	
		9	5	1	6	1	3

(c) *BL and LL (30 and 34)*. Patients showed comparable response. In none of the patients was there complete recovery of motor or sensory functions.

No. of patients	Symptoms and signs	Pain relief	Motor recovery		Sensory recovery		No change in neurological function
			Partial	Complete	Partial	Complete	
		60	30	0	40	0	24

There was significant improvement in neurological function in well over half the patients. Again there was no recurrence after 1 year of continuous therapy.

Eyes (Iritis/Iridocyclitis/Scleritis)

Ophthalmological complications associated with ENL reaction were seen in 16 patients. Apart from mydriatics no other local therapy was given. All the patients found relief of symptoms in 4 weeks and marked improvement at the end of 12 weeks. They continued to improve for 18 months. Visual acuity improved by at least 1 line on Snellen's chart in all the patients.

Epistaxis—Nasal Discharge—“Blocking” of the nose

Ten patients with BL leprosy and 20 patients with LL leprosy had epistaxis, profuse nasal catarrh and difficulty in breathing because of blocking of the nose. The epistaxis cleared when the reaction came under control. Nasal discharge and blocking of the nose improved gradually over a 6 month period. Nasal discharge was noticed to have a brownish discolouration between 12 and 16 weeks of commencement of treatment.

Hoarseness of voice and haemoptysis

This was seen in 10 lepromatous leprosy patients. The haemoptysis cleared in 8 weeks while there was gradual improvement in hoarseness of voice over a period of 18 months.

Pregnancy and Lamprene

Three women who had been on Lamprene for management of severe, chronic ENL became pregnant at 3 months, 9 months and a year after initiation of therapy with Lamprene and continued with Lamprene 100 mg daily throughout

pregnancy and puereperium. No untoward effects were observed either in the mother or the foetus except for somewhat darker colour of the skin of the offspring, more than can be accounted for by the ethnic background. The pigmentation gradually faded away over a one year period.

Clearance of Myco. leprae

Fifty patients with BL and LL leprosy were available for follow-up over a 5 year period. Forty of them became skin smear negative between 1 and 5 years from initiation of treatment. Average drop in Bacterial Index (Ridley's Scale) was 1+ per year of treatment, comparable to that seen in patients on dapsone 100 mg daily.

Side-effects

The occurrence of red-brown pigmentation was seen in all the patients within 12 weeks of initiation of treatment. Dry, scaly, ichthyotic changes in the skin were seen in the extensor surfaces of the upper and lower extremities in over 75% of patients. This improved with immersion in water for 15 min followed by application of a thin layer of vegetable oil or vaseline. In a number of patients partial regrowth of eyebrows was a welcome effect.

Gastrointestinal tolerance was good when daily dose did not exceed 300 mg. Among the 120 patients 2 patients developed recurrent, colicky abdominal pain after 6 months and 18 months of regular intake of Lamprene. Barium meal studies showed narrowing of the terminal ileum, and dilatation of proximal loop of ileum. There was no change in the absorptive functions of the small intestine. At laparotomy, about 6 in of terminal ileum appeared thickened and oedematous. There were a few enlarged mesenteric lymph nodes. Biopsy of the glands as well as terminal ileum showed non-specific granuloma characterized by the presence of foreign body giant cells and lymphocytes. The sections also showed crystals of Lamprene in the granulomata. No AFB were grown on culture. Lamprene was withdrawn from these patients and the symptoms cleared up in 8 to 10 weeks.

The sweat, urine, tears, nasal discharge, semen and breast milk developed varying degrees of brownish discolouration.

By slit-lamp microscopy one could demonstrate crystals of clofazimine in the iris, conjunctiva, sclera and cornea about 6 months after initiation of therapy. In patients who had more than 6 months of continuous therapy about 25% of patients developed asymptomatic bluish discolouration of the lens. These changes in the eye were reversible and cleared up over a period of 6 to 12 months after cessation of therapy with Lamprene.

Acknowledgements

I am grateful to Ciba-Geigy, Basel, for making this study possible. It is a pleasure to acknowledge my indebtedness to Mrs S. Karat for help with biopsies, neurological assessments including EMG studies, to the many house physicians who have helped with the day to day care, the laboratory and physiotherapy staff for their help.

References

- Browne, S. G. (1965). *Lepr. Rev.* 36, 9.
- Browne, S. G. and Hogerzeil, L. M. (1962a). *Lepr. Rev.* 33, 6.
- Browne, S. G. and Hogerzeil, L. M. (1962b). *Lepr. Rev.* 33, 182.
- Hastings, R. C. and Trautman, J. R. (1968). *Lepr. Rev.* 39, 3.
- Karat, A. B. A., Aubn Jeevaratnam, Karat, S. and Rao, P. S. S. (1970). *Br. med. J.* 1, 198.
- Karat, A. B. A., Aubn Jeevaratnam, Karat, S. and Rao, P. S. S. (1971). *Br. med. J.* 4, 514.

The Effect of Long-term Steroid Therapy on Patients Treated with Clofazimine (Lamprene)

L. M. HOGERZEIL AND N. PRABHUDAS

*Victoria Hospital, Dichpalli 503 175,
Nizamabad District, Andhra Pradesh, India*

A study was undertaken in 18 leprosy patients and 31 controls to find out if Lamprene can prevent a flare-up of the infection with *Myco. leprae* during long-term steroid therapy. All patients were either BL or LL; some were given daily Lamprene 100 mg and prednisone 10 mg because of persistent reactions, others twice weekly Lamprene 100 mg and daily prednisone 10 mg for the same reason. The duration of treatment varied from 6 to 23 months. The control patients were given Lamprene only, either daily 100 mg or twice weekly 100 mg. Their reactions were less severe and therefore they did not require prednisone. It was found that in both groups (Lamprene plus prednisone and Lamprene only) there was a satisfactory reduction of the MI (Morphological Index) to zero or less than 1%. But as regards the BI (Bacteriological Index) the patients on Lamprene plus prednisone did clearly better than the patients on Lamprene only. It thus appears that long-term steroid therapy has no adverse effect on the BI and MI of lepromatous patients, provided that they are treated with Lamprene at the same time.

Introduction

It is a well known fact that during long-term steroid therapy an undiagnosed and therefore untreated infection with *Myco. tuberculosis* may flare up. With this in mind a study was undertaken in 18 leprosy patients on long-term steroid therapy to find out if Lamprene does prevent a flare-up of the infection with *Myco. leprae*.

Materials and Methods

The patients were divided in 4 groups:

- | | |
|---|----|
| (1) Patients on daily Lamprene and steroids | 12 |
| (2) Patients on bi-weekly Lamprene and steroids | 6 |
| (3) Patients on daily Lamprene | 8 |
| (4) Patients on bi-weekly Lamprene | 33 |

The total number of patients studied was 49, all of them LL or BL. Some patients first belonged to one of the 4 groups and later to another.

Group 4: Lamprene twice weekly 100 mg

- (a) Thirty patients suffering from reaction (ENL and fever), 8 of whom were found to be suffering from tuberculosis as well.
- (b) Three patients with resistance against DDS.

If in spite of bi-weekly Lamprene reactions continued to occur, Lamprene was increased to 100 mg daily.

Group 3: Lamprene daily 100 mg

- (a) Seven patients suffering from reaction, 5 of them with concomitant tuberculosis.
- (b) One patient with resistance against DDS.

As Lamprene is an expensive drug and not always freely obtainable in India, it was sometimes impossible to increase the dosage to 100 mg daily to suppress reactions. In that case steroids (prednisone) were given according to a standard routine, starting with 40 mg daily and tapering off in 4 weeks to 10 mg daily.

Group 2: Lamprene twice weekly 100 mg and prednisone (40 to 10 mg) daily

- (a) Four patients with chronic neuritis.
- (b) Two patients with chronic reaction, one of them suffering from tuberculosis as well.

If in spite of bi-weekly Lamprene reactions continued to occur, Lamprene was increased to 100 mg daily.

Group 1: Lamprene 100 mg daily and prednisone (40 to) 10 mg daily

- (a) Seven patients with chronic reaction.
- (b) Five patients with chronic neuritis.
Seven patients in this group with extremely severe reaction and/or neuritis suffered from tuberculosis as well.

As far as possible bacteriological smears were examined every 3 months and only patients with at least 6 months treatment of the same type and with at least 3 smears were included in the various groups.

Results

In all patients there was a satisfactory reduction of the MI to less than 1% and in most cases to zero.

The average decline of the BI was as follows:

- Group 1:* Daily Lamprene and prednisone: 47% per annum, varying from 12 to 84%.
- Group 2:* Bi-weekly Lamprene and prednisone: 54% per annum, in 1 patient the BI increased by 14%, in the others there was a decline of up to 100%.
- Group 3:* Daily Lamprene: 25% per annum, in 2 patients the BI increased by 8 and 10% respectively, in the others there was a decline of up to 100%.
- Group 4:* Bi-weekly Lamprene: 37% per annum, in one patient the BI increased by 5%, in the others there was a decline of up to 100%.

TABLE 1
Group 1: Daily Lamprene and prednisone

	Period in months	First smear BI-MI	Last smear BI-MI	Decline BI per annum
1. M., BL, 1958, chronic neuritis	18	3.3-0.0	1.6-0.0	34%
2. G., BL, 1959, chronic neuritis	8	3.0-0.0	1.5-0.0	75%
3. D., LL, 1963, chronic reaction	10	4.5-0.0	3.5-0.0	27%
4. Y., LL, 1963, chronic reaction, tb	6	4.5-0.3	2.6-0.0	84%
5. K., BL, 1962, chronic neuritis, tb	8	3.1-0.0	2.1-0.0	48%
6. D., LL, 1954, chronic reaction, tb	19	3.5-0.0	1.1-0.0	43%
7. T., LL, 1941, chronic reaction, tb	13	3.1-0.0	1.8-0.0	39%
8. N., BL, 1954, chronic neuritis, tb	6	5.0-0.3	4.3-0.1	28%
9. S., BL, 1954, chronic neuritis	16	2.8-0.0	0.3-0.0	67%
10. L., LL, 1937, chronic reaction	9	2.6-0.0	1.5-0.0	56%
11. S., LL, 1956, chronic reaction, tb	21	3.5-0.0	0.5-0.0	49%
12. P., LL, 1928, chronic reaction, tb	23	4.6-0.3	3.5-0.0	12%
				562
				Average: 47%

TABLE 2
Group 2: Bi-weekly Lamprene and prednisone

	Period in months	First smear BI-MI	Last smear BI-MI	Decline BI per annum
1. D., LL, 1961, chronic reaction, tb	6	3.5-0.0	3.0-0.1	29%
2. A., BL, 1954, chronic neuritis	6	3.6-0.0	1.8-0.0	100%
3. I., BL, 1953, chronic neuritis	8	2.1-0.0	2.3-0.2	-14%
4. L., LL, 1937, chronic reaction	7	5.5-0.6	3.8-0.0	53%
5. G., BL, 1957, chronic neuritis	6	3.8-1.2	2.0-0.0	95%
6. S., BL, 1954, chronic neuritis	9	4.1-0.3	2.3-0.0	59%
				322
				Average: 54%

TABLE 3
Group 3: Daily Lamprene

	Period in months	First smear BI-MI	Last smear BI-MI	Decline BI per annum
1. M., LL, 1947, chronic reaction, tb	7	4.8-1.0	4.3-0.0	18%
2. J., LL, 1945, DDS resistant	6	5.0-2.3	4.6-0.3	16%
3. B., LL, 1959, chronic reaction	8	3.1-0.2	2.6-0.0	24%
4. R., LL, 1954, chronic reaction	7	4.3-0.5	4.5-0.2	-8%
5. V., LL, 1961, chronic reaction, tb	7	4.5-0.2	3.6-0.3	34%
6. D. LL., 1961, chronic reaction, tb	9	4.1-0.1	0.3-0.0	124%
7. N., BL, 1954, chronic reaction, tb	9	5.2-3.0	5.1-0.3	3%
8. T., LL, 1941, chronic reaction, tb	10	3.5-0.7	3.8-0.0	-10%
				201
				Average: 25%

TABLE 4
Group 4: Bi-weekly Lamprene

	Period in months	First smear BI-MI	Last smear BI-MI	Decline BI per annum
1. R., LL, 1959, chronic reaction	11	2.5-0.3	0.3-0.0	96%
2. K., LL, 1944, chronic reaction	12	4.1-0.6	4.1-0.2	0%
3. M., BL, 1947, chronic reaction	9	1.5-0.0	0.0-0.0	133%
4. R., LL, 1942, chronic reaction, tb	19	4.8-0.0	2.0-0.0	37%
5. B., LL, 1934, chronic reaction	7	4.1-0.6	3.5-0.3	25%
6. A., LL, 1937, chronic reaction, tb	22	3.0-0.0	0.0-0.0	55%
7. S., LL, 1050, chreotic reaction	28	4.5-0.2	0.8-0.0	35%
8. S., LL, 1949, chronic reaction	23	4.8-0.1	1.6-0.0	35%
9. J., LL, 1946, chronic reaction	9	5.0-0.1	2.6-0.0	64%
10. M., LL, 1945, chronic reaction	36	4.5-8.0	0.6-0.0	29%
11. B., LL, 1935, chronic reaction	25	5.0-1.0	4.8-0.5	2%
12. C., LL, 1935, chronic reaction, tb	7	3.8-0.0	2.3-0.0	68%
13. R., BL, 1951, chronic reaction	17	5.0-0.0	3.8-0.2	17%
14. Y., LL, 1937, DDS resistant	22	4.6-0.0	3.8-0.1	9%
15. S., LL, 1930, chronic reaction	18	4.6-0.0	2.1-0.0	36%
16. P., LL, 1952, chronic reaction	18	3.5-0.0	3.0-0.0	10%
17. H., LL, 1943, chronic reaction	27	5.3-4.0	1.0-0.0	36%
18. S., LL, 1947, chronic reaction	11	4.3-0.6	2.1-0.0	56%
19. V., LL, 1935, DDS resistant	6	4.6-1.5	4.3-0.0	13%
20. S., BL, 1940, chronic reaction	7	5.0-0.3	4.1-0.1	31%
21. Y., LL, 1955, chronic reaction	6	5.0-0.5	2.8-0.0	88%
22. S., LL, 1933, chronic reaction	7	4.0-0.0	3.6-0.0	17%
23. S., LL, 1943, chronic reaction	15	5.5-0.6	3.3-0.0	32%
24. M., LL, 1918, DDS resistant	9	4.0-1.1	3.6-0.0	13%
25. S., LL, 1950, chronic reaction	15	5.0-0.0	2.6-0.0	38%
26. S., LL, 1954, chronic reaction, tb	9	5.1-4.0	5.3-1.6	-5%
27. Y., LL, 1950, chronic reaction, tb	7	3.1-0.0	2.0-0.0	61%
28. A., BL, 1954, chronic reaction	15	5.0-0.0	2.3-0.0	43%
29. G., LL, 1939, chronic reaction	10	5.1-0.3	3.5-0.2	38%
30. P., LL, 1930, chronic reaction	16	5.1-1.5	3.3-0.0	26%
31. S., LL, 1947, chronic reaction, tb	28	2.1-0.0	0.0-0.0	43%
32. Y., LL, 1963, chronic reaction, tb	10	5.1-6.0	3.6-0.0	35%
33. D., LL, 1961, chronic reaction, tb	8	5.4-6.0	5.0-0.2	11%

1227

Average: 37%

Summary

	Average decline BI
Group 1: Daily Lamprene and prednisone	47% (tb patients 43%).
Group 2: Bi-weekly Lamprene and prednisone	54% (tb patients 29%).
Group 3: Daily Lamprene	25% (tb patients 34%).
Group 4: Bi-weekly Lamprene	37% (tb patients 38%).

Discussion

In both groups, with and without prednisone, a few patients showed a slight increase in BI. It is interesting to note that group 1 (daily Lamprene and

prednisone) seemed to do better than group 3 (daily Lamprene only) and that group 2 (bi-weekly Lamprene and prednisone) seemed to do better than group 4 (bi-weekly Lamprene only).

As the average decline of the BI in the patients with tuberculosis was about the same as the average decline of BI in the whole group, it does not seem likely that treatment of tuberculosis with streptomycin, INH and thiosemicarbazone had much influence on the reduction of the BI in these patients.

Open Trial with Clofazimine in the Management of Recurrent Lepra Reaction and of Sulphone Sensitive Cases: A Preliminary Report*

K. RAMANUJAM, C. G. S. IYER AND G. RAMU

Central Leprosy Institute, P.O. Tirumani, Chingleput 603001, S. India

An open trial to assess the value of clofazimine in the management of cases of lepromatous leprosy with recurrent lepra reaction and those who are sulphone sensitive was commenced in February, 1973. Thalidomide was used as the drug in the control subjects. Up to the end of August, 1974, 61 cases have been admitted into the study. In the majority of instances the drug had been found to be effective. In 3 instances clofazimine failed to confer beneficial effects. Six cases in whom the maintenance dose of the drug was stopped after 52 weeks of continued control of the reactive state, have not revealed any recurrence of reaction.

The Investigation

A study was undertaken to assess the therapeutic value of clofazimine (CLF) with the following objectives, using Thalidomide (TLD) as the control drug: (a) To assess the value of clofazimine in the management of recurrent lepra reaction and (b) to ascertain whether this drug can increase tolerance to DDS in cases of lepromatous leprosy, who are sulphone sensitive and prone to recurrent reaction.

Plan of the study

The investigation has been planned as a continuous one in order to deal with both the objectives (a) and (b). Cases of lepromatous leprosy subject to recurrent episodes of lepra reaction will receive clofazimine or thalidomide during Part (a) of the investigation, lasting for 8 weeks. It is expected that the reactive episodes will be controlled within the 8 weeks' period, with either of these 2 drugs. Thereafter the same patient serves as subject for Part (b) of the trial. If any of

* This investigation received financial support from the WHO.

these cases fail to respond to therapy in the 8 weeks' period, the drug is considered a failure, and the patient taken off the trial. Once the patients are transferred to Part (b) of the trial and the reaction is under control, steroid dependent patients are weaned from steroid, DDS treatment is inducted and gradually increased and the dose of clofazimine/thalidomide reduced progressively until the case on clofazimine continues to receive a maintenance dose of 100 mg of the drug per day and those on thalidomide, a dose of 25 to 50 mg/day. The dose of DDS is increased to the maximum dose of 10 mg/kg body weight/week or to the limit of tolerance.

Subjects for the study

Adult male patients with lepromatous leprosy who had become subjects of recurrent reactive episodes and were sulphone sensitive constituted the subjects for the study. Patients who had become steroid dependent for the control of their reactive states were also eligible for the trial. Allocation of subjects to the trial (clofazimine) or control (thalidomide) group was done by randomization.

Dosage

In Part (a) of the investigation clofazimine was administered in a dose of 100 mg 3 times a day for the maximum period of 8 weeks. The patients in the control group received 100 mg of thalidomide thrice a day for the same period.

In Part (b) of the trial induction of specific treatment with DDS was commenced with a small dose and gradually built up as indicated above and the dose of anti-reaction drug, clofazimine or thalidomide, was progressively reduced till the patients received a maintenance dose of 100 mg of clofazimine or 25 to 50 mg of thalidomide per day.

Duration of trial

The duration of Part (a) of the trial was for 8 weeks and of Part (b), 52 weeks.

Side-effects

Occurrence of side-effects in respect of the drugs was recorded in suitably drawn up proformae.

Records

Details in respect of the frequency, duration and severity of reactive episodes prior to entry into the study, details of reactive phases while in the trial, clinical and bacteriological progress under treatment and finding of laboratory investigation such as haemogram, urinalysis and liver function tests were recorded in suitable proformae.

Laboratory investigations

The preliminary investigation consisted of haemogram, urinalysis, stools examination, biochemical investigations, BI and MI, and skin biopsy. All the investigations except the last were repeated once a quarter. Skin biopsy was repeated as and when necessary.

Assessment of progress

The progress of cases under treatment was suitably recorded and the results assessed according to pre-determined criteria. For Part (a) of the investigation, the progress of cases in relation to the control of frequency and severity of reactive episodes was recorded. For Part (b), the periodical assessment included the presence or absence of reactive episodes, ability to tolerate DDS with reference to its dosage and continuity of treatment, and clinical and bacteriological progress under such treatment.

Removal from the study

Cases who failed to register a satisfactory response within 8 weeks in Part (a) of the investigation and those unable to tolerate even minimum doses of DDS in Part (b) of the study were taken out of the study and counted as failures.

Findings of the study

The investigation was commenced on 20 February, 1973. Up to the end of August, 1974, 61 cases were included in the study. Of these 61 cases, 52 who had been on the trial for more than 8 weeks have been taken up for analysis. The categorization of these 52 cases with regard to the chief manifestation of reactive episode is as under:

Cases of recurrent Lepra Reaction (RLR) with mostly skin manifestations:	25
Cases of recurrent Lepra Reaction (RLR) with mostly skin manifestations and steroid dependent:	7
Cases of Recurrent Pustular Lepra Reaction:	6
Cases of Recurrent Pustular Lepra Reaction and steroid dependent:	7
Cases of RLR with neuritis as the main manifestation:	2
Cases of RLR with neuritis as the main manifestation and steroid dependent:	3
Case of RLR with predominantly osseous manifestation and steroid dependent:	
Case of RLR with predominantly lymph adenitis:	

Of the 61 cases included so far, 5 cases failed to respond to treatment during 8 weeks of Part (a) of the trial—3 on clofazimine and 2 on thalidomide, and hence were taken out of the study. Five cases (2 on clofazimine and 3 on thalidomide) absconded after recording very satisfactory progress.

Six cases receiving clofazimine and 7 cases thalidomide in maintenance doses, and DDS in the optimum dose, were taken off the anti-reaction drug (clofazimine or thalidomide) after the reactions were controlled, and remained controlled for 52 weeks. The cases who were on clofazimine continue to be free from reaction. All the 7 cases who had been on thalidomide have shown a relapse of the reactive state.

The findings of the study up-to-date indicate:

(i) Both clofazimine and thalidomide possess anti-inflammatory properties and are generally capable of controlling recurrent reactive episodes in lepromatous leprosy, irrespective of the predominant manifestation of reaction, except for pustular skin lesions which called for the concurrent administration of antibiotics.

(ii) Of the 2 drugs, thalidomide appears to exert the desired effect quicker.

(iii) Both the drugs permit weaning of patients from steroid dependence.

(iv) Both the drugs increase the tolerance of patients to DDS.

(v) In view of the fact that clofazimine takes as long as 8–12 weeks to exert its anti-inflammatory effect, in very severe reactions or where painful manifestations are predominant it was mandatory to supplement clofazimine initially with cortico-steroids to obtain quick relief.

(vi) Reappearance of manifestations of reaction were observed in an occasional case with both the drugs when the dose was being reduced, or while the patient was on maintenance dose of either drug.

(vii) While generally either drug was effective in controlling recurrent reactive episodes, there were instances where they failed to achieve the desired effect.

(viii) Bacteriologically, in the subjects who had been on the trial for 6 to 19 months and receiving DDS in conventional dose, improvement was observed in both the groups, this being more appreciable in the clofazimine group.

(ix) Side-effects included pigmentation of the skin and mucous membrane, colouration of urine, stools and sweat and development of ichthyotic skin over the extremities in cases on clofazimine; dryness of nasal and buccal mucosa, somnolence and very occasionally bradycardia with or without irregular pulse in cases receiving thalidomide. In none of the cases were the side-effects severe enough to warrant interference with the continued administration of the drug.

(x) The follow-up of the 13 cases in whom the anti-reaction drug was withdrawn after control of reactions showed that the beneficial effect conferred by clofazimine are more long-lasting, presumably due to retention of the drug in the RE cells, these acting as depots of clofazimine from which the drug was released slowly thereby exerting its reaction suppressing effect. On the other hand, the anti-reaction properties of thalidomide seem to be short lived as evidenced by the recurrence of reaction in all the 7 cases soon after the cessation of the drug.

Rifampicin: The Investigation of a Bactericidal Antileprosy Drug

R. J. W. REES

National Institute for Medical Research
Mill Hill, London, NW7 1AA

The purpose of this paper is first to present briefly some general conclusions that have emerged from our experience in the use of rifampicin mainly in the Leprosy Research Unit, National Leprosy Control Centre, Sungei Buloh, Malaysia, and more recently in the Medical Research Council Leprosy Research Project, Addis Ababa, Ethiopia; and secondly, to report in more detail on some of the special studies from which this experience has been derived.

We have treated about 100 patients with rifampicin in the past 6 years. Almost all of them have been suffering from active lepromatous leprosy (LL-LI: Ridley and Jopling, 1966; Ridley and Waters, 1969); some had received no previous treatment, but the majority had developed dapsone resistance. However, data from such dapsone resistant cases with active disease should in general be applicable to all patients with lepromatous leprosy.

General conclusions from these studies may be summarized as follows:

- (1) The Morphological Index (MI) falls more rapidly than in patients treated with dapsone.
- (2) Clinical improvement in the first 6 months or so of treatment is more rapid than under dapsone therapy.
- (3) Over a period of up to 4 years the fall in the Bacterial Index (BI) is no more rapid than that seen in patients treated with dapsone or clofazimine.
- (4) Contrary to our expectations, erythema nodosum leprosum (ENL) is no more frequent or severe than under dapsone therapy.

Rifampicin was originally tested in the mouse footpad for activity against *Mycobacterium leprae* and it was shown to be equally effective against both dapsone sensitive and dapsone resistant strains (Rees, Pearson and Waters, 1970; Rees, personal communication). A very rapid fall in the MI (to baseline values within 4 weeks) was observed in our initial, pilot, clinical trial, implying that the drug possessed powerful bactericidal activity (Rees, Pearson and Waters, 1970). These experimental findings have been confirmed and extended by Holmes and Hilson, 1972; Shepard *et al.*, 1971 and Shepard, Levy and Fasal, 1972*a,b*).

The next phase of our investigations was designed to determine the rate at which rifampicin killed *Myco. leprae* in man. Patients with active lepromatous leprosy were treated with rifampicin 600 mg daily or dapsone 100 mg daily, and *Myco. leprae* obtained from biopsies of skin taken at intervals during the trial were monitored for the presence of viable bacilli by mouse footpad inoculation.

This study (Rees, Pearson and Waters, 1970) showed that *Myc. leprae* in the skin was rapidly killed by rifampicin since after only 3–24 days treatment viable bacilli could no longer be recovered, whereas in contrast viable bacilli were still recovered after 69 days treatment with dapsone. Similar or even more rapid killing of *Myc. leprae* in the skin of rifampicin treated patients has been reported by Shepard, Levy and Fasal, 1972a,b and Levy, Shepard and Fasal, 1973.

With this clear evidence from experimental and clinical studies that rifampicin was highly bactericidal against *Myc. leprae* on daily doses of 600 mg in man, or its equivalent in animals, subsidiary and exploratory clinical trials were undertaken to study the efficacy of lower daily doses (20, 60 and 150 mg rifampicin) and 600 mg doses given intermittently. These modifications seem justified on the basis of the high activity of rifampicin against *Myc. leprae*, but also had an essentially practical approach because of the very high cost of the drug.

The pilot trial of smaller doses of rifampicin was designed entirely to determine whether doses less than 600 mg daily were active. Therefore the trial lasted only 2 months and was assessed primarily on bacteriological criteria by measuring the viability of *Myc. leprae* in the skin by the MI and mouse footpad test. By these criteria all 3 lower doses were shown to be active against *Myc. leprae*, although their rate of killing was slower than that obtained with 600 mg rifampicin daily. These short-term results do not prove the efficacy of low dose rifampicin therapy for long-term treatment of lepromatous leprosy. However, the results are important in showing that rifampicin is still bactericidal at a dose of 20 mg daily, and therefore this dose in combination with dapsone for a limited initial period might prove highly efficacious, as related to the small increased cost.

The second and probably more important exploratory clinical trial is concerned with rifampicin therapy on an intermittent basis because of its high bactericidal activity against *Myc. leprae*. Our intermittent rifampicin treatment trials have been started in Malaysia and Ethiopia and are based on a dosage of 600 mg rifampicin on 2 consecutive days once a month. These are in too early a stage to report clinical results. Unfortunately, in the field of tuberculosis chemotherapy it is well recognized that intermittent rifampicin regimens give rise to a high proportion of "adverse immunological-type reactions" frequently associated with circulating rifampicin-dependent antibodies (Aquinas *et al.*, 1972). In tuberculosis these adverse reactions have occurred in intermittent rifampicin therapy given once weekly and are more frequent when the dose of rifampicin exceeds 600 mg. There is no experience on the intermittent regimen we have chosen and therefore it is encouraging that to date no adverse reactions have occurred and no circulating rifampicin-dependent antibodies have been detected in some 30 patients who have been given once monthly rifampicin over a period of about 12 months.

The final part of this paper is a progress report on the study described at the 10th International Leprosy Congress, Bergen, in 1973 (Rees *et al.*, 1973). The advent of a bactericidal drug offered hope that patients could be cured by shorter periods of therapy than are currently employed using dapsone. We investigated this possibility by studying groups of patients treated with rifampicin 600 mg daily (combined with thiambutosine) for 6, 12 and 24 months. Each patient was subjected to biopsy of the skin, peripheral nerve, striated muscle, and smooth (dartos) muscle, and the specimens inoculated into the footpads of thymectomized-irradiated and normal mice. These tissues were chosen as preferred sites where there is good evidence that *Myc. leprae* persists in spite of

dapsone therapy (Pearson, Rees and Weddell, 1970; Waters *et al.*, 1974). Our hope was that, after 2 years of treatment (or possibly less) no viable bacilli would be detected in these sites. If this were the case, it would be justifiable to discontinue antileprosy treatment, while continuing careful clinical observation together with repeated site monitoring in mice to detect relapses at the earliest possible moment.

The results of these studies have clearly shown that unfortunately our hopes of a quick "cure" by rifampicin have been disappointing. Thus, in 6 patients given rifampicin for 6 months, 10 given rifampicin for 12 months and 10 patients given rifampicin for 2 years, a proportion still harboured living bacilli after each period of treatment at one or other of the selected sites as demonstrated by their ability to multiply in the footpads of mice. To date, bacilli isolated in mice from 3 of the rifampicin treated patients have been shown on mouse passage to be rifampicin sensitive. There is clearly a persistor problem with rifampicin, as with dapsone and other antileprosy drugs, and 2 years is not long enough to "cure" patients with lepromatous leprosy.

It is still possible that rifampicin will "cure" lepromatous leprosy more quickly than dapsone; maybe 3 years treatment will be enough. These studies are continuing. However, patients with lepromatous leprosy are known to have very low specific cell-mediated immunity with which to deal with their bacilli, and 2 years treatment with a highly bactericidal drug, such as rifampicin, has not sterilized their tissues of viable *Myco. leprae*. One must conclude, not with an answer but a question: can patients with lepromatous leprosy ever be cured by chemotherapy alone?

Acknowledgements

All the data presented in this paper is part of coordinated chemotherapeutic trials undertaken by the Medical Research Council at the Leprosy Research Unit in Malaysia and more recently in Ethiopia. The trials reported here were coordinated from the National Institute for Medical Research, London, and the clinical conduct and expertise undertaken by Drs J. M. H. Pearson and M. F. R. Waters. The mouse footpad studies were undertaken in London on refrigerated tissues despatched by air. The assessments of rifampicin-dependent antibodies were undertaken by Dr Sheila Worledge of the Department of Haematology, Royal Postgraduate Medical School, Hammersmith. Messrs Gruppo Lepetit of Milan generously provided free all the rifampicin.

References

- Aquinas, M., Alan, W. G. L., Horsfall, P. A. L., Jenkins, P. K., Wong, Hung-yan, Girling, D., Tall, R. and Fox, W. (1972). Adverse reactions to daily and intermittent rifampicin regimens for pulmonary tuberculosis in Hong Kong. *Br. med. J.* **1**, 765.
- Holmes, I. B. and Hilton, G. R. F. (1972). The effect of rifampicin and dapsone on experimental *Mycobacterium leprae* infections; minimum inhibitory concentrations and bactericidal action. *J. med. Microbiol.* **5**, 251.
- Levy, L., Shepard, C. C. and Fasal, P. (1973). Death of *Myco. leprae* following treatment of leprosy patients with 1500 mg in a single dose. *Int. J. Lepr.* **41**, 490.
- Pearson, J. M. H., Rees, R. J. W. and Weddell, A. G. M. (1970). *Mycobacterium leprae* in the striated muscle of patients with leprosy. *Lepr. Rev.* **41**, 155.
- Rees, R. J. W., Pearson, J. M. H. and Waters, M. F. R. (1970). Experimental and clinical studies on rifampicin in the treatment of leprosy. *Br. med. J.* **1**, 89.

- Rees, R. J. W., Waters, M. F. R., Pearson, J. M. H., Helmy, H. S., McDougall, A. C., Weddell, A. G. M. and Edwards, Rose (1973). Rifampicin: Assessment of a bactericidal drug in the treatment of lepromatous leprosy. *Int. J. Lepr.* **41**, 681.
- Ridley, D. S. and Jopling, W. H. (1966). Classification of leprosy according to immunity. A five-group system. *Int. J. Lepr.* **34**, 255.
- Ridley, D. S. and Waters, M. F. R. (1969). Significance of variations within the lepromatous group. *Lepr. Rev.* **40**, 143.
- Shepard, C. C., Levy, L. and Faisal, P. (1972a). Rapid bactericidal effect of rifampicin on *Mycobacterium leprae*. *Am. J. trop. Med. Hyg.* **21**, 446.
- Shepard, C. C., Levy, L. and Faisal, P. (1972b). Rifampicin and *Myco. leprae*. *Int. J. Lepr.* **40**, 459.
- Shepard, C. C., Walker, L. L., Van Lanningham, R. M. and Redus, M. (1971). Kinetic testing of drugs against *Mycobacterium leprae* in mice. Activity of cephaloridine, rifampicin, streptovaricin, and viomycin. *Am. J. trop. Med. Hyg.* **20**, 616.
- Waters, M. F. R., Rees, R. J. W., McDougall, A. C. and Weddell, A. G. M. (1974). Ten years of dapsone in lepromatous leprosy: Clinical, bacteriological and histological assessment and the findings of viable leprosy bacilli. *Lepr. Rev.* **45**, 288.

The Use of Rifampicin in the Treatment of Leprosy

E. J. SAERENS

*University of Antwerp, Dept. of Int. Medicine,
Universiteitsplein 1, Wilrijk, Belgium*

Rifampicin is the most active drug in the experimental mouse footpad infection with *Myc. leprae* and in the treatment of human lepromatous leprosy as judged by the rapid decline in Morphological Index.

Its definite place in the overall treatment of human leprosy needs however to be further ascertained through controlled clinical trials exploring different therapeutics, also intermittent and therefore less expensive regimens associated with careful patient monitoring for side-effects.

As an introduction to our discussion planned for tomorrow, I would like to raise four questions that have received only incomplete answers to my knowledge, and that I hope may provoke suggestions and lead to further investigations.

The first introductory question is: how active is rifampicin as an agent against Myco. leprae under experimental conditions? This question may seem superfluous after all the work that has been done and published by many of those here present. We do know that rifampicin administration decreases very rapidly the number of viable bacilli or is followed by a delay in growth in the mouse footpad model, and also that its minimal inhibitory concentration is somewhere in the range of 0.06 to 0.12 mcg/ml and that much higher serum levels can be reached by oral administration, as well in mice as in men.

We also know from comparative investigations that the effect of a single dose of rifampicin is of the same magnitude as that obtained by DDS given continuously for 2 months. An equally favourable impression is gained from the experimental model developed in this institute and using *Myc. marinum*.

Existing models with *Myc. leprae* have, however, their limitations: for instance the bacteriological yield does not seem to allow any deduction as far as frequency of selection of resistant mutants is concerned.

The armadillo and to a lesser extent some rat strains might provide a more suitable model in this regard but to my knowledge this question remains open. This could nevertheless be of considerable importance in the extrapolation of experimental therapeutic animal data to human therapy, (for example when we think in terms of relapse in tuberculosis due to selection of resistant mutants under monotherapy).

I am aware of the fact that if little attention has been given to the subject, it is not mainly because of lack of concern but because of lack of an appropriate model and suitable standards of comparison.

I would now like to turn to *the second question: how active is rifampicin in the therapy of human leprosy?* A few hundreds of patients either treated unsuccessfully with other drugs or previously untreated have been subjected to rifampicin administration and monitored mainly in open trials or more rarely in controlled trials. Dosage has varied from 150 to 1.200 mg per administration and the total duration has ranged from a few months to more than 2 years. Treatment regimens have consisted of continuous daily or varied intermittent schemes.

Evaluation of therapeutic results has been based on clinical criteria and on bacteriological criteria. If one accepts the evaluation of the Morphological Index (on smears or preferably on serial skin biopsies) all or not followed by inoculation into the mouse footpad, as a major criterium of therapeutic effect then the overall conclusion is that within 2 to 3 months of rifampicin at a dosage level of about 10 mg/kg in continuous daily administration or 15 mg/kg in intermittent administration, a bactericidal effect is achieved. Once again, however, we are limited by the available methodology.

In antibiotic therapy success and cure have often been attributed too exclusively to the rather simplistic assumption that a serum level in excess of the m.i.c. for the causative microorganism suffices.

The measurable and well documented decrease in viable bacilli in mouse footpads or even human skin lesions, when appropriate doses of rifampicin are administered seems to corroborate this idea.

We are all aware, however, that in the case of leprosy this is not a sufficient or final answer. It is already documented that relapses in patients under long standing DDS therapy have occurred and are most likely due to development originating from the so-called "dormant bacilli" located in muscle fibres and nerve sheaths. Little is known about the possible effect of rifampicin on these bacilli although some results have been claimed when rifampicin was used in association with other drugs.

Recent communications have drawn attention to the fact that DDS is acetylated and that as with INH (isoniazid) there may exist slow and rapid acetylators. So far no therapeutic relevance of this metabolic pattern is known. Rifampicin on the other hand is mainly de-acetylated to an active des-acetyl rifampicin, and if combined administration would be considered an investigation into combined pharmacokinetics might be indicated.

At least 2 additional types of information are lacking:

- (a) We need to know more about rifampicin tissue penetration (e.g. in nerve and muscle fibres) and even more about rifampicin's intracellular and even probably intralysosomal penetration.
- (b) We need to know more about "optimal" dosage, whether rifampicin is used alone or in combination.

For evident reasons related to the available evaluation criteria the main attention has till now been focused on active lepromatous leprosy.

The number of patients with borderline or tuberculoid forms of the disease is, however, far in excess of those with lepromatous leprosy, and it remains therefore a challenge to investigate the use of rifampicin in such cases provided suitable evaluation methods can be developed. In fact we are confronted with the paradoxical situation that rifampicin is a most, if not the most, active drug against *Myc. leprae* and in lepromatous leprosy, but we know neither whether rifampicin is or can be a curative drug nor how long it should be used.

The third question is: how safe is rifampicin in the therapy of leprosy? In trying to provide an answer to this question we can first look at the considerable amount of data accumulated in the treatment of tuberculosis. Generally speaking one can say that rifampicin is a well tolerated and safe drug when administered continuously; there is no haematological, oto-vestibular or renal toxicity, and the data about hepatic side-effects do not exceed a few per cent of patients treated with the drug. Jaundice and or a deterioration in the hepatic function remain contra-indications for the use of rifampicin. The available data about leprosy do not differ substantially. Leprosy therapy is, however, confronted with some peculiar aspects related to the disease itself, one of them being reactive episodes. Different authors agree that under rifampicin administration the incidence of reactions has been similar to that under DDS therapy and its intensity did not exclude continuation of therapy. Investigational use of highly successful intermittent rifampicin regimens in tuberculosis has been accompanied by several reports on side-effects of a different nature than those that were known under continuous therapy.

