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VOLUME XXXVIII NO. 4 OCTOBER 1967

PRINCIPAL CONTENTS

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LEPROSY REVIEW

VOLUME XXXVIII NO. 4 OCTOBER 1967

Contents

All communications re *Leprosy Review* and all subscriptions should be sent to the Editor.

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Editorial

ERRATA. We wish to draw attention to *errata* in the July issue of *Leprosy Review* in the paper 'The Significance of *Mycobacterium leprae* in the Nasal Mucosa with Special Reference to Chinese Leprosy Patients' by Dr. C. S. Goodwin.

p. 183, under the heading (*e*)

'Assessment of the duration of the disease after treatment'

should read

'Assessment of the duration of the disease *before* treatment'

p. 186, left-hand col. line 9-10

'Leprosy bacilli in the nose are probably spread . . .'

should read

'Leprosy bacilli are probably spread . . .'

p. 186, right-hand col. line 11

'. . . in all patients with other forms of leprosy . . .'

should read

'. . . in all patients with *these* forms of leprosy . . .'

p. 186, right-hand col. line 16

'Skin lesions and the nasal mucosa . . .'

should read

'Skin lesions and *not* the nasal mucosa . . .'

Leprosy Review is pleased to carry on the fine work of the late Dr. P. Glyn Griffiths on Polybactrin and Cicatrin by publishing a paper in this issue by Dr. I. A. Susman on a practical trial of these drugs in Togo. Dr. Susman's results support Dr. Griffiths' findings.

We wish to congratulate the World Health Organization on their new permanent headquarters building in the Avenue Appia, Geneva. The builidng was inaugurated on 7 May, 1966, and the staff of WHO is now fully installed. We have just received the World Health Organization Album and find it extremely fascinating. It gives pictures of the new building and full information about the day-to-day work of the organization and of its international activities. Copies of the Album can be ordered from WHO sales agents or from booksellers and the price is Sw. fr. 6, U.S. $2 or 10 shillings. Alternatively, they can be ordered direct from the World Health Organization, Distribution and Sales, Avenue Appia, 1211 Geneva 27, Switzerland, with an extra charge for postage.

We wish to congratulate Dr. Meny Bergel and his staff on the XV Anniversary of the founding of the Laboratorio de Investigaciones Leprológicas in Rosario, Argentina. The institution is well equipped, has a good library and has published 52 scientific papers in various journals. Dr. Bergel is well known for his ideas about iodism in the diet in leprosy and we think more attention should be given to this aspect by other leprosy workers.

We have received the ELEP Bulletin, No. 1, July 1967. The Bulletin gives a comprehensive summary of the chief centres of leprosy work throughout the world and shows that ELEP is obviously interested in forwarding leprosy work in all its aspects. We have had occasion previously to point out the valuable work being done by this Committee and we recommend that interested organizations should contact the Secretary General of ELEP in Brussels.

We would like to express our gratitude and thanks, and those of many of our subscribers in India, to Mr. Pyare Lall, Honorary Assistant Secretary of the Hind Kusht Nivaran Sangh, New Delhi, for he has been most helpful in transmitting subscriptions to *Leprosy Review* on behalf of leprosy workers in India.

Lep. Rev. (1967) **38**, 4, 213-220

Some Results of the Treatment of Plantar Ulcers with Polybactrin and Cicatrin

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INTRODUCTION

The plantar ulcer is a condition only too well known to those working in the domain of leprosy. Treatment of such ulcers is a big problem especially to those working in the field and without all the necessary facilities of surgery, physiotherapy, shoe-making, etc., available.

That treatment is difficult is shown by the large number of different applications and forms of treatment listed in the various textbooks and numerous articles written on the subject. The treatments vary also according to the stage and severity of the lesion, including involvement of underlying bone. Complete rest and plaster casts are now well-tried methods of dealing with plantar ulcers. However, these are not really very practical for large numbers of patients who cannot be hospitalised or for whom the facilities for plastering do not conveniently exist. Similarly, orthopaedic or plastic surgical procedures can only be carried out at special centres. What is required for the majority of plantar ulcer sufferers is a treatment which can be carried out at home or at an out-patient clinic with little inconvenience to the patient himself and with little extra burden on the medical personnel.

The common sites of plantar ulceration are as follows:—

I and II metatarsal heads.
Tubercle at base V metatarsal.
The calcaneal tubercles at the heel.
The head of the proximal phalanx of the great toe.
The terminal phalanges of the toes.

Three of the major factors in the causation of plantar ulceration are sensory loss, motor loss, and vasomotor loss. Of these 3 factors, only the third lends itself to a possibility of practical correction in the field. Vaidyanathan[1] has already reported on the usefulness of a vasodilator (nicotinic acid) in the treatment of plantar trophic ulcers. Given intravenously, it had a better effect than administered orally. Lauret and Kerbastard[2] also attributed the good results they obtained in treating perforating ulcers to the vasodilatory action of the intraveous injections of dehydrocholate of sodium which they gave. Priscol has also been given by perineural injection causing trophic ulcers of the sole to heal with prolonged treatment—Mathur, Sehgal and Rao[3].

It has been shown that topical applications of certain amino-acids can accelerate tissue healing and epithelialisation—Sullivan[4], Brunsting and Simonsen[5]—by their local absorption and utilisation causing an increased blood supply to the part stimulating cell proliferation —Neunhoeffer[6], Bronner and Fargel[7].

Griffiths[8] used both Cicatrin and Polybactrin to treat successfully 2 leprosy patients with large ulcers of the thigh and leg.

This paper is to indicate some results of a trial of Polybactrin and Cicatrin in the treatment of trophic plantar ulcers in leprosy patients.

PHARMACOLOGY

Polybactrin is an antibiotic powder, each g. of which contains:—

Neomycin Sulphate (as base)	330 mg.
Polymyxin 'B' Sulphate	100,000 units
Zinc Bacitracin	25,000 units

—pressurised with Dichlorotetrafluoroethane and Dichlorodifluoromethane.

* Until September 14th, 1967.

Cicatrin is an amino-acid antibiotic powder or cream, each g. of which contains:—

Neomycin Sulphate	3.3 mg. base
Zinc Bacitracin	250 units
l-Cysteine	2 mg.
Glycine	10 mg.
dl-Threonine	1 mg.

METHOD

Nine patients were chosen arbitrarily who had plantar ulceration of both feet, all of more than one year's duration. Five further patients were chosen with one foot only ulcerated but which was present for 6 years or more without complete healing. Amongst these 14 patients, 27 ulcers were taken into account plus one ulcer which developed later. Seventeen were treated and 11 untreated. The patients were residents of a leprosy village where there was no facility for hospitalisation.

The application of the medicaments was made twice weekly during the first 6 weeks and then once weekly during the next 7 weeks of the trial. A light gauze dressing and bandage were applied in each case. None of the patients was put at absolute rest but they were all asked to try not to do any unnecessary walking about during the period of treatment.

Those who had bilateral ulcers were given treatment for one foot only (the foot with the larger ulcer being chosen) and the other was dressed without any application of medicament.

Some of the ulcers were treated with either Polybactrin, Cicatrin powder or Cicatrin cream, and others with both Polybactrin and Cicatrin powder or Polybactrin and Cicatrin cream. The frequency of the medicaments used depended upon their availability.

Photographs of the ulcerated feet were taken on the day the treatment was commenced, on the 40th day and again on the 90th day of treatment.

RESULTS

The accompanying photographs show the results in 5 of the patients with bilateral ulceration and in the one patient with unilateral ulceration. This history and treatment is given with each photograph. The results of the other 8 patients with bilateral ulceration are also similarly presented although without photographs.

The results were classified according to the increase or reduction in size of the ulcers as follows:—

BAD—Increase or no reduction.

FAIR—Reduction up to 45%.

GOOD—Reduction between 45% and 90%.

EXCELLENT—Reduction more than 90%.

The results are summarised in Table 1.

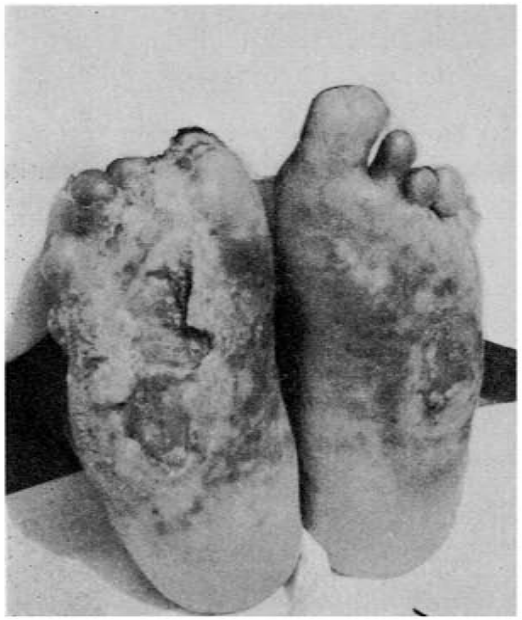
It can, therefore, be seen that all the ulcers which were not treated with the drugs under trial increased in size after 40 days except 2 which remained stationary (Patients 915 and 1102) and 2 which showed some decrease (24.2% in Patient 889 and 17% in Patient 569). In Patient 807, a new ulcer was formed during the first 40 days of treatment and this showed an increase in size after 90 days. In addition, after 90 days, only one remained stationary (Patient 915), whilst Patient 1102 now showed an increase in size of the untreated ulcer. Also, at this time, Patients 889 and 569 continued to show a diminution in size of the untreated ulcers of 43.2% and 17% of the areas, respectively. Patient 108's ulcer which had increased after 40 days had diminished by 24.4% after 90 days (without treatment).

Thus, no treatment produced 9 'bad' and 2 'fair' results after 40 days and 8 'bad' and 3 'fair' results after 90 days.

In the treated ulcers, though the healing in most cases was not complete, except in Patients 915 and 569 after 40 days, and in addition in Patients 1102 and 807 after 90 days, the marked improvement in nearly all the patients treated with Polybactrin and Cicatrin, especially the latter, has prompted the presentation of this paper. In fact, the treated ulcers provided 9 'fair', 2 'good' and 6 'excellent' results after 40 days and then only 1 'bad', 5 'fair, 4 'good' and 7 'excellent' results after 90 days. Most of the ulcers treated also showed a decrease in

TABLE I

Patient	*Type of Leprosy*	*Duration of Ulcer(s) (Years)*	*Uni- or Bi-lateral Ulceration*	*Medicament used or No Treatment (NIL)*	*Results after 40 days*	*Results after 90 days*
M 108	Tub.	Rt 20 Lt 15	Bil.	Polybactrin spray only NIL	Reduced 11.1% = FAIR Increased = BAD	No change from original = BAD Reduced 24.4% = FAIR
M 491	Tub.	15	Bil.	Polybactrin spray only NIL	Reduced 26.5% = FAIR Increased = BAD	Reduced 49.0% = GOOD Increased = BAD
M 805	Lep.	6	Uni.	Polybactrin spray plus Cicatrin cream	Reduced 98.6% = EXCELLENT	Reduced 99.0% = EXCELLENT
M 889	Lep.	8	Bil.	Polybactrin spray plus Cicatrin powder NIL NIL	Reduced 44.4% = FAIR Reduced 24.2% = FAIR Increased = BAD	Reduced 63.0% = GOOD Reduced 43.2% = FAIR Increased = BAD
M 915	Tub.	7	Bil.	Polybactrin spray plus Cicatrin powder NIL	Reduced 100% = EXCELLENT No change = BAD	Reduced 100% = EXCELLENT Increased = BAD
M 1102	Lep.	1+	Bil.	Polybactrin spray plus Cicatrin powder NIL	(1) Reduced 99.0% = EXCELLENT (2) Reduced 99.0% = EXCELLENT No change = BAD	(1) Reduced 100% = EXCELLENT (2) Reduced 99.0% = EXCELLENT Increased = BAD
M 617	Lep.	18	Uni.	Polybactrin spray plus Cicatrin powder	(1) Reduced 60.0% = GOOD (2) Reduced 33.0% = FAIR (3) Reduction in oedema and profundity = FAIR	(1) Reduced 40.0% = FAIR (2) Reduced 50.0% = GOOD (3) Reduction in oedema and profundity = FAIR
M 1071	Lep.	2	Bil.	Cicatrin powder only NIL	Reduced 87.5% = GOOD Increased = BAD	Reduced 99.0% = EXCELLENT Increased = BAD
M 1183	Lep.	3	Bil.	Cicatrin powder only NIL	Reduced 40.0% = FAIR Increased = BAD	Reduced 70.0% = GOOD Increased = BAD
M 807	Lep.	8	Bil.	Cicatrin powder only NIL	Reduced 99.0% = EXCELLENT (1) Increased = BAD (2) New ulcer = BAD	Reduced 100% = EXCELLENT (1) Increased = BAD (2) Increased = BAD
M 1229	Tub.	6	Uni.	Cicatrin powder only	Reduced 28.6% = FAIR	Reduced 42.8% = FAIR
M 129	Tub.	18	Uni.	Cicatrin powder only	No change in size but granulating = FAIR	No change but continued granulations = FAIR
M 569	Lep.	9	Bil.	Cicatrin cream only NIL	Reduced 100% = EXCELLENT Reduced 17.0% = FAIR	Reduced 100% = EXCELLENT Reduced 17.0% = FAIR
F 800	Lep.	8	Uni.	Cicatrin cream only	Reduced 28.6% = FAIR	Reduced 3.1% = FAIR



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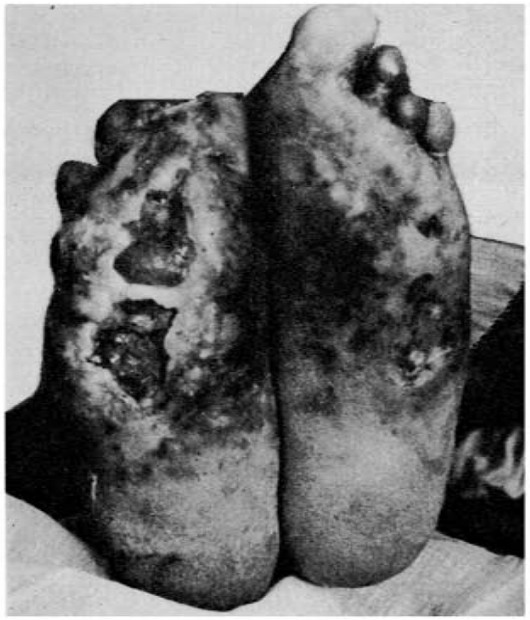

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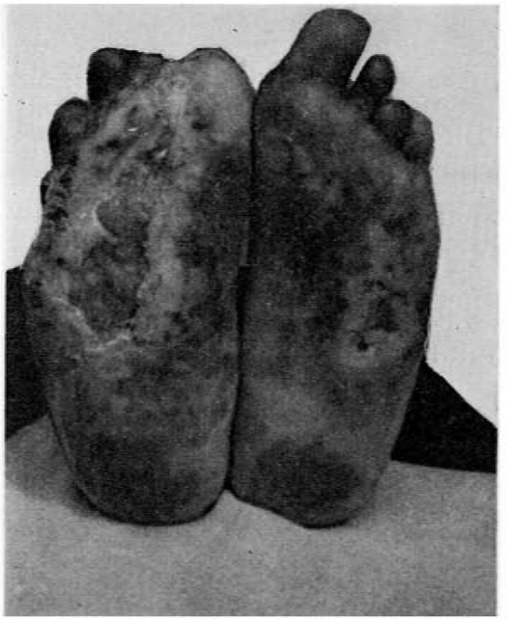
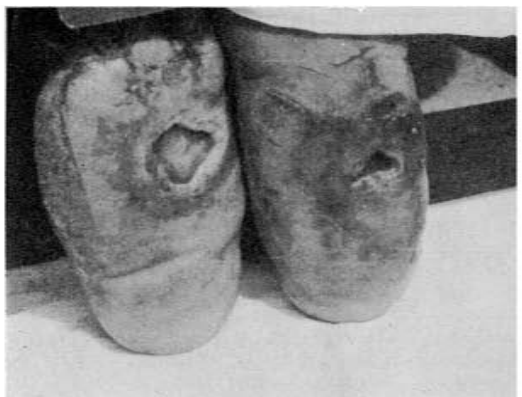


28th June 1967

PATIENT 108: Male. 60 years. Tuberculoid. Admitted 1951. History of ulcers: Right 20 years, Left 15 years.

