

LEPROSY REVIEW

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VOL. XXXII. No. 3

JULY 1961

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Letters to the Editor
Abstracts
Reports
Review

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Edited by DR. J. ROSS INNES, Medical Secretary of the British Leprosy Relief Association, 8 Portman Street, London, W.1, to whom all communications should be sent. The Association does not accept any responsibility for views expressed by writers.

Contributors of original articles will receive 25 loose reprints free, but more formal bound reprints must be ordered at time of submitting the article, and the cost reimbursed later.

EDITORIAL

1. First Mexican Congress of Dermatology

Dr. Fernando Latapí, Secretary of the Mexican Society of Dermatology, informs us that this Society will celebrate the 25th anniversary of its foundation in September 1961 and in honour of this is organizing the First Mexican Congress of Dermatology to take place 30 August to 2 September. The themes of the Congress will be: Dermatology in Mexico, Therapeutics in Dermatology, Surgery of the Skin, Tropical Dermatology (with presentation of clinical cases) and certain free themes. There will also be a session devoted to the most common skin diseases in Mexico and their relation to general medicine. The President of the Congress will be Dr. F. Latapí, the Vice-President Dr. P. Lavalle, the Secretary Dr. A. Saúl, and the Treasurer Dr. J. Peniche. All correspondence should be directed to PASCUA DERMATOLOGY CENTRE, Dr. Garciadiego Street No. 21, Mexico 7, D.F.

2. Decorations for Leprologists in Brazil

By Decree of 2.12.60 the President of the Republic of Brazil, Dr. JUSCELINO KUBITSCHKE DE OLIVEIRA, M.D. decorated as Officers of the National Order of Medical Merit the following leprologists and sanitarian co-workers in Leprosy Control in Brazil:

Dr. ANTONIO GONÇALVES PERYASSU, the famous entomologist who intensified leprosy control as Delegate of Federal Public Health in Pará; Dr. FRANCISCO E. A. RABELLO, the creator of the concept of polar classification in leprosy at the Cairo Congress of 1938; Dr. HERACLIDES C. DE SOUZA-ARAÚJO who has worked since 1915 in the study, control, and teaching of leprosy in Brazil; Dr. JANDUHY CARNEIRO, author of the project for the National Campaign against Leprosy; Dr. JOSÉ P. B. COSTA who as director of health of the state of Rio Grande do Sul founded the Itapoan leprosarium; Dr. LAFAYETTE DE FREITAS who as director of rural sanitation intensified leprosy control in various states; Dr. MAYA FAILLACE, technician in leprosy of the public health department of the state of Rio Grande do Sul; Dr. ORESTES DINIZ, director of the national leprosy service; Dr. SAMUEL LIBANIO who founded the Santa Isabel Leprosarium when director of health of the state of Minas Gerais; Dr. THEOPHILO DE ALMEIDA who was first director of Curupaity leprosarium, Rio de Janeiro (1928–1940). The Decree ascribes the honour to “their notable and relevant services done on behalf of the national public health”. By another Decree of December 1960 the President extended the same decoration to Dr. HOWARD WINDSOR WADE, President of the International Leprosy Association.

In addition, Dr. H. C. de Souza-Araújo, who kindly supplied the above information, has given the present day staffing in public health as follows:

Ministry of Health:	Dr. CATETE PINHEIRO, M.D., M.P.H.
Director of Health:	Dr. BICHAT RODRIGUES, M.D., C.P.H.
Director of the National Leprosy Service:	Dr. JOAO BAPTISTA RISI, M.D., C.P.H.
	Address: Rua São Cristóvão 1298, Rio de Janeiro, E.G.
Chief of Institute of Leprology:	Dr. CANDIDO SILVA, M.D., C.P.H.
Chief of Central Dispensary:	Dr. AVELINO MIGUEZ ALONSO, M.D.

THE DISTRIBUTION OF 35S-LABELLED ETISUL IN THE SKIN AS INDICATED BY AUTORADIOGRAPHY

by D. G. JAMISON and ELISABETH PALMER
(*Department of Human Anatomy, Oxford*)

The treatment of tuberculosis with "Etisul" (diethyl dithiol isophthalate) was shown by Davies and Driver (1956/7) to be highly successful and this suggested that it might also be useful in the treatment of leprosy. The initial clinical trials in cases with leprosy were carried out by Davey and Hogerzeil (1959) by inunction through the skin and they found the drug to be a useful chemo-therapeutic agent. Although it has not proved to be universally successful in the treatment of all cases and has certain drawbacks, there is no doubt that it has a place in the treatment of leprosy at the moment. For this reason it was considered worth while to determine whether one or more of the tissue components in the skin had a particular affinity for the drug. The work of Snow (1959) has established that 35S-labelled diethyl disulphide can be detected in all body tissues by the assay method after either subcutaneous injection or oral administration in mice and guinea pigs. To map the distribution of "Etisul" in human skin a 35S-labelled preparation was used in the treatment of four patients with leprosy and skin biopsies taken at various intervals following its inunction. These were sectioned in a plane vertical to the surface and the position of the radio-active molecules determined in relation to the various skin layers (and the tissue elements within them) by autoradiography.

Material

Four cases of leprosy with commonly encountered forms of the disease were selected from among the leprosy patients of the Sudan Interior Mission leprosy settlement in Katsina, Northern Nigeria. Three of the cases were under treatment with dapsone and one with sulphetrone and all appeared to be responding more or less satisfactorily to treatment as judged clinically. None had as yet been treated with "Etisul".

Case 1. (No. 130)

A male aged 30 who was admitted with dimorphous leprosy in 1956 and, despite treatment, in 1959 his ulnar had become sufficiently involved to require neurolysis.

Case 2. (No. 131)

A male aged 38 who was admitted with multiple dimorphous patches in 1960.

Case 3. (No. 132)

A male aged 25 who was admitted 3 months previously with a single hypo-pigmented patch over his face which had almost completely disappeared at the time of examination.

Case 4. (No. 133)

A male aged 27 who was admitted in 1955 with lepromatous leprosy. His response to treatment was low and he went into "reaction" as soon as the dose of dapsone was increased sufficiently to become effective. For this reason sulphetrone therapy had to be substituted in 1959.

Method of Treatment with "Etisul"

The skin covering the arm and forearm on one side of the body was scrubbed for 10 minutes with a soft nailbrush in soap and water. It was then examined clinically. Skin lesions of any kind were recorded and the state of the ulnar, median and radial nerves was determined by palpation. A suitable area was chosen for taking biopsies and the sensory activity of the skin carefully determined. 4.6 ml of "Etisul" containing 50 μ C of 35S was then brushed over the shoulder, the extensor surfaces of the arm, forearm and hand. The concentration of 35S was well within the limits of safety laid down by the International Commission for Radiological Protection, according to which 100 μ C of 35S is the maximum permissible dose, assuming that 10% of the initial dose will be concentrated in the skin.

3 four-millimeter punch biopsies were taken from each patient at 3, 6, and 24 hours after the application and fixed in neutral formalin for 13 days. Each specimen was then cut in half: one half being embedded in wax and cut into sections which were stained either with haematoxylin and eosin or with carbol-fuchsin by the Fite-Faraco method. The other half was cut on a freezing microtome into a series of 50 sections which were mounted serially, alternate sections being prepared for autoradiography and silver-staining for nerve fibres. The sections destined for autoradiography were briefly washed in distilled water and transferred to microscope slides on which there was a thin layer of gelatine and allowed to dry. They were then covered with Kodak autoradiographic Stripping, AR.10, and left in the dark for periods of 1, 2, 6 and 8 weeks, then developed, fixed and stained with either haematoxylin or toluidin blue.

Observations

For the purpose of this investigation skin was removed from a selected (standard) area on the back of the forearm in every patient so that the basic histological and neurological patterns would be as comparable as possible from one case to another.

PLATE I

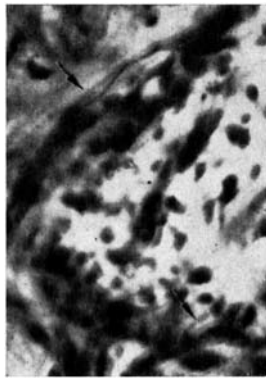


FIG. 1



FIG. 2

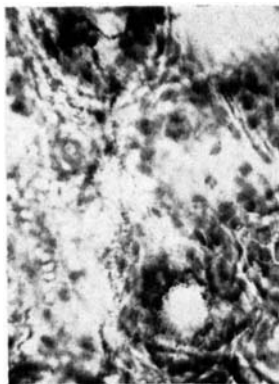


FIG. 3

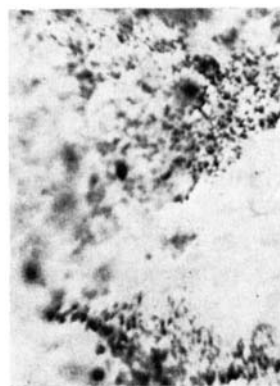


FIG. 4

- FIG. 1 Case 1 (130) A single nerve fibre accompanied by large Schwann nuclei in an enlarged sheath of Schwann. 50 μ section, stained Bielschowsky Schofield. x 550
- FIG. 2 Case 1 (130) Autoradiograph of a hairshaft, cut slightly obliquely, showing an accumulation of silver particles between the shaft and the external root sheath in a section from a biopsy 3 hours after treatment. x 550
- FIG. 3 Case 2 (131) Autoradiographs of the sweat gland ducts, cut transversely, the lumen and some of the cells outlined by silver particles. Some silver particles are also outlining cells in the connective tissue around the ducts. Section from a biopsy taken 24 hours after treatment. x 550
- FIG. 4 Case 3 (132) Autoradiograph from a skin biopsy taken 3 hours after treatment. Silver particles are concentrated over the outer root sheath and are also seen outlining individual cells. x 1300

Case 1

At the time of examination the patient appeared in good health and had no signs of "reaction" to the dapsone he was taking. Following the stripping of his ulnar nerve 9 months previously there had been a steady improvement in the strength of his hand and at the time of examination only slight weakness and wasting of the ulnar muscles was observed. However, sensory acuity was considerably diminished over the dorsal surface of his forearm. The biopsy was taken from the area already selected as standard. This removed skin showed no outward signs of disease whatever. In sections stained with haematoxylin/eosin however there was a sub-epidermal cellular infiltrate and the neuro-vascular bundles were heavily infiltrated with cells, as were the skin structures related to skin appendages. The infiltrate was composed of epithelioid cells, plasma cells and lymphocytes. In some portions of the neurovascular bundles there was connective tissue proliferation and aggregations of fibroblasts. In the section stained with carbolfuchsin there were no acid-fast bacilli to be seen. In the sections stained with silver many regenerating nerve fibres were to be seen but relatively few degenerating ones. The Schwann sheath and the Schwann nuclei were enlarged (Fig. 1).

The autoradiographs made from sections of the biopsy taken three hours after application of 35S-labelled Etisul revealed that radio-active particles had been concentrated between the hair shaft and the external root sheath (Fig. 2) and in mast cells accompanying the superficial blood vessels just beneath the epidermis. In section from biopsies taken 6 hours after application the radio-active particles had concentrated in the cells composing the sub-epidermal infiltrate and also in the cells forming the coils and ducts of the sweat glands. In sections taken 24 hours after application the radio-active particles were again seen concentrated in the cells of the sub-epidermal infiltrate, as well as those surrounding the neuro-vascular bundles. Concentrations of radio-active particles were also seen in the cells composing the outer root sheath of hair follicles and on the whole activity was greater than in the two previous biopsies.

Case 2

This patient still had a depigmented macule on the extensor surface of his left forearm but the majority of those present on admission were now no longer visible. Sensory testing showed that the area of depigmentation on the back of the left forearm was completely anaesthetic to light touch.

The sections from the biopsy taken from the selected zone of the forearm (which happened to be within the depigmented area) stained with haematoxylin/eosin showed small patches of sub-epidermal infiltrate as a slight aggregation of cells around the neurovascular

bundles. The sub-epidermal infiltrate consisted mainly of macrophages containing melanin granules as well as numerous mast cells. No acid-fast bacilli were seen in the sections stained with carbol fuchsin. The sections stained with silver that there were no nerve fibres just beneath the epidermis and in the deeper layer of the dermis there were seen nerve bundles containing only fine axons and many empty Schwann tubes.

The autoradiographs made from sections of the biopsy taken three hours after the application of ³⁵S-labelled Etisul showed that there had been a concentration of radio-active particles throughout the sub-epidermal region which contained the cellular infiltrate and also to a lesser extent in the connective tissue zones which contained no adventitial cells. In the autoradiographs from sections taken 6 hours after treatment, radio-active particles were most concentrated in tissue mast cells in the dermis and in cells forming the sweat gland coils in the deeper layers of the dermis. At 24 hours after treatment radio-active particles were found to be denser in the cells of the sub-epidermal infiltrate than had been the case in sections from the two previous biopsies, and particles were again concentrated in the cells of the coils and ducts of the sweat glands (Fig. 3).

Case 3

The patch on the patient's face was only just visible and no other clinical signs of leprosy could be detected. Sensory tests over the back of the right forearm showed a slight but significant degree of misreference when compared with that found in this region in average normal subjects, but there was no anaesthesia to light touch. Sections from the biopsy stained with haematoxylin/eosin showed that there was a small increase in the number of cells surrounding all the neuro-vascular bundles in the dermis; those stained with silver showed a full complement of nerve fibres but the Schwann cells were larger than normal. Some of the deeper nerve bundles contained a few fine axons which had clearly regenerated and they also contained a number of empty Schwann tubes. No acid-fast bacilli were seen in the carbol-fuchsin stained sections.

The autoradiographs from sections of the biopsy taken 3 hours after treatment showed that there was a concentration of radio-active particles surrounding the shaft of the hair itself, but there was also a concentration around the cells forming the outer root sheath (Fig. 4) and the individual cells were outlined by particles of exposed silver. After 6 hours treatment biopsies showed that radio-activity was almost entirely confined in and around mast cells and other cells seen in the connective tissue forming the dermis. After 24 hours treatment the picture was similar but the concentration of radio-active particles was far denser. In addition, radio-active particles

PLATE II

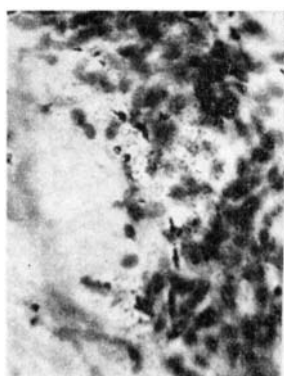


FIG. 5

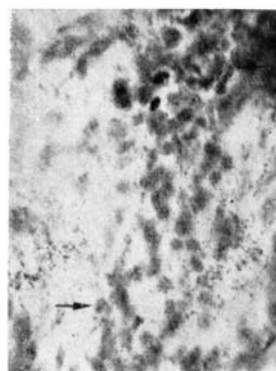


FIG. 6

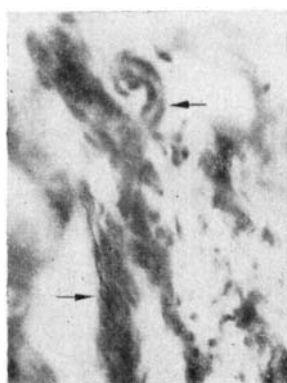


FIG. 7

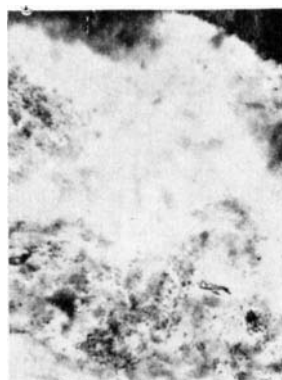


FIG. 8

- FIG. 5 Case 3 (132) An autoradiograph from a skin biopsy taken 24 hours after treatment. Silver particles are seen above the cells forming the infiltrate in the dermis. x 550
- FIG. 6 Case 3 (132) Autoradiograph from a skin biopsy taken 24 hours after treatment. The silver particles are concentrated above the nerve bundle and the cells forming the neuro-vascular infiltrate. x 550
- FIG. 7 Case 3 (132) The adjoining section to that shown in Fig. 6. The silver-stained preparation shows the same nerve bundle and its position in the infiltrate. x 550
- FIG. 8 Case 4 (133) Autoradiograph from a skin biopsy taken 24 hours after treatment. Silver particles are clearly seen above the lepromatous infiltrate in the sub-epidermis. x 550

were now seen to be concentrated in large numbers in the ducts leading from the sweat glands and also in the cells forming the infiltrate surrounding these ducts.

Case 4

On examination, this case showed signs of diffuse lepromatous infiltration and he had no generalized reaction to sulphetrone. Sensory testing over the back of the forearm showed no diminution of sensory acuity.

Sections from the biopsy stained with haematoxylin/eosin showed heavy infiltration of cells around the neuro-vascular bundles and around the tissues of the skin appendages. The infiltrate was particularly dense around the sweat gland cells of the deeper dermis and the infiltrate consisted chiefly of plasma cells, lymphocytes, mast cells and fibrocytes. In some zones of the infiltrate collagen fibres had been laid down. No acid-fast bacilli were seen in the sections stained with carbol-fuchsin. Sections stained with silver showed that the skin was supplied with a normal complement of nerve fibres throughout.

Autoradiographs from biopsies taken 3 hours after treatment showed that there had been little concentration of radio-active particles in the sub-epidermal tissues or in relation to the ducts of the sweat glands. 6 hours after treatment the picture had not changed appreciably, except that the radio-active particles were now more concentrated in the sub-epidermal region. 24 hours after treatment the radio-active particles were seen densely concentrated in and around the cells forming the infiltrate around the neuro-vascular bundles and fewer particles were seen in the cells forming the infiltrate deeper in the dermis (Fig. 5).

In an attempt to follow the distribution of radio-active particles in the skin 48 hours after treatment further biopsies were taken from the standard region on the treated side and a single specimen was also taken from the contra-lateral side of the body. Radio-active particles were present in small numbers in the cells surrounding the neuro-vascular bundles on the untreated side and on the treated side particles were also present in the cells of the sweat gland coils and the cells surrounding the neuro-vascular bundles in the deep dermis.

Discussion

It is known that the thickness of the epidermis varies greatly from one part of the body to another and it also seems probable that there are slight variations related to sex and age in any given region, but these are not very extensive. Because of this we chose a standard area of skin taken from males between the ages of 25 and 37 years. The site chosen was the extensor surface of the forearm where the

epidermal thickness is fairly uniform throughout, and the density of innervation is also uniform.

In each case the 35S-labelled Etisul was applied by brush only from the shoulder to the back of the hand and the liquid allowed to penetrate the skin without additional inunction. Care was taken to prevent loss of Etisul by keeping the patients out of the sun to prevent sweating and keeping the arm completely at rest in a horizontal position for 20 minutes following the application of the drug. At the end of this time the liquid had disappeared from the surface of the skin.

In Fig. 2 which is from a section of a biopsy taken three hours after the application of the drug, there is a large concentration of "exposed" silver particles between the hair shaft and the external root sheath close to the epidermis. In other sections taken after a comparable time interval following application of the drug small concentration of exposed silver particles were found in the sub-epidermal region. This suggests that the drug enters the skin directly through the epidermis and possibly by passing down beside the hair shafts emerging through the epidermis.

Six hours after application of the drug the radio-active particles had become more concentrated in mast cells and in the connective tissue elements composing the infiltrate. It appeared that the concentration of radio-activity was always greatest in the regions where there was reason to suppose that cells were actively accumulating or multiplying.

In cases 132 and 133, in which the sub-epidermal nerve plexus was present, it was possible to show that in sections from biopsies taken 24 hours after treatment there was a concentration of "exposed" silver particles in the position occupied by these nerve bundles. Since they were surrounded by adventitial cells it was not possible to determine the relationship between the particles and any particular nerve element (Figs. 6 and 7).

Twenty-four hours after application of the drug radio-active particles were much more concentrated in and around the adventitial cells characteristic of leprosy in the skin (Fig. 8). They had also been in high concentration in the cells and lumen of the sweat gland ducts. This was also the case after 48 hours. These findings suggest that radio-active particles contained in the drug are partly excreted in the sweat, but some must enter the bloodstream to appear on the opposite side of the body after 48 hours. Lechat (1960) found that Etisul was excreted in the sweat for up to two days after its initial application and this fits in well with our own observations.

The rapid penetration of radio-active sulphur into the skin and its selective localisation in the pathological zones parallels our clinical findings with unlabelled Etisul. In biopsies which we examined from patients under treatment with this drug (Jamison, Palmer and Vollum

1961) it was the rapid reduction in the number of cells surrounding the neuro-vascular bundles which was so noticeable.

The radio-active Etisul used in this investigation was generously supplied by the Imperial Chemical Industries Ltd.

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TRIAL OF A VASODILATOR ON TROPHIC ULCERS.

By E. P. VAIDYANATHAN, M.B.B.S.

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Polambakkam, South India*

Introduction

We are faced with the problem of treating plantar trophic ulcers in leprosy. These cases occupy a larger number of hospital beds than cases such as lepra reaction or any other concurrent disease.

Treatments of the ulcers are many according to the extent of the lesion, discharge from the ulcer, and the involvement of the underlying bone. Ulcers without discharge or involvement of bone can successfully be treated with full cast plaster of paris bandage to the leg applied at the roadside clinic itself, but patients having chronic recurrent ulcers with marked oedema of the foot and serious discharge cannot be treated with plaster of paris immobilisation and they need prolonged hospitalisation and special treatment.

It is known that sclerosis and fibrosis lead to extra-vascular compression and narrowing of the blood vessels in the region of the trophic ulcers. DHARMENDRA, SEN, & CHATTERJI² hold that diminution in the blood supply is a fundamental cause of persistent ulceration.

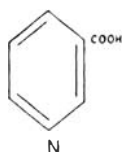
LAURET and KERBASTARD³ treated 17 perforating ulcers with trichloroacetic acid and salicylic acid externally and intravenous injection of Dycholium (dehydrocholate of sodium). They attribute the good results to the antiseptic and epithelial softening actions of the acid and the vasodilatation brought about by the bile salts.

PATERSON⁴ from a series of angiographs concluded that there is dilatation of the arteriovenous shunts and sometimes there is defective filling of the digital arteries due to short circuit of blood.

Hence it was felt that any drug which would increase the blood flow to the affected part might promote quicker healing of these ulcers. This led me to the trial of nicotinic acid, a vasodilator drug, in the treatment of plantar trophic ulcers which forms the subject of this paper.

Pharmacology

Pyridine B—carboxylic acid is nicotinic acid having the following formula:



Nicotinic acid is capable of producing marked vasodilation particularly of the capillary bed.

For the purpose of this trial Pelonin of the Glaxo laboratories was used.

Selection of material for study

Each case was selected on the following criterion:

Secondary infection and bony involvement were absent and the ulcers had serous discharge.

The patients were of all types of leprosy and all of them were on sulphone treatment.

The method

The patient was seated on a high stool with the leg hanging down and a pneumatic cuff of the sphygmomanometer was applied over the thigh at a pressure of 110 mg. of mercury. 100 mg. of nicotinic acid, i.e., two ampoules of 50 mg. Pelonin, each ampoule containing 2 ml. was injected into the long saphenous vein in the leg which had the ulcer, keeping the pneumatic tourniquet on for five minutes to prevent the drug from flowing proximally. The treatment was given only thrice weekly and the ulcers were dressed with dry sterile gauze on alternate days. The patients were not strictly confined to bed. They were not aware that a trial was being made.

As a control, a few cases were given 4 ml. of distilled water intravenously, instead of Pelonin.

The blood pressures of the individuals were recorded before and after the administration of the drug.

Results

In the nicotinic acid group, out of 18 ulcers, 4 healed within 10 days, 8 healed within 22 days, 3 healed in 30 days and the rest within 60 days. Whereas in the control group with distilled water, out of 9 ulcers, only 2 healed within 30 days and the rest did not show any sign of improvement even after 30 days.

Nicotinic acid group—See table I.

Control group—See table II.

TABLE I

<i>S. No.</i>	<i>Name</i>	<i>Sex and Age</i>	<i>Type</i>	<i>Site of ulcer</i>	<i>Size of ulcer (Length × Breadth × Depth)</i>	<i>Duration of Ulcer</i>	<i>Duration of Treatment</i>	<i>No. of Injections given</i>	<i>Remark</i>
1	S.	Male/30	Polyneuritic	Lateral edge of foot 4th and 5th metatarsals	4 cm × 3 cm × 1 cm	3 years	60 days	24	Healed
2	C.	Male/60	Polyneuritic	Head of 2nd metatarsal	2 cm × 2 cm × 5 mm	1 year	11 days	5	..
3	V.	Female/37	Polyneuritic	Heads 2nd, 3rd and 4th metatarsals	3 cm × 2 cm × 1 cm	9 months	41 days	15	..
4	L.	Male/25	Tuberculoid	Head of 2nd metatarsal	4 mm × 3 mm × 2 mm	7 months	30 days	12	..
				Head of 5th metatarsal	1 cm × 1 cm × 1 mm	7 months	20 days	9	..
5	A.	Male/29	Polyneuritic	Head of 1st metatarsal (New)	1.5cm × 1.5cm × 9 mm	6 months	25 days	10	..
6	A.	Male/35	Borderline	Head of 1st metatarsal	2.5cm × 2.5cm × 2 cm	5 months	22 days	9	..
				Heads 3rd, 4th metatarsals	2.5cm × 2.5cm × 1 cm	4 months	14 days	6	..
7	S.	Male/16	Borderline	Heads of 3rd, 4th metatarsals	1 cm × 1 cm × 1 cm	3 months	23 days	9	..
8	K.	Male/15	Indeterminate	Head of 2nd metatarsal	2 cm × 1.5cm × 1 cm	2 months	16 days	7	..
9	D.	Male/43	Lepromatous	Head of 1st metatarsal	1 mm × 1 mm × 1 cm	2 months	10 days	4	..
10	P.	Female/28	Tuberculoid	Shaft of 5th metatarsal and Heel	2 cm × 2 cm × 1 mm	2 months	7 days	3	..
					2 cm × 2 cm × 2 mm	30 days	10 days	4	..
11	K.	Male/35	Lepromatous	Base of terminals phalanx of great toe	1 cm × 1 cm × 1 mm	2 months	33 days	13	..
12	D.	Male/32	Tuberculoid	Head of 2nd metatarsal (New)	1.3cm × 1 cm × 1 cm	2 months	5 days	2	..
13	C.	Male/39	Lepromatous	Heads of 4th, 5th metatarsals	3 cm × 2 cm × 1.5cm	2 months	45 days	16	..
14	A.	Male/31	Tuberculoid	Base of terminal phalanx of great toe	2.6cm × 1.9cm × 1 cm	45 days	19 days	8	..
15	K.	Male/36	Tuberculoid	Base of terminal phalanx of great toe	1.5cm × 1 mm × 2 mm	45 days	14 days	6	..