The intensity and incidence of these side-effects seem to be related to dosage and interval of doses. The most frequent of these side-effects is the so-called flu-syndrome with fever and arthralgia. Appearing within a few hours following rifampicin administration, it generally did not require interruption of therapy and could be managed in most cases by reduction in dosage or by a switch to continuous daily therapy.

The more serious side-effects such as thrombocytopenia, purpura, and anuria, which are fortunately rare, require immediate interruption of rifampicin therapy and forbid its further use.

Quite evidently these reports are a cause of justified concern; even more since similar accidents may occur under a rifampicin therapy that has been interrupted and restarted accidentally.

The clinical aspects of these side-effects have suggested that rifampicin induced immune complexes may be responsible.

In team work with a group of investigators of the University of Leuven, Dr Stevens and Dr Verbist, we are trying to investigate this hypothesis further. We know that rifampicin as such is not an antigen although it can probably conjugate with proteins and then elicit antibodies. Antigen-antibody reactions with mobilization of complement or activation of complement components are by analogy with other clinical syndromes considered to be involved in the different side reactions observed. Several teams of investigators have tried to monitor these immunological aspects in patients under rifampicin therapy in tuberculosis. One indirect method is based on complement fixation in a haemagglutination technique. The one which we use is based on immune complex precipitation (Ouchterlony).

The latter is certainly more specific but requires also the use of a stable rifampicin conjugate which is difficult to prepare.

Ongoing studies aim to look into the quantitative aspects and into the kinetics of this phenomenon. The precise relation between the clinical side-effects and the immune-complexes is not yet clearly established. We can only say that most likely it is not the mere presence of these "antibodies" (they might even be present spontaneously) that is responsible for the incidents, but most probably a critical ratio between antibodies and the hapten-carrier.

A lower incidence or practical absence of the side-effects just described has

been observed in certain geographical areas (Zaire), and the hypothesis has been formulated that a different immunological reactivity could be involved.

These data, as mentioned, stem from tuberculosis research, and once more we are compelled to keep in mind the particular aspects of leprosy in its varied clinical manifestations. Little if any side-effects, and certainly no serious side-effects have, as far as I know, been reported in lepromatous patients under intermittent rifampicin therapy. The available information suggests in my opinion for the time being, 2 leads:

(1) A practical one: namely that any form of intermittent rifampicin therapy should be supervised with a close monitoring of the patients.

(2) An investigational one, which we are planning and which is aimed at looking into the immunological reactivity of different leprosy patients before and during rifampicin therapy, with special regard to the presence or formation of these antibodies.

My fourth and last question is directly linked up with the previous ones. How practical is rifampicin in the therapy of human leprosy? The answer is evidently not only linked up with activity or efficacy and safety but also with socio-economic factors.

It has been ironically said that the major side-effect of rifampicin is its price. A large scale continuous daily use of rifampicin in the therapy of leprosy, mainly in developing countries, seems therefore wishful thinking.

The overall cost of therapy, however, is not just a matter of cost of chemotherapy but also of mobilizing the few available medical and paramedical personnel and facilities. Therefore any short therapy whether initial or definite that could reduce infectivity and substitute to any significant extent the life-long therapy regimens that are available now seems worth investigating.

The development of a short safe intermittent regimen could very well be a valid alternative even if it has to include an expensive drug.

Within short range I therefore dare suggest that further controlled trials be set up to investigate efficacy and safety of intermittent rifampicin or rifampicin containing regimens of different duration. Whenever possible these trials should be associated with immunological studies and optimally with a prolonged follow-up of patients.

Further ahead it is to be expected that new rifamycin derivatives with different pharmacokinetic properties will become available, first for animal investigation, and hopefully later for human use.

In summary it is my opinion that rifampicin has provided us with an extraordinarily active drug in lepromatous leprosy but that further research is mandatory to define its proper place and limitations in the overall therapy of leprosy.

A Controlled Clinical Trial of Continuous and Intermittent Rifampicin Therapy During an Initial Three Months Period in Lepromatous leprosy: Final Analysis

S. R. PATTYN

*University of Antwerp, UIA, Institute for Tropical Medicine,
Antwerp, Belgium*

M. T. ROLLIER AND R. ROLLIER

Service National de léprologie, Casablanca, Maroc

E. J. SAERENS AND P. DOCKX

University of Antwerp, UIA, Antwerp, Belgium

A controlled clinical trial was organized as a 3 months introductory treatment of lepromatous leprosy, comparing the following treatment regimens administered in the hospital: dapsone 100 mg daily, rifampicin 450 mg daily, rifampicin 900 mg once a week and clofazimine 300 mg once a week. Thereafter the patients were discharged, and treated with standard dapsone 100 mg in routine self-administration. Clinical, biological and microbiological assessments were performed at the start and after 1, 2, 3, 6, 9 months of treatment. BI and MI were determined on a blind basis. One hundred and twenty-nine patients were admitted to the trial, 93 remaining for final analysis. Results show that from a microbiological standpoint the 2 rifampicin groups behaved similarly, their MI reaching minimum levels within one month, as compared with 3 to 6 months in the case of dapsone and clofazimine treated groups, the clofazimine group being the slowest. Clinical improvement was somewhat more rapid in the RMP groups, especially the cicatrization of soft palate ulcerations and in the daily rifampicin group the regression of peripheral anaesthesia. There was somewhat more ENL, although not statistically significant, after rifampicin weekly. There were no other complications associated with any of the treatment schedules. The results show that intermittent once weekly rifampicin treatment is as efficient as daily therapy, and that the period of treatment may even be shortened to 2 months, thus reducing further the total amount of drug administered. Clofazimine 300 mg once a week induces too slow an improvement, although it could be useful as an addition for combined introductory intermittent therapy.

Nasal smears may be as sensitive indicators of the bacteriological evolution under drug treatment as are skin biopsies.

Introduction

Results of treatment of chronic infectious diseases can be much improved if treatment can be supervised. Supervision of treatment is practicable only when it is intermittent. Intermittent treatment has a further advantage in reducing the total amount of drug administered.

Acedapsone is at this moment the drug which lends itself to the longest intermittency in the therapy of leprosy. However, as discussed previously (Pattyn, 1972) the administration of acedapsone in the treatment of multi-bacillary forms of the disease should be preceded by an introductory phase that is rapidly bactericidal.

Rifampicin is a rapidly bactericidal drug for *Myco. leprae* (Rees *et al.*, 1970, Shepard *et al.*, 1972) when administered in daily doses. From experiments in mice it is known (Pattyn *et al.*, 1974) that it is also active when given intermittently.

We therefore initiated a controlled clinical trial to compare the effect of daily administration of rifampicin with a once weekly administration. A weekly administration of clofazimine was also included in the trial whereas classical dapsone therapy was the reference treatment. Preliminary results on this trial have been published elsewhere (Pattyn *et al.*, 1974).

Organization of the Trial

Selection of patients

Patients were selected at the out-patient department of dermatology at Casablanca, where 200 new leprosy patients a year are seen, nearly half of them suffering from lepromatous or borderline lepromatous forms of disease. These were hospitalized for investigation and eventual inclusion in the trial.

Pretreatment investigations

The severity of skin involvement was estimated and graded: for erythematous lesions, 2 for infiltrated plaques and 3 for nodular lesions. The degree of anaesthesia of the extremities was also graded into categories: 0 for absence of anaesthesia, 1 for finger or toe anaesthesia, 2 for forearm or leg anaesthesia and 3 for anaesthesia of the whole member.

Routine haematological examinations were performed including red blood cell count, haemoglobin and haematocrit determination, erythrocyte sedimentation rate (ESR), and a chest X-ray was taken. Smears were prepared from the nasal mucosa, the ear-lobes and the skin of the forehead. A skin biopsy from a clearcut lesion was taken and fixed in 10% formalin.

Criteria for admission

For inclusion in the trial patients had to conform to the following conditions: to be adults with previously untreated lepromatous or near lepromatous leprosy, not to suffer from concomitant tuberculosis, and to show in their biopsies a Morphological Index (MI) higher than 0.10 to ascertain clearer results. The trial started in May, 1972, the last patients entered the trial in May, 1974.

Chemotherapeutic regimens

Using a table of random numbers, patients were admitted to one of the following treatment regimens administered during their 3 months hospitalization.

RMP 450: rifampicin 8–10 mg/kg body weight 450 mg daily.

RMP 900: rifampicin 15 mg/kg body weight, 900 mg, once a week.

CLO 300: clofazimine 300 mg once a week.

DDS 100: dapsone 100 mg daily (starting with a lower dose and reaching the 100 mg dosage after 2 weeks).

All drugs were administered in the early morning about 1 hour after breakfast.

After 3 months patients were discharged from the hospital and treated by the classical dapsone therapy, 100 mg daily in self-administration. The drug is given to them at each out-patient control visit.

Management of patients

During the hospitalization period, dermatological, neurological, haematological examinations and skin biopsies were repeated after 1, 2 and 3 months. All biopsies were sent to Antwerp. During the out-patient period, patients were invited to return to the hospital after a further 3 months for examinations as above. Thereafter patients are expected to return to the hospital every 6 months. In this trial patients were followed for at least 6 months.

Bacteriological procedures

Code numbered biopsies were sent to Antwerp where they were examined after haematoxylin-eosin and Ziehl-Neelsen (Fite-Faraco technique) staining. Bacterial and morphologic indices (BI and MI) were recorded without any knowledge of the treatment schedule or clinical status of the patients. Data of these determinations were communicated and stained slides were sent to Casablanca.

Clinical assessments

Patients were examined monthly, when weight and ESR were recorded, and clinical improvement and sensibility of the extremities were evaluated. The degree of resolution in lepromatous infiltration was recorded as 0 when unchanged, 1 for discrete improvement, 2 for easily visible improvement, 3 for a reduction in infiltration by 50%, 4 for nearly complete resolution, and 5 for a total disappearance of any cutaneous signs, "W" if the condition was worsening or if erythema nodosum (ENL) developed.

The occurrence of ENL was also noted during the follow-up period, as were all other complaints made by the patients.

Results

Exclusions

A total of 129 patients participated in the trial (Table 1). From these, 19 had to be excluded from the final analysis because of a MI below 0.10 at the start of

treatment, 16 patients had to be excluded because a group of biopsies was lost during air transport and finally 1 was excluded because the clinical file was unavailable.

Table 2 shows the distribution of the 93 patients remaining for final analysis within each treatment group. The number of males largely exceeds the number of females, reflecting the difference in sex distribution of leprosy as seen in Morocco. Mean age, body weight and ESR in each group are comparable (Table 3). The degree of skin involvement (Table 4) and anaesthesia was moderate in most patients and not significantly different between the different treatment groups.

TABLE 1
Population studied

	Male	Female	Total
Patients admitted into trial	95	34	129
Excluded from analysis:			
MI 0.10	14	5	19
Biopsies lost by accident	13	3	16
Files unavailable	1		1
Total remaining for analysis	67	26	93

TABLE 2
Distribution of patients among treatment groups

	RMP 450	RMP 900	CLO 300	DDS 100
Number of patients	25	25	21	22
male : female	15 : 10	18 : 7	17 : 4	17 : 5
Average age (male)	35.8	32.3	40.4	39.0
max - min.	65-14	55-16	61-16	72-20
Average age (female)	38.7	25.7	42.2	42.4
max - min.	62-15	53-17	50-15	75-17

TABLE 3
Weight and ESR of patients

	RMP 450	RMP 900	CLO 300	DDS 100
Weight average	53.6	55.3	55.0	55.1
	80/37	92/39	80/39	70/41
ESR average	62/87	42/66	54/85	60/85
Extremes max.	140/144	115/130	121/142	130/135
Extremes min.	7/18	5/12	4/10	5/15

TABLE 4

Degree of skin involvement and anaesthesia of extremities

		RMP 450	RMP 900	CLO 300	DDS 100
Degree of skin involvement at start	1	9	3	5	4
	2	15	21	15	18
	3	1	1	1	—
Degree of anaesthesia at start	0	7	8	4	6
	1	16	17	14	12
	2	2	—	3	4
	3	—	—	—	—

Evolution of MI and BI

Figure 1 shows the evolution of BI and MI during 6 months for each regimen. The mean MI before treatment was slightly lower in the DDS and CLO groups. The evolution of MI in the 2 RMP regimens differs significantly from that in the other 2 regimens: it fell down under 0.10 within 1 month for both RMP regimens while this is only the case after 2 months for DDS 100 and 3 months for CLO 300. Minimal values for the MI were reached after 1 month for RMP 450, 2 months for RMP 900, but not within 3 months for the CLO and DDS groups.

In the preliminary data previously published (Pattyn *et al.*, 1974) mention was made of a comparison of the MI determined independently in Antwerp and Casablanca. A small difference was noted between the 2 readings but the general trend was entirely comparable. The complete figures confirm the preliminary findings: values were slightly higher in Casablanca, but the evolution was the same (Fig. 2). The BI in the nose smears (Table 5) also fell more rapidly in the 2 RMP regimens: from more than 4.0 before treatment to 2.0 within 1 month. However,

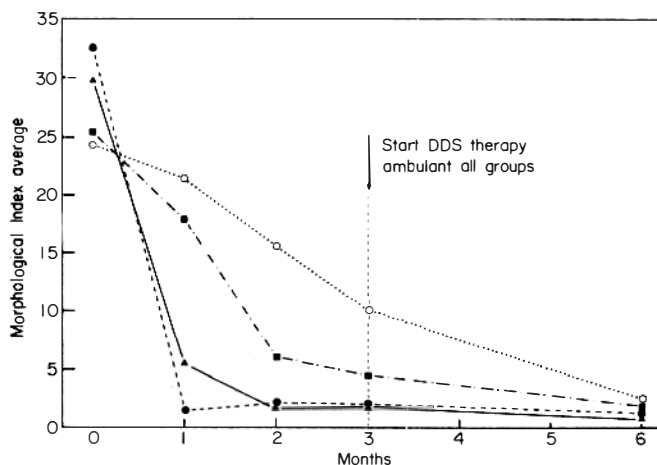


Fig. 1. Evolution of MI and BI during treatment. (▲---▲) RAMP 900/W; (●---●) RAMP 450/D; (■-.-.-■) DDS 100/D; (○...○) CLO 300/W.

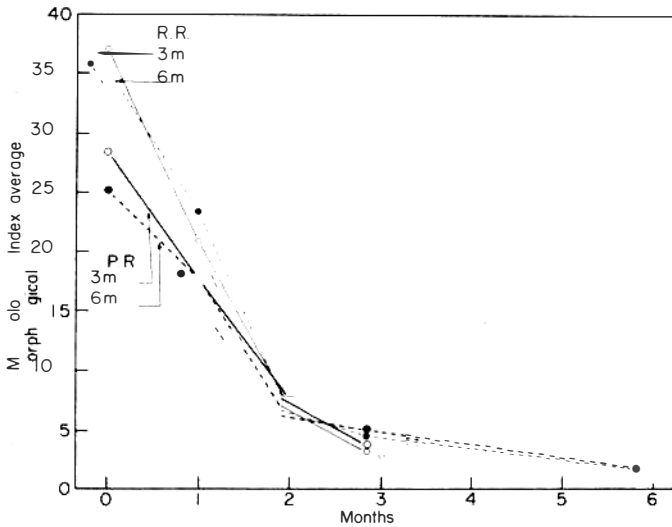


Fig. 2. Comparison of 2 different biopsy evaluations (at 3 and 6 months) R. R. Rollier reading; P. R. Pattyn reading.

TABLE 5

Evolution of BI and MI in nose smears

	RMP 450	RMP 900	CLO 300	DDS 100
BI				
Start	4.7	4.4	3.8	3.2
1 month	2	1.9	3.6	3.1
2 months	1.8	2.4	3.3	2.5
3 months	1.7	1.5	2.6	1.9
MI				
Start	0.34	0.34	0.22	0.20
1 month	0.01	0.02	0.18	0.20
2 months	<0.01	0.01	0.05	0.09
3 months	<0.01	<0.01	0.02	0.01

after 3 months there is no notable difference between the RMP and DDS treated patients. Again the CLO 300 group lags behind in this respect also.

As was the case in the skin the MI in the nose smears at the start was somewhat higher in the RMP treated patients. Within 1 month the MI in these patients reached baseline levels, while this situation was reached in the CLO and DDS groups at the third month only. The BI in the skin did not change during the observation period (Table 6).

Clinical evolution

Due to circumstances, some clinical data are lacking, reducing the number of patients available for this analysis. Table 7 shows the evolution of body weight

TABLE 6
Evolution of BI during treatment (mean values)

	RMP 450	RMP 900	CLO 300	DDS 100
Start	4.7	4.5	4.8	4.5
1 month	4.7	4.3	4.5	4.2
2 months	4.1	4.7	4.3	4.3
3 months	3.6	4.5	4.7	4.3
6 months	4.1	4.1	4.1	4.3

TABLE 7
Evolution of weight and ESR during treatment

	RMP 450	RMP 900	CLO 300	DDS 100
Weight average				
Start	53.6	55.3	55.0	55.1
1 month	53.8	55.5	55.3	55.8
2 months	55.0	56.8	54.1	56.7
3 months	55.6	57.4	54.2	57.3
ESR average				
Start	62/87	42/66	54/85	60/85
1 month	64/88	51/69	57/80	56/84
2 months	54/80	57/82	67/90	63/87
3 months	56/79	52/72	65/85	63/88

and ESR. There is some weight increase in all treatment regimens except for CLO 300 while the values for ESR are lower for the RMP 450 only, these differences are not significant.

Figure 3 shows the histogram, depicting the degree of reduction of infiltration of the cutaneous lesions. The fastest rate of improvement is observed in the RMP 450 regimen, followed by the RMP 900 and DDS 100 regimens, while the CLO 300 regimen leads manifestly to a slower improvement. There is a parallelism between the fall of the MI in the different groups and the rate of cutaneous improvement.

As can be seen from Table 8, improvement of anaesthesia of the extremities was much faster in the RMP 450 regimen: at 6 months 17 out of 19 patients showed a considerable improvement in this respect, while this was only so for roughly half the patients on the other 3 regimens. Table 9 shows the number of ENL episodes during the first 3 months, the next 3 months and later. One patient in each of the RMP 900 and CLO 300 groups was suffering from this condition at the start of treatment. There was a non-significant greater number of ENL episodes during the first 6 months of treatment within the RMP 900 group; the numbers of ENL within the other groups are absolutely comparable.

At the start of treatment a considerable number of patients had rhinitis, even haemorrhagic (Table 10). This condition also improved more rapidly among the RMP treated patients, but this is difficult to quantify and is therefore not

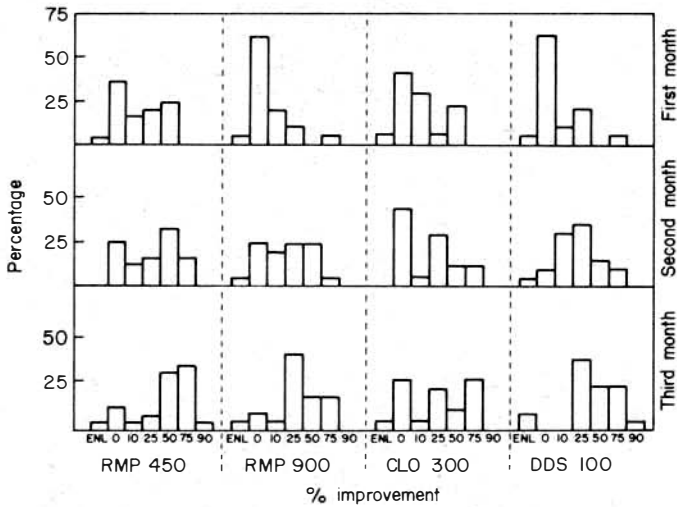


Fig. 3. Clinical improvement during first 3 months of treatment.

TABLE 8

Evolution of anaesthesia of extremities during the first 3 months of treatment

	Improvement	Status quo	No. at start	Total
RMP 450	16	2	6	24
RMP 900	9	6	8	23
CLO 300	7	7	4	18
DDS 100	9	7	6	22

TABLE 9

Incidence of ENL

	RMP 450	RMP 900	CLO 300	DDS 100
ENL				
Start	1	0	1	0
First 3 months	2	3	1	2
4-6 months	1	6	3	3
After 6 months	1	1	1	3

recorded. Ulcerations of soft palate were present in some patients, cicatrization of these was clearly more rapid within the RMP 900 group, while in the CLO 300 and DDS 100 groups, these lesions were not healed in some patients after 3 months of treatment.

Other complications

Table 11 shows all complications and the subjective complaints noted during the first 3 months of treatment. Especially important here, are symptoms which

TABLE 10
Evolution of nose lesions

	RMP 450	RMP 900	CLO 300	DDS 100
Start				
Total	25	25	21	22
Rhinitis	14	13	9	10
Haemorrh. rhin.	11	9	10	12
Palate ulcer.	7	5	4	8
Palate cicatr.				
1 month	4	5	1	6
2 months	1		1	
3 months	1			
unknown	1			
Palate non-cicatr.			2	2

TABLE 11
Clinical complications during the first 3 months of treatment

	RMP 450	RMP 900	CLO 300	DDS 100
Arthralgia	3		2	1
Fever (headache)	1	1	1	
Jaundice				1
Morbilloform erythema	1			
Neuralgia		1		
Pruritus		2		1
Stomach pains			2	
Bronchitis				1
Cystitis			1	
Increased ESR at 2 months				1
Zona			1	

could be expressions of complications of the intermittent administration of RMP. Serious complications such as thrombocytopenia and anuria were not observed. In no instance had the therapeutic regimen to be interrupted or changed. One case of icterus occurred in the DDS group after 2 months treatment. Arthralgias and febrile episodes occurred as frequently in those patients not receiving as those taking RMP. One patient on dapsone had a sudden unexplained increase in his ESR at 2 months, which disappeared at 3 months.

Discussion

The evolution of the reference dapsone treatment is as could be expected from studies previously performed by other authors (Shepard *et al.*, 1968; Rees, 1965) 100 days of treatment being necessary to obtain maximal measurable bactericidal effect.

The results of the RMP 450 regimen are also consistent with previous experience, namely a rapid decline of the MI, within 1 month of treatment (Rees *et al.*, 1970; Shepard *et al.*, 1972; Pattyn *et al.*, 1972). Our results show that with

patients whose average weight does not exceed 60 kg, a dosage of 450 mg daily may be sufficient. Intermittent administration of RMP, 900 mg once weekly produces an identical decline of the MI in skin biopsies and nose smears, and the same fall in the BI in the latter. The regression of anaesthesia was significantly more rapid in the daily RMP regimens, compared with the three other groups.

The greater number of ENL episodes observed with the RMP 900 regimen, especially during the second trimester after the start of treatment, is not statistically significant. This should be investigated on a greater number of patients.

The weekly administration of RMP was not associated with any significant side-effect. This must be attributed to the relatively low dose of the drug administered and the short duration: most side-effects have been observed after more than 3 months intermittent therapy (Gyselen, 1971).

The total amount of rifampicin administered during 3 months in the RMP 900 regimen has been but one fourth of the total amount administered in the continuous regimen: 10.8 g compared with 40.5 g. The results of the present trial, and those of experiments in mice (Pattyn and Saerens, 1974) allow the conclusion that the intermittent administration of RMP may be reduced to a period of 2 months, or a total amount of 7.2 g.

The important question of necessity for combined therapy during the initial phase was not considered in this short term trial and can only be resolved by very long term trials (Committee on experimental therapy, 10th International Congress for Leprosy, Bergen 1973). An effort will be made to follow as long as possible the patients who participated in the present trial.

From a theoretical point of view and in analogy with the situation in tuberculosis (Pattyn, 1972) combined drug therapy is probably unavoidable in the initial phase of treatment of multibacillary leprosy. Since there is no antagonism between dapsone and rifampicin in their activity on *Myc. leprae* (Shepard, 1973), one could probably administer acedapsone from the very start and even add weekly injections of thiambutosine for 2 or 3 months, provided this does not result in clinical complications. This was not done in the present trial because it was first necessary to assure that the weekly RMP regimen compared favourably with the daily administration of the drug.

Clofazimine in a dosage of 300 mg once weekly was clearly the least effective treatment both in terms of bacteriological results as in clinical improvement. But it might be useful as a component of the initial combined introductory treatment referred to above. One other important result of the present study is that nasal smears may constitute a parameter as important as skin biopsies to monitor the effect of drug treatment of multibacillary forms of the disease. Although it is difficult to standardize nasal smears, their BI diminished significantly within the first months of treatment with RMP and reached comparable values after 3 months in all treatment groups. This may be in direct relationship with the healing of the rhinitis in lepromatous leprosy. In the clofazimine treated patients the MI in the nose smears fell significantly more rapidly than in the skin. One may wonder if this is the result of a concentration of the drug in the nasal mucosa.

The treatment of multibacillary leprosy can be conducted in an analogous way as is presently done for tuberculosis: a short term introductory therapy rapidly bactericidal, intermittent (preferably combined) and therefore supervisable, followed by long term intermittent treatment with acedapsone, which should provide fool proof treatment of the disease.

Acknowledgement

This work was supported by a grant from the Damiaanfonds, Brussels, Belgium.

References

- Pattyn, S. R. (1972). Comments on the chemotherapy of leprosy as influenced by present knowledge of *M. leprae*. *Lepr. Rev.* **43**, 126-136.
- Pattyn, S. R., Rollier, R., Rollier, M. R., De Muynck, A., Janssens, P. G., Verdoolaege-Van Loo (1972). Correlation of laboratory and clinical data during treatment of leprosy. *Ann. Soc. Belge Méd. Trop.* **52**, 537-548.
- Pattyn, S. R., Rollier, R., Saerens, E. J., Rollier, M. R. (1974). Initial three months continuous and intermittent therapy in lepromatous leprosy. A controlled clinical trial. Preliminary data. *Ann. Soc. Belge Méd. Trop.* **54**, 43-49.
- Rees, R. J. W., Pearson, J. M. H., Waters, M. F. R. (1970). Experimental and clinical studies on rifampicin in treatment of leprosy. *Br. med. J.* **1**, 89-92.
- Shepard, C. C. (1972). Combinations of drugs against *M. leprae*. *Int. J. Lepr.* **40**, 33-39.
- Shepard, C. C., Levy, L., Fasal, P. (1972). Rapid bactericidal effect of rifampicin on *M. leprae*. *Am. J. trop. Med. Hyg.* **21**, 446-449.

Antibiotics in Leprosy, with Special Reference to Rifampicin

D. V. A. OPROMOLLA AND C. J. S. TONELLO

*Hospital Airmores, Rodovia Bauru-Jau, km 385, Caixa Postal 62,
Bauru – E.S. Paulo, Brazil*

The authors record the results obtained with various antibiotics, in particular the rifamycins, in the treatment of leprosy.

Improvement was most obvious and rapid in those patients whose disease was getting worse, and in whom bacterioscopy showed morphologically typical solid and long bacilli.

They analyse the results obtained with rifampicin in daily doses of 600 to 900 mg observed for varying lengths of time. They conclude that rifampicin should not be used alone. In cases resistant to other drugs, former treatment should be maintained in conjunction with the antibiotic until the reactivation is controlled. In patients who have had no previous treatment the antibiotic could be given in addition to sulphones, but not for longer than 120 days.

We have tested several antibiotics in leprosy treatment, including cycloserine, oxytetracycline, doxycycline, kanamycin and several rifamycins (See Table 1). The clinical results were uniformly good during an observation period of 12 months. In the majority of these drugs, maximum therapeutic effects were noted within the first 4 months, after which improvement was slower. The best results were obtained in patients who were experiencing a worsening of their disease. There were no differences in the incidence of ENL. During the period of observation no patients got worse.

In spite of the fact that according to some authors oxytetracycline does not exhibit anti-leprotic activity, and Shepard and Godal were unable to observe that it occasioned any inhibition in the growth of bacilli in the mouse footpad, the clinical and bacteriological results in our patients were good, and some of them could be called excellent. We agree with Weinstein (1967) when he affirms, "The only expressive indication of therapeutic effect is a favourable clinical response" (referring to the lack of correlation between the concentration of sulphonamides in the blood and the therapeutic effects observed). The bacteriological results follow the same pattern of response as that seen with the other antibiotics studied. Thus the Bacteriological Indices did not change much after a year's observation, and the Morphological Indices showed a clear predominance of degenerate bacilli at the end of this time.

The rifamycins acted similarly to the other antibiotics studied. The excellent response observed with rifamycin SV given intramuscularly, mainly to patients who were obviously getting worse, made Souza Lima and ourselves conclude in 1963 that, "The result of these experiments, in some ways surprisingly favourable if we consider the relatively short period of experimentation, opens up new roads in the field of therapeutic investigations of leprosy".



Fig. 1. Before treatment.



Fig. 2. After 20 days of treatment.



Fig. 3. Before treatment.



Fig. 4. After 30 days of treatment.

Rifampycin SV given intravenously confirmed these findings of high activity; in spite of the small number of cases studied, convincing clinical responses were observed within short periods of treatment (see Figs 1 and 2). The bacteriological status after one year of treatment with this antibiotic showed the same pattern as that of the others.

We conclude, therefore, that the antibiotics, particularly the rifamycins, are active in patients whose disease is worsening, and where solid staining and long bacilli predominate. We also conclude that maximum activity is observed in the first 4 months of treatment.

TABLE 1

Antibiotic	Daily dosage	Route of administration	Number of patients	Duration of treatment (months)
Cycloserine + INH	1.0 g	oral	32	12
Rifamycin SV	1.0 g	IM	10	12
Rifamycin SV	1.0 g	IV	5	12
Rifamycin SV + DDS + Sulfadimethoxine	1.0 g 100 mg 500 mg	IV oral oral	5	12
Oxytetracycline	200 mg	IM	22	12
Kanamycin	1.0 g	IM	10	3
Doxycycline	100 mg	oral	14	4-8
Rifampicin	600 - 900 mg	oral	52	1-28

TABLE 2

Rifampicin 600-900 mg daily	
Duration of treatment (months)	Number of patients
1-4	18
5-8	11
9-12	10
13-16	2
17-28	12

With the advent of rifampicin (derived from rifamycin SV), which is given orally, we have begun therapeutic schemes on the basis of the conclusions mentioned above. In our hospital routine, patients who do not respond to sulphones and other drugs, and whose disease is clearly degenerating, have received rifampicin in daily doses of 600 to 900 mg. At the moment 53 patients are being observed, of whom 32 have lepromatous leprosy and fulfil the above requirements. Of the remainder, 9 were receiving drugs other than sulphones, but because these drugs were no longer available, and in spite of the patients' improvement, they were given rifampicin; 6 had received no previous treatment for leprosy, and 6 with "borderline" leprosy continued to present active lesions in

spite of long periods of treatment with sulphones and other drugs. The duration of treatment and the number of patients in each category are indicated in Table 2.

Clinically, those patients who presented with recent reactivation of old lesions or with new lesions improved rapidly, while those whose reactivation was of longer duration improved more slowly. In all the patients who had already been under treatment for 1 year, old lesions remain, improved but still active (Figs 3 and 4).

The response of those patients who were improving slowly with other drugs and who began treatment with the antibiotic, continues to be favourable, but slow and less obvious.

In those patients who had received no previous treatment for leprosy, the group with a large number of lesions of short duration, most of which were in the same stage, improved rapidly, until after 4 months the lesions were no longer active. The others with lesions already dormant improved also, but more slowly.

The patients with "borderline" leprosy did not develop new lesions, and the existing lesions improved gradually. The bacteriological status in all these patients does not differ essentially from that observed with rifamycin SV, in other words Bacteriological Indices were only slightly different after 1 year of treatment, and Morphological Indices showed a predominance of degenerate bacilli.

A point worthy of note is that in patients with relapsed lepromatous leprosy who after a year still present active lesions, the Morphological Index does not return to zero as many reports indicate. A certain proportion of solid bacilli persisted in the smears.

The clinical and bacteriological findings permit us to make the following observations:

(1) The existence of resistance to rifampicin has already been described in tuberculosis, and the persistence of morphologically normal bacilli after a year of treatment suggests that resistance also occurs in leprosy.

(2) This antibiotic should not be used alone.

(3) In the cases resistant to other drugs, rifampicin should be used in conjunction with the drug in previous use until the new lesions disappear. If reactivation occurs again, the same combination of drugs should be given.

(4) In patients who have had no previous treatment for leprosy, rifampicin should be used in conjunction with sulphone for the first 4 months, after which treatment should proceed with a sulphone alone, bearing in mind the compatibility of the 2 drugs given simultaneously as demonstrated by Shepard.

(5) Rifampicin is well tolerated, but its high cost limits its use except in special cases. It should be used with caution, and with the aim of preventing the emergence of resistant strains, which would further limit its area of usefulness.

References

- Languillon, J. (1971). Activité de deux antituberculeux: La rifampicine et l'ethambutol dans la maladie de Hansen. *Acta Leprol.* **46-47**, 123-131.
- Leiker, D. L. and Kamp, H. (1970). First results of treatment of leprosy with rifadin. *Lepr. Rev.* **41**, 25-30.
- Lima, L. S. and Opromolla, D. V. A. (1963). First results on the treatment of leprosy with rifamycin SV. *Chemotherapy* **7**, 668-678.
- Opromolla, D. V. A. (1963). Primeiros resultados com a "Rifamicine SV" na lepra lepromatosa. In *Congresso Internacional de Leprologia*, 8^o., Rio de Janeiro, Vol. 2, pp. 346-355.
- Opromolla, D. V. A. and Almeida, S. C. (1965). Primeiros resultados do Tratamento da Leprea com a Kanamicina. *Revta Bras. Leprol.* **33**, 3-21.

- Opromolla, D. V. A. *et al.* (1965). A terramicina na lepra. *Revta Bras. Lepról.* 33, 3-21.
- Opromolla, D. V. A. and Quagliato, R. (1960). A "Serociclina" na lepra. Observacao em 32 casos. *Revta Bras. Lepról.* 28, 185-198.
- Opromolla, D. V. A. (1972). Contribuicao ao Estudo da Lepra (Hanseníase)—Tese de Doutorado apresentada à Faculdade de Odontologia de Bauru—Bauru/S.P.
- Rees, R. J. W., Pearson, J. M. H. and Waters, M. F. R. (1970). Experimental and clinical studies on rifampicin in treatment of leprosy. *Br med. J.* 1, 89-92. *J. Christian Med. Ass. India* 45, 415.
- Shepard, C. C., Levy, L. and Fasal, P. (1972) Rifampicin and *M. leprae*. In *Joint Leprosy Research Conference, 7^a*, Tokyo *Int J. Lepr.* 40, 459-460.
- Weinstein, L. (1967). Quimioterapia das doenças microbianas. In *As bases farmacológicas da terapeutica*. 3rd ed. (Eds L. S. Goodman and A. Gilman) p. 1041. Rio de Janeiro, G.B: Koogan.

The Effect of a Single Dose of Rifampicin on the Infectivity of the Nasal Discharge in Leprosy (Preliminary Communication)

L. M. HOGERZEIL

*Victoria Hospital, Dichpalli 503 175
Nizamabad District, Andhra Pradesh, India*

and

R. J. W. REES

*National Institute for Medical Research,
The Ridgeway, Mill Hill, London, NW7, 1AA, England*

This study was undertaken in London (Rees) and Dichpalli, India (Hogerzeil). Twenty-four hour nose blows before and after a single dose of rifampicin, 30 mg per kg body weight, were sent on ice from Dichpalli to London for inoculation into mouse footpads. The final results from mice are not yet available, but total counts and morphology of *Myc. leprae* from the nasal discharges before and after rifampicin suggest that within 4 days of a single dose of rifampicin the infectivity of patients was considerably reduced.

Results of Leprosy Control Project, Malawi

B. DAVID MOLESWORTH

Lepra Control Project, Malawi

An intensive Leprosy Control Project in Southern Malawi. Using standard dapsone therapy, the effect on the bacilliferous cases was assessed and has produced a very considerable impact.

From the figures it is obvious the time factor is long and, therefore, any shortening of this period, practical for mass campaigns, would be of the greatest importance.

From 1966 to 1973 LEPROA has undertaken an intensive Control Project in part of Southern Malawi with a population of 1.3 million in an area of about 2000 square miles lying 16° South latitude.

The leprosy prevalence is in the region of 15–20 per thousand. By the end of 1973, 13,000 cases had been recorded, some had already received varying amounts of dapsone treatment, the majority had received none (Fig. 1).

Treatment was on an out-patient basis, with weekly visits and the patient given 7 days supply. Once confidence was well established, this was extended to fortnightly, or, in some difficult areas, monthly visits.

Dapsone was the routine drug used in doses of 100 mg daily, reduced to 25 mg daily in 1969. A few cases had a thiozemicarbazone/isoniazid tablet in addition if their MI or BI appeared to be “sticking”.

Attendance overall is 50% and Ellard has shown that, nearly all the dapsone issued is consumed by this 50% of regular attenders. Defaulting is as much a disease as leprosy and a persistent defaulter remains so in spite of costly and time consuming measures. Persistent defaulters account for 66% of those cases showing no response or becoming worse.

For social reasons, many of this group are in the 20-40 year olds.

The object of this paper is to show the impact of this intensive control programme, and to this end, the bacilliferous cases have been selected as giving a precise measurement.

The laboratory records of 2280 bacilliferous cases, lepromatous, borderline, and a few tuberculoids in reaction show that:

76% become negative.

13% show the expected improvement.

11% showed no improvement or became worse, indicated by a rise in BI or MI.

Solid forms were still present in 7% of cases, that is 154 cases, and of these 68 were in the most recent group with less than 3 years' treatment.

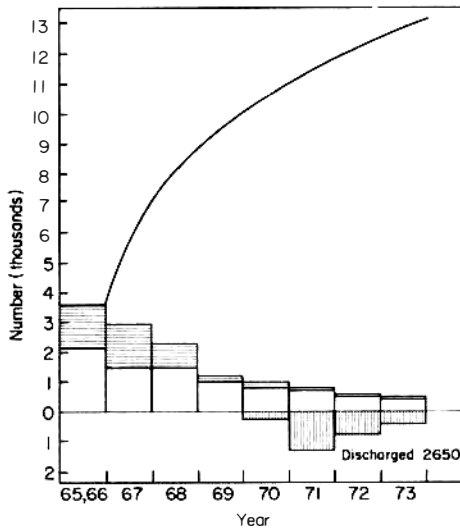


Fig. 1. Registered patients, 1965-1973. ■ some previous treatment; □ new, untreated; ▨ discharged.

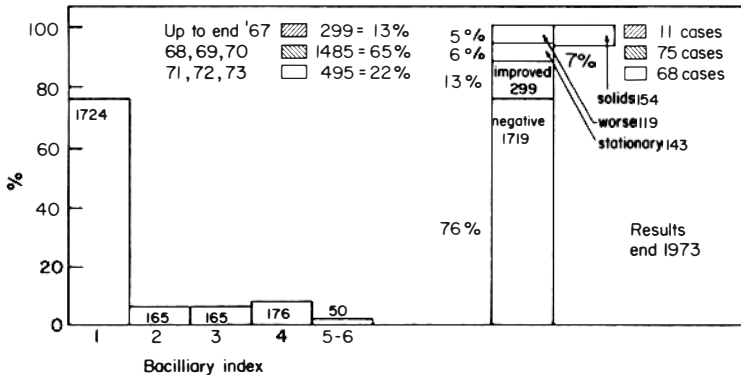


Fig. 2. Bacilliferous cases 2280.

As has been stated, two-thirds of the non-improving group are explicable on grounds of insufficient treatment, but one-third are regular and are candidates for other drug regimes or methods of administration.

Figure 1 shows the overall picture with a reduction of case load from 3500 to 500 annually. Untreated cases have fallen from 2100 to 450, and to discover a partially treated case, apart from those returning from abroad or moving into the area, is now a rarity.