Right: 3.0 cm. × 9.0 cm. ——Polybactrin spray—> 3.0 cm. × 8.0 cm.—Reduced 3.0 sq. cm. (11.1%) ——Polybactrin spray—> 3.0 cm. × 9.0 cm.—No change from original

Left: 1.7 cm. × 3.5 cm. ——Nil—> 1.7 cm. × 3.8 cm.—Increased 0.51 sq. cm. ——Nil—>1.5 cm. × 3.0 cm.—Reduced 1.45 sq. cm. (24.4%)



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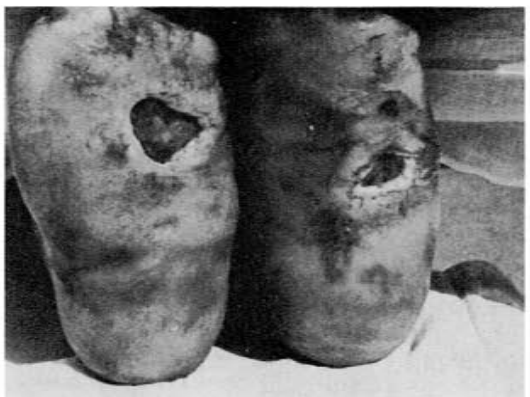

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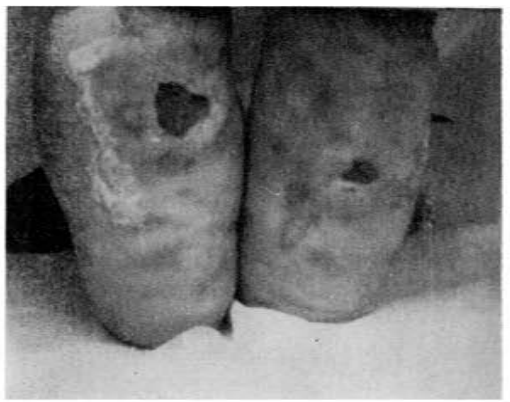
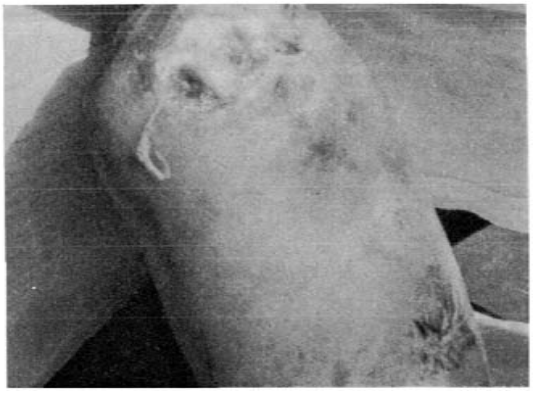


28th June 1967

PATIENT 491: Male. 40 years. Tuberculoid. Admitted 1964. History of ulcers: 15 years.

Right: 3.5 cm. × 3.5 cm. ——Polybactrin spray—> 3.0 cm. × 3.0 cm.—Reduced 3.25 sq. cm. (26.5%) ——Polybactrin spray—> 2.5 cm. × 2.5 cm.—Reduced 6.0 sq. cm. (49.0%)

Left: 0.6 cm. × 2.3 cm. ——Nil—> 0.8 cm. × 2.3 cm.—Increased 0.46 sq. cm. ——Nil—>1.0 cm. × 1.5 cm.—Increased 0.12 sq. cm.



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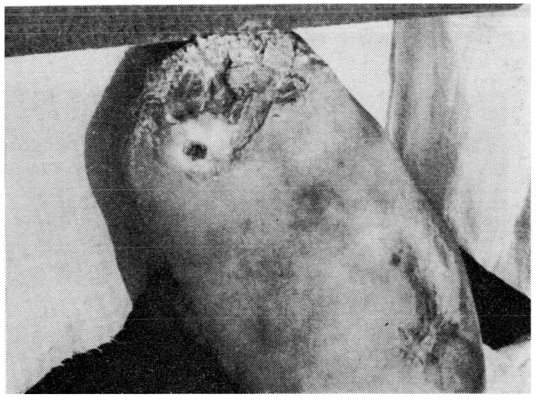

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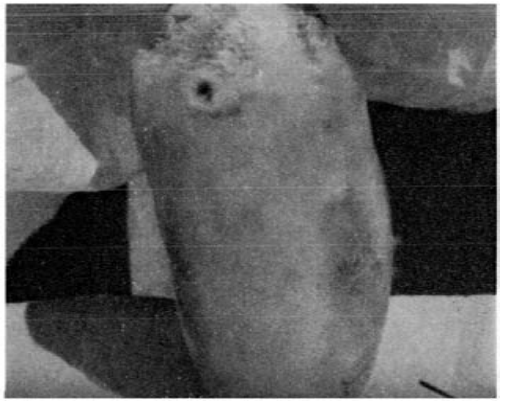
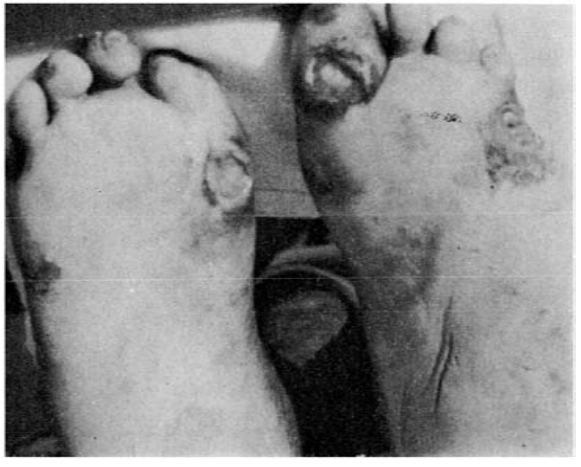


28th June 1967

PATIENT 805: Male. 67 years. Lepromatous. Admitted 1952. History of ulcer: 6 years.

Right: 5.8 cm. × 3.0 cm. ——Polybactrin spray plus Cicatrin cream—> 0.5 cm. × 0.5 cm.—Reduced 17.15 sq. cm. (98.6%) ——Polybactrin spray plus Cicatrin cream—> 0.4 cm. × 0.4 cm.—Reduced 17.24 sq. cm. (99.0%)



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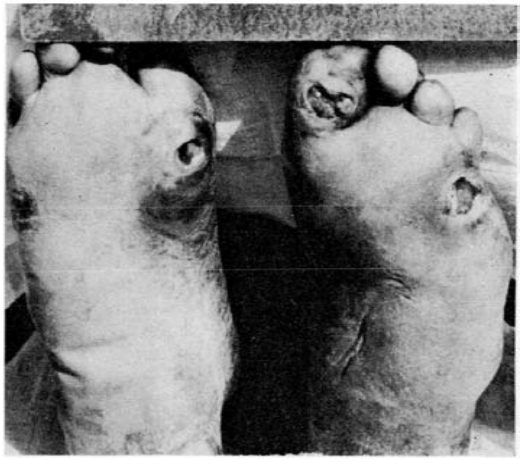

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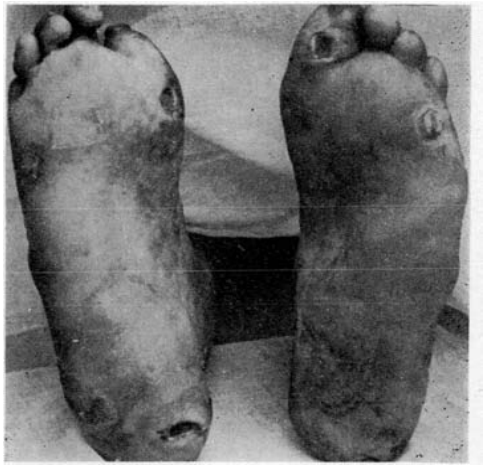


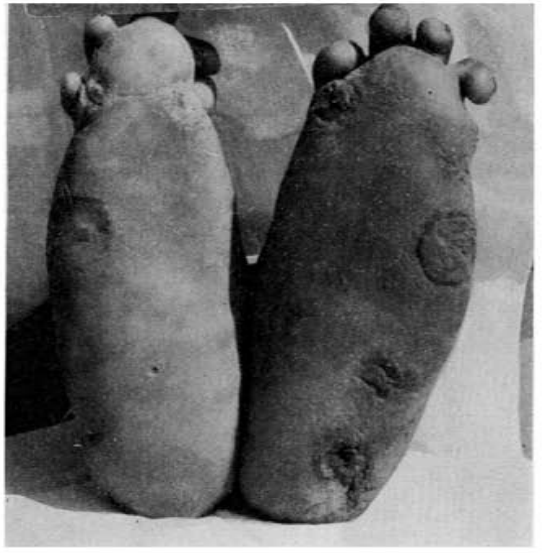
28th June 1967

PATIENT 889: Male. 42 years. Lepromatous. Admitted 1955. History of ulcers: 8 years.

Right: 1.8 cm. × 1.8 cm. ——Polybactrin spray plus Cicatrin powder—> 1.5 cm. × 1.2 cm.—Reduced 1.44 sq. cm. (44.4%) ——Polybactrin spray plus Cicatrin powder—> 1.2 cm. × 1.0 cm.—Reduced 2.04 sq. cm. (63.0%)

Left: 2.2 cm. × 1.2 cm. (gt. toe) ——Nil—> 2.0 cm. × 1.0 cm.—Reduced 0.64 sq. cm. (24.2%) ——Nil—> 1.5 cm. × 1.0 cm.—Reduced 1.14 sq. cm. (43.2%)
0.5 cm. × 0.5 cm. (4th mt.) ——Nil—> 1.5 cm. × 1.2 cm.—Increased 1.55 sq. cm. ——Nil—> 1.0 cm. × 0.5 cm.—Increased 0.25 sq. cm.

9th May 1967

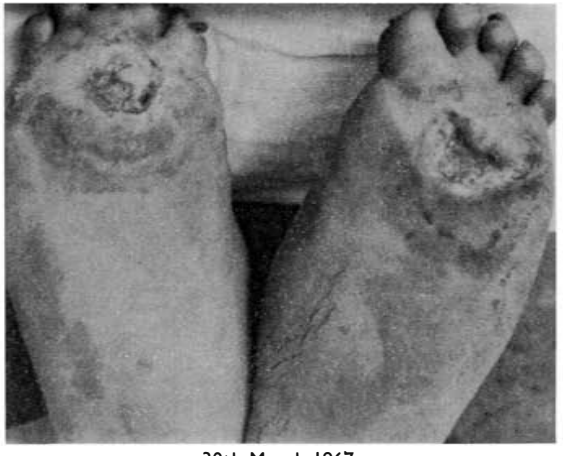


28th June 1967

PATIENT 915: Male. 52 years. Tuberculoid. Admitted 1956. History of ulcers: 7 years.

Right: 0.5 cm. × 0.2 cm. (5th mt.) ——Polybactrin spray plus Cicatrin powder—> Healed (100%) ——Polybactrin spray plus Cicatrin powder—> Healed (100%)

Left: 0.5 cm. × 0.5 cm. (Calc.) ——Nil—> 0.5 cm. × 0.5 cm.—No change ——Nil—> 0.5 cm. × 0.5 cm.—No change



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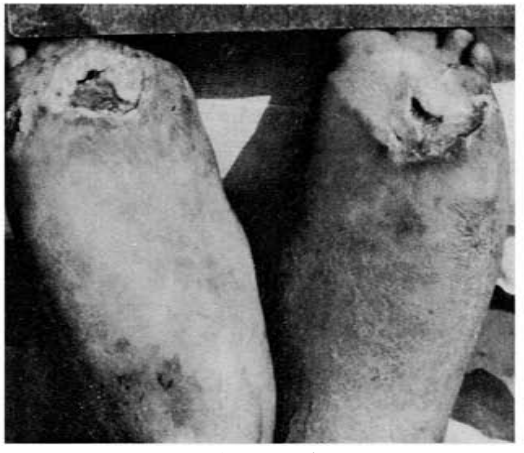

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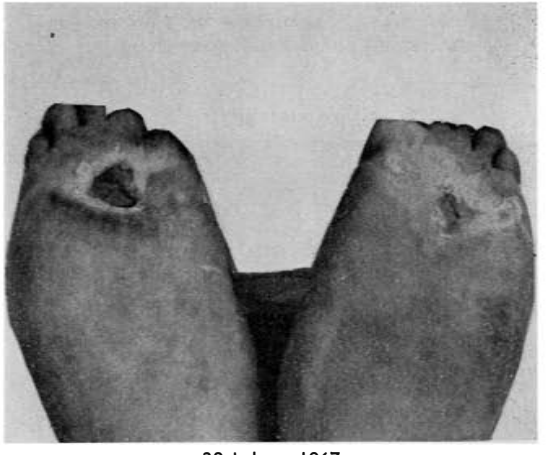

28th June 1967

PATIENT 1071: Male. 25 years. Lepromatous. Admitted 1961. History of ulcers: 2 years.

Right: 2.5 cm. × 3.0 cm. ——Nil—> 3.0 cm. × 3.5 cm.—Increased 3.0 sq. cm. ——Nil—> 3.0 cm. × 3.0 cm.—Increased 1.5 sq. cm.

Left: 4.0 cm. × 2.0 cm. ——Cicatrin powder—> 1.0 cm. × 1.0 cm.—Reduced 7.0 sq. cm. (87.5%) ——Cicatrin powder—> Almost healed (99.0%)

depth after 40 days and this improvement continued.

All the patients themselves were very enthusiastic about the treatment, being delighted with the amount of progress made in the healing of their ulcers within the space of some few weeks, whereas previously they had shown no sign of improvement during several years.

All the patients continued on their normal dosage of Dapsone during the ulcer treatments.

DISCUSSION

One of the most difficult problems in the treatment of leprosy patients is the specific treatment of plantar ulcers. Surgery and special footwear play an important part but facilities for their provision are not always possible.