Side effects

Soon after releasing the cuff, in the nicotinic acid group, all of them had flushing and some had gastric discomfort, which lasted for a few minutes.

Discussion and conclusions

The results with nicotinic acid were encouraging. Fresh crops of healthy granulation tissue were seen sprouting up in the ulcers on the third day. As seen in table I, ulcers of short duration and the first ulcers healed rapidly. 11 patients who were admitted for skin diseases who had also ulcers without bony involvement were given Pelonin 100 mg. daily orally as part of their treatment for the skin disease. It was noted that these ulcers took on an average about two months to heal in spite of local dressings. CAVER¹ tried Roniacol, a vasodilator orally in 3 plantar ulcers and found no significant improvement. Ulcers treated with distilled water also took a long time to heal and healthy granulation tissue as seen in ulcers treated with nicotinic acid was not present.

These findings lead me to conclude that:

1. Vasodilatation plays a greater part than previously thought in healing of the ulcers.
2. Nicotinic acid is a useful drug for the treatment of plantar ulcers.
3. Nicotinic acid given intravenously has a better effect than administered orally.

Summary

1. A vasodilator, nicotinic acid (Pelonin) was tried intravenously for the treatment of plantar trophic ulcers without local dressings.
2. 15 persons with 18 ulcers were put on nicotinic acid.
3. 5 persons with 9 ulcers were kept as control with distilled water injections.
4. 11 cases were treated with nicotinic acid orally.
5. Healing of the ulcers were quicker in the nicotinic acid group (intravenous), and the first ulcers more rapidly.

Acknowledgment

Grateful thanks are due to Dr. (Miss) C. Vellut, Medical Officer in charge, for supplying the drug for trial and permitting me to publish this article. Thanks are due to Dr. K. Ramanujam of Madras for his useful suggestions, criticisms and comments.

I am also thankful to the staff of this centre who helped me and to the patients without whose co-operation this work would not have been possible.

TABLE II
(CONTROL GROUP)

<i>S. No.</i>	<i>Name</i>	<i>Sex and Age</i>	<i>Type</i>	<i>Site of ulcer</i>	<i>Size of ulcer (Length × Breadth × Depth)</i>	<i>Duration of Ulcer</i>	<i>Duration of Treatment</i>	<i>Remark</i>
1	S.	Male/38	Lepromatous	Head of 1st metatarsal	2 cm × 1 cm × 2 mm	20 days	60 days	Not healed
2	M.	Male/42	Lepromatous	Head of 3rd metatarsal	2 cm × 2 cm × 1 mm	6 months	45 days	„
				Head of 1st metatarsal	2 cm × 2 cm × 3 mm	2 months	30 days	„
				Shaft of 3rd metatarsal	1 mm × 1 mm × 0.2cm	2 months	30 days	„
3	P.	Male/40	Tuberculoid	Head of 2nd metatarsal	1.5cm × 1 cm × 1 cm	6 months	60 days	„
				Heel	2.5cm × 2 cm × 2 cm	6 months	60 days	„
4	M.	Male/45	Tuberculoid	Head of 5th metatarsal (New)	1 cm × 2 cm × 0.2cm	1 month	28 days	Healed
5	G.	Male/39	Tuberculoid	Head of 1st metatarsal (New)	3 cm × 3 cm × 2 mm	1 month	30 days	Not healed
				Head of 5th metatarsal (New)	2 cm × 1.5cm × 1 mm	1 month	30 days	Healed

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PRELIMINARY NOTE ON A SERIES OF CASES OF LEPROMATOUS LEPROSY TREATED WITH ETISUL

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A considerable amount of work and experience has been built up in various countries in the use of Etisul by inunction particularly in lepromatous leprosy. Hitherto this work has been limited by the high cost of the drug but a liquid form is now available at a very much reduced cost.

In general our small series of 22 cases in Ankaful Leprosarium in Ghana confirmed the findings hitherto reported, namely a rapid fall in the number of solid forms of *M. leprae* in the smears followed by a slower reduction in the bacillary index which, however, was well in advance of the reduction obtained in similar cases treated with DDS alone. There was definite clinical improvement and a very remarkable absence of "reactions" even in cases which had hitherto proved intractable.

At the start of the series untreated cases were selected and all received 5 grammes of Etisul thrice weekly in addition to their routine treatment with oral DDS 100 mg. daily.

Two cases, both boys, who did produce an acute exacerbation of ENL with dermatitis were receiving DPT (Ciba 1906). This was withdrawn and after the reaction had subsided, Etisul plus DDS were started with no untoward results. Both these cases were so debilitated and their leprosy so acute that Ciba 1906 had originally been chosen in preference to DDS for fear of precipitating further reaction.

Two other cases are worth special note in that they had had already three and five years treatment respectively with a very stormy history of repeated ENL and neuritis both so severe and frequent that no effective anti-leprosy treatment had been possible. Etisul was given and produced a rapid improvement and the dose of DDS was gradually increased to 100 mg. daily. Neither case at the time of writing has had any further neuritis or ENL and both have shown marked clinical improvement with a fall of bacteriological index from 2.5 to 0.75, and 2.1 to 1.3 respectively.

Ulnar neuritis occurred in one case, unfortunately not reported by him, with the result of an early clawing of the 4th and 5th fingers of that side.

Etisul treatment was very popular and the idea of "rubbing in the medicine" on the affected spots seemed entirely logical to the

patients. The smell worried the staff much more than the recipients.

After nine months' experience with Etisul as a cream, a liquid form was sent to us for trial. Five of the original series were changed to the new form and seven new patients were admitted to this second series.

Bottles containing 250 cc. of the liquid were supplied, thus instead of tubes, a five-gramme dose was dispensed to the patient from a graduated measure supplied with each bottle. We found old penicillin vials were ideal for receiving the dose, dispensing was quick and easy and there was little or no wastage.

All patients liked the treatment and the old cases were unanimous in preferring the oily form which they said was easier to rub in; once more it was only the staff who complained about the smell.

Nearly all mentioned a burning sensation after inunction but were not worried by it, in fact they felt it did them good. Three cases stated they felt feverish following inunction but this was not confirmed by the thermometer. One case developed a dermatitis which subsided and although it occurred again after the second inunction did not do so after the third, otherwise there were no complications of any severity other than occasional mild ENL.

Results

Of the 22 cases in the trial 21 have shown improvement, some very marked. This improvement must not be confused with a well-oiled appearance following treatment.

Twenty-one have shown a reduction in the bacteriological index though in one other case this was only very slight. With true lepromatous cases we have not yet achieved a negative in the year of the trial. The improvement in the bacteriological index ranged from 75% down to 0% with the average 40%.

Solid forms of *M. leprae* which, in the untreated cases were often as high as 90%, disappeared from the smears in as little as one month but in two cases a few (5%) recurred sporadically for as much as ten months. The average time was three months.

Six cases showing most marked improvement (over 60%) in the bacterial index were found to have a blood sulphone level of 0.4 mgm. per cent or over, and though a low blood sulphone level did not preclude a good response, three cases showing least improvement had levels below 0.25 mg. per cent.

Conclusions

We feel from this series that Etisul is an extremely useful additive to sulphone therapy producing a more rapid clinical and bacteriological improvement with minimal intolerance or reactional episodes.

Its effectivity appears dependant on an adequate blood sulphone level. The liquid form, at its much lower cost, gives the possibility

of wider use, especially if the total time of treatment is reduced thereby with the possibility of shortening the period of infectivity of positive cases.

Acknowledgement

I would like to thank the Chief Medical Officer, Ministry of Health, for permission to publish this note and Imperial Chemical Industries Ltd. for the generous supplies of Etisul; also Mr. J. A. K. Yankah, A.M.I.L.T., i/c of the Laboratory at Ankaful Leprosarium for his careful and detailed work involved by this series.

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STUDIES ON THE NEURO-HISTOLOGICAL CHANGES IN THE MEISSNER CORPUSCLE IN LEPROSY

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The Meissner corpuscle is one of the most complex cutaneous sensory receptors. In spite of extensive work on the role and the distribution of the nerve fibres in the Meissner corpuscle on normal individuals for nearly a century, there is still substantial controversy over the nature of the nerve termination and function of the corpuscle.

CAUNA (1956-B) conducted an interesting investigation on the nerve supply and their endings in Meissner corpuscles on material classified into various age and occupational groups (manual workers) in both sexes. He observed in old age the nerve endings are restricted to the distal end of the corpuscle, the rest of it consisting of twisted bundles of nerve fibres. In manual workers he observed that the nerve endings are reduced in number, but at the same time intra-corporcular nerve fibres showed neurofibrillar expansions.

The present work is an investigation of nerve supply and their changes in Meissner corpuscles in leprosy, since Meissner corpuscles act as a selective touch receptor and are primarily designed for tactile discrimination. An attempt has also been made to study the location of the bacilli in these receptors in relation to the neuro-fibrillary processes.

Material and method

Twenty-four pieces of skin were taken from the distal pad of the fingers from 24 patients showing typical lesions of leprosy, 14 from the lepromatous and 10 from tuberculoid cases. There were no visible lesions anywhere on the finger pads. Biopsies were also taken from the lesions of each patient to confirm histologically the type of lesion. Most of the specimens were taken from the back and a few from the forearm. Tissues were fixed in 10% neutral formalin and frozen sections were taken at 20 micron thickness and stained by the method described by BALA SUBRAMANYAN, JAYARAJ and GASS (1954) for nerve fibres. 20 sections were taken from each specimen

for this study. Remaining tissues were processed for paraffin sections. Sections were stained with hematoxylin and eosin and for acid fast bacilli by the method described by JAYARAJ (1955). As a control 3 specimens were taken from the distal pad of the fingers of manual workers.

Results

Changes in the Meissner corpuscle in lepromatous leprosy. The stem fibres ending in Meissner corpuscle show certain complexity and fragmentation. Most of the corpuscles receive single medullated nerve fibres which end with branching. Occasionally two medullated nerve fibres are seen ascending and ramifying in a most fragmented condition. The neural fragments are seen scattered all over the dermal papillae and they seem to line up with the neurofibrillary process of the corpuscle. In few cases Meissner corpuscles show the free fading filaments in the connective tissue. Bulbous fragments of the fibrillary structure are also found in the papillae, deep in the epithelium. In early lepromatous leprosy, the nerve endings in Meissner corpuscles undergo less damage compared to advanced lepromatous leprosy. Most of the corpuscles in this stage of leprosy show normal neurofibrillary structure.

Paraffin sections stained for acid fast bacilli show that the bacilli are situated alongside the visible fibrillary ramification in the Meissner corpuscles. They are found abundant in early lepromatous leprosy. In advanced lepromatous leprosy the bacilli are found less in number.

Changes in tuberculoid leprosy. The degenerated nerve fibres ascend in a most difficult course towards the papillary region where they usually end as naked fading filaments. Most of the fibres break up into several segments which disintegrate in the illformed corpuscle. In a few specimens complete destruction of Meissner corpuscles are noticed. Several neural fragments are found in corpuscles and they are highly macerated and are not connected to the stem fibre. The epidermis is much flattened and the papillary regions are collapsed.

The paraffin sections stained for acid fast bacilli have not shown the presence of bacilli.

Changes in Manual Workers. The ascending stem fibres reach the papillary region without any changes compared to normal individuals. The ramification of the fine nerve filaments show expansion in the end bulbs. The papillary regions are slightly compressed.

Discussion

Meissner corpuscles contain a series of nerve fibres. The stem fibres ascend within the capsule and branch in layers in between the cells parallel to the surface of the capsule and to their stem fibres.

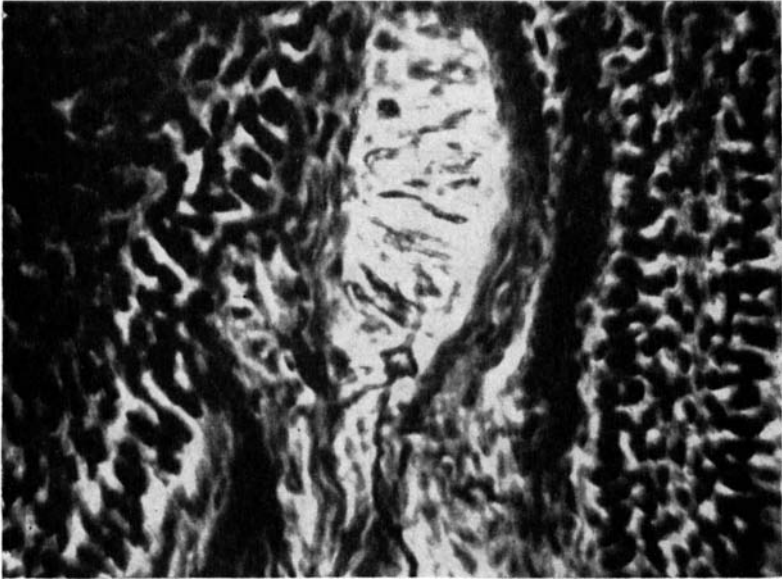


Fig. 1. A Meissner corpuscle in the dermal papillae showing normal neuro-fibrillary coiling with little of terminal thickening in the corpuscle. Distal pad of middle finger, male, 30 years, manual worker. x400.

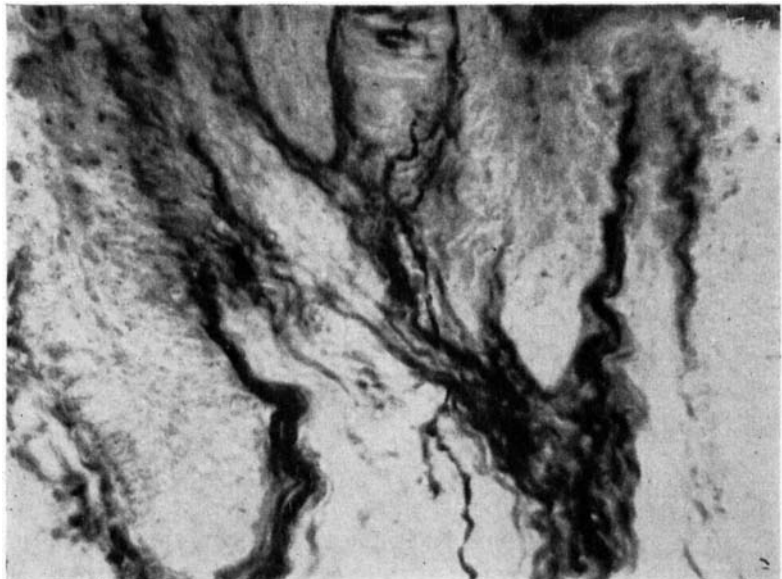


Fig. 2. A Meissner corpuscle in the dermal papillae showing a single myelinated stem fibre ascending from the subcutaneous tissue to the corpuscle where it branches as fading nerve filament. On the top of the corpuscle thickened fibrillary structure is seen disconnected to the stem fibre. Distal pad of the ring finger, male, 28 years, advanced lepromatous leprosy. x400.

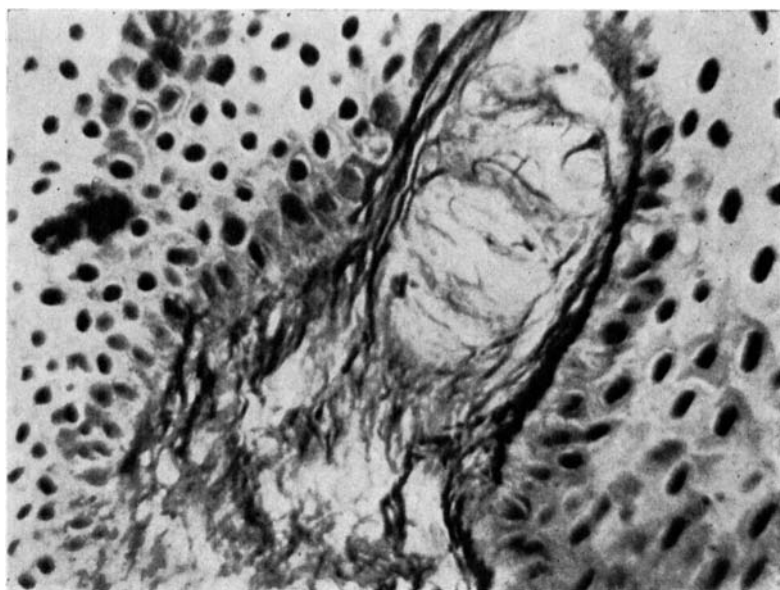


Fig. 3. A Meissner corpuscle in the dermal papillae showing a single stem fibre ascending into the corpuscle where it ramifies with partially fading nerve filaments without much structural alteration. Distal pad of the middle finger, male, 30 years, advanced lepromatous leprosy. x400.

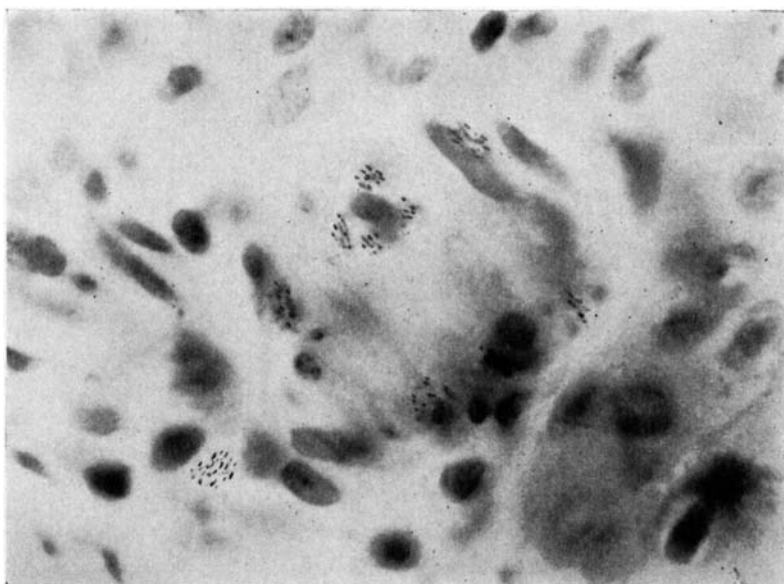


Fig. 4. Meissner corpuscle in the dermal papillae shows the clumps of bacilli situated alongside the neurofibrillary processes in the corpuscle. Paraffin section stained for acid-fast bacilli. Distal pad of the ring finger, male, 25 years. Early lepromatous leprosy. x900.

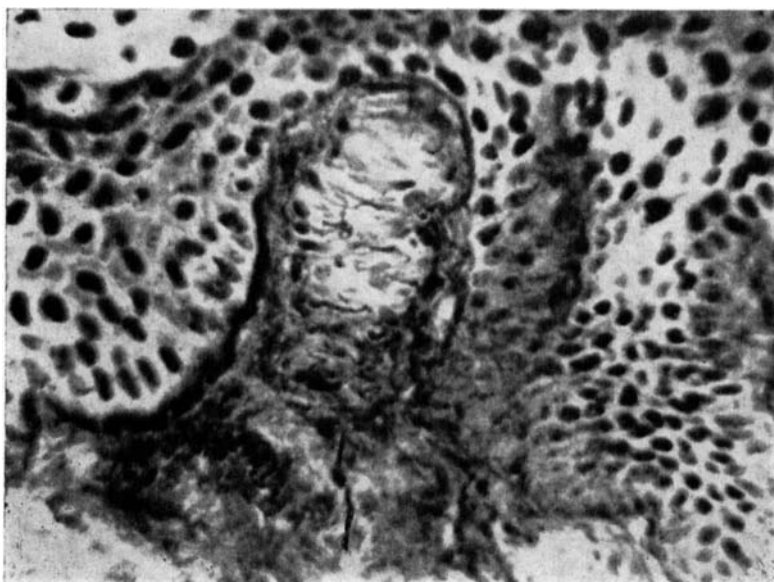


Fig. 5. Meissner corpuscle in the dermal papillae showing a single ascending nerve fibre ramifying in the corpuscle with partially fading filaments. Several neural segments are seen. Distal pad of the ring finger. Male, 36 years. Early lepromatous leprosy. x400.

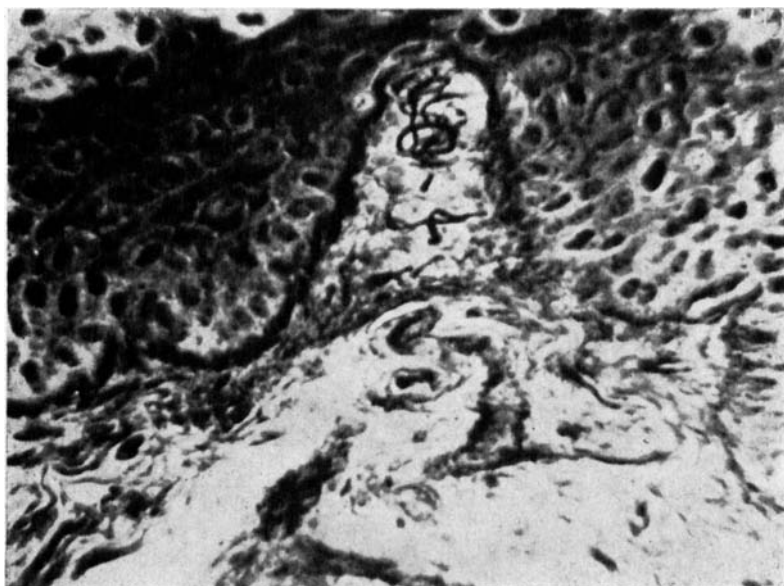


Fig. 6. Meissner corpuscle showing a myelinated single fibre ascending right up to the dermal papillae with limited coiling. The whole process looks myelinated. Distal pad of the ring finger. Male, 28 years. Lepromatous leprosy. x400.

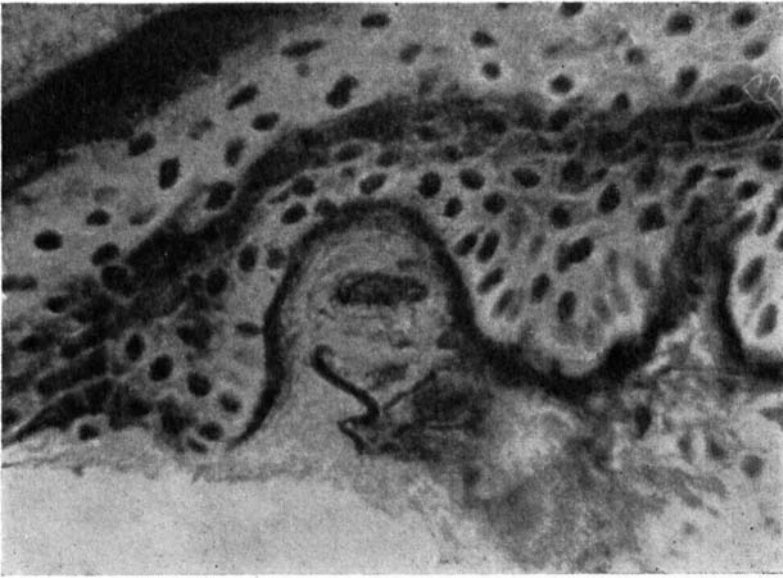


Fig. 7. Meissner corpuscle showing two myelinated nerve fibres ascending into the flattened dermal papillae and ramifying with faded nerve filament. A thickened neural element is seen in the middle of the corpuscle unconnected to the stem fibre. Distal pad of the middle finger. Male, 37 years. Lepromatous leprosy. x400.

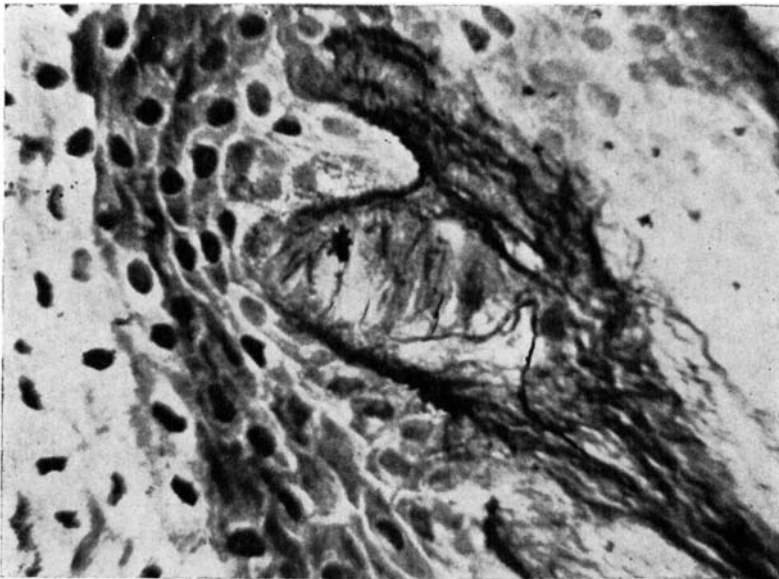


Fig. 8. Meissner corpuscle showing a single stem fibre ascending into the corpuscle and branching with number of neural segments and feeding filaments. Distal pad of the middle finger. Male, 28 years. Tuberculoid leprosy. x400.

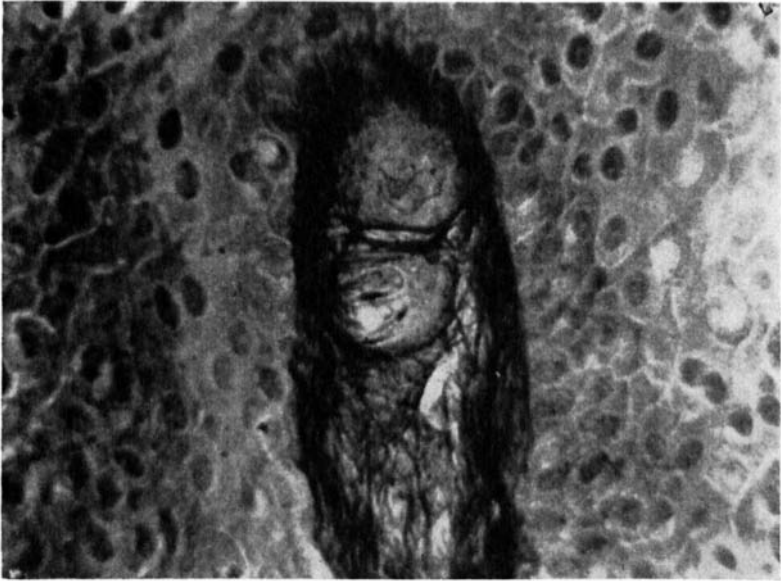


Fig. 9. Meissner corpuscle in the dermal papillae showing the corpuscle embedded in the connective tissue elements and the neural fragments situated in the centre of the lobulated corpuscle. Distal pad of the ring finger. Male, 30 years. Tuberculoid leprosy. x400.