Discharges are nearly all tuberculoid cases and so far, as a matter of policy, no women of childbearing age have been discharged to ensure dapsone cover for pregnancies.



Fig. 3. Group BI<2+, 1724 cases.

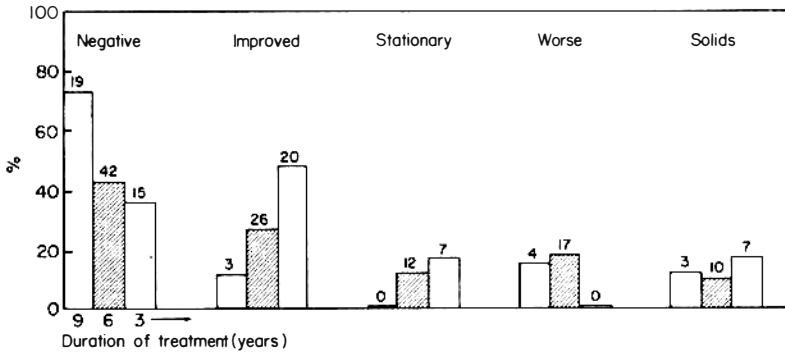


Fig. 4. Group BI2+, 165 cases.

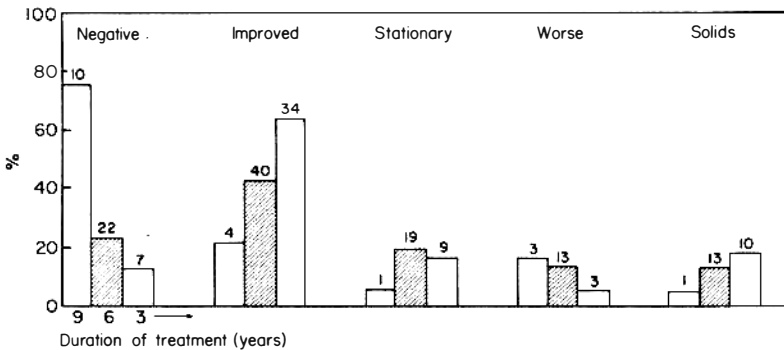


Fig. 5. Group BI3+, 165 cases.

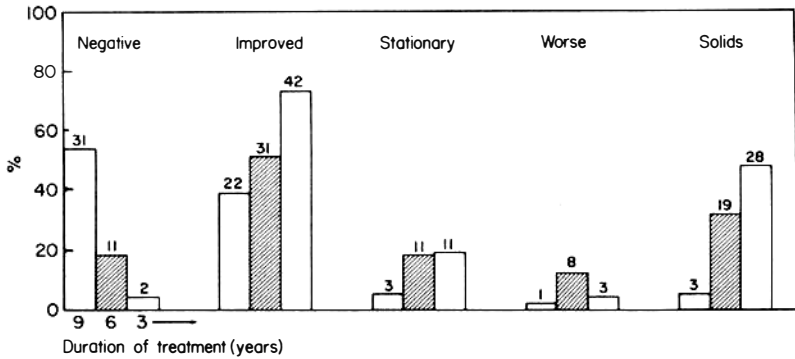


Fig. 6. Group BI4+, 176 cases.

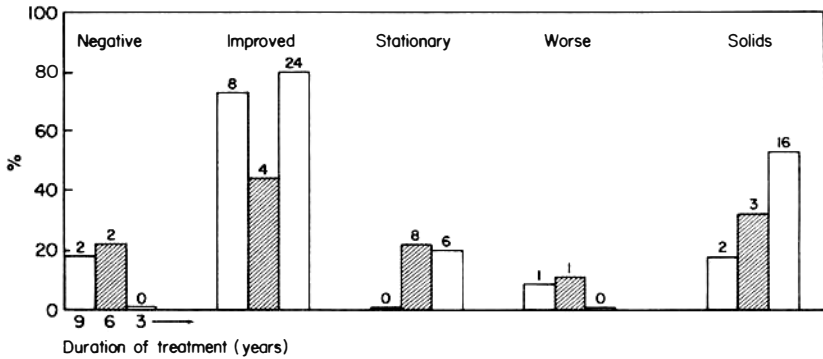


Fig. 7. Groups BI5+ and 6+, 50 cases.

In Fig. 2, of the total of 2280 bacilliferous cases, 76% show a BI of less than 2 on the Ridley scale. The right hand columns show the overall results obtained.

Cases have been divided into three year groups; the most recent going back to January 1971, 495 cases; the second group back to January 1968, 1486 cases, and the oldest group before December 1967, many of whom had received dapsone before the Project began.

Figures 3-7 show the effect of treatment on groups divided according to BI and duration of treatment.

In the largest group with BI of less than 2, negativity had been achieved in a very high percentage of cases; likewise, since the group contained many old cases who had discontinued treatment, it produces many of the relapses.

The BI and MI are obviously related to the duration of treatment and at the higher levels improvement in BI is far more rapidly obtained than negativity.

In addition to the above figures:

- 320 cases from beyond our area were transferred for treatment elsewhere;
- 131 came once and have not been seen since;
- 150 deaths.

2. Current Concerns in the Chemotherapy of Leprosy (B) Combined Therapy

Combined Therapy in Leprosy

J. C. GATTI

*Chief of the Center of Leprology, Chair of Infectious Diseases,
Faculty of Medicine of Buenos Aires, Maipu 863, 5^o Piso - D^{to} A,
Buenos Aires, Argentina*

We are submitting here our trials with combined therapy in leprosy. The following combinations of drugs were used.

- (a) Dapsone 25 mg daily plus rifampicin 300 mg daily in 43 out-patients, of whom 32 had lepromatous leprosy;
- (b) Dapsone 50 mg or 100 mg daily plus rifampicin 300 mg daily in 70 in-patients with lepromatous leprosy in the Sanatorio Colonia Baldomero Sommer.
- (c) Dapsone 25 mg daily plus clofazimine 200 mg weekly in 38 outpatients with lepromatous leprosy.
- (d) In addition, comment is made on 4 patients with lepromatous leprosy in whom the addition of dapsone to clofazimine resulted in an improvement in bacteriological status.

We believe that combined therapy is useful because it not only produces clinical and bacteriological improvement in patients with lepromatous leprosy, but also induces fewer and less severe reactional episodes. Furthermore, it has a lower tendency to favour the development of resistance.

Introduction

The introduction of an increasing number of drugs in the treatment of leprosy during the last three decades has been largely on theoretical grounds because of a lack of knowledge of the responsible organism, *Myco. leprae*, and of the pathogenesis of the disease. The effectiveness of single drugs like dapsone, the long acting sulphonamides, thiambutosine, thiacetazone, ethionamide, etc., is decreased by the reactional states they often appear to induce and by the emergence of resistant forms. Some of these drugs e.g. ethionamide demonstrate crossed resistance with other drugs.

We therefore need a form of combined therapy for use in the multibacillary forms of leprosy that can be compared with use in tuberculosis. In this disease it has been shown that after a preliminary period of treatment with 2 or 3 drugs the number of bacilli decreases dramatically, and therefore the incidence of resistance.

The present ideas about combined therapy began to gain currency in Rio de Janeiro in 1963, when the Therapeutic Committee of the VIII International Leprosy Congress advised its use; it was again asserted in London, 1968. The Therapeutic Committee of the Tenth International Leprosy Congress (Bergen, 1973) stated regarding combined therapy. "Concurrent administration of drugs like thiambutosine, long acting sulphonamides, thiosemicarbazone, clofazimine and rifampicin along with dapsone has been tried in the treatment of leprosy with

a view to obtain a synergistic effect and also to prevent the development of sulphone resistance. The results of the trials are not uniform, some found the combined treatment better than dapsone alone, while others did not notice any substantial difference." Further, it says regarding resistance, "Clofazimine and rifampicin, either alone or in combination with dapsone (or other drugs such as thiambutosine or ethionamide) have been found to be effective in the management of cases". Its criteria are based on the observation that the real effectiveness of the first-line drugs (sulphone, long acting and repository sulphonamides, clofazimine and thiambutosine) is frequently reduced by the reactional states that often necessitate the reduction of the dose or the change of drug, or even the stopping of the specific medication.

We wanted to obtain a synergistic effect, and prevent the development of sulphone resistance, or resistance to the first line drug with which treatment began. We believe that in the use of combined therapy the therapeutic effect of each drug should be considered, the indications for it, and the counter-indications against it ("Leprosy Treatment Actualization", Second National Leprosy Meeting, Buenos Aires, November 1968).

Our experience with combined therapy began 9 years ago ("First trials on lepromatous patients treatment with associated medication"—J. C. Gatti, J. E. Cardama, M. H. Farina, L. M. Balina, F. F. Wilkinson, O. Bianchi and J. J. Avila. *El Dia Medico Practico* 20-VIII-65 P. 4, and *Leprologia* 1965-X (2) 179.). At first we combined dapsone with sulphamethoxy-pyridazine or sulphamethoxy-diazine in the following ways:

- (1) Ingestion of 1 pill daily; dapsone 25 mg, sulphamethoxydiazine 250 mg, excipient to 500 mg
- (2) Ingestion of 1 pill daily; dapsone 25 mg, sulphamethoxy-pyridazine 250 mg, excipient to 500 mg.

After 6 months we concluded, "They are useful medications and of great future in the leprologic field and they justify going on with the first trials". Nine years after those first patients were treated we can state that the clinical, bacteriological and histological effects are, in more than 50 patients with all types of leprosy, similar to those found with sulphone, with a better tolerance to the drug and fewer reactional phenomena. Furthermore, we think this combined therapy is useful in patients with sulphone resistant bacilli.

Our present combined therapy. 1. Dapsone plus rifampicin

(a) Out-patient trials

Dose

Dapsone 25 mg daily with rifampicin 300 mg daily.

Number of cases

Total: 43 patients (all out-patients) classified thus:

- 32 lepromatous
- 3 tuberculoid
- 1 borderline
- 4 indeterminate
- 2 reactional tuberculoid
- 1 reactional lepromatous (ENL).

Period under observation

Between 3 and 24 months.

Tolerance

Generally good. Eight patients developed ENL of variable intensity. We have always tried to administer thalidomide concurrently, trying not to stop the specific medication; in some cases we had to reduce it for a few days. One patient developed symptoms of ulnar neuritis (epitrochlear pain). One patient developed gastric and hepatic disturbance.

Results

Of 3 tuberculoid cases treated from 4 to 10 months, 2 showed complete resolution. The third patient showed improvement in skin lesions, but developed acute neuritis which was treated with clofazimine 100 mg/day, since we consider this useful in neuritis.

Most of the patients with lepromatous leprosy showed obvious clinical improvement, mainly in the nodules, and seen after the first few months. Bacteriological improvement was similar to that with dapsone, but was most evident in early cases like the 4 with indeterminate leprosy, the borderline and the early lepromatous. Patients with advanced lepromatous leprosy and those already showing resistance to the initial therapy have shown less improvement in Morphological and Bacteriological Index. Nevertheless, 4 of these cases had negative smears after 12 months with this therapy.

Histology

In 5 patients with lepromatous leprosy treated for more than 1 year, the histopathology showed an obvious decrease of the lepromatous infiltration, with fewer Virchow cells and fewer bacilli, which were fragmented and granular.

Two patients with reactional tuberculoid leprosy improved clinically and bacteriologically after 2 months. The one patient with reactional lepromatous leprosy needed additional thalidomide in order to control the reaction.

(b) In-patient trials

The following trial has been made in Sanatorio Baldomero Sommer by Drs R. O. Manzi, I. Simonovich, J. Ganopol and R. L. Guaraz.

The in-patients chosen have lepromatous leprosy (L2, L3) and have received sulphone for 3 to 10 years in a dose from 50 to 100 mg/day. Nevertheless these patients did not improve clinically and bacteriologically. It was therefore decided to use rifampicin 300 mg/day and dapsone 50–100 mg/day, except in those patients with severe reactional states or kidney impairment who received 25 mg dapsone. Rifampicin was used at a dose of 300 mg daily because it is expensive and because of the visceral lesions some patients had. It was combined with dapsone to diminish the risk of resistance, but this is a low dose when compared with that customary in tuberculosis. These 70 patients included 24 with previous reactions who also received thalidomide.

Methods

The most important lesions observed were, nasal obstruction, nodules, infiltration, reactions and loss of voice. Investigations included clinical control, photography, skin smears and histopathology. Patients were between 20 and 63 years old, and were treated for from 3 to 15 months.

Twenty-four patients presented reactional states during the trial; they were given thalidomide 100 to 300 mg/day in addition to the combined therapy.

Results

Nasal obstruction This was the first symptom to disappear; this was evident in from 7 to 15 days.

Nodules New nodules did not develop during the treatment. Old nodules began to subside within 15 to 30 days and resolution was obvious after 3–4 months.

Infiltration The infiltration lessened within 15 days, and resolution was obvious after 4 months. One of the patients stopped the treatment. One month later he developed an infiltrated lesion on the buttocks the size of the palm of the hand, which disappeared when he resumed treatment. Twelve patients who had itching, epistaxis, joint pains, ulcers and loss of voice improved in a similar way.

Reactions In 6 out of the 24 patients, the reactional states were less violent and less frequent, so that thalidomide could be stopped. The other 18 patients had no obvious changes in their reactional state.

Smears After 2 months, 90% had negative nasal smears, in 10% the B.I. and M.I. improved. Skin smears improved less rapidly than the clinical lesions, but the M.I. decreased.

Conclusions

- (1) Tolerance to this combined therapy was good.
- (2) The results varied between good and excellent in all patients.
- (3) Ninety per cent had negative nasal smears in 2 months.
- (4) The B.I. presented no evident changes, but there were important falls in the M.I.
- (5) After 15 months of treatment, resistance to this form of treatment had not developed.
- (6) Trials should be continued to assess long term results.

Our Present Combined Therapy 2. Dapsone with clofazimine

Dose

Dapsone 25 mg/day plus clofazimine 200 mg/week.

Number of cases and clinical types

Thirty-eight patients with lepromatous leprosy, all out-patients, of whom 16 had had no previous treatment, and 22 had become resistant to the first therapy, having been treated for more than 5 years.

Period of observation

Between 6 and 35 months.

Tolerance

Good. The typical pigmentation after clofazimine was not so evident as with the usual dose of the drug. Three patients developed ENL. They improved after receiving thalidomide in addition.

Results

No new lesions developed. In all cases after the first month of treatment, lesions began to lose their infiltration and the nodules began to get smaller. This was quite evident during the sixth month, when these lesions were definitely atrophic and the surface was wrinkled by folds. After the first month, bacteriological improvement was confirmed in regard to the number and morphology of bacilli. Bacilli decreased in number and they became granular.

Histology

After 6 months biopsies showed histological improvement. There was a decrease in the number of Virchow cells and the appearance of fibroblasts.

Interesting points

A report was made at the IX International Leprosy Congress (London, 1968) on 30 patients treated with clofazimine. Interesting points in the subsequent progress of 4 of these patients deserve mention.

Case No. 1 Lepromatous. He received clofazimine 300 mg/day for 16 months. Smears became negative. Clofazimine was then reduced to 200 mg/day for 11 months, and smears became positive again, but when we associated dapsone 25 mg/day with clofazimine 200 mg/week, smears became negative in 3 months.

Case No. 2 Lepromatous. He received clofazimine 100 mg/day for 26 months without bacteriological improvement. After that we associated dapsone 25 mg/day with clofazimine 200 mg/week and smears became negative in 6 months.

Case No. 3 Lepromatous. He received clofazimine 100 mg/day for 37 months with the following bacteriological result; the B.I. fell from 4 to 3. The M.I. rose from 1 to 4. After that we combined dapsone 25 mg/day with clofazimine 200 mg/week for 6 months, and smears became negative.

Case No. 4 Lepromatous. He received clofazimine 100 mg/day for 28 months, at which point the B.I. had fallen from 5 to 2 but the M.I. had risen from 3 to 7. After that dapsone 25 mg/day was combined with clofazimine 200 mg/week and smears became negative after 4 months.

Conclusion

We believe that combined therapy is useful because it not only leads to clinical and bacteriological improvement in patients with lepromatous leprosy, but also to reduction in reactional episodes both in number and intensity. Furthermore, there appears to be a diminished risk of the development of drug resistant forms of the bacillus, and also of overcoming the effects of true drug resistance of genetic origin.

Acknowledgement

We gratefully acknowledge the help given by Dr Manzi and others of the Sanatorio Colonia Baldomero Sommer, and also the contribution from Drs J. E. Cardama and L. M. Balina and others of the Skin and Leprosy Service of the Muniz Hospital.

Preliminary Experience with Combined Therapy using Rifampicin and Isoprodian (L73A)

E. FREERKSEN

Forschungsinstitut Borstel, 2061 Borstel, West Germany

We should like to present to you some findings in leprosy patients which were not obtained by conventional trials, but by the results of treatment with the same combined therapy as used at different centres and consisting of rifampicin + Isoprodian. We did not have the intention of comparing this form of medication with others; we wanted to help several groups of dangerously ill patients by giving them a highly effective treatment.

Our conviction that the above-mentioned treatment represents the most effective therapy today, is based on our experimental results and on some clinical random trials carried out earlier. I know very well that in so doing I violate an old habit; this is why I have briefly to substantiate this opinion.

What significance can trials still have today? Prior to the early nineteen-forties there did in fact not exist any effective chemotherapy. At this moment in history leprologists encountered the sulphones, i.e. a real chemotherapeutic agent, for the first time, and it became possible to assess a drug against the background "Nil". Only under such conditions could trials in the classical sense be undertaken. Today we have at our disposal several effective substances. Therefore we no longer need to decide between "activity" and "inactivity", but rather have to distinguish degrees of efficiency by comparison.

This becomes more difficult and complicated from the technical point of view, when the differences in activity are small. For this reason we may use only those patients who can furnish any useful criteria for a comparative study. This is why, above all, lepromatous cases or at least bacteriologically positive ones are suitable for such trials, since the decrease in the number of bacteria provides the most important criterion for the assessment of anti-bacterial activity. Starting from the principle that all antileprosy drugs available today are active because of their inhibition of bacterial multiplication or killing power, we have to concede that no drug now available will accelerate the rate of clearance of bacteria from the tissues. The period of time taken for this to happen, could be regarded as a parameter. The morphological changes in the bacteria and their quantitative estimation (MI) are often in use. But our knowledge in this field is scantier than often believed.

(1) Trials in the form used in the past are to be justified not only in respect of the bacteriological criteria, but also regarding the choice of the patients. In order to satisfy the minimum requirements for statistical interpretation, we need at

least 3 groups if only one new substance is to be assessed, i.e. (a) 1 untreated control group, (b) 1 group treated with a substance of known activity and (c) a third group treated with the substance to be tested. For statistical reasons, each of these 3 groups should consist of at least 30 cases who must be strictly comparable in all essential respects. That means about 100 cases per trial carried out in the most simple manner. I have seen many leprosy patients and leprosaria, but up to now I have not found 100 identical cases in the same hospital, who could be used for such a trial. That is why I hold the opinion that scientifically acceptable trials are no longer possible. Trials with groups consisting of 4 or 8 or even 20 cases, observed only over a period of a few months are thus of no scientific value and do not furnish sufficient information because only slight (but practically essential) differences in effectiveness will be compared, even with highly effective forms of medication.

Although for technical and quantitative reasons true scientific trials are impossible, we should seriously question ourselves, whether such trials could at all be justified. Could we as doctors allow—just for the sake of scientific reasons—that one group of patients remain untreated, although they need treatment?

(2) The demand that only patients who have not had previous treatment should be taken into such trials is based on a reasonable foundation. But how to find 100 such cases, who have not even had dapsone? In the leprosaria I visited I have hardly come across any untreated patient with lepromatous leprosy; we are always dealing with patients who have had treatment somehow and at sometime or other except for those few fresh cases who often do not fit into the trial protocol. This demand for non-treated cases is theoretically correct, but not attainable in practice.

(3) All our patients we shall show—with a few exceptions—have had previous treatment, the results of which in each individual patient serve as control data. At the outset of combined therapy, our cases were bacteriologically positive and the clear majority lepromatous. Nearly all of them were previously treated with dapsone, not only for 6 or 12 *months* but often for a period of 6, 12 or even 20 *years*. At the beginning of our therapy all these cases were still highly positive. The previous treatment had been ineffective.

(4) During this colloquium we should clearly define the decisive criteria for the effectiveness of a prescribed treatment. In treating almost identical cases receiving 25 mg of dapsone or 100 mg dapsone or rifampicin or even rifampicin in combination you will probably not notice any bacteriological differences at all during the first 3 or even 6 months—and if any do exist, they can be irrelevant for statistical purposes or difficult to standardize.

The actual and decisive criterion determining the value of a therapy in the case of infectious diseases such as leprosy and all the other mycobacterioses (including tuberculosis) is the absence of relapse. We cannot alter the period of time necessary for this proof. One year remains 1 year and 5 years remain 5 years; today we simply should not judge definitely the value of different forms of therapy showing relatively similar initial effectiveness. That goes naturally for the form of treatment reported here.

(5) The absence of relapses can only be observed and investigated, if we are courageous enough to stop treatment at a given point of time. This is permissible only if the patients can remain under observation for a long time after withdrawal of treatment. This is also only possible under special and rare circumstances and

where therapy can be started should relapses occur. The point of time, chosen arbitrarily, but not without foundation, for stopping treatment arrives when 6 successive monthly bacteriological tests are negative.

(6) As mentioned above, we think that too great a reliance on the morphological changes of the bacteria (MI) as a criterion for the effectivity of a therapy is open to question. We know that nearly all species of mycobacteria investigated for this purpose, reveal the ability to adapt to changing environmental conditions, first of all by granulation, fragmentation, etc. Chemotherapeutic agents themselves represent an environmental influence on the mycobacteria in (living) media. On the other hand (especially under insufficient treatment) the recurrence of all bacterial forms can be possible. The best criterion of a therapeutic effect is tissue clearance demonstrated repeatedly. That is why the decisive criterion is not the MI, but the reduction to zero of the BI. All our investigations were carried out in accordance with the concept I explained in detail in September, 1972 (Freerksen, E. and M. Rosenfeld: Fundamental data, methods and goals of present research on the treatment of leprosy. *Z. Tropenmedizin* 24 (1973), 17-25).

Treatment of Leprosy with Rifampicin and Isoprodian (L73A)

J. TERCICIO DE LAS AGUAS

Sanatorio de Fontilles, Alicante, Spain

A total of 27 patients with lepromatous leprosy were treated, 13 with rifampicin, 600 mg per day, and 14 with rifampicin 600 mg per day plus Isoprodian, 2 tablets per day. Clinical improvement was excellent in both groups, bacteriological improvement not so good, as judged by the Morphological and Bacteriological Indices. It was greater in the first group, which had treatment for a longer period.

In general, tolerance was excellent. Reactions occurred in both groups, but were more frequent in the second.

The present study was made on two groups of patients.

Group I Rifampicin

The first group consisted of 13 patients, 12 male and 1 female. Seven patients were very advanced in their disease, and after many years of treatment with sulphone had relapsed, mainly as a result of stopping treatment. Six patients were in the early stages of their disease, and had had no treatment. All 13 patients were strongly positive bacteriologically. They were all treated with rifampicin only, 600 mg per day, and were observed from 2 to 37 months. Results are tabulated as follows.

Case No.	Period of treatment	Results of bacteriology	Clinical results	Reaction	Tolerance
1	37 months	Mucus negative	Excellent	2	Good
2	30 months	Nil	Good	3	Good
3	18 months	Reactivation	Good	2	Good
4	17 months	Nil	Good	Nil	Good
5	16 months	Slight improvement	Excellent	Nil	Good
6	16 months	Slight improvement	Excellent	1	Good
7	15 months	Slight improvement	Passable	3	Good
8	15 months	Slight improvement	Excellent	2	Good
9	14 months	Slight improvement	Good	3	Good
10	14 months	Slight improvement	Good	Nil	Good
11	11 months	Mucus negative	Good	Nil	Good
12	12 months	Slight improvement	Slight	Nil	Good
13	2 months	Nil	Slight	1	Good



Fig. 1. Before treatment.

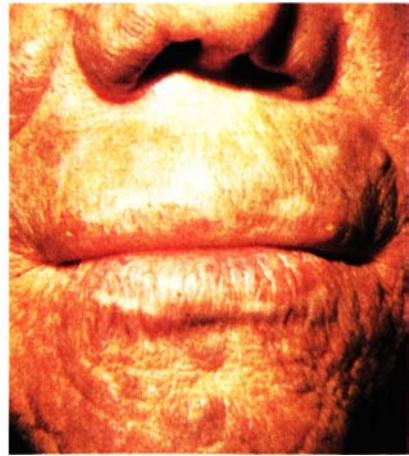


Fig. 2. After 6 months of treatment with rifampicin.

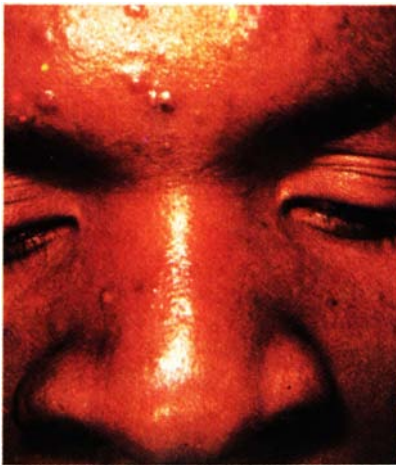


Fig. 3. Before treatment.



Fig. 4. After 4 months of treatment with rifampicin.

Observations

Clinical improvement was remarkable in all patients, especially marked in the nodules, the nasal mucosa and the eyes. This improvement was noted between the fourth and tenth week after beginning treatment. Complete resolution of the cutaneous lesions of those patients with very advanced or longstanding leprosy takes a long time. For instance, case No. 1 had treatment for 37 months.

Reduction in bacteriological activity was not as noticeable or as rapid as clinical improvement. The nasal mucosa became negative in two cases; No. 1 after 30 months of treatment, and No. 11 after 8 months. Bacteriological improvement occurred in the majority of cases, being greater in those who had suffered from leprosy for a shorter time and whose clinical lesions were of moderate degree. The

improvement in the Bacteriological and Morphological Indices was variable. In general, tolerance was good, and no side-effects were observed in relation to the stomach, liver or haemopoietic system. Reactions occurred in 8 patients.

Conclusions

Rifampicin is an excellent drug with activity on the clinical manifestations, especially nodules, the nasopharyngeal mucosa and in the eye. There is improvement in the neural lesions, but this is not as rapid as in the skin or nasal mucosa.

On the basis of experience with these patients, we can affirm that in contrast to the sulphones, the activity of rifampicin is similar, both in untreated patients and those who have had leprosy for a short time on the one hand, and in patients on the other hand who have had leprosy for a long period or who present in relapse as a result of negligence or deficient sulphone treatment. Most of the in-patients in this series have been early cases. For complete resolution of even such early lesions, the period of treatment needed is likely to be similar to that required with the sulphones.

Reaction is less frequent with rifampicin than with the sulphones. We have given thalidomide during reaction, continuing with the specific treatment, but reducing the dose for some days.

In general, tolerance, including hepatic tolerance, has been excellent. Further observation is necessary to obtain a precise evaluation of the activity of this drug.

The bacteriological improvement in patients treated with rifampicin is not better than in those treated with sulphones. This is the case with patients who have longstanding leprosy with widespread lesions and those who relapse after prolonged sulphone treatment. With a long period of treatment it is possible that resistance might occur.

Group II Rifampicin plus Isoprodian

This group consisted of 14 patients, 10 male and 4 female, all of them suffering from lepromatous leprosy, and highly positive bacteriologically. These patients were given 600 mg rifampicin and 2 tablets of Isoprodian daily, and kept under observation for from 3 to 9 months. Results may be tabulated as follows.

Case No.	Period of treatment	Results of bacteriology	Clinical results	Reaction	Tolerance
1	9 months	Good	Good	Nil	Good
2	6 months	Nil	Good	2	Good
3	6 months	Nil	Good	4	Good
4	6 months	Reactivation	Good	1	Good
5	6 months	Nil	Good	2	Good
6	6 months	Slight improvement	Good	Nil	Good
7	6 months	Reactivation	Good	6	Good
8	6 months	Slight improvement	Good	6	Good
9	6 months	Slight improvement	Very good	1	Good
10	5 months	Nil	Good	2	Good
11	5 months	Slight improvement	Slight	3	Good
12	4 months	Nil	Nil	3	Good
13	4 months	Nil	Good	1	Good
14	3 months	Nil	Slight	1	Good

Conclusions

Experience with the second group is shorter than with the first, the duration of treatment being only from 3 to 9 months. In general, clinical improvement was remarkable and rapid in 13 patients the only exception being patient No. 12, who has persistent reactional polyneuritis. Bacteriological improvement was less marked than in the first group because of the shorter period of treatment. Tolerance was good in all patients. The number of reactions was higher in this group, all except two suffering from reactional episodes. In some patients the outbreaks were persistent, necessitating thalidomide throughout. We are of the opinion that the frequent reactions were caused by the presence of dapsons in the composition of Isoprodian. In the second group a longer period of observation is necessary before a definite judgment can be given.

Clinical and Bacteriological Effects of Rifampicin in Combination with L73A in Leprosy: Observation for Six Months

SEIJI INNAMI

Leprocomio Santa Isabel, Sapucay, Paraguay

OSCAR R. LEGUIZAMÓN

Centro de Salud No. 1., Asunción, Paraguay

and

ARNALDO E. ALVARENGA

Departamento de Lepra, Ministerio de Salud Pública y Bienestar Social, Asunción, Paraguay

Therapeutic effects of rifampicin in combination with L73A were observed both clinically and bacteriologically in 30 patients with lepromatous leprosy for 6 months.

It was evident that the fall of BI was gradual and the decrease of MI was rapid in practically all cases. One of the most favourable signs of clinical improvement was the flattening and absorption of nodules and other raised skin lesions in a short time. ENL was observed in about 33%, mild dizziness was seen frequently as a side effect.

Introduction

At the request of Prof. Freerksen, treatment with rifampicin in combination with L73A was carried out in 30 selected lepromatous leprosy patients for a period of 6 months. All other anti-leprosy drugs were stopped for 1 month before the start of administration. Daily dosage of 600 mg rifampicin and 4 tablets of L73A were administered orally except on Sunday.

Twenty-six out of 30 cases completed the scheduled treatment for 6 months. Four cases were suspended from the trial for various reasons.

Results

Changes of BI and MI of Myco. leprae during rifampicin and L73A therapy

These are shown in Table 1.

The fall of BI was gradual in all cases, and 3 out of 30 cases became

bacteriologically negative at 6 months. On the other hand the MI decreased very rapidly. The improvement in MI was seen in almost all cases within 3 months, and the average value of MI decreased from 12.6% to 5.0% at 6 months.

TABLE 1
The changes of BI and MI of Myco. leprae treated with rifampicin and L73A

Patients number	Months of treatment					
	Initial		3 months		6 months	
	BI+	MI%	BI+	MI%	BI+	MI%
1	5	15	5	11	5	9
2	3	4	2	3	2	1
3	4	12	4	6	3	5
4	2	7	1	1	0	0
5	5	18	5	7	—	—
6	5	23	4	10	4	7
7	3	6	2	2	2	2
8	3	9	3	5	2	5
9	5	31	4	18	4	7
10	3	12	—	—	—	—
11	3	7	3	5	2	5
12	3	8	2	5	2	5
13	5	16	5	9	4	6
14	5	25	4	12	4	15
15	3	6	1	2	0	—
16	4	18	4	11	3	7
17	4	17	4	12	3	8
18	5	21	5	11	5	9
19	4	6	4	3	3	3
20	4	14	4	8	4	6
21	2	4	2	0	0	0
22	4	13	3	7	3	5
23	3	9	3	5	2	5
24	4	9	—	—	—	—
25	4	9	4	6	3	5
26	3	7	—	—	—	—
27	3	8	3	3	2	2
28	5	23	3	11	3	7
29	4	13	4	8	3	3
30	3	7	3	5	3	3
Average	3.8	12.6	3.4	6.9	2.7	5.0

Clinical results

Effective	15 cases
Unchanged	14 cases
Worse	0 case
Dead	1 case
Total	30 cases

One of the most striking signs of clinical improvement was the flattening and absorption of nodules and other raised skin lesions within 6 months.

ENL during the treatment

Ten patients experienced ENL while under treatment.

Severe ENL	4 cases
Mild ENL	6 cases

All cases were controlled by thalidomide or by diminished dosage of L73A.

Side effects during the treatment

Side effects were observed in 11 cases.

Mild dizziness	6 cases
Gastric disturbances	2 cases
Headache	2 cases
Pruritus	1 case
Total	11 cases

These side effects frequently occurred after the pause of administration on Sunday.

Tolerance and non-tolerance of rifampicin and L73A

Tolerance	26 cases
Non-tolerance	4 cases
Total	30 cases

Rifampicin and L73A treatment had to be interrupted in 4 cases for the following reasons:

Severe iridocyclitis in 1 case, epilepsy-like seizure in 1 case, severe polyneuritis in 1 case, and death in 1 case. The patient who died had been suspended from treatment for 1 week because of ENL after 2 months of treatment. Death with some symptoms of toxicity occurred shortly after the intake of rifampicin and L73A after the pause of administration.

Laboratory examinations

Increase of SGOT and GPT	2 cases
Continued proteinuria	5 cases
Severe signs of anaemia	1 case
Total	8 cases

Summary

Therapeutic effects of rifampicin in combination with L73A were observed both clinically and bacteriologically on 30 patients with lepromatous leprosy for 6 months.

It was evident that the fall of BI was gradual and the decrease of MI was rapid in practically all cases. One of the most favourable signs of clinical improvement

was that nodules and other raised skin elevations became absorbed and flattened out in a short time.

ENL was observed in about 33%. Mild dizziness was seen frequently as a side effect. Careful attention must be paid to liver function, proteinuria and anaemia during the treatment.

Though we have no comparison with other control groups, the clinical and bacteriological results of the treatment indicate strongly that the best and rapid effects may be expected in cases of lepromatous leprosy with nodules or raised skin elevations.

Acknowledgements

We are greatly indebted for the cooperation of Dr Felipe Gimenez, Haematologist, Mrs G. Schrammen—Secretary of Department of Leprosy, Ministry of Health and Welfare, and nurses—sisters of Leprosarium Santa Isabel.

Treatment of Leprosy with Rifampicin and Isoprodian in 38 Patients at St. Thomas Hospital, Chetput, South India

M. ASCHHOFF

*St Thomas Hospital and Leprosy Centre,
Chetput, 606801, India*

A clinical and bacteriological study is described of rifampicin in a dose of 300–600 mg daily combined with Isoprodian 2–3 tablets daily in 38 patients, 30 of them lepromatous in type, and continued for periods up to 16 months. Clinical and neurological improvement was general, in some cases outstanding. Bacteriological improvement was inconstant. A rapid decline in Morphological Index to 1% or less was usual within 6 months. In some cases the decline in Bacteriological Index was outstanding, superior to that experienced in patients receiving clofazimine or high dose dapsone, but in other cases this was not so.

Side effects included mild hepatitis with jaundice in the first few weeks of treatment, which did not demand withdrawal from the trial. There was 1 case of exfoliative dermatitis, and 3 patients were withdrawn from the trial on account of severe reactions resulting in paralysis.

At our institution, engaged in field work in a rural area in South India since 1960, rifampicin was used in combination with Isoprodian and studied in 38 patients. They received 300–600 mg rifampicin and 2–3 tablets Isoprodian daily according to their body weight. Detailed laboratory investigations carried out monthly included, ESR, haemoglobin, leucocyte and differential blood cell count, Takata, SGPT, SGOT, serum bilirubin, total serum protein, cadmium, fasting blood sugar, urine status, sputum and stool tests. Clinical assessments including chest X ray were undertaken at regular intervals. Out of 38 patients selected, 25 were males and 13 females, all in the age group 8–55 years.

Thirty patients were classified as suffering from leprosy of L type, 6 of B type, 1 T type in reaction, 1 T in a state of healing. This last patient was selected because she was 1 of 2 patients having simultaneous tuberculosis, 1 of them pulmonary, 1 of them spinal.

Thirty-two patients had had previous anti-leprosy treatment, many of them for several years, and either did not respond to it, showed signs of intolerance, or had repeated reactional episodes. They were known to us as “problem patients”. Six patients assured us they had had no previous anti-leprosy treatment whatever.

* This work was undertaken in collaboration with Professor E. Freerksen, Director of the Research Institute Borstel, West Germany.

The duration of the trial is as follows:

16 months	22 patients
15 months	7 patients
14 months	2 patients
9 months	1 patient
6 months	6 patients

Treatment had to be stopped in 5 of the 38 patients for the following reasons:
 (1) One patient withdrew on her own initiative. She had an abortion, was irregular in attendance, and subsequently put on dapsone.

(2) One patient developed severe exfoliative dermatitis after 2 months' treatment and was transferred to treatment with clofazimine.

(3) Three patients experienced frequent reactions with neuritis resulting in paralysis.

Two groups of patients, only mildly bacteriologically positive at the onset of the trial, were treated as follows.

The first, consisting of 4 patients (2 lepromatous, 1 borderline, 1 T in reaction) BI 0.5, were given the combined treatment for 6 months. By the time all were completely negative in their BI. No further treatment was given and the patients have subsequently been kept under regular observation for 9–10 months. They are all clinically without signs of activity, and skin smears continue to be negative.

The second group consisted of 3 patients of lepromatous type with BI 0.5 together with 1 patient T in type with tuberculosis of the spine, and added to the trial for that reason, even though the BI was zero. The 3 lepromatous patients all became negative within 3 months of combined therapy, which was continued for a further 3 months, and then treatment was continued with dapsone 600 mg per week. All continue in good health, with skin smears negative, though the patient with tuberculosis has been irregular in attendance for follow up.

In 2 patients, 1 of them a child of 8 years, both with lepromatous leprosy, we were anxious regarding liability to reactions, and Lamprene was added to the drug combination from the start. Clinical improvement in 6 months is considerable, and in both the MI has come down to 1% and 2% respectively. In the child the BI has fallen from 4.14 to 2.42, but remains steady in the other (adult age 35) patient at 3.16.

One patient actually in a state of reaction received rifampicin and Lamprene right from the start. After 6 months her BI is still 4.85, but her MI fell to 2% within 5 months.

These small groups are the exceptions. The major group was treated and still is being treated with the combination of rifampicin and Isoprodian. In 3 out of 4 borderline cases the patients have improved considerably clinically during a treatment period of 6–15 months. Negative smears were found after 2 months in 2 patients previously treated with other drugs, and after 6 months in 1 patient receiving his first anti-leprosy treatment. The patient with pulmonary tuberculosis became sputum negative after 3 months. A fourth patient, a boy of 12 years, classified as BL also improved very well clinically, and after 1 month became smear-negative, but subsequently a few bacilli were found.

Out of the 18 patients with lepromatous leprosy, 2 of them Nos 7 and 8, who were mildly positive at the start of treatment, became negative within 1 year, 6 improved considerably within 16 months, their BI having come down from 5.0 to 1.0 or 0.5, the MI being 0%. In 9 other patients, who have been continuing

treatment for 11–16 months, the MI is zero, but the BI shows scarcely any change as yet. One patient shows no response either in MI or BI after 6 months.

Further Observations

Sensory assessment

Fifty per cent of patients receiving the drug combination had at the onset anaesthesia to light touch to some extent in hands or feet or both. In 10 patients this had developed within the past 1–2 years, and these regained sensation at least partially, notably in the thumb-index finger web space.

Regrowth of eyebrows

Out of the 21 patients showing loss of eyebrows 8 showed moderate regrowth. One male patient aged 28 years had scanty regrowth of his beard.

Muscle power

Six patients out of 18 showed some improvement in the muscle power in the hands, confirmed by electrical studies. Here too the paresis was of recent origin, occurring within the previous 6 months to 3 years.