Within the limitations of this trial, there were indications that Polybactrin spray, Cicatrin powder and Cicatrin cream can produce promising results in the healing of trophic plantar ulcers in leprosy patients, even those ulcers of very long standing. In the above series, it appeared that Polybactrin spray combined with Cicatrin powder or cream gave the best results, whereas Polybactrin spray on its own gave the less promising results. Cicatrin powder or Cicatrin cream alone also produced very good results. These results can be tabulated as follows:—

Hence, after 40 days of one of the above treatments, there were no 'bad' results, 52.9% were 'fair', 11.8% were 'good' and 35.3% were 'excellent'. After 90 days treatment, 5.9% (one patient) showed a 'bad' result, 29.4% were 'fair', 23.5% were 'good' and 41.2% showed 'excellent' results.

Of course, one must not lose sight of the fact that once ulcers are healed, great care must be taken to prevent a recurrence. Thus, the application of whatever medicaments does not obviate the need for the provision of special shoes for all such healed feet.

Furthermore, one cannot emphasise too strongly or too often that 'prevention is better than cure'.

And finally, the cost of the drugs employed must at present be a factor limiting their widespread use.

SUMMARY

Nine leprosy patients with plantar ulceration of both feet and 5 with unilateral ulceration were chosen for treatment with Polybactrin spray, Cicatrin powder and Cicatrin cream. In those with bilateral ulceration, only one foot was treated. Seventeen ulcers were treated in all. The results after 6 weeks and then 13 weeks of treatment are presented. All the ulcers treated, except one, showed definite improve-

Results of 17 ulcers treated:

	BAD		*FAIR*		*GOOD*		*EXCELLENT*	
	After 40 days	*After 90 days*	*After 40 days*	*After 90 days*	*After 40 days*	*After 90 days*	*After 40 days*	*After 90 days*
Polybactrin spray only	—	1	2	—	—	1	—	—
Polybactrin spray plus Cicatrin cream ..	—	—	—	—	—	—	1	1
Polybactrin spray plus Cicatrin powder ..	—	—	3	2	1	2	3	3
Cicatrin powder only	—	—	3	2	1	1	1	2
Cicatrin cream only	—	—	1	1	—	—	1	1
	—	1	9	5	2	4	6	7
	0%	5.9%	52.9%	29.4%	11.8%	23.5%	35.3%	41.2%

ment. After 90 days, 7 of the ulcers in this paper (that is, 41.2%) showed excellent results (between 90% and 100% reduction in size), especially taking into the account the fact that all these ulcers were chronic of very long duration.

Although these drugs appear to be encouraging in the treatment of plantar ulcers in leprosy patients, they are not the last word in such treatment by a long way ! Also, the cost of such drugs for local application must be a prohibitive factor. However, they appear to be worthy of further trials.

ACKNOWLEDGEMENTS

I am very grateful to Calmic Ltd., Crewe, Cheshire, for supplying the Polybactrin and Cicatrin for this trial. I am also grateful to my ward, Frank Elliott, for the taking and provision of all the photographs.

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Lep. Rev. (1967) **38**, 4, 221-223

The Treatment of Lepromatous Leprosy and Erythema Nodosum Leprosum with the Cytostatic Drugs Ancyte* and Vercyte*

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INTRODUCTION

Having carried out clinical trials on the immunosuppressive effects in leprosy of cytostatics such as cyclophosphamide (Davison *et al.*, 1964) and procarbazine (Schulz and Falkson (*a*) 1965, (*b*) 1965, (*c*) 1966), we decided to investigate the effect of 2 new cytostatic piperazine derivatives on erythema nodosum leprosum.

Vercyte (A-8103 or N,N^1-Bis (3 bromopropionyl) piperazine) is a neutral amide. The halogens in this compound are not particularly reactive in contrast with the halogens in the nitrogen mustards. Ancyte (A-20968 or N,N^1-bis (3 methane sulfonyloxypropanoyl) piperazine) is an analogue of Vercyte and is also a neutral amide. These compounds differ in structure from other previously used anti-cancer drugs. They both show marked anti-tumour effect in animals and man. Although both agents have myelosuppressive effect at the dosage used in this study these effects develop slowly and are quickly reversible.

MATERIALS AND METHODS

Six patients with lepromatous leprosy with erythema nodosum leprosum were treated with Vercyte followed by Ancyte. All 6 patients had had severe continuous ENL despite corticosteroid administration for from 15-36 months before treatment was started. Corticosteroid treatment was continued throughout the period of treatment with Vercyte and Ancyte.

One mgm. per kg. per day of Vercyte was given to the patients for 5 weeks. Three and a half weeks after the Vercyte was stopped 2.5 mgm./kg. of Ancyte was given 3 times a week for 13 weeks to 5 patients (Nos. 1, 3, 4, 5 and 6) and for 4 weeks to one patient (No. 2). The drugs were given by mouth. Blood counts were done at weekly intervals. The age, sex, total dose of Vercyte and Ancyte, lowest white cell count during treatment with the 2 drugs are given in Table 1.

The duration of standard antileprosy treatment before the piperazine derivates were given is shown in Table 1. It can be seen that treatment had in one instance already been given for 5 years. During the treatment with Vercyte and Ancyte treatment with sulfone was continued in 5 patients (Nos. 1, 2, 3, 4 and 6) and thiambutosine in one patient (No. 5).

Bacterial indices were done at monthly intervals.

RESULTS

During the 5 weeks treatment with Vercyte no significant decrease was observed in the occurrence of erythema nodosum leprosum. No toxic effects attributable to Vercyte were

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† In receipt of a grant from the National Cancer Association of South Africa.

TABLE 1

Details of Treatment with Ancyte and Vercyte

No.	*Age*	*Sex*	*Duration of Previous Treatment in months*	*Total dose Vercyte in mgm.*	*Lowest White cell count on Vercyte per mm.*^{3}	*Total dose Ancyte in mgm.*	*Lowest White cell count on Ancyte per mm.*^{3}
1	35	M	51	2040	4700	5850	5050
2	42	M	22	1800	6450	2062.5	5830
3	49	M	46	2160	6000	5850	5750
4	15	M	26	1260	7150	3900	7000
5	12	M	65	1260	6000	3900	5900
6	27	M	31	2160	5000	5850	5100

encountered. None of the patients became leukopenic but the average white cell count decreased from 10,800 to 6,850 per mm.^{3} In the $3\frac{1}{2}$ weeks observation periods following discontinuation of Vercyte, most patients experienced a worsening of the ENL, despite the fact that there had been no significant improvement on treatment.

During treatment with Ancyte for 12 weeks in 5 patients and 4 weeks in one patient, all 6 patients continued to develop new ENL. Patient No. 2 complained of weakness and dizziness which he ascribed to the drug, which was stopped at his request. The symptoms disappeared 2 weeks after the Ancyte was stopped. Neither subjective nor objective side effects occurred in the other patients. The average white cell count at the start of Ancyte administration was 9,500 and at the end of treatment was 10,900 per mm.

All 6 patients continued to suffer from the same amount of ENL during treatment and as the reactions continued to be severe it was considered that a trial of longer than 3 months was not justified. An interesting observation was, however, that 3 patients had a severe exacerbation of the ENL after the Vercyte was stopped and before the Ancyte was started.

There was no significant change in the bacterial indicies before and after the administration of Vercyte and Ancyte.

DISCUSSION

Clinical and bacteriological response to dapsone may only follow after years of treatment in lepromatous leprosy. Erythema nodosum leprosum develops in 30% of our lepromatous patients. We reported suppression of acute reactions in 5 out of 8 patients who were treated with large intravenous doses of cyclophosphamide together with dapsone (Davison *et al.*, 1964). None of 9 patients treated with small oral doses of cyclophosphamide for up to 146 days and none of 6 patients treated with small oral doses of procarbazine for up to 36 weeks (Schulz and Falkson, 1965a) showed a decrease in ENL. Both cyclophosphamide and procarbazine suppress immune response. Therapeutic response to cyclophosphamide and procarbazine in cancer is seldom adequate unless a concentration of the drug, high enough to cause leukopenia is achieved. Drug concentration of this order was not considered justified in a non-malignant disease.

The dosages of Vercyte and Ancyte used in this trial are the same as those originally recommended in clinical cancer trials. These doses did not cause leukopenia in our patients with leprosy. The combination of Vercyte with corticosteroids can cause sudden and severe leukopenia in patients with blastic transformation in acute myeloid leukemia (van Dyk *et al.*, 1967). The total dose of Ancyte and Vercyte administered during 21 weeks is considered adequate for evaluation in our trial and we conclude that at this dosage range no beneficial effect is obtained in ENL. Higher doses are not considered justifiable in the treatment of ENL because of the possibility of thrombocytopenia and severe diarrhoea.

SUMMARY

Six patients with lepromatous leprosy and severe recurrent ENL were given a course of treatment first with Vercyte and after a $3\frac{1}{2}$ weeks break with Ancyte. No significant side effects were encountered and no therapeutic benefit was observed. After withdrawal of Vercyte 3 patients had severe exacerbations of ENL.

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Antimicrobial Therapy of Experimental Human Leprosy *(Myco. leprae)* Infection in the Mouse Foot Pad

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Interest has arisen in recent years in a remarkably consistent method for the transmission of leprosy (*M. leprae*) from man to mice which was first described by Shepard (1960, 1962). This finding was confirmed by other workers who used specimens of leprosy organisms obtained from patients in different countries (Rees, 1964; Pattyn and Janssens, 1965; Pattyn, 1965; Shepard and McRae, 1965). Unfortunately the lesion produced was always microscopic. Briefly, in a high proportion of mice challenged in their foot pads with between 10 and 10^5 organisms, a mild form of infection was induced that developed very slowly and then regressed. In fact, multiplication only progressed to a limit of 10^6-10^7 organisms for each foot and then stopped. However, inocula equal to this value (or even higher) did not undergo any increase.

The object of the present investigation was to examine the efficiency of the above technique as a routine method for determining antimicrobial activity. In order to undertake this fully a wide choice of compounds was used including a few of uncertain or unknown effectiveness against human infection.

MATERIALS AND METHODS

Source of M. leprae

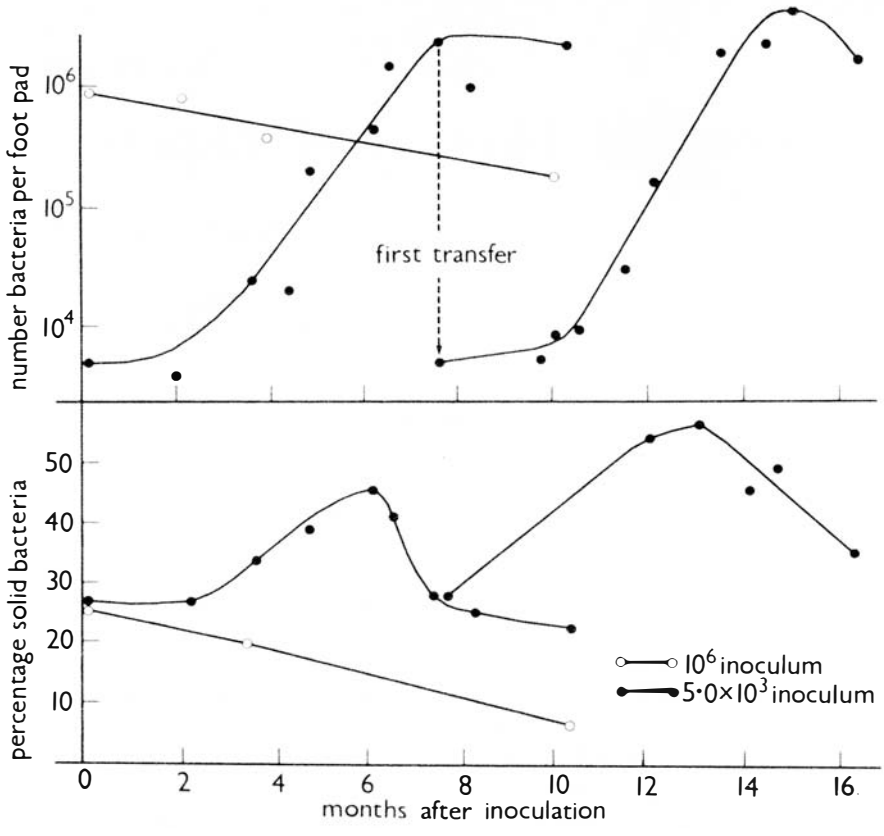
The specimens of *M. leprae* used in the present investigation were obtained from 2 different sources and each contained a fairly high proportion of solid (viable) forms (Rees and Valentine, 1962). Firstly, 3 specimens were extracted from biopsy material taken from untreated lepromatous patients in Malaya and these were supplied by the Medical Research Council through the courtesy of Dr. R. J. W. Rees (London, England). Secondly, 2 specimens were isolated from previously infected mice and these were kindly sent by Dr. C. C. Shepard (Atlanta, U.S.A.). All the specimens were dispatched (on ice at 0°C) by air to London and were used for challenge within 3 days of removal from the host. Specimens of *M. leprae* bacteria were supplied in the form of a suspension, these failed to grow when seeded on to Lowenstein-Jensens medium even after 6 months incubation at 37° or 32°C.

Animals

Albino mice (mostly males) of about 6 weeks of age and derived from the I.C.I. pathogen free strain were used throughout.

Inoculation

The technique devised by Shepard was used to transfer leprosy to mice. Our own particular experimental methods for inoculation and subsequent harvesting of the organisms have been given in detail elsewhere (Gaugas, 1967). In order to induce infection each mouse was challenged in both its hind foot pads with an inoculum of 5.0×10^3 organisms. The fresh human biopsy isolates were used as the first or subsequent mouse transfers.



LEGEND TO FIGURE

Graph giving the growth curves (inoculum 5.0×10^3 bacteria) for the first and subsequent transfer of a fresh specimen of *M. leprae* in the mouse hind foot pad. No increase was obtained from an inoculum of 10^6 bacteria. The total number of bacteria recovered as well as the corresponding percentage solid (i.e., viable) bacteria (ordinates) is plotted against time in months after inoculation (abscissa). Each point represents 1-6 foot pad estimations.

Drug Treatment

Administration of drugs was either by subcutaneous (s.c.) injection where each dose was usually dissolved in 0.2 ml. of sterile saline, or alternatively mixed in a powdered diet (i.e., orally). The regimen in the diet was based on a previous finding that mice ate 250 gm./kg. of food every day regardless of the amount offered. Treatment was generally given for 5-7 days a week and lasted until the maximal level of organisms was reached in the foot pads of untreated control mice after 7-9 months. At this juncture treated mice were killed and the foot pad content of organisms was estimated separately for each mouse. Groups of 12-30 surviving mice were used to determine the effectiveness of each course of treatment usually against a single specimen of *M. leprae*.

RESULTS

All the specimens of *M. leprae* behaved in a characteristic and predictable manner and this is illustrated (single example) by the growth curve in Fig 1. In order to obtain quantitative data on the infection it was necessary to continue checking the foot pad yield of organisms monthly. Here, from a convenient inoculum of 5.0×10^3 (26% solid) organisms the limit of slightly above 10^6 (24% solid) was reached after about $7\frac{1}{2}$ months. The infection, as expected, could be transferred from mouse to mouse. In contrast, a challenge dose of 10^6 organisms failed to undergo multiplication.