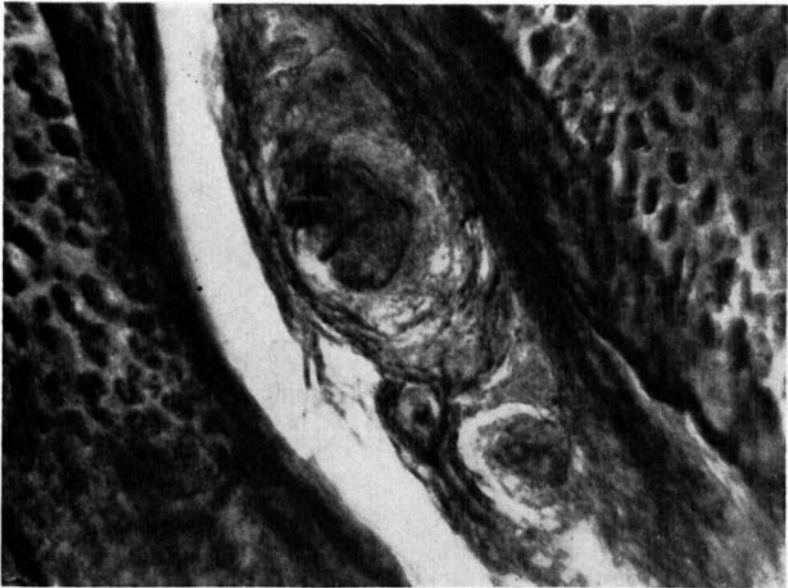


Fig. 10. Meissner corpuscle in the dermal papillae showing the neural mass in the centre of the corpuscle with structural collapse. The two stem fibres which reach the corpuscle show degenerated changes and are not connected to the fine neural elements situated in the centre of the corpuscle. Distal pad of the middle finger. Male, 22 years. Tuberculoid. x400.

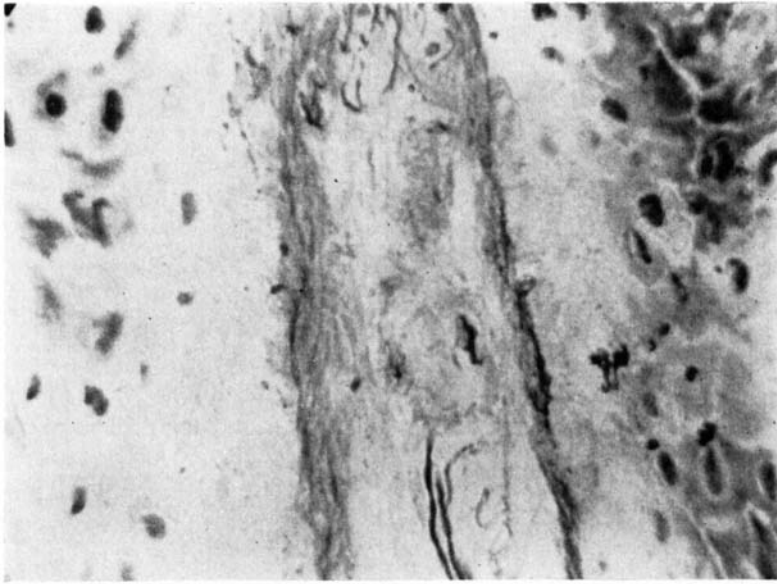


Fig. 11. Two stem fibres are seen ascending in the dermal papillae. The ramifying neural filaments are destroyed and a few nerve filaments are seen deep in the dermal papillae unconnected to the stem fibres. Distal pad of the ring finger. Male, 30 years. Tuberculoid. x400.

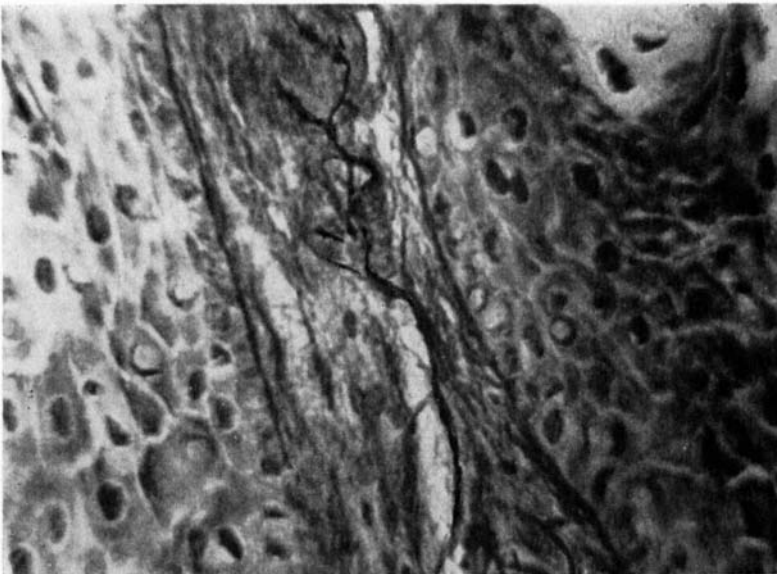


Fig. 12. A single nerve fibre is seen ascending into dermal papillae with irregular branching and embedded into the connective tissue elements. Distal pad of the ring finger. Male, 40 years. Tuberculoid. x400.

Direct pressure will produce stimulation to all these fibres. WEDDELL (1941a) showed the pattern of cutaneous innervation in relation to cutaneous sensibility and brought out the clinical significance of the pattern of cutaneous innervation. He demonstrated that the density of innervation of skin varies from place to place and that tactile acuity is dependant upon both the numbers of compact encapsulated nerve endings and the number of pre-terminal nerve fibres per unit field serving them. He further observed that in hairy skin, there are normally no receptor bodies like Meissner corpuscle other than the nerve endings related to hairs. In non-hairy areas, Meissner corpuscles and their functional status determine the tactile acuity of the concerned area.

In leprosy the changes in Meissner corpuscles are of considerable interest. Alteration of the Meissner corpuscles in manual workers has been reported by CAUNA (1956 B). However there are no reports in detail in the literature on the changes of Meissner corpuscles in leprosy. In recent years a considerable amount of work has been done on nerve changes in leprosy. GASS and BALSUBRAMANYAN (1954) studied the damage of nerves in different kinds of leprosy lesions. BALSUBRAMANYAN, JAYARAJ and GASS (1954) demonstrated the acid fast bacilli in the myelinated nerve fibres. GAULT, JAYARAJ and GASS (1955) demonstrated the bacillus containing capillaries and axons by treatment for alkaline and acid phosphatases. They observed that the bulbous swelling of axons are filled up with bacilli. KHANOLKAR (1951) brought out the theory that the bacilli invade the fine nerve and travel into the axons. MUKHERJI *et al* in a study by the acid phosphatase method described by GAULT, JAYARAJ and GASS (1955), observed parenchymatous degeneration of fibres in lepromatous leprosy and thought it to be possibly of toxic origin. They further observed that the changes in tuberculoid leprosy start with perineural infiltration in the finer nerves near the epidermis. The compact perineural infiltration, they found, penetrated into the thicker nerve and brought about fragmentation of fibres which lead to Wallerian degeneration. In the lepromatous lesions, they found no fragmentation of fibres. They observed that location of bacilli in the cutaneous nerves was mainly in the inter-fibre spaces, but in the lepromatous lesions they were occasionally encountered in the different parts of a nerve fibre, such as myelin sheath, Schwann sheath, Schwann cell and faintly stained axon. JAYARAJ and CHAUDHURY (1959) reported the existence of nerve fibres even in advanced lepromatous leprosy in the most superficial layers of the epithelial and sub-epithelial regions. The present observation shows that in Meissner corpuscles in early lepromatous leprosy the bacilli invade the whole processes of the corpuscles when the corpuscle maintains its normal ramification of fine axons. In the later stages the bacilli are not found in these corpuscles and are found more in stem fibres. However the

structural ramification of the fine nerve fibres in Meissner corpuscles is always maintained in lepromatous leprosy without much alteration and damage. In tuberculoid leprosy the stem fibres that enter into the corpuscles show more segmentation and they do not branch and ramify into the capsule. The continuity of the fine fibres is not seen. It looks as if the corpuscle is completely damaged in this type of leprosy.

Summary

1. Biopsies from distal pad of the fingers from 24 leprosy patients comprising 14 lepromatous and 10 tuberculoid were studied by cytological and nerve staining methods.
2. It was found that the terminal fibres in Meissner corpuscles undergo characteristic changes in leprosy. In early lepromatous leprosy abundant bacilli were found alongside of the neuro-fibrillary ramification and the corpuscles look almost normal. Whereas in advanced lepromatous leprosy, bacilli were not found in Meissner's corpuscles and the corpuscle was found slightly damaged.
3. In tuberculoid leprosy the fading filaments are commonly found in the corpuscle. The papilla that occupies the corpuscle is compressed causing severe damage to the corpuscle. The ascending stem fibres which reach the papillae undergo severe damage by way of fragmentation leaving several neural filaments far away in the papillary region not connected to the stem fibre.
4. It is generally assumed that the receptor mechanism does play a part in alteration of sensory modalities more in tuberculoid type of leprosy and less in lepromatous leprosy. There is a tendency for regaining the structural and functional status of Meissner corpuscles in lepromatous leprosy when the disease process is arrested. The possibilities in regaining the functional and structural status in tuberculoid leprosy are far less.

Acknowledgments

Our grateful thanks are due to Dr. V. Subrahmanyam, D.Sc., F.R.I.C., F.N.I., Director, Central Food Technological Research Institute, for kindly offering all facilities and encouragements to this investigation and to Dr. R. V. Wardekar, B.Sc., M.D., Secretary, Gandhi Memorial Leprosy Foundation, for kind permission to do this investigation. We are also indebted to Dr. M. Swaminathan, D.Sc., F.N.I., Assistant Director, Central Food Technological Research Institute, Mysore, for his kind and valued encouragements.

We express our gratitude to Mr. K. V. Achyuta Rao, for his aid with the photographic work.

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DIAGNOSIS OF LEPROSY

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(Reprinted by courtesy of the Editors of TRIANGLE,
the Sandoz Journal of Medical Science)

Leprosy is a chronic infective disease which presents a characteristic and easily recognisable picture in its advanced stages. It is not difficult then to diagnose it, if the possibility of infection with *M. leprae* is borne in mind. However, it is surprising, even in countries where leprosy is endemic, how frequently the disease is misdiagnosed. In countries where the disease is not commonly seen, leprosy patients are treated sometimes for years, as suffering from nervous disorders. It has also been suggested that as a person declared to be suffering from leprosy unfortunately becomes a marked man in his community, "one should not make a diagnosis of leprosy unless the signs are unequivocal" (COCHRANE¹).

The real difficulty in diagnosis arises when leprosy is in the early stages, not necessarily in terms of the duration of the infection, but in the unfolding of its clinical manifestations. It is, however, important to arrive at a correct diagnosis, because it is during these early stages that the disease is amenable to well-conceived treatment, and most of the deformities and other untoward complications which develop in the wake of its advance can be prevented.

The diagnosis of leprosy in these stages demands an answer to three questions which have to be solved in the following sequence: (a) Is the person concerned suffering from leprosy? (b) If the answer is in the affirmative, it is necessary to ascertain the type of disease with which he is afflicted. Is it a "malignant" or lepromatous type, a "benign" or lepride type, or do the signs and symptoms suggest that the malady belongs to the dimorphous or "intermediate" group? (c) Is the disease progressing and active: is it quiescent or in an arrested phase? * These questions can only be solved after a careful clinical, bacteriological, histopathological and immunological study of the patient. It is necessary, however, to point out that it is not often feasible to carry out all the examinations on each and every patient, nor will the technical facilities available to the examining doctor in most places permit them. Under such circumstances a clinician relies on his experience and acumen and often makes a fairly shrewd estimate of the patient's morbid condition.

* At the Manila Conference (1931) it was decided to restrict the application of the term "arrested" to cases which had remained bacteriologically and clinically free from active disease for a period of at least two years; to those cases which had remained free for a period of three months or two years, the term "quiescent" was to be applied.

The diagnostic investigations are based on a knowledge of the mode of entry of the infecting organisms and the pathological alterations which follow their proliferation in human tissues. A brief outline of our present-day ideas on this subject is therefore given below.

It has recently been shown that the infecting organisms enter the skin and are taken up by regenerating nerve fibres which are present in the dermis and epidermis, particularly in small, growing children. The leprosy bacilli multiply in the axoplasm of the nerve fibres, enter the body of the SCHWANN cells and often remain dormant in that sheltered location for long periods of time. Under the stimulus of certain supervening changes in the functions of the body, as during adolescence, puberty, pregnancy and the onset of mild maladies, the bacilli begin to proliferate in the nerve fibres and appear in large numbers in the intercalated zones, from which they burst out in the endo and perineural tissues. There, they are taken up by histiocytes which gradually become transformed either into lepra cells or into epithelioid cells depending upon the immunological response of the host to the presence of leprosy bacilli.

The pathological alterations and the subsequent signs which are observed in the nerves and the skin are dependent upon the distribution of the inflammatory exudate in them (whether as compact aggregates (nodular) broad patches (infiltrating) or as diffuse sheets), and upon the functional impairment of the nerve supply to the cutaneous blood vessels and to the deeper cells of the epidermis. In lepromatous leprosy, the alterations in nerves are probably due to pressure exerted by thickly packed lepra cells in the endo and perineural tissues. The nerve affections in this type of disease develop rather slowly; they are often transient and sometimes reversible. In the tuberculoid type, on the other hand, there is necrosis of the cells of the inflammatory exudate, involving the nerve fibres, the collagen material and the perineural tissues, as a result of the activity and evolution of the epithelioid cells. The consequent changes manifest themselves in a more lasting or even permanent damage to the affected nerves and secondary changes in the skin supplied by them. The changes in the bigger nerves lead to their thickening, with attendant pain and tenderness, sometimes terminating in the formation of a necrotic mass, or a so-called "nerve abscess", in the tuberculoid type of the disease. The damage to the sensory, reflex, sympathetic and motor nerve fibres manifests itself in characteristic dryness and roughness of the skin, anhydrosis, loss of sensation, wasting and paralysis of certain muscles. The gross signs of these changes are facial paralysis, lagophthalmos, corneal anaesthesia, wrist drop and foot drop. The affected tissues are particularly liable to secondary infection, wasting and atrophy. Spontaneous blisters in the anaesthetic areas, ulceration of the skin, extensive osteoporosis and osteo-

necrosis of the affected bones are the results of these secondary changes. All these, however, are late manifestations. The earliest changes are those associated with hypopigmentation and certain types of sensory disturbances in the skin. These have been vaguely described as anaesthesias which usually set in, in the following order: alterations in thermal, tactile, pain and pressure sensations.

Clinical examination

This is the most readily available diagnostic procedure. It can be carried out by a practising physician, and does not entail the use of costly equipment or elaborate techniques. A complete and methodical examination of the whole patient is essential. The entire surface of the body has to be systematically examined in bright daylight, and the sensory performance and alterations in the thickness, feel and sensitivity of certain nerves carefully determined. The examining eye, the palpating hand, a feather or a tuft of cotton-wool, a pin and two glass test tubes with hot and cold water, are the sole requisites. It is, however, a matter of prime importance that the physician should know what to look for in a patient suffering from leprosy. The extension, arrest, or even regression of the disease can only be ascertained if as complete a history as possible is obtained and careful records are maintained of all the clinical observations that have been made at more or less regular, periodic examinations.

The leprosy patient usually sees his physician for one or both of the two following physical signs: (1) numbness or loss of sensation in some part of the body and (2) one or more spots, patches, or even large areas of hypopigmentation of the skin. If at the same time the presence of a large number of acid-fast bacilli can be demonstrated in the skin, the diagnosis of leprosy becomes almost indisputable. Such bacilli, however, are not readily seen in a smear obtained from an incision, and to arrive at a reliable diagnosis other evidence has to be collected. For this purpose one examines the cutaneous nerves arising from the suspected spot, and other superficially placed nerves like (a) the great auricular, (b) the ulnar and (c) the radial. It is possible to differentiate the lepromatous, the tuberculoid and the dimorphous macules from one another on the basis of the physical signs and symptoms presented by the patient. As an illustration the clinical features of the three lesions may now be considered:

Tuberculoid macules. The lesions are few in number and tend to be large and asymmetrical in their distribution. They are commonly found on the face, lateral aspect of the extremities, buttocks and scapulae. The lesions are hypopigmented and show sharply defined edges, clearly demarcated from the adjoining normal skin (Fig. 1). Macules on the extremities and buttocks feel dry to the touch and show anhydrosis. Sometimes they possess a scaly or rough surface,

and anaesthesia either to light touch or warmth is present. Enlargement of the ulnar or common peroneal is also seen. Sometimes there are areas of anaesthesia on the extremities along the course of the major cutaneous nerves, and in cases of long duration this anaesthesia is fairly pronounced.

Lepromatous macules. The lesions are not confined to the face, buttocks, scapulae etc., but are diffusely scattered over the body in an almost symmetrical manner. Pre-leproma macules are usually small and numerous. Their periphery is hazy in outline and fades imperceptibly into the surrounding normal skin. There is hardly any difference in the texture of the skin over the macules from the normal skin around them (Fig. 2). They appear shiny and there is no anhydrosis.

In diffuse lepromatous leprosy it is difficult to detect the affected area due to the gradual coalescence of several ill-defined macules. In such cases the ear-lobes are usually thickened and shiny, and the eyebrows show loss of hair.

Dimorphous macules. In distribution, in appearance and in size these lesions show certain features of both tuberculoid and lepromatous macular leprosy. Some of the macules have vague edges and show slight loss of tactile and thermal sensation. With the progress of the disease large and small lesions, symmetrically distributed, appear on the body (Fig. 3). The larger macules usually show loss of sensibility and their edges are fairly definite. The majority of these lesions are small, generally with indefinite edges. The texture of the skin of the macules is usually rough and occasionally presents a curious creased or wrinkled appearance.



FIG. 1. A typical macule of tuberculoid leprosy. Patient was lepromin positive.



FIG. 2. Multiple macules in lepromatous leprosy. Patient was lepromin negative.

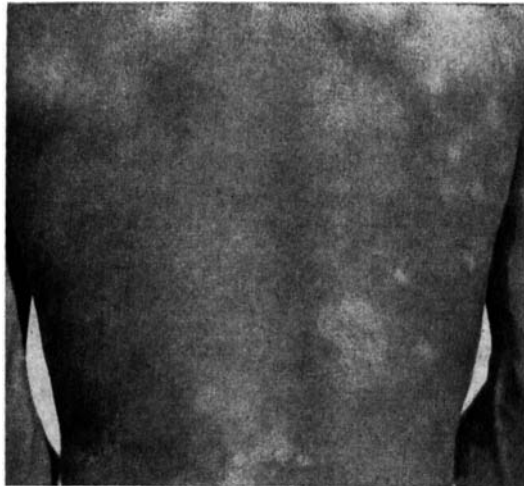


FIG. 3. Macules in dimorphous leprosy, showing features intermediate between the types shown in Figures 1 and 2. Lepromin was weakly positive.

Bacteriological examination

The bacteriological examination in leprosy has not progressed beyond a relatively simple procedure, because the causative organism cannot be cultivated on artificial nutrient media, and the disease

cannot be transmitted to laboratory animals. Therefore the examination involves a microscopic study of smears obtained by superficial incision of the skin. The material is taken by one of the following three methods: In the routine or standard technique a small superficial cut is made in the skin near the advancing edge of the suspected lesion. The blood or lymph which exudes is wiped away and the cut surface scraped with the blade of the scalpel. The material collected on the scalpel is transferred to a microscopic slide and a uniformly thick smear is made from it. The slide is fixed and stained by the ZIEHL-NIELSEN technique. The dried smear is then carefully examined under a microscope for the presence of acid-fast bacilli and for the type of inflammatory cells. Some leprologists recommend a deeper cut down to the subcutaneous tissue. We prefer a small piece of tissue $4 \times 3 \times 4$ mm. in size for the concentration technique. Instead of a scalpel, a 4 mm. diameter punch may be used for the biopsy. Our patients prefer the punch method of biopsy. It should, however, be pointed out that the punch biopsy is not suitable for histological examination, as there is always a certain amount of crushing of the tissue in the process. The tissue is kept for 3–4 hours in one per cent acetic acid solution which partly fixes it and facilitates the detachment of the epidermis. The tissue left after peeling off the epidermis is minced in a pressure mincer with the addition of 3–4 ml. of normal saline. The supernatant fluid is vigorously shaken after 25 drops of petroleum ether/ethyl ether mixture 1:10 have been added to float the micro-organisms to the top layer. Smears are prepared from this layer and fixed in CARNOY's fixative, dried and stained for 3–4 minutes in an aqueous solution containing 0.3 per cent auramine, 0.3 per cent phenol and 6 per cent absolute alcohol. The smears are decolourised for 3–4 minutes in 70 per cent alcohol containing 0.5 per cent of hydrochloric acid and 0.5 per cent of sodium chloride. After a brief rinse in water, the smears are dried and examined under a fluorescence microscope using $40 \times$ objective and $10 \times$ eyepiece. If the auramine-stained smears are kept in ultra-violet light for more than half an hour, the intensity of the fluorescence gradually fades. However, the smears can be restained with auramine solution. The smears can also be stained by the ZIEHL-NIELSEN technique after staining with auramine solution, but the process cannot be reversed. This technique has given us uniformly good results and we have been able to demonstrate acid-fast bacilli from almost all the lesions of active and even quiescent* leprosy².

Histopathological examination

A piece of tissue is taken from the selected area. The skin is cleaned and infiltrated with local anaesthetic. After about 5 minutes a suture of sterile thread is passed through the superficial layer of

* See p.158 re Manila Conference.

the corium at one of the extreme ends of the proposed biopsy. The thread is used to steady the piece of tissue to be removed and to avoid the use of forceps which always crush the intended biopsy and often spoil a good portion of it for histological examination. The thread is gently pulled and an elliptical incision in the skin down to the subcutaneous tissue is made with a sharp sterile scalpel. A piece of skin measuring approximately 1.5 cm long and 0.5 cm wide is obtained without squeezing the tissue, and is immediately transferred to the fixative.

For examination of the biopsy material with an electron microscope, the fixation, dehydration and impregnation are carried out by different techniques which permit the preparation of ultra-thin sections 25-50 μ thick with an ultra-microtome. This is a complicated process which need not be described here.

In the earliest stages of the disease the microscope does not reveal any abnormal features, though a careful search occasionally reveals the presence of histiocytes with one or two intact or fragmented acid-fast bacilli in their cytoplasm. Sometimes the cytoplasm stains diffusely with the basic dye which does not decolourise with weak acid. These cells have been seen by us only in the early stages of leprosy and have been termed "fuchsinophil" cells. At a slightly later stage a non-specific type of cellular exudate is seen in the microscopic preparations which present more characteristic features of infection with *M.leprae*. After the disease has progressed further it is possible to identify the tissue reaction and to distinguish a leproma, a tuberculoid or a dimorphous lesion. In the early stages of the lepromatous type of disease it is observed that the axoplasm of some cutaneous nerves has undergone degenerative changes, with leprosy bacilli lying in the disintegrated tissue; the sheath of SCHWANN is collapsed and converted into a ribbon-like band (BÜNGNER's band). *M.leprae* are usually found in large numbers in the nerve fibres and in the endo- and perineural tissues. The bacilli are ingested by the histiocytes which are gradually transformed into lepra (VIRCHOW's) cells. The transformation of the histiocytes is a result of multiplication of the mycobacteria within the cell cytoplasm and their envelopment with electron-opaque lipid material. As a result of the metabolic activity of the bacilli, electron-transparent material begins to show itself in the lipid droplets and forms clear zones to the micro-organisms. These clear zones fuse until the whole cytoplasm of the inflammatory cell assumes a foam-like or soap-bubble appearance. In between the lepra cells, groups of mononuclear and plasma cells are often encountered.

In the tuberculoid lesion the dermis is invaded by foci of productive inflammatory exudate mainly comprising mononuclear cells and histiocytes. The most characteristic feature of the inflammatory reaction is the transformation of these histiocytes into epithelioid

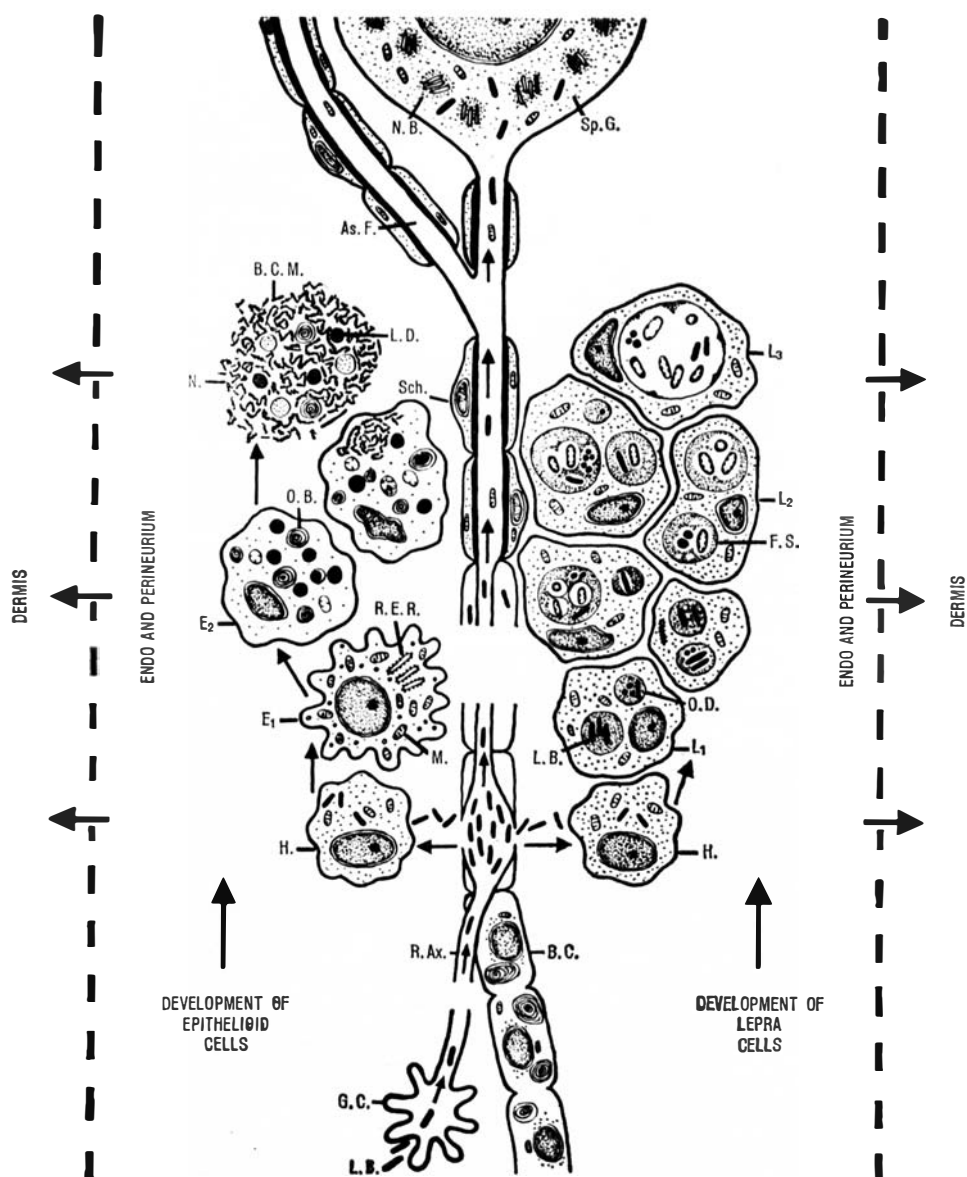


FIG. 4. Diagram of the histological findings in leprosy. As.F.=Ascending fibre; B.C.=BUNGER's band; B.C.M.=Broken cell membrane; E₁=Epithelioid cell (1st stage); E₂=Epithelioid cell (2nd stage); F.S.=Foamy structure; G.C.=Growth cone; H=Histiocyte; L₁=Lepra cell (1st stage); L₂=Lepra cell (2nd stage); L₃=Lepra cell (3rd stage); L.B.=Leprosy bacillus; L.D.=Lipid droplet; M.=Mitochondria; N.=Necrotic mass; N.B.=NISSL body; O.B.=Onion body; O.D.=Opaque droplet; R.Ax.=Regenerating axon; R.E.R.=Rough surfaced endoplasmic reticulum; Sch.=SCHWANN's cell; Sp.G.=Spinal ganglion cell.



