LEPROSY REVIEW

The Quarterly Publication of
THE BRITISH LEPROSY RELIEF ASSOCIATION

VOL. XXX. NO. 2 APRIL 1959

Principal Contents

8 PORTMAN STREET, LONDON, W.1

Price: Three Shillings and Sixpence, plus postage
Annual Subscription: Fifteen Shillings, including postage

LEPROSY REVIEW

VOL. XXX, No. 2. APRIL, 1959

CONTENTS

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

Anti-leprosy therapy today

Among the abiding impressions of the outstanding VII International Congress of Leprology held in Tokyo in November, 1958, perhaps the most powerful and stimulating was that of the extraordinary richness of the reports and suggestions on new drugs suitable for the treatment of leprosy.

There was no attack on the standard treatment by the sulphones. On the contrary, it was made abundantly clear that this group of chemical compounds had revolutionised the treatment of leprosy, and could even be used as a definite method of leprosy control when used in mass campaigns over a wide area. The surge of activity and interest in new drugs springs partly from the *success* of the sulphones. The old moderate estimate of the incidence of leprosy has had to be revised repeatedly under the impact of the leprosy patients who come forward to receive a good treatment, and repeated surveys have added to our knowledge of incidence. In 1955, the estimate of world incidence of leprosy was 10,000,000 cases. Now, in 1959, the figure of 20,000,000 is being mentioned for the first time. Against this background most workers find the trusty sulphones too slow in action, and begin to search for some other drug which will do the job quickly, either in its own right, or combined with the sulphones.

Here is a list of a few of the *new anti-leprosy drugs* with short comments:

1. Diphenylthiourea derivatives, exemplified by Ciba 1906 (also called DPT by T. F. Davey) are of great interest. DPT has been under trial in human leprosy for almost four years, and is emerging as a new basic drug for leprosy.
2. Diethyl dithiol isophthalate or "Etisul" (to which Davey has also given the short name of ETIP) has been under trial for about ten months. It shows in some cases an especially rapid action in reducing the bacterial index. At about the fourth month drug resistance develops. It is given by inunction. Davey thinks its combination with DDS or with DPT will result in material shortening of the time taken for total treatment.
3. Sodium ethyl thiosulphate or ET has been reported on by E. del Pianto. This is a related drug to ETIP, but can be given by mouth for a much longer period. Del Pianto found it well tolerated, effective, and safer and quicker than DDS.
4. The antibiotics viomycin, cycloserine, and kanamycin were reported on by Baccareda-Boy, Rollier, and Yanigasawa and others. They all seem to be effective in human leprosy, but perhaps with much the same value as streptomycin in leprosy, maybe rather more effective.

5. Diaminodiphenyl sulphoxide or DDSO was described by Davey and others as having about the same value as DDS, with advantages in special cases.
6. Buu-Hoi reported on the effects of the isonicotinylhydrazones and found an effectiveness in leprosy lower than DDSO. Hirano found that similar hydrazones were effective in murine leprosy and in tuberculosis of guinea pigs, in particular isonicotinyl-3, 4-diethoxybenzal hydrazone. This is less toxic, has a striking effect on murine leprosy, and may be of value in the treatment of human leprosy.
7. Miyazaki described the value of photo-sensitizing dyestuffs as a secondary treatment of leprosy because of their action to stimulate all body cells, and hence to strengthen resistance.

The above are only a few of the flowers that bloom in the therapeutic garden. The first and second mentioned provide an obvious case for trial in combination, and the third also should be brought into combined research with the first and second.

The *treatment of lepra reactions* is ever a concern to those who deal with leprosy patients. Such reactions have increased greatly since the sulphones were introduced. There are very many anti-allergic and purely empirical medicines in use against them. Most workers now agree on the value of the corticosteroids, and some suggest nivaquin or camoquin as a useful addition to the list.

For some time *Antigen Marianum* has been tried in the treatment of leprosy, but the evidence so far does not suggest that it has any real place. The same applies to the drug, pyrazinamide.

In any description of the modern therapy of leprosy, the advance in methods for surgical repair of deformities (Brand, Ikeda and others), along with thinking out of practical methods of prevention, must be hailed as one of its best features.