The Table summarises the effect of various antimicrobial compounds (3 loosely defined classes) against this particular form of infection. It also enables a direct comparison to be made

TABLE 1

Results of antimicrobial therapy of *M. leprae* in the mouse

	Dose	*Effect*	*Previous Investigation**
1. ANTI-LEPROSY DRUGS			
Dapsone	25 mg/kg orally	Complete	0.1% complete, Shepard and Chang (1962) 0.025% complete, Rees (1965b), Pattyn and Royackers (1965) 0.00001% complete, Shepard (1966)
Solapsone	2.5 mg/kg s.c.	Complete	
	0.25 mg/kg s.c.	Partial	
Sulphormethoxine	25 mg/kg orally		0.1% active, Rees (1965a)
Sulphadimethoxine	75 mg/kg orally		0.1% (thrice weekly), Rees (1965a)
B663(M) phenazine	25 mg/kg orally		0.1% complete, Shepard and Chang (1964) 0.006% complete, Rees (1965a)
Thiacetazone	250 mg/kg orally	Complete	0.1% partial, Shepard and Chang (1964) 0.1% active, Rees (1965a)
Thiambutosine	250 mg/kg orally		0.1% inactive, Shepard and Chang (1964)
	2.5 mg/kg s.c. twice weekly in oil		0.1% partial, Rees (1965b) 0.1% complete, Pattyn and Royackers (1965)
SU 3068 Ciba	150 mg/kg orally		
2. ANTI-TUBERCULOSIS DRUGS			
Capreomycin	25 mg/kg s.c.		10 mg/mouse/day complete, Shepard (1964)
Isoniazid	25 mg/kg orally		0.01% complete, Shepard and Chang (1964)
Oxydiazolone	250 mg/kg orally		
PAS	150 mg/kg orally	Complete	0.06% complete, Shepard and Chang (1964)
Streptomycin	2.5 mg/kg s.c.		2 mg/mouse/day complete, Shepard and Chang (1964)
Streptovaricin	150 mg/kg orally		
Viomycin	100 mg/kg s.c.		
3. BROAD SPECTRUM ANTIMICROBIALS			
Cephaloridine	300 mg/kg s.c.	Complete	
Rifamycin	150 mg s.c.	Complete	
Gentamicin	165 mg/kg s.c.	Partial	
Morphazinamide	75 mg/kg orally	Ineffective	
Tetracycline	75 mg/kg s.c.	Ineffective	
	75 mg/kg orally	Ineffective	

* Generally expressed as percentage of drug in diet.

with the results previously published by other workers who used the same screening technique. At first in our laboratory each compound was tested at its maximum tolerated dose (M.T.D.) for the mouse. Subsequently most of the compounds with a beneficial effect were tested with lower doses and only these later results are listed in the table. It can be seen that all the anti-leprosy drugs and all the anti-tuberculosis drugs we used prevented the multiplication of human leprosy organisms in the mouse. In addition, 2 broad spectrum antimicrobials cephaloridine and rifamycin also had the same effect. Previously thiambutosine was reported to be ineffective by Shepard and Chang (1964). However, this was not at first confirmed by Rees (1965a) but he later (1965b) observed irregular behaviour where some experiments resulted in complete inhibition and others resulted in partial or absence of activity. As he suggested, it is possible that this may be due to poor absorption in the mouse. In our own experiments complete inhibition was obtained for 2 specimens of *M. leprae*, one obtained from each of the above authors. In addition, subcutaneous administration (bi-weekly) of the drug suspended in arachis oil was also found to be effective. Due to the above discrepancy the thiazoline derivative of this compound, SU 3068 Ciba, was also tested since it is more soluble. Here also complete inhibition was observed.

It is noteworthy that the lower dose of solapsone prevented bacterial multiplication in just over half the number of animals treated. This was regarded as a partial effect. Hence the minimal effective dose (M.E.D.) must be slightly above this value of 0.25 mg./kg. body weight. This result correlates reasonably well with that for a related compound, dapsone, recently found by Shepard, McRae and Habas (1966) to have a complete effect even at the very low concentration of 0.00001% in the diet. In fact, we found dapsone (25 mg./kg.) effective even if given only for the first $2\frac{1}{2}$ months of the infection (although this result is not included in the Table). It is interesting that the human leprosy organism is very susceptible to sulphones. In this respect it is unlike any other pathogenic mycobacterium.

Information relevant to the pharmacology, toxicity and range of susceptible pathogens of the antimicrobials mentioned is readily available in the literature.

DISCUSSION

The mouse foot pad type of leprosy infection is easily cured from its inception by treating with a wide variety of antimicrobials, perhaps too easily in contrast to the disease in man. In human patients the problem is different since here infection, often with massive bacillary concentration, is already established before therapy begins. Moreover, the foot pad infection was too mild for assessing the value of combined drug therapy (if given for the duration of the infection). Nevertheless, the experimental infection does provide the only means readily available to date for the screening of potential anti-leprosy drugs other than in human subjects. This is because the organism responsible for leprosy in man cannot be grown on bacteriological media. One useful application of the mouse foot pad technique has already been demonstrated by Pettit and Rees (1964) and also by Adams and Waters (1966) where the occurrence of dapsone resistant *M. leprae* organisms from human patients (a total of 4 patients) was detected experimentally rather than by clinical observation. As a matter of interest the former patients then responded successfully to phenazine B 663 treatment (Pettit and Rees, 1966).

As a safeguard before starting trials with a new drug on human patients it would be desirable to determine the M.E.D. required to stop multiplication of leprosy organisms in the mouse foot pad, and then compare this result with that of related compounds (if any). When such a list has been finally compiled it is possible that a relative pattern of antimicrobial effect against leprosy infection may emerge approaching that already known for man. Owing to the long duration of the experiments and in the light of the experience gained it is recommended that extremely low doses of the compound should be given at the outset. Such a diversion

from the routinely accepted method is probably due to the uniquely long generation time of about 26 days for *M. leprae* under these conditions, as well as the mildness of the infection in the mouse.

Finally in the future, attempts must be made to induce a more massive type of leprosy infection in experimental animals. At present, the key to inducing a more progressive leprosy disease appears to be by the use of powerful immunosuppressive treatment. Recently some success has been achieved along these lines by Rees (1965, 1966) and also by Gaugas (1967) where thymectomy plus x-irradiation of adult mice markedly enhanced susceptibility to infection in the foot pad. Advantages are to be found in a more reliable way of testing the effectiveness of anti-leprosy drugs in so far as this may be more discriminating. It would also allow the usefulness of combined therapy to be evaluated in the experimental animal.

SUMMARY

In the present investigation Shepard's original method for transmission of human leprosy (*M. leprae*) to the mouse was confirmed. As expected a very mild form of infection was induced. This model was used to test the effectiveness of antimicrobial therapy. At largely arbitrary dose ranges treatment with dapsone, solapsone, sulphormethoxine, sulphadimethoxine, B663(M) phenazine, thiacetazone, thiambutosine, SU 3068, capreomycin, isoniazid, oxydiazolone, PAS, streptomycin, streptovaricin, viomycin, cephaloridine and rifamycin completely suppressed the development of the mild infection, but tetracycline or morphazinamide had no inhibitory effect; gentamicin had only a partial effect. The suitability of this method for the screening of compounds is discussed.

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Calcification of Superficial Nerves in Leprosy

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M. leprae has got a special predilection for the superficial nerves. The pattern of histopathological changes which ultimately emerge as a result of its lodgement in the nerve tissue has been described by some workers[6 13]. No mention has been made about the calcification of nerves in leprosy even in the comprehensive text-book by Cochrane and Davey[3]. However, some workers[1 2 4 5 7 8 9 10 11 12 15 16] have reported stray cases of its occurrence in neuritic leprosy. The study on the radiological evidence of calcification of nerves as such has not been thoroughly undertaken.

The present study was carried out to find the radiological evidence of macroscopic calcification and its probable relationship to its prognosis.

MATERIALS AND METHODS

Fifty patients, comprising 35 with tuberculoid, 10 with neuritic and 5 with leprotic nerve abscesses formed the subject for the study. These patients were collected from the 'Dermatologic' section of Sir Sunder Lal Hospital, Banaras Hindu University. The diagnosis in each case was made on clinical grounds. The involvement of the ulnar nerve at the elbow region in the form of thickening and tenderness or the formation of nerve abscess was the common denominator in all cases. All the patients were invariably on therapy with Diamino-diphenyl-sulphone sometime or another.

Radiological antero-posterior view of the affected elbow region was taken considering the following factors as tabulated below:—

K.V.	*M.A.S.*	*F.F.D.*	*Screen film*
40	8	36″	Yes

The above factors were taken into account for the X-rays of soft tissue, though the non-screened films are claimed to be ideal but in our results we found comparable contrast with the screened films to the best of our satisfaction. As a standard, small focus was chosen for radiographs of the series.

OBSERVATIONS

No evidence of radiological calcification was seen in any of our patients (Figs. 1 and 2). However, in 5 patients irregular, increased soft tissue shadow was seen in radiographs at the level of lower one third of the humerus in the region of the ulnar nerve on the medial side (Fig. 3). The patients with leprotic nerve abscesses were confirmed at operation as reported earlier by one of the authors[14].

DISCUSSION

Calcification of superficial nerves in leprosy is extremely rare and has been infrequently reported. It has been observed exclusively in the neuritic variety by most of the workers[1 2 4 5 7 8 9 10 11 12 15 16]. Some workers[1 2 5 10 13] found oval blobs of calcification conforming to the calcification of old nerve abscesses. However, Trapnell[16] and Ramanujam and Ramu[12] have reported one case each where calcification was seen radiologically in the nerve as such.

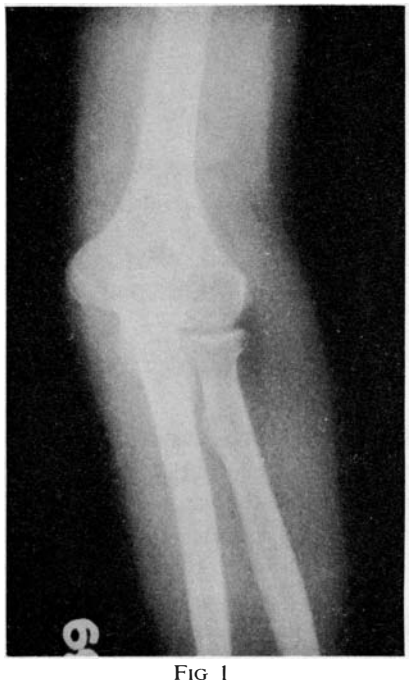

FIG 1

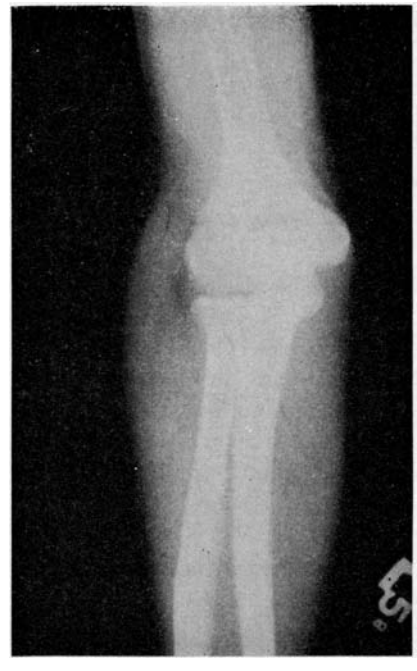

FIG 2

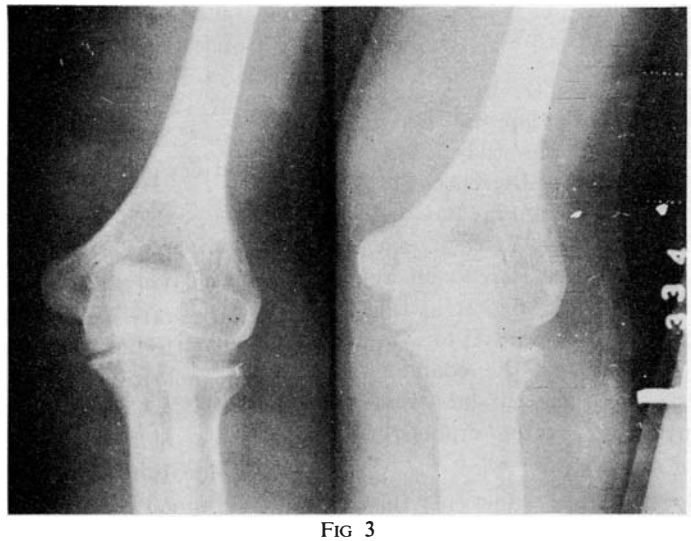

FIG 3

In our series, on the other hand, comprising different stages of the disease no macroscopic radiological calcification was seen including those of nerve abscesses which are reported to be extremely rare[14]. Our observations, therefore, do not support the findings of the earlier workers.

No adequate explanation for the absence of calcification in our series could be given. It seems plausible that the therapy with Diaminodiphenyl-sulphone has changed the pattern of natural course of the disease resulting in lesser degenerative changes in the nerve tissue, thus limiting the chances of deposition of calcium. The marked degenerative changes in the nerve are supposed to be the pre-requisite for dystrophic calcification.

It is unlikely that calcification of nerves in leprosy will help in the evaluation of its prognosis.

SUMMARY

Fifty patients in different stages of leprosy were studied for the evidence of macroscopic radiological calcification in superficial nerves. No calcification was seen in any of our patients.

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Some Observations on the Age at Onset of Leprosy

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Age at onset in leprosy still remains disputed and has not received the attention it deserves. There is a wide variability of results among the various authors. The age at onset is important for early diagnosis and treatment and will define the period which should receive the special attention of the public health workers for prevention and control of leprosy. While interpreting the age at onset, a careful interrogation of relatives or friends is essential for those patients who are unable to give correct dates due to low levels of intelligence, poor or failing memory or for those who cannot give their correct ages.

The present study in Lucknow was carried on outpatients'* new patients coming from the city itself or nearby adjoining areas. The lepromatous rate in Northern India has been reported to vary from 20 to 25% or even 30% (Mulick *et al.*, 1957; Chandy *et al.*, 1963; Sharma and Prasad, 1964).

RESULTS

The age at onset by sex and type found in the present study is given in Table 1 and 2 respectively.

Nearly one-fourth of the total patients (28.8%) were below 20 years of age; also in the 2 sexes and among the lepromatous and non-lepromatous the distribution was the same. 9.2% of patients were 50 years of age or above (Table 2).

Nearly half of the patients (45.2%) were in the 15-29 years of age group, below and above which decline was noted (Table 1).

Table 3 and the frequency polygon depict comparison of the age at onset reported by Cochrane (1947, quoted by Badger, 1959) and Mohd. Ali (1964) in Madras State said to be highly endemic; Badger (1959) from the endemic states of U.S.A.; study by the present authors at Lucknow reported to have low endemicity; and by Sharma and Prasad (1964) at Barabanki which adjoins Lucknow but has relatively a higher endemnicity.

Cochrane (1947, quoted by Badger, 1959) states 'it is our firm conviction that the great majority of those acquiring leprosy are infected and show manifestations of the disease before the age of 15'. Muir (1948, quoted by Badger, 1959) is of the view that 'like tuberculosis infection, leprosy is most common in the first few years of life'. Rogers and Muir (1946, quoted by Badger, 1959) hold that children and young adults up to the age of 20 years are most susceptible to infection by leprosy, while Doull (1957, quoted by Badger, 1959) holds that 'greater susceptibility of young children is indicated by their relative higher risk when exposed in the household'. Mohd. Ali (1964) on the contrary holds that, assuming 10 years as the incubation period, about 50% of patients under his study (i.e., 1,760 patients) had got infected

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Refers to outpatients' department of Leprosy Hospital, Nishatganj, Lucknow, where the study was carried out and the present enquiry comprised of a part of thesis for M.D. examination of Lucknow University by the first author.