Side-effects

(1) Several patients showed a mild form of hepatitis with jaundice during the first few weeks of treatment, but recovered under usual care without any interruption of the rifampicin combination treatment in some cases and only very brief interruption in others.

(2) ENL and neuritis were seen and treated with thalidomide and Mogadon; 3 patients had to be withdrawn from the trial on account of repeated severe reactions resulting in paralysis (mentioned above).

(3) One patient developed exfoliative dermatitis and had to discontinue.

Anaemia, leucopenia and thrombocytopenia were not seen.

Experience with Other Drugs

Lamprene

Eight patients with lepromatous leprosy and high BI have been under Lamprene treatment for 9–27 months. In 1 of these the BI became negative after 19 months, but the others still have a BI of 2.0 or 3.0.

Lamprene followed by high dose dapsone

Nine patients were treated with Lamprene for 1–18 months because of frequent reactional episodes and then put on DDS 600 mg per week. No severe reaction occurred subsequently. Three patients achieved a negative BI within 18 months of starting Lamprene, 5 have improved, and 1 has remained in *statu quo*.

TABLE 1

Therapy forms	List No.	Name	Age	Record No.	Pre-treatment (years)	Type	Bact.
Rifampicin + Isoprodian	1	CH	23	12815/73	2	BB/TBC	+
	2	A	35	3119/74	0.5	BB	+
	3	D	31	14527/67	5.6	LL	+
	4	K	41	54372	10.9	LL	+
	5	R	20	7756/67	5.5	LL	+
	6	S	26		0.5	LL	+
	7	E	15	4092/70	3.2	LL	+
	8	A	32	12672/67	10.5	LL	+
	9	K	20	5063/73	—	BL	+
	10	N	44	5255/69	11.9	LL	+
	11	TS	55	2187/72	1.3	LL	+
	12	ST	12	5227/73	—	BL	+
	13	S	33	1258/68	12.8	LL	+
	14	A	32	12911/69	3.6	LL	+
	15	CH	45	1227/68	12.5	LL	+
	16	E	19	7815/66	12.6	LL	+
	17	N	35	7131/66	6.5	LL	+
	18	I	46	4071/67	2.2	LL	+
	19	P	46	1079/72	12.7	LL	+
	20	E	41	4848/67	12.5	LL	+
	21	R	8	1556/71	6.3	LL	+
	22	M	46	3667/74	—	LL	+
Rifampicin + Lamprene	1	SH	36	1856/74	1	LL	+
Rifampicin + Isoprodian + Lamprene	1	N	8	2898/74	0	LL	+
	2	M	35	3037/74	6/12	LL	+
Rifampicin + Isoprodian 6 months followed by DDS (100 mg daily)	1	B	18	5427/73	10/12	LL	+
	2	V	31	8069/72	1.4	LL	+
	3	R	35	9274/70	3.5	LL	+
	4	CH	40	2130/73	3/12	TT/TBC	—
Rifampicin + Isoprodian 6 months followed by observation only	1	Y	14	10482/70	2.6	LL	+
	2	P	40	4178/70	12.5	LL	+
	3	R	8	4773/73	1/12	BB	+
	4	P	30	9253/72	4/12	TR	+

High dose dapsone.

Thirty-two patients who did not become negative under low dose DDS or had frequent reactional episodes were treated with high dose dapsone. Thirty of them were of lepromatous type, 2 borderline. All were placed on 600 mg dapsone per week without build up. Eleven became negative within 1 year, 12 improved and 9 remained in *statu quo* after 1 year. Reactions were few and mild only, so that treatment was sustained.

Acknowledgement

I would like to thank my colleagues and all the staff at St. Thomas Hospital for their great interest in this work and their devoted cooperation: Professor Freerksen for his guidance, and the German Leprosy Relief Association, Wuerzburg, for supplying us with the required drugs and for support and encouragement.

Rifampicin and Isoprodian in Combination in the Treatment of Leprosy

G. DEPASQUALE

*St. Luke's Hospital, Department of Dermatology,
La Valetta, Malta*

Reviewing the progress over a 2 year period of 192 Maltese patients treated with rifampicin combined with Isoprodian, a much quicker response to therapy was observed than with any other type of therapy used earlier. The combination was effective even in cases previously treated for a number of years, though early cases seem to show the speediest response to treatment. The combination of drugs was well tolerated, and reactions could be controlled with the use of thalidomide without interruption of therapy. The therapy was most acceptable to patients.

Since the start of the Leprosy Eradication Programme in July 1972, the standard treatment of leprosy in Malta has been a combination of rifampicin and Isoprodian (= Prothionamide + isoniazid + dapsone).

One hundred and ninety-two patients, most of which had been treated previously for a number of years, were included in the programme from the start, while 18 other patients including 13 fresh cases were included at later stages. "Fresh cases" here refers to cases of recent diagnosis that have not received any previous treatment.

If one starts by studying the bacteriological results of this particular group of patients, one observes:

- (a) there is a steady decrease in bacterial counts following treatment in practically all patients,
- (b) as a general rule, the lower the initial count of bacteria the earlier is negativity reached,
- (c) there seems to be no relation between age of the patients and their response to treatment.

Similar observations can be made on consideration of the large group of patients that were included in the programme from its start. There is great variation in the duration of treatment necessary before negativity in the sense of tissue clearance is reached. Even after 2 years of treatment we have a group of 20 patients who are at present not negative in this sense.

On detailed study one observes that as a general rule the longer standing the disease is, the longer the period of treatment required to achieve negativity. From the clinical point of view, the effects of therapy are seen earlier. Ulcerating

nodules were observed to heal rapidly—sometimes in a matter of days after initiation of the treatment. The nodules themselves regressed at a later stage, while in some cases hard fibrotic nodules although decreased in size, did not disappear completely. Nasal obstruction and hoarseness were also relieved early in the course of treatment. Patients previously suffering from anaesthesia, reported marked improvement. Hair growth was observed in some patients who had been suffering from alopecia initially. Of particular importance is the fact that most patients reported that they were feeling physically much better after starting treatment.

Nausea and other gastric disturbances were reported initially by 44 patients (i.e. 20.9%). However these side-effects subsided in almost all cases without interruption of therapy. Anaemia of moderate severity was recorded in 3 cases. In 1 of these cases the anaemia appeared 2 months after treatment had been discontinued. Mild anaemia occurred in 12 other cases. Jaundice appeared in 2 patients. Treatment was suspended until the jaundice cleared and it did not recur when treatment was restarted; according to our records serum bilirubin is slightly raised even in the untreated leprosy patients.

Lepra reactions occurred in 21 cases, mostly moderate to mild in severity. These reactions receded spontaneously or following the administration of thalidomide. Two patients suffered severe reactions requiring hospitalization. Corticosteroids were never used.

In general, we have observed a much quicker response to therapy with the use of rifampicin and Isoprodian than with any other type of therapy used earlier. The combination was effective even in cases previously treated for a number of years. However, early freshly diagnosed cases seemed to show a quicker response to treatment. The combination was well tolerated and reactions could be controlled with the use of thalidomide without interruption of therapy. Finally, the therapy was acceptable to the patients and they were very happy to carry on with the treatment as long as we advised it.

Preliminary Experience with Rifampicin and Isoprodian (L73A)—Combination in Lepromatous Leprosy

M. HAMZAH AND A. KOSASIH

*Department of Dermatology, University of Indonesia,
Jakarta, Indonesia*

Nineteen male patients suffering from lepromatous leprosy are being treated with rifampicin and Isoprodian. So far, 8 patients have completed 6 months of follow-up, 5 patients have received treatment for less than 6 months and another 6 patients have just started treatment.

Out of 13 patients under treatment, 10 patients so far have become bacteriologically negative, accompanied by clinical improvement, especially in the macular, nodular and diffuse types of infiltration, whereas miliary and lenticular types of infiltration improved slightly.

Side-effects were mild, except in 1 patient who dropped out because of severe vomiting.

Laboratory examinations showed no significant changes in the blood picture and the initial high value of ESR gradually decreased.

Introduction

Those who have devoted a long time to the treatment of leprosy are aware of the inadequacies of present day therapy. Even the drug most widely applied at the present time, namely dapsone, is still under research to find out the most efficient dose requirements, and the search for a more efficient drug continues.

Experiments of various combinations of drugs have been made, both using known as well as combinations of completely new drugs in the treatment of leprosy. In the present experiment the therapy applied is a combination of drugs composed of rifampicin and Isoprodian (L73A). Rifampicin was applied for the first time in leprosy in 1965. Each tablet of Isoprodian used in this investigation contains a combination of 3 drugs, namely dapsone 50 mg, *Isoniazid* 250 mg and 250 mg Prothionamide.

Dapsone is the most widely applied drug, *Isoniazid* is not a drug to be applied routinely in leprosy.

Prothionamide is a drug applied for the first time in leprosy in Indonesia.

Materials and Methods

The experiment was carried out at the General Hospital in Jakarta (RSTM), subdivision for leprosy outpatient Department.

It was intended to treat at least 20 patients, all male, and of the lepromatous type, with complete follow-up examination.

The reason why only male patients were chosen was the fact that thalidomide would be used in the event of lepra reaction. These patients were chosen carefully in order to minimize drop-outs, and considering the need for frequent follow-up examinations.

Each new patient was given the following examinations:

- (1) 10 ml of blood was drawn for examination of Hb, leucocyte count, BSR, differential count, thrombocyte count, SGOT and SGPT
- (2) A direct smear of the lesion for bacterioscopic examination
- (3) A skin biopsy for histopathological examination
- (4) A coloured photograph of the lesion

All these examinations were done at the same day whenever possible.

Follow-up examinations were undertaken monthly to evaluate the clinical progress, observe side-effects, and perform the same laboratory procedures as mentioned above. Treatment accompanied by 6 times follow-up would be completed in 6-7 months.

The treatment was started in September, 1973, by using rifampicin 2×300 mg/day and 3×1 tablet of L73A. Later on, treatment was modified to 2×300 mg rifampicin and 2 tablets of Isoprodian (1 tablet of Isoprodian is equal to 2 tablets of L73A used formerly) with 1 day pause within each week, namely on Sunday. This quantity of drug was given in a single dose with breakfast. However, when the single dose treatment was difficult, patients were allowed to take the drug in divided doses. This dose was given to patients whose body weight was more than 40 kg, whereas patients weighing less than 40 kg were given half of the dose.

Results

This preliminary report relates to the results of the treatment of 13 male lepromatous patients at ages varying between 11 and 65 years.

Eight patients have completed the 6 times follow-up. Five patients are under treatment for the duration of less than 6 times follow-up, specified as follows: Two patients have reached the 5th follow-up, 2 patients have reached the 4th follow-up and 1 patient has reached the 2nd follow-up.

It is hoped that all these patients will manage to complete the treatment in due time. Another 6 patients have just started treatment. Besides these patients there were 6 patients who have stopped the treatment in the early phases of treatment for the following reasons:

Two patients rejected the second biopsy, 1 patient because of the occurrence of a big keloid on the biopsy scar, 1 patient because of severe vomiting, restlessness and insomnia, whereas 2 patients have not returned for unknown reasons.

Clinical Results

The skin lesions found were in the form of erythematous macules of numular size, usually spread over the trunk, sometimes on the arms and thighs, diffuse infiltration and erythematous nodules usually found on the face, ear, extremities

and sometimes on the trunk; and smaller nodular lesions of miliary and lenticular size, usually found on the ear, and in 1 patient occurring on the lips, while in another patient found spread over the back and limbs.

During the first weeks of treatment, improvement of the lesions was readily seen, especially the nodules and diffuse infiltrations, whereas with nodular lesions of miliar and lenticular size very slight or no improvement was observed.

Macular lesions disappeared without leaving a mark. Diffuse infiltrated lesions and nodules partly disappeared without leaving a mark, partly leaving macules, partly leaving a wrinkled skin the colour of which is normal or bluish.

In addition, there was also infiltration which underwent only a slight change either in terms of thickness or colouring.

Relating to this improvement, there was a difference both individually and topographically. Relating to the changes in miliary and lenticular noduli, a slight improvement took place except in the erythema.

Infiltrates that took a long time to regress were those localized on the ear, face and the distal part of the extremities.

Notes on patients of interest

(1) A. L., age 65. After 6 follow-up examinations no trace of infiltration was to be seen on the skin, except that a few bullae were always found, appearing and vanishing, containing clear or haemorrhagic fluid mainly on the palm of the right hand, sometimes on the palm of the left hand and on the sole of the infected foot. This lesion occurred immediately before the treatment and during the treatment.

(2) M. M., age 31. After 6 follow-up examinations persistent lesions remained in the form of nodules of miliary size in both ears, infiltration of the lower right leg with edema.

Persistent painful enlargement of the right femoral gland occurred 3 months after the treatment. This patient appeared to suffer from active tuberculosis at the 5th follow-up, with the occurrence of haemoptosis. A sputum direct smear examination showed a negative result, while the result of culture is still awaited.

(3) W. A., age 50. Before treatment there were lesions in the form of nodules spread over the whole body and the existence of facies leonina. During the treatment a few lesions changed to become erosive, excoriative and ulcerative after the 1st follow-up for a period of approximately 1 month at the 6th examination. Now, the lesions have become hyper-pigmented macules, wrinkled and encircled by small infiltrates which were somewhat erythematous.

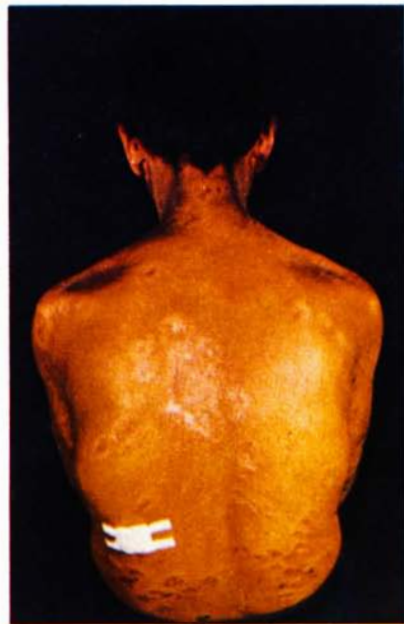
(4) M. R., age 37. At the sixth monthly examination, the noduli of miliar and lenticular size on the back, breast, upper arm and neck persist.

(5) Z. A., age 30. At the sixth monthly examination the lesions remained unchanged in the form of miliary nodules on the upper and lower lip and on the nose. Both ears were irregularly thickened with shiny face due to the presence of a diffuse infiltrate of bluish colour. The fingers as well as the skin covering the extensor part of the arm and the lower third of the leg were also shiny and of a bluish colour.

(6) A. G., age 42. Prior to this trial he was treated with Conteben for 1½ years, with Ciba 1906 during 1½ years, with Lamprene for 15 months and with dapsone for 1 month, without any progress. After 5 months with this new method of treatment progress was quite satisfactory. It was seen objectively that the oedema on the lower leg disappeared entirely and there was improvement in all



(a)



(c)



(b)



(d)

infiltrations. The infiltration on the body disappeared fast leaving indistinct macules; infiltration on the face became thinner although it took a little more time becoming pink coloured but lighter than the initial red colour.

(7) G. T., age 43. Has completed 4 times follow-up. This patient underwent a gallstone operation 1967 and prior to this he was admitted to this hospital for 3 months because of epigastric pain. During the first weeks of the treatment, he complained of nausea, but later on this complaint disappeared without special treatment. After the 3rd follow-up, the patient was suffering from a serious illness with high fever accompanied by vomiting and diarrhoea. The general condition got worse, his weight dropped by 8 kg to 49 kg. During his serious illness, the lesions on the skin did not increase although leprosy treatment was stopped for the time being.

Leprosy Reaction

A mild leprosy reaction occurred in 3 patients but disappeared without special medication so that treatment could be continued without interruption. Details are as follows.

(1) A. A., age 60. From the 1st month onwards some nodules occurred but appeared and vanished, mainly on the extensor part of the arm, sometimes on the palm of the hand and on the lower leg.

(2) S. K., age 11. At end of the 3rd month after having completed the 6th follow-up, some nodules appeared on both underarms and on the extensor part of the leg as well as on the chest.

(3) S. L., age 32. At the 1st follow-up, 3 new nodules were seen on the extensor part of the left arm and 2 appeared on the palm of the hand. They disappeared slowly and no further new nodules occurred.

Side-effects

The side-effects found were nausea, vomiting, dizziness, weakness and insomnia, all of which disappeared without special treatment, except that 1 dropped out because of severe vomiting as reported above.

Bacteriological Findings

Out of the 8 patients who have completed 6 months of follow-up, 3 patients were still bacteriologically positive, viz.:

(1) Z. A., age 30, with several globi in the earlobes and solid forms of bacilli still present.

(2) M. T., age 30, with some globi in the earlobes.

(3) S. K., age 11, still with solid bacilli at the 6th follow-up but no globus.

Other patients:

(4) M. M., age 31, negative for bacilli at the 6th follow-up

(5) M. A., age 50, negative for bacilli at the 6th follow-up

(6) A. L., age 65, negative for bacilli at the 6th follow-up

(7) M. R., age 37, negative for bacilli at the 5th follow-up

(8) W. A., age 53, negative for bacilli at the 3rd follow-up.

Eight patients who had not reached the 6th follow-up gave the following results:

- (1) A. N., age 60, negative for bacilli at the 4th follow-up
- (2) G. T., age 43, negative for bacilli at the 5th follow-up
- (3) S. L., age 32, negative for bacilli at the 4th follow-up
- (4) A. G., age 42, negative for bacilli at the 1st follow-up
- (5) A. B., age 31, negative for bacilli at the 1st follow-up.

All these 13 patients started with globi in their smears except the 2 last cases.

Histopathological Results

Histopathological examination during treatment revealed involution of leproma with reduction of the infiltration, bacilli became granular and fragmented, and disappeared with the presence of fibrosis. The presence or absence of bacilli in the histopathological specimens was in conformity with the smear results.

Laboratory Results

There are no significant changes in the haemoglobin, leucocyte count, differential count, thrombocyte, SGOT and SGPT during the treatment. The initial high value of ESR gradually decreased during treatment.

Discussion

Compared with the treatment with dapsone as "drug of choice", consisting of a maintenance dose of 350 mg per week in accordance with the regulation of the 10th International Congress of Leprosy, the treatment which we are here describing could be regarded as a "bulldozer" treatment, considering the doses, combination of drugs and price.

Rifampicin 600 mg per day is a costly treatment involving a price which either cannot be paid by most of the patients, or only with difficulty. However, if the results are satisfactory, it will still be worth-while.

The treatment of patients with the lepromatous type is considered by some to be a life-long treatment. We know that the lepromatous type is a contagious type. Life-long treatment and contagiousness are the two main factors stimulating research with the "bulldozer" treatment with the aim of shortening the duration of treatment and hastening the process of conversion to the non-infectious conditions, while at the same time reducing emergence of lepra reaction and possibility of sequelae consisting of diverse forms of deformity.

Compared with other drugs this treatment is able to heal the lesions of nodular lesions of miliary and lenticular size and in the healing of the infiltration in the ear and the face it seemed that a longer time of treatment was needed.

A distinct healing with this drug was obtained with the patient A. G., 42 years old, who had been treated with other drugs approximately five years without success.

On the contrary there were 2 patients in whom globus, granular/fragmented as well as solid forms of Hansen's bacillus were still found.

Lepra reaction was slight so that treatment with a specific drug was not needed.

Concerning side-effects such as nausea, vomiting and dizziness, such symptoms are understandable considering the high doses given once daily.

The provisional conclusion of this research was that a longer time was needed to evaluate the efficiency of this kind of treatment.

Acknowledgement

We are very much indebted to Prof. Freerksen, Director of the Forschungsinstitut Borstel and his staff for their excellent assistance and for the availability of the drugs used in this investigation.

References

- Cochrane, R. G. and Davey, T. F. (1964). *Leprosy in Theory and Practice*, 2nd ed. Baltimore: The Williams and Wilkins Company.
- Leiker, D. L. (1971). Chemotherapy of Leprosy. *Int. J. Lepr.* **39**, 462-466.
- Opromolla and Souza Lima (1965). Congresso International de Leprologia—Rio de Janeiro.
- Rees, R. J. W. and Pearson, J. M. H. (1970). Experimental and clinical studies of rifampicin in treatment of leprosy. (Preliminary communications). *Br. med. J.* **1**, 89-92.
- Shepard, C. C. (1971). The first decade in experimental leprosy. *Bull. Wld Hlth Org.* **44**, 821-827.
- Wilkinson, F. F., Gaco, J. and Stantabaya, E. (1971). Therapy of leprosy with rifampicin. *Int. J. Lepr.* **40**, 53-57.

Preliminary Experience with Rifampicin and Isoprodian in Combination in Leprosy Treatment

H. N. KRENZIEN

Balaka Leprosy Hospital, Malawi

Sixty-seven patients with lepromatous leprosy were given combined treatment with rifampicin and Isoprodian at Balaka Leprosy Hospital in Malawi, and experience during the first 15 months is described. Administration was orally according to body weight. Several criteria of control were applied. In addition to routine skin smears, serial biopsies were taken simultaneously, homogenized, the bacilli counted and the bacillary load of the skin calculated per mg of tissue. Clinical improvement from moderate to dramatic occurred in all patients in a matter of months. The fall of the BI was on average 1 unit on Ridley's scale, the homogenate counts indicate a bacilli reduction of more than 90% after 1 year of treatment. A comparison of the simultaneously taken skin smears and biopsy counts is undertaken. The frequency of reactional states under combined therapy and the relationship to secondary parasitic infectious diseases is described. Side-effects were mostly transitory, in 5 cases the combination tablet Isoprodian was discontinued. Some patients showed slightly elevated liver enzymes. However, more biochemical investigation is needed with regard to liver and kidney function under this therapy.

Since June, 1973 a combined therapy which has been developed on an experimental basis at the Forschungsinstitut Borstel has been applied at Balaka Leprosy Hospital in Malawi to patients with lepromatous leprosy.

Drugs, Application, Dosage

The antimycobacterial effective drugs of this combination are rifampicin, isoniazid, prothionamide and dapsone. The drugs were given orally after breakfast in the morning in one dosage according to kg/bodyweight, rifampicin in the dosage of 10 mg, isoniazid and prothionamide 5 mg and dapsone 2 per kg bodyweight. The average patient with a bodyweight of 60 kg received accordingly 2 capsules rifampicin, 300 mg each, and 2 tablets of Isoprodian, the combined tablet of INH, PTH and DDS. Medications were given daily except on Sundays to ensure the elimination of the drugs or their metabolic products.

Criteria of Control

Several criteria of control have been used. Besides the clinical examination, serial photos have been taken at intervals to document progress. Before the start of therapy and during therapy routine skin smears and small biopsies have been taken at monthly intervals. The biopsies are used to quantitative determination of

the bacilli in the skin and for histological examination.

The amount of bacilli in the skin biopsies is counted with the same method which is used by Shepard and Rees in their mouse footpad experiments. After taking the biopsy the material is fixed in 4% formalin and later divided into 2 parts. One is to be used for cryo-sections, the other one is homogenized in Belco tissue grinders for the bacilli count. Before starting homogenizing, the biopsy is weighed on an analytic scale, the average weight of the skin biopsies varies between 15–40 mg. The tissue is then homogenized in the volume of 1 ml 0.1% albumin/dist. water in tissue grinders. Having reached a fine suspension 5 μ l of the homogenate are equally distributed on spot-slides. The slides are air-dried, fixed on a heating plate, Ziehl-Neelsen stained and the bacilli counted under high power. Finally the amount of bacilli is calculated per mg/tissue.

Section of Patients

From June 1973 to August 1974, 67 lepromatous patients have been taken under the combined therapy and by the end of this year 100 patients will be included. Forty-eight cases had been previously treated with dapsone 19 were new, previously untreated patients. In 13 patients the duration of previous treatment lasted up to 5 years, the majority of 35 cases had been previously for between 5 and 25 years with dapsone on different therapy schedules. During the last 7–8 years most of them had 25 mg DDS daily as this schedule was used throughout the country of Malawi since 1965. One section of the patients had

TABLE 1
Distribution of patients as between untreated and previously treated groups

Total patients		67
Previously untreated		19
Treated previously		
No. of years	No. of patients	
0–5	13	
6–10	14	
11–15	8	
16–20	5	
21–25	8	
	Total	48

TABLE 2
Age- and sex-distribution of 67 patients taken under combined therapy. All had lepromatous leprosy

Total patients	Age groups	No. of patients
67	0–14 years	3
(52♂)	15–39 years	33
15♀)	40–59 years	30
	60 and over	1

been hospitalized for several years in different leprosaria, which ensured regular treatment to a certain degree. However, irregularity in taking the previous treatment certainly must be considered, although the majority of the cases previously treated but unregistered claimed to have taken their dapsons regularly over all the years as out-patients.

The age- and sex-distribution of the patients was as follows: 52 out of 67 patients are male, 15 patients are female. Three children with lepromatous are within the age-group up to 14 years, the majority are in the age-groups 15–39 and 40–59 years. One patient was more than 60 years old at the beginning of therapy.

Clinical Results

In all 67 cases a clinical improvement was seen not only by the examiner but by the patients themselves. This seems to me very important and one reason for the good attendance at the out-patient clinics. The time and degree of the clinical improvement varied from the dramatic within a short time of 1 to 3 months to slow clinical improvement within 12 months and longer.

The reddish succulent papules and nodules from new, previously untreated cases, and from obviously relapsed cases disappeared early, whereas the subsidence of old indurative lesions took longer, at least 12 months or more. There are examples of an impressive dramatic clinical improvement in cases treated previously with dapsons for many years whose physiognomy changed from week to week to the better, all papules on the body subsided within three months; these patients never came into reactional states. (The author demonstrated numerous photos comparing the patients before and after treatment.)

Bacteriological Results

The skin smears of most patients gave a Bacteriological Index of between 4+ and 5+ on Ridley's logarithmic scale before therapy.

Figure 1 gives the mean results of skin smears at 3-monthly intervals, the figures in brackets giving the number of patients. The figure for the first quarter

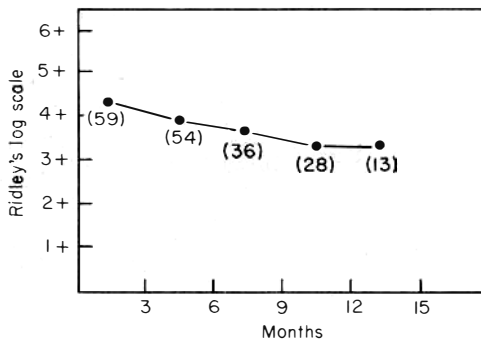


Fig. 1. Decrease of BI with combined therapy. Mean skin smears before combined therapy and up to 15 months after. The figures in brackets indicate the number of patients investigated. The average fall of the BI was 1 unit of the Ridley scale within 12 months.

of the year includes the mean of the figure at the start and those after 1 and 2 months, so that the total of skin smears taken into consideration amounts to $59 \times 3 = 177$ smears. The figure shows the slow decrease of the BI after 12–15 months of combined therapy. The BI had gone down on average 1 unit of Ridley's scale, in this case from 4.4+ to 3.4+.

In Fig. 2 the bacilli counts are plotted against time after treatment. The first 3 counts of the first quarter were chosen as starting point = 100%. The figures in brackets again give the number of patients on whom the results are based. The biopsy counts demonstrate a rapid decrease within the first 12 months of therapy, which means an elimination of more than 90% of the bacillary load of the skin within the first year.

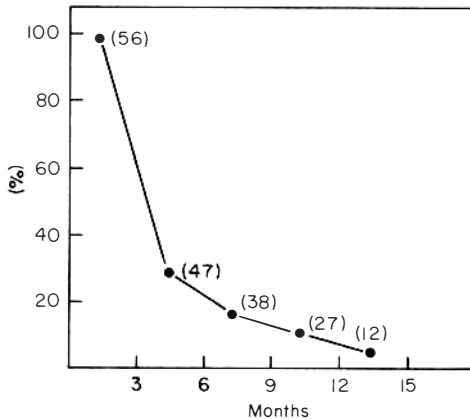


Fig. 2. Decrease of homogenate counts after treatment with rifampicin and Isoprodian. The averages of biopsy count No. 1–3, 4–6, 7–9, 10–12 and 13–15 are plotted against months of treatment. After 12 months of treatment the counts indicate an elimination of more than 90% of the bacilli load before therapy.

Table 3 shows the actual figures of all homogenate counts before therapy, at

TABLE 3
Elimination of Myco. leprae with rifampicin and Isoprodian

Time	Count/bacilli/mg tissue		% left	Reduction rate
Before treatment				
	4.94×10^5	(64)	100	0
After months of treatment				
1	3.24×10^5	(60)	65.6	34.4
3	1.31×10^5	(51)	26.5	73.5
6	6.27×10^4	(32)	12.7	87.3
9	3.03×10^4	(22)	6.1	93.9
12	9.29×10^3	(9)	1.9	98.1

The actual figures of the biopsy counts before and after x months of treatment. The figures in brackets give the number of patients upon which the mean counts are based.

the end of the 1st, 3rd, 6th, 9th and 12th month of the year. In brackets the number of patients investigated, next to that the percentage of the remaining amount of bacilli and the reduction rate. At the end of the 12th month a reduction rate of 98% is reached on average, which means that only 2% of the bacillary load before therapy is left.

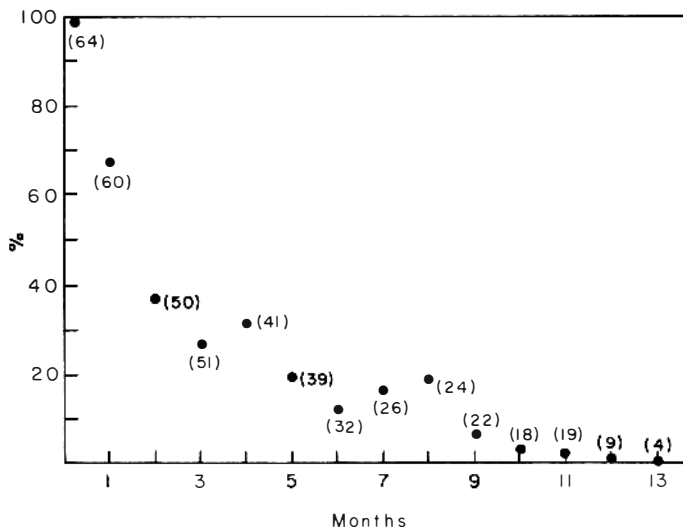


Fig. 3. Elimination of *Myco. leprae* with rifampicin and Isoprodian. Homogenate counts before therapy and thereafter in monthly intervals plotted against time. Figures in brackets indicate the number of patients investigated.

In Fig. 3 the means of all monthly homogenate counts are plotted against time. The graph indicates that the elimination of bacilli follows the shape of a hyperbola, the elimination of 50% of the bacilli being already reached between the 1st and 2nd month after the therapy. After 10 months of therapy all mean counts fall below the 10% mark compared with counts before therapy. No

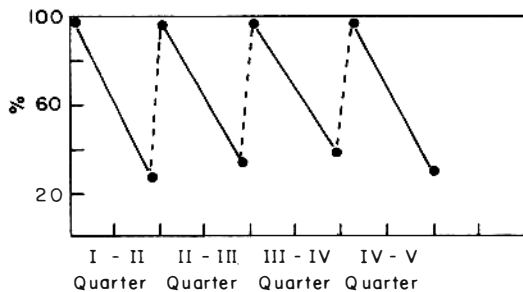


Fig. 4. Bacilli-reduction (relative %), quarterly comparison. A quarterly comparison shows that the reduction rate between 2 quarters of treatment amounts always 60-70%, when the count of the preceding quarter is brought again to 100%.

difference in the reduction rates could be seen between previously treated and new previously untreated cases.

Fig. 4 shows the average in percentage of the homogenate counts from all patients in quarterly comparisons. The means of the first 3 biopsy counts are compared with the corresponding figures of the 2nd quarter, the result of the 2nd quarter with that of the 3rd quarter etc., hereby is the preceding mean count always brought to 100%.

Remarkable is that the reduction rates are all within the same range between 60–70%.

As the data of a large number of biopsy counts and simultaneously taken skin smears were available all counts were compared with corresponding skin smears.

Table 4 gives the information about the actual number of bacilli belonging to a result on Ridley's log scale. The figures in brackets give you the amount of investigations upon which the results are based. Ridley's 2+ to 2.9+ means that you can expect an average of 6×10^3 bacilli per mg of skin tissue, 3+ to 4+ corresponds to 9×10^3 up to 9×10^4 bacilli per mg of tissue. From 4+ to 5+ only an increase of half a log, i.e. from 5+ upwards only 20 comparable results were available, the corresponding figure is 6.7×10^5 bacilli/mg of tissue.

TABLE 4
Quantitative comparison

Routine skin smear (Ridley's log scale)	Biopsy counts (No. bacilli/mg)	No. of patients
2 -2.9	6.48×10^3	(36)
3 -3.5	9.15×10^3	(50)
3.6-4	9.20×10^4	(96)
4.1-4.5	1.82×10^5	(134)
4.6-5	4.88×10^5	(56)
5.1-5.5	6.72×10^5	(20)

On the left side the figures of Ridley's log scale from 2+ to 5.5+. The right side shows the corresponding biopsy counts with the actual number of bacilli/mg tissue. The figures in brackets give the number of patients investigated.

Morphological Indices

The Morphological Index was followed up after medication with the combined therapy in 31 patients in whom skin smears were taken weekly. The white symbols on Fig. 5 show Morphological Indices before therapy, the black spots any positive result after the beginning of the combined therapy. The MIs were distributed between 1 and 25% before therapy. The decrease to zero in the MI took place within 12 weeks in all patients. In reading the MIs only solid and unsolid forms were differentiated. The weekly follow-up showed clearly that there is a relationship between the height of the MI and the length of time until negativity. In this respect, no difference in morphological response was found between previously treated and new, previously untreated patients.

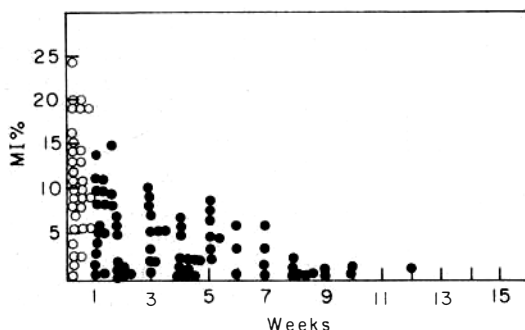


Fig. 5. Decrease of MI with combined therapy rifampicin and Isoprodian. The weekly follow-up of the MI after combined therapy. Each white circle (on the slide red) gives the percentage of solids before therapy, the black circles any positive MI after therapy. The last positive MI is seen after 12 weeks.

Reactional States

The frequency of reactional states is shown in Fig. 6. Out of 67 patients, 23 showed reactional states during the observation period of 15 months. This includes those patients who were admitted because of reactions and then treated with the combined therapy. The type of reaction varied between pure neuritis, reaction type I and reaction type II. In 4 cases isolated symptoms of neuritis dominated, 2 cases with reaction type I and the remaining 17 were classified as reaction type II with ENL. Out of these 19, 7 reactions occurred in new, previously untreated cases and 12 in previously treated cases, most of whom had had several reactions previously.

Secondary parasitic infections

Fifty-eight out of 67 patients were started on the combined therapy in the hospital after being checked for diseases other than leprosy. This included in all cases urine and stool analysis as routine examination for parasitic infections.

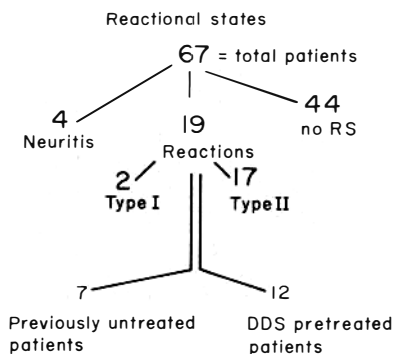


Fig. 6. The frequency of reactional states among the 67 lepromatous patients.

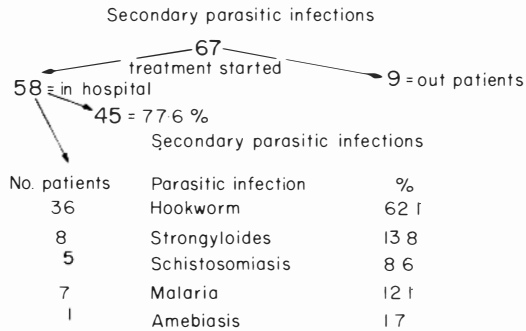


Fig. 7. The frequency of secondary parasitic infectious diseases checked during the first weeks when admitted in the hospital.

Forty-five out of 58 cases (77.6%) showed secondary parasitic infections. The incidence of the different parasitic infections is given in Fig. 7; the frequency of parasitic infections among those 19 patients with reactional states is shown in Table 5.

Four patients were free from parasitic infection, 15 patients had at least 1 or even 3 parasitic infectious diseases at the same time besides lepromatous leprosy.

TABLE 5

The relationship between patients with reactional states and their possible reason—the secondary infectious diseases

Reactions—secondary parasitic infections	
No. patients	No. sec. par. inf.
4	0
7	1
5	2
3	3

Side-effects

As the equipment for biochemical investigations arrived only recently, liver and kidney function tests on patients under combined therapy are still in the early stages. So far 17 patients under combined therapy have been tested for SGOT and SGPT levels. Of these 9 showed slightly elevated results in SGOT and 6 moderate elevations in SGPT after different length of therapy. Alkaline phosphatase was determined in 14 patients after different periods of therapy and in 3 cases slight elevation was found. Although the number of investigations is very limited and no test before the beginning of therapy had been possible, this could be an indicator for hepatotoxic reaction and further investigations are necessary. The actual figures for the enzyme activities are shown in Figs 8 and 9.

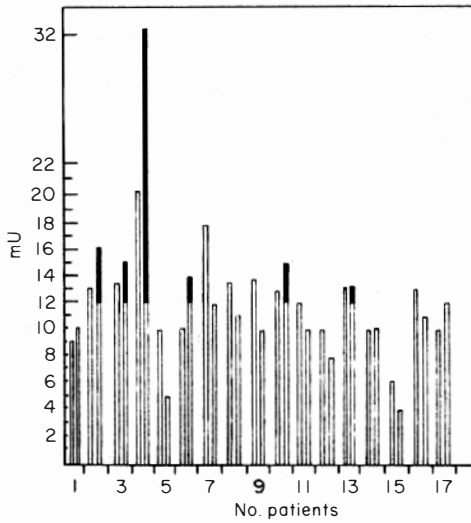


Fig. 8. Enzyme activity under combined therapy (Merkotest Micro-method). SGOT and SGPT investigated in 17 patients after different lengths of treatment with rifampicin and Isoprodian.

□ = Elevated SGOT; ■ = Elevated SGPT.

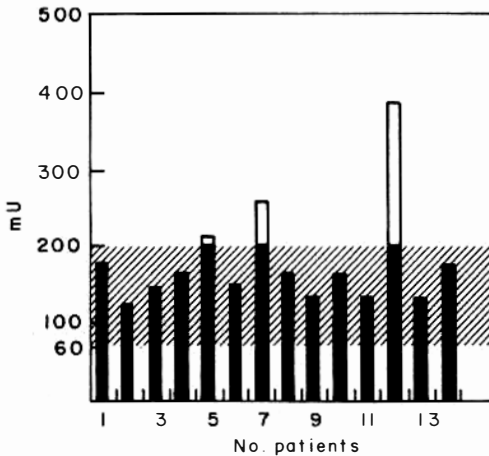


Fig. 9. Enzyme activity under combined therapy (Merckotest Micro-method). The alkaline phosphatase slightly elevated in 3 patients out of 14 investigated after different lengths of treatment with rifampicin and Isoprodian.

□ = Elevated alkaline phosphatase.