FIG. 6. Advanced foamy cells in a lepromatous great auricular nerve. In the cytoplasm of lepra cells, many degenerated leprosy bacilli are seen embedded in oval electron-transparent zones. The cell wall of the degenerated bacilli is swollen and the bacillary cytoplasm is fragmented. Magnification: 10,000 x. A: Degenerated leprosy bacilli. B: Electron-transparent zone. C: Mitochondria. D: Nucleus. (Electron micrograph).

bacilli or other cells or tissue which come within the range of their activity. The collagen fibres and nerve twigs which are involved in this process undergo degenerative changes and dissolution. The nerve fibres show WALLERIAN degeneration in the early stages and, later, necrosis, when they are incorporated in the substance of the epithelioid tubercle formation. These lesions are characterised by a scarcity of the mycobacteria in the inflammatory tissue (Fig. 4).

The dimorphous lesion presents mixed features of the above two

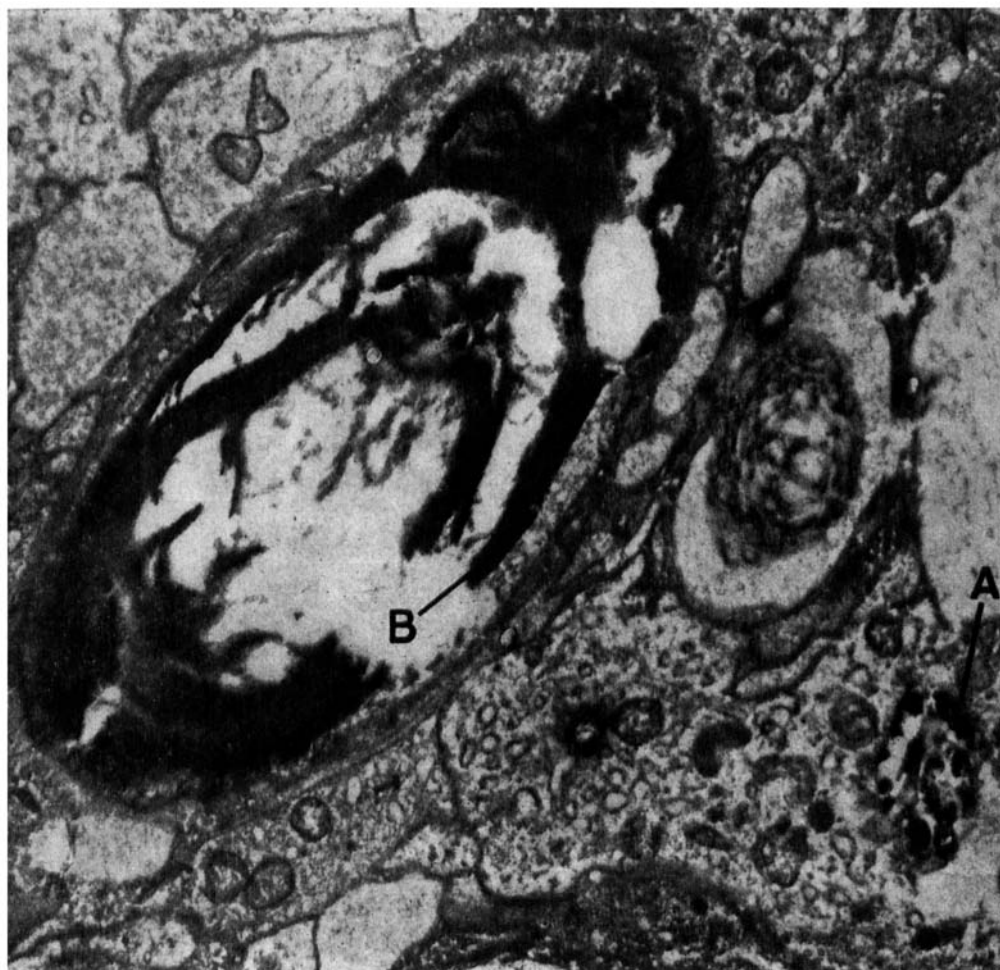


FIG. 5. Lepromatous lesion in a great auricular nerve. A group of leprosy bacilli is seen in a iepra cell of the endoneural space. These bacilli have not yet degenerated and have a more or less homogenous bacillary cytoplasm and nuclear apparatus. Various stages of a degeneration of the myelin sheath are observed. Magnification: 28,000 x. A: Leprosy bacilli. B: Degenerating myelin sheath. (Electron micrograph).

cells and occasional giant cells round a core of fine nerve twigs. These cells are rather large with faintly acidophilic and finely granular cytoplasm. Under the electron microscope the ultra-thin section shows that the cytoplasm contains smooth-surfaced endoplasmic reticulum and evenly scattered lipoid dust comprising weakly osmio-philic droplets. The epithelioid cells are fragile and the cell wall often cracks, leading to a spilling of the cytoplasmic contents into the intercellular tissue. The epithelioid cells engulf and rapidly destroy

types in the same or different lesions in the same person; it is an intermediate response to the infection of the host tissues with leprosy bacilli.

Immunological examination

Even the most refined techniques available at the present time fail to reveal the presence of antibodies to *M.leprae* in the sera of patients. Further the uterine horns of guinea-pigs which have been sensitised to *M.leprae* do not contract when "shocked" with a small dose of mycobacterial antigen. Therefore it can be stated that our present techniques are incapable of detecting antibodies to *M.leprae* in leprosy patients and in immunised experimental animals. A technique which has often been used is a skin reaction to lepromin, a product prepared from lepromatous nodules. The reaction is positive in tuberculoid patients and negative in lepromatous patients. As pointed out by FELDMAN³ "there is much about the lepromin reaction that is nebulous and purely presumptive. Until more definite information is available, the exact situation pertaining to the capability to react to lepromin must remain the realm of speculation".

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THE USE OF PARAFFIN IN LEPROSY

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Introduction

Paraffin can be very useful in the management of symptoms secondary to leprosy. Yet the observations of this author made while a staff member of the National Leprosarium, Carville, Louisiana indicate that there is not widespread use by medical missionaries in this field.

Several readily recognizable circumstances may contribute to this void, such as budgetary problems, lack of library facilities or professionally trained personnel. It is not the purpose of this paper to deal with these aspects.

It is hoped that this paper will serve as a guide for the use of paraffin in leprosy. The information contained herein has been written in the light of the modern paraffin unit as it is known in the United States of America. Although these may not be available or practical in many locations, little need be said about the ingenuity, resourcefulness or ability to improvise of those workers found in these areas. Specific information regarding one means of substitution of equipment will be found in reference 5 of the bibliography.

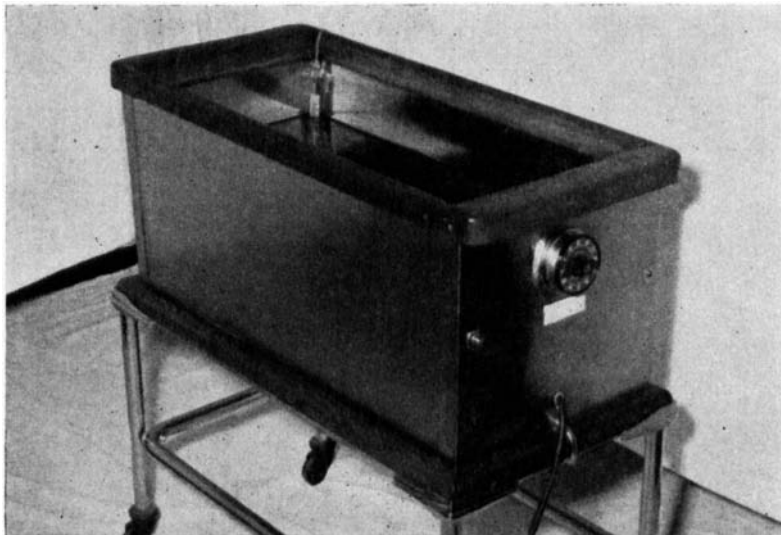


FIG. A. The paraffin unit, showing a thermometer in the bath at far corner.

Historical

The use of paraffin for therapeutic purposes dates back to 1829¹. Incorporated into gauze to form what was then called a paraffin dressing, its major use was in the treatment of burns. During the early 1900's the formula for the mixture was a closely guarded secret. Today, pure paraffin is used of a specific melting point (MP) ranging from 48°–58° C. To this is added a specific amount of pine oil or light petrolatum. Originally the baths were heated by gas. Since 1926 a thermostatically controlled electrical heating unit has been commonly used.

Frequency of use

At the National Leprosarium paraffin is used extensively. More than 4,000 treatments were administered during 1957, which is an average of 337 per month. As many as 22 treatments have been administered from one unit in a single day.

Sanitary aspects

During such intensive use one might justly be concerned with the sanitary aspects. Culture samples taken from our unit for upper extremities immediately following immersion of an extremity and at ten-minute intervals for a total of six samples, all proved negative. The temperature of operation (53°C.) is above that at which bacteria, with few exceptions, will grow. In this regard, two practices are worthy of mention.

1. Prior to immersion, the part to be treated is washed with soap and water and then thoroughly dried.
2. At the close of each work day, the temperature of the bath is increased to 82°–93°C.

Techniques of application

1. *Continuous immersion*: The extremity is immersed to the desired level and is kept immersed throughout the treatment. A thin layer of paraffin congeals over the surface of the part, forming a "glove" or "stocking". The joints and digits are not moved during treatment as this would cause the glove to tear or crack. Such cracks allow melted paraffin to leak into the glove causing a hot spot on the skin. For this reason some persons prefer to remove the part at least once prior to continuous immersion. The congealed layer is of lower temperature than the melted paraffin, thus allowing treatment without burning the skin.
2. *Dip immersion*: In this method a thicker glove is formed by repeated brief dips. The patient is instructed not to move the

joints in order not to crack this glove. Following a minimum of six dips, the part is immersed for the duration of the treatment.

3. *Dip wrap:* The extremity is dipped in and out of the bath to produce ten to twelve layers of paraffin, being careful not to crack these layers as they are applied. The part is then wrapped in a thin sheet of clear plastic (20" \times 24"). This prevents the paraffin from adhering to the towel, a common complaint. A large bath towel is then wrapped over the plastic to retain heat, and is secured by means of a two-inch spring clip. This prevents the towel from working loose until treatment is completed. When the 20-minute treatment duration has elapsed, the plastic sheeting is removed and rinsed. After drying it is ready to be used again.
4. *Brush wrap:* Occasionally the part being treated is not easily immersed. Then the paraffin may be "painted" on with an ordinary one- or two-inch paint brush. Following application of ten to twelve layers of paraffin, the area is covered with towels or a blanket for the prescribed treatment time.

Physical findings

Upon immersion of an extremity into the molten paraffin, solidification occurs on the immersed part. This is a result of heat loss from that layer of paraffin in contact with the skin. LAMPERT² measured the temperature differences of this layer of congealed



FIG. 1. Clear plastic sheeting is wrapped about the treated extremity.

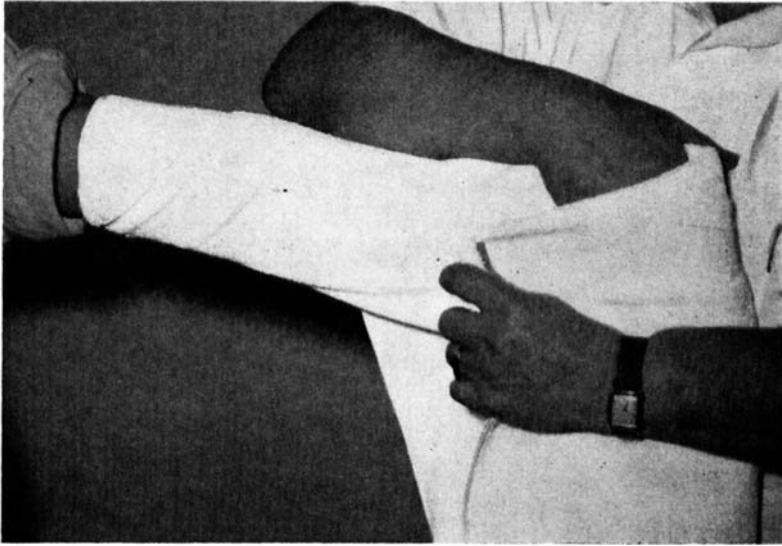


FIG. 2. A large bath towel is then wrapped over the plastic to retain heat.

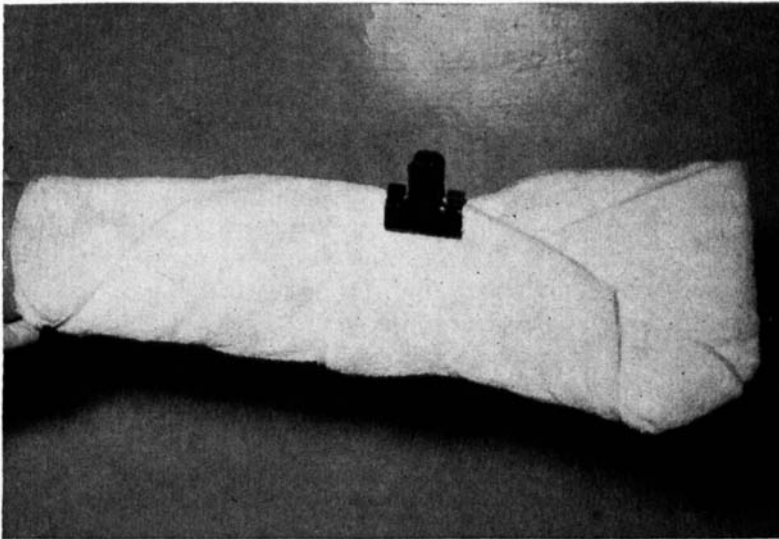


FIG. 3. The towel is secured by means of a two-inch spring clip.

paraffin as compared to the melted paraffin. The findings of his study bear out the theoretical explanation of why the application of melted paraffin produces no burn.

ACTUAL TEMPERATURES OF APPLIED PARAFFIN (LAMPERT)

<i>Time (of application)</i>	<i>Temperature of paraffin*</i>
few seconds	55°C.
2 minutes	43.9°C.
3 minutes	41.5°C.

*Applied in the form of paraffin packs.

There is on record a treatment given with paraffin at 82°C. with no burn resulting³, however, this report states that the bath was too uncomfortable to tolerate continuous immersion of the part. The skin temperature of the part during treatment has been studied^{1,3} using a galvanometer and thermocouple. ZEITER reported skin temperature as found in various techniques of paraffin application. In dip wrap, the skin temperature fell from 48.8°C. (the average temperature during the first 60 seconds of application) to 43.3°C. at five minutes and 40.5°C. at ten minutes.

VOGEL and WEINSTEIN report a skin temperature rise of 11.1 to 13.9 degree immediately following conventional paraffin pack technique and then slowly decreased in temperature as the treatment progresses¹.

SEDWITZ made similar studies on the reflex effect upon the untreated extremity. He found paraffin applications to one extremity caused the opposite extremity to react at once with an elevation of skin temperature of 1.4 degrees. Even though a slow decrease in the temperature followed, it remained elevated by 0.47 degree for thirty minutes from the time of the initial application⁴.

LAMPERT² suggests that the heat produces sweat, thus forming a protective layer between the skin and paraffin, and preventing significant contact between the two. As the temperature of the paraffin rapidly drops following application, and as the circulatory system disperses heat from the extremity, temperature of the paraffin during most of treatment is well within tolerance.

Still another theory is related to the low specific heat of the paraffin^{1, 3, 4, 5}. The contention is that heat yielded per unit mass is significantly less than that produced by water (specific heat of 1.0°) of the same temperature. However, upon application, the temperature of paraffin is lowered to the hardening point, a significant amount of heat is released (heat of fusion) and transferred to

the skin. Solidified paraffin is a poor thermal conductor, and acts as an insulator to the part being treated. In immersion type treatments this prevents the melted paraffin of high temperature from actually contacting the skin.

Ingredients

With regard to the formula used, several variations of the proportions of oil to paraffin are in use. However, the one which has been used for several years at the National Leprosarium is as follows:

Paraffin of 53°C. MP—seven (7) parts (53 lbs.).

Oil (light petrolatum)—one (1) part (1 gallon).

This formula offers a mixture with an operational MP of 53°C. The MP of any mixture may be lowered by the addition of a greater proportion of oil than in the above formula.



FIG. 4. The congealed paraffin forms a glove.

Indications

Paraffin may be prescribed when local heat is desirable. The liquid immersion treatment has the asset of affecting all the convolutions, folds, and angled surfaces of an extremity simultaneously. Although not conclusive, heat is said to have a sedative effect and may help to relax muscle spasm⁶. In addition to use in general medical and surgical conditions, several operative procedures and secondary symptoms common to leprosy may be treated by paraffin applications. This may be the sole treating agent or it may be

coupled with other modalities of physical medicine, namely massage and exercise.

Dyshidrosis

Dyshidrosis, commonly seen in leprosy, leaves the skin dry, tight, and prone to crack on ordinary movements. Paraffin may be used regularly to improve skin texture and prevent cracking. Satisfaction is frequently expressed by the patient following this treatment.

Neuritis

At Carville, paraffin has been the treatment of choice for chronic and sub-acute neuritis.

Nerve transposition

Should a surgical transposition of a nerve be carried out, paraffin is again employed following complete healing of the incised area. Its use usually precedes massage and exercise, which are directed at prevention of adhesions, reduction of edema, and muscle strengthening.

Muscle-tendon transfer

In patients who are candidates for muscle-tendon transfers, physical therapy employing paraffin is prescribed both pre- and post-operatively. The pre-operative aims of treatment are:

1. Maintain or increase joint range of motion.
2. Maintain or increase muscle-tendon length.
3. Lubricate and soften atrophic skin.

Post-operative care is directed toward:

1. Re-education of the tendon transfer procedure.
2. Prevention of adhesions.
3. Reduce stiffness from casting or bandaging.

Hydrotherapy is usually employed initially following removal of bandages or casts. Paraffin is resumed following healing of incisions. It renders the skin oily, soft and pliable, providing excellent condition for massage.

Therapeutic exercise

It is often desirable to precede exercise with an application of heat. This is particularly true where stretching of contracted joints is of primary importance. Here again paraffin has been used with great frequency.

Contra-indications

Contra-indication for the use of paraffin are few. However, these should receive due regard. They are:

1. Open skin lesions.
2. Sensory loss or impairment.

Discussion

The paraffin bath, which has been used for well over a century now, allows for a great number of patient treatments when employing the dip-wrap technique of application. Although there are no objections to other techniques of application, in a centre where many treatments are to be administered during the course of a day, this method has proved to be most expedient. It must also be mentioned that the drip-wrap method of treatment will allow the patient to go elsewhere on other business or treatment during the course of his twenty-minute paraffin treatment time.

It will be noticed that the contra-indications occur with great frequency in a given population of leprosy patients. In spite of sensory loss, patients have been treated over a number of years with no record of a burn. It will be noted that the temperature is maintained at 53°C. This is a full five degrees below the recommended operating temperature of units used for patients with no sensory loss. By frequent observation of the temperature, patients are never treated in the unit should the temperature rise above the 53°C. level. A raised grill covering the bottom of the unit prevents the treated part from directly contacting the bottom, where the heating element is located, and therefore, the warmest part of the unit. This comes as an integral part of the unit as it is sold in the United States of America.

The physical findings have been discussed at length. Supportive information regarding temperature studies and other pertinent investigative projects are included. The ingredients, no longer held secret, may vary as to proportion of oil to paraffin. A satisfactory formula has been offered.

Patient evaluation and treatment is the sole responsibility of the physician. It is he who directs a prescription for paraffin treatments to the physical therapist.

Many secondary complications of leprosy which have been successfully treated with paraffin at Carville have been listed. This is not meant to be an all-inclusive listing. Nor should it serve as a stereotype guide for treatment. One can readily see that this topic has been treated extremely lightly. However, this is not the purpose of this paper. These are merely cited to demonstrate the usefulness of paraffin in the management of the leprosy patient.

Conclusions

Topical application of heat to the extremities, by means of the paraffin bath, is a useful treatment in complications of leprosy. The paraffin bath permits accurate temperature control, giving maximum benefit from the use of heat.

Methods and their applicability are described. Excellent symptomatic improvement and limited physical improvement can be obtained. Equally important is its use as an adjunct in preventing deformity.

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USEFUL APPLIANCE (PYLON) FOR BELOW-KNEE AMPUTATIONS

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Where the services of a limb maker and monies are not immediately and readily available for the construction of complex and expensive appliances, resort is made to other devices. The pylon is such a device that meets most requirements for successful walking.

As soon as the stump can bear pressure the pylon consisting of a moulded plaster shell (socket), a shank and cuff suspension is constructed (Fig. 1). The pylon can be constructed within a hospital's facilities and with inexpensive available materials. Basic materials required are plaster, wood, leather and four metal strips (aluminium or stainless steel). Other materials include stockinette, wood screws, rubber and a few carpenter's tools such as a level, screwdriver, saw and pliers.

This pylon is light, durable and has no joints. It provides efficient function and wearing comfort to the amputee. Pylons are usually intended for temporary use to shorten the period of inactivity while waiting to be fitted with permanent appliances; however, it could be used as a permanent appliance. This device has been employed at the United States Public Health Service Hospital, Carville, Louisiana, as a temporary measure while waiting for completion of permanent prostheses. The skills learned while using the pylon are valuable and useful for any subsequent prosthesis. During its use the amputee adjusts to weight-bearing on the stump, learns to balance and walk in parallel bars. The pylon's use enables the gait training programme to start sooner by eliminating unnecessary waiting, thus proving to be a psychological boost to the amputee.

The amputee's ambulation time should be gradually increased within tolerance to practical limits. Starting with 10 minutes, ambulation time should be graduated so the amputee can wear the pylon during entire days' activities.

During the early stages of the pylon's use, one must watch for pressure signs. If pressure signs are present, the socket is readily sanded in appropriate areas to relieve excessive pressure points. If stockinette of double thickness is used and plaster is applied properly, pressure signs will be few, if any.

Few critical measurements are necessary for successful completion of the pylon. The over-all length and joint level measurements are taken to correspond with the normal leg.

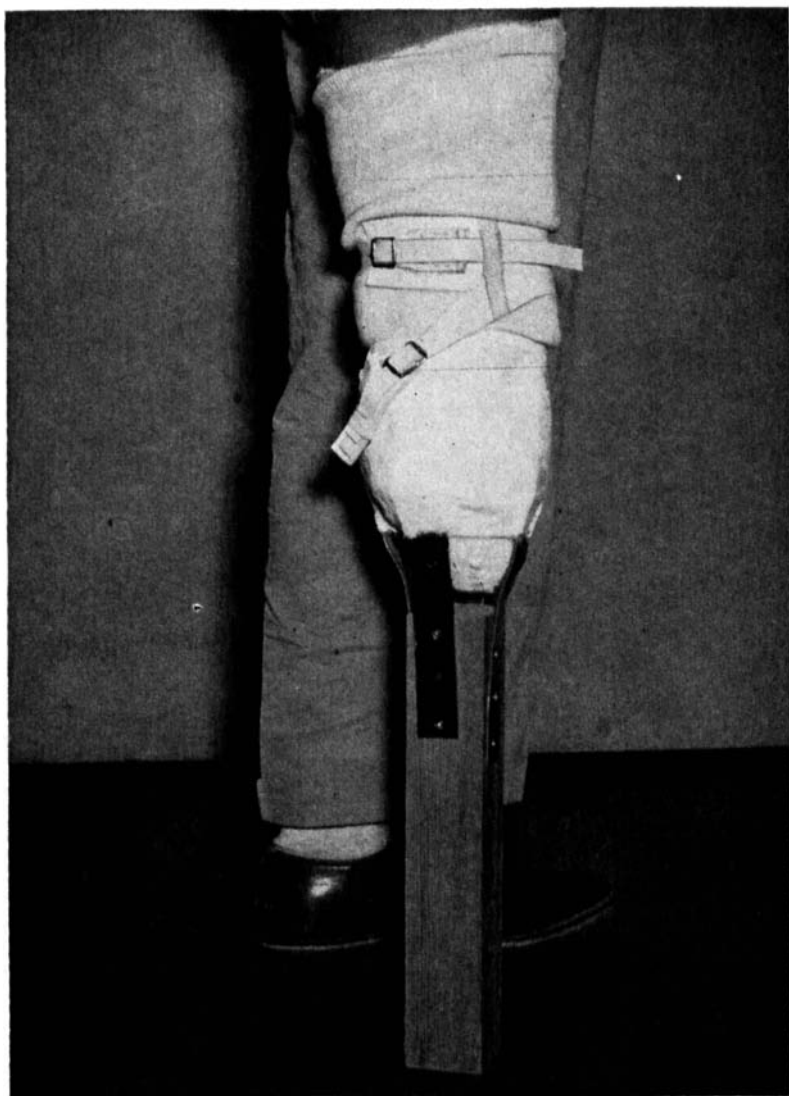


FIG 1. Useful appliance (pylon) for below-knee amputations.