TABLE 1

Distribution of age at onset* by sex and type

Age Groups in years	MALES		FEMALES		TOTAL			LEPROMATOUS		NON-LEPROMATOUS	
	Number	%	Number	%	Number	%		Number	%	Number	%
0-4	1	0.5	1	1.8	2	0.8		—	—	2	1.0
5-9	9	4.6	3	5.5	12	4.8		1	1.9	11	5.6
10-14	16	8.2	4	7.3	20	8.0		5	9.6	15	7.8
15-19	30	15.4	8	14.5	38	15.2		8	15.4	30	15.0
20-24	34	17.4	10	18.2	44	17.6	45.2	13	25.0	31	15.1
25-29	23	11.8	8	14.5	31	12.4		7	13.5	24	12.1
30-34	17	8.7	5	9.1	22	8.8		7	13.5	15	7.8
35-39	19	9.7	5	9.1	24	9.6		1	1.9	23	11.6
40-44	14	7.2	2	3.6	16	6.4		1	1.9	15	7.8
45-49	17	8.7	1	1.8	18	7.2		4	7.7	14	7.1
Over 49	15	7.7	8	14.5	23	9.2		5	9.6	18	9.1
Total	195	99.9	55	99.9	250	100.0		52	100.0	198	100.0
Mean	28.45	—	27.90	—	28.34	—		27.50	—	28.55	—
S.D.	13.00	—	13.63	—	13.13	—		12.28		13.34	—

* The age at onset has been worked out on the basis of deducting probable duration of disease from the present age (i.e., what the patient has reported in the outpatients' department).

TABLE 2

Percentage distribution of age at onset for the three distinct age groups (by sex and type)

Age groups in years	DISTRIBUTION BY SEX			DISTRIBUTION BY TYPE	
	Males	Females	Total	Lepromatous	Non-Lepromatous
0-19	28.7	29.1	28.8	26.9	29.4
20-49	63.3	56.3	62.0	63.5	61.5
50 years and over	7.7	14.5	9.2	9.6	9.1

after they had passed their 20th year of life thereby showing that leprosy is not a children's disease.

The results of the present study are similar to those undertaken in the U.S.A. (Badger, 1959) where the rising trend is more marked and sustained with advancing years of life (Table 3). Higher percentage of population of the older age groups in the U.S.A. may account for this difference.

Figures of the 2 studies undertaken in a highly endemic area, i.e., the Madras State, by Cochrane (1947, quoted by Badger, 1959) and Mohd. Ali (1964) at different periods, indicate the age of onset to be below 10 years of age in nearly 15 to 20% of the patients. Comparative figures by different authors in Table 3 for the lesser endemic areas of U.P. and U.S.A. vary from 3 to 5%, about 3 times less than the figures found in the Madras State, showing thereby an earlier age predisposition in highly endemic zones.

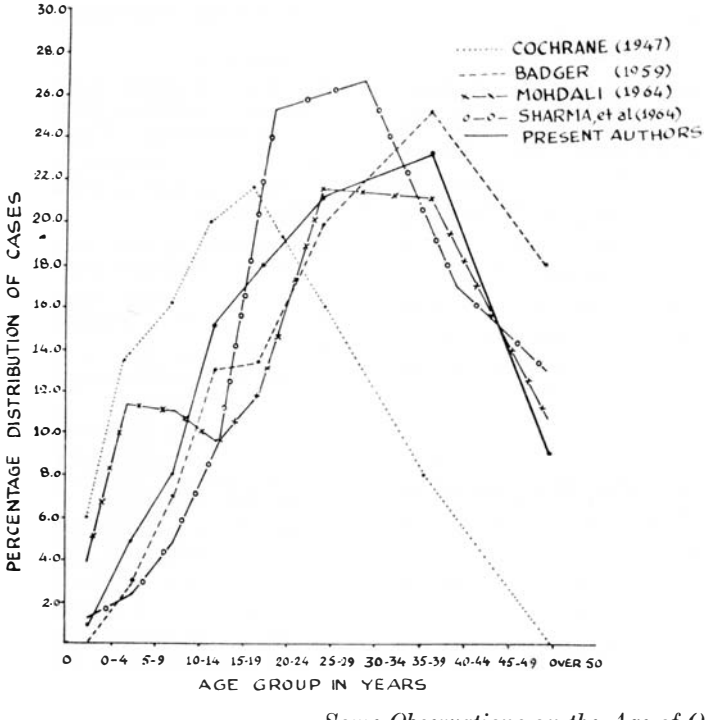
It is worth while to observe that 41.3% of the patients fell in the 10 years age group of 15-24 years in Cochrane's Madras study (Cochrane, 1947, quoted by Badger, 1959), 51.8% in the 20 years age group of 20-39 years in that of Sharma and Prasad (1964), 42.5% in the 25 years age group of 25-49 in Mohd. Ali's (1964) study in Chingleput (Madras State), 44.4% in the 25 years age group of 25-49 years in the present study, and 45% in the 25 years age group

TABLE 3

Showing comparative study of percentage distribution of age at onset in different areas by different workers

Age at onset in years	*Madras State (Cochrane, 1947. quoted by Badger, 1959)*	*Chingleput District of Madras State (Mohd. Ali, 1964)*	*Lucknow Study (Present authors)*	*Barabanki Study (Sharma and Prasad, 1964)*	*Endemic states of USA (Badger, 1959)*
0-4	6.3	3.8	0.8	1.2	0.1
5-9	13.4	11.3	4.8	2.4	3.0
10-14	15.9	11.0	8.0	4.8	7.0
15-19	19.8 } 41.3	9.5	15.2	9.6	13.2
20-24	21.5 }	12.2	17.6	20-29 yrs. 25.3 } 51.8	13.4
25-34	16.1	21.6 } 42.5	21.2 } 44.4	30-39 yrs. 26.5 }	19.8 } 45.0
35-49	7.0	20.9 }	23.2 }	40-49 yrs. 16.9	25.2 }
50 years and above		10.4	9.2	13.2	17.8
Under 10	19.7	15.1	5.6	3.6	3.1
Under 20	55.4	35 6	28.8	18.0	23.3
Over 10	80.3	84.9	91 4	96.4	96.4
Over 20	44.6	64.4	71·2	81.9	76.3
Over 35	7.0	31.3	32.4	30.1	43.0
Over 49		10.4	9.2	13.2	17.8

FREQUENCY POLYGON SHOWING PERCENTAGE DISTRIBUTION OF AGE OF ONSET IN DIFFERENT AREAS BY DIFFERENT WORKERS



of 25-49 years in the U.S.A. study (Badger, 1959). Thus in nearly 40-50% of the total number of patients the age at onset was in young or younger age groups in the studies under reference and the greater the endemicity the lower was the age of onset.

It will be seen from the above that there is a variation in the age at onset in the two Madras studies (Cochrane, 1947, quoted by Badger, 1959; and Mohd. Ali, 1964) and the 2 studies undertaken in Uttar Pradesh (Sharma and Prasad, 1964, and the present study). According to Badger (1959), the age of onset is seen to vary in different countries, in different parts of the same country and even in the same areas at different times.

Further, in a much larger percentage of patients the age at onset was found at a lower age in childhood, i.e., below 10 years in Madras studies, while the figures in studies from Uttar Pradesh fell between the Madras and the U.S.A. studies. It was revealed in the present study that in the majority of instances the infectious contact was a result of infection from without the household in those giving positive histories of contact (Varma, 1964). This was also the finding of Sharma and Prasad (1964).

All the above mentioned studies show that 30-40% of patients reported the age at onset after they had passed their 35th year of life, excepting in Cochrane's study (1947, quoted by Badger, 1959) where it was 7%. Mohd. Ali (1964) refers to the incubation period of leprosy as a subject of much controversy—Rogers (quoted by Mohd. Ali, 1964) suggesting 3-5 years, Badger (1959) 3-4 years, recent Japanese studies (quoted by Mohd. Ali, 1964) putting it at 8 years, and the longest perhaps up to 20 years (Dharmendra, 1960). 23.2% of patients reported the age at onset falling within the age group between 35-49 years and 9.2% above 49 years in the present study. With regard to the patients in these 2 later groups there can be little doubt that they could not have developed the disease consequent to childhood infection.

In the absence of reliable diagnostic tests for estimation of immunity to leprosy and individual resistance patterns (variable response to infection) it would not be safe to propose a fixed limit for the age at onset. Moreover, principles of universal acceptability cannot be formulated especially when the country presents widely differing spectra of psycho-socio-cultural and economic strata (Varma and Prasad, 1966). However, the vulnerability to infection as evinced by variability in age at onset is suggestive of the involvement of multiple factors (individual as well as community factors). The community infection, i.e., availability of infectious contacts to susceptible hosts, probably determines the childhood, adult or geriatric predominance.

SUMMARY

The authors have attempted to analyse the age at onset reported by various workers the world over along with their own findings. They suggest that the availability of infectious contacts probably determines the age at onset in a community. There is ample evidence to suggest that adulthood infection is by no means as rare as it is often thought to be.

It may not be safe to suggest a definite age at onset in the absence of reliable tests for determining immunity status.

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The Presence of *M. Leprae* in Human Milk

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In the pathogenesis of leprosy inunction or inoculation through the skin is still thought to be the chief method by which the bacillus enters the body. Evidence for entrance by the respiratory and alimentary portals is believed to be lacking. For example, Spickett[1] referring to the paper of Weddell and Palmer[2] on the pathogenesis of leprosy wrote:—

> 'The evidence of Weddell and Palmer does appear to establish that *M. leprae* may be disseminated throughout the body by the circulation, and this being so one of the major problems connected with a respiratory or alimentary portal of entry is solved. However, this does not in any sense provide evidence that such portals of entry are used and it is difficult to see how the type of evidence that Weddell and Palmer have produced can provide such evidence.'

Again, Badger[3] writes:—

> 'Occasionally one sees reference to possible indirect contact transmission through *food*, clothing, insect vectors, etc. Concrete and definite information relative to such transmission is lacking.' (Italics—mine.)

In view of these remarks, the following patient will be of interest.

In May this year a Nepali woman, aged 22 years, came into my consulting room carrying her 6 months old baby. She complained of swelling of the face and 'pins and needles' sensation in hands and feet for one year, developing when she was about 3 months pregnant. This was her first child. My clinical notes are as follows:—

Skin

The skin of the face is slightly erythematous and shows a diffuse, generalised infiltration. Both ear lobes are swollen. There is a broad based erythematous, shiny nodule about 1 cm. across situated on the chin to the right of the mid-line. The skin of the chest, back and front, and of the neck shows multitudes of small, slightly hypopigmented coalescing macules symmetrically distributed.

Nerves	*R*	*L*
Auricular	+2	—ive
Ulnar	+1	—ive
Radial	+1	+1
Peroneal	+1	+2

Anaesthesia

No obvious impairment of tactile and pain sensations in the extremeties. Thermal sense not tested.

Slit Skin Scrapings

One from each ear lobe. Both showed massive infection with acid fast bacilli; that is, innumerable bacilli and numbers of globi in every field. At least 50% of the bacilli were judged to be in good well-staining solid rods.

Diagnosis

Lepromatous leprosy in very active stage.

Therapy

The patient was started on DDS 30 mgm. per week and given 3 months' supply as she had come from a considerable distance.

Later, it occurred to me that I had let slip the opportunity to examine the patient's breast milk. However, 2 months later she turned up again bringing her baby.

Examination of Breast Milk

Both breasts were fairly full. The nipples were normal and there appeared to be no cracks or fissures. A small stream of milk was ejected

from the left nipple by slight digital pressure. Then a few more drops were gently expressed, one being caught on a freshly cleaned laboratory slide. This one drop was distributed over almost the whole slide by means of a platinum loop previously sterilised by making it red hot in a spirit flame. The slide was fixed and stained in the usual way for AFB.

Using a Vickers binocular microscope equipped with a movable stage, a thorough search of the slide was made. A group of 12 well stained shortened rods was soon found, and the remainder of a total of 118 acid fast bacilli were counted by searching approximately 2,650 fields, occupying about 2/3rds of the whole smear, thus averaging 1 bacillus in 22 fields.

An experienced Japanese bacteriologist, Dr. Ivawmura, a member of our hospital staff, checked some of my findings. There could be no doubt at all in our minds that the bacilli we had seen in this woman's milk were indeed *M. leprae*. The same arrangements or formations of bacilli were seen in the milk as can be seen in skin smears from active lepromatous leprosy. For example, bacilli lying side by side like cigars in a box, or a cluster of 12 well stained shortened rods, and pairs of slightly shortened bacilli lying parallel with a little gap between each pair. Others were found singly—full length, well stained, solid rods. Three which were judged to be solid rods were lying head to head in the shape of a letter 'Y' each one well stained. Fragmented bacilli were also very characteristic. Details of the bacillary count are given as follows:—

9.2%	consisted of	11 solid rods
69.7%	,,	82 fragmented bacilli
19.5%	,,	23 short rods
1.6%	,,	2 granules
	Total	118

Control

Just to check that my staining technique was not at fault, I prepared another slide of the milk of a healthy lactating woman. I used the same set of stains, the same solution of 10% sulphuric acid. None of these had been changed or replenished since preparing the slide from the lepromatous woman's milk. A search of 1,500 fields (approx.) was negative. I was, however, impressed with the numbers of white cells present, which Dr. Ivawmura identified as lymphocytes and plasma cells. This led to a discussion about bacilli in breast milk, and there emerged the comparison between the breast milk of a woman suffering from miliary tuberculosis and that of a woman suffering from lepromatous leprosy, referred to later in this paper.

DISCUSSION

It seems clear that if ever this woman's child develops leprosy the main portal of entry will have been the alimentary canal. Skin-to-skin contact or the mother's clothes wrapped about the child may play their part in transmitting the disease, but, by comparison with the breast milk, it would seem to be a very minor part. In about a minim of its mother's milk at least 118 acid fast bacilli were present. This could, perhaps, mean that in a 4 ounce feed approximately 2 million bacilli are present. Whether or not this is so, it seems certain that this child is consuming countless bacilli.

This finding lends significance to bacilli which might get trapped in the nasal muscosa. One way by which their deeper penetration into the body could occur would be by secretions from the naso-pharynx passing into the alimentary canal.

Thus, in the light of Professor Weddell's findings[2], supported by the evidence given above, a mental picture emerges. Some of these bacilli are probably finding their way from this child's alimentary canal into the blood stream. They will then pass to some of his Schwann cells. Here they will lie dormant during the so-called 'silent' or 'latent' period. In another paper on the pathogenesis of leprosy[4], Professor Weddell has likened the Schwann cell to a 'refrigerator'. At the end of the incubation period or period of 'refrigeration', the bacilli emerge. Then, according to the degree of tissue resistance, leprosy could develop in one of its forms. At length it decides to display itself: pins

and needles sensation, an area of hypo-aesthesia, an enlarged cutaneous nerve, a patch, or an area of generalised diffuse erythematous infiltration, such as the skin of the face.