Clinical side-effects were in most cases transitory. Complaints differed from abdominal discomfort, stomach ache, loss of appetite and constipation to headache. Nausea, vomiting and heart palpitations necessitating in 5 cases the withdrawal of Isoprodian. All subjective side-effects stopped after that procedure, so it seems very likely that the abdominal side-effects were due to the prothionamide in the combination tablet Isoprodian.

Acknowledgements

For advice and support I am grateful to Prof. Dr E. Freerksen, Forschungsinstitut Borstel, and Deutsches Aussaetzigen Hilfswerk, Wuerzburg; I owe thanks to my wife for the extensive laboratory work needed for this investigation.

Report of Combined Therapy in Leprosy with Rifampicin and Isoprodian Conducted at the Bisidimo-Center, Ethiopia*

R. ROHDE

Forschungsinstitut Borstel, 2061 Borstel, West Germany

On the basis of experimental results by the Borstel Research Institute, 62 patients (BL and LL cases) from the Bisidimo-Center, Ethiopia, received a combination of rifampicin and Isoprodian for a definite length of time under control and clinical conditions. In the same way 18 patients under dapsone monotherapy could be observed.

During treatment good improvement could be seen under both medications, however, the improvement was better under the combined therapy. Side-effects were exceptional; reactions occurred in both groups.

After therapy had to be discontinued, regular controls of the patients were arranged. In the dapsone group a deterioration was soon found, and treatment had to be continued; After combined therapy, however, the trend of improvement continued, the clinical and bacteriological improvement has shown to be progressive; up to now (in many cases more than 2 years after treatment was stopped) no persistent signs of relapse could be found. The patients will continue under further observation.

On the basis of experimental results by the Borstel Research Institute and after first clinical experience was available, 62 leprosy patients from the Bisidimo-Center, Ethiopia, were given an antimycobacterial combined therapy for a definite length of time.

The combined therapy consisted of rifampicin and Isoprodian. The latter is a ready-made combination of prothionamide, dapsone and isoniazid. Before Isoprodian was available, the combination partners of rifampicin were given singly and instead of dapsone a trimethoprim-sulphonamide preparation was used in the combination. The patients all suffered from the lepromatous type of leprosy (BL and LL cases), the Bacteriological Index was highly positive. Most of the patients were new cases, a smaller group had received dapsone therapy previously however, with unsatisfying results. During the time of therapy the patients were admitted to the hospital and the medication was given daily under personal control, rifampicin 10 mg/kg body weight, Isoprodian 2-4 tablets according to body weight. Under the same conditions a group of 18 control patients was under observation, receiving dapsone therapy in a high daily dosage—11 patients received 25 mg, 7 patients 100 mg dapsone daily. For bacteriological diagnosis

* This investigation received financial support from the German Leprosy Relief Association.

skin smears were done fortnightly and biopsies were taken monthly. Besides the routine laboratory examinations a photographic documentation was undertaken.

The duration of stay in the hospital and consequently the time of treatment was limited to $\frac{1}{4}$ or $\frac{1}{2}$ year respectively as the patients wanted to return to their villages and refused to stay any longer in the Center. However, further control was possible, their clinical and bacteriological status was regularly registered and documented by photography. The cases will also be followed-up in the future.

Clinical Results

During the time of treatment an obvious improvement could be seen in both groups (combined therapy and dapsone monotherapy). Those patients, however, that had improved most, could be found in the combined therapy group. Reactions were present in both groups, in more severe cases thalidomide was given with remarkably good results, cortisones were not used, the therapy was not interrupted, and the medication was not reduced in dosage. The preliminary high values for leucocyte count and ESR turned to normal under treatment, but in the combined therapy group this was more evident and quicker. With the exception of 4 cases who became infected during a virus-hepatitis epidemic (2 patients of the dapsone group and 2 patients of the combined therapy group) in no case could an impairment of the liver-function be found, there were as well no signs of a toxic anaemia and no impairment of the kidney function. The drugs were very well tolerated, and side effects were exceptional. Under rifampicin and Isoprodian 70% of the patients were without any complaints during 3 months' treatment.

After therapy was discontinued it could be noticed during the continued follow-up that those patients who had received the combined therapy showed a progressive clinical improvement; they were without complaints, the aspect of the disease showed a step by step improvement up to the present. In many cases a period of 2 years after the initial treatment can be surveyed already. A quite different situation can be seen in the group that had received the dapsone monotherapy; after a short period of improvement in most cases a deterioration followed that made continuation of treatment necessary.

Bacteriological Results

The bacteriological results during the time of therapy and the period after therapy correspond with the results of the clinical observations. During the therapy a slow decrease in the Bacteriological Index took place. The rate of decrease was better under combined therapy than under dapsone monotherapy. The Morphological Index became negative in most patients during the first weeks, the most rapid decrease again being observed under combined therapy.

In the period of follow-up after the course of therapy it was found that in those patients who had received the combined therapy a further and progressive decrease of the Bacteriological Index was evident; 1 year after therapy about 50% of the patients became bacteriologically negative. In the dapsone group a different situation was found. In most patients a deterioration of the bacteriological findings followed an initial improvement the Bacteriological Index showed an increase and the Morphological Index became positive again.

As example of these bacteriological and clinical aspects results in 2 smaller therapy groups are shown on the following 2 figures. The photographs document the outstanding clinical improvement of leprosy patients after a short-term treatment with the combined therapy.

Figs 1 and 2 show the comparison of 2 groups with the longest survey-time after therapy.
 Group 1: 18 patients, dapsone monotherapy (0.5 or 2 mg/kg), 3 months.

Group 2: 16 patients, combined therapy, 3 months, rifampicin (10 mg/kg), Ethionamide (10 mg/kg), isoniazid (5 mg/kg), Trimethoprim-Sulphonamide (20 mg/kg).

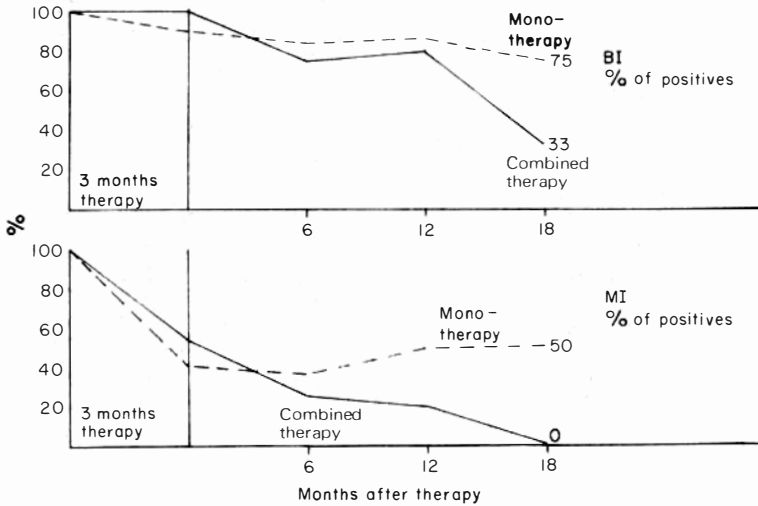


Fig. 1. Bacteriological results. The percentage of BI and MI positive cases show initially the same course, ½ and 1 year respectively after therapy a change occurs. After combined therapy the initial trend continues through the time without treatment in direction of bacterial negativity, In opposite the trend after dapsone monotherapy changes and leads back again to the condition of origin; this corresponds with the observation of the clinical appearance.

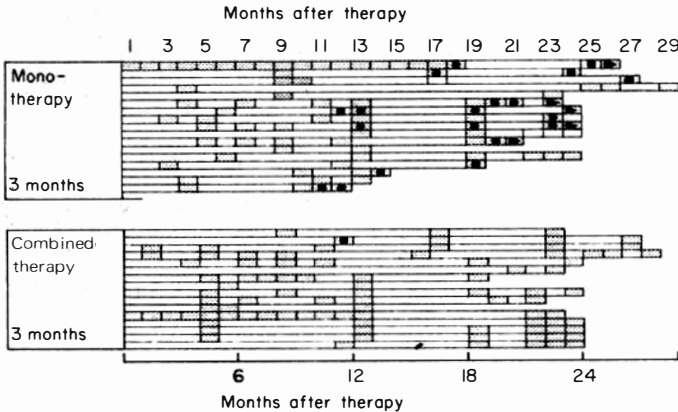


Fig. 2. Clinical symptoms. The reappearance of new and persistent symptoms (lepromata and patches) after therapy was discontinued was only noticed after short dapsone monotherapy. In these patients treatment was started again. Such new persistent symptoms were not found until now after 3 months' combined therapy, not even in those patients who were treated before unsuccessfully for many years with monotherapy.

Each line shows the time after therapy of each patient. Each grey field is a visit to this patient and a control of his clinical and bacteriological status.

(●) the appearance of new lepromata or patches; (►) shows that the patient is under treatment again.

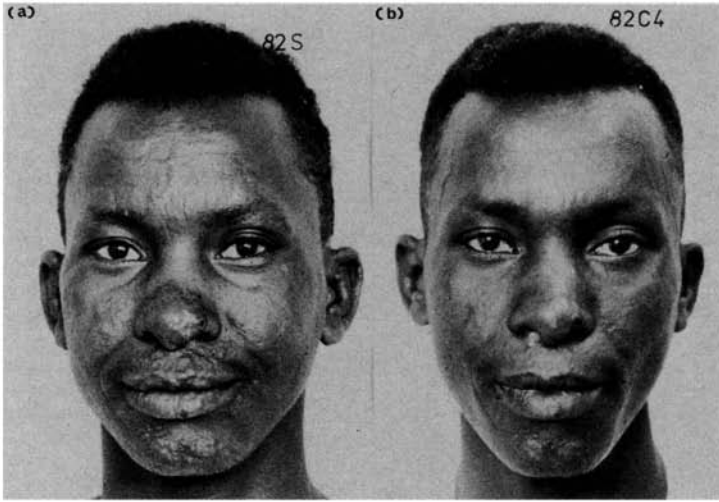


Fig. 3. Patient No. 82, not pretreated. (a) Before treatment. (b) After 3 months' combined therapy and a 4 months' period without further treatment.



Fig. 4. Patient No. 58, not pretreated. (a) Before treatment BI 1.1×10^6 bacteria/mg skin biopsy MI 7.7%. (b) After a 7 months' combined therapy and a 9 months' period without further treatment. BI negative.

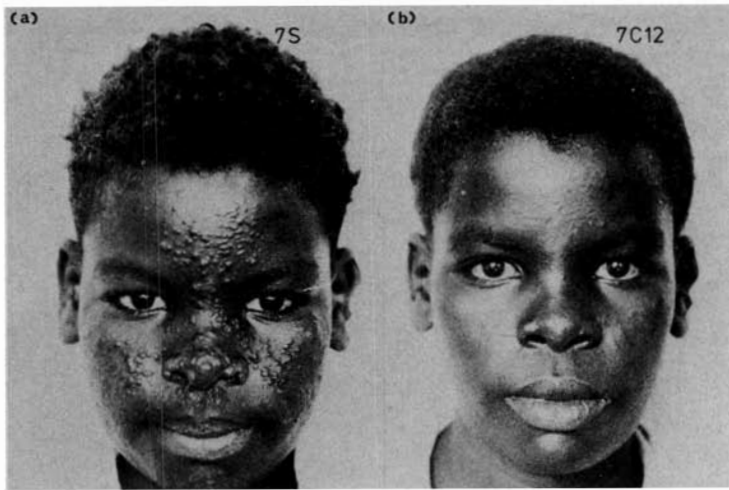


Fig. 5. Patient No. 7, not pretreated. (a) before treatment. BI 5.6×10^5 bacteria/mg skin biopsy. (b) After a 7 months' combined therapy and a 12 months' period without further treatment. BI negative.



Fig. 6. Patient No. 2, not pretreated. (a) Before treatment BI 1.7×10^4 bacteria/mg skin biopsy. (b) After a 7 months' combined therapy and a 12 months' period without further treatment. BI negative.



Fig. 7. Patient No. 51, regularly pretreated with dapsone and Ciba 1906 for 10 years. (a) Before treatment, BI 1.1×10^6 bacteria/mg skin biopsy, MI 11%. (b) After 3 months' combined therapy and 13 months' period without further treatment. BI 5.1×10^3 , MI negative.

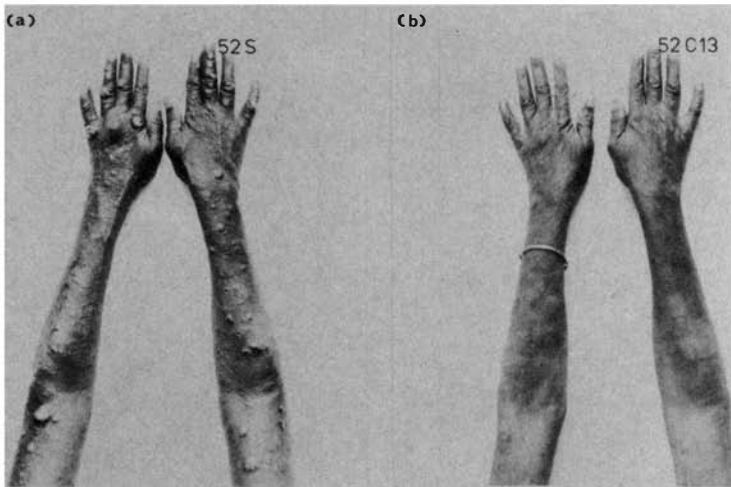


Fig. 8. Patient No. 52, regularly pretreated with dapsone and Ciba 1906 for 9 years. (a) Before treatment. (b) After 3 months' combined therapy and 13 months' period without further treatment.



Fig. 9. Patient No. 56, not pretreated. (a) Before treatment. (b) After 3 months' combined therapy and 12 months' period without further treatment. The regrowth of eyebrows is remarkable.

Preliminary Report of a Drug Trial Conducted at Leprosy Relief Rural Centre, Chettipatty, South India

E. VOMSTEIN

Leprosy Relief Rural Centre, Chettipatty P.O., South India

The drug combination (rifampicin + Isoprodian) therapy continues for 7 cases, it has been stopped for 19 cases—out of which 10 cases receive dapsona treatment ranging from 25 to 400 mg/week, the other 9 cases are without DDS subjected to further observation and follow-up.

All, but 2 cases could again resume work which for some of them had not been possible for years gone by.

The experience gained till now with the drug combination therapy rifampicin + Isoprodian allows us to state that it no doubt means a noteworthy progress. This is especially so in those L and BL cases who never could tolerate and constantly reacted adversely to all the anti-leprosy drugs that are commonly in use.

These patients hitherto constitute an insurmountable medical and social problem.

On 22 May, 1973, a trial was started with the combination of rifampicin and Isoprodian which was introduced by Professor Freerksen for leprosy therapy. Thirty-two patients were selected—29 males and 3 females. These patients were admitted to our hospital for a few weeks before and after commencement of the drug trial to allow close clinical observation and check-up. After being discharged, they reported every 2 weeks for treatment and examination.

Type

L, 29 cases BL, 2 cases TM, 1 case

Ranges from 15 to 60 years

Below 15 years	1 case	male		Type L
20 to 30 years	15 cases	13 males	2 females	Type L
31 to 40 years	9 cases	8 males	1 female	Type L
41 to 50 years	5 cases	5 males		Type: 2 L, 2 BL, 1 TM
51 to 60 years	2 cases	2 males		Type L

Total cases 32

Duration of Disease

5 to 20 years

Groups

The cases were divided into 3 groups:

Group 1: 4 cases—2 BL and 2 L type.

No specific treatment had been taken previously (i.e. dapsone or any other anti-leprosy treatment). These patients⁴ reported to us only a short time previously and were continuously in a reactional state.

Group 2: 12 cases—11 L and 1 TM type.

Treated with a single anti-leprosy drug previously (e.g. dapsone or sulphetrone) with doubtful and unsatisfactory results. With the exception of the TM case, all the others had suffered from chronic reaction with repeated ENL.

Group 3: 16 cases—L type.

No specific treatment was tolerated (e.g. dapsone orally, sulphetrone parenterally, thiambutosine, thiosemicarbazone, Stibenol—Fantorin). In all these patients the disease was long standing with chronic reaction, and most of them suffered from severe intermittent exacerbations and widespread ulcerations.

Nerves

Twenty-three cases of groups 2 and 3 presented nerve involvement. Two cases with single nerve thickened, but not tender. Fourteen cases with multiple nerves thickened, but not tender. Seven cases with multiple nerves thickened and tender (active neuritis).

It was not possible to stabilize the condition of the cases in group 3, not even to a minimum tolerable degree. Two of these cases were steroid dependent, 2 cases depended on steroid cum thalidomide and 2 cases were thalidomide dependent.

Withdrawal

Three cases were withdrawn (2 males and 1 female) from the drug trial after 2 weeks and 4 months respectively because of severe reaction.

Apart from the pathological changes that pertain to *Myco. leprae* in these advanced and chronic reactional cases, no other pathological findings were evident on preliminary examination.

Dosage

The dosage schedule was as follows:

Body weight (kg)	Isoprodian tablets	Rifampicin (mg)
16	1	300
17 to 33	2	300
34 to 49	3	600
50 to 66	4	600

The drug combination was administered orally after breakfast 6 days in the week. During the course of the first 6 months the dosage was reduced if the patient had any side-effects such as nausea or vomiting, and increased to the usual dosage later, thus the maintenance dose was reached and continued till the end of treatment.

Role of Other Drugs

Thalidomide

(1) Initially, together with the new drug combination, a short course of thalidomide (400 mg twice a day which was gradually tapered off) was given to 6 cases (5 L and 1 BL type) in order to control reaction. They were satisfactorily stabilized thereafter and did not require further use of thalidomide.

(2) Twenty cases (1 BL, 18 L and 1 TM type) received short courses of thalidomide, not more than 200 mg/day, which was gradually reduced and then withdrawn after 6 to 7 days to control mild reactions, neuritis and ENL.

(3) Two cases (L type) remain thalidomide dependent, with a maintenance dose of 100 mg/day and 50 mg/day respectively.

Prednisolone

One female L case was given prednisolone instead of thalidomide. None of the patients are dependent on steroids any longer.

Apart from occasional gastric discomfort with vomiting in 2 cases, no pathological symptoms and changes were observed or reported which could undoubtedly be interpreted as sequelae of the drug combination.

A few patients suffered from anorexia with sudden loss of body weight after 11 to 12 months of treatment. After withdrawal there was quick recovery.

Results

There was especially marked improvement in the clinical condition in all the cases during the first 3 months. It is understood that we have to a large extent to rely on the visual evidence only. Infiltrations diminished or subsided, skin lesions flattened, became less erythematous, texture and pigmentation of the skin regained normal appearance in many cases. Ulcerations healed within a relatively short time. Neural involvement was negligible at the end of treatment.

In 1 patient, admitted in severe condition with the integument of the extremities destroyed by ulceration, and ulcers widely scattered all over the trunk (duration and former treatment not known to us); after treatment with the new drug combination the ulcerations healed up. At present this patient is on dapsone 100 mg/week, but he is thalidomide dependent.

Special Observations

A peculiar finding observed during the course of the drug trial was partial new hair growth on eyebrows, eye-lashes, forearms, lower limbs, upper lips, chin, chest and over the patches on the legs and elbows. One patient developed a pleural empyema (right side) 1 month after the drug combination was stopped. The cause could not be definitely diagnosed. The effusion was sanguinous-purulent. Surgical

treatment-rib resection with drainage was performed. Despite the initially toxic condition there occurred no reactivation of *Myco. leprae* and skin smears on this patient were found to be negative after 3 months of the drug trial.

Two patients who suffered from severe attacks of malaria of mixed type (*P. vivax* and *P. falciparum*) did not suffer a relapse of *Myco. leprae*. This is remarkable because from experience we know that intercurrent diseases invariably used to provoke exacerbation, with mild to very severe reactions in patients of this kind.

Surgery

In 3 cases surgery was performed (hand, foot and gynecomastia) without any complications and with excellent results.

Laboratory Findings

All the patients had monthly examinations of urine, blood and stool. Skin smears were also done monthly. Skin biopsies of 4 L cases—2 males and 2 females—were taken and sent to Borstel for examination, as follows:

Patient No.	Type	Sex	Skin Biopsy No.	
13	L	male		10/74
23	L	female	6/74,	25/74
24	L	female	7/74,	14/74
30	L	male		8/74

Corresponding with the clinical findings, the BI in most of the cases showed marked improvement after 3 months. Six of the 8 patients who became negative were so already after 3 months.

All the patients of the negative group have remained stable, despite intercurrent occurrence of other diseases like malaria, pleural empyema, etc.

Patient No. 29 of OB (occasional bacilli) group still requires short courses of thalidomide now and again. He is on dapsone medication now.

Of the 0.16 group in the BI only 1 case is unstable, patient No. 1. This patient is thalidomide dependent. It cannot be ruled out that he was irregular in taking the medicine during the time when he was not hospitalized.

Patient No. 15. Thalidomide dependent (see formerly mentioned history).

Patient No. 5. Very unreliable. Probably he has not taken his medication regularly.

Patient No. 25 and No. 17. Very unstable, irregular attendance.

Short Histories of Four Patients

Patient No. 23

Name: B., Age: about 34 years, female, Type L. Skin biopsy Nos 6/74 and 25/74.

On treatment with us since January, 1968. Nodular lepromatous in chronic

TABLE 1
Bacteriological and Granular Index

Patient No.	Sex	Type	Onset		After 3 months		After 1 year	
			BI ^a	GI ^b	BI ^a	GI ^b	BI ^a	GI ^b
2	male	L	0.66	32%	-ve		-ve	
9	male	L	0.66	40%	-ve		-ve	
12	male	BL	0.16	71%	-ve			
13	male	L	1.66	28%	0.83	80%	-ve	
18	male	TM	-ve		-ve		-ve	
20	male	L	0.33	82%	-ve		-ve	
23	female	L	1.16	42%	-ve		-ve	
24	female	L	0.66	53%	-ve		-ve	
26	male	L	1.00	22%	0.83	55%	-ve	
22	male	L	-ve		-ve			
8	male	L	0.83	42%	1.00	65%	OB	98%
29	male	L	1.00	37%	0.33	72%	OB	98%
3	male	L	1.16	20%	1.00	52%	0.16	98%
7	male	L	1.16	30%	0.66	60%	0.16	96%
10	male	L	1.33	12%	0.16	90%	0.16	98%
11	male	L	1.16	32%	0.66	57%	0.16	97%
19	male	L	0.16	79%	1.00	50%	0.16	98%
4	male	BL	1.00	22%	0.83	37%	0.5	87%
6	male	L	1.00	37%	1.00	62%	0.5	78%
28	male	L	1.00	30%	0.66	55%	0.5	82%
27	male	L	1.00	15%	1.00	56%	0.83	72%
1	male	L	1.16	10%	1.00	25%	1.00	25%
21	male	L	1.66	12%	1.16	20%	1.00	38%
16	male	L	1.00	35%	1.00	67%	1.00	60%
17	male	L	1.00	20%	1.00	35%		
25	male	L	1.00	22%	0.83	30%	1.00	27%
5	male	L	1.33	15%	1.00	35%	1.16	22%
14	male	L	2.00	11%	1.16	34%	1.5	60%
15	male	L	1.66	10%	0.66	45%	1.5	60%

^aBI: The mean score of the 6 smears taken from:

(1) the lesion, (2) right ear, (3) left ear, (4) forehead (5) right cheek and (6) left cheek, in the Bacterial Index (BI) of the patients.

^bGI: The Granularity Index (GI) is divided into 3 groups:

(1) solid, (2) fragmented, (3) granular (SFG).

The mean score of the granular bacilli only found in the 6 smears is given.

The results (BI and GI) are read under the ordinary medical microscope using the oil immersion objective. Smears stained with Ziehl-Neelsen's stain using 10% sulphuric acid as the decolourizer.

reaction; repeated severe exacerbations leading to precarious condition; ulceration of lepromas, involvement of lymph glands, enlargement with tenderness of liver and spleen; life saving administration of steroids; no specific anti-leprosy treatment tolerated. Patient was steroid dependent which had to be given continuously in varying dosages. At the beginning of the drug combination

trial with rifampicin and Isoprodian, prednisolone was withdrawn. Only twice was a short course needed during the drug trial period.

Skin smear. Beginning 1.16, after 3 months negative, at present negative. Combined treatment stopped after 12 months (May, 1974). Attack of Malaria (*P. vivax* and *P. falciparum*) subsided with adequate routine treatment without complications. Now on dapsone 175 mg/week; no re-activation of *Myco. leprae*.

Patient No. 24

Name: K., Age: 24 years, female, Type L¹ (macular lepromatous). Onset of the disease in 1966. Treatment taken at Government Hospital, Salem. Skin biopsy Nos 7/74 and 14/74.

First admission in our Centre in 1968 in a severe condition, with dermatitis exfoliativa and 9 months hospitalization. Thereafter tentative introduction of dapsone treatment which was not tolerated. Patient was in chronic reaction. January, 1972, primary pulmonary tuberculosis of right lung verified. Routine TB treatment with streptomycin, PAS and INH was given. Occasional mild reaction with ENL of short duration. Dapsone orally was introduced again by end of 1972, 50 mg/week. No complications during drug trial period of RMP + Isoprodian. Clinically and radiologically no more pathological findings in the lungs.

Skin smear. Onset 0.66 after 3 months negative, after 1 year negative. Now on dapsone 300 mg/week and follow-up.

Patient No. 13

Name: K., Age: 40 years, male, Type L (macular lepromatous). Skin biopsy No. 10/74.

Under treatment since 1961, received up to 200 mg/week dapsone, attendance very irregular till 1969. In October 1969, severe reaction occurred with ulceration of the skin lesions and bilateral ulnar neuritis. Reaction controlled with thalidomide. Treatment with "Ciba 1906" (thiambutosine). Repeated recurrence of reactions. No improvement. Combined therapy of rifampicin + Isoprodian was well tolerated. After introductory phase, thalidomide was completely withdrawn and not required again. Clinically much improved—disfiguring scars and hyperpigmentations diminished. Both ulnar nerves quiescent. Follow-up—under further observation.

Skin smear. Onset 1.66, after 3 months 0.83, after 1 year negative.

Occupation. Coolie, working capacity restored. No specific treatment at present.

Patient No. 29

Name: M., Age: 24 years, male, Type L. Biopsy No. 8/74.

Suffering from leprosy for the past 15 years. Treatment with us since 1965. Oral treatment with dapsone was first tolerated up to dosage of 150 mg/week. First admission in February 1965 with severe reaction. After that date follows a history of chronic reaction with severe exacerbations and nerve involvement. Futile attempts of treatment with several recommended anti-leprosy drugs (thiourea, carbazone, INH, Ciba 1906, Fantorin, PAT (Pot. Ammonium

Tartrate) and since 1970 thalidomide dependent. Steroid—prednisolone, and thalidomide were withdrawn during drug trial period. Short courses of thalidomide were given to control reaction occasionally when required.

Skin smear. Onset 1.00, after 3 months 0.33, after 1 year OB (occasional bacilli). Patient now on dapsone 400 mg/week, under further observation and follow-up.

The Leprosy Eradication Programme of Malta

G. DEPASQUALE

St Luke's Hospital, Dept. of Dermatology, La Valetta, Malta

An eradication programme ideally requires a closed community with close collaboration from all authorities concerned in order to enable the examination of all known, registered cases; early detection of cases and starting therapy with an effective, quick-acting medication to reduce the possibility of dissemination of the disease; and the facility to follow-up the patients on a long term basis. These requirements having been satisfied in the Malta Programme, one has to carry on with observation of all patients for the next few years in order to evaluate fully the results achieved.

In July 1972 a Leprosy Eradication Programme was started in the Maltese Islands with the cooperation of the Sovereign Military Order of Malta, the German Leprosy Relief Association, the Borstel Research Institute and the Ministry of Health.

The eradication programme is based on experimental and clinical studies resulting in a therapeutical method which, at least at present, can be viewed as the most effective one. It consists of a combination of rifampicin and Isoprodian (Prothionamide + isoniazid + DDS). Since the medication is administered entirely orally, and is as a general rule well tolerated, the programme could be started and carried out on an out-patient basis.

Until recent years, DDS has been the only available drug in the treatment of leprosy, from a practical point of view. Like other anti-leprosy drugs used so far, DDS is a bacteriostatic agent, limiting the reproduction of bacteria rather than killing them. This has been the rationale of lifelong therapy in dealing with leprosy.

The situation has changed with the introduction of rifampicin and the discovery of suitable combination partners. Thus a bactericidal combination enables a quicker and more intensive therapeutic effect. Treatment need no longer be a lifelong process but can be terminated in accordance with the clinical and bacteriological results of the individual case. These were the scientific prerequisites for conducting an eradication programme, which naturally differs in purpose and method from a general control programme. On termination of therapy, subsequent observation and control of all cases has to be carried out, thus allowing a fuller evaluation of the results.

The question of control of patients, which is of such great importance in an eradication programme, proved to be no problem in the Maltese Islands. The population of *c.* 32,000 is fairly stable with very minimal movements. The patients have been very cooperative and regular in attendance. Patients normally

attend once every 2 weeks at the Department of Venereology and Dermatology, St. Luke's Hospital, where they are examined and given the medicaments. Patients in Gozo, the sister island, and St. Bartholomew Hospital, are visited weekly. Home visits, when necessary, are no great difficulty due to the short distances. Patients are only admitted to hospital if suffering from a severe reaction or some complicating illness: these occasions were infrequent. Most reactions that occurred receded spontaneously or with the administration of thalidomide: steroids were never deemed necessary.

Skin smears and biopsies are taken every month from each patient. The smears and biopsies are examined at the Borstel Research Institute, while smears are also examined in Malta. An evaluation system is used integrating the smear results with those of homogenised samples and histological sections of biopsies.

When the programme was started in the second half of 1972, a total of 217 cases were registered. Subsequent adjustment of the registration list for different reasons (dubious diagnosis, movement, death, concomitant disease e.g. carcinoma, heart disease, mental disease, etc.) left 195 cases for consideration. Due to intolerance phenomena or outright refusal of treatment, 3 patients appeared to be untreatable. The remaining 192 patients form the first part of the programme. Eighteen other patients presented themselves when the project was already under way, and form an additional part of the programme.

In conformity with the character of the eradication programme, all patients were treated with the same medication, irrespective of severity of the disease, type and duration of pretreatment, age, sex, etc. Likewise, all patients were subjected to the same bacteriological evaluation system referred to above.

Of the 192 patients forming part 1 of the programme: 64 cases (34%) were found to be "Negative", that is to say, that at no stage have their smears and biopsies exhibited any bacteria or acid-fast material. One hundred and twenty-eight cases (66%) were found to be "Positive". In the group of 64 negative cases, treatment has been discontinued and the patients are observed every 3 months for negativity and the absence of relapse.

Of the 128 positive cases, 108 patients have reached bacteriological negativity in the sense of tissue clearance through treatment. Treatment has been discontinued in all these cases and they too are observed every 3 months for negativity and the absence of relapse. Twenty patients have not reached complete negativity in the sense of tissue clearance, but both the Bacteriological Indices and the Morphological Indices are greatly reduced. The steady decrease in the number of germs is not only demonstrated by the absolute numbers and the indices but also by the fact that the monthly controls have quite often revealed negativity in the sense of tissue clearance. These patients remain under treatment for a further period of time. Some of the patients in this group showing unsatisfactory results might be failing to take the medication regularly. On the other hand, one cannot exclude the fact that, as is seen in other diseases, some patients fail to show satisfactory results despite regular intake of the medication. A modification of therapy may have to be considered for these patients.

The group of 18 cases forming the second part of the programme, although being a heterogenous group due to the staggered initiation of treatment, enables us to make certain interesting observations. The group is composed of 5 long-standing cases that had been treated regularly or otherwise, and 13 fresh cases. Fresh cases show, as a rule, a much quicker response to therapy and the B.I. and M.I. decrease more rapidly. Clinical improvement, although related to the

decrease in the number of bacteria, usually precedes bacterial negativation. The organism requires a relatively long time span to eliminate the acid-fast material. Its duration is not exclusively but decisively dependent upon the number of germs at the initiation of therapy.

DISCUSSION

Discussion

PART I. CRITERIA FOR THE ASSESSMENT OF DRUG ACTIVITY

- I.1. Clinical Criteria
- I.2. Bacteriological Assessment of Drug Activity
- I.3. Animal Models

Dr Browne

Our first theme for discussion is the criteria for the assessment of drug activity. Later we shall be dealing with other aspects, in particular clinical trials and the practical problems of chemotherapy. I would remind you of a sentence in one of the letters sent to you earlier; the aim of the meeting will be to compare the results of the relatively large number of studies recently undertaken, to evaluate these studies, and to make recommendations and suggestions for future work.

What are the criteria that we should observe as we attempt to assess the activity of a drug? We will start with the clinical criteria, go on to bacteriological criteria and then compare animal studies, footpad activity for instance, with clinical response. Yesterday we heard that sometimes these two facets of investigation are not "superposable" (to use a very good French word). We should also examine both clinically and bacteriologically the importance of "persisters", viable persisters, in different organs because this will determine the duration of treatment, the declaration of non-infectivity, and of the reduction to the minimum of the risk of relapse. I hope we shall have time to think of the activity of the various groups of drugs that we have been considering yesterday and today, i.e. particularly the sulphones, clofazimine, rifampicin and Transfer Factor. At the end of this, we shall discuss "Combined therapy", the pros and cons, whether, as we look on the world as a whole, we can recommend combined therapy, or whether, wearing blinkers and with partial blindness, we will persist in the advocacy of monotherapy in a chronic mycobacterial disease in which we wholeheartedly invite the emergence of numerous cases of drug resistance in the future. Now we will begin with the criteria for the assessment of drug activity.

I.1. Clinical Criteria

Dr Krenzien

Yesterday Professor Pattyn showed in his controlled trial an objective criterion concerning the clinical observation. I should like to ask him if he will be so kind as to explain what is involved in this objective control criterion.

Prof. Pattyn

This is purely an evaluation of the degree of skin involvement in terms of infiltration and extent of skin lesions. This criterion is indeed difficult to measure very precisely, but it was noted as such by the clinicians.

Dr Browne

We remember the Leonard Wood Memorial trials of olden days and how they lumped together so many clinical criteria, some of which were due directly to the drug, some to the body reaction to the drug or even to the development of cell-mediated immunity, and some to the results of fibrosis. Now I'd very much like Dr Davey and Dr Leiker to give us some ideas of their assessment of drug activity from the clinical standpoint.

Dr Davey

Without any doubt I would look first in the patients' noses, because I am quite convinced that if we are beginning to study a new drug in a person who has untreated lepromatous leprosy, the first signs of improvement are going to be in relation to his nasal discharge and the state of his nasal mucosa. We should expect to see a change there within three weeks to a month at any rate and with rifampicin probably before that. This is my experience in India. After that I would expect to see a steady reduction in lepromatous infiltration obvious first in the most recent lesions, last in the most fibrotic lesions. One would look for this, of course, on the face where it is readily seen, and also especially on the extensor surfaces of the limbs. At the same time one would turn one's attention to the nervous side; there should be no extension of anaesthesia, one would hope before very long to see the beginning of improvement in nerve enlargement, etc. The suggestion that in the long term, absence of relapse should come into our assessment is important I think. Another valuable criterion is the regrowth of hair.

Dr Leiker

Those who are familiar with the old literature undoubtedly know that even in the period of chaulmoogra oil the clinical appearance of the patient changed remarkably, often the patients were considered as cured. Now I had the privilege of working for some time in Indonesia in an area where leprosy treatment had not been introduced. After the surveys, it was not possible to introduce leprosy treatment immediately. I came back a few years later and I noticed marked changes in many patients for the better. I regard the clinical criteria as most unreliable. Here we have seen an impressive series of photographs with marked clinical improvement, on the other hand, I have also seen many patients who have to be classified as borderline or borderline-lepromatous. In these patients spontaneous clinical changes are very common; marked skin lesions may disappear spontaneously and nearly completely.

Dr Davey

I would like also to comment on that: in the last 24 hours I have seen a large number of photographs of borderline cases and I would not consider these at all suitable for pilot drug trials.

Dr Pearson

The major problem to me in assessing clinical improvement is how to quantify it. It is very easy to look at slides before and after and say the patient is improving well or satisfactorily and get a rough idea whether one drug is better than another, but it is almost impossible to put this improvement into figures. I think that the only way in which this can be done is by Dr Ridley's technique of examining serial biopsies, taken from the same lesion or comparable lesions and

assessing the area, the proportion of the biopsy, affected by the infiltrate or granuloma.

Prof. Saerens

I have the impression that photography is being used for the evaluation of clinical assessment. Why can't we standardize photography as has been done in X-ray photographs for instance? Why can't we learn in this respect from biometricians?

Prof. Freerksen

The effect of a therapy should not solely be judged according to a patient's general clinical improvement, since the latter cannot be standardized. In this respect I quite agree with Professor Saerens and Dr Pearson. The clinical improvement is, however, very important for the patient and his position in society. In our experience, clinical improvement means a relationship to what you can find with other objective methods. This should also be a matter of discussion. A therapy which does not cause any clinical improvement is, in my opinion, of no real value.

In the case of leprosy an impartial and independent registration of phenomena appearing in the clinical picture can only be achieved by means of photographs. However, only outward changes can be registered by photographs. Any changes taking place inside the body cannot be demonstrated by this method. A series of photographs must be taken, one every month, for instance, or every three months. As far as the exterior pathological phenomena of the skin are concerned, the importance of serial photos resembles that of X-ray exposures in the case of pulmonary tuberculosis. Here again the pathological phenomena can only be registered and compared, but not standardized.

Dr Browne

Dr Karat—you have been engaged in drug trials in South India.

Dr Karat

I find it extremely difficult to quantify clinical improvement in patients. Flattening of evidently raised lesions is obviously like the changes in the quantity of nasal discharge that Dr Davey referred to. But I believe that these are very superficial and inadequate criteria for the assessment of therapeutic response, because they do not bear a constant relationship to the change in the bacteriological status of the patient. For the same reason we have also found that the assessment of enlargement of nerves is a very unreliable index, because there is no correlation between the size of the peripheral nerve and its function. We have assessed this using new techniques of electro-myography. More often we have been surprised to find perfectly normally functioning nerves despite gross thickening. That is why I think that clinical assessments can only demonstrate whether a patient looks better, the same or worse, but cannot quantify into terms which can be used by doctors working in different areas of the world.

Dr Ramanujam

We are familiar with the numerical evaluation of clinical progress from time to time. We still follow the traditional method of charting cases, that is representing the clinical condition of the patients on a suitable proforma. We divide the human body into seven areas; the head, the trunk, the two upper extremities, the

buttocks and the two lower extremities. Depending on the predominant type of skin lesion present in these areas, we give them "clinical scores". If there are essentially macular lesions we give them the score of one, if there are areas of diffuse infiltrations we give the clinical score of two, if in addition to diffuse infiltration we find nodules we give a clinical score of three. If the nodules are predominant manifestations we give a clinical score of four. Patients are assessed clinically in our triple trials once in three months and this assessment of the clinical condition on the proforma is done without reference to the previous condition of the patients. In addition to this giving of clinical scores, we note on the chart of these patients, the condition of the peripheral nerves not only regarding their size but also with reference to the presence of tenderness and otherwise, anaesthesia in the peripheral part of the limbs, and also deformities present, if any. We find this way of recording clinical assessment quite useful. This is, of course, only a qualitative assessment. We know that in patients who show very good clinical improvement, the bacteriological changes may not be in conformity with it, but, however, by comparing the chart every three months it gives us an idea whether the patient is progressing satisfactorily or not.