The amputee is placed in a sitting position on a table with knee of leg to be fitted several inches or cms. beyond table's edge, and flexed to 25 degrees. This position emphasizes identification of bony prominences, the patellar tendon and hamstring tendons, thus ensuring reduced pressure to popliteal area and avoiding interference with knee flexion.¹

Stockinette of double thickness and stitched at one end is placed over stump, knee and lower thigh to form a stump sock. The stockinette should be free from wrinkles which cause undesirable roughness in socket's interior.

One-one half rolls of plaster-impregnated bandage gauze (or plaster-impregnated stockinette) are applied in a series of circumferential wraps. The plaster is smoothed and worked around bony prominences with each wrap. The proximal portion of the socket should not be higher than the tibial plateau or distal portion of the patella, while the distal portion of the socket should allow the stump end to be exposed and non-weight-bearing. The patellar tendon and medial and lateral flares of the tibial condyles are good weight-bearing areas. As the plaster hardens, the thumb tips are pressed inwardly on both sides of the patellar tendon causing indentations while the fingers compress the popliteal tissues. The finger impressions made in the popliteal area serve to push the patellar tendon against the shelf (indentations) formed by the thumb tips.

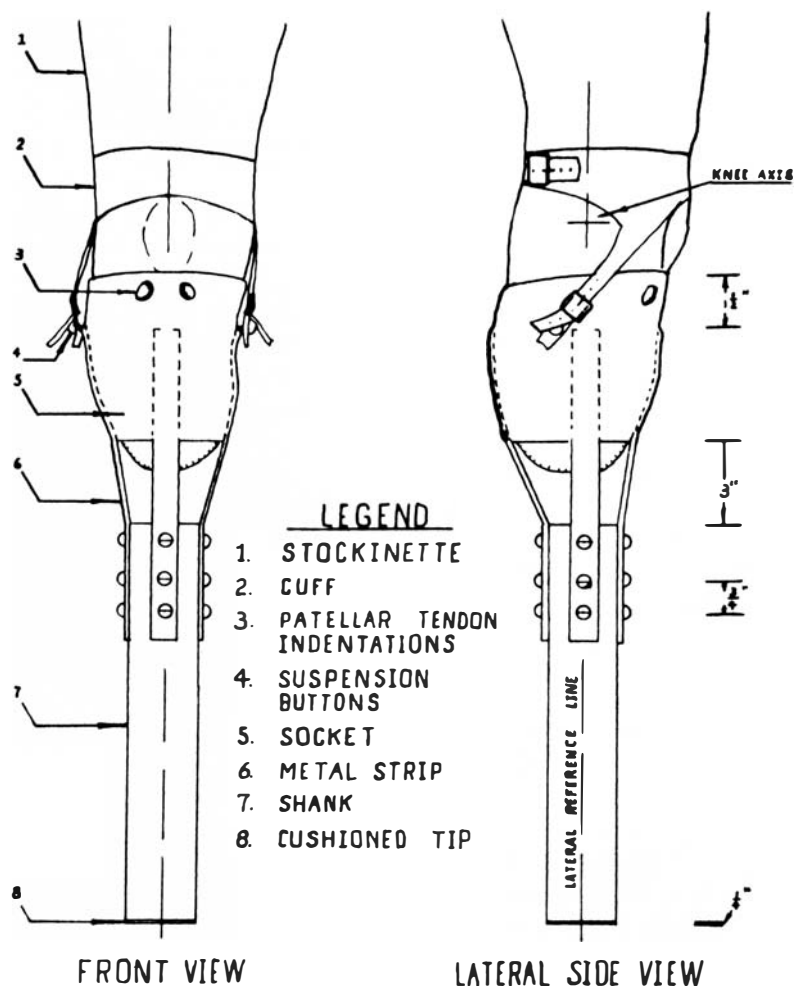


FIG. 2. Below-knee pylon with cuff suspension.

When the plaster has hardened, lateral and medial vertical reference lines corresponding to the knee axis are marked on the socket as are the anterior and posterior mid lines (Fig. 2). These reference lines aid in determining the position of the metal strips for socket-shank attachment. The socket is then removed from the amputee.

Next, the 4 metal strips ($10 \times 1 \times \frac{1}{8}$ inches or $25.4 \times 2.54 \times 0.16$ cm) are fashioned to the socket's contour. One-half of each metal strip's length is secured to the socket over marked reference lines by circumscribing the socket with $\frac{1}{2}$ of a plaster roll.

After the metal strips are thoroughly secured, 3 holes (corresponding to screw's diameter) are drilled $\frac{1}{2}$ - $\frac{3}{4}$ inch (1.27 cm to 1.91 cm) apart at unsecured end of each metal strip. This will serve for socket-shank attachment.

The wood shank ($2 \times 2 \times 18$ inches, or $5.08 \times 5.08 \times 45.72$ cm) is placed between the unsecured ends of the 4 metal strips. A distance of 3 inches (7.62 cm) must separate shank from distal portion of socket to prevent stump tip rubbing against the shank. When the shank has been properly positioned, it is secured to the 4 metal strips by means of screws.

The length of the shank is determined the following day (to allow plaster to set). The amputee is seated in a standard chair with knee of normal leg flexed to 90 degrees and with a shoe on the foot. The distance from the tibial plateau (top rim of socket) to the floor is measured and transferred to the pylon. The extra shank length is sawed off $\frac{1}{4}$ inch (0.64 cm) shorter than measured distance to permit attachment of rubber tip. The rubber is compressed during the stance phase of walking, thus allowing for shock absorption.

The pylon and stump sock are placed on the stump. The height of the pylon can be checked for error by having the patient seated, both knees flexed to 90 degrees and laying a carpenter's level across the knees.² If an error has been made the cushioned tip can be altered to bring the legs to proper length.

When a below-knee amputee stands, the body's centre of gravity changes from that of a normal subject; as a result, the pylon will often shift laterally when the thrust of body-weight is borne. When this occurs the medial metal strip is repositioned lower on the shank by changing the screw position. This will compensate for the change in the body's centre of gravity.

The cuff is adequate for suspending the pylon to the below-knee amputee. Two small leather straps ($1\frac{1}{2} \times \frac{1}{2}$ inches, or 3.81×1.27 cm) with tabs and buckle are manufactured (Fig. 3). This pattern can be reversed when cuff for left leg is desired. The cuff encircles the knee and rests against upper patellar edge. This serves to lock the patella in position for maintaining pylon in proper position. When body-weight is borne, the patella rests against the socket indentations

provided during initial moulding. When the leg is raised in walking, the patella rests against the cuff preventing pylon from falling off. The cuff should be loose upon sitting and snug upon standing.

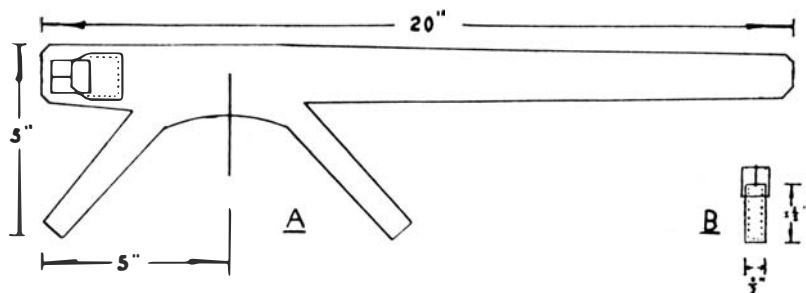


FIG. 3. A—Right knee cuff with tabs. B—Socket strap.

The cuff tabs are adjusted to the socket after the amputee stands on the pylon with body-weight evenly distributed on both legs and cuff is fastened. Pull cuff tabs down on both sides of the knee to their natural position against the socket. Mark the outline of the tabs on the socket. A 1-inch (2.54 cm) wood screw (suspension button) is inserted directly behind the lateral and medial vertical reference lines (posterior to knee axis) and slightly below top rim of the socket. The screws may be reinforced with small plaster strips. These screws anchor the cuff tabs to the socket.

The pylon is completed and ready to be worn by the amputee for gait training.

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2. HOOGE, J., "An Experimental Below-The-Knee Prosthesis", *The Physical Therapy Review*, 38, 326-30 (May 1958).

A STUDY OF VADRINE, ALONE AND COMBINED WITH SULPHETRONE

by

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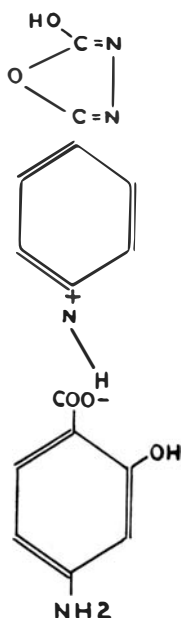
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Introduction

Vadrine of Messrs. Geistlich Ltd. has been reported on previously by JOPLING, W. H., and RIDLEY, D. S., in 1958, who tried it in leprosy patients. It is 2-pyridyl- (4)-1, 3, 4,-oxydiazalone-(5) p-amino salicylate with the following formula:

In the Philafrica Mission in Angola in September 1955 we also began a trial of this drug and treated 40 cases up to May 1960. We have chosen to report on 20 of these cases, mainly because the lepromatous element was important in these 20 cases. For primary drug trials we think that tuberculoid cases should not be selected, because there is a tendency to spontaneous healing in tuberculoid cases, and it is not easy to give a fair clinical assessment. The 20 selected cases have been treated for an average period of 33 months (18 to 50 months). The usual physical and laboratory examinations were given to all cases. During the trial the bacterial index was estimated every 3 months, and photographs and skin biopsies were taken every 6 months. The average dose given of Vadrine was 30 mg./kg. of body weight, as the optimum dose appears to be between 30 and 40 mg./kg.

Lepromatous reactions of the ENL type occurred in 6 of the 20 selected cases, and there were milder reactions in 6 others. Mild anaemia occurred under treatment in 8 cases, but this improved without the exhibition of iron. There was 1 case with marked anaemia. There was 1 case of nephritis which responded well to ordinary treatment and which seemed to have no relationship to the taking of Vadrine. A sensation of burning in the feet and sometimes in the legs was the only possible symptom relatable to the drug. This occurred in 8 cases during the 2nd and 3rd years of treatment. There were breaks in the treatment of 3 cases, leading to serious clinical and bacterial index deterioration. The replacement of Vadrine produced a definite improvement in each case. In most cases under treatment lepromatous lesions flattened and the infiltrations progressively disappeared. In 3 cases ulcer healing was prompt after Vadrine had been begun. On Vadrine all the patients felt better and fitter. Bacilli showed changes in form and tended to become beaded,



and histological improvement was present but slower, appearing at least 1 year after the beginning of treatment. General improvement after the first year was less spectacular but it continued slowly. *Results* after the second year were classified as follows, excellent in 3, good in 4, satisfactory in 7, stationary in 5, and bad in 1. In 10 cases the *lepromin* reaction became slightly positive, after being negative at the beginning, and in 4 of these 10 cases there was a greater predominance of the dimorphous features along with the lepromin test improvement. We think that most leprosy cases pass through a "dimorphous zone", in evolution either towards lepromatous or tuberculoid leprosy. Such cases as transform into lepromatous leprosy show dimorphous features previously masked by the lepromatous element as the latter begins to clear. In such circumstances, as these cases pass into the atypical tuberculoid zone of the dimorphous spectrum one would expect the lepromin reaction to transform from a negative to a positive.

Fig. 1 shows a graph of the improvement under Vadrine treatment. It will be noted that in the first 6 to 12 months the bacterial improvement under Vadrine was comparable to that under DDS, but after 12 months, the improvement began to lag behind that seen under DDS and Ciba-1906. After 18 months the improvement curve tended to remain level. Of the 20 cases, 4 had no relapse up to this time and 2 were stationary with an eventual slight deterioration. The 12 other cases showed clinical deterioration after 22 months of treatment with Vadrine alone. The earliest relapse occurred 14 months after the beginning of treatment and the latest was at 36

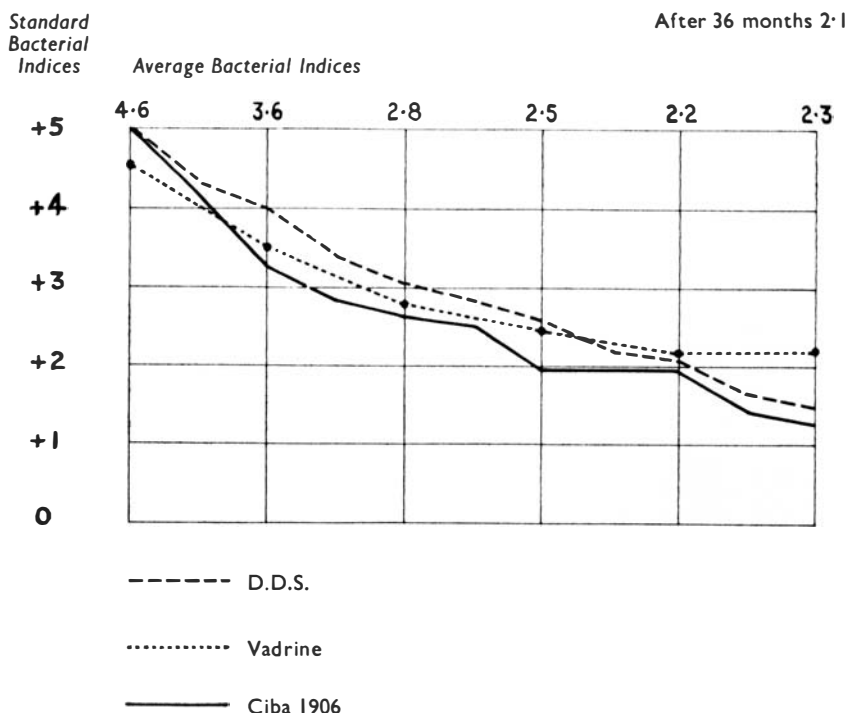


FIG. 1. Chart Showing the Average Bacteriological Index of 18 Cases on Vadrine Therapy at six-monthly intervals.

months. One case had 47 months' treatment without any evidence of deterioration. Clinical deterioration preceded bacterial or histopathological and showed itself by new lesions appearing and old lesions exacerbating. Hence we thought that Vadrine should be combined with Sulphetrone in the hope of preventing the resistance to Vadrine which appeared after about 18 months. We found evidence that this was so.

Illustrative cases

Because there is not space for all cases, notes of 2 cases under treatment are here given. 1 under Vadrine alone, 1 under Vadrine plus sulphetrone.

Case under Vadrine Treatment alone

Case 1. FELIZ CHISSINGUI. No. 658, Jamba. Male, aged 35 years.

This patient was admitted into the leprosarium on 26th November, 1956. Macules had appeared on the right arm and thigh a year prior to admission. On examination the body was seen to be covered with small diffuse macules, typical of lepromatous leprosy, small nodules on the edge of the ears, and infiltration of the lobes of the ears was also seen. Treatment commenced in February 1957, and the dosage given was 1200 mgms. daily, that is 22 mgm./kg. body weight. The following is the histopathological report on the biopsy taken before treatment began.

Patients under Vadrine alone (FELIZ) and Vadrine plus
Sulphetrone (NAVAYA)



FELIZ Dimorphous



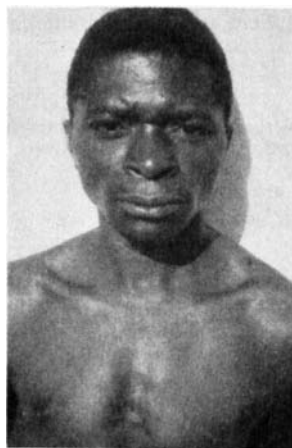
FELIZ Dimorphous



NAVAYA Leproma



FELIZ Healing leproma



FELIZ Healing leproma



NAVAYA Leproma,
commencing resolution

Lab. No. 2596.

H.E. SECTION: A gross infiltration is seen with a relatively clear sub-epidermal zone. The granuloma consists of well-developed macrophages and considerable round celled infiltration is seen. These round cells occur in collections and among them are fairly numerous plasma cells. In one area near to a hair follicle and fairly superficial there is a small focus with round cells in the periphery and epithelioid cells in the centre. There is some evidence of foamy cell change, but this is not conspicuous. Nerves, generally speaking, are well-seen and uninvolved. However, there are some nerves in which there is a certain amount of cellular involvement, but in the Fite Faraco section the increase of the cellular infiltrate appears to be largely in cells of Schwann.

F.F. STAIN: Fairly numerous acid-fast bacilli seen throughout the section, showing no morphological change.

DIAGNOSIS: This is an active case with lepromatous features. Activity is shown by the presence of fairly numerous plasma cells, but there is also some evidence of epithelioid cell formation and round celled infiltration which is much more than one would ordinarily see. There is also further evidence of a commencing lymphocytic response. Nevertheless, the histology is predominantly lepromatous.

In April 1957 it was noted that, while there was some clinical improvement, macular lesions were more evident and were slightly elevated, and definite paraesthesia developed on the extremities. In August 1957 the patient showed blisters on the feet and on the right hand. There was also some reaction on the ears, which had become swollen and showed some desquamation and crust formation. The macules had changed their characteristics somewhat, and showed elevation and some erythema. The biopsy report on tissue taken in August 1957 was as follows:

Lab. No. 2847.

H.E. SECTION: There is a massive infiltration occupying about 80 per cent. of the total area of the corium with a relatively clear sub-epidermal zone. The granulomatous infiltration consists almost entirely of epithelioid cells with, here and there, an occasional giant cell. Amidst this epithelioid granulomatous tissue there are foci of round cells and plasma cells, but there is no true tubercle formation. Nerves are quite unrecognizable.

F.F. STAIN: Scanty acid-fast bacilli seen here and there in the section and are generally arranged singly and show no morphological change.

DIAGNOSIS: This is a very active dimorphous lesion towards the tuberculoid end of the spectrum rather than the lepromatous, although the tuberculoid features—except for the fact that most of the cells are epithelioid with an occasional giant cell—are not very marked.

A photograph was taken in August 1957 and showed definite macular lesions on the chest. Unfortunately, the first photograph, taken before therapy commenced, was lost in the post. In January 1958 there was considerable improvement and the macular lesions were much less conspicuous. The following is a biopsy report on tissue taken in January 1958:

Lab. No. 2955.

H.E. SECTION: A diffusely scattered infiltration is seen underneath the epidermis of moderate intensity, extending into the deeper parts of the corium, but in this area the infiltration is only slight. The infiltration consists largely of histiocytes and round cells, and there is some evidence of foamy cell change. In one area in the vicinity of a hair follicle round celled infiltration is more marked.

F.F. STAIN: No acid-fast bacilli seen.

DIAGNOSIS: In the absence of definite acid-fast bacilli this is a difficult section on which to give a diagnosis, but the picture is consistent with a resolving lepromatous lesion. The fact that there do not seem to be any nerves cut across in the section might suggest a previous dimorphous lesion,* but in the absence of evidence one must conclude that the biopsy is taken from a resolving or healing lepromatous case.*

* It is to be noted that biopsy readings are made without access to clinical notes and, therefore, I (R.G.C.) would not know when I gave the report, the findings of the previous biopsy—2847.

The patient continued to make substantial progress. He was taking 1,200 mgms. Vadrine daily until 1959, when he started taking 1,600 mgms. daily.

The bacteriological indices were as follows:

January 1957	—	5.0
March 1957	—	1.1
August 1957	—	0.5
5 negatives were then recorded.		
November 1958	—	0.1

From October 1959 to January 1960 all bacteriological investigations were negative.

The Mitsuda reaction in January 1957 was negative, and in February 1959 it was slightly positive. A biopsy of the lepromin reaction showed essentially lepromatous histology.

Comments

In the first instance this case appeared to be lepromatous, but with treatment the lepromatous features began to subside and the previous dimorphous lesions that were masked by the ascendancy of the lepromatous element in dimorphous leprosy began to assert themselves. It is interesting to note that the lepromin reaction changed from a negative reaction to a slightly positive reaction. This need not have been significant, for the biopsy of the lepromin reaction in 1959 indicated essentially lepromatous features, but, nevertheless, there was in all the biopsies some indication of a dimorphous element in the tissue response—the patient remaining negative up to May 1960.

Vadrine plus Sulphetrone (50 per cent aqueous solution) Treatment

Case 5. NAVAYA NANGA, No. 627, Jamba. Female, aged 45 years.

This patient was admitted into the leprosarium in August 1955. It was stated that the first signs of leprosy were noted a year previously, when the patient felt a sensation of heat in the body. In May 1955 tiny nodules appeared on the face. After a time her condition deteriorated and she applied to the institution for admission. On admission she patient presented the following clinical signs: gross nodulation of the ears, smaller nodules on the face, partial loss of the eyebrows and some infiltration of the forearms, but no nodulation of the trunk. The lepromin test was negative to both reactions. The following is a report on tissue taken at the time of admission:

Lab. No. 2368.

H.E. SECTION: There is a gross infiltration throughout the epidermis, leaving a moderately narrow, free, sub-epidermal zone. The infiltrate consists of

macrophages and round cells. Plasma cells are not conspicuous. The nerve changes are interesting in that there is marked proliferation of the perineurium and yet the nerve shows considerable cellular invasion. Foamy cell change is not conspicuous.

F.F. STAIN: Fairly numerous acid-fast bacilli seen with little morphological change.

DIAGNOSIS: This section is probably taken from a lepromatous case although the histological evidence suggests that it may be very near to the borderline end of the lepromatous spectrum.

It will be noted that mention has been made of the state of the nerves in the tissues, indicating that they showed more cellular infiltration than one would normally expect to see in a straight lepromatous case, and, therefore, it is suggestive that the patient had passed through the dimorphous zone in the evolution of the disease towards lepromatous leprosy, as so often happens in our experience.

The patient commenced Vadrine therapy on 28th September 1956 having had no appreciable treatment with DDS previously. She was given 1,200 mgms. Vadrine daily during the first two months, followed by 1,600 mgms. daily, which is 30 mgms./Kg. body weight. A biopsy was taken in January 1957 and the following is the report:

Lab. No. 2600.

H.E. SECTION: There is a moderate to gross infiltration seen underneath the epidermis, leaving a relatively clear sub-epidermal zone. In the superficial parts of the dermis the infiltrate is seen and consists of a small area of foamy cell change amidst which there is seen fairly numerous round cells. As one looks deeper into the dermis the granulomatous infiltration becomes more marked and extends to the subcutaneous fatty tissue. Amidst the foamy cells are numerous round cells and a few plasma cells. Nerves, while not grossly invaded, show considerable cellular increase and some infiltration between the nerve bundles. There is considerable proliferation of the perineurium.

F.F. STAIN: Fairly numerous acid-fast bacilli seen, showing gross morphological change.

DIAGNOSIS: This has the appearance of a moderate lepromatous lesion, showing commencing resolution under therapy.

The next biopsy was taken in April 1957 and showed comparatively little alteration:

Lab. No. 2817.

H.E. SECTION: There is a generalized infiltration throughout the corium, leaving a narrow, relatively clear, sub-epidermal zone. The granulomatous infiltrate occupies about 60 per cent of the whole of the corium. The infiltrating cells are chiefly histiocytes and macrophages. There is a certain amount of foamy cell change. Here and there are more definite foci. These are associated with the skin appendages and consist of epithelioid and round cells and an occasional small giant cell. Nerves, by and large, are well seen, although there is considerable increase in Schwann cells. The epithelioid foci appear as if they are in connection with a nerve, but no nerve tissue is discernible.

F.F. STAIN: Acid-fast bacilli are seen throughout the section in moderate numbers except in areas where there are epithelioid cells. The *M. leprae* show some morphological change.

DIAGNOSIS: This is a lepromatous case showing some activity, with evidence that it either shows dimorphous signs clinically or else it has passed from dimorphous leprosy to lepromatous leprosy. I do not think there is enough

evidence to say that it is a dimorphous case on the lepromatous side of the spectrum. There is some evidence of the influence of therapy, as the *M. leprae* look to be rather broken up.

It is interesting to note that the biopsy report suggests that the dimorphous features, which may have originally been manifest, have now been completely suppressed, as the patient passed into lepromatous leprosy. A biopsy was taken six months later in October 1957. This showed that practically all the bacilli had disappeared. The following is the report:

Lab. No. 2909.

H.E. SECTION: There is a diffusely scattered infiltration of slight to moderate intensity underneath the epidermis. While the sub-epidermal zone is relatively free from infiltration, there is no clear-cut free space. The infiltrating cells are chiefly round cells and histiocytes, but there is some evidence of a concentration of the cellular infiltration around the appendages of the skin, particularly the hair follicles. Nerves are recognizable, but there is a considerable cellular increase (round cells and histiocytes), but no definite tuberculoid structure or characteristic proliferation of the perineurium as seen in lepromatous lesions.

F.F. STAIN: There was one acid-fast bacillus seen in a nerve.

DIAGNOSIS: This is a difficult section to interpret, but it is obviously a lesion improving under therapy. While there are no definite dimorphous features in the section, the fact that the nerves show a greater cellular increase than one would normally find in lepromatous leprosy is suggestive that this is a healing case with evidence of residual dimorphous lesions.

Subsequent to this, the patient's condition began to deteriorate. First, very occasional acid-fast bacilli appeared in the section. Many of these bacilli were not granular, but were well developed, indicating that the patient's clinical condition had deteriorated, and that the bacilli were returning to the rod-shaped form. This was further evidence that Vadrine probably had had its maximum effect.

Conclusions

During the experimental period of 4 years, we found that Vadrine appeared to have a definite action in lepromatous leprosy during the first 2 years, the results being comparable to, or slightly better than those seen in DDS therapy over a similar period. The effect of the drug becomes less obvious at the end of 2 years and little improvement is seen after that time.

We think that Vadrine has advantages in its rapid action in the first 12 to 18 months, its lack of toxicity and side effects and its reactions are at a minimum. The optimum dose of Vadrine seems to be 30 to 40 mg./kg. body weight. We found evidence that Vadrine is useful in those cases which show intolerance to sulphone therapy. We think that it is inadvisable to continue Vadrine therapy for more than 2 years. There is some evidence that combination with sulphones prolongs the useful period, but this evidence is not yet conclusive. On signs appearing of clinical and bacterial deterioration we think a change of treatment is advisable.