This picture may be a faulty one, but in the light of the findings and evidence already referred to, there seems to be enough truth in it to highlight the tremendous importance of preventative treatment, especially in the case of children of lepromatous mothers. My own line as regards this mother and her child will be to:—

1. Treat the mother vigorously with DDS.
2. Find out if the child has a natural immunity to tuberculosis. If not, to give BCG inoculation, repeating, if necessary, at regular intervals in order to maintain a positive Mantoux reaction.
3. Give regular prophylactic doses of DDS to the child.
   If at all possible, to continue *both* these lines of preventative treatment to the child *until well past adolescence.*

We have been following these lines of attack in a nearby Government leprosy settlement for several years. They are suggested by Browne[5]. In the light of the evidence given in this paper, prolonged preventative treatment is emphasised.

As regards the mother of this child, it seems that a specific comparison can be made between the breast milk of a woman suffering from miliary tuberculosis and that of a woman suffering from lepromatous leprosy. This comparison is made on the basis of 2 established facts:—

1. That *M. leprae* can be *seen* in the *lumen* of blood vessels of persons with very active lepromatous leprosy. I have 4 biopsies of my patients which demonstrate this.
2. That *M. tuberculosis* have been found in the breast milk of women suffering from miliary tuberculosis, and that this finding has been reported in Japanese medical journals.

Therefore, it can be said that, just as the *M. tuberculosis* can pass in the blood stream to the mamary gland and occasionally be found in the breast milk of a woman suffering from miliary tuberculosis, so it is possible for the *M. leprae* to pass in the blood stream to the milk of this woman who is suffering from very active lepromatous leprosy.

It is hoped that workers in the field of leprosy will check on this finding by examination of the milk of every lactating woman suffering from lepromatous leprosy that they come across, especially those whose skin smears show both a high bacillary and a high morphological index. It is suggested that a small quantity of breast milk could be placed in a refrigerator, so that a number of smears could be examined at leisure.

Further investigation must be made to show if this is an occasional or a constant happening in lactating women suffering from lepromatous leprosy.

In lactating women suffering from other forms of leprosy which clinically and histopathologically could be shown to lie between the lepromatous end of the spectrum and the borderline zone, one could postulate that the bacilli, if present at all, would be increasingly difficult to find in the milk, by reason of their fewness, the nearer the patient approaches the borderline zone.

SUMMARY

Attention is drawn to the view held by leprologists that there is a lack of evidence to show that the alimentary canal may be a portal of entry for the *M. leprae.* Findings which appear to be definite evidence are submitted. The bearing of this evidence on the importance of preventative treatment is emphasised. Leprologists are urged to check the evidence given.

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I wish to express my thanks to Dr. Ivawmura for checking the microscope findings, and for drawing my attention to the relevant facts in tuberculosis.

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CONTINUATION NOTES

SUMMARY OF PAST NOTES

2nd May, 1967. Date of *first* visit to O.Ps, when she brought her 6 months old baby. Found to be suffering from very active lepromatous leprosy—one year history since she became pregnant. M.I. 50-60%. B.I. +4. Started on DDS 30 mgm. per week and given 3 months' supply. Unfortunately did not think to examine the breast milk on this occasion.

8th July, 1967. Date of *second* visit to O.Ps. A total dose of DDS 270 mgm. had been taken since first visit. Breast milk examined, 118 acid fast bacilli of which 9.2% were solid rods, were present in approximately one minim of breast milk. Had I examined the milk at the first visit before any treatment had been given, it is highly probable that the number of bacilli and proportion of solid rods would have been much higher. Prescribed DDS 60 mgm. per week.

CONTINUATION NOTE

29th July, 1967. Date of *third* visit. Since the second visit a further 180 mgm. of DDS had been taken.

Repeat Examination of Breast Milk. Three milk smears made as follows:—

1. An ordinary smear, fixed and stained in the usual way using 10% sulphuric acid to decolourise. 1,500 microscopic fields searched. I could find *no* acid fast bacilli. I did find 4 irregularly stained very short fragmented acid fast organisms—each consisting of 2 granules, or having the appearance of a very short bipolate rod broken in the middle. These might have been bacillary debris.

2. An ordinary smear—in this case 0.5% HCl in 70% alcohol was used for decolourising. Same number of fields searched. No acid fast bacilli found.

3. A smear made from the sediment of an electrically centrifuged portion of milk (15,000 revs. per min. for 20 mins.). A very thick smear was made from the sediment. 700 fields searched. No acid fast bacilli found in solid rod form, but I did find 3 very short irregularly stained rods and 10 granules. I think that these represent bacillary debris.

Repeat skin smear from right ear lobe of mother: showed numerous AFB in every field and globi in nearly every field. The M.I. was judged to be at least 60%.

Biopsy

A very deep skin biopsy with as much subcutaneous tissue as possible was taken from the broad based nodule on the right side of the chin and fixed in F-Z solution for 16 hours before transfer to com. spt. This was sent to the Leprosy Study Centre in London. In it, I hope it will be possible to demonstrate the presence of bacilli in lumen of the blood vessels.

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Nerve Abscess in Lepromatous Leprosy —Report of a Patient

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Nerve abscess is quite well known in the tuberculoid type of leprosy and is analgous to the 'cold abscess' of tuberculosis, but its existence in lepromatous type of leprosy has always been in doubt. Hughes[4] states that nerve abscess is found only in the tuberculoid type of leprosy. However, Austin[1] has seen nerve abscess in 2 patients with lepromatous leprosy but failed to make the necessary investigations. The lepromatous patient with nerve abscess which Muir[7] had recorded belongs to the 'cold abscess' type and the patient is thought to be 'neural' to start with. Wade[10] in 1939 had mentioned 2 lepromatous leprosy patients with nerve abscesses which differed grossly and histologically from 'the cold abscess' seen in tuberculoid patients. Later, in an editorial in the same journal in 1953 Wade[11] had asked to report any patient with lepromatous nerve abscess proved histologically. Subsequantly Sato[8] in 1956 reported a patient with lepromatous leprosy with a cutaneous nerve abscess which histologically showed lepromatous granuloma with abundant bacilli but hardly any polymorphonuclear leucocytes.

In this paper we report a patient with lepromatous leprosy presenting with erythema nodosum leprosum (ENL) and having an acute nerve abscess proved histologically.

C.M.C.H. 399299: A 29-year-old male patient with lepromatous leprosy presented with a complaint of having painful nodules all over the body off and on for 3 years. He was diagnosed as a leprosy patient 3 years ago while having fever and arthritis and was treated with Diamino Diphenyl Sulphone (DDS). This treatment precipitated an attack of ENL. Since then he had had recurrent attacks of ENL On examination there was diffuse fine infiltration and erythema of the skin of the trunk, face and extremities. Bilateral glove and stocking anaesthesia was present. There was also oedema of the hands and feet. The right ulnar nerve was thickened and painful. Scattered tender nodules were present all over the body. One of these was biopsied.

INVESTIGATIONS

Skin smears were done according to the Wade's technique[9] and graded as per Cochrane's method[2].

Ear	1 plus
Forehead	1 plus
Cheek	1 plus
Arm	1 plus
Chest	Only occasional bacilli
Back	Only occasional bacilli
Buttock	Only occasional bacilli

Urine examination showed no abnormality.

HISTOPATHOLOGICAL REPORT

The biopsy consisted of an elliptical piece of skin measuring 2 cm. long. The tissue was bisected and it revealed a nodule in the subcutaneous tissue measuring 0.4 cm. in diameter. It was fixed in 10% formalin, processed and several paraffin sections were made. Haematoxylin and Eosin stain, acid fast stain according to the Fite's method[3], Loyes myelin stain and

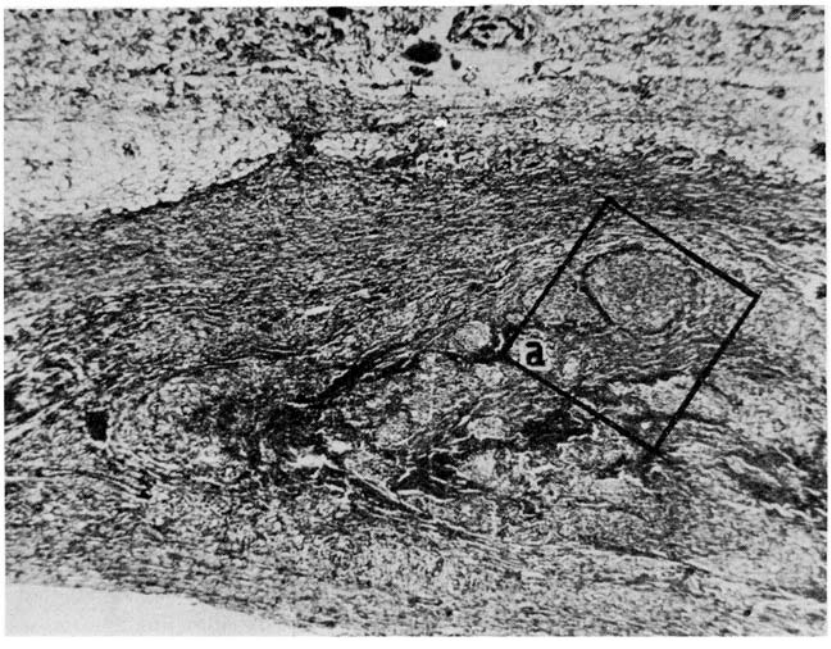

FIG. 1

Photomicropgraph of the subcutaneous nodule to show the abscess involving the nerve.
(H & E × 30.)

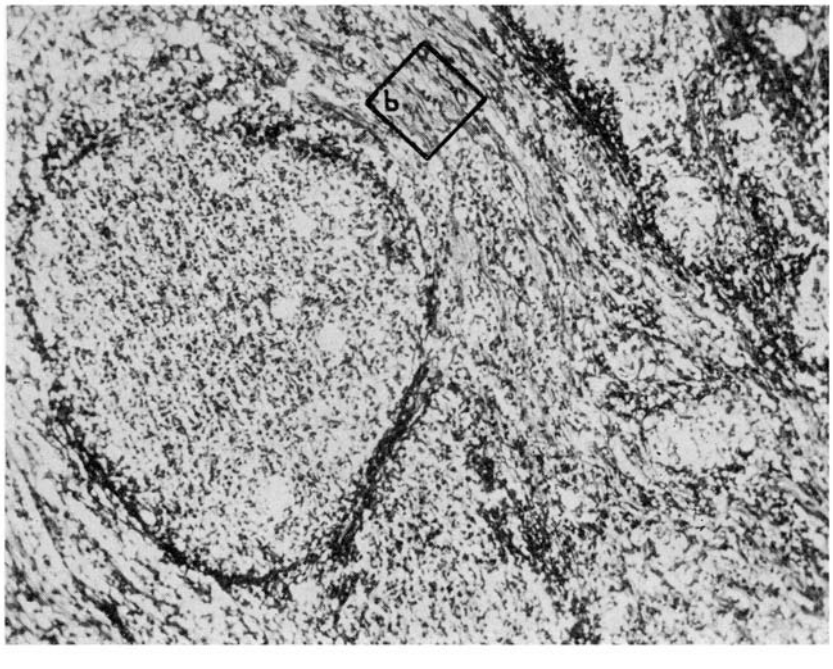

FIG. 2

Field in Fig. 1 magnified to show a part of the abscess composed almost entirely of polymorphonuclear leucocytes.
(H & E × 150.)

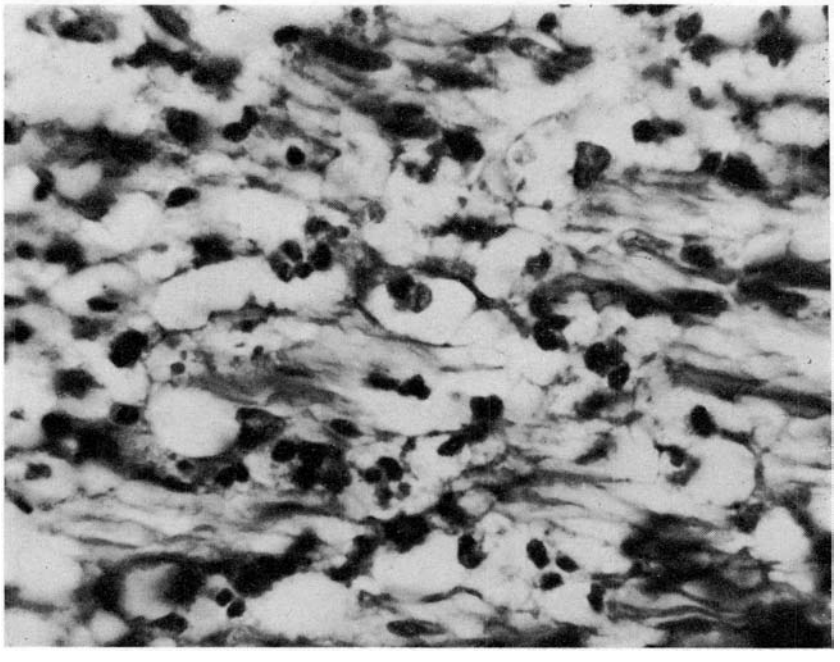

FIG. 3

Field in Fig. 2 magnified to show the nerve bundle infiltrated with numerous polymorphonuclear leucocytes.
(H & E × 1100.)

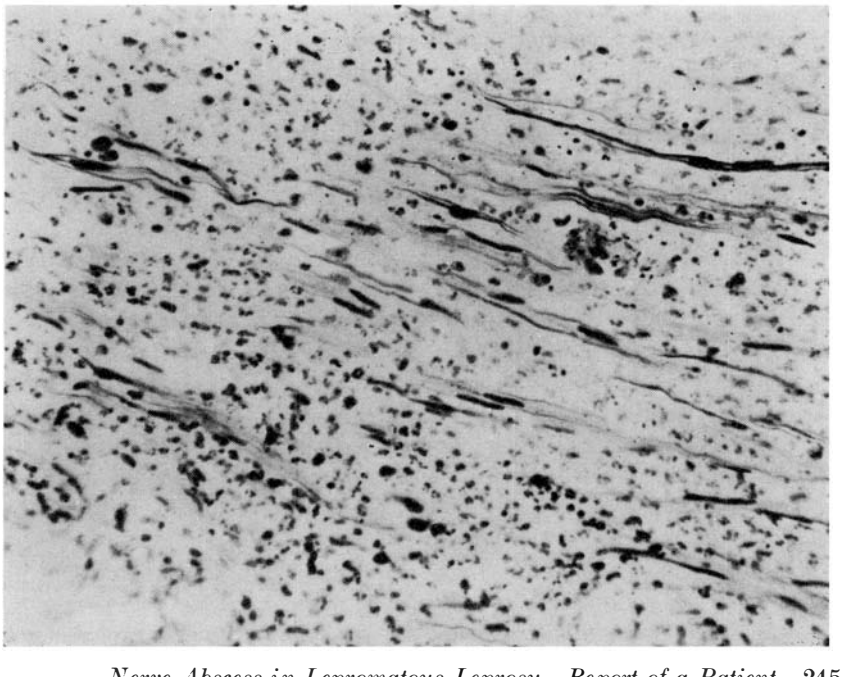

FIG 4.