Dr Rees

Can I add to what Dr Ramanujam has just said? By and large, in the trials with which the Medical Research Council are concerned, our policy has been very similar to his, and includes what other leprologists have said here, but there is one important addition which must be mentioned, namely that in all our trials clinical progress is judged by an independent assessor. It is very important to have an independent clinical assessor who is not seeing the patient from day to day, as only in this way is maximum objectivity assured. The assessor examines the patient at the beginning. On each subsequent occasion he first examines the patient, and having made notes, he is given successive photographs, together with his previous notes. His guidance that the patient is improving or deteriorating is of course qualitative, but his independence is important not only from the standpoint of the total pattern to which Professor Freerksen has referred, but also because it enables the group responsible for the patient from day to day to be sure that they are not missing deterioration, an aspect obviously important from the ethical point of view.

Dr Browne

There are only about four centres in the world where competent independent observers can be found within an easy geographical range. This state of affairs is perhaps a reflection on our lack of enthusiasm in leprosy.

Dr Krenzien

Within my relatively short experience in clinical leprosy it is quite obvious to me that there always exists a delay between clinical improvement and the bacteriological response of the host. I think that this might be different under treatment with different drugs. For instance rifampicin causes a quick response of the host within four weeks. Clinical improvement takes a much longer time under standard therapy with dapsone only. This is why we should always note precisely the duration of time for clinical improvement to appear. With some drugs, such as Lamprene, rifampicin and combined therapy, it is typical that clinical improvement will appear within a very short period of time. Of course, the bacteriological response, the decrease of the BI, takes much longer.

Dr Browne

I would like us to return to those peripheral nerves which in the past have been gauged as an important indication of improvement. A lot would depend naturally upon the precise form of leprosy, whether pure lepromatous or subpolar, and the precise duration of leprosy as well as the degree of fibrosis within the nerve, which would account for the persistence of tenderness on palpation. The increase in the extent of cutaneous anaesthesia and paralysis may coincide with clinical improvement in other areas. I would like Dr Davey to take up this aspect which is really an extension of one of his earlier remarks.

Dr Davey

I do not think changes in nerve enlargement are an important criterion of progress really, because you can get extension of anaesthesia during a successful course of treatment, but I do believe that diminution in nerve tenderness in the early stages may be more helpful. My own feeling is of course that we are seriously limited where the assessment of clinical improvement is concerned and can really only say that the patient is improving or getting worse.

Prof. Azulay

It is very difficult to demonstrate clinical improvement by photograph. For us leprologists the clinical improvement is of value, but we have other and better criteria; for the patients themselves the clinical criterion is the most important one, the reason why he comes to the doctor. There may be drugs that act against the bacilli and of course improve the clinical appearance, but there are also drugs that act against the bacilli and against the infiltration, and this fact is of significance.

Dr Pearson

We need to remember that when we are measuring clinical improvement in a long term trial, i.e. one to three years, the clinical improvement is not basically a measure of the continuing effect of the drug; it is a measure of the effect of the host in clearing the results of the infection. It measures the continued action of the drug on the small number of persisting bacilli. Improvement after the initial period is primarily a measure of what the body is doing and not of what the drug is doing.

Dr Jopling

May I just revert for a minute to the question of nerve thickening? The subsiding of nerve thickening can be of very great value in assessing the progress of a borderline or tuberculoid case. Here we have granulomatous involvement of the nerve; the granuloma is absorbed as the result of treatment, the nerve very definitely subsides and can give a very useful assessment of the response to treatment. But I do agree, as Dr Davey says, in a lepromatous case this does not apply; in a lepromatous case, even successfully responding to treatment, there may be steady increase in nerve thickening as well as increase in areas of anaesthesia and in muscle paralysis.

Dr Browne

I would like to take up Dr Pearson's point because we have not yet explained why dapsone is remarkably efficacious in some cases of tuberculoid leprosy and the

sulphonamides, too, as Dr Languillon pointed out. We are dependent not upon the bacteriostatic activity of the drug but on something else. When we are assessing clinical improvement under treatment, what are our criteria then, Dr Pearson?

Dr Pearson

I think I'd query whether even in tuberculoid leprosy all the bacilli are fragmented. If one looks in the right places, that is, in particular, nerves which are liable to be enlarged and damaged in three months' time, but are not now, or dermal nerves in the area just outside tuberculoid lesions, one will find occasionally small numbers of viable bacilli. After all, much tuberculoid leprosy is not usually self-limiting because the patches enlarge, and I still think that even tuberculoid leprosy is caused basically by the presence of leprosy bacilli. Killing the bacilli or stopping their multiplying by any drug is the prerequisite for curing the disease.

I.2. Bacteriological Assessment of Drug Activity

Dr Browne

Since the clinicians seem to be limited, I think we had better go along to the bacteriologists now and to those who are concerned with the bacteriological assessment of drug activity in leprosy. We have heard a lot about MIs and BIs, and one of our participants went so far as to suggest that the MI should be abolished. Perhaps he would like to take up that assertion.

Dr Karat

In my experience there has been no consistent relationship between the number of solidly staining organisms present in a given biopsy homogenate and the cultivation of those bacilli in the footpads of mice. I believe that, while there is a change in the appearance of bacilli under treatment, interpretation of the change as indicating non-viability is premature.

Dr Ridley

I think that any index which depends on staining bacteria is notoriously open to difficulties and to change from one set of conditions in one laboratory to another, due to slight differences in technique. I was particularly aware of this myself when I found that indexing, which I have found to be extraordinarily constant, suddenly showed an increase of five times in the apparent rate of progress of lepromas; I traced this to a change in the alteration of the maximal Bacterial Index in sections from six to six and a half.

While I am speaking, could I also mention the question of the granuloma which two colleagues have referred to and which Dr Pearson said he thought was a good index of clinical improvement, with which I agree, because after all it is infiltration in nodules, which for the most part the clinician is looking at, unless there is a reaction present. This can be quite accurately estimated. Prof. Azulay said that he thought that some drugs acted on the granuloma, others on the bacilli. I am not sure if that is true, but it is interesting that in the trial of clofazimine versus dapsone which I referred to yesterday, the Granuloma Index was the only one which showed any difference between the two drugs.

Dr Browne

Dr Ridley, may I ask you kindly to amplify that phrase, "certain slight differences in technique"? I think it would be most helpful to all of us if Dr Ridley would give us a résumé of the slight differences in technique to which he refers.

Dr Ridley

Well, this goes back mainly to the questions of staining. The differences are just too numerous; we have written papers about this. Differences in the technique of making smears, the way they are spread, the way they are fixed, the temperature at which they are stained, the time of differentiation, all these things have a most definite effect on any sort of bacterial index. There is after all no absolute point at which a bacillus is converted from acid-fast to non-fast, and it is obviously difficult to determine the exact point at which it ceases to be viable. Mere acid-fastness is useful, but after that, bacilli are still present for a long time when they are no longer acid-fast at all; if you use a silver stain you can see bacilli, even solid stained bacilli, when there is no acid fastness whatever.

Prof. Freerksen

When talking about the so-called "effect" of chemotherapy, we have to consider another point which is often neglected. Strictly speaking we are using chemical substances capable of inhibiting in macro-organisms the growth of micro-organisms, or even killing them. The activity of such substances is, however, not directed against the disease itself, nor are the substances able to eliminate dead bacteria from the body. This is one of the organisms' properties and cannot be influenced by means of chemotherapeutic substances. The disappearance of dead bacteria from the body during treatment therefore indicates only indirectly the therapeutic activity, but is nevertheless of remarkable importance. It is apparently very difficult for the organism to disintegrate mycobacteria. Disintegration may perhaps be easier with living than with dead bacteria, since the body can react more strongly with the former than with the latter. Chemotherapeutic substances therefore cannot be compared with "true" pharmaceutical substances, neither be submitted to the same test methods.

When finding acid-fast bacteria in homogeneous material in biopsies and sections we cannot distinguish whether these bacteria were already dead or still alive in the tissue. It is typical for all mycobacteria that by alteration of the medium they undergo considerable morphological changes interpreted as phenomena of adaptation. When chemotherapeutic substances are applied to an organism, the "tissue medium" is rendered unfavourable for the growth of leprosy bacilli. The same thing happens when bacteria are transferred from one culture to another or from one experimental animal to another. This phenomenon is not restricted to *Myco. leprae*; it is common to all mycobacterial species we have studied with regard to this property.

Another symptom of adaptation to a new medium can be the loss of acid-fastness. This means that living mycobacteria may be present even if we do not find any acid-fast bacteria.

As to the double or multiple effect of medicaments several points have to be considered. Apart from their antibacterial activity all antibacterial substances possess a pharmacological and toxicological effect. A classical example of this is the orally administered antidiabetic substances which were not found by research in the glucose field, but rather through chemotherapeutic research (sulphona-

mides). They were only discovered because quite apart from the tests regarding the antibacterial activity of these substances, their biological aspects were also taken into consideration. In such tests the antibacterial aspect may prove to be of no interest at all.

Another aspect of this multiple activity is indicated by the fact that an antibacterial substance may have a very *specific* inhibitory effect, as for example, isoniazid, which is highly active only against *Myc. tuberculosis*, but hardly effective against any other mycobacterial species, while on the other hand rifampicin is a broad range antibiotic used almost universally in antibacterial therapy. I especially noticed this yesterday when the effect upon nasal discharge was mentioned. Nasal discharges are always induced by mixed infection, i.e. they are not purely “leprosy”. This also applies to many ulcers. The broad range antibiotic rifampicin covers leprosy as well as tuberculosis, but also many “unspecific” diseases. Furthermore, it must be considered that certain antibacterial substances mutually intensify their action. Here again we are dealing with a “multiple activity”.

Dr Walter

To have a redefinition of our criteria for therapeutic trials, one could for instance introduce two phases. The first one would be a relatively short “anti-bacterial” phase in which the morphological changes in the bacilli due to the treatment could be measured. The clinical side would not be so very important. This phase could last from 20 to 48 weeks. It would be followed by the “therapeutic” phase, in which the BI would be measured and the clinical improvement assessed. Even if we don't know exactly the final meaning of the morphological changes, we can be quite sure that the activity of the drugs introduced is definitely shown by the changes in the Morphological Index. This would give us some quite valuable measurement for a short time-period. If the first phase shows clearly that there is a significant change as compared with the established value of standard dapsone treatment we would perhaps not need control cases in many instances. We could measure the effect of a new drug by comparison with dapsone therapy. This is why we should distinguish between a short, “antibacterial phase”, and the therapeutic phase which might last two years or longer.

Prof. Azulay

I had one female patient in whom I made the diagnosis of borderline leprosy. At that time I was using thiacetazone (TBI) in leprosy treatment. The patient was improving, but the supply of TBI came to an end, so I gave her dapsone and she improved much more than with TBI. I found out that the patient did not suffer from leprosy, but from premycosis fungoides which developed into mycosis fungoides. From that mistake I learned that dapsone was helping much more than TBI and is likely to have a cytostatic effect, too. Furthermore I discovered that several cytostatic drugs have some similarity to dapsone. In clinical use all cases of premycosis fungoides showed that dapsone stops the course of the mycosis fungoides or decreases the speed of the evolution of this disease. We also administered dapsone to patients with psoriasis, as some people will give nitroretaxate, and obtained good results. This is why I am quite sure that dapsone has a cytostatic effect, too.

Prof. Pattyn

Concerning the MI. It has been stated frequently that we are handicapped in leprosy by the fact that we cannot cultivate the bacillus and I would stress that the discussion on the MI is a very nice illustration of this. What do the tuberculosis doctors do in their controlled trials? Their main parameter for assessment is cultivation of the bacilli during treatment, not X-ray photographs, because these are not sufficiently reliable. In leprosy unfortunately we cannot do this. We can isolate bacilli in the mouse footpad, but the technique is much more complicated than is the case of cultivation of tubercle bacilli. This is why we confine our attention to something less good, namely, the MI. It is less good, because it is a morphological assessment. As has been stressed by Dr Ridley, all morphological assessments are extremely dependent on very small details in technique. The MI in my eyes is the second step down from the optimum, the optimum being the cultivation of the bacillus. We are in need of some sort of biochemical reaction that we would undertake on say a cryostatic slide of leprous tissue in order to have some more biochemical way to determine viability. But up till now we do not have these means, so we have to try everything else we have and we are very well aware of the fact that everything else other than the mouse footpad is less good.

Dr Rees

May I first of all say that Professor Pattyn has stated very well the relative importance, and limitations, of the MI as an indirect morphological method for assessing the viability of *Myc. leprae*. However, in spite of the technical difficulties in interpretation and staining associated with the MI, it is based on sound bacteriological criteria which seem always to be ignored when the subject is discussed. Since in this Colloquium the same basic principles of the MI are being challenged, I would like to clarify the scientific evidence and assess the practical value of the MI. When *Myc. leprae* from patients are examined by electron microscopy, as whole or sectioned preparations, bacillary forms are seen with intact cell walls containing either a complete and well structured or a disorganized and variably deficient cytoplasm distributed irregularly within the cell wall. Since the latter picture of all other species of bacteria was seen only in degenerating and non-viable organisms, it was concluded that such changes were incompatible with viability of *Myc. leprae*. Having identified individual organisms with these various morphological features in the electron microscope, the same preparation was stained with carbon fuchsin and re-examined in the electron microscope. These studies showed that bacilli with homogeneous and well structured cytoplasm stained uniformly and "solidly" with carbol fuchsin, whereas, organisms showing degenerative changes in their cytoplasm with only partial cytoplasmic residues, stained irregularly with carbol fuchsin. Thus these detailed comparisons on the morphological appearances of individual organisms at the level of electron microscopy provided irrefutable evidence that bacilli showing irregular staining identified those organisms that, in their pre-stained condition, showed degenerative changes incompatible with viability. Incidentally, these direct comparative studies of stained and unstained bacilli established that the acid-fastness of *Myc. leprae*, and for that matter other mycobacteria, applied only to the cytoplasmic moiety and that the cell walls of mycobacteria are not acid-fast, since organisms which had degenerated and lost all their cytoplasmic content were no longer acid-fast. On the basis of our original studies at the level

of electron microscopy we extrapolate the criteria of irregular staining to light microscopy as a degenerative percentage on the basis that organisms in this category were incapable of life. By this definition we were well aware that of the organisms that still stained uniformly with carbol fuchsin some were not necessarily "viable", since they might have died more recently without having lost sufficient cytoplasmic content to stain irregularly. Therefore our original "degenerate index" represented a maximal index of viable organisms. On the other hand, clinicians chose to present the index in the opposite direction—i.e. the Morphological Index (MI), as the proportion of solidly staining organisms, and equating this to the proportion of viable bacilli. For the reasons given, therefore, the MI, however carefully assessed, could over-estimate the proportion of living *Myco. leprae*. However, on the basis of our original, and entirely morphological indices, it has since been established with the mouse footpad infection that under well-defined criteria there is a very good correlation between the MI of a suspension of *Myco. leprae* and the ability of the organisms to multiply in the mouse. Therefore, as the mouse infection is the only means of culturing *Myco. leprae* it must at present be accepted as strong supporting evidence for the reliability of the MI as a measure of *Myco. leprae* viability. However, Professor Pattyn has quite rightly stated that the MI is only second best to *in vivo* assessment by mouse inoculation. Since there are few laboratories throughout the world that can undertake the mouse footpad infection, the MI provided an apparently simple indirect method for determining the viability of *Myco. leprae*. Unfortunately, as has already been clearly stated by Dr Ridley, the MI has so many technical difficulties that by and large it cannot be easily accomplished or standardized as a routine procedure. For a proper assessment the MI can only be assessed by high-class microscopy and, moreover, unless well standardized preparations of carbol fuchsin are available, the methods of staining and fixation of the smears can influence considerably the interpretation of solid and irregular staining. These variabilities unfortunately exclude the use of the MI for routine field studies. However, I believe that the MI still has an important place in centres concerned with chemotherapeutic trials. For while such centres may not be in a position to standardize their methods of staining with other centres and, therefore, with untreated patients they may well have very variable figures for their initial MIs, whatever criteria they use there are no technical details that I know of which would fail to show a very significant fall in the Morphological Index to approximately 0 following a six month treatment with dapsone or an equivalent active drug.

Dr Leiker

I have encountered the same difficulties which Dr Ridley has mentioned concerning the MI. This is the reason why I switched over from the MI to the GI for the time being. It is impossible to standardize the technique to such an extent that we can definitely distinguish between completely solidly stained bacilli and those which are slightly fragmented. Nobody can tell whether the slightly fragmented ones are alive or not, but it is possible after some training to recognize granular bacilli with reasonable certainty. For this reason I believe that this is basically the same principle, a more convenient way of expressing the changes in the morphology, just a practical thing. Secondly, concerning the Granuloma Index quantification of the degree of infiltration, we again encountered difficulties. In the biopsy specimen it is quite possible to measure the degree of granuloma. This

offers fairly constant results in pure lepromatous cases. But in borderline-lepromatous cases it becomes more difficult and in borderline ones even more so. In these types of leprosy the clinical lesions are different, it is not an entirely generalized disease, it is to some extent localized. Under the microscope the granuloma, too, is not generalized but localized. When taking successive biopsies, we may take the first biopsy in large part from the infiltrated area in the corium, the next biopsy we may take just a little bit outside the infiltrated part and it seems that there is some improvement, because there is less infiltration as compared with the first biopsy. This is why I think that in clinical trials it is extremely important to separate two groups; to assess (a) the purely lepromatous cases including all the criteria such as granuloma index, and (b) the borderline-lepromatous cases which I believe have a place in clinical trials.

Dr Ridley

Could I just say that I agree with all that Dr Rees said? I did say that acid-fast stain had proved useful in showing a correlation with viability and when I went on to mention silver stains I should like to make it clear that I was talking about staining in a general sense and that the loss of acid-fastness did not mean that bacilli had disappeared altogether, and in fact that there is no sudden end point to bacterial treatment.

Prof. Freerksen

I should briefly like to support Dr Rees' opinion and slightly extend what he said in one particular point: We are not dealing with single bacteria, but rather with a whole bacterial population in the diseased body. With or without treatment this population contains all forms of bacteria in different ratios. During an effective treatment the number of solid forms gradually decreases. It is futile to discuss the question whether they are alive or dead, because nobody knows it. Of course we have to base our judgement on bacteriological data in the case of leprosy, since we are dealing with an infectious disease. But tuberculosis is also a mycobacterial disease and also in populations of *Myco. tuberculosis* all forms are to be seen. If the curative effect would solely be judged by the disappearance of bacteria from the tissues, we would never have cured any patient.

Dr Browne

I think we all agree that the MI is a useful indication of the efficacy of a drug, but that there must be impeccable standardization of technique, if possible between different laboratories and certainly within the same laboratory by the same competent and trustworthy technician. I don't think that many of us would have any doubts as to the usefulness of the BI not as an indication of the efficacy of a drug, but rather of the competence of the body in clearing bacilli, which does not depend directly upon the activity of the drug itself. In this connection, the subject of animal studies should be mentioned and whether there is a definite correlation or not between footpad activity in the mouse and the clinical response. This does affect us tremendously in our practical application of the results of investigations of the activity of different drugs in human leprosy.

I.3. Animal Models

Dr Browne

We should say a word or two about animal models and their use in the assessment of drug activity in leprosy. We have heard a lot about the mouse footpad and

something about the armadillo, but there are other animal models, some of which should be re-examined, some of which are coming into their own for the first time.

Dr Walter

Perhaps one could make a distinction between established animal models for leprosy and those which are potential animal models. We take the mouse as an established animal model—with limitations—and the armadillo with a question mark. The range of susceptibility in the mouse is about 99 or 98%, in the armadillo between 40-60%. Other animals may finally become suitable models for leprosy, such as Dr Convit's hamster, the chipmunk in Korea and others. In this context, I would like to ask Prof. Freerksen to say a few words about the hedgehog as a laboratory animal, because it is very important to find an animal model which can easily be kept in captivity and which provides sufficient amount of *Myco. leprae*.

Prof. Freerksen

There is no doubt that we need experimental animals in chemotherapeutic research, but it is very difficult to choose the right type of experimental animal for leprosy studies. Moreover we do not possess the large quantities of animals necessary for such field experiments. A method which has proved to be very useful and even indispensable is the mouse footpad test employed by Shepard and Rees. In mice, however, there will be no generalization, and the clinical picture we obtain is not the one we call "leprosy" in human beings. This may perhaps be not quite so important. Robert Koch's claim that pathogenic bacteria must induce exactly the same disease in experimental animals as in humans is ideal, yet can hardly ever be realized. Everybody dealing with experimental animals knows that, for instance, the tuberculosis induced in mice has only a slight similarity to the one observed in human beings. The tuberculosis of the guinea-pig differs just as much from that of the rabbit. In leprosy there are no decisive criteria for the choice of experimental animals. Just as in trying to grow the bacteria on culture media, we have to rely here on the hazard selection of possible animals. There is almost no type of animal which has not been used in such trials. Here the conviction plays a part that leprosy bacteria prefer low temperatures. This was mentioned yesterday, but I should like to repeat it today believing personally that this is wrong. This opinion is based upon the fact that leprosy bacteria preferably manifest themselves in the nerves and skin layers situated at the periphery of the body. But they may also appear within the body, in the bone marrow, for instance, as was demonstrated again today by Dr Karat. The temperatures there are certainly not low. We have made the experience that leprosy bacteria multiply in the hedgehog. This animal, too, is only a model, but it is an accessible and cheap living medium suitable for animal trials on a large scale.

Dr Walter

Prof. Freerksen, can you give us some specific data concerning multiplication time, generation time, number of hedgehogs under test, etc.?

Prof. Freerksen

Up to now we have only infected 26 hedgehogs, this is why I would not like to give any further comment. The information I have given should only be seen as an initiative to the study of the hedgehog as a laboratory animal.

PART II. CURRENT CONCERNS IN THERAPEUTIC RESEARCH

- II.1. Persistent *Myco. leprae*
- II.2. Drug Resistance
- II.3. Combined Therapy
- II.4. Transfer Factor

II.1. Persistent *Myco. leprae*

Prof. Saerens

I should like to ask Dr Rees about the problem of persistent bacilli. You presented three series of patients treated for 6 months, 12 months and 18 months, and I was more or less struck by the impression that the longer therapy was continued the greater the percentage of persisters, which seems paradoxical on the face of it. Compared with the situation in tuberculosis we can say that the longer the therapy, the higher the risk of resistant mutants appearing. You showed that in three cases the bacilli were still sensitive. We shall have to wait for further data, but may we ask whether these three cases belonged to the same group and whether you have any further comment on these data?

Dr Rees

You are correct, Dr Saerens, to date our data show a higher proportion of "takes" in mice inoculated with bacilli from patients after receiving two years of rifampicin, compared with bacilli recovered from patients receiving rifampicin for 12 or 6 months. However, the numbers are small and are not statistically significant. Moreover, bacilli isolated in mice from three patients are all sensitive still to rifampicin, albeit these strains have come from patients treated for only six months with rifampicin. While I would agree that it would be more likely for resistance to be manifested in isolates from patients treated up to two years, the results of these tests are not yet available. While at this early stage of our studies we cannot rule out the possibility that some bacilli we are isolating are rifampicin-resistant, I must remind you that in this special study all the patients are receiving rifampicin *plus* thiambutosine. By giving combined therapy it is unlikely that drug resistance to rifampicin will occur.

Dr Ellard

I would like to make a few comments concerning the continued persistence of viable drug-sensitive leprosy bacilli in sites such as peripheral nerve and striated muscle despite long-term treatment with dapsone or rifampicin. All the evidence suggests that both drugs readily diffuse into most body tissues, and in a recent experimental study both drugs were shown to penetrate readily into the sciatic nerves of the dog and sheep. It must therefore be concluded that the persistence of these viable drug-sensitive leprosy bacilli cannot be due to inadequate tissue penetration of either drug. A more probable explanation is that a significant proportion of the leprosy bacilli in such tissue sites are dormant and as a consequence are physiologically resistant to killing by either drug. Dapsone is in any case primarily a bacteriostatic drug, while it is known that rifampicin has very little bactericidal activity *in vitro* against non-growing *Myco. tuberculosis*. This aspect of the chemotherapy of leprosy may therefore be similar to that encountered in the chemotherapy of tuberculosis, where it is apparent that drugs

such as isoniazid and rifampicin that are highly bactericidal against actively growing *Myco. tuberculosis* are unable to kill dormant bacilli. Experience in the treatment of tuberculosis however indicates that the drug pyrazinamide is capable of killing near-dormant tubercle bacilli. Unfortunately experimental evidence indicates that when doses of pyrazinamide are given that are well tolerated in man, the concentrations of the drug attained in the body fail to prevent multiplication of *Myco. leprae* in the mouse footpad. I would suggest therefore that one of the most important areas of chemotherapy research would be to try and find an analogue of pyrazinamide with significant activity against *Myco. leprae*.

Prof. Freerksen

The opinion that antibacterial substances might have no influence on "dormant bacilli", is widespread but never proved. Physiological saline is no culture medium, in which bacteria could multiply. They thus remain "dormant" as shown in Table 1.

TABLE 1

Subcultures after action of rifampicin + isoniazid in different doses after 14 days' contact

1 mg/ml <i>Myco. tub.</i> H ₃₇ Rv in	/ml INH + RAMP	time of contact	Subcultures (0.1 of 10 ⁰) on Löwenstein-Jensen egg-medium*		
			after 3	4	6 weeks
Saline	100 + 100	14 days	-----	-----	-----
	50 + 50		-----	-----	-----
	10 + 10		-----	-----	-----
	5 + 5		-----	-----	-----
	0 + 0		*** ** ** **	*** ** ** **	*** ** ** **
Lockemann medium	100 + 100	14 days	-----	-----	-----
	50 + 50		-----	-----	-----
	10 + 10		-----	-----	-----
	5 + 5		-----	-----	-----
	0 + 0		*** ** ** **	*** ** ** **	*** ** ** **

This very simple but clear-cut experiment shows that isoniazid + rifampicin will have a bactericidal effect in bactericidal concentrations, even if the bacteria have no multiplication metabolism, that is they are "dormant". No matter if the first culture has been given into a medium or physiological saline. The "dormant bacilli" without multiplication-metabolism were killed in this experiment, too.

Whether antileprosy drugs exert any action upon "dormant bacilli", cannot be ascertained *in vivo*, and whether a substance has a bacteriostatic or bactericidal effect, not in animal tests. The reaction between bacterium and macro-organism leads finally from bacteriostasis to bactericidal activity. This process is supported and accelerated by chemotherapy; otherwise we all would be no longer above ground; virulent micro-organisms would have eaten up all macro-organisms!

Dr Ellard

All I can say is that the ability of single drugs to kill *Myco. tuberculosis in vitro* has been demonstrated conclusively by numerous groups of workers. Furthermore since several groups have shown that rifampicin specifically inhibits bacterial

DNA-dependent RNA polymerase, it is clear that its antibacterial activity is dependent on the bacteria being in a state of active growth.

Dr Browne

From the point of view of the public health worker and the clinician, persistent bacilli are not a problem, but they are a problem to the individual patient who may relapse and thereafter become a public health problem. We are convinced that the active drugs, despite the proliferation of a certain number of persisters, are active in leprosy and will help the individual patient.

II.2. Drug Resistance

Dr Browne

Another problem is posed by the increasing occurrence of drug resistance in the world. Sooner or later whether we work in Malaysia or in Britain we shall have to face this problem. It is becoming increasingly serious, as we were reminded yesterday. Fortunately we have two drugs that up to the present have been able to control bacillary proliferation in those patients showing dapsone-resistant bacilli. But the day will come when we shall have resistant forms due to clofazimine and rifampicin.

Dr Pearson

There is quite a lot of drug resistance; I am thinking particularly of dapsone resistance. We have a series of about 100 proved cases in Malaysia; about 140, mostly not proved, but clinically of the same pattern, in the clinic where I work in Addis Ababa. The interesting thing is the time that it takes, 10 years, 15 years, 20 years from the start of treatment for relapse to appear, for resistant strains to multiply and emerge. There is some suggestion that in Ethiopia lower dosage of dapsone has been used in general in leprosy treatment than in Malaysia and that the clinical signs of drug resistance come out sooner. The mean time is about 7 or 8 years in Addis Ababa, about 15 years in Malaysia. In out-patient control centres irregular treatment is also of course more likely, and therefore dapsone resistance is more likely to happen in patients under out-patient therapy. The important thing it seems to me is first of all to get an estimate of how serious the problem is. Our current figures suggest that somewhere round about 5% of patients with lepromatous leprosy, sooner or later will probably get dapsone resistance. This is, of course, very provisional, but such numbers are sufficient to make a major impact on the management of lepromatous leprosy in a big leprosy treatment centre. Drug resistance only seems to happen in lepromatous cases, presumably because it is only in lepromatous leprosy that there is a sufficiently high bacillary population for there to be a reasonable number of spontaneous mutants initially.

Dr Browne

I think your figures of 5% will certainly have to be raised. The percentage of those patients who were in the mid-forties' drug trials in Carville, Louisiana, and now have drug resistant forms is about 50%. I think a patient of mine still holds the world record—four years and four months from the initiation of treatment to the development of proven resistance.

Dr Pearson

One thing to add is that *the important thing is prevention*, and I am convinced that lepromatous patients should be started off at least on dual drug therapy in an attempt to reduce the incidence of dapsone resistance.

Dr Browne

In how many countries in the world is it possible to afford such therapy? Leprosy is only one of the many problems confronting these poor developing countries.

Prof. Pattyn

I think that we should refer to what we have learned from tuberculosis. I invite all those who are not “contaminated by tuberculosis”, as you said yesterday, to get contaminated as soon as possible and to read something about how the modern treatment of tuberculosis was found out, why it was established and why it should be as it is. As has just been said in multibacillary cases it is a “must” to start treatment with combined therapy in order to prevent resistance. The only difference is that leprosy has such a long generation time, and instead of taking one year, more or less, to become evident as in tuberculosis, resistance in leprosy takes a decade.

Dr van der Meulen

I would like to ask Dr Karat if he thinks that early detection of resistance will be possible by examining slides of bone marrow, because he said yesterday that bacilli will remain viable much longer in the bone marrow.

Dr Karat

One can certainly demonstrate the bacilli in the bone marrow, and as I tried to indicate earlier, we could not find a clear relation between the staining characteristics of those bacilli and their viability. If one is looking for “persisters”, certainly bone marrow will be one site which one should seriously consider.

Dr Urbancik

In tuberculosis we have already got in Germany in some laboratories about 6 to 8% of rifampicin resistant strains. If rifampicin is going to be administered in leprosy on its own, we can probably expect resistant strains of *Myc. leprae* within a few years.

Dr Rees

I entirely agree with the previous speaker that from the vast experience in the field of tuberculosis which has shown that monotherapy inevitably results in a high incidence of drug resistance, initial monotherapy in the treatment of lepromatous leprosy by rifampicin, or for that matter any new antileprosy drug, is unjustifiable as routine treatment for an appreciable number of patients. I would like to reinforce this recommendation by briefly recapitulating the present picture of dapsone resistance in leprosy which is only beginning to unfold. From the data I and Dr Pearson have presented from detailed studies on drug resistance in Malaysia and Ethiopia respectively, including proof from dapsone sensitivity tests using the mouse infection model, it is clear that: (1) While relapse due to the emergence of dapsone resistance in a minority of patients presents as early as 3-5 years, in the vast majority the mean time to emergence of drug resistance is

many years—probably 15. In Malaysia where dapsone has been used systematically for 25 years, even in the patients maintained for this number of years on dapsone, some are still relapsing with dapsone resistant leprosy. (2) There is increasingly good scientific evidence that the incidence of sulphone resistance is higher in irregularly treated patients. (3) There is equally good evidence that the incidence of sulphone resistance is higher in patients receiving lower doses of dapsone (lower than 100 mg daily) or where lower doses have been administered by treatment with some of the di-substituted sulphones, such as sulphethrone, where all such derivatives are equivalent to giving 5-20 mg of dapsone. The picture presently presented of dapsone resistance is based entirely on monotherapy, which initially seemed perfectly justifiable because early relapses did not occur. The more recent revelation of the very long incubation period preceding the occurrence of dapsone resistance is as pernicious and frightening as was the revelation and realization of the prolonged exposure necessary for revealing the carcinogenesis of many environmental factors, industrial chemicals or drugs. There can be no doubt that we are only beginning to inherit an ever-increasing dapsone resistant problem, and although resistance to thiambutosine and thiacetazone becomes apparent within 2-3 years, it cannot and must not be assumed that the prolonged period of evolution will be unique to dapsone. It could apply to rifampicin or to any other new antileprosy drug introduced. It should be the duty of all of us responsible for future developments in the chemotherapy of leprosy to insist on initial combined therapy for all new patients with lepromatous leprosy.

Dr Browne

Would anybody like to comment on the recommendation that patients with lepromatous leprosy should continue treatment for life, after apparent clinical and bacteriological quiescence has been achieved? Would you expect there to be a greater proportion of resistant cases as result of this therapy?

Prof. Freerksen

“Resistance” has no absolute rate, but means a gradually differentiated sensitivity restriction. The problem therefore is whether the existing sensitivity is high enough if compared with the applied dose of an antibacterial substance. When stating that a patient is resistant against dapsone one must therefore mention at the same time the doses of the antibacterial substance administered. There may for instance be resistance against dapsone at a dosage rate of 0.1 mg/kg body weight, but sensitivity at 1 mg/kg. Resistance occurs more easily when bacteriostatic agents are used in small doses. It is therefore a great mistake to administer too low doses of antibacterial substances. Big problems also arise with regard to the statement that the effectiveness of a therapy determines its duration. The more intensive the therapy and the smaller the number of germs, the shorter the treatment time. Patients pretreated with dapsone for years or even decades who were still bacteriologically positive at the outset of the therapy we recommended are a distinct proof that the therapeutic effect of dapsone was unsatisfactory.

Our therapeutic results show that bacteriologically negative results can be obtained at variable intervals. There were patients who already became negative after two months and remained so during the observation period. And there are others who are still positive after a treatment period of two years. We do not know the reason for this phenomenon. It may be possible that the patients have not swallowed the medicament given to them, but this seems not to be the only

reason. I personally think that it is useless to apply the same therapy over a period longer than two to three years. If a patient is still bacteriologically positive at the end of those two or three years of treatment, the therapy should be changed.

Dr Browne

Should we continue with an effective treatment, after clinical and bacteriological quiescence has apparently been achieved?

Prof. Freerksen

According to our experience the time necessary for treatment differs from one patient to another. It therefore has to be decided in each individual case at what time treatment should be stopped. This is very difficult, since we do not possess any absolutely relevant criteria characterizing a successful cure in each individual case. At the present level of our experience, we must have the courage to terminate a treatment after a sufficiently long observation period during which the patient remains negative and to investigate then thoroughly the occurrence of relapse. This, of course, must be done in hospitals chosen for this purpose and with the help of suitable doctors. This method is justified as long as a patient can be observed for a period of two to five years. In the case of relapse the patient must of course be treated again. After a short-term treatment this does not offer any problem, since the bacteria remained sensitive.

Dr Rees

Dr Browne has posed a logical and practical question. It is this—bearing in mind that among patients treated with dapsone for many years there is evidence that some will relapse with dapsone resistance, others apparently harbour a few persisters, but viable organisms, that when treatment is stopped will eventually result in the recurrence of active disease. In the latter case the infection is sulphone sensitive and the patients will again respond to dapsone therapy. His question is basically whether these two possible deleterious outcomes will more likely be overcome, or enhanced, by prolonging dapsone therapy indefinitely. Before attempting to answer this question I must stress that these problems only apply to patients with lepromatous leprosy and that from the studies of our own group in Malaysia we entirely agree that both possibilities do occur. However, while both phenomena can occur in lepromatous patients treated with dapsone, fortunately they only occur in a proportion, and since there is no routine investigation for predetermining such cases we can only live with the problem and not prevent it in patients that currently are at this stage of therapy. Therefore, the short answer is to continue maintenance doses of dapsone indefinitely in lepromatous patients already started on sulphone therapy. However, for all newly identified patients with lepromatous leprosy we should be able to prevent the emergence of dapsone resistance by initiating them on a course of dapsone combined with another antileprosy drug and then followed by dapsone alone. Such combined therapy will, on the other hand, not necessarily obliterate a residual persister population of viable organisms, which are drug sensitive, and will multiply when therapy is stopped. The question of whether such drug sensitive persisters can ever be completely eradicated in all patients with lepromatous leprosy still remains a question of the future. Hitherto, dapsone and other antileprosy drugs are believed to be predominantly bacteriostatic and therefore a bactericidal drug, such as rifampicin, may obliterate such persisters, and only

further prolonged studies will answer this important question. If rifampicin or other bactericidal antileprosy drugs fail to do so, then it is likely that a proportion of patients with lepromatous leprosy will never be sterilized by chemotherapy alone and will require, if such a procedure can be devised, a form of immunotherapy which in combination with chemotherapy will enable the host to contribute to the eradication of persisters.

Dr Walter

Life-long treatment has partly been recommended by WHO because we have no alternative. At the time being we really have only one simple first line drug available. All other drugs for practical purposes cannot be used at the moment for a period of three, four or five years for reasons which we don't have to spell out in detail here. We know definitely that the majority of patients who have been treated regularly for a period of five years at an average, become negative by routine methods. How far they are negative to the last bone, the last muscle we don't know, but we assume they are not. So we have to go on treating them.

II.3. Combined Therapy

Dr Browne

I should like us to spend a short time debating the pros and cons of combined therapy. Does combined therapy postpone the appearance of resistance, does it reduce the duration of infectivity, or the duration of treatment; does it make for rapid bacillary clearance and does it prevent or indefinitely postpone the onset of peripheral nerve damage? These are questions that have long troubled those working in the clinical field, and it has been suggested that combined therapy will help. What could we recommend for further investigations?

Dr Molesworth

I should like to say just a word about some earlier experience of combined therapy. Somewhere about 1955 in Malaya, we tried one series of 25 untreated patients on dapsone, another on thiacetazone (TBI), each drug alone, and finally a third series on the two drugs in combination. We gave marks only for those who improved bacteriologically, clinically and histopathologically. I was working at the time with Dr Hale from Singapore University and he did the biopsies while I did the BI. Now we found that in the dapsone group six cases out of 25 had shown improvement in all three aspects, in the TBI group three, and of the combined treatment group, 14. Whenever I have found a case on dapsone, the BI has fallen steadily but sooner or later has stopped and then continued without further fall; when we have added thiacetazone, or as we do in Malawi at the moment, a combination tablet of isoniazid and thiacetazone, the period of infectivity is shortened, the bacillary load falls and the patient progresses. We are very strong advocates for combined therapy. Particularly do I insist on this in Malawi where we have got over 200 cases on DADDS.

Dr Ramanujam

In our treatment of lepromatous cases for the past 20 years we have come across an occasional case where in spite of the patient receiving adequate sulphone

therapy under controlled conditions, there has been some progress, but later on the progress ceased with no further fall in the Bacteriological Index as just mentioned by Dr Molesworth. The only other drug we could ever consider and which we could combine with dapsone was thiacetazone, and we did this in quite a number of cases. I cannot give you the exact figures, such as the maximum dose of dapsone the patients had received previously; but we administered thiacetazone in a dose of 100-150 mg per day in a single dose. All these cases have registered considerable clinical improvement, although bacteriologically the improvement is rather slow. We have not encountered side-effects of thiacetazone as observed especially in the treatment for tuberculosis. Under the existing conditions in India we find it very useful to combine dapsone with one or two other substances in patients who do not respond as we would have expected them to do.

Prof. Freerksen

We should not simply talk about combined therapy as such, but always specify *which* combinations of drugs are meant. Not all combinations are good. Since we never have a sufficient number of equal, comparable cases, it cannot be demonstrated by the usual clinical trials that a certain combination is more valuable than another or better than a highly effective single substance. An investigation with 10 or 20 cases divided into several groups, is not worth-while. The simplest trial must be made up of three groups (untreated cases, treated cases and control group) consisting of at least 30 cases each, i.e. about 100 patients altogether. None of us would be in a position to carry out such a trial.