In addition to Vadrine being a useful initial treatment in cases which show intolerance to sulphone therapy, we think there is also some evidence that even after 2 years its combination with sulphones enhances the effectiveness of the therapy.

We point out that no drug has yet been discovered which is uniformly successful in every case of leprosy. The sulphone group of drugs are of great value in most cases of leprosy but there are still a few patients who fail to respond to them by adequate improvement and about 10 to 16% do not respond at all. Alternative drugs are called for in this group of cases and it would seem that Vadrine could be used as one of these drugs, either alone or in combination with one of the sulphones, our preference being parenteral Sulphetrone. It looks as if the therapy of leprosy is now beginning to run parallel to that of tuberculosis, and the logical approach to the treatment of an active lepromatous case is to use a rapidly-acting drug such as Etisul for 3 months, followed by Vadrine, combined with one of the sulphones (probably Sulphetrone). Finally, at the end of 2 years of continuous treatment with Vadrine and Sulphetrone, the patient may be put on diphenylthiourea (Ciba-1906). For the adequate approach to the therapy of leprosy it is essential that the physician should have a number of drugs available so that he may change or combine them in order to avoid drug resistance.

Acknowledgments

We express our appreciation to Geistlich & Sons Ltd., Wolhusen, Switzerland, for their supply of Vadrine (S131) used in this trial.

Reference

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VADRINE COMBINED WITH SULPHONE IN THE TREATMENT OF LEPROMATOUS LEPROSY

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Vadrine (the p-aminosalicylate of 2-pyridyl-(4)-1, 3, 4,-oxydiazolone-(5)) was found to possess appreciable activity in lepromatous leprosy in a small trial of 7 patients (Jopling and Ridley, 1958), but the subsequent development of drug resistance in the majority after 9-15 months' treatment discouraged us from carrying out further trials of the compound used alone. However, because of the very promising initial response in some of these patients, and the complete absence of toxic effects, we decided to give Vadrine a trial in combination with sulphone.

Method

Five lepromatous patients admitted consecutively to the Jordan Hospital (2 European, 1 West Indian, 1 Nigerian, 1 Indian) received Vadrine together with standard doses of sulphone. They had not been treated previously. In the hope of minimising the chances of Vadrine-resistant strains of bacilli emerging, the dosage was increased more rapidly than in the previous trial, as follows:

1st week: One tablet of 200mg. twice daily (400mg./day).

2nd week: Two tablets of 200mg. twice daily (800mg./day).

3rd week: Three tablets of 200mg. twice daily (1200mg./day).

4th week: Four tablets of 200mg. twice daily (1600mg./day).

Dosage was not increased further once it reached 40mg./kg./day, i.e. 2000mg./day for a 50kg. patient. On the larger dosage we were able to use 500mg. tablets instead of 200mg.

Clinical progress was observed and recorded at weekly intervals, photographs were taken before treatment and subsequently every 6 months, and bacteriological progress was assessed by carrying out 6-8 skin smears and 2 skin biopsies every 6 months.

The small number of new admissions did not permit the concurrent treatment of control cases on sulphone alone, and it was therefore necessary to evaluate the progress of our 5 patients against our well documented records of previously admitted similar lepromatous patients who had received sulphone therapy.

Clinical results

During the first 6 months all 5 patients made excellent clinical improvement, and by the end of this period all macules had disappeared and the majority of plaques and nodules had become flattened and impalpable. The rate of improvement appeared to be more rapid than that which could have been expected from sulphone alone; in fact, the improvement after 6 months was comparable with that which we would have expected after 12 months' treatment with sulphone alone. During the course of the next 6 months the remaining skin lesions disappeared leaving no trace apart from pigmentation in some instances, but the paucity and smallness of the remaining lesions at this stage made it difficult to compare subsequent progress with that which would have been expected from sulphone alone.

Erythema nodosum leprosum (ENL) developed in 3 patients during the first year causing serious interruption of treatment from the beginning of the second 6 months in Case 3 (see below) and during the second year in Cases 4 and 5, thus making further evaluation of therapy impossible.

Bacteriological results

As in the earlier trial, combined bacteriological and histological progress was assessed on an index obtained from biopsies of skin lesions. The results are as follows:

<i>Case</i>	<i>Percentage Fall in Biopsy Index</i>	
	<i>1st 6 months</i>	<i>2nd 6 months</i>
1	64	20
2	27	41
3	57	25
4	55	50
5	27	56
Mean	46	28

The corresponding figures for a series of 16 similar cases treated at the Jordan Hospital with sulphone alone are 33% for the first period of 6 months and 23% for the second; for another series of 28 lepromatous cases treated in overseas institutions but analysed by the same method, the corresponding figures are 30% and 22%. The difference between the figures 46% for Vadrine plus sulphone and 33% or 30% for sulphone alone during the first 6 months accords with clinical impressions of the superior progress of the Vadrine cases during this period. In the second 6-monthly period the results are normally more erratic and the mean fall lower than in the first period because of the onset of ENL. Four out of 5 patients continued

to make excellent bacteriological and histological progress during this second period even though two of them developed mild ENL. In the fifth patient (Case 3) ENL was sufficiently severe to necessitate interruption of treatment, and there was a bacteriological (though not a clinical) relapse. This has caused the mean fall in the index for the second period to be lowered to 28%, which is only a little better than the expected figure for sulphone alone. It would probably have been justifiable to exclude this patient on account of the interruption of treatment, in which case the mean figure would have been 42% which is substantially better than the expected 22% or 23% for sulphone. However, in view of the individual variation in response, a larger series would have been needed to establish that the differences were statistically significant.

An interesting aspect of the figures is that one of these 5 patients, and one from the previous trial of Vadrine alone, showed two consecutive improvements of 50% or more for the first and second periods. This is an exceptional event which has never previously been observed at the Jordan Hospital.

Conclusion

The trial was too small to be conclusive, but the results suggest that the combination of Vadrine and sulphone is substantially superior to sulphone alone for the first stages of the treatment of lepromatous leprosy, or until the onset of ENL. As far as is known Vadrine has no toxic effects or contra-indications.

Acknowledgments

Our thanks are due to the Physicians at the Hospital for Tropical Diseases for their co-operation and permission to report on their patients; to Miss Marian Wise for preparing the histological sections, and to Edward Geistlich & Sons, Ltd., Wolhusen, Switzerland, for generous supplies of Vadrine.

Reference

JOPLING, W. H. and RIDLEY, D. S. (1958), *Leprosy Review*, **29**, 143.

THE TREATMENT OF LEPROMATOUS LEPROSY WITH NEOVADRINE AND VADRINE IN COMBINATION WITH DDS

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Neovadrine and Vadrine are related compounds. The former is 2-pyridyl-(4)-1, 3, 4,-oxydiazolone-(5) and Vadrine is the p-amino-salicylate.

For the trial we chose 21 lepromatous cases without borderline features, and gave to 10 Neovadrine combined with DDS and to 11 Vadrine combined with DDS. Previous treatment in 15 cases had been DDS alone for varying periods. Biopsies were taken of all cases at the beginning of the trial, and biopsies were again taken 6 months later in order to establish the Biopsy Index and percentage fall for the period. During the trial clinical and bacterial examinations were made at intervals of 3 months, the first assessment at 9 months, and the second 3 months later. Results were compared with those of DDS. Dosage of Neovadrine and Vadrine began with 1 tablet daily of 200 mg. increasing by 1 tablet weekly to a maximum of 20 mg. per kg. of body weight and 40 mg./kg. per day, respectively. This combined with 100 mg. DDS daily.

Conclusions

Evaluation of the efficacy of Neovadrine/DDS and Vadrine/DDS compared with DDS, depends on clinical impressions and bacteriological studies. These methods leave much to be desired, but are sufficient to formulate an opinion, whether, or not, the combinations, by virtue of increased effect, should replace DDS.

The yardstick of comparison is based on a study of a large number of lepromatous cases treated with DDS over the past 10 years.

The clinical impression gained, in this small series of cases, after 21 months of treatment, suggests a slightly better response, and manifested equally by both combinations. Cases Nos. 12 and 17 show an accelerated response. This phenomenon, however, can also occur with DDS, no doubt the result of mutation of immunological response in some individuals.

Examination of the Biopsy Index shows a mean percentage fall of 41% in six months, which compares favourably with results from elsewhere (RIDLEY). Unfortunately no figures are available for our own DDS cases.

TABLE OF RESULTS

Case No.	Sex	Age	Stage of Disease			Previous treatment with DDS	21 months of combined treatment NeoV/DDS or V/DDS	Bacteriology						Biopsy Index			Reactions		Comparative study of results				
			Advanced	Mod. Ad.	Early			Skin smears			Nasal smears			Initial	After 6 mos.	% Fall	R.A.C.	S.R.N.	Improvement exceeds DDS	On a Par after 9 mos.	Exceed DDS after 21 mos.	On a Par after 21 mos.	Remarks
								Initial	After 9 mos.	Latest	Initial	After 9 mos.	Latest										
African	1	M	12			6 mos.	NeoV/DDS	+5	+5	+5	+5	+1	Neg.	5	3.2	36							
"	2	M	28		+	6 mos.	NeoV/DDS	+5	+5	+5	+5	+1	+1	4.5	2.8	38			+				
"	3	M	30			4 mos.	NeoV/DDS	+5	+5	+5	+5	+1	Neg.	4.5	2.7	40			+				
"	4	M	19			5 mos.	NeoV/DDS	+5	+5	+5	+5	+1	Neg.	4	1	75	+		+				
"	5	M	20			5 mos.	NeoV/DDS	+5	+5	+5	+5	+3	+2	4	3.6	10		+					
"	6	M	16			4 mos.	NeoV/DDS	+5	+1	+3	+5	Neg.	Neg.	1	0.3	70			+				
"	7	M	42		+	4 mos.	NeoV/DDS	+5	+5	+5	+3	+3	+3	6	0.6	90		+	+				
"	8	M	14			3 mos.	NeoV/DDS	+5	+5	+5	+5	+4	Neg.	4	1.7	57			+				
"	9	M	38			Nil	NeoV/DDS	+5	+5	+5	+5	+1	Neg.						+				
"	10	F	24			Nil	NeoV/DDS	+5	+5	+5	+5	+2	+1	5.4	2.8	48		+					
"	11	M	45			2 mos.	V/DDS	+5	+2	+4	+5	Neg.	Neg.	.45	.23	49			+				
"	12	M	35		+	2 mos.	V/DDS	+5	+2	+1	+5	Neg.	Neg.	.24	.09	62			+				
"	13	M	45			Nil	V/DDS	+5	+4	+5	+2	Neg.	+1	.25	.08	68			+				
"	14	F	34			6 mos.	V/DDS	+5	+5	+5	+5	+3	Neg.	.5	.08	84							
"	15	F	20			5 mos.	V/DDS	+5	+3	+5	+5	Neg.	Neg.	3.6	2.3	36	+		+				
"	16	F	22	+		5 mos.	V/DDS	+5	+5	+5	+5	+1	+1	4	3	25							
"	17	F	36			4 mos.	V/DDS	+5	+5	+2	+5	Neg.	Neg.	.5	1	—50							
"	18	F	40			5 mos.	V/DDS	+5	+5	+5	+1	Neg.	Neg.	1.8	1.4	22		+					
"	19	M	35			Nil	V/DDS 11 mos.	+5	+5	+5	+5	+1		3	.1	97			+				
"	20	M	15			Nil	V/DDS	+5	+5	+4	+5	+2	Neg.	.75	2.8	—73							
"	21	M	34			Nil	V/DDS	+5	+5	+5	+5	Neg.	Neg.	5	2.8	44							

R.A.C.—Reactionary Anaemia Complex. S.R.N.—Symptomless Reactionary Nodules. P—Pregnant.

Cases 6, 11, 13 and 15 showed bacteriological worsening of the skin smears after an average interval of 12 months, suggesting the emergence of resistant strains, and further indicates that the p-aminosalicylate component of Vadrine, likewise, is unable to prevent this.

Of note is the absence of toxicity attributable to these compounds. The incidence of cases with symptomless reactionary nodules is not exceptional. Case No. 15 experienced a more severe reaction, probably the result of pregnancy.

The efficacy of the combinations suggests an initial augmented bacteriostatic effect, unfortunately shortlived, but nevertheless useful. The phase of gradual resorption of infiltrates and bacterial clearing continues, and depends to a large extent on the individual's varied tissue responses. A forecast of the ultimate time interval required for arrest of the disease, suggests that a slight reduction only, compared with DDS, can be expected. This hardly warrants their routine usage for the treatment of lepromatous leprosy.

Summary

The Oxydiazolones appear to be non-toxic when used in combination with DDS.

Their adjuvant action suggests an initial additive effect only, followed later by bacteriological worsening, suggesting the emergence of resistant organisms. The p. aminosalicylate component of Vadrine does not prevent this.

It is unlikely that the ultimate duration of treatment required will be appreciably reduced compared with DDS.

Acknowledgments

I wish to express thanks to Ed. Geistlich Sons Ltd., Wolhusen, Switzerland, for their generous supplies of Neovadrine and Vadrine, and Drs. Jopling and Ridley for their co-operation and for undertaking the Biopsy Index studies.

Thanks are due to the Director of Medical Services, Southern Rhodesia, for permission to publish.

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RIDLEY, D. S., (1958), *Leprosy Rev.*, vol. 29, No. 1, p. 45.

DIAMINO-DIPHENYL SULPHOXIDE IN THE TREATMENT OF LEPROSY: A DEFINITIVE REPORT ON EXPANDED TRIALS

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Further experience gained in the treatment of leprosy with Diamino-diphenyl sulphoxide (DDSO) in the Research Unit at Uzuakoli and in several neighbouring leprosy settlements, subsequent to the progress report by Davey *et al.* (1957), has substantiated certain of the earlier findings and has amplified the tentative conclusions reached concerning the toxic qualities of the product.

Cognisant of the warning contained in the above report that certain observed abnormalities might prove serious at higher dose levels, and having been informed that the drug was potentially toxic, the Tokyo Congress (1958) passed a Technical Resolution to the effect that further studies of the drug, especially its toxicity and its use in the later stages of treatment, should be undertaken.

This definitive report on expanded trials with DDSO embodies the results of further study and attempts to answer outstanding questions regarding toxicity and therapeutic value.

It is recalled that DDSO was recognized as a bactericidal agent principally through the investigations of Fournneau *et al.* (1937) Buttler *et al.* (1938), and that Buu-Hoi *et al.* (1955) first used the drug in the treatment of leprosy. In addition to Davey *et al.* (1957) in Eastern Nigeria, Laviron *et al.* (1957) and others have employed the drug elsewhere.

On the analogy of the good results obtained with Dapsone in the treatment of dermatitis herpetiformis, DDSO has been given for this condition (Alexander, 1958).

Choice of patients

The patients who took part in this expanded trial represented a typical cross-section of leprosy as it occurs among patients seeking admission into settlements in Southern Nigeria. They were unselected as regards age, sex and duration of the disease. Most of them had received no previous treatment.

The following settlements co-operated with Uzuakoli: Oji River, Isoba, Itu, Uburu, Abakaliki and Ossiomo.

Clinical forms of leprosy

Lepromatous	64
Borderline	6
Tuberculoid	44
Indeterminate	8
	<hr/> 122 <hr/>

Some of the patients originally classified as "lepromatous" or "tuberculoid" subsequently developed borderline features.

Dosage of the drug

For the purposes of the pilot trial, it was inferred that since the molecular structure of DDSO resembled that of Dapsone, dosage scales should be similar to those employed with Dapsone. The scales then adopted were continued throughout the present trial.

Adult patients received the drug in the following doses during a cautious build-up (which has been held to minimize the risk of toxic complications, especially dermatitis): 70 patients received 100 mgm. twice weekly for 3 weeks; 200 mgm. twice weekly for 3 weeks; and 300 mgm. twice weekly thereafter; 37 patients received 100 mgm. daily for six days a week; 7 children received 50 mgm. daily, and 8 adolescents received 200 mgm. twice weekly, as definitive doses.

The average weight of the adults was 124 lbs. (56.4 kg.), and the average age was 33 years.

Controls

For the first 24 months of the trial at Uzuakoli, patients under treatment with DDSO were paired with patients undergoing standard Dapsone treatment. Once the absolute efficacy of the drug had been established, precise comparative studies with paired patients were discontinued.

It was at first considered that the therapeutic action of DDSO was somewhat different from that of Dapsone in the following respects: with similar doses the clinical and bacteriological improvement was greater; smaller doses were effective; the toxic signs followed a different pattern, anaemia being less marked and liver damage occurring relatively late; DDSO was thought not to precipitate neuritis and lepra reaction as frequently as did Dapsone.

Further experience has not substantiated the earlier impressions, except as regards toxicity: specifically, a pattern of kidney damage became apparent to which detailed reference will later be made.

Duration of treatment

Treatment was continued with DDSO for an average of 36 months for bacteriologically positive patients and for 30 months for the bacteriologically negative.

Progress under therapy: Clinical

As with other treatments for leprosy, clinical progress has not been uninterrupted in all cases. Several patients admitted to treatment in an active or progressive phase of the disease showed some exacerbation before steady improvement became established.

The results of treatment in this expanded trial do not differ materially from those obtained in patients receiving Dapsone in standard doses. Taking all clinical criteria into consideration, the following assessment of progress was made in those who continued treatment with the drug till the end of the trial.

Excellent	23
Good	65
Fair or Slight	17
		—	105

In the remaining 17 patients, treatment was discontinued for the following reasons:

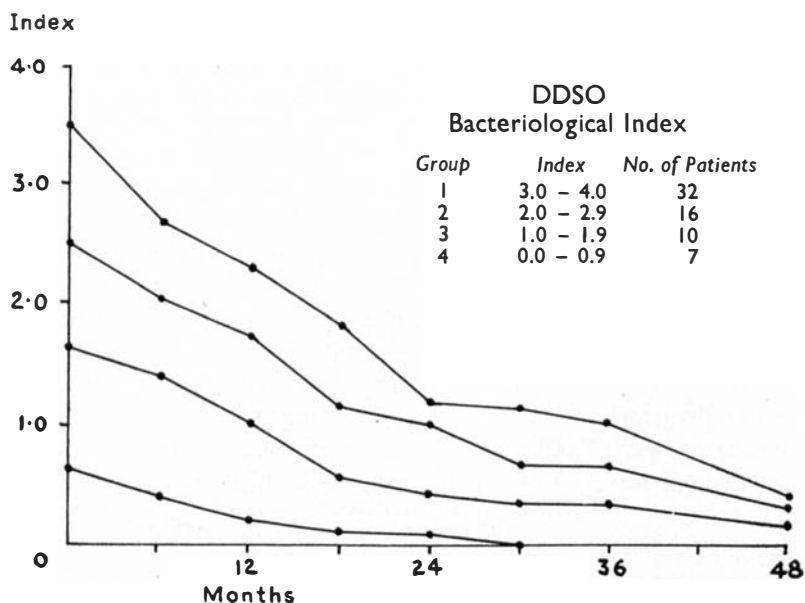
Haematuria	8
Dermatitis	4
Severe lepra reaction	1
Psychosis (including one patient with hepatitis)	2
Hepatitis	1
Death (from Yellow Fever)	1

Of the 70 Uzuakoli patients, 27 who had received no drug but DDSO were discharged symptom-free, and 16 out of 33 bacteriologically negative patients were considered to require further treatment after having received the drug for 30 months. Subsequent progress has been without incident in these patients, and similar to that expected if Dapsone had been the drug originally employed.

Bacteriological

Most bacteriologically positive patients had smears examined at eight sites at monthly intervals. The collated results are expressed in the accompanying figure.

The rate of morphological degeneration of the *M. leprae* in the routine smears resembled the pattern habitually observed in patients under Dapsone therapy.



After making progress similar to that of other patients with disease of comparable severity, 4 patients suddenly showed an increase in the Bacteriological Index, with reappearance of *M. leprae* of normal morphology in the routine smears. Normal bacilli were first seen in the nasal mucosa in one patient, in the cutaneous lesions in another, and in both skin and ear lobes in the remaining two patients. The raised Index persisted for a variable period before returning to the pre-existing level and then resuming its downward trend; normal bacilli usually disappeared as the Index fell. The sustained nature of the elevation would suggest that the findings were not fortuitously dependent on the hazards of smearing but may be explicable on other grounds.

The increase occurred in all four patients in the rainy season; all had lepra reaction with erythema nodosum at the time; one of them was suffering from severe anaemia which had necessitated reduction in the dose of drug.

Serial No.	Age	B.I. on admission	Length of treatment before B.I. rose	B.I. in the month before the rise	Raised B.I.	Duration of raised B.I. before return to pre-existing level
9750	6	2.8	34 months	2.6	3.4	16 months
9749	6	1.8	11 „	1.5	2.0	11 „
9769	12	3.0	27 „	0.9	1.7	27 „
2474	40	3.4	26 „	0.8	1.6	25 „

Relapses

Of the total of 47 patients who have been discharged from Uzuakoli with the disease clinically arrested (27 having received DDSO only), 35 have attended subsequently for examination, most of them more than once. Of these, 3 patients have relapsed, 2, 10 and 12 months respectively after discharge; there are almost certainly no relapses apart from these three. In two of the three, *M. leprae* were found in the smears: one of them had been bacteriologically negative for 14 months before discharge, and the other had never been positive. Bacilli were present in the ear-lobes of both patients, and also in the skin lesion in one, and in the nasal mucosa in the other.

All three relapses were in patients whose lesions have subsequently shown Borderline features, indicating immunological instability. The duration of treatment with DDSO (none having received any other treatment) had been 25, 26 and 38 months. In retrospect, it is evident that treatment of these patients should have continued for longer.

Toxicity

Since DDSO possesses no obvious advantage over Dapsone in the treatment of leprosy, and since it is, moreover, at least twice as expensive to manufacture, its sphere of use will be determined by its toxicity and the incidence of undesirable side-effects.

Anaemia

In addition to the signs of slight initial reduction in haemoglobin levels already reported, two patients under therapy experienced more severe anaemia.

Dermatitis

Several types of cutaneous reaction to DDSO were noted: in four patients they were sufficiently severe to warrant suppression of the drug.

1. A papular irritating dermatitis in two patients. In one, the dermatitis recurred with every administration of the drug; a slow desensitization with aqueous Solapsone was successful, and treatment was eventually resumed.
2. A diffuse melanosis, facial in one patient, and generalized on the trunk in two others;
3. A discrete hypermelanotic macular rash, in one patient, similar to the cases reported by Browne (1959, 1960) with Dapsone and Solapsone;

4. Marked hypermelanosis of lepromatous infiltration was seen on the face, particularly the forehead and cheeks, in two patients.

Three patients showed parallergic sensitivity to DDSO and to Dapsone; one of them was also sensitive to Ditophal ("Etisul"), and another to both Ditophal and the barbiturates. On the other hand, one patient who was sensitive to Dapsone, received DDSO for 20 months before developing dermatitis.

Lepra reaction

Fourteen of the 64 lepromatous patients under treatment developed lepra reaction with erythema nodosum, of varying severity.

Iritis

Two patients had iritis.

Neuritis

Twenty-four patients developed neuritis of one or more main superficial nerve trunks during the trial.

Psychosis

Three patients, with no obvious history of mental instability, developed psychotic symptoms. In two, although clinical progress had been satisfactory in other respects, treatment with the drug had to be abandoned.

Hepatitis

Two patients developed clinical signs of liver damage, after two years of treatment.

Schlesinger's test (for urobilin) was performed every month on all Uzuakoli patients. From the 16th to the 25th months inclusive, this delicate test was positive on 47 occasions, and in 6 patients definitely abnormal findings were reported on 10 occasions between the 20th and 26th months: in 2 of these the liver was slightly enlarged and tender.

One patient died after a brief illness characterized by pyrexia, jaundice and coma, with massive albuminuria. The liver showed the typical histological picture of Yellow Fever.

Kidney damage

The toxic action of DDSO on the kidneys, already suspected, has been confirmed.

In the majority of the 70 Uzuakoli patients concerning whom detailed laboratory data were available, albuminuria was discovered

on at least one occasion during the course of treatment. In the last 12 months of the trial a "clean" specimen of urine obtained from all patients having a trace of albumin, failed to show albumin in approximately one-half of the specimens. In about one-half of the remainder, the albumin may have arisen in tissues other than glomeruli or tubules, for, in addition to epithelial cells and leucocytes, these specimens contained one of the following: gonococci, spermatozoa, oxalate or triple phosphate crystals, *Trichomonas vaginalis*. No schistosome ova were found, and no crystals other than those mentioned.

A total of 36 patients had albuminuria, probably of renal origin, at some period during the trial. In 28, a "faint trace" was recorded at least once, but in seven of these erythrocytes were present in the deposit after centrifugation, and in two, casts were found. All seven patients whose urine contained "1 plus" of albumin at least once, passed erythrocytes in the specimen that contained albumin, and two had casts in addition. In the single specimen in which the amount of albumin was returned as "2 plus", erythrocytes and casts were also present.

The erythrocytes were generally scanty, under 3 per field (of the $\frac{1}{8}$ -inch objective) of the deposit after centrifugation; they occurred mainly from the 11th to the 13th months of treatment, and from the 22nd to the 24th, but few months were entirely exempt.

In the course of the trial DDSO was discontinued in eight patients because of persistent microscopic haematuria. After improvement in the urinary condition, another anti-leprosy treatment was instituted.

When the nephrotoxic action of the drug was beyond doubt, the trial was concluded. Thereafter slight albuminuria persisted in 12 patients intermittently for some months (1 to 19); in two patients, microscopic haematuria persisted for 2 and 5 months respectively, and casts were found in one of the latter up till 2 months.

The presence of erythrocytes in the urine was not related to the reaction of the urine; nor to pyuria—infection with resistant organisms can thus be excluded. It could not be correlated with the dose/body-weight ratio, or with the frequency of administration of the drug.

Dysuria and strangury were absent, except in one patient, who complained of these symptoms after the drug had been suppressed.

The blood urea was estimated in 25 patients, in 16 of them twice. In all cases, it was within normal limits. In nine patients, the second examination gave slightly lower readings than the first performed six months previously.

It is inferred from these findings that the unchanged drug or certain of its metabolites have a nephrotoxic action, slight or moderately severe, and usually transient, in a regrettably high pro-

portion of patients receiving standard doses of DDSO for the prolonged periods necessary for the adequate treatment of leprosy.