Fragmented nerve fibres are seen densely infiltrated with polymorphonuclear leucocytes.
The tissue is oedematous.
(Bodian × 150.)

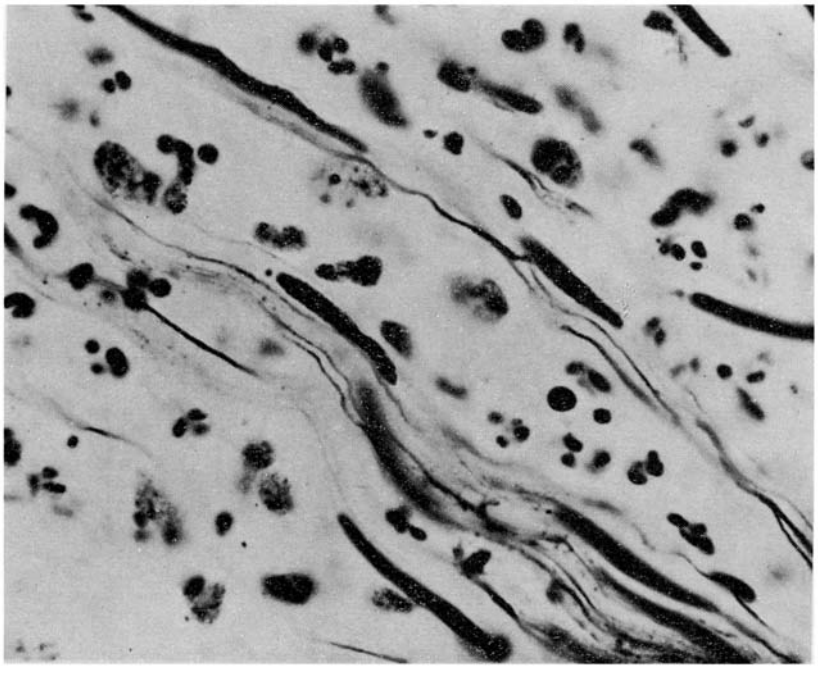

FIG. 5

Higher power photomicrograph to show clearly the fragmented nerve fibres infiltrated with numerous polymorphs. (Bodian × 1100.)

Bodian stain for axis cylinders in paraffin sections were prepared.

Histopathological examination showed epidermis with some proliferation of the prickle cell layer. In the corium were focal collections of inflammatory cells consisting of mainly lymphocytes and plasma cells. They were collected around skin appendages. There was marked increase in vascularity and the blood vessels were also surrounded by the inflammatory cells.

The chief lesion was a nodule in the subcutaneous tissue.

The nodule consisted of a subcutaneously placed nerve showing pronounced oedema and severe inflammation. Large collections of foamy macrophages with markedly vacuolated cytoplasm had infiltrated the nerve separating widely the nerve fibres. The nerve was also diffusely infiltrated with numerous neutrophilic polymorphonuclear leucocytes which in areas were densely packed together to form abscesses.

There was endothelial proliferation with formation of new capillaries. In the myelin stain total demyelination of the nerve fibres was seen. The Bodian preparation showed much fragmentation and destruction of nerve fibres. A few fragmented remanants of the axons were made out.

Numerous acid fast bacilli were present inside Schwann cells. Most of them were broken and granular. The macrophages did not show any bacilli.

COMMENTS

This patient with lepromatous leprosy presents all the features of lepromatous nerve abscess the histopathological appearance of which has been predicted by several others earlier. Muir[3] had suggested that the nerve abscess in lepromatous leprosy should be like the skin nodule in 'lepra reaction' containing pus filled with leucocytes and a large number of acid fast bacilli. Wade[7] suggested that 'the nerve abscess in the cutaneous type (lepromatous type) is an acute condition and admittedly due to a lepra reaction phenomenon'. In this patient the nerve abscess occurred during an attack of

erythema nodosum leprosum and the nerve was densely packed with neutrophilic polymorphonuclear leucocytes forming an abscess. Acid fast stain showed numerous acid fast bacilli.

Erythema nodosum leprosum is thought to be a hypersensitivity reaction. The exact pathogenesis of the phenomenon is not well understood. In our experience most of the ENL lesions occur in an already existing granuloma of macrophages containing acid fast bacilli which are mostly broken and granulated.[5] The well known site of ENL is the skin. However, one of the authors has seen ENL-like reaction in the lymph nodes which are extensively replaced by lepromatous granulation tissue[6].

The nerve seen in the patient under report showed a lepromatous granuloma together with an abscess composed of polymorphonuclear leucocytes. Numerous broken and granular bacilli were also present in the Schwann cells. This nerve lesion is present in association with numerous other skin nodules typical of ENL. Therefore, it proves beyond doubt for the first time that ENL-like reaction with abscess formation takes place in the nerve tissue also.

SUMMARY

An acute subcutaenous nerve abscess in a patient with lepromatous leprosy is presented. Histopathological appearance of the nerve abscess is typical of the ENL with lepromatous granuloma infiltrated with large collection of polymorphonuclear leucocytes.

ACKNOWLEDGEMENTS

We acknowledge with thanks the technical help received from Mr. R. Shanthakumar and Mr. S. Jesudoss and the secretarial help from Mr. K. George William.

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Report

Report of the Health Division, Ministry of Health, United Republic of Tanzania, 1965. Section on Leprosy.

The control of leprosy in Tanzania is based on the principle that the most effective measure is early treatment. The campaign has accordingly been centred on the rural dispensary and increased emphasis placed on the training of Rural Medical Aids in the diagnosis and treatment of the disease. Modern leprosaria or leprosy hospitals exist in all areas of high leprosy prevalence with the exception of the Kigoma Region, and the coverage afforded by these hospitals and the rural dispensaries resulted, in 1965, in approximately 50% of the total estimated patients in the country receiving treatment. The routine mass treatment standardized at all out-patient centres has consisted of oral dapsone in one of 2 schedules: 50 mgm. daily for 6 days a week when the patient can be given 1-2 months' supply to take at his home, or (more usually) up to 400 mgm. taken in a single dose at dispensaries holding a weekly leprosy clinic.

Abstracts

1. **Physiotherapy and Leprosy,** by DAVID J. WARD. *J. Rehab. in Asia*, 1967, **8**, 2, 35-38.

The author gives a brief outline of the physical conditions caused by leprosy which call for treatment by physiotherapists before and after surgery. He suggests future line for research by physiotherapists and stresses the need for more fully trained physiotherapists as well as paramedical workers, especially in India. This is a very valuable paper as it has so many practical suggestions.

The following 9 abstracts are reprinted with permission from *Trop. Dis. Bull.*, 1967, **64**, 4:

2. **El programa de control de la lepra en el Ecuador** (Programme of Control of Leprosy in Ecuador), by E. BLUM GUTIERREZ. *Rev. Ecuatoriana de Hig. y Med. Trop.* Guayaquil. 1966, May-Aug., **23**, 2, 183-8, 2 graphs.

This paper reviews characteristics of regional variations of leprosy in Ecuador and merits study in the original. Between 1963 and 1966, 420,000 persons were examined and 978 new patients were recorded, mainly from 4 areas of the country.

J. R. Innes.

3. **Leprous Lymphadenitis. Demonstration of Tuberculoid Lesions,** by K. V. DESIKAN and C. K. JOB. *Inter. J. Lepr.*, Wash., 1966, Apr.-June, **34**, 2, 147-54, 8 figs. (17 refs.).

It is known that lepromatous leprosy frequently involves the regional lymph nodes draining affected parts of the skin, and that these glands are sometimes enlarged. This also occurs in tuberculoid leprosy, but no histological lesions have ever been found in the glands in this latter type. This paper reports the finding of such lesions, and describes the histology of lymph glands in all types of leprosy.

The histology of the lepromatous and borderline groups was similar to that described by earlier workers (this *Bulletin*, 1954, v. 51, 274; 1959, v. 56, 447). In all groups, the histological appearances corresponded fairly closely to those of skin lesions. The largest of the biopsied nodes in tuberculoid patients measures $2 \times 1 \times 1$ cm. The lymph nodes of this group showed the presence of granulomas composed of clusters of epithelioid and giant cells even in true polar (TT) patients. There was no caseation. Acid-fast bacilli (AFB) were found in 1 out of 8 biopsies in the borderline-tuberculoid (BT) group but in none of 5 TT glands. Cultures for AFB were all negative.

D. S. Ridley.

4. **Secondary Amyloidosis in Leprosy,** by S. KRISHNAMURTHY and C. K. JOB. *Inter. J. Lepr.*, Wash., 1966, Apr.-June, **34**, 2, 155-8, 4 figs.

Amyloidosis is known to be a possible complication of prolonged infection with leprosy, but it is rare in the East. Nevertheless, 2 out of 25 autopsies from 27 patients who died of leprosy in India revealed secondary deposits of amyloid in the kidney, liver, spleen and adrenals. In both patients the leprosy was of the lepromatous type and both had nephrotic symptoms. Nine of the other 23 autopsies showed that the patients had had tuberculosis in addition to leprosy; but no amyloidosis. It is concluded that the incidence of amyloidosis appears to be lower in India than in Western countries.

D. S. Ridley.

5. (**Serological Tests with Sera from Patients with Lepromatous Leprosy during Periods of Exacerbation**) by G. V. MERTSLIN and V. N. STRUCHKOVA. *Vestnik Dermat. i Venerol.*, Moscow, 1966, **40**, 10, 41-3. (In Russian.) English summary (7 lines).

The author studied serological reactions in 22 patients suffering from lepromatous leprosy, and found that the CFT (in the Mertslin modification) became gradually

negative during effective treatment with antileprosy drugs but usually sharply intensified in exacerbations.

Serological tests for syphilis often become positive in patients suffering from leprosy, and these show a decrease during effective treatment.

W. Odrzywolski.

6. **Classification of Leprosy according to Immunity. A Five-Group System,** by D. S. Ridley and W. H. Jopling. *Inter. J. Lepr.*, Wash., 1966, July-Sept., **34**, 3, 255-73, 21 figs. (20 refs.)

In their summary to this important paper the authors state that:—

'The tuberculoid-lepromatous classification of leprosy is recognized to be an expression of the patient's resistance to the infection. As such its object must be a statement of his resistance.'

Resistance can be assessed by the lepromin test, and indirectly by the therapeutic response in patients who are bacteriologically positive, and by the stability of the infection. The conclusions drawn can be correlated with other features, such as histological findings, suitable for the definition of groups. On this basis 5 groups have been strictly defined.

This system is intended for the use of research workers and those who have full facilities for the investigation of patients. It complements the simple clinical classification that is needed by others.

This is a careful study and should be consulted in the original. The paper is illustrated with 11 clinical photographs and 10 photomicrographs.

J. R. Innes.

7. **The Karimui Trial of BCG. 2. Tuberculin Reactions in a Leprosy-Endemic but Tuberculosis-Free Population,** by G. C. Scott, S. G. Wigley and D. A. Russell. *Inter. J. Lepr.*, Wash., 1966, Apr.-June, **34**, 2, 139-46. (25 refs.)

The authors chose the Karimui area in the Eastern Highlands of the Territory of Papua and New Guinea for a 'blind' controlled trial of the efficacy of BCG as a prophylactic against leprosy because it is an area where leprosy is endemic and tuberculosis is absent (for a preliminary report see this *Bulletin*, 1965, v. 62, 537). Tuberculin surveys indicate that infection with *Mycobacterium tuberculosis* at some time in the past may have resulted in a small number of positive tuberculin reactions. 'Clinical evidence of infection with *M. leprae* is not associated with tuberculin reactivity, nor is presumed latent or inapparent infection, nor the tuberculoid form of the disease when compared to all other types.' The variation in natural tuberculin reactivity is about 1% per annum. Details are given in 6 tables, which include figures showing the tuberculin positivity among members of 'leprous and non-leprous' households, the tuberculin reactivity of persons with and without leprosy and the frequency distribution of the diameter of positive tuberculin reactions by age, sex, leprosy status and membership of a leprous household.

J. R. Innes.

8. **La régression tuberculoïde dans la lèpre lépromateuse** (Tuberculoid Regression in Lepromatous Leprosy), by J. Languillon. *Bull. Soc. Path. Exot.*, 1965, Sept.-Oct., **58**, 5, 780-88. (12 refs.)

The possibility of lepromatous leprosy changing into the tuberculoid form has long intrigued leprologists, and the histological and immunological bases for such a change have been well examined by Wade (*Inter. J. Lepr.*, 1955, v. 23, 443) and others.

After a brief review of the literature, the author describes the clinical history of 5 patients (from the Institut Marchoux, Bamako, Mali), and presents evidence that he considers sufficiently cogent to justify the assertion that 'tuberculoid regression' occurred. All 5 patients had leprosy diagnosed as lepromatous on clinical grounds, but in one the original diagnosis had been indeterminate leprosy with tuberculoid features. In this latter patient the lepromin reaction was slightly positive, varying from 4 to 5 mm. In the remaining 4 patients, the lepromin reaction had initially been negative (the actual diameter of any response occurring not being given), but in 3 of them it became positive (3, 4 and 7 mm. in diameter) after the 'tubreculoid regression' described. A summary of the histological findings suggests that the multibacillary lepra or Virchow cells were replaced by epithelioid and possibly giant cells—supporting evidence of a change in the immunological pattern.

The clinical findings were roughly in keeping with previously reported examples of this phenomenon. After a period of treatment (with sulphamethoxypyridazine sulphamethoxine (3 patients) or injectable thiambutosine) varying from 3 to 20 months, an exacerbation occurred in the existing lepromatous lesions. When the acute inflammatory phase subsided, the lesions became well defined, resembling those of reactional tuberculoid or major tuberculoid leprosy. At the same time the peripheral nerve trunks passed through a phase of enlargement and tenderness, with appropriate neurological results.

With previous writers on the subject, the author attributes the underlying change in clinical and immunological state to the existence in these patients of a latent or potential resistance that was not revealed by the initial lepromin testing. His 'para-lepromatous' classification corresponds to the 'BL' of Ridley and Jopling (see above, abstract no. 6) and the 'lepromatous with borderline features' of other leprologists.

S. G. Browne.

9. **Observations on the Macular Series in African Leprosy,** by S. G. Browne. *Inter. J. Lepr.*, Wash., 1966, Apr.-June, **34**, 2, 175-8.

Completely flat and well-defined leprosy lesions, uniformly hypopigmented and showing some degree of tactile loss, may be pathologically dissimilar. The bacteriological findings vary within wide limits, and the histological appearances may differ likewise. All such lesions might be termed 'macular tuberculoid' if the clinical aspects were the sole criterion.

In Africa, a high proportion of these macular lesions would conform to Leiker's 'low-resistant tuberculoid' form (this *Bulletin*, 1965, v. 62, 760), but some appear to fit better into the Indian 'maculo-anesthetic' description (*ibid.*, 1964, v. 61, 676). Others, again, indistinguishable on purely clinical grounds from these, are in reality far from the tuberculoid pole when the bacteriological and histological findings are taken into consideration.

The proportions of these diverse macular manifestations of leprosy, all non-lepromatous, may vary from country to country. Their pathological interest is matched by their epidemiological importance.

This paper is of particular interest and value, and is recommended for personal perusal.