Finally, help in therapy of leprosy may well come from the side of pathology and bacteriology. S.W.A. Kuper at the Congress described a histological finding with injections of BCG, in lepromatous patients, of a distinct trend towards the lymphocytic type of cellular reaction, suggesting that a systemic immunological response had been elicited. A clinical trial under controlled conditions is taking place this year in Thailand, India, and Africa on lepromatous patients, to ascertain whether BCG injections at intervals do in fact raise the resistance of patients on the usual basic therapy, as compared with those not given BCG. K. R. Chatterjee has demonstrated successful transmission of *M. leprae* to a laboratory animal, a laboratory-bred strain of hybrid black mice. Various workers this year will seek to confirm this finding, and its establishment would provide us with a most valuable tool in therapeutic research, especially in the screening of new drugs for leprosy.

A New Book on Leprosy

We hail the new book, "Leprosy in Theory and Practice", edited by R. G. Cochrane with a foreword by Sir George McRobert, and published by Messrs. Wright of Bristol, with 407 pages and 184 figures. This book represents a landmark for all leprologists and those interested in leprosy relief, and likewise for scientists in other disciplines who have found that leprosy impinges on their own work. Dr. Cochrane has adopted the plan of a symposium by 24 different contributors. He himself is responsible for 11 chapters and two appendices. The other contributors deal with various sections of the subject and of particular interest is the space given to radiographic appearances of the bones in leprosy. A careful study of deformity in leprosy and its prevention by physiotherapy, and recent investigations into sensory and histological changes in leprosy are included. The general effect of this stimulating book will be that a great deal of hard thinking will go on among those who read it, and equally beneficial arguments whenever the readers meet together. The new orientation of leprosy as part of general science, and as part of the world problem of humanity, is underlined by this work. The book is undoubtedly of the greatest value and should be in the hands of every worker.

References

More information about the new drugs mentioned will be found in Therapy section of Report of Proceedings of VII International Congress of Leprology, *Leprosy Review*, **30**, 1: Jan. 1959, pp. 17-29 also: DAVEY, T. F. and HOGERZEIL, L. M. Ibid. pp. 61-72.

THE MORPHOLOGY OF MYCOBACTERIUM LEPRAE

H. C. DE SOUZA-ARAUJO, M.D., DR. P.H.

Instituto Oswaldo Cruz, Rio de Janeiro

Introduction

The morphology of *M. leprae* as revealed by classical optics was described by F. Löhnis[1] after a review of the literature from 1838 to 1918, and completed in 1923 by A. Paldrock[2], but electron and phase contrast microscopy brought considerable progress. This paper is a confirmation of that presented to the VI International Congress of Leprology in October, 1953[3].

Materials and Methods

For this study we used serum obtained from the skin of various lesions of erythema nodosum leprosum (hereinafter called ENL) of a female patient of white race, of 44 years of age, who was clinically L_2N_2 type and while on sulphone treatment had twice a year lepra reactions of ENL type which were difficult to control. We also used fresh suspensions in sterile distilled water of triturated lepromas of human and murine origin, as also human lepromin and lepromas kept in 40% glycerin in water for a few days. For phase contrast microscopy we used two drops of fresh suspensions of lepromas between common glasco slides covered with thin slides of the kind used for sections. For electron microscopy we used the same suspensions after they had been centrifuged twice and filtered through sterile gauze: they were then placed on collodium film on a metallic grid (a mesh of stainless steel wire) and dried in an incubator at 40° C., and then placed in the electron microscope, which was RCA, type EMU-2C, 50,000 volts. The electron micrographs were taken at a magnification of 4,000 to 7,800 X.

Structure of M. leprae

See Plates 1 to 4. (The electron micrographs of Plate 1 were made by Dr. Penna Franca, and those of Plates 2, 3, and 4 by Dr. Hans Muth, Chief of the Physical Research Laboratory of the Instituto Oswaldo Cruz. The author is greatly indebted to these two colleagues).