Earlier reports concerning kidney damage with the drug have been made. Kimmig (1948) declared that its potential toxicity for the kidney rendered its use inadvisable in human disease; but Buttle *et al.* (1938), and Laviron *et al.* (1957) did not consider it more toxic than Dapsone.

Alexander (1958) using DDSO for dermatitis herpetiformis, in relatively high doses up to 200 mgm. daily, mainly in elderly patients, reported a high incidence of urinary complications after a short period of treatment. Haematuria was noted in 3 patients out of 11, frequency of micturition in 7, dysuria in 4. The urine contained *Esch. coli* in 2 patients and *Staph. aureus* in one.

It is known that DDSO is partly converted into Dapsone and excreted as such (Levi & Snow, 1960), but it is unlikely that this moiety could account for the toxic effects noted in such a high proportion of patients, since it is distinctly uncommon for Dapsone in standard doses to cause haematuria in leprosy patients on prolonged treatment. Combes and Reisch (1957) reported 3 patients who developed "cystitis" under Dapsone therapy, and Verma (1958) reported one. Van Ketel (1960) recorded three urinary tract infections among 13 patients treated with Dapsone (Cf. Alexander's cases, referred to above, of the same disease treated with DDSO); but Kroichik and Tumasheva (1960) specifically mention the absence of urinary tract infections in 54 patients treated with Dapsone for psoriasis and other dermatoses.

Conclusions

1. Diamino-diphenyl sulphoxide has a definite anti-leprosy action in doses of the order of 300 mgm. twice weekly or 100 mgm. daily by the mouth.
2. Clinical improvement is obtained in all varieties of leprosy.
3. Reduction in the Bacteriological Index and disappearance of morphologically normal *M. leprae* generally follow a consistent pattern.
4. The clinical and bacteriological amelioration is similar in all respects to that with Dapsone.
5. The incidence of such side-effects as anaemia, psychosis, lepra reaction and erythema nodosum and hepatitis appears to be similar to that in comparable groups of patients undergoing Dapsone therapy.
6. The incidence of dermatitis is higher with DDSO than with Dapsone.
7. In a high proportion of patients who receive standard doses of the drug over prolonged periods, DDSO has a direct nephrotoxic

action shown by the occurrence of albuminuria, and haematuria, and the passage of casts.

8. Notwithstanding its therapeutic efficacy in the treatment of all types of leprosy, the nephrotoxic action of the drug renders its further use inadvisable.

Acknowledgments

Our thanks are due to the Medical Officers who, in leprosy settlements in the Eastern Region of Nigeria, co-operated in this trial: Drs. A. S. Garrett, K. Ellis and W. F. Ross (Oji River); M. G. Corcos, and A. Paklikowski (Isoba); M. Phillips (Itu); A. McDonald (Uburu); M. Chambers, E. Fern and D. McLoughlin (Abakaliki); and B. Nicholson at Ossiomo in the Western Region.

Special thanks are expressed to Dr. L. M. Hogerzeil, Area Superintendent of Owerri Province, Uzuakoli Settlement, for his ready help during the trial. The Yellow Fever services of the Yaba Federal Laboratory were responsible for the histological diagnosis of Yellow Fever in the case recorded.

We acknowledge with gratitude the generous supply of Diamino-diphenyl sulphoxide placed at our disposal by Messrs. Imperial Chemical Industries (Pharmaceuticals) Ltd., and particularly the help of Dr. J. Michael Mungavin.

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LEPROSY IN BALI, INDONESIA

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Medical Secretary, The Mission to Lepers

The following information is abstracted from reports sent to The Mission to Lepers by Dr. E. SPENCER REED, Government Leprosy Officer, Den Pasar, Bali, Indonesia.

Bali is a diamond-shaped island, about 85 miles by 55 miles, lying at the Eastern tip of Java, with a population of about 2,000,000 people. The religion is predominantly Balinese Hindu and this permeates to the very core of the lives of the people in the villages.

Government Leprosaria

There are six leprosaria sited around the island. The number of in-patients in December 1959 was 292; in December 1960 it was 277. Most of these patients have gross deformities and mutilations. The accommodation provided is rough and simple, but generous rations keep the patients remarkably happy.

Medical supervision is carried out by the Leprosy Officer once a month, by an assistant once a week, and by a "dresser" daily.

These leprosaria are mainly social homes for the aged, the destitute and the maimed, and for orphans. They do not come within the planning of leprosy eradication.

Clinical Unit

A Clinical Unit was completed at Den Pasar in 1959, and is the organizing centre for the anti-leprosy campaign. It provides 28 beds for the admission of patients from the out-patient clinics, who are needing treatment for complications or for intercurrent infections. It provides accommodation for the treatment of out-patients; 12 rooms for patients employed to assist with the work; offices, dispensary and laboratory, and store rooms.

In the first ten months following the opening of the ward unit 50 patients were admitted, and 28 were still under treatment at the time the report was written. The conditions for which the patients were admitted were as follows:

1. For reaction conditions	29 patients
2. For grossly infected ulcers	7 patients
3. For malnutrition and neglect	3 patients
4. For acute infections	9 patients
5. For spiritual rehabilitation	1 patient
6. For operation for ectropion	1 patient

Treatment places

Arrangements have been made to give treatments at some 95 places, including 34 general hospitals and polyclinics, 26 shelters of bamboo and coconut (mostly provided by the villages and erected by the patients themselves), 20 under roadside trees, or in the houses of patients, 6 in connection with the Government leprosaria, and 1 at the special clinical unit.

Dr. Reed writes, "Headway at last seems to have been made in the last area in Bali where there is not only a high incidence of leprosy, but also a strong resistance to any efforts to provide places for treatment. Now two locally elected officials have proved most helpful, and something will almost certainly be done in the near future. This will mean that our first objective has been attained—the provision of places at which patients can get treatment within reasonable walking distance (up to 3–4 miles) of their homes".

Workers

The finding, employment and training of suitable men to assist with this programme has provided Dr. Reed with many problems, and inherent difficulties have been greatly increased by rising prices and widespread economic disturbances. Trained and untrained workers have been employed, and on the whole the untrained workers have proved the more satisfactory for "nearly all have now caught the spirit of the campaign which is so important in winning the confidence of the patients and ensuring regularity in their attendance; they are now giving out the DDS tablets conscientiously, and, mostly, accurately".

"But the brightest side of the picture is the willing help given by some of the more intelligent patients of the younger generation, most of whom have now been to school for a period. One of these is the only reliable person available to do such administrative work as the accurate keeping of the central register. These patients are invaluable also in encouraging new ones to attend regularly, as they will take the trouble to explain patiently just what is involved".

Transport

All available forms of transport are used by those attending to the patients in the clinics. The Government has provided a jeep and two motor cycles which are used to visit the more distant places in the mountains. Other workers use motorised bicycles, a number of which were supplied by UNICEF and by The Mission to Lepers. Yet others use the buses or the local hospital jeep. Petrol and maintenance is met by Government grants with some assistance from The Mission to Lepers.

Two new areas were opened up during 1960, one of them being a small island 20 miles off the coast and reached only by outrigger canoe. "This island is mountainous without any roads so visiting means a 60-mile trek, with only bare boards as a bed at night, and plain rice without meat or vegetables for meals". However in three special tours undertaken either by the doctor or the male nurse 75 new patients were found.

Attendance

The number of patients who were being treated at the end of December 1960 was 2,141. This includes both the 298 who were living in the government leprosaria, and 1,843 attending the clinics.

Those attending the clinics are classified as follows:

	<i>Lepromatous</i>	<i>Tuberculoid</i>	<i>Indeterminate</i>	<i>Total</i>
Male	382	806	14	1,202
Female	154	482	5	641
				<hr/> 1,843 <hr/>

The number of voluntary new patients brought under treatment since the campaign started in Sept. 1956 is				1,658
Adding the number registered in Sept. 1956		1,074
				<hr/>
		the total is	...	2,732 <hr/>

Treatment

In the majority of cases DDS has been found the treatment of choice. Induction is begun for all patients with 25mg. twice weekly for the first month. This is increased to 50 mg. for the second month, then to 100 mg. and in the 4th month two 100 mg. tablets are given on two days in each week.

Supplies of Ciba-1906 were also made available and were found of great value in the treatment of patients with tuberculoid reaction conditions. On the other hand 16 out of 18 cases admitted to the ward for persistent minor lepra and/or ENL episodes show as much intolerance to this drug as to DDS. All these cases are now on a lengthy course of desensitization by intramuscular injections of 50% Sulphetrone solution twice weekly, a method found most successful in earlier years before the ward was opened for the six reaction cases that lived within walking distance of the clinic. 100% of these patients have now tolerated full doses of DDS for over a year without any discomfort.

Progress

Some indication of the progress that has been made is shown by the fact that "in one area where treatment has been given longest, and where there is no prejudice against new patients coming forward for treatment, there were 250 cases of "arrest" last year, while new patients totalled 100".

29% of these new patients however already had developed some degree of minor disability when they presented themselves. Many of these conditions would respond to treatment.

Severe mutilations were present in only 3% of the new patients, and this figure compares very favourably with that of 28% of the total in 1956.

Certificates of arrest have so far been issued to 376 patients.

Propaganda and Public Opinion

Dr. Reed reports "Almost a medico-social revolution has taken place in the attitude of the community towards patients and their illness mainly owing to the remarkable effect of DDS in preventing hideous deformities, which surely are the main cause of the world-wide fear of the illness. This means that it is now rare for a patient to be hounded out of his occupation. Even those with pre-treatment deformities have learnt to compensate for these in a remarkable way so that to all intents and purposes all our out-patients are employable, and all but a very few lazy ones do in fact perform traditional family and community duties.

In fact, recently a new problem has arisen. Attendances in a widespread area suddenly fell, the reason being that the patients had been included in the village work list for communal rice gathering. One of these villages was fanatical in its attitude to the illness only a few years ago.

The very fact that patients are getting better before their eyes is perhaps the most important reason for the changing attitude; but a tape recorder has also been used to give talks in Balinese in villages where prejudice has been most marked. 10,000 information leaflets have also been distributed.

Home Visits

Arrangements made for visiting the homes of patients have not been carried out as conscientiously as is desired. Such visits are needed to find out the reason for failure to attend regularly at the clinics; and to make yearly examinations of contacts of lepromatous patients.

WHO Survey

During 1960 Dr. Reed helped organise a WHO "Pilot Project"

in return for which he was provided with free supplies of DDS and the use of a station wagon. Three erstwhile yaws campaign workers were specially trained to detect the early signs of leprosy. In the course of the year 73,000 persons were examined, amongst whom 24 new leprosy cases were found.

Dr. Reed's conclusions confirm those of other experienced leprosy workers that the most practical and economical way to get new patients is to establish treatment centres in those areas where leprosy is known to exist. Within one or two years the good results of treatment are sufficiently self-advertising to draw in voluntarily an increasing number of shy and as yet unknown patients. Contact tracing of these patients by a good conscientious worker can then lead to excellent results.

Supplies of Sulphetrone from B. W. & Co., of Ciba 1906 from Ciba, of Etisul from I.C.I. are gratefully acknowledged, as well as the support of the Head of the Bali Health Department, of UNICEF and of The Mission to Lepers.

THE MISSION TO LEPERS IN-PATIENT UNIT
OF THE KYUNGBUK UNIVERSITY HOSPITAL,
TAEGU, KOREA
JAN. 1st—DEC. 31st, 1960

G. K. WILSON, M.B., B.S.

On 5th December, 1959, Dr. Han of the Ministry of Health and Social Affairs of the Republic of Korea opened The Mission to Lepers In-patient Unit in the Kyungbuk University Hospital Compound.

The purpose of this 4-bed unit was to supplement the work of the out-patient clinics begun in 1957 by the Rev. C. M. and Mrs. Lloyd and Miss Grace Bennett, S.R.N., by providing more specialised care of patients with lepra reactions and other complications. A further aim was to find out whether this would prove a satisfactory method of meeting this need; and as far as possible to assess how great the need might be.

The unit is part of the Government General Hospital with its attached Medical School and is thus in a most strategic position both medically and spiritually. The consultant services of all departments are available as well as the facilities of the operating theatre, the X-ray, clinical and surgical pathology, and pharmacy departments. The leprosy centre is, in fact, a Leprosy Department of the General Hospital, and as such is treated like any other department.

Details of the work undertaken in this department during 1960 are as follows:

Admission

30 patients were admitted, two of whom were readmitted for other conditions than those treated on the first occasion.

Ages ranged from 17 to 59 years.

Sex

Of the 32 admission 24 were male, 8 female.

Classification

Indeterminate	2	Tuberculoid	10
Borderline	0	Lepromatous	20

Bacillary Index

19 patients were negative, of whom 7 were classified as lepromatous, 10 as tuberculoid and 2 indeterminate.

Source

9 patients were admitted from the Taegu Clinic, 16 from the mobile clinics and 5 from leprosy colonies lacking facilities for the treatment indicated.

Duration of stay varied from 1 to 63 days. The average stay for reaction cases was 33 days; for those on whom operations were done for foot ulceration it was 36.1 days.

Operations

21 operations were performed. Two patients each had two operations; one had three (and a fourth in 1961).

Conditions for which patients were admitted

Reaction	5	Injuries	2
Anaemia	1	Liver abscess	1
Neuritis	2	Amputation forearm	1
Nephritis...	1	Incision finger	1
Foot ulceration	8	Hepatitis	1
Carcinoma	2	Ovarian cyst	1
Hydrocele	2	Cataract	4

25% of admissions were for conditions other than those directly or indirectly due to leprosy.

The operations performed on the 30 patients admitted were for *other conditions than leprosy*:—

- (1) Ovarian cystectomy.
- (2) Halstead's Mastectomy for carcinoma of breast.
- (3) Gastro-jejunostomy for inoperable carcinoma of the stomach.
- (4) Hydrocele sac excision.
- (5) Hydrocele sac excision with epididymectomy and orchidec-tomy.
- (6) Herniorrhaphy.
- (7) Laparotomy and drainage of liver abscess.

for complications of leprosy:—

- (1) (2) (3) Curettage of sequestra in foot ulceration.
- (4) Metatarsectomy of 5th digit.
- (5) Amputation of 1st and 2nd digits to the Navicular bone.
- (6) Transverse mid-metatarsal amputation.
- (7) Amputation of forearm for gangrene.
- (8) Ulnar nerve sheath stripping fo neuritis.
- (9) Eyebrow transplant.
- (10) Secondary suture of wounds.

Ophthalmic operations:—

Cataract operations on 4 patients.

Results

Reactions. Although general measures were tried at first, pyrexia did not respond until Stibophen was used. Including the patient who was admitted with anaemia, and who developed lepra reaction during his stay, haemoglobin values in 4 of the 6 patients were below 65%, and gave poor response to iron therapy. 4 of the 6 patients were lepromatous.

Acute Neuritis. One of the two patients was discharged after five days, but continued to have intermittent neuritis. The other patient had relief from pain for 3 months following the nerve sheath stripping operation; later the pain was much less than before the operation.

Nephritis (Bright's disease Type II). There was a satisfactory initial response to treatment, albuminuria becoming minimal after 26 days. Albuminuria had disappeared after five months.

Foot ulceration. Six operations were done under spinal anaesthesia. One was cauterised and trimmed without an anaesthetic. In three the results have so far been satisfactory; in two the results are not yet known. One in a woman who was pregnant healed without operation.

In two patients the ulcers were over the lateral malleoli, a common site due to the Korean habit of sitting cross-legged and unprotected on a hard, and often very hot floor.

Carcinoma. The patient with carcinoma of the breast showed no signs of metastases 10 months later, when she was admitted for foot ulceration. The patient with the inoperable carcinoma of the stomach died a month after a gastro-jejunostomy.

Hydrocele. In both patients the results appear satisfactory. One patient had had a herniorrhaphy without release of symptoms, so the hydrocele sac was excised together with diseased epididymis and testis. This patient had eyebrow transplants done, and was in the ward for 63 days.

Injuries and burns. One patient was a girl of 17 with multiple burns on hands and legs. The other was a boy of 19 who had allowed a fellow-patient to remove not only the whole of his third finger, but also the metacarpal bone as well, the exposed wound being left to granulate. Secondary suture was performed to this and another smaller wound.

Liver Abscess. This patient was admitted from the Roman Catholic leprosy colony about 20 miles away. A laparotomy was done followed by drainage of the abscess.

Amputation of the Forearm. This patient was admitted from the Roman Catholic colony. Gangrene had developed and amputation of the forearm was undertaken.

Incision of Finger. The patient came 200 miles with a cyanosed septic finger. Lateral incision relieved the pressure and the finger recovered.

Hepatitis. This patient had jaundice and diminished liver function, both of which returned to normal. He also developed psychotic disturbances so has been put on DPT.

Ovarian Cyst. Unfortunately there was such delay before the operation could be undertaken and the patient died under the anaesthetic.

Cataract. Extractions were performed on four patients. One was successful in the patient who developed an inoperable carcinoma of the stomach. Two cases have not returned since the operation. One was referred from a leprosy colony from which no further report has been received.

Comments

The four-bed unit has met the need for which it was planned; it has proved that patients will come for in-patient treatment and that this is a satisfactory way of meeting the need.

The total need is still difficult to assess; emergency treatment was needed for some patients whom we could not admit. At the end of the year there was a waiting list of 15 and only those in most urgent need could be admitted. Further the numbers attending the clinics are steadily increasing; in addition it is found that the worst sufferers concentrate in numerous small leprosy villages from which we need must admit patients for special care and attention.

The growth of the out-patient clinics begun in March 1957 is shown in the following figures:—

March 1958	245	patients	were	treated.
March 1959	413	„	„	„
March 1960	578	„	„	„
Nov. 1960	660	„	„	„

Conclusions

The co-operation of the University Hospital has made for success in this experiment. It is hoped that this co-operation may continue and make possible an expansion of the unit to 15-20 beds to help meet the need not only for the emergency treatment of out-patients, but also for reconstructive and plastic surgery. This work has not as yet been undertaken, but its importance is realised especially for those patients who return home after attending clinics.

The value of the centre for the training of medical students is also appreciated, as it is possible for them to learn to treat leprosy as another disease, and leprosy patients as any other patients but perhaps even more in need of personal interest, care and help.

LETTERS TO THE EDITOR

I. Dr. R. CHAUSSINAND of Institut Pasteur, Paris, writes about the article "Is Leprosy Transmitted by Arthropods?" (by Prof. NIELS DUNGAL of Reykjavik, Iceland, in *Lep. Rev.* 32, 1, pp.28-35). CHAUSSINAND says, "In this article Prof. DUNGAL declares concerning the routes of penetration of the Hansen bacillus that 'CHAUSSINAND and many others with him have incriminated the inhalation of nasal droplets of mucus from infective patients, as in tuberculosis' " (p.29). However, I have always affirmed the contrary, both in my articles and in my books. So in the paragraph in the two editions of *de la Lèpre*, to which DUNGAL refers, is expressed in the following terms, "Most leprologists now consider at the present time that the penetration of the Hansen bacillus through the mucosae is exceptional. They base themselves on the fact that mucosal lesions are never observed at the beginning of the disease. Furthermore, leprosy patients with the benign type of leprosy only infrequently show changes in the pituitary and buccopharyngeal mucosae, and just as in leprosy patients with the malign type of leprosy, the appearance of these lesions always occurs after that of skin and nerve lesions. On the other hand, there is no hint that the Hansen bacillus may enter the body through the pituitary buccopharyngeal and laryngeal mucosae or through the mucosa of the stomach, intestine, and lungs".

As for the various arguments presented in this article, I do not agree with NIELS DUNGAL when he states in connection with my theory on the antagonism between tuberculosis and leprosy: "this theory would explain much, but is difficult to prove".

The phenomenon of crossed premunition between 2 infections relatively akin in nature is determined by the pathogenic agent which infected the body in the first place. This contamination thus renders the body ready to defend itself, in certain measure, against a later attack by the second pathogenic germ. To obtain clinical observations which are conclusive, it is then indispensable in each case to know the primary contaminating agent. There is no room for doubt in this matter, if one is presented with a leprosy patient in whom the tuberculin reactions are negative. On the other hand, the problem will be practically insoluble when the leprosy patient reacts to tuberculin. It is then generally impossible to be certain of the nature of the initial bacillary infection. It is however evident that this crossed premunition is relative and its intensity differs from one subject to the other. The degree of para-immunity of the body against the second infection depends on the degree of acquired immunity against the first infection. A bacillary impregnation which has not provoked any phenomenon of specific immunity cannot produce a para-immunity. So the organism of a lepromatous case of leprosy,

anergic to lepromin, which presents no immunity to the Hansen bacillus, will never achieve premunition by means of its leprosy against a later infection due to the Koch bacillus. The degree and the very existence of the specific antileprosy immunity or especially the antituberculous immunity, which can benefit the body at the moment of its contamination by the second germ, are very often impossible to determine retrospectively. Doubtless this antagonism between tuberculosis and leprosy is not the sole cause for the progressive evolution of the leprosy. Other factors, varying from one country to another, enter in to play a role more or less important. I think we can obtain a valuable clinical hint on the problem of relative para-immunity between leprosy and tuberculosis when one studies the different countries where the two infections are endemic, and the percentage of patients attacked by advancing pulmonary tuberculosis, on the one hand in tuberculoid leprosy patients strongly allergic to lepromin and on the other hand in anergic lepromatous leprosy patients who are anergic to lepromin. The causes of error are considerably equalised in the two groups, if the second group is numerically important and well matched, and if the percentage of advancing pulmonary tuberculosis is significantly high in the group of lepromatous cases. It is especially clear that leprosy cases attacked with active pulmonary tuberculosis should be taken into account. Leprosy patients which do not show any tuberculinic allergy or benign or regressive lesions of tuberculosis should be excluded from these statistics, since this para-immunity can only be relative. Also there should be excluded such patients who have had an antileprosy therapy of the nature of streptomycin, INH, or other drugs very active against tuberculosis.

As for the para-immunity between tuberculosis and leprosy, it is very difficult to obtain a useful indication unless these researches deal with subjects reacting to tuberculin or having been vaccinated or re-vaccinated with BCG, at least 2 years before the appearance of clinical lesions of leprosy. Subjects negative to tuberculin and not vaccinated with BCG should then furnish a higher percentage of leprosy cases and especially of indeterminate or lepromatous leprosy. Whereas among subjects reacting to tuberculin or vaccinated by BCG, after at least 3 years, the cases of leprosy should be rarer and mostly tuberculoid in type.

It is certain that it is difficult to prove the existence of an antagonism between tuberculosis and leprosy but the search for this proof is indeed worth trying, for it will bring, as NIELS DUNGAL justly says, valuable clarification of leprosy epidemiology.

2. Prof. NIELS DUNGAL has seen this letter and replies as follows:

I am sorry to have misunderstood or misquoted Dr. CHAUSINAND's teaching on the possible part of entrance of the *M. leprae*.

I accept with great pleasure and full satisfaction Dr. CHAUSSINAND's quotation from his book on Leprosy, that he with the majority of leprologists thinks that *M.leprae* "does only exceptionally penetrate the mucous membranes".

This is in full agreement with my views as expressed in my paper in question, for if *M.leprae* does not pass through the mucous membranes it must pass through the skin or a lesion in the skin to enter the body. The all important question is how that happens, and that is what all of us should like to know. I have just tried to bring forth some arguments how that transport might be brought about, as none of us seems to accredit the *M.leprae* with a skin penetrating power by itself. Scratches might do it, but insect pricks fit, in my opinion, better in with many observed cases of transmission.

The cross-immunity, between tuberculosis and leprosy is a big chapter which is difficult to discuss fruitfully. In this country I have come to the conclusion that the majority of population has been free from tuberculosis in this century, just at the time that leprosy was being eradicated. We are therefore unable to maintain that tuberculosis has had anything to do with the termination of leprosy here, But, of course, that does not disprove Dr. CHAUSSINAND's theory for other countries.

3. *Correction.* Dr. R. CHAUSSINAND writes pointing out that in his article "Classification of Leprosy", pp.74-81, Vol. 32, No. 2, April 1961 of *Leprosy Review*, in Section 2 p.78 the title "binary classification" used in the text should be replaced by "secondary classification". The word "binary" therefore should be replaced by "secondary" throughout the text of Section 2 of Dr. Chaussinand's article. This error is regretted.

We reproduce here in the original the letter of Dr. Chaussinand. "Cher Dr. Ross Innes,

"Dans le deuxième chapitre de mon article sur la Classification de la lèpre, vous avez traduit le mot français 'secondaire' par le mot 'binary'. Or, en français, ces adjectifs ont une signification totalement différente et je suppose qu'il en est de même en anglais:

" 'secondaire' signifie en français 'qui vient en seconde ligne ou qui ne vient qu'en second lieu'.

" 'binaire' signifie en français, "qui est composé de deux unités".

"Donc une classification binaire est une classification composée de deux unités (lèpre maligne et lèpre bénigne, par exemple).

"Au contraire, une classification secondaire est une sous-classification, qui ne vient qu'en second lieu, après la classification primaire, et qui peut être composée d'un nombre variable d'unités.

"Les deux termes ne sont donc pas interchangeables.

"En conséquence, je prie les lecteurs de mon article de vouloir bien rectifier eux-mêmes, le mot 'binary' devant être remplacé par le

mot 'secondary' partout où il figure dans le deuxième chapitre de mon article, titre compris.

"Toutefois, à part ce léger désaccord linguistique, je me plais à reconnaître que votre traduction est parfaite et je vous présente mes compliments et mes très vifs remerciements.

R. CHAUSSINAND".

4. Vellore Conference on Rehabilitation of Leprosy Patients

Dr. E. W. PRICE, F.R.C.S., kindly provided an account of this conference which we incorporated in the editorial of the April *Leprosy Review*. He wishes us to state that he also was present and took part in the conference.

5. Dr. D. LEIKER of Rotterdam has just returned from a 5-months trip to West Africa, mainly Nigeria, and wishes to correct an error in Table 10, in his paper on Netherlands New Guinea, "Epidemiological and Immunological Surveys." This paper was published in *Leprosy Review* **31**, 4, October 1960, pp.241-259. This Table 10 on p.252 should be amended as follows: The right half of the Table should read:

<i>Males</i>			<i>Females</i>				
	0—4	5—9	10—14	15—19	20—39	40+	<i>Total</i>
	30	22	7	10	60	10	139
	30	22	7	10	59	10	138
	0	0	0	0	0	0	0
	0	0	0	0	1	0	1

Also on p.242 "between 1800 and 1805" should be "between 1800 and 1850".