J. R. Innes.

10. **La mise en évidence des troubles de la sudation dans la lèpre par l'hygrophotographie** (The Demonstration of Disorders of Sweating in Leprosy by Hygrophotography), by H. A. Floch, M. Duchassin and J. Sivadjian *Arch. Inst. Pasteur de la Guyane Française et de l'Inini. Publication No.* 492. 1965, June, 10 pp., 5 figs.

Having mentioned that disorders of sweating are but lightly touched on in works on leprosy, the authors record their experiences in applying the technique of hygrophotography in investigating the sweat pattern of the skin of 17 patients suffering from various kinds of leprosy (Sivadjian, *Anneé Biol.*, 1960, v. 36, 199). They consider this test superior to the tests usually employed (exercise, pilocarpine, histamine, and so forth).

An emulsion of the double iodide of silver and mercury has the property of undergoing a colour change from yellow to black on exposure to light, and of becoming yellow again when in contact with water. A film treated with this emulsion, held in close contact with the skin, will indicate by punctate change of colour (to yellow) the openings of the sweat glands.

The authors found that this demonstration of impaired sweating function showed that in lepromatous leprosy damage to sweat glands might be more widespread than the macules themselves, even in the absence of sensory impairment. In tuberculoid leprosy, the areas of impaired sweating corresponded generally to the visible lesions; but in one patient there was a definite area of impaired sweating that corresponded to no pigmentary or sensory changes apparent in the skin. In such patients, hygrophotography appeared to be a more searching test of early damage to the cutaneous adnexa by leprosy than the usual tests for sensory impairment.

S. G. Browne.

The following 6 abstracts are reprinted with permission from *Trop. Dis. Bull.*, 1967, **64**, 5:

11. **WHO Epidemiologic Random Sample Surveys of Leprosy in Northern Nigeria (Katsina), Cameroon and Thailand (Khon Kaen),** by L. M. Bechelli V. Martinez Dominguez, and K. M. Patwary. *Inter. J. Lepr.*, 1966, **34**, 3, 223-43.

12. **WHO Surveys of Disabilities in Leprosy in Northern Nigeria (Katsina), Cameroon and Thailand (Khon Kaen),** by V. Martinez Dominguez, L. M. Bechelli and K. M. Patwary. *Ibid.*, 244-54.

With a statistician as a member of the 3-man WHO Leprosy Advisory Team, carefully planned surveys of representative areas of 3 countries have been carried out. After a detailed account of the geography and population of each area, the methods are fully delineated. Statistically valid sample sizes were chosen, as detailed in an appendix, and care was taken to ensure that 100% of each sample was examined.

In Cameroon, 14,473 people were examined, in north-east Thailand, 16,568 people and in Katsina, Northern Nigeria, 24,538 people were examined, 500 patients being examined per day. The results are given in 17 tables, and cannot be easily summarized. (Much of the information could have been more effectively presented as histograms.) The prevalence of leprosy per 1,000 inhabitants was found to be 12.37 in north-east Thailand, 25.84 in Cameroon, and 28.73 in Katsina. However, the number of lepromatous patients per 1,000 inhabitants, the 'lepromatous rate', was 4.58 in Thailand, 2.90 in Cameroon and 2.08 in Katsina. In Cameroon, 55.6% of the leprosy patients were diagnosed as having tuberculoid leprosy, in Katsina 48.3%, and in Thailand 38.5%. The leprosy prevalence rate was higher in females in Katsina, higher in males in Cameroon, and in Thailand the rate in males and females was similar. However, males had a significantly higher lepromatous rate than females. An analysis is made of possible reasons for different sex rates. The leprosy prevalence in different age-groups and the age of onset of leprosy in the 3 areas is detailed. The lepromatous rate was found to be much higher in the older age-groups. In the 2 ethnic groups in Katsina no significant difference was found in leprosy prevalence and lepromatous rates.

The frequency and type of leprosy disability was also studied and its relation to the different forms of leprosy, and its frequency in different sex, age and ethnic groups. Disabilities were classified according to the scheme proposed by the Second WHO Expert Committee in Leprosy (this *Bulletin*, 1960, v. 57, 598).

Eleven tables contain the findings and these should be studied in the original. In Katsina, 23.4% of leprosy patients were found to have some kind of disability of the hands, feet or face, which indicates a total of over 100,000 disabled leprosy patients in Northern Nigeria. In Cameroon, 35.6% of leprosy patients had some disability, giving a probable total of 30,000 leprosy disabled in the country. In north-east Thailand 41.5% of leprosy patients had some disability, although 25% suffered only from Grade 1 disability. In Katsina, 37.8% had some hand disability, 10% having partial loss of fingers; 30.4% had some foot disability, 8.7% having plantar ulcers; and 15% had some facial 'disability', 9.4% having nasal collapse, lagophthalmos or considerable loss of vision.

In Cameroon, 43.4% had some hand disability, 33% having partial or gross loss of fingers; 47.9%

had foot disability, 25% having partial or gross loss of the foot; and 14.8% had facial disability, 8% having nasal collapse with or without lagophthalmos. In Thailand, 52.2% had hand disability, 20% having partial finger loss; 55.1% had foot disability, 8.3% having plantar ulcers with or without some foot paralysis; and 33.9% had facial disability, 10% having lagophthalmos. No involvement of the larynx was found in Cameroon or Thailand, and only 0.9% in Nigeria. In Thailand, pure neural patients were relatively frequent, although in some of these patients leprosy bacilli were found in smears from ear lobes. Disabilities were slightly more frequent in males; and much more frequent in older people. The considerable economic and social effect of leprosy disabilities is emphasized. The WHO survey team recommend that prevention and treatment of disabilities, at least by simple methods, should be started as soon as possible.

(The application of strict statistical significance tests to leprosy studies is to be welcomed; but a consistent reporting of the value of P, or the level of significance such as in footnote 8, would be clearer than lits of χ^2 when the value of v is not immediately mentioned. These papers merit close study, and many epidemiological opinions can be tested against their findings.)

C. S. Goodwin.

13. **Study of Contacts of Leprosy,** by S. Ghosh and B. K. Das. *Bull. Calcutta Sch. Trop. Med.*, 1966, **14**, 2, 56, 58.

In Calcutta, 1,671 house contacts of 507 'infectious' leprosy patients were examined. Typical leprosy lesions were found in 31 adults and suspicious skin lesions in 407 persons including 103 children. The suspicious skin lesions were scaly 'without complete anaesthesia' and did not itch. Forty-three people with such lesions were able to be examined 'completely', by slit-scrape skin smear in 'ten places, both arms, forearms, thighs, legs, chest, back and suspected lesion'; a biopsy specimen of the lesion was taken and the lepromin test performed. All but 2 of this group were under the age of 17 years. In one of the suspected patches bacilli were found by skin smear; and in a further 7 cases bacilli were found by a concentration method by chloroform extraction of the skin biopsy specimen. The lepromin reaction was positive in 26 subjects. Histologically, cellular infiltration with epineural infiltration was found in the 8 bacteriologically positive persons and in one further subject who was lepromin-negative. Forty-two contacts with no skin lesions were examined completely, all but 6 being aged less than 17 years. Skin smears revealed no acid-fast bacilli, but by the concentration method, a few acid-fast bacilli were found in 17 cases (40%). The lepromin reaction was positive in these 17 subject and also in a further 6. Skin biopsy specimens from the left arm revealed a variation from the normal histological picture in 13 persons, all lepromin-positive.

C. S. Goodwin.

14. **Pure Polyneuritic Leprosy of Tuberculoid Type,** by Dharmendra and K. Ramanujam. *Lepr. India*, 1966, **38**, 3, 152-8.

Full case reports including histological findings in nerves of 4 patients with polyneuritic tuberculoid leprosy with no skin lesions are presented. While admitting that the first published full description of a patient of pure neural tuberculoid leprosy was by Jopling and Morgan-Hughes (this *Bulletin*, 1966, v. 63, 166), the authors emphasize that pure polyneuritic leprosy has been recognized by Indian leprologists in their classification since 1953. Three of the 4 patients had nerve involvement both in the arms and the legs; the lateral popliteal, the ulnar, median and superficial radial nerves were most frequently affected. A history of anaesthesia or paralysis, together with thickening of the nerve was found (but in one patient with scars of nerve abscesses no sensory or motor loss is mentioned). It is concluded that histological confirmation of pure polyneuritic leprosy is unnecessary (although in the first case reported it was essential). The lepromin reaction is considered to indicate the classification when a clinical diagnosis is made (but clearer reporting of the reaction is desirable —namely, the exact days of reading and the diameter of the infiltration).

These instructive case reports are a welcome addition to the literature on pure neural leprosy.

C. S. Goodwin.

15. **A terramicina na lepra** (Terramycin in Leprosy, D. V. A. Opromolla, J. P. Mendes and L. de Souza Lima *Revta Bras. Leprol.*, 1965, **33**, 1/4, 3-21, 5 coloured figs. on 4 pls. English summary.

The authors report on oxytetracycline (Terramycin) in the treatment of lepromatous leprosy in Brazil. In addition to their case notes they give some excellent figures which are in effect colour photographs. They gave their 22 patients treatment by the intramuscular route of injections of 100 mgm. every 12 hours for about 12 months, and initial dermatological examination and histological examination of biopsies at regular intervals. The results were very good. Sixteen nasal smears were positive before treatment but only one was positive at the final examination. In nearly all the skin smears the bacillary index was reduced.

J. R. Innes.

16. **Tratamento sintomático da reação leprótica com o sulfato de hidroxicloroquina** (Symptomatic Treatment of Lepra Reaction by Hydroxychloroquine Sulphate), by N. Proença. *Revta Bras. Leprol.*, 1965, **33**, 1 4, 35-44. English summary.

The author investigated the action of hydroxychloroquine sulphate in the treatment of lepra reaction and in spite of numerous favourable references in the literature to the action of antimalarial drugs was unable to show positive results.

J. R. Innes.

The following 4 abstracts are reprinted with permission from *Trop. Dis. Bull.*, 1967, **64**, 6:

17. **Traitement de la maladie de Hansen par la sulforthomidine** (The treatment of Hansen's disease with sulphormethoxine), by J. LANGUILLON. *Méd. Trop.*, 1966, **26**, 4, 331-41.

The author treated 25 leprosy patients with sulphormethoxine (Fanasil, sulphorthomidine). All were untreated and suffering from active disease. Thirteen patients with bacillary positive lepromatous leprosy (of whom 2 were probably suffering from the borderline type, to judge from response to treatment) were given the drug for 36 months; of 12 with tuberculoid leprosy (6 major and 6 minor), 9 had treatment for 36 months and 3 for 24 months. A dose of 1.50 gm. weekly was found to be necessary to maintain a hypothetically desirable blood level of 30 mgm. per litre.

All the 12 patients suffering from tuberculoid leprosy were assessed as clinically cured at the end of the treatment. All 13 with lepromatous leprosy were greatly improved, both clinically and bacteriologically. In 11 patients, the nasal mucosa became bacteriologically negative, and in 7 the skin. The disease in 7 patients was considered to be 'arrested'.

Acute exacerbation taking the form of erythema nodosum leprosum or acute ulnar neuritis occurred in 5 patients, but in each instance the condition was rapidly controlled without interruption of treatment. The drug was well tolerated.

The author concludes that this product given orally at a weekly dose of 1.50 gm. is suitable for mass treatment.

S. G. Browne.

18. **Studies on sulfone resistance in leprosy,** by J. H. S. PETTIT, R. J. W. REES and D. S. RIDLEY. **1. Detection of cases** (PETTIT, REES and RIDLEY), *Inter. J. Lepr.*, 1966, **34**, 4, 375-90. **2. Treatment with a riminophenazine derivative** (B663) (PETTIT and REES). *Ibid.*, 391-7.

1. The authors made an extensive search in one of the biggest leprosaria in the world, namely Sungei Buloh, and discovered evidence of 9 patients with lepromatous leprosy who displayed resistance to sulphone treatment, shown by an absence of a satisfactory fall in the bacterial index and in the morphological index. The patients were studied in an investigation unit at which special attention was given to an injectable form of sulphone (300 mgm. twice a week) and also to tests of sensitivity to DDS by the mouse footpaid method. The period of the tests was 6 months. Only 4 of the patients failed to respond satisfactorily. It was found that only the strains of *Mycobacterium leprae* in the 4 patients who failed to improve were insensitive to DDS and that the histological picture in patients with drug resistance was essentially that of relapsing leprosy or very acute leprosy.

2. In the second part of the paper the authors report that when 3 of the patients with proved DDS-resistant leprosy infections were treated for one year with the riminophenazine derivative B663 (300 mgm. daily for 6 days a week) all slowed clinical, bacteriological and histological improvement which has been maintained for 28 months. The results show that active leprosy resulting from resistance to one drug can still respond satisfactorily to a different type of drug as is the case with drug resistance in other bacterial infections. In this limited study B663 showed no toxicity but the degree of skin discoloration was disconcerting in Chinese patients.

These papers are of great interest and value and should be studied in the original.

J. R. Innes.

19. **Sur la chimiorésistance du bacille de Hansen et le traitement de la lèpre par des associations médicamenteuses** (Chemoresistance of Hansen's bacillus and treatment of leprosy with combinations of drugs), by H. A. FLOCH. *Bull. Soc. Path. Exot.*, 1966, **59**, 2, 188-92.

The author repeats the opinion that he, in common with other workers, reached some years ago that on clinical grounds resistance to drugs used in leprosy was by no means uncommon. Without referring to the recent conclusive demonstration of dapsone-resistance by means of the mouse foot-pad inoculation technique (this *Bulletin*. 1965, v. 62, 108), he suggests that—on analogy with therapy in other conditions—combinations of drugs should be used wherever possible against multibacillary leprosy in order to prevent the emergence of drug-resistant strains. He suggests that excellent results are obtainable by giving, in addition to dapsone, such drugs as thiambutosine, long-acting sulphonamides, thiacetazone or an antibiotic (cycloserine, streptomycin or rifamycin). (No supporting evidence is adduced for the conclusions reached, but the author's practical advice should be heeded.)

S. G. Browne.

20. **Use of corticosteroids in persistent 'lepra reaction',** by S. KUNDU and S. GHOSH. *Bull. Calcutta Sch. Trop. Med.*, 1966, **14**, 1, 16-17.

Eighteen highly bacilliferous patients with 'persistent' leprosy reactional episodes which were uncontrolled by intravenous antimonials were treated with betamethasone, 2 mgm. daily, in divided doses, for the first week, 1.5 mgm. daily for the second, 1.0 mgm. for the third week and then 0.5 mgm. daily 'till the reaction was well controlled in about 4-6 weeks'. In all the patients there was remission of fever, subsidence of skin lesions and limb swelling, and marked symptomatic relief. The 'reaction was controlled within 7-10 days', at which time 50% aqueous sulphetrone injections, 0.25 ml., were started bi-weekly 'till 6 such'. The sulphetrone was increased by 0.25 ml. every second week to a final dose of 2.5 ml. or 4 ml. When the final dose of sulphetrone was achieved 'the dosage of prednisolone was gradually reduced and ultimately the drug was discontinued'. (There is no previous mention of prednisolone, and the dosage schemes described are contradictory.) The only side-effect of betamethasone was 'heaviness of the body', and it is stated that complete adrenal suppression was not produced. It is concluded that betamethasone effectively controls lepra reaction and allows the re-introduction of sulphone therapy.

C. S. Goodwin.

(1967)

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