Dr Karat

I have a few observations to make on combined therapy. First I will take up thiacetazone. As Dr Ramanujam mentioned, this is a drug which is easily available in India and is very cheap. That was the reason why it was chosen for study, secondly it was widely accepted in the domiciliary treatment of tuberculosis. The design of the study was to compare three groups of patients: (1) standard treatment with dapsone, 100 mg; (2) dapsone plus thiacetazone; and (3) thiacetazone and isoniazid. Few observations reviewing our findings; first, we could not record any significant difference between the three groups of patients I have now described in relation to elimination of bacilli. Secondly, there was a marked increase in peripheral neuropathy in patients treated with the combination of thiacetazone and isoniazid as compared to the other groups. The figures approached 10% and the patients under study were of the order of 200, so that the findings are significant.

I should like to refer to one other combination of drugs which we have used on occasion. This was in highly bacilliferous untreated lepromatous leprosy patients who presented with severe respiratory symptoms and some of whom had ulcerating leprosy nodules. In this context three months' study of dapsone versus dapsone and daily 1 g streptomycin produced a striking difference (a) in the clinical resolution of lesions, (b) in the amelioration of respiratory symptoms, (c) in the fall in Morphological Index and (d) in the fall in the Bacterial Index. The progress, as far as the Bacterial Index was concerned, seemed to attain a plateau between three and six months from the onset of treatment.

Dr Pearson

I think one must ask why we are using double therapy. There are two possible reasons. The first is the possibility of getting a quicker cure, a quicker response.

On analogy with tuberculosis, I understand that this is unlikely. When two drugs are used against tuberculosis the initial response I believe is no more rapid than that of the best one used alone. Two drugs are used in order to prevent the emergence of resistance. This is the second reason for using combined therapy, and again by analogy with tuberculosis, it seems to me highly probable that it will have this effect against *Myc. leprae* also. I can see no reason why double therapy in leprosy should be less effective than double therapy in tuberculosis. But this applies merely to lepromatous leprosy. There are plenty of data for us to know that in non-lepromatous leprosy, drug resistance is likely at worst to be only a very occasional, rare phenomenon.

Dr Rees

May I take a few minutes of this discussion to present a number of general and particular basic principles in bacteriology and chemotherapy which are relevant to our present discussions on drug resistance in leprosy?

The first refers to choosing alternative drugs for relapsing patients. Several papers have been presented at this Colloquium where such patients have been given alternative drugs without considering the basic principles of cross resistance between drugs of similar chemical structure and mode of action. Thus for the Chemotherapy of leprosy, dapsone and all other sulphone derivatives, long-acting sulphonamides and acedapsone (DADDS) can be grouped together as having a common mode of action against *Myc. leprae*. Therefore, any leprosy patient who relapses under rigorously supervised treatment with one of any of these drugs in this group will not benefit from any other of the drugs in this same group because they have the same mode of action and will show cross resistance. The same basic principle applies to the thioureas i.e. thiambutosine and thiacetazone, with similar essential chemical structures and mode of action, and therefore a patient resistant to one will show cross resistance to the other member of this thiourea series. On the other hand, the mode of action of the thioureas is completely different from that of the sulpha-group of drugs and therefore there is no cross resistance between the two groups, and they are compatible alternative groups of drugs. On present evidence and known modes of action the three other important antileprosy drugs, i.e. clofazimine, rifampicin and streptomycin, have no common features and therefore among themselves are compatible alternative drugs. Likewise, these three drugs are entirely different in their modes of action against bacteria in general, or *Myc. leprae* in particular, with the sulpha- or thiourea-groups of antileprosy drugs. There have been many references to the use of combined therapy in leprosy in our discussions.

I have a feeling that many clinicians think of combined therapy primarily as a method for obtaining a significant increase in therapeutic activity and therefore as a means of obtaining more rapid cures. There is no significant evidence for this where combined therapy has been used in the chemotherapy of other bacterial infections, or in particular, where combined therapy is routinely used in tuberculosis. The paramount importance of using combined therapy, with striking advantage, is in reducing the incidence of drug resistance resulting from monotherapy, to insignificant proportions. The efficacy of combined therapy is based on sound bacteriological principles and is highly relevant to the chemotherapy of leprosy. Drug resistance results from the presence of a very small proportion of organisms in a bacterial population that are resistant to a particular drug and with the passage of time multiply sufficiently to repopulate the patient

entirely with resistant organisms. The small proportion of such drug resistant mutants seldom exceeds one in a million (10^{-6}). Therefore, if two drugs with entirely different modes of action are given at the same time, then at most the chances of resistant mutants occurring to both drugs would be at best not more than the product of two proportions, i.e. one in a million million (10^{-12}). It is therefore on the basis of such an astronomically small proportion of dual resistant mutants existing in a bacterial population that combined therapy has proved highly beneficial. Clearly the advantage of combined therapy in almost completely excluding the possibility of the emergence of drug resistance, outweighs any small advantages which might result from the efficacy of combined therapy *per se*. These basic principles, which are highly relevant to the chemotherapy of tuberculosis, are likely to apply equally to the chemotherapy of lepromatous leprosy now that we know monotherapy results in drug resistance. Likewise, these basic bacteriological principles also explain why the need for using combined therapy applies only to patients with lepromatous type leprosy. While in the latter type of leprosy the bacterial population is high, and would be expected to contain a significant proportion of drug resistant mutants, in non-lepromatous leprosy the bacterial population is very much smaller and therefore few, if any, drug resistant mutants would be present.

My last point, though not directly concerned with drug resistance, is concerned with a basic principle pertinent to all trials. I refer here to the necessity of control trials for a meaningful assessment of any new drug or new combination of drugs. We have all heard in this Colloquium beneficial results being claimed for a new triple therapy, including rifampicin, from six Centres around the world. All six claim essentially rapid improvement, yet in none of these trials is this claim supported by a controlled comparison. Such an omission is unjustifiable in any circumstances, but is especially so in the particular trials undertaken because of the wide variations in type of leprosy and prior treatments, of the patients under study and because the triple therapies have included rifampicin. All six trials therefore have ignored the well-established knowledge on the variation in the response of patients within the leprosy spectrum, the problems associated with including treated and untreated patients in the same trial, and the well-established evidence based on control trials, which has already shown rifampicin, administered alone, to be more bactericidal than dapsone or any other antileprosy drug. Therefore, on the basis of these accepted principles, none of the claims being made for this triple therapy can be justified, or even accepted as being true, without including a properly matched group of patients treated by rifampicin alone. Regarding the problem of drug resistance in leprosy, this particular triple therapy regimen might well be advantageous, but from what we already know about resistance in leprosy, the type of controlled trials required would have to be undertaken on previously untreated patients and would have to continue for many years. The six trials on triple therapy fit none of these essential requirements.

Prof. Freerksen

In general, the most important reason for the use of combined therapy are the following:

- (1) An intensification of the action reducing the time of treatment and thus avoiding relapses.

- (2) Up to now there do not exist any antimycobacterial medicaments inducing a bactericidal effect, but there are potential bactericidal substances. Bactericidal action can be approached by combining appropriate substances. It can easily be shown that rifampicin administered alone does not nearly attain the results achieved by rifampicin in combination with special substances (i.e. not all).
- (3) Combined therapy ensures more safety regarding the therapeutic effect, because it prevents the development of resistant organisms and bacterial populations showing reduced sensitivity.

Dr Browne

Recalling WHO trials in which I was engaged 10 and more years ago, we were not able to prove any of those objects and the trials did not continue long enough to demonstrate the indefinite postponement of the emergence of resistant strains. We must still do a lot more work on this matter.

Dr Gatti

We have already over 100 patients with all types of leprosy, most of them being lepromatous cases, being treated with the combination of rifampicin plus dapson. In 40 cases we gave a combination of dapson plus clofazimine. We believe that combined treatment is useful, because it produces both clinical and bacteriological improvement and a lower incidence of leprosy reactions. When we used rifampicin, 600 mg alone, reactions were very frequent. Up to now we have had no reactional episodes with this combination. In our experience with combined therapy, reaction is less intensive and we see also less risk of developing resistance.

Dr Krenzien

I should like to reply to Dr Rees' comments on our Borstel-papers this morning. I can only certify my own paper. It was not my intention to compare rifampicin and the combination therapy, which includes rifampicin and three other drugs. The major reason is the second one which Dr Pearson pointed out, and not to achieve a quicker elimination of the bacillary load of the patients under combined therapy. When we compare our results with those you obtained with rifampicin monotherapy, we may come to the conclusion that there is no difference in the speed of elimination of the bacillary load between single therapy and combined therapy. The major advantage would be the prevention of resistance. You did not have the same numbers as I had, but we use the same method, we counted the bacilli. You came to the result that you eliminate round about 90% in the first year and this is exactly what I found also.

Prof. Azulay

I think we have here a very important problem, but it is very difficult to say whether a drug combination is good or not. Each antibiotic has a special way of acting. Two bactericidal antibiotics help each other, sometimes a bactericidal plus a bacteriostatic drug help each other. It should be easy by laboratory trials to find out which combination is the most effective. But in leprosy we encounter a special problem because we do not know exactly in which phase of the bacterial life cycle the antibiotic is acting. This is why we can only guess or find out empirically by trials over a long period, which combination of drugs is good or

not. Another point should be mentioned in this context, because it is of more interest than combined therapy, namely alternative treatment, sulphone after clofazimine, after rifampicin and so on. This problem has been neglected till now.

Dr Gatti

We had a few cases treated with clofazimine over a period of 24 months, in whom the Bacterial Index became negative. One patient under clofazimine treatment however still showed positive findings on bacilloscopy. Under combined therapy with dapson and clofazimine over a period of six months, the findings on bacilloscopy became negative. I think that in this sphere many a question arises. One combination of drugs is not equivalent to another.

Dr Browne

Are you suggesting that this is a possible case of resistance to clofazimine?

Dr Gatti

I am not sure, but my experience is that this patient was a problem.

Dr Browne

Is there anybody else with similar experience of bacterial recrudescence during clofazimine therapy?

Dr Molesworth

We had a patient who was one of our control group on a 100 mg of dapson daily and who produced clinical resistance after two years, with the reappearance of solid staining bacilli, the reappearance of nodules and general degeneration. We gave her Lamprene (clofazimine), and clinically we immediately began to get a response, but no fall whatever occurred in the BI which was 5, and the MI remained steady at about 3 to 4%. After another period of about two years, quite by chance, I suggested putting her on dapson as well, and the combination produced an immediate result which is being maintained, so that both BI and MI have now fallen. Clinically she has maintained a very satisfactory response.

Prof. Saerens

I would like to raise another question in connection with combined therapy. If we do accept as logical the idea of combined therapy, but if we think on the other hand of the socio-economic aspects, the use of rifampicin would probably mean intermittent therapy. Not all drugs seem to be suitable as intermittent companion drugs. This problem should be investigated. We may expect this to be the case for the sulphones, but we really do not know. For tuberculosis it has meant a lot of work, and Prof. Mitchison in England has done a lot of work to find out suitable companion drugs in intermittent therapy. In this respect we hardly know anything in relation to leprosy. Intermittent therapy is likely to be one of the partial solutions to the problem of therapy in leprosy.

Dr Urbancik

I had the honour to serve in a WHO tuberculosis centre in South America and thus would like to stress the point that combined therapy might be of definite advantage in leprosy, because leprosy is very often found together with tuberculosis, and laboratory facilities in that part of the world and in developing

countries are not good. It is often impossible to recognize tuberculosis but it is much more simple to recognize leprosy. Thus by combined treatment which is directed not against one but against more than one mycobacteriosis, at the same time, we can reach a better result.

Prof. Freerksen

In order to avoid any misunderstanding we need distinct definitions when discussing a problem. This especially applies to our definition of the terms "effect" or "cure". And we must also be well aware of the aim of our therapy. In my opinion we should distinguish at least three levels:

- (1) Control of epidemics as leprosy control in the classical sense
- (2) Individual treatment
- (3) Eradication

These three objectives require different and not necessarily comparable procedures. Yet it is certain that the application of well-elaborated therapeutic methods at hospital level will be the best way to perceive what should be done in order to cure the individual patient and to prevent reinfections. An effective short-term therapy healing and simultaneously neutralizing the individual patient is the best protection against reinfection. The best epidemiological work can thus be done by means of highly effective therapy.

II.4. Transfer Factor

Dr Browne

Dr Ridley, will you please make some remarks on transfer factor?

Dr Ridley

I just thought as you mentioned this subject that I would mention a small study I have done recently relating the number of lymphocytes in skin lesions to immunological performance of the patient. A certain number of lymphocytes, not unexpectedly, are necessary to achieve any sort of good immunological performance. But unexpectedly over and above that level there is no effect, there is no relationship between the number of lymphocytes and performance, that is antibacterial performance. On the other hand a large number of lymphocytes does appear to give some sort of stability to a patient and prevent his downgrading in untreated patients or to increase the chances of upgrading with treatment. The point I want to make is that the number of lymphocytes is not an absolute number, but is related to the size of the lesion, and it seems to me therefore, that if one took a patient in the still fairly advanced stage of the disease, the dose of transfer factor required would be enormous and would have to be sustained. If there is a place for immuno-therapy in leprosy, it seems to me more likely that it would be found at a later stage of treatment when the disease has undergone regression and at that time it is possible that an effective upgrading or reversal reaction would be induced which might conceivably prevent a relapse.

Dr Karat

I have just two observations to make. In reference to Bullock's work in the United States, acceleration of the reversal process appeared after administration of

transfer factor. I should like to ask Dr Ridley, whether he had the opportunity to distinguish between B and T lymphocytes in the context in which he described just now.

Dr Ridley

Just to answer Dr Karat's question. It is not possible to distinguish between T and B lymphocytes.

Dr Rees

From all the studies that I am aware of on the use of transfer factor in lepromatous leprosy, with one exception, all have shown minimal benefit. The one exception is the trial being carried out by Dr Hastings and his colleagues at Carville. In their studies they have, unlike the other trials, been administering transfer factor regularly over a significantly longer period, for many months. Their admittedly limited experience has shown that prolonged therapy with transfer factor resulted in a significant drop in the BI associated with a significant lymphocytic infiltration of the skin lesions.

Dr Languillon

It is very interesting to combine with chemotherapy a therapy which gives a stimulation of immunity. I have used a preparation named Ducton. I gave this by intramuscular injection, 5 ml every two days to two borderline cases. When treating these two patients with dapsone, with sulphonamides, with Lamprene, I observed every time a borderline reaction with infiltration of lesions, ulceration and many bacilli in the nose and skin. I gave this treatment with Ducton alone during a period of two months. I obtained a total regression of the lesions and both nose and skin became bacteriologically negative in both cases. A friend of mine in Bamako used the same treatment in association with dapsone and obtained better results with the association of Ducton and dapsone than with dapsone alone. I think that this drug gives a very good stimulation of the property of macrophages in the treatment of leprosy.

Prof. Azulay

I agree with Dr Ridley that it is impossible to make a differentiation between T and B lymphocytes on the slides. But, those who have experience in the histopathology of leprosy know that there are some cases of lepromatous leprosy that have a huge number of plasmocytes; there are also other lepromatous cases that have few plasmocytes. As far as we know from immunological study, the plasmocyte is nothing else than a B lymphocyte that has changed its morphology. On the other hand, tuberculoid cases have no plasmocytes. Nevertheless we see one or two plasmocytes in slides from tuberculoid cases. I wonder if those cases with relapse have more plasmocytes than those who respond better to the treatment.

Dr Browne

I must say that I was certainly impressed by the histological evidence produced by our Korean colleague and also by the hint recently that there may be some drugs that will influence the development of T lymphocytes inducing them to take on unexpected properties which may be more than transient, but this work is still in the press.

PART III CLINICAL TRIALS

- III.1. Choice of patients
- III.2. Duration of trials
- III.3. Duration of therapy
- III.4. Criteria for non-infectivity
- III.5. Intermittent versus continuous therapy: toxicity and side-effects

III.1. Choice of Patients

Dr Browne

We think now in particular of clinical trials in leprosy and the choice of patients. We have had some observations about the need for patients with lepromatous leprosy, high MI, and high BI, previously untreated. Dr Pearson said that there also should be trials using non-lepromatous leprosy. Would anybody like to pursue these questions?

Dr Pearson

When planning a trial we have to decide what we want to know. If it is whether a drug works in killing bacilli, then one chooses patients with lepromatous leprosy. If it is for other things, such as comparing the incidence of complications, or of reactions on different regimes, you have to decide what response you want to study and choose the appropriate group of patients. The only really important thing is whether a drug cures the disease. The only way to establish this is by giving treatment for a period and then stopping it, and seeing whether the disease is cured. For this type of trial I think that non-lepromatous leprosy is the most suitable type of disease to choose, because such trials can be undertaken and results obtained in a reasonably short time.

Dr Ridley

This is an interesting idea. I think that more information is wanted about the incidence of relapse in tuberculoid patients without treatment.

Prof. Azulay

It might be an interesting idea, but I really don't think it will be worthwhile pursuing because the rate of relapse in tuberculoid cases is very, very low. You will spend too much time, maybe 20 years, in deciding if a therapy is good or not on that basis. I have been working in leprosy for more than 30 years and I can tell you that in tuberculoid leprosy relapse is very rare.

Dr Pearson

Maybe we should not choose polar tuberculoid but rather a type of disease that gives a measurable relapse rate in a reasonable period. Let us look at it from that point of view.

Dr Walter

Dr Pearson's idea to include tuberculoid cases in a trial for testing new drugs is a good one. However it is not only Dr Pearson's idea. Others have put forward this idea too. Dr Languillon has published several papers on the use of long-acting sulphonamides in tuberculoid leprosy. The question is by which criteria of

measure in the early stages without waiting for three or four years until we can histologically confirm a more or less definite cure.

Can we measure in the early stages the effect of the drug? If somebody could find out this, I think we would have some worthwhile result. Possibly we could use another drug, even for a very short time in tuberculoid leprosy; but how can we measure it?

Dr Davey

I was just going to refer to the point that Dr Azulay made earlier. In the presulphone days, we had very large numbers of TT and BT patients on treatment in Nigeria who did very well indeed on chaulmoogra oil treatment, and relapses were very rare among them. The disease just disappeared. The very first paper I ever published was one in the International Journal round about 1939 reporting on a group of about 70 isolated patients across the whole spectrum of leprosy who for reasons outside our control, had to be left to their own devices for two years with no treatment whatever. These were people whose leprosy was sufficiently marked for them to be well known objects in the community and therefore were isolated. After two years the interesting point was that though they had no therapy of any description there were several of these people who had resolved completely, and others had very much improved. So we do have very serious problems when we try to use tuberculoid and near-tuberculoid patients in any form of drug trial.

Dr Browne

There is shortly to be published in *Leprosy Review* a report of 2700 cases of self-resolving leprosy.

Dr. Languillon

I have treated many hundreds of patients with leprosy of tuberculoid form for 17 years with sulphonamides. I have never seen relapses among these patients. They were also treated with dapsone, and relapse was very, very rare. I agree with Dr Azulay, the relapse of the polar tuberculoid form is also very rare in Dakar.

Dr Ramanujam

We have followed up cases of tuberculoid leprosy from 1939 till 1956 when sulphone treatment was available to all patients. This is a special reference to all kinds of tuberculoid leprosy in children and the follow-up study shows that in the vast majority this disease resolves spontaneously. The children were followed for seven years afterwards and there was not even one instance of relapse. I am not able to give you figures of relapses in other patients with tuberculoid leprosy because in our experience classical tuberculoid leprosy is becoming very infrequent in that part of the country where I am working. Dr Pearson made a modification in his suggestion for trials especially to study the incidence of relapses. He said that instead of TT we would like BT cases to be under surveillance for a long period of time. Here I would like to mention that since 1965 we have had a longitudinal trial in borderline cases using very small doses of dapsone ranging from 1.25 to 2.5 mg per day, that is 240 cases in a 20 years' follow-up study. Recent assessment of these cases revealed a relapse rate of 8.8%. We presented these results in one of the seminars held at our institute. At that time the question was posed to me whether this relapse was possibly due to the

small doses of dapsone. From the literature I learned that Dr Davey reported a relapse rate of 29% in the Tokyo Congress in inadequately treated borderline and indeterminate cases. We have information with regard to the relapse rate in the unstable forms of leprosy. Relapse is a very serious problem in lepromatous cases with which we are all concerned, and if you propose to concentrate on the less serious forms of leprosy, we could possibly lose the main issue.

Dr Krenzien

Concerning the selection of patients for control trials, I had out of 67 patients, 48 who were pretreated while 19 were new cases. I found up to now no difference between the previously treated cases and the new cases as to the fall of the BI, even if the counting method was used. This would be an argument to start control trials with a mixture of previously treated and new cases, because we get the same situation in both.

Dr Browne

I too would add a point that already has been made today, namely that we should be most careful in our classification of patients. If we include those with borderline elements and call them lepromatous, then our results are dubious to a very serious degree.

III.2. Duration of Trials

Dr Browne

I think we should say a word or two about the duration of trials we would recommend, and concentrate on lepromatous leprosy in pilot trials. For how long should an initial trial be undertaken? Then for the definitive trial on a wider scale, multi-centre if possible, what should be our recommendations? Some people have suggested that it is possible to obtain definite indications within a few weeks or months.

Prof. Azulay

I had a group of cases, treated with clofazimine over five years, all BI negative and clinically very well. Do you believe that we can withdraw treatment under these circumstances?

Prof. Pattyn

As Dr Pearson said earlier, much depends on the purpose of the trial in question. At the Bergen Congress the Panel on experimental chemotherapy divided trials into three or four groups, very short ones, short ones, long-term ones and very long-term ones. A very short trial can fulfil the purpose of determining the activity of a compound that has previously been tested in the laboratory, a short-term trial can determine short term toxicity effects and things like that, while a very long-term trial will provide information about what is happening in terms of relapses and resistance. Everything depends upon the question, what is the precise purpose of the trial.

Dr Karat

The duration of a trial will depend on the purpose we have in mind, for instance to determine whether a given compound shown to exert some effect in animal

experiments, is active in man. From my own personal experience I know that trials lasting less than six months are not very valuable, because of sampling errors, the techniques, all the various things I have mentioned this morning.

Prof. Freerksen

I think we must differentiate between the time necessary for the treatment of a single case and the duration of a trial. These are two entirely different matters. The duration of a trial depends on the objective we have in mind. Short-term trials can be carried out with a view to studying the activity of a substance during treatment, but in this case the subsequent period without therapy obviously also belongs to the trial, because no trial is complete without the consideration of relapses. In fact, we do not know how long we have to treat a patient and which medication should be applied in order to obtain complete healing. The decisive criterion is the absence of relapses, which can only be studied over a long period during which the patient remains untreated.

Therapeutic methods exhibiting relapses during treatment are obviously of no value. But here we require a clear definition of what is meant by the term "relapse".

It is relatively simple to organize trials providing answers to precise questions. Their interpretation, however, is quite a different matter. Nobody knows exactly how long a patient should be treated, since this has never been sufficiently studied because nobody wants to incur the risk of withdrawing treatment. Dr Azulay has therefore raised a decisive question.

Dr Languillon

If we administer combined therapy with rifampicin and Isoprodian, the trial can be stopped after three to five months, when the Morphological Index is negative, because all bacilli are destroyed and no solid or granular forms are to be seen. Then it would be enough to continue treatment with dapsone *per os*, or better by injection of DADDS every two months. But for the treatment in lepromatous cases it is absolutely necessary to continue treatment for life, because I have seen many patients with lepromatous leprosy which was inactive but when treatment was stopped, after one, two, five years, relapses have appeared

III.3. Duration of Therapy

Dr Browne

Dr Walter, can you be so kind as to summarize briefly the recommendations of the WHO regarding duration of treatment.

Dr Walter

These recommendations are more or less known; namely, five years of regular treatment after negativity has been achieved. However, in lepromatous cases it is recommended that treatment be continued for life. In our discussion we seem to have gone a bit in a vicious circle regarding the alternatives. We have not found any alternatives so far as mass treatment is concerned. The term "mass treatment" is a bit unfortunate, since we are not really doing mass treatment, which implies

treatment of a whole population. We have to distinguish this procedure from the one for cases which do not tolerate easily the generally recommended treatment with dapsone.

Dr Browne

When one looks hard one can always find fragmented bacilli and the only way of defining complete bacteriological negativity is to kill the patient and section all his tissues, when you would certainly find some bacilli in the bone marrow, the liver, the spleen, the lymphatic nodes and between nerve fibres. From the public health point of view this person is no longer a menace. From the individual point of view he may relapse. The group at Sungei Buloh is discussing the possibility and the ethical desirability of ceasing treatment after bacteriological negativity has been achieved. Would that be justifiable?

Dr Rees

Since I am of the British Medical Research Council and responsible for the Leprosy Research Unit you referred to at Sungei Buloh, I would like to comment and justify the point you have challenged. Let me first recapitulate what Dr Browne has said, which clearly relates to his vast experience and that of other leprologists, that some lepromatous patients treated with dapsone for many years, and in spite of negative skin smears, may relapse with active disease when taken off treatment. Excluding the possibility that such patients might have been reinfected it must be concluded that their relapse arises from a residue of living bacilli somewhere in their body tissues. While I am well aware that among clinicians this subject has led to heated controversy and the presentation of somewhat mystical alternative hypotheses, I will present evidence in support of basic bacteriological principles. In other bacterial, and particularly mycobacterial infections, it has been well established that small populations of living and drug-sensitive organisms can persist in the tissues in spite of adequate chemotherapy. Therefore, there is nothing unique about relapses occurring in lepromatous patients after stopping treatment, in spite of many years of therapy. In leprosy the routine bacteriological assessment is made from skin scrapes and therefore on a quantitative basis, based on the assessment of stained skin smears, there could be a small number of organisms present even when a skin smear assessment by routine examination is negative. This is simply a question of numbers of acid-fast bacilli present related to the volume of smears examined and the time allocated. The same discrepancy applies to the examination of smears of sputum from patients with pulmonary tuberculosis. Cultures are more sensitive. In leprosy the examination of skin scrapes would particularly apply if viable persisters existed in sites other than the skin, and likewise would apply if the small number of such persisters were concentrated specifically within the cells of nerves or plain muscle in the skin, rather than uniformly throughout the skin tissue. There is good histological evidence, and mouse footpad infectivity evidence, to suggest that the latter situation is relevant. Namely, that well-stained bacilli in small numbers may particularly be seen only in dermal nerves and arrector pili muscle fibres or in peripheral nerves and striated and smooth muscle fibres in parts of the body other than the skin. Clearly therefore negative skin scrapes could well be only a

question of small numbers of persistor bacilli, below the number detectable by routine microscopy. There is good evidence using the mouse footpad infection to support this explanation. Thus it has been established that skin sites negative on microscopy as skin smears, when biopsied and homogenized and injected into mice produce positive infections. Likewise, similar patients with skin smear negativity have been shown to harbour living *Myc. lepræ* capable of multiplying in the mouse, when biopsies are taken from muscle or peripheral nerve or scrotal skin (including dartos smooth muscle). In fact, our own studies at Sungei Buloh have shown that 7 of 12 lepromatous patients maintained on full dapsone therapy for 10 years have from one or other of these biopsy sites produced infection in mice. This evidence is of paramount importance since it clearly shows, as in tuberculosis, the presence of a few viable persistor bacilli in patients treated with chemotherapy for many years, and establishes the mouse infection technique as being more sensitive than routine stained skin smear techniques.

Thus our experimental studies are in line with the experience of leprologists who are familiar with relapse occurring when skin negative patients are taken off dapsone. Unfortunately, the routine application of the mouse infection is not generally available. Our own special studies fully justify continued dapsone therapy long after, if not indefinitely, skin negativity is reached in patients with lepromatous leprosy.

However, having presented evidence that the mouse footpad infection is more sensitive than stained skin scrapes for identifying persisting viable bacilli within the skin or other tissues, it is surely justifiable to use the mouse to monitor and compare the efficacy of other antileprosy drugs. Therefore, if a new antileprosy drug is monitored in the mouse, and inoculation of homogenates from the skin or other tissue sites fails to reveal the presence of living bacilli, it would be reasonable to conclude that the new drug was more beneficial than dapsone. On this basis we consider that if a new drug monitored this way in mice gave completely negative results, it would then be justifiable to withdraw treatment as long as the patient could be regularly monitored using the mouse test. On the basis of our present knowledge we consider this justifiable and moreover the only way that a new drug could be shown in patients to be more effective than dapsone.

Dr Browne

There are two points I should like to make from the chair. One is that in the mouse we have a wonderful model, but it may not pick up every living organism. Chang and other workers suggested that organisms that we would call non-viable on morphological examination, would not grow in the mouse, but in the human they might grow. The other observation is a very practical one. In a developing country with 40 pence per head per year to spend on all medical services, including leprosy, can rifampicin be used for a shorter period to reduce drastically the bacillary load and render the patient non-contagious? Is it a practical possibility then to use rifampicin, say, for a fortnight and then to switch to dapsone? This is perhaps not the ideal, but is this a practical possibility for a developing country with 40 pence per annum per head to spend on all medical services?

Dr Ellard, would you consider it advisable to give one dose of rifampicin, perhaps 1 g, or 1.5 g, and then dapsone to patients in a rural situation who can be visited only once in three months by an itinerating medical officer?

Dr Ellard

My answer would be yes.

Prof. Pattyn

I think we have now started talking about optimal things to do in reality. If you pose the question in terms of what do we do in a situation where we can reach the patients only once every three months, then definitely it would be worthwhile to add a dose of rifampicin at the start. Whether this is the absolute level optimum, we do not know at the moment. But choosing between DADDS alone from the start in the multibacillary patients, or DADDS plus one dose of rifampicin, I think that the latter possibility is certainly the best one.

Dr Walter

It is definitely most desirable, and there is no doubt about it from the public health point of view, to have a drug which reduces or terminates infectivity in a very short time. On the other hand we cannot possibly base our recommendations on the experience gained in 50 cases. We need more trials to be carried out in a proper way by independent workers for longer periods with greater numbers of patients, before we can make practical recommendations on this particular subject.

Prof. Freerksen

Being physicians we should not let economic questions interfere too early with scientific or medical ones. Our duty is to find out the best method for the patient. The administrative authorities should then examine whether our suggestions can be put into practice. May I raise here a concrete question regarding this situation: Should we prefer bactericidal or bacteriostatic substances in leprosy treatment? All of you seem to hold the opinion that preference should by all means be given to bactericidal substances. Since we know, however, that bactericidal substances are not automatically bactericidal medicaments, yet that we can approach the bactericidal effect by using the right combinations (not any and every combination), should we not consequently give preference to combined therapy instead of single substances?

It is easy to demonstrate that single substances do not induce any bactericidal effect whereas combinations do, at least *in vitro*. In my opinion we have no other alternative to practising combined therapy. It is not difficult to show that combinations with rifampicin are more effective than rifampicin alone as has been demonstrated in Figs 10, 11, 13 and 14 of my first Paper (p. 25). Of course this can neither be examined nor proved at hospital on the basis of a few cases differing moreover in anamnesis and method of treatment. Such studies which unfortunately are rather common nowadays have no informative value.

Prof. Saerens

I don't think that we all are convinced that combined therapy is more bactericidal than one drug alone. On this point I don't agree.

Prof. Freerksen

The question whether we should choose combined therapy or single substances is no longer a matter of conviction, since in our time there is no doubt that combinations prove to be more effective than single substances. I am not aware of any exception as far as mycobacterial infections are concerned.

Prof. Saerens

It is a question of interpreting facts.

Dr Ellard

I should like to remind the audience that many workers, including my colleagues Dr Dickinson and Prof. Mitchison, have shown that single drugs such as isoniazid, rifampicin or streptomycin have a marked bactericidal effect against logarithmic cultures of *Myc. tuberculosis*. Continued exposure to concentrations of these drugs attained in the body with normal therapeutic doses can result in the killing of from 90 to 99.9% of the viable organisms.

Dr Browne

We have not yet answered your question, Prof. Azulay. Shall we advise to stop treatment?

Dr Karat

I should like to make a suggestion: to study the bone marrow of all your 20 patients, keep the negative ones under surveillance and stop the treatment. In all other cases continue treatment. Then you have at least two groups with certain known facts whom you can compare twice a year.

Dr Jopling

I would suggest that this is the stage to introduce acedapsone therapy into this group of patients described by Prof. Azulay.

III.4. Criteria for Non-infectivity

Dr Browne

We should deal briefly now with the criteria for non-infectivity, the criteria for freedom from risk of relapse and the criteria for stopping treatment.

The criteria for non-infectivity: are there any clinical criteria that would help? Do we rely on laboratory data, in particular the presence of morphologically normal, presumably viable organisms, in the discharge from open ulceration or from the nasal mucosa? These are very practical and very important questions. When can we say that a patient is no longer contagious, when can he work in school, or in a restaurant, etc.? These are practical problems. When, as in Hong Kong, can we say a patient may be admitted to a factory and to a high-rise apartment? Freedom from risk of relapse is rather more important and rather more difficult to define.

Dr Pearson

The only way to find out is to do it, carefully classifying the patients so that one can obtain relapse rates after different periods of treatment in different types of leprosy. There may be enough data for us to get some reasonable guesses already available in the world. It would be nice if this could be assembled in one place.

Dr Walter

The point I would like to make is that when such studies are undertaken we should keep in mind that a certain percentage of so-called relapses may in fact be reinfections which are difficult to separate.

Dr Browne

Dr Davey wrote years ago in a paper from Eastern Nigeria that the danger of relapse was particularly great in patients with intermediate types of leprosy. Would you like to add to that?

Dr Davey

I have still firmly that opinion, but I have nothing further to add. I have not been in India long enough to have any firm judgement there.

III.5. Intermittent v. Continuous Therapy: Toxicity and Side-effects

Prof. Saerens

As far as safety of intermittent therapy is concerned, I should like to remind you that the data which we have on tuberculosis have dealt with intervals of administration of one week, as the longest interval. I mentioned yesterday that the intervals seem to be an important factor in the incidence of side-effects. Now for micro-biological reasons one could think of leprosy in terms of a monthly interval or a bi-weekly interval. We don't know if this would not increase the risk of side-effects.

We should be very cautious. There are more side-effects when the interval is one week versus twice weekly. We don't know anything if we would increase the interval to two weeks, three weeks or four weeks. This needs investigation.

Dr Browne

Would you like to comment on the possibility of toxic symptoms arising if a single dose of rifampicin is given at three monthly intervals?

Prof. Saerens

We don't know anything about it. Such an investigation has never been done. If we extrapolate from what we know we should be cautious.

Dr Rees

I entirely agree with Dr Saerens answer. However, from our knowledge in the chemotherapy of tuberculosis it has been well established that the manifestations of rifampicin toxicity are directly related to the length of time between intermittent treatment up to a period of seven days *and* dosage. Namely, the higher the dose in intermittent therapy with rifampicin the greater the incidence of toxicity. Doses of 600 mg were least toxic. Because in leprosy we are hopeful that doses of rifampicin at intervals of one month may be beneficial, intervals of such magnitude and their predisposition to toxicity is completely unknown. At present we are undertaking trials in leprosy using a dose of 600 mg on two consecutive days at intervals of one month, and currently we have no evidence of clinical toxicity or the presence of rifampicin antibodies.

Prof. Saerens

We know that within the first three to four months of any intermittent therapy the incidence of side-effects is small. Most appear after five or six months of intermittent therapy. Dr Rees, how long do you intend to go on with monthly administration?

Dr Rees

This is initially six months.

I think it is justified to be cautious. On the other hand we have also to take into consideration not only the periodicity of the administration but also possibly the number of administrations. What we know is that side-effects appear after a given number of administrations and maybe, if this number is spread over a very prolonged period of time, we will not see anything for several years. We just don't know, it is very difficult to make any guess on this matter.

Dr Hogerzeil

This touches on a practical question. If we give 1500 mg rifampicin in one dose to a patient, should we warn him against taking a further dose of rifampicin later on? At present, in our circumstances, it is not very likely that he would soon be treated with another dose of it, but what I want to ask Prof. Saerens is, do you think that after a single dose of 1500 mg rifampicin the patient ought to watch out against a second dose?

Prof. Saerens

I am afraid, we have no answer. We are naturally afraid of possible severe and maybe fatal accidents, but these have occurred under two different types of circumstances; one under very well monitored intermittent therapy, where different factors have been shown to be implicated, as I mentioned yesterday; and the other one in patients who had been on continuous therapy for a very long time and then accidentally stopped their therapy and started it again without warning anybody, or else their doctor started the therapy again. In the previous period very considerable doses of rifampicin had been taken in all cases. We don't know if one dose could be enough to provoke complications.

Prof. Freerksen

We have experience with about 200 patients many of whom have been treated with rifampicin combination over a period of two years without any toxic symptoms.

Dr Pearson

I have about ten patients treated for about a year with rifampicin 600 mg on two consecutive days once a month. So far no evidence of immunological toxicity has been reported.

Dr Terencio de las Aguas

In my experience over three years with rifampicin I have seen no side-effects. In contrast, with clofazimine in common with other leprologists I very often observed phenomena in the skin. I should like to know the etiology of these phenomena.

Prof. Azulay

During a five years' treatment programme, all our patients had ichthyosis-like lesions. They treated their lesions with oil, and that is all. This is not due to a regression of oedema as was thought at one time.

Dr Jopling

I commonly see this complication in London with my patients who have been on treatment with clofazimine, and therefore I don't think we can postulate any question of silicone or grasses or any such adventitious agents.

Dr Browne

It is very common in the African, from Ethiopia to Sierra Leone.

Dr Karat

One hundred per cent of patients in our country develop the same skin problems. We did wonder whether there was some relationship to the level of unsaturated fatty acid in the human body because of the affinity of clofazimine for fatty tissue. I had put forward this suggestion to Geigy's who tell me that it is very expensive to investigate patients for levels of unsaturated fatty acid before and after treatment with clofazimine.

Dr Ramanujam

Also in our series of cases whom we had treated with clofazimine, we have very often encountered recurrent lepra-reactions. It is true that an ichthyotic skin condition becomes exaggerated in patients on clofazimine. We found that when the dose of clofazimine was reduced and finally stopped, this condition tended to disappear.

Dr Browne

A good treatment is rehydration in simple bowls of water, for then the liquid will be retained in the epidermis by means of a thin layer of lanolin.

Dr Leiker

I am a little bit worried about the combination of rifampicin and ethionamide. With both drugs liver complications are seen. Among the four patients in this second triple trial I mentioned, one patient developed a severe toxic hepatitis; he survived, but this is a warning to be careful, and we have to keep in mind that the possibility exists that by combining these two drugs, the risk becomes greater than in using one drug.

Dr Pearson

I think it was Dr Karat who mentioned two cases of ilio-ulceration mimicking Crohn's disease in patients treated with Lamprene. In retrospect I have seen one case that could also have this. I think it would be worth keeping an eye open for that in our patients treated with clofazimine.

Dr Molesworth

We had one patient on clofazimine, not actually one of mine, but in a neighbouring leprosarium, who produced a violent and fatal gastric haemorrhage

following his second or third dose. We did a post mortem and except for the very engorged gastric mucosa there was no obvious lesion which could have caused it. I merely report it, I have not seen it again.

PART IV PRACTICAL PROBLEMS OF CHEMOTHERAPY IN LEPROSY

- IV.1. Clinical and laboratory control in field projects
- IV.2. Prevention
- IV.3. Combined leprosy and tuberculosis control
- IV.4. Practicability

IV.1 Clinical and Laboratory Control in Field Projects

Dr Browne

Now on to practical problems of chemotherapy in leprosy. I should like us to discuss first of all clinical and laboratory control in field projects. Many of you are engaged in field projects in leprosy. What is the kind of clinical and laboratory control that you would consider essential in any field project? How often should the doctor go around, how often should smears be taken, how often should biopsies be taken, what kind of control should there be? what are the minimum requirements for an effective leprosy treatment scheme?