6. Mr. G. T. Harimurthi writes as regards Dr. DHARMENDRA's new book as follows:

"The arrangements for the sale of his book 'Notes on Leprosy' have been finalised, and the book will now be available for sale from the Central Leprosy Teaching & Research Institute, Tirumani, Chingleput P.O. India, at the price of Rs.8/- per copy exclusive of postage".

7. Dr. J. M. B. GARROD, Director, East African Leprosy Research Centre, writes:

"Your point about light interfering with staining and causing fading deserves to be more widely known. It obviously applies to

places outside E. Africa as a number of people have noted it, Corcos from Nigeria, Dharmendra and Mukerjee from India, Davison and Kooij from S. Africa and my own experience in Rhodesia. It is well known here and precautions are always taken to guard against it, both before and after staining. After staining if a quantity of slides are to be examined they are put in a box or tray with a lid when they are removed from the slide cabinet or drying cabinet”.

References

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DHARMENDRA and MUKERJEE, N., Memoria del V Congreso Intern. de la Lepra 1948, (quoted by Corcos).
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ABSTRACTS

Multiple Puncture Vaccination with Freeze-Dried BCG Vaccine in School Children. M. I. GRIFFITHS, T. W. BRINDLE, E. H. GORDON, T. HOLME and B. JONES. Brit. Med. J., Feb. 25, 1961, pp. 536-539.

The authors used British freeze-dried BCG to vaccinate 2,535 school children in Cheshire between February 1959 and June 1960. They found that multipuncture vaccination with freeze-dried BCG was less effective than intradermal vaccination with a less concentrated freeze-dried vaccination. They also found that heat had a deleterious effect on the vaccine, and that after heat sterilization adequate time for cooling is necessary.

Scope of Plastic Surgery in Leprosy. H. N. ANTIA, Trans. of the Internat. Soc. of Plastic Surgeons, 1960, pp. 547-555.

Dr. Antia, who is Honorary Plastic Surgeon to the J.J. Group of Hospitals, Bombay, and also to Kondhwa Leprosy Hospital, Poona, describes some of the remarkable advances in the scope and technique of plastic surgery. *Nose:* the most evident deformity in leprosy is sunken or *saddle nose*, which nevertheless has the fortunate peculiarity that the skin of the nose is intact in its entirety. For reconstruction there is the very satisfactory operation of postnasal epithelial inlay of GILLIES. Minor nasal depression can be corrected by a bone graft without an epithelial inlay.

Lagophthalmos is due to a selective paralysis of the orbicularis oculi branch of the facial nerve. The result is paralytic ectropion of the lower lid and incomplete closure of the eye. Again, GILLIES' operation of using a temporalis musculo-fascial sling, using an innervated slip of the temporalis, gives a very satisfactory and permanent result (unlike lateral tarsorrhaphy in former use).

Loss of eyebrows is a common stigma of leprosy and can be corrected by an island scalp flap with the anterior branch of the temporal artery as a subcutaneous pedicle, or a transposition flap can be used. A face lift operation can be used for *premature facial wrinkling*, and the elongated *nodules of the ears* trimmed to a normal shape. In the *hand* ulnar and median nerve paralysis is typical but in this the long flexors and extensors are usually spared. This makes possible the operation of sublimis transfer on the many-tailed extensor graft replacement operation of BRAND, which gives consistently successful results with the help of good physiotherapy. In a fully developed claw hand there is loss of the web space, which must be re-established before an opponens transfer can be done for the thumb. A transposition flap from the dorsum gives adequate elongation of the web. Flexion contractures of the fingers due to

burns require Wolff grafting, cross-finger flap, or amputation of a finger, and using its skin to correct the deformities of adjacent fingers. Loss of thumb will require elongation by a "cocked hat" type of operation, and if all fingers and thumb are lost, deepening of the web by excision of the index metacarpal will allow the patient enough pinch to make him independent for feeding and toilet. The chronic plantar *ulcers of the feet* can be healed by local flaps or by a cross-leg flap if more extensive. Anaesthesia for all the above operations has been local, or brachial plexus block, or spinal block. There is often anaesthesia there already, and Pethidine injections suffice. There are many other reconstructive and plastic operations called for in leprosy patients, but facilities so far are very limited and there are very few surgeons who are available. Dr. Antia illustrates his paper with numerous illustrations which alone make his case for more facilities and more colleagues in this enormous and highly successful field of surgery, of which he is one of the pioneers.

The Feldsher in the USSR. WHO Chronicle 15, 3, March 1961, pp. 86-88. This account is based on an article by E. D. ASHURKOV, A. ZHUK and Y. LISITSIN, in *Aspects of Public Health Nursing*, p. 152.

The feldsher is in the USSR an important type of auxiliary medical worker, and belongs there to the "medium-grade class, which also includes nurses, midwives, laboratory assistants, dental technicians, etc. There have been feldshers in Russia since the 18th century but they became more numerous and important when the rural (zemstvo) public health services developed, wherein they assisted and even replaced doctors. In some rural areas they worked alone, in others they were supervised by the zemstvo doctor. The feldsher system was retained after 1917, so that in 1958 there were in Russia 343,000 feldshers, including feldsher-midwives and feldsher-sanitarians. They are integrated into the centres of 74,000 medical districts. The modern feldshers are well trained and still act as assistants to doctors but it seems mainly as independent doctors. Their training seems as comprehensive as that given to a medical student, but over a less period of time (2½ to 4 years). (It is probably this class of officer who in Russia provides the primary casefinding and care of tuberculosis and leprosy patients.)

Estado Actual de la Lepra en el Salvador C.A. (Present State of Leprosy in El Salvador, Central America). A. C. ANAYA, Boletín de la Sociedad de Derm. y Sifil. 17, 2 & 3, June-September 1960, 00. 84-91.

After five journeys of investigation in 1960 the author reported 50 new cases and gives the names of 11 out of 14 departments of the

country where leprosy is now endemic. The department most heavily attacked is Chalatenango with a leprosy rate of 461 per thousand, where the leprosy belongs mainly to three families and their relatives and contacts. Also La Unión and San Miguel are heavily attacked, with 196 and 152 per thousand, respectively. The disease mostly presents in the second and third decades of life, but there are two children under 6 years of age and several old people. The male incidence predominates—129 male to 49 female cases. Most of the leprosy is found in the poor, in ill-nourished labourers who live in huts in deplorable hygienic conditions. The lepromatous type predominates (in 95 of the 178 diagnosed cases). In most cases which have been studied since 1953 the author found abolition of the reflexes at the base of the tongue, and in the pharynx and larynx and the vomit reflex—this has not been seen reported by any other author. The author got BCG vaccination given in the endemic zones of the country. He thinks it is necessary that all doctors and medical students should familiarize themselves with the chief symptoms and signs of leprosy, so as to be able to make a sure early diagnosis and begin suitable treatment as early as possible. Because of these 178 leprosy cases diagnosed and treated, and a probable extra 400 undiagnosed cases, he thinks it right that a committee of two or three doctors should be set up in order to launch a full antileprosy campaign. Drug treatment is more or less satisfactory and many patients can receive supervised domiciliary or ambulatory treatment. Such a campaign would be practicable in El Salvador and not heavily expensive.

Sarcoidosis and Leprosy. D. GERAINT JAMES and W. H. JOPLING. *J. of Trop. Med. & Hyg.* London 63, 22; February 1961, pp. 42-46.

The authors point out that in tropical practice leprosy is recognised but sarcoidosis missed, even though sarcoidosis has a higher incidence in the coloured races. There are certain similarities between the two diseases which might cause confusion in diagnosis. *Sarcoidosis* is a systemic granulomatous disease of undetermined aetiology and²pathogenesis. The parts most often involved are the mediastinal and peripheral lymph nodes, lungs, liver spleen, skin, eyes, bones of the phalanges, and the parotid glands. Sarcoid tissue is made up of follicles of epithelioid cells, occasional giant cells and little or no central necrosis. When stained the epithelioid cells have pale-staining vesicular nuclei, cytoplasm which stains pink, and cell boundaries are clearly demarcated. Giant cells are either of foreign body type or Langhans type and they may have various inclusions. If there is a focus of necrosis it is central and of the fibrinoid type, and is inconspicuous. The sarcoid follicles are usually spherical and often bounded by a scanty rim of lymphocytes. The persistence of

fine fibrils passing through the centre of the follicle is often revealed by reticulin stains. Helpful in distinguishing sarcoid tissue from tuberculous is the absence of acid-fast bacilli, caseation or calcification. It is well known that sarcoid tissue may develop as a reaction to neoplasms, reticuloses, infections, chemicals and trauma, but in that case the reaction is not distinctive and the onus of diagnosis rests on the clinician, not the pathologist. He has to distinguish a non-specific local sarcoid tissue reaction from the generalized reticulo-endothelial disorder which is sarcoidosis. Whenever sarcoid-like tissue has been obtained from any site, search of other systems must be carried on such as skin, eyes, lymph nodes, and spleen, with chest or bone X-rays as well. The Kveim test and serum globulin and urinary calcium levels may be helpful.

Leprosy is a contagious granulomatous disease in which the causal agent is accepted to be *M. leprae*. It primarily involves peripheral nerves but the skin and other organs and tissues may also be affected. In tuberculoid and borderline leprosy the changes are either confined to nerves or may involve skin as well. In tuberculoid and near-tuberculoid cases the histology is similar to that of sarcoidosis, and absence of acid-fast bacilli heightens the similarity. Usually bacilli are present in borderline leprosy and tend to increase as the case approaches the lepromatous end of the spectrum. Lepromatous leprosy veers away from any confusion with sarcoidosis, for it is a systemic disease affecting nerves, skin, reticulo-endothelial system, oral and upper respiratory mucosa, the eyes, bones and testes. The affected tissues show a distinctive histology of vacuolated cells in different stages of development from mononuclear cells (histiocytes) to typical Virchow foam cells (macrophages) with numerous acid-fast bacilli some lying singly and others packed in greatly swollen macrophages to form globi, or in smaller bundles and groups.

Differential diagnosis. In the skin, lesions of the two diseases are often very similar. The first step in distinguishing them is to *test the skin lesions for anaesthesia* to pain, light touch, and sensation to heat and cold, because such sensory impairment favours the diagnosis of tuberculoid or borderline leprosy. Lepromatous lesions are not anaesthetic, but a skin smear from one of the lesions stained by Z.N., will always show acid-fast bacilli, and additional evidence is the *finding of one or more thickened peripheral nerves*. By silver impregnation staining techniques it may be possible to demonstrate axonal degeneration in or near the granuloma, which is typical of leprosy. Conversely, the presence of normal cutaneous nerves in or near the granuloma is evidence against leprosy. The differentiation from borderline leprosy is less difficult, as cutaneous nerves are readily seen, and cellular infiltration within the nerves is not so intense, and the nerves are more likely to be swollen than destroyed. It is possible to

demonstrate acid-fast bacilli lying singly within the nerves and in the dermis.

Skin plaques may undergo transient erysipeloid swelling and redness in both sarcoidosis and leprosy of any type, but only in leprosy is this reaction liable to progress to ulceration.

Mucosae. The nasal mucosa may sustain lepromatous or sarcoid nodulation; the former ulcerates and gives off a bloody nasal discharge, whereas the sarcoid does not. The same applies to the buccal and other upper mucosa.

Hair. Loss of scalp and body hair does not occur in sarcoidosis but in tuberculoid leprosy a plaque in a hairy site loses local hair and borderline also has lesser degrees of hair loss in plaques. Lepromatous has no local skin loss over a lesion of the skin but in advanced cases there is deficient hair in eyebrows, even in eyelashes, and in Japan even alopecia is reported.

Eyes. In both diseases there may be involvement of cornea, iris, and ciliary body, and lead to eventual blindness; also common to both are superficial punctate keratitis, and iridocyclitis, also chronic adhesive iridocyclitis with episodes of the acute form, leading to secondary glaucoma. Retinal deposits may be seen in both diseases. A useful point is that the cornea in sarcoidosis is dry and irritating whereas in leprosy the cornea is likely to be anaesthetic. Facial nerve damage is much more common in leprosy, so the seventh nerve should be tested. A combination of facial weakness and corneal anaesthesia is diagnostic of leprosy.

Reticulo-endothelial system. In leprosy, unlike sarcoidosis, lymph node enlargement occurs only in one type, the lepromatous, and liver and spleen are not enlarged detectably, while lymph gland enlargement is typical only of inguinal, femoral and epitrochlear glands.

Nerves. Thickened peripheral nerves are typical of leprosy of any type, palpable where the nerves lie superficial in their course. There may be caseation in nerves in tuberculoid leprosy. Neural sarcoidosis is uncommon, and peripheral neuritis is rare and does not lead to deformities such as in leprosy.

Bones. In leprosy there is aseptic necrosis which usually starts in the terminal phalanges of the fingers so that they thin and gradually disappear. The absorption goes from the distal one upwards. The metacarpal and carpal bones are spared. In the feet there is a common concentric absorption of the heads of one or more metatarsals, and Charcot joints may later appear. Later true septic necrosis, and deep trophic ulceration of anaesthetic hands and feet may commonly occur, atrophy of anterior nasal spine and generalised osteoporosis, claw hand, etc. are common late changes, whereas in sarcoidosis bony changes consist only of innocent punched-out phalangeal cysts, occasionally with swelling of the digits, but usually revealed by

routine radiography. In sarcoidosis bone absorption with consequent deformity is rare; likewise there is an absence of anaesthesia of hands and feet.

Lungs. Lung changes are common in sarcoidosis, e.g. early bilateral hilar adenopathy which either clears up or goes on to diffuse mottling. Lung changes in leprosy probably do not occur but full studies should be done to make sure of this.

Kidneys. In the later stages of lepromatous leprosy there may be chronic glomerulo-nephritis or secondary amyloidosis, but in sarcoidosis the common change is nephrocalcinosis, with raised levels of serum and urinary calcium.

Testes. These are not involved in sarcoidosis but in lepromatous leprosy the testes contain large numbers of bacilli and in late cases become shrunken, with sterility but not impotence. The urine contains a raised level of FSH from the anterior pituitary, but the urinary 17-ketosteroids are within normal limits. Later the testicular interstitial cells are damaged, causing impaired secretion of testosterone with resulting impotence, gynaecomastia, osteoporosis, and diminished output of urinary ketosteroids. During a reactional state there may be additional acute epididymo-orchitis in one or both testes.

Reactional States occur in both diseases, of a type of erythema nodosum. This in leprosy is confined to the lepromatous and has features of erythema nodosum, fever, swollen joints, bone pains, swelling and tenderness of one or more lymph glands, epistaxis, epididymo-orchitis, and acute irido-cyclitis. The nodes of erythema on the face, arm and thighs may fade in a few days or become necrotic and ulcerate. The reaction is most likely to occur during the course of antileprosy therapy, or be triggered off by some inter-current infection, stress, or smallpox or tuberculin vaccination. It never occurs early in the disease, but later when most of the infecting bacilli are granular and fragmented. There is anaemia, raised serum globulin and BSR and a polymorph leucocytosis. But in sarcoidosis an acute reaction always presents early in the course. The lesions do not present in crops, they persist for one to six weeks and are confined to the legs and less commonly the arms. There may be an antigen-antibody reaction in both diseases from chemical breakdown products, in leprosy from the disintegrating bacilli, in sarcoidosis from mycolic acid, or even pine pollen.

Skin Tests. The percentage of positive reactors to the tuberculin test in leprosy patients has been found to tally with or be lower than that in the healthy population, and tuberculoid and lepromatous cases react much the same. In sarcoidosis two-thirds of sarcoid patients are insensitive to 100 units of ID tuberculin. With depot tuberculin of 5 unites in oil three-quarters of those negative to the ordinary tuberculin test have tuberculin hypersensitivity. BCG

vaccination of Mantoux-negative sarcoid patients does not convert to tuberculin hypersensitivity. Leprosy patients convert normally as in healthy subjects. The *Kveim Test* and the *Lepromin Test* have striking similarities in that antigen injected I.D. leads to a very delayed reaction. Biopsy of the resulting nodule at the end of about one month reveals a granulomatous reaction. A positive Kveim test provides strong evidence of sarcoidosis but the lepromin reaction is often positive in healthy subjects, and has no place in diagnosis, only in prognosis and classification of leprosy cases. It is negative in lepromatous leprosy and in most borderline, but always positive in the tuberculoid and near-tuberculoid borderline. The authors tried the Kveim Test in a small number of leprosy patients of different types and found it negative, but KOOIJ has reported positive results in tuberculoid leprosy but negative in lepromatous.

Treatment. Corticosteroids are useful in both diseases and the only agents known to act in sarcoidosis: they have little or no effect in the later stages of sarcoidosis. In leprosy they are very useful in the ENL type of reaction, and there is a separate basic therapy for the disease. For clinical lesions where there is no corroborative evidence a therapeutic trial with corticosteroid is justifiable.

Reaction in Leprosy. G. RAMU. The Licentiate, Ambala **10**, 11, February 1961, pp. 369-378.

The author made a study of 79 cases of various types of leprosy reactions during the course of the disease or during treatment. These reactions were found during regular observation of 418 leprosy patients. The subjects at risk had a diet very deficient in proteins, and the Vitamins A and C, but no correlation was observed in their reaction cases with diet. Concomitant infections had some slight influence in causing reactions, and sulphone therapy. He found that reactions are more common in the first 18 months of sulphone therapy. In treatment he recommends simple palliative measures, and caution in using ACTH and cortisone, and anti-malarial drugs (camoquin and chloroquin) are better than many others previously used.

Angiography in Leprosy. S. P. BASU et al. Indian J. of Radiology, **14**, 4; November 1960, pp. 180-189.

Basu and colleagues did arteriography of 20 non-lepromatous leprosy cases, and had 9 control cases. There was a definite circulatory stasis in the digits, which did not depend on duration of the disease. In cases with associated bone absorption, the vessels appeared thinner, and there was delay in emptying due to venous stasis. In control cases in which there was poor filling of the digital vessels it was noticed that a shunt took place.

A Review of 79 Leprosy Patients Seen in London. C. J. STEVENSON. Brit. Med. J. of 1st April, 1961, pp. 925-928.

Dr. Stevenson is senior registrar of St. John's Hospital for Diseases of the Skin in London and describes and discusses the 79 cases that he has seen. He found that two-thirds of the cases were immigrants to U.K. during the past 10 years. The countries of origin were 42 from India (of which 27 were Anglo-Indian, 10 Indian, and 5 European stock), 8 originated in Britain (but had worked overseas in endemic zones); 6 from Cyprus, 4 each from West Africa and Malaya, 3 each from Pakistan, Ceylon, and West Indies; 2 from Malta; and 1 each from Austria (who had worked overseas in an endemic area) and 1 each from Aden, Hong Kong, and Malaya. In 22 cases symptoms were present before arrival in Great Britain. The author states that at some time while these patients were under observation in this country, acid-fast bacilli were found in the skin in at least one-third of them. These would be potentially infective. Although some cases are self-healing, others progress to more serious and permanent complications.

Preliminary Trial with Etisul in Northern Nigeria. D. G. JAMISON, E. PALMER and R. L. VOLLUM. Trans. Roy. Soc. of Trop. Med. & Hyg. 55, 2; March 1961, pp. 142-148.

The authors tried Etisul by inunction on 4 patients at Katsina. In all 4 patients there was marked improvement in the general health of the patient, although the clinical signs of leprosy still persisted to some extent. The bacteriological index in the smears showed a progressive reduction, most marked during the first six weeks of treatment and associated with an alteration in the appearance of the bacilli, which became granular. There was a consistent pattern of changes in the appearance of the cellular infiltrate in the skin biopsies, taken from the same region, as treatment proceeded. This consisted of (1) a reduction in the number of bacilli present in the infiltrate; (2) a reduction in the number of foamy cells; (3) a replacement of the lepromatous infiltrate by fibroblasts and lymphocytes. The authors think that intensive inunction with Etisul over the body for 3 to 4 months in conjunction with DDS may prove to be the best treatment for leprosy. With large doses of Etisul they saw reactions in children and temporary discontinuance in such cases may be called for.

The Influence of Hypnotherapy on the Excretion of 17-Ketosteroids in Patients Affected with Diffuse Neurodermatitis. M. M. ZHELTAKOV, G. Y. SHARAPOVA and Y. K. SKRIPKIN: Vestnikh Dermatologii i Venerologii, Moscow, 1961, No. 1, p. 13-17.

The authors think that therapy by hypnosis is one of the best for patients with diffuse neurodermatitis. As the skin process resolved

they noted a more marked and more intense excretion of 17-ketosteroids as compared to treatment with more routine desensitizing agents. They think that hypnosis therapy has a favourable effect on the central nervous system and a stimulating action on the adrenal cortex.

Problems of Rehabilitation of the Leprosy Patient in a High Prevalence Area of Africa. M. F. LECHAT, F. PUISSANT, *Journal of Chronic Diseases*, St. Louis, **13**, 3, March 1961, pp. 221–227.

The authors formerly worked in Yonda Leprosarium, Coquilhatville, Congo Republic. They point out that more than three million leprosy patients are in Africa and about 300,000 in the Congo Republic. There are 72 leprosaria in the Congo, with about 16,600 in-patients and 270,000 were treated at out-patient centres. At Yonda leprosarium there are about 850 patients and now treatment is reported to be continuing by nurses. Out-patient treatment in rural areas is probably disorganised. After current political difficulties are settled it may be assumed that treatment of leprosy will go on. The authors comment that the sulphones were the basis of former treatment and are effective but very slow in their action. Etisul was tried at Yonda and gave promise of being more rapidly effective. The authors point out the very considerable physical disabilities and deformities which occur in even the medically cured cases of leprosy, osteitis, nerve damage, ulcers, and contractures and suggest that Yonda could be revived with international aid and become a main centre of rehabilitation of such cases, using special equipment and personnel trained in physiotherapy and reconstructive and plastic surgery, and giving job training for rehabilitation of the patients. The repair and rehabilitation of the foot is for the agricultural worker as important as the hand. Physiotherapists and surgeons who volunteer for this work perhaps may be sent for training under the auspices of WHO. (At the moment the centre of such training might be India, where such work under BRAND is well understood in theory and practice.—*Editor*.)

Treatment of Initial Forms of Leprosy by 7522 RP (Sultirene): First Results. A. BASSET, R. CAMAIN, Mme BASSET and A. M. SOW. *Bull. de la Soc. Méd. d'Afrique Noire de langue française*, **5**, 4, 4th quarter 1960, pp. 461–465.

The authors tried this drug 7522 RP (Sultirene) which is sulphomethopyraxine. SCHNEIDER in 1958 reported on it after trial in Bamako on different forms of leprosy that its action seemed comparable to that of the sulphones in lepromatous cases, but seemed superior in tuberculoid cases. The authors therefore tried it in 35 patients with tuberculoid or indeterminate leprosy. Of these cases 20 were retained, as some were lost when they gave up treatment on

the appearance of early clinical improvement. The new drug was always well tolerated and there was no change in the blood picture. The dosage was oral, 3 tablets of 250 mg. daily, every second day. In most cases reactions were unimportant. In many cases clinical improvement showed itself in the first weeks and clinical cure could be spoken of in six months. Sultirene is valuable in having (unlike DDS) an early favourable result in these forms of leprosy. However, histological sections showed that the early improvement was not parallel in the skin and long treatment is still necessary.

REPORTS

Colony of Fiji—Annual Report of the Medical Dept. 1959 (received March 1960).

This Report contains several references to leprosy and the report of the Central Leprosy Hospital, Makogai. The number of cases was less than 320 at the end of 1959. Some 40 patients had been transferred for continued treatment to the Gilbert Is. but there have been many discharges. The number of cases notified remained fairly steady (26 in 1954, 36 in 1955, 40 in 1956, 44 in 1957, 39 in 1958, 40 in 1959) and hidden foci of the disease are considered to exist. The staff at Makogai consists of 1 Senior Medical Officer, 2 clerical staff, 7 overseers, 41 subordinate staff, 23 nursing sisters and 11 assistant nursing sisters. The total number of beds in Makogai is 622 but at end of 1959 there were 317 in-patients. During the 48 years of its existence there have been 3,815 patients and 1,94 cases of arrest of the disease. In 1959 131 were discharged, the highest number recorded. The races of the patients were Fijians, Indians, Europeans, part-Europeans, Chinese and others. The proportion of children admitted continues to decline. The lepromatous rate remains high, about 58%. In treatment at Makogai DDS by mouth remains the chief method, and small scale trials have been made of DPT or Ciba-1906 and of Etisul. In the latter the abnoxious smell of the drug proved unpopular and hindered a fuller trial. DPT by mouth gave favourable results.

Hind Kusht Nivaran Sangh (Indian Leprosy Association) 1959 Annual Report.

The Chairman, Rajkumari Amrit Kaur, gave a report containing such a magnificently inclusive survey of leprosy work in India that no abstract could possibly do it justice and it is so valuable that readers are recommended to obtain their own copies from Hind Kusht Nivaran Sangh, New Delhi.

Lake Bunyoni Leprosarium, Report for 1960.

This leprosarium of the CMS lies on islands and mainlands of Lake Bunyoni in the Kigezi District of Uganda. Dr. H. C. Parry reports that 321 patients received treatment during 1960 and there were 28 patients discharged, 25 of them without disability. For discharge the criteria are strict. The outward signs of leprosy having vanished, the patient must have been under observation for at least 12 months without specific treatment and 6 or more monthly consecutive negative smears must have been obtained. Dr. Parry approves of this strictness, because in 1960 there were 10 relapses, in spite of every care. In the laboratory increased care has been

given to the making and staining of smears. Dressing of ulcers still remains a large part of the daily care of the patients. The out-patient department remains very active, with 6,531 attendances during the year. The dispensary has been greatly improved in stocks and facilities, and the general work greatly improved. Members of the District Council (African Local Govt.) visited the leprosarium in December and showed great interest. The leprosarium receives aid from Central and Local Government Grants and from BELRA and the Mission to Lepers. The percentage of types of leprosy among those treated was lepromatous 57%, tuberculoid 30%, indeterminate 8% and borderline 4%.

REVIEW

The Treatment of Tropical Diseases, W. H. JOPLING. Published by Messrs. John Wright and Sons Ltd. 1960, 202 pages, price 20/-.

Dr. Jopling of the Hospital for Tropical Diseases has written this compact handbook of the therapy of tropical diseases for the practitioner in the tropics in mind. It is so intensely practical and up to date that it will be a godsend, and we expect that in emergency the layman in the tropics will find it the same. Nothing important is left out which may turn up in tropical experience. Thus we find a sensible and thorough account of leprosy and its therapy, even in its most modern aspects. Malaria is dealt with particularly well. For brevity and clarity this book is a sheer delight, as well as informativeness, and should receive wide use.