PLATE 1

Three electron micrographs of a fresh suspension of leproma from a F. aet. 16 years, before any anti-leprosy treatment was given. No. 1 shows a compact mass of bacilli surrounded by a well-defined sheet of gloea, and two free granules. No. 2 shows two bundles of bacilli in palisade, also surrounded by gloea. No. 3 shows two bacilli, one of which is homogeneous, with a clear sheet of gloea double the usual size. All the bacilli were carbonized by the electron beam, and hence became opaque and appear as compact black masses, and the gloea became white, coagulated by the electron bombardment. All three figures suggest the fusion of the gloea of each bacillus.

Magnification 22,500 *x*

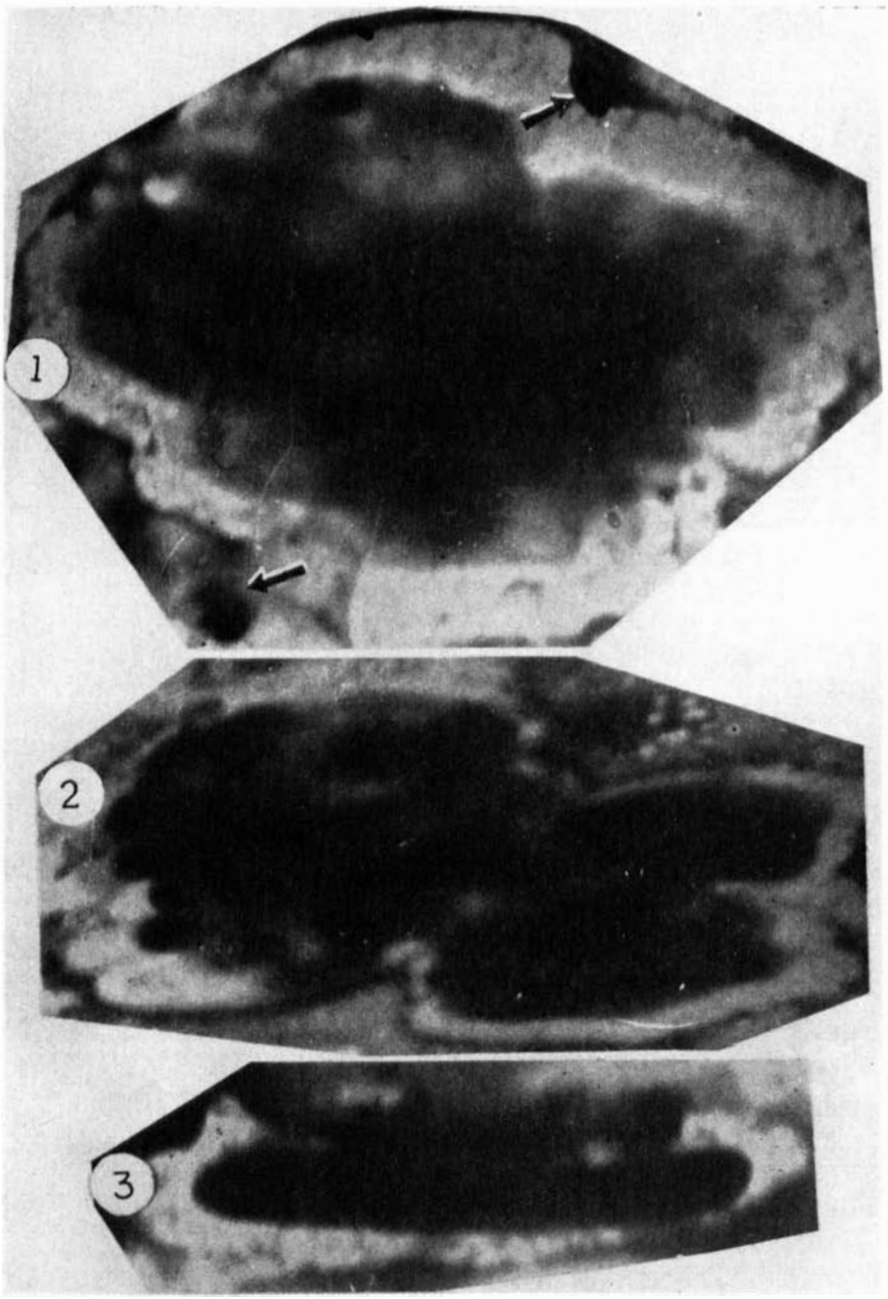


Plate 1 *Morphology of* Mycobacterium leprae. *Magnification 22,500 x.*

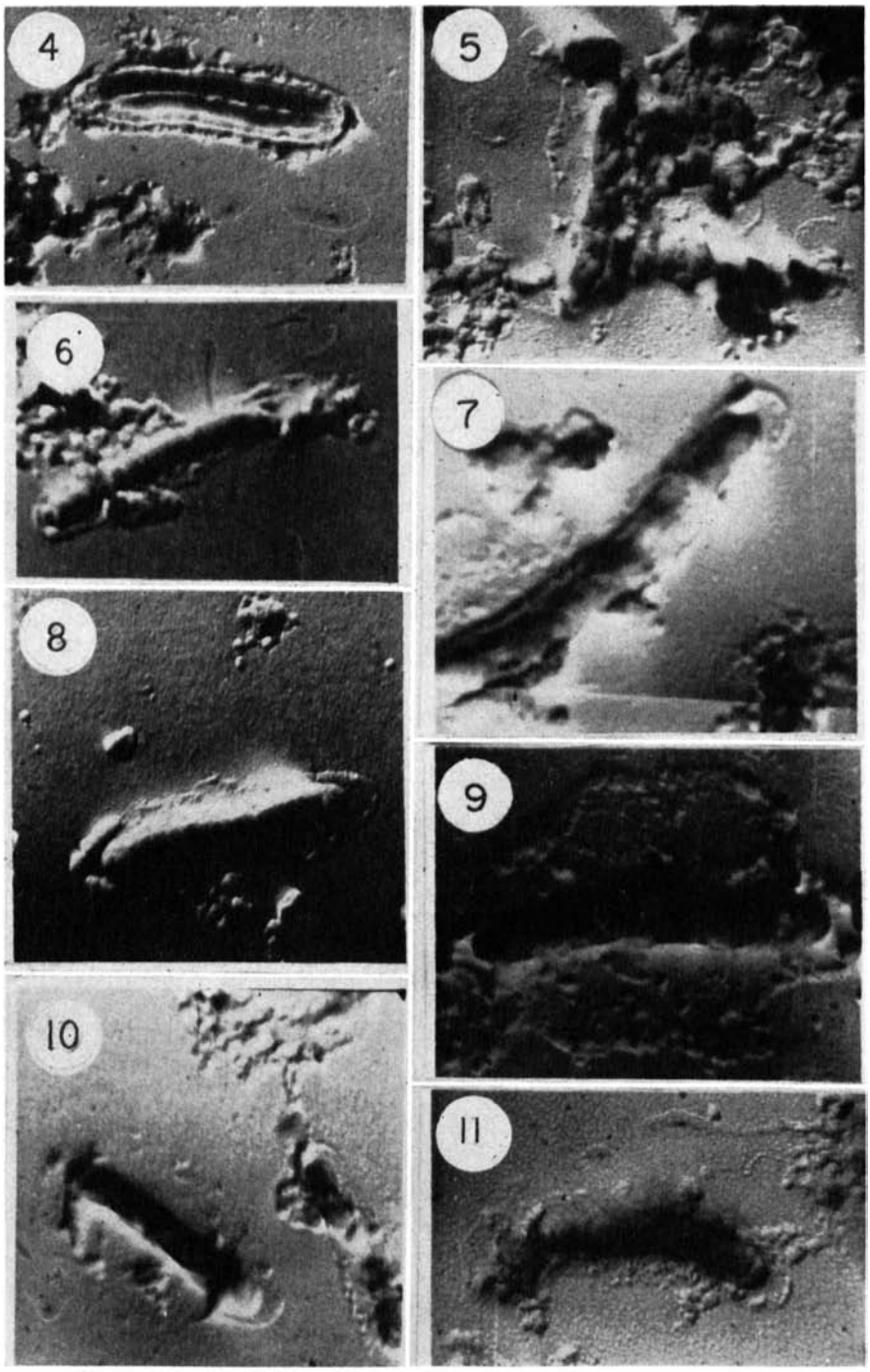


Plate 2

Lepromа in 40% glycerin-water. Shaded.