Dr Molesworth

The set up we have in South Malawi covers a million and a quarter people and about 2000 sq miles. We now have 13,000 cases who have passed through our mesh; each one has been charted in detail. Each possibly bacilliferous case has had smears done, and if necessary repeated, and all bacilliferous cases have had repeated smears done. We have had to limit biopsies, simply for the time factor, to aid the diagnosis or to assess progress in research groups. The routine treatment has been carried out faithfully by the staff, not so faithfully by the patients, and as a result we have not been able to increase beyond an average of 50% regular attenders. The work that was done on our cases showed that nearly all the dapsone that we gave out was consumed by this 50% of cases. I have always thought that 50% was too low to achieve control. The lepromatous cases appear rather better at attending, because they see more obvious reason for it than do the non-lepromatous, who may have just an anaesthetic patch with a bit of an edge which does not worry them at all. The results are quite effective in those with a lower BI, they are inevitably slower in those with higher BI.

Dr Browne

How frequently do you take skin smears?

Dr Molesworth

In bacilliferous cases one every six months and more frequently in any trial case.

Dr Ellard

In response to the point Dr Molesworth made about the possibility of malabsorption of dapsone occurring. I should like to say that, as far as I am

aware, no case has ever been proved of a patient failing to absorb ingested dapsone. There is therefore no reason for trying to estimate dapsone plasma levels when a patient appears not to be progressing as well as he should on dapsone treatment. The essential point is to ensure that the patient is actually swallowing the dapsone tablets he is being given. Ideally every dose should be given under full supervision, but usually this is impracticable. We have recently devised a urine-test method for monitoring the regularity with which leprosy patients take their prescribed dapsone tablets, which can be used to provide evidence as to how serious a problem irregular drug ingestion is. I would entirely agree with Dr Molesworth that there are some patients who won't take their dapsone tablets whatever you do and that in their case it would be best to give dapsone by injection.

Dr Browne

I have three observations to make. (1) I have seen dapsone tablets in the stools, very hard. (2) Patients in a certain country that shall be nameless, hid dapsone tablets under the tongue despite swallowing a draught of water, they then would spit them out and sell them on the local market. Others would actually swallow the tablet in front of the doctor, and then regorge it. But they got only half the price for such a tablet in the local market because it was bile-stained!

Dr Languillon

In Senegal we have now an average of 40,000 leprosy patients, among them 8% lepromatous cases. They are visited once a year, they receive dapsone 600 mg once a week. It is necessary that they take the tablets in front of the nurse because if we don't act like that they frequently don't take the tablets. Once a year we take a nasal smear and a skin smear; no biopsies were taken. The contacts of the lepromatous cases are also visited at the same interval and receive 5 mg/kg body weight dapsone weekly as prophylaxis after BCG vaccination.

Dr Browne

Dr Hogerzeil, what are you able to do in the way of a laboratory cover?

Dr Hogerzeil

We see our patients once every three months, but as some of them have to travel very far, we don't hesitate to send dapsone by post for instance, because we would rather take risks and reach at least 50% of our patients.

Dr Karat

In the control programme with which I was associated for several years, 75 to 85% of patients attended for treatment for more than 42 weeks per year of therapy. We collected 2000 random samples of urine at these clinics and examined them for metabolites of dapsone. To our surprise we found metabolites in 80%. We also conducted a survey of absentees in our programme, and in our experience the absentees were patients with skin lesions either of the indeterminate or tuberculoid variety. There was a small group of patients with severe deformity who had no means of transport. I just wonder how many of the reported 50% absentees were so deformed that they could not get to the clinic. They also may be patients who feel that their deformities are not being attended to by the control programme.

Dr Pearson

In Ethiopia we have two control schemes. One, in the area around Addis Ababa which is sponsored by ALERT, is involved in training, and has considerably more facilities, a larger number of people, a bigger variety of drugs available, and it is easier to get shoes, in other words it is more comprehensive than the leprosy control programme for the rest of Ethiopia, which is very basic, issuing dapsone, but very little else. For what it is worth, the attendance rates in the two control schemes are very close to identical. Under the conditions that we are working in, it looks as if special attention to feet ulcers and so on does not necessarily encourage increased clinic attendance. I was surprised that this does seem to be the case.

Dr Walter

I think it would perhaps be enough to have smears once a year, provided they are taken properly.

Prof. Pattyn

What has remained of the study of Lechat made more than 20 years ago? He found that from a strategical point of view it was sufficient and necessary to make only one smear from one ear lobe for survey purposes.

Dr Browne

Most of Lechat's records were lost in Iyonda, but we had comparable records in which we compared each of the six cutaneous sites and the two nasal septum sites. We found, that if you have limited time and resources, then two sites, (ear lobe and the edge of an active lesion) will give you the best information of bacillary activity. You don't increase it by adopting Cochrane's method of sixteen smears every three months.

IV.2. Prevention

Dr Browne

Are there any practicable methods that we could adopt to prevent leprosy in exposed populations? Where the prevalence rates are higher than 1/1000, everybody must be considered to be exposed. We have thought of acedapone and BCG, dapsone prophylaxis. Is there a place for, say, one dose of rifampicin for contacts of index cases who were lepromatous upon diagnosis? Are there any other methods that would suggest themselves to you, acedapone for instance; could we achieve whole population coverage with prophylactic or therapeutic acedapone?

Prof. Azulay

BCG is known to be a non-specific immunological agent; it should be helpful as a prophylactic measure. My experience with BCG in infants resulted in 97% of Mitsuda positives; of their mothers, less than 70% were Mitsuda positive, which seems to me very important. After 12 negative smears, I gave BCG to lepromatous cases. Thirty-five per cent showed a weak lepromin positive reaction. I think that BCG should be considered under immunological aspects.

Dr Walter

Concerning the result of chemoprophylaxis that Dr Ramanujam has described, I would like to add that similar results were obtained by Dr Lara in the Philippines in a WHO-assisted study involving about 600 children observed for a period of five years.

IV.3. Combined Leprosy and Tuberculosis Control

Dr Browne

We ought now to spend a few minutes discussing some projects in which two diseases are attacked by the same medical and auxiliary team. The two diseases are both mycobacterial diseases, leprosy and tuberculosis. There are various schemes in operation around the world, and there are suggestions for other schemes in which these two diseases are attacked. I should like some observations on this kind of project, advantages and disadvantages, possible dangers of the polyvalent clinics. Perhaps those of you with some experience would share your views with us.

Dr Ramanujam

I should like to mention a project in India to assess the value of BCG in prevention of leprosy and to study the inter-relation between tuberculosis and leprosy under surveillance. It has been carried out in cooperation with the Tuberculosis Provincial Trial in the Chingleput district. We thought there should be advantages in combining this BCG provincial trial in leprosy with the tuberculosis provincial trial because much fieldwork will be done with the tuberculosis people and the population will also be ready for examination for the presence of leprosy. Unfortunately the entire population was not surveyed for the presence of leprosy prior to the vaccination procedures, which would have been ideal. Nevertheless the examination of the population is going on and we hope that it will be possible to examine 150,000 at least once in $2\frac{1}{2}$ years. The future results will show how useful such a joint enterprise will be.

Dr Ellard

I should like to say something about recent developments in the treatment of tuberculosis that may be relevant to the feasibility of combined treatment schemes for the two diseases. In many rural areas the most satisfactory form of antituberculosis chemotherapy consists of two months initial supervised, and often hospitalized, daily treatment with streptomycin, plus isoniazid plus thiacetazone, followed by 10 months daily self-administered treatment with isoniazid plus thiacetazone. However, although this is a highly effective regimen when given under controlled clinical trial conditions, in practice it is much less successful because of the failure of many patients to collect or take their prescribed treatment regularly. In some urban and semi-urban situations these problems may be overcome by basing treatment on fully supervised twice-weekly doses of streptomycin plus isoniazid, but such a treatment scheme is impracticable in the rural areas where most patients live.

Recent clinical trials have therefore investigated whether effective regimens can be found that can cure tuberculosis within a substantially shorter time and several regimens have now been shown to be highly effective when given for as little as six months. Rifampicin appears to be a vital component of the most effective

regimens evaluated so far and future studies are likely to be concerned with establishing whether the amount of rifampicin required for effective short-course treatment can be reduced to a level that is financially practical and whether effective short-course regimens can be found requiring less than six months treatment. By contrast all the evidence suggests that with the drugs at present available, the treatment of lepromatous patients must be continued for many years.

Prof. Freerksen

We have shown that the combined therapy we mainly apply in leprosy is at the same time the most effective treatment against tuberculosis. In some cases where leprosy patients also suffered from tuberculosis—extrapulmonary or pulmonary—both diseases could be cured without any additional treatment. Meanwhile numerous cases of pure tuberculosis are successfully treated. In paucibacilliferous cases treatment with Isoprodian is sufficient. It is as effective as the therapy RAMP + INH + EMB in tuberculosis.

I believe that it would be too early to conceive a general programme for all of us today. But it is necessary to examine systematically whether leprosy treatment and tuberculosis treatment—or rather the control of these two diseases—could be approached as one single task.

Dr Molesworth

We have exactly such a pilot project starting in Malawi in a central area where we presume that there is a 15/1000 prevalence of leprosy, which is probably at least that of tuberculosis. Hitherto all tuberculosis treatment has been confined to the clinics. The idea is to combine in our mobile units the double function of leprosy control and treatment with tuberculosis treatment and control. The diagnosis of leprosy often takes a long time, sometimes it is easy and quick but with our system of charting, it takes a certain amount of time. The diagnosis of tuberculosis on the other hand should be reduced to the positive sputum, and those are the cases we treat. If we are certain that the person has tuberculosis, in spite of two negative sputa, then he will be referred to the district hospital where an X-ray examination and further laboratory facilities are available. Whether the programme will work or not depends on the dedication of the teams concerned. In fact they will have to work out a *modus operandi* of the timing factor, because otherwise the tuberculosis worker is going to finish his treatment and his case finding quickly, whereas the leprosy doctor is still looking for small macules. Alternatively the leprosy worker has finished and the tuberculosis worker is still wandering around.

What will happen I just don't know, but I believe firmly that this project is feasible and practicable.

Dr Browne

I have heard the objection that patients with lepromatous leprosy would stand a higher risk of contracting pulmonary tuberculosis if they are exposed in the same clinic week by week to those suffering from open tuberculosis.

Dr Molesworth

This is true.

IV.4. Practicability

Dr Browne

The last point to discuss is the practicability of the treatment we advise: injections or oral treatment, daily, weekly, monthly, three monthly treatment; how to encourage regularity and perseverance and how to do all this on 40 pence per head per year for all medical services, including leprosy.

Dr Hogerzeil

There is indeed a very small budget per head of population in developing countries, but the patients are much more willing to contribute than we are inclined to believe. In the area where I am working about 25% of our budget comes from the patients themselves without any reservation at all. It is one of the things I am always happy to show to our visitors because if you look at our outpatient department you will find very many beggars from the streets of Hyderabad and Bombay who appear to have nothing to give, but they produce a certain amount which will cover their treatment for a whole year. It is a kind of a medical insurance, including if necessary orthopaedic reconstruction of their hands, being operated on by a highly skilled surgeon from Vellore or elsewhere. It doesn't make any difference whether they get tuberculosis, for they are then treated in hospital for three months daily with streptomycin, all this is included and they know it. This comes as a great surprise to many people who treat leprosy in India. As far as I know we have the highest income of all leprosy hospitals in India from our patients, without any pressure at all, because never has any patient been refused treatment on economic grounds or inability to offer payment. Twenty per cent of our patients don't pay anything at all and they get exactly the same care and attention as others. The second point I would like to mention is that while such projects as we have discussed here aim at the highest standards, I couldn't help thinking about the contrast which we have to contend with in rural areas, often a hundred miles away from the nearest centre. A scientist or a research worker hates making a compromise; I would say that the field worker's life is just one continued compromise. It would be lovely if from this meeting some practical suggestions came about regarding the acceptability of compromise. For instance, when we were working in Nigeria, if I am right, we had a certain meaning about a relapse rate of 6% of our patients over a considerably long period.

I quite agree that it is good for a lepromatous patient to get life-long treatment, but how can we do so in India with $\frac{3}{4}$ million patients in our state. One demoralizes the patient by saying that he has to go on taking drugs for life. What about our borderline cases? Do we really have to keep them on for five or seven years? I am very happy indeed with what Dr Pearson has said, to have courage and send the patient away if you know that you cannot have a reasonable amount of supervision. On the other hand it is wonderful to hear about the treatment with rifampicin. But the suggestion of giving only one high dose treatment was really not done on scientific grounds, but only prompted by the fact that unless we manage to do something important for the patients in one single blow (which is 1500 mg in our case), we won't be able to do anything at all. We can't even give a patient four capsules daily for a week. That would come to 210 rupees, and it will constitute more than a month's wages.

When we come for instance to the treatment of reactions, many people have

said with justifiable pride “We never had to resort to corticosteroids among our reaction patients”, but I would plead for the compromise of giving corticosteroids. I have considerable experience with corticosteroids as a dermatologist. We must not say that all corticosteroids in reactions are taboo, because the patients are going to become steroid-dependent. From this viewpoint we always have to make compromises in the duration of treatment, compromises in the way of giving corticosteroids, risking perhaps in one of a hundred a dependence, compromise in the choice of drug and so on.

Dr Pearson

One of the things that might help in reducing the costs of a leprosy control programme is in reducing the costs of maintaining staff. The costs of the drugs, of the ordinary ones, don't really come into it. I think it is possible that by lengthening the period between visits of staff, the costs of running a programme could be considerably reduced. This would have to be balanced—you have to see a patient a certain number of times to establish the necessary relationship with him so that he continues treatment and so on. In my experience, a surprising number of patients in Malaya who lived many miles away, several hundred miles, became used to being given one year's supply of dapsone at a time. They came up for their annual visits regularly within a few days, and this was over five or six years. Maybe our patients are different, more sophisticated, but I think this is something that would be worth serious consideration in reducing the costs, or making money available for other things.

Dr Browne

When surveying leprosy in the mountainous valleys of Nepal I met a man who walked for 41 days to get treatment, over mountains up to 12,500 ft high. We cannot possibly think of that man coming every week for his treatment. Another little comment comes from French West Africa where “auto-traitement”, self-treatment, is a most practical proposition in places where roads are non-existent for nine months in a year, where the population is sparsely scattered and where the medical occupation is so embryonic that one doctor can pay a visit only once a year during the dry season when there are roads, to patients who need his help. By enlisting the aid of literate village chiefs it is possible to conduct a leprosy control service even in such a situation. The literate chief has a supply of dapsone tablets and a list of patients who need treatment. When they have run out of tablets, they walk to him, perhaps for several days, and get their drugs. The number of tablets is inscribed in an almost illiterate hand in the register. This may be the only possibility of getting leprosy and tuberculosis treatment to the villagers who need it. It is a far cry from the sophisticated developed clinics of Addis Ababa or Sungei Buloh or Chingleput, but it is the only practicable proposition for millions of our fellow citizens in this world.

In conclusion, I should like to thank all who have participated in the discussions and in the most helpful listening, as all those who have come to the front will doubtless agree. I now adjourn this Colloquium, and know I express the feelings of us all when I offer our most grateful thanks to Professor Freerksen, to Dr Thumim, and also to our able translators, unseen, but not unheard, who have helped us tremendously, and to everyone else concerned. Thank you very much.

List of Participants

Dr A. E. ALVARENGA
Ministerio de Salud Publica
y Bienestar Social
Departamento de Lepra
Asuncion
PARAGUAY

Dr P. AREND
Chemie Grünenthal
519 Stolberg
WEST GERMANY

Dr M. ASCHHOFF
St. Thomas Hospital and
Leprosy Centre
Chettupattu, 606 801 N.A. Dt
Tamil Nadu
SOUTH INDIA

Dr M. ASHRAF
Chief of Endemic Diseases Section
Ministry of Health
Tripoli
LIBYAN ARAB REPUBLIC

Prof. Dr R. B. AZULAY
Av. Atlantica 3130/701
Rio de Janeiro GB-ZC-07
BRAZIL

Dr A. J. M. BAAR
Academisch Ziekenhuis
Dermatologische Kliniek
Oostersingel 59
Groningen
NETHERLANDS

Carl Wolfgang Graf von BALLESTREM
Via Condotti, Palazzo di Malta
Rome
ITALY

Hubert Graf von BALLESTREM
Präsident des Deutschen
Aussätzigen-Hilfwerkes e.V.
53 Bonn
Schumannstrasse 49
WEST GERMANY

Dr L. BOCK
Forschungsinstitut
2061 Borstel
WEST GERMANY

Dr S. G. BROWNE
The Leprosy Study Centre
57a Wimpole Street
London, W.1
ENGLAND

Prof. Dr F. H. CASELITZ
Chefarzt des Bakteriologischen Instituts am
Allgemeinen Krankenhaus Altona
2000 Hamburg 50
Paul-Ehrlich-Strasse 1
WEST GERMANY

K. DAMM
Forschungsinstitut
2061 Borstel
WEST GERMANY

Dr T. F. DAVEY
12 Garland Avenue
Emsworth, Hants. PO10 7QA
ENGLAND

Dr G. DEPASQUALE
St. Luke's Hospital
Dept. of Dermatology
La Valetta
MALTA

Dr T. T. DHOL
Rheumaheilstätte
Orthopädische Abteilung
2357 Bad Bramstedt
WEST GERMANY

Prof. Dr P. DOCKX
Universitaire Instelling Antwerpen
Department KVS
Universiteitsplein 1
B-2610 Wilrijk
BELGIUM

Dr G. A. ELLARD
Medical Research Council Unit
for Laboratory Studies of Tuberculosis
Royal Post Graduate Medical School
Ducane Road
London, W.12
ENGLAND

Dr E. FASSKE
Forschungsinstitut
2061 Borstel
WEST GERMANY

Dr R. FETTING
Forschungsinstitut
2061 Borstel
WEST GERMANY

Dr G. FOWST
Gruppo Lepetit spa.
Via R. Lepetit, 8
I-20124 Milan
ITALY

Dr H. FRANZ
Saarstickstoff-Fatol GmbH
6685 Schiffweiler/Saar
WEST GERMANY

Prof. Dr E. FREERKSEN
Direktor des Forschungsinstitutes Borstel
2061 Borstel
WEST GERMANY

Dr E. FREERKSEN
Forschungsinstitut
2061 Borstel
WEST GERMANY

Dr R. FREERKSEN
Forschungsinstitut
2061 Borstel
WEST GERMANY

Dr J. C. GATTI
Sociedad Argentina de Leprologia
Maipu 836, 5° Piso-d^{to}-A
Buenos Aires
ARGENTINA

Prof. Dr M. GILBERT
Secrétaire Général du Comité
International de l'Ordre de Malte
pour l'Assistance aux Lépreux
3, Place Claparède
Geneve
SWITZERLAND

Dr M. HAMZAH
University of Indonesia
Faculty of Medicine
Dermato-Venerology Dept.
6 Salemba Raya
Jakarta
INDONESIA

Dr A. HARTMAN
Academisch Ziekenhuis
Dermatologische Kliniek
Oostersingel 59
Groningen
NETHERLANDS

Dr A HAVEL
Forschungsinstitut
2061 Borstel
WEST GERMANY

Dr L. M. HOGERZEIL
Victoria Hospital
Dichpalli 503 175
Nizamabad District
Andhra Pradesh
INDIA

Dr E. JENSEN
Rockwinkeler Landstrasse 8
28 Bremen-Oberneuland
WEST GERMANY

Dr W. H. JOPLING
Hospital for Tropical Diseases
4, St. Pancras Way
London, NW1 OPE
ENGLAND

Dr G. KALLISTRATOS
Forschungsinstitut
2061 Borstel
WEST GERMANY

M. KARAGOUNIS
Forschungsinstitut
2061 Borstel
WEST GERMANY

Dr A. B. A. KARAT
Consultant Physician
St. Catherine's Hospital
Church Road
Birkenhead L42 0LQ
ENGLAND

Dr I. KAZDA
Forschungsinstitut
2061 Borstel
WEST GERMANY

Dr W. KLEINERT
Allgemeines Krankenhaus
Harburg
21 Hamburg 90
Eissendorfer Pferdeweg 52
WEST GERMANY

Prof. Dr A. H. KLOKKE
Academisch Ziekenhuis
Dermatologische Kliniek
Oostersingel 59
Groningen
NETHERLANDS

H. KOBER
Geschäftsführendes Vorstandsmitglied des
Deutschen Aussätzigen-Hilfswerks o.v.
Postfach 348
87 Würzburg
WEST GERMANY

Dr R. KOOIJ
Ruychrocklaan 96
Den Haag
NETHERLANDS

Dr A. KOSASIH
University of Indonesia
Faculty of Medicine
Dermato-Venereology Department
6 Salemba Raya
Jakarta
INDONESIA

Dr H. KÖLBEL
Forschungsinstitut
2061 Borstel
WEST GERMANY

Dr H.-N. KRENZIEN
Balaka Leprosy Hospital
P.O. Box 78
Balaka
MALAWI

Dr J. LANGUILLON
Institut Leprologie
Appliquée de Dakar
B. P. 11023, CD Annva
Dakar
SENEGAL

Dr D. L. LEIKER
Royal Tropical Institute
Mauritskade 57
Amsterdam
NETHERLANDS

Dr B. MATTHIESSEN
2000 Hamburg
Adolfstrasse 21
WEST GERMANY

Prof. G. MEISSNER
Forschungsinstitut
2061 Borstel
WEST GERMANY

Prof. J. MEISSNER
Forschungsinstitut
2061 Borstel
WEST GERMANY

Dr van der MEULEN
Academisch Ziekenhuis
Dermatologische Kliniek
Oostersingel 59
Groningen
NETHERLANDS

Dr D. B. MOLESWORTH
Lepra Control Project
P.O. Box 496
Blantyre
MALAWI

Dr H. J. MUSEHOLD
Forschungsinstitut
2061 Borstel
WEST GERMANY

Dr D. V. A. OPROMOLLA
Hospital Aimorés
Rodovia Bauru-Jaú, km 385
Caixa Postal 62
Bauru, E.S. Paulo
BRAZIL

Dr E. H. Orłowski
Chefarzt der Forschungsklinik des
Forschungsinstitutes Borstel
2061 Borstel
WEST GERMANY

M. ORŁOWSKI
2061 Süfeld
WEST GERMANY

J. PAPENHAGEN
Forschungsinstitut
2061 Borstel
WEST GERMANY

Prof. Dr S. PATTYN
Instituut voor Tropische
Geneeskunde Prins Leopold
Nationalestraat 155
B-2000 Antwerpen
BELGIUM

Dr J. M. H. PEARSON
M.R.C. Leprosy Project
Armauer Hansen Research Institute
P.O. Box 1005
Addis Ababa
ETHIOPIA

Dr M. PETERS
Forschungsinstitut
2061 Borstel
WEST GERMANY

Dr R. PFAU
M.A. Leprosy Centre, A.M. 21
off Frere Road opp. Naveed-Clinic
Karachi 3
PARKISTAN

Dr K. RAMANUJAM
10 Doraiswamy Road
Theogarayanagar
Madras-17
Tamil Nadu
INDIA

Dr R. J. W. REES
National Institute for Medical Research
The Ridgeway, Mill Hill
London, NW7 1AA
ENGLAND

Dr A. REMIEN
Forschungsinstitut
2061 Borstel
WEST GERMANY

R. ROHDE
Forschungsinstitut
2061 Borstel
WEST GERMANY

M. ROSENFELD
Forschungsinstitut
2061 Borstel
WEST GERMANY

Dr D. S. RIDLEY
Hospital for Tropical Diseases
4 St. Pancras Way
London, NW1
ENGLAND

Prof. Dr E. J. SAERENS
65 Av. de la Niveole
B-1020 Brussels
BELGIUM

Dr J. SEYDEL
Forschungsinstitut
2061 Borstel
WEST GERMANY

Dr R. SZALAY
Forschungsinstitut
2061 Borstel
WEST GERMANY

Dr K. J. SCHAPER
Forschungsinstitut
2061 Borstel
WEST GERMANY

Dr K. H. SCHRODER
Forschungsinstitut
2061 Borstel
WEST GERMANY

Dr J. TERCICIO DE LAS AGUAS
Sanatorio Fontilles
Alicante
SPAIN

Dr J. THUMIM
Forschungsinstitut
2061 Borstel
WEST GERMANY

Dr A. TRUMELLINI
Gruppo Lepetit spa.
Via R. Lepetit, 8
I-20124 Milan
ITALY

Dr R. URBANCIK
Schwarzwald-Sanatorium der BfA
7542 Schömburg
WEST GERMANY

Dr J. WALTER
World Health Organization
Leprosy Unit
CH-1211 Geneve 27
SWITZERLAND

Dr Dr F. WEGENER
87 Würzburg
Lerchenweg 14
WEST GERMANY

Index

SUPPLEMENT

A

- Address of welcome. E. FREERKSEN 1
ALVARENGA, ARNALDO E., *see* INNAMI, SEIJI 169
Antibiotics in leprosy, with special reference to rifampicin 141
ASCHHOFF, M., Treatment of leprosy with rifampicin and Isoprodian in
38 patients at St. Thomas Hospital, Chetput, South India 173
Assessment of treatment procedures by means of bacteriological and
histological examinations. M. ROSENFELD 53
AZULAY, R. D., Discussion 225,228,243,246,247,249,257,260,261
AZULAY, R. D., DA SILVA, N. C., ZEO, A., DE JESUS, M. and
FRANCA, C. B., Personal experience with clofazimine in the
treatment of leprosy 99

B

- BROWNE, S. G., The Second International Leprosy Colloquium, Borstel. 3
—, Discussion 222,223,224,225,226,227,231,235,236,237,238,239,243,244,
245,246,247,248,249,250,251,252,254,255,257,258,259,260,262,263,264

C

- Chemotherapeutic trials in patients with non-lepromatous leprosy. JOHN
M. H. PEARSON 63
— and their assessments. R. J. W. REES 17
Clinical and bacteriological effects of rifampicin in combination with
L73A in leprosy: observation for six months. SEIJI INNAMI,
OSCAR R. LEGUIZAMÓN and ARNALDO E. ALVARENGA 169
— trials 247
Combined therapy in leprosy. J. C. GATTI 155
Controlled clinical trial of continuous and intermittent rifampicin therapy
during an initial three months period in lepromatous leprosy: final
analysis, A. S. R. PATTYN, M. T. ROLLIER, R. ROLLIER, E. J.
SAERENS and P. DOCKX 129

Criteria for the assessment of drug activity	221
Current concerns in therapeutic research	233

D

DA SILVA, N. C., <i>see</i> AZULAY, R. D.	99
DAVEY, T. F., Discussion	222,225,248,255
DE JESUS, M., <i>see</i> AZULAY, R. D.	99
DEPASQUALE, G., Rifampicin and Isoprodian in combination in the treatment of leprosy	179
—, The Leprosy Eradication Programme of Malta	215
Discussion	221
DOCKX, P., <i>see</i> PATTYN, S. R.	129

E

Effect of long-term steroid therapy on patients treated with clofazimine (Lamprene). L. M. HOGERZEIL and N. PRABHUDAS	111
—, a single dose of rifampicin on the infectivity of the nasal discharge in leprosy (preliminary communication). L. M. HOGERZEIL and R. J. W. REES	147
—, mono treatment and combined treatment on the morphology of <i>Myc. leprae</i> in the skin. D. L. LEIKER	73
ELLARD, G. A., Pharmacological aspects of the chemotherapy of leprosy	41
—, Discussion	233,234,253,254,258,261

F

FRANCA, C. B., <i>see</i> AZULAY, R. D.	99
FREERKSEN, E., Address of welcome	1
—, The technique of evaluating anti-leprosy medications at the Fors- chungsinstitut Borstel	25
—, Preliminary experience with combined therapy using rifampicin and Isoprodian (L73A)	161
—, Discussion	223,227,231,232,234,237,238,240,242,245,250,253,256,262

G

GATTI, J. C., Combined therapy in leprosy	155
—, Discussion	243,244

H

- HAMZAH, M. and KOSASIH, A., Preliminary experience with rifampicin and Isoprodian (L73A)—combination in lepromatous leprosy . . . 181
- HOGERZEIL, L. M. and PRABHUDAS, N., Effect of long-term steroid therapy on patients treated with clofazimine (Lamprene) . . . 111
- and REES, R. J. W., The effect of a single dose of rifampicin on the infectivity of the nasal discharge in leprosy (preliminary communication) 147
- , Discussion 256,259,263

I

- INNAMI, SEIJI, LEGUIZAMÓN, OSCAR R. and ALVARENGA, ARNALDO E., Clinical and bacteriological effects of rifampicin in combination with L73A in leprosy: observation for six months. . . . 169
- IYER, G. G. S., *see* RAMANUJAM, K. 85,93,117

J

- JOPLING, W. H. Discussion 225,254,257

K

- KARAT, A. B. A., Viability of *Myco. leprae* in the skin and bone marrow of patients with lepromatous leprosy while on dapsone or Lamprene.
A. B. A. KARAT 69
- , Low dose dapsone therapy in lepromatous leprosy 89
- , Long-term follow-up of clofazimine (Lamprene) in the management of reactive phases of leprosy 105
- , Discussion 223,226,236,240,245,249,254,257,259
- KOSASIH, A., *see* HAMZAH, M. 181
- KRENZIEN, H. N., Preliminary experience with rifampicin and Isoprodian in combination in leprosy treatment 189
- , Discussion 221,224,243,249

L

- LANGUILLON, J., Treatment of leprosy with clofazimine, rifampicin and Bayrena 81
- , Discussion 246,248,250,259
- LEGUIZAMÓN, OSCAR R., *see* INNAMI, SEIJI 169
- LEIKER, D. L., Effect of mono treatment and combined treatment on the morphology of *Myco. leprae* in the skin 73
- , Discussion 222,230,257

Leprosy Eradication Programme of Malta, The., G. DEPASQUALE	215
List of participants	265
Long-term follow-up of clofazimine (Lamprene) in the management of reactive phases of leprosy. A. B. A. KARAT	105
Low dose dapsone therapy in lepromatous leprosy. A. B. A. KARAT	89

M

MEULEN, VAN DER, Discussion	236
MOLESWORTH, B. DAVID, Results of Leprosy Control Project, Malawi	149
—, Discussion	239,244,257,258,262

N

NOUSSITOU, F. M., <i>see</i> WALTER, J.	9
---	---

O

Open trial with clofazimine in the management of recurrent lepra reaction and of sulphone sensitive cases: a preliminary report. K. RAMANUJAM, C. G. S. IYER and G. RAMU	117
OPROMOLLA, D. V. A. and TONELLO, C. J. S., Antibiotics in leprosy, with special reference to rifampicin	141

P

PATTYN, S. R., Discussion	221,229,236,249,253,260
PATTYN, S. R., ROLLIER, M. T., ROLLIER, R., SAERENS, E. J. and DOCKX, P., A controlled clinical trial of continuous and inter- mittent rifampicin therapy during an initial three months period in lepromatous leprosy: final analysis	129
PEARSON, JOHN M. H., Chemotherapeutic trials in patients with non-lepromatous leprosy	63
—, Discussion	222,225,226,235,236,240,247,254,256,257,260,264
Personal experience with clofazimine in the treatment of leprosy. R. D. AZULAY, N. C. DA SILVA, A. ZEO, M. DE JESUS and C. B. FRANCA	99
Pharmacological aspects of the chemotherapy of leprosy. G. A. ELLARD	41
PRABHUDAS, N., <i>see</i> HOGERZEIL, L. M.	111
Practical problems of chemotherapy in leprosy	258
Preliminary experience with combined therapy using rifampicin and Isoprodian (L73A). E. FREERKSEN	161
— with rifampicin and Isoprodian (L73A)—combination in lepromatous leprosy. M. HAMZAH and A. KOSASIH	181
— with rifampicin and Isoprodian in combination in leprosy treatment. H. N. KRENZIEN	189

Preliminary report on a therapeutic trial with acedapsone in lepromatous leprosy, A. K. RAMANUJAM, C. G. S. IYER and G. RAMU	85
-- of a drug trial conducted at Leprosy Relief Rural Centre, Chettipatty, South India. E. VOMSTEIN	207
Problems in the design of medium and long-term therapeutic trials. D. S. RIDLEY	59

R

RAMANUJAM, K., IYER, C. G. S. and RAMU, G., A preliminary report on a therapeutic trial with acedapsone in lepromatous leprosy	85
--- A report on a controlled clinical trial with conventional and one third conventional dose of dapsone administered orally once a week in lepromatous patients	93
--- Open trial with clofazimine in the management of recurrent Lepra reaction and of sulphone sensitive cases: a preliminary report	117
---, Discussion	223,239,248,257,261
RAMU, G., <i>see</i> RAMANUJAM, K.	85,93,117
REES, R. J. W., Chemotherapeutic trials and their assessments	17
--, Rifampicin: the investigation of a bactericidal antileprosy drug	121
--, Discussion	224,229,233,236,238,241,246,251,255,256
--, <i>see</i> HOGERZEIL, L. M.	147
Report of combined therapy in leprosy with rifampicin and Isoprodian Conducted at the Bisidimo-Center, Ethiopia. R. ROHDE	199
- on a controlled clinical trial with conventional and one third conventional dose of dapsone administered orally once a week in lepromatous patients, A. K. RAMANUJAM, C. G. S. IYER and G. RAMU	93
Results of Leprosy Control Project, Malawi. B. DAVID MOLESWORTH	149
RIDLEY, D. S., Problems in the design of medium and long-term therapeutic trials	59
--, Discussion	226,227,231,245,246,247
Rifampicin: the investigation of a bactericidal antileprosy drug. R. J. W. REES	121
--, and Isoprodian in combination in the treatment of leprosy. G. DEPASQUALE	179
ROHDE, R., Report of combined therapy in leprosy with rifampicin and Isoprodian conducted at the Bisidimo-Center, Ethiopia	199
Role of WHO in antileprosy drug trials, The. J. WALTER, F. M. NOUSSITOU and H. SANSARRICQ	9
ROLLIER, M. T., <i>see</i> PATTYN, S. R.	129
ROLLIER, R., <i>see</i> ROLLIER, M. T.	129
ROSENFELD, M., Assessment of treatment procedures by means of bacteriological and histological examinations	53

S

- SAERENS, E. J., The use of rifampicin in the treatment of leprosy . . . 125
 —, Discussion 223,233,244,253,254,255,256
 —, *see* PATTYN, S. R. 129
 SANSARRICQ, H., *see* WALTER, J 9
 Second International Leprosy Colloquium, Borstel, The. S. G. BROWNE, . . . 3

T

- Technique of evaluating anti-leprosy medications at the Forschungsinstitut
 Borstel, The. E. FREERKSEN 25
 TERCENIO DE LAS AGUAS, J., Treatment of leprosy with rifampicin
 and Isoprodian (L73A) 165
 —, Discussion 256
 TONELLO, C. J. S., *see* OPROMOLLA, D. V. A. 141
 Treatment of leprosy with clofazimine, rifampicin and Bayrena. J.
 LANGUILLON 81
 — with rifampicin and Isoprodian (L73A). J. TERCENIO DE LAS
 AGUAS 165
 — with rifampicin and Isoprodian in 38 patients at St. Thomas
 Hospital, Chetput, South India. M. ASCHHOFF 173

U

- URBANCIK, R., Discussion 236,244
 Use of rifampicin in the treatment of leprosy, The. E. J. SAERENS . . . 125

V

- Viability of *Myc. leprae* in the skin and bone marrow of patients with
 lepromatous leprosy while on dapsone or Lamprene. A. B. A.
 KARAT 69
 VOMSTEIN, E., Preliminary report of a drug trial conducted at Leprosy
 Relief Rural Centre, Chettipatty, South India 207

W

- WALTER, J., Discussion 228,232,239,247,250,253,255,260,261
 WALTER, J., NOUSSITOU, F. M. and SANSARRICQ, H., The role of
 WHO in antileprosy drug trials 9

Z

- ZEO, A., *see* AZULAY, R. D. 99

The Physiology and Pathophysiology of the Skin

Volume 3

edited by A. Jarrett

Department of Dermatology, University College Hospital Medical School, London, England

January 1975, xviii + 448 pp., £13.00/\$34.50 0.12.380603.8

With the proliferation of papers and monographs on normal and abnormal skin physiology throughout widely diversified journals of different disciplines, a need has arisen for a comprehensive survey to bring together contemporary knowledge and thinking in a form that the practising dermatologist can relate to some of his clinical problems. It is the aim of this series to fulfil this need. Divided into two sections, the present volume concerns itself with both the dermis and the dendritic cells of the epidermis. The first section, on the dermis, gives an account of the chemistry of collagen and elastic tissues. The ageing process of the dermis is considered and the physical nature of the dermis in the living skin is discussed in some detail. Diseases affecting collagen and elastic tissues are described from the standpoint of their pathogenesis and pathophysiology, and there is also chapter on the comparative physiology of the dermis. An account of the dermal cell population is given in the last chapter of this section.

The second part of this volume, devoted to the dendritic cells of the epidermis, considers, in particular the melanocyte both from its biological aspects and its association with human and animal pigmentary disturbances. The relationship of the melanocyte and the Langerhans cell and the nature of malignant melanomata are also discussed.

It is envisaged that *The Physiology and Pathophysiology of the Skin* will be completed in not less than five or six volumes, and in its totality the series will form the most comprehensive and up-to-date work available on the skin and its functions. Dermatologists, and pathologists who wish to understand something of the disordered physiology underlying the cutaneous disorders requiring their diagnosis, will welcome this work as an invaluable addition to their bookshelves. Its usefulness should also extend to biologists and all other scientists who share an interest in this field of research.

Contents

The Physiology of the Dermis

- A. Jarrett: The chemistry and molecular biology of collagen.
- A. Jarrett: The elastic tissue of the dermis.
- A. Jarrett: The physical nature of the dermis in living skin.
- R. I. C. Spearman: The comparative biology of collagenous tissues.
- A. Jarrett: Ageing of the dermis.

The Pathophysiology of the Dermis

- A. Jarrett: The collagenoses.
- A. Jarrett: Cutaneous elastoses.
- T. J. Ryan: Vasculitis.
- A. Jarrett: Dermal cell populations and their pathological responses.

The Dendritic Cell Population of the Epidermis

- P. A. Riley: Melanin and melanocytes.
- P. A. Riley: Embryonic origin and abnormalities of melanocytes.
- P. A. Riley: The biochemistry of pigment formation.
- P. A. Riley: Pathological disturbances of pigmentation.
- P. A. Riley: The Langerhans cell.
- P. A. Riley: Melanoma.

Author Index. Subject Index.

Academic Press

London New York San Francisco

A Subsidiary of Harcourt Brace Jovanovich, Publishers

24-28 Oval Road, London NW1, England 111 Fifth Avenue, New York, NY 10003, USA

Australian office: P.O. Box 300, North Ryde, NSW 2113, Australia

® **Lamprene Geigy** Effective in all forms and in all stages of **leprosy**



Anti-inflammatory action

References:

1. Browne, S.G., *Int. J. Leprosy* 34, 289 (1966)
2. Waters, M.F.R., *Leprosy Review* 40, 21 (1969)
3. Hastings et al., *Leprosy Review* 39, 3 (1968)
4. Warren, H.A., *Leprosy Review* 39, 61 (1968)
5. Pfalzgraff, R.E., *Int. J. Leprosy* 40, 392 (1972)
6. Languillon, J., *Médecine d'Afrique noire* 22, 825 (1975)

For further information, see the Prescriber's Guide to
GEIGY Pharmaceuticals

011 LAM 7474e

clear improvement

in skin and nerve lesions¹

no bacterial resistance²

prevents

lepra reactions³

treats

ENL and leprotic iritis⁴
often caused by other
anti-leprotic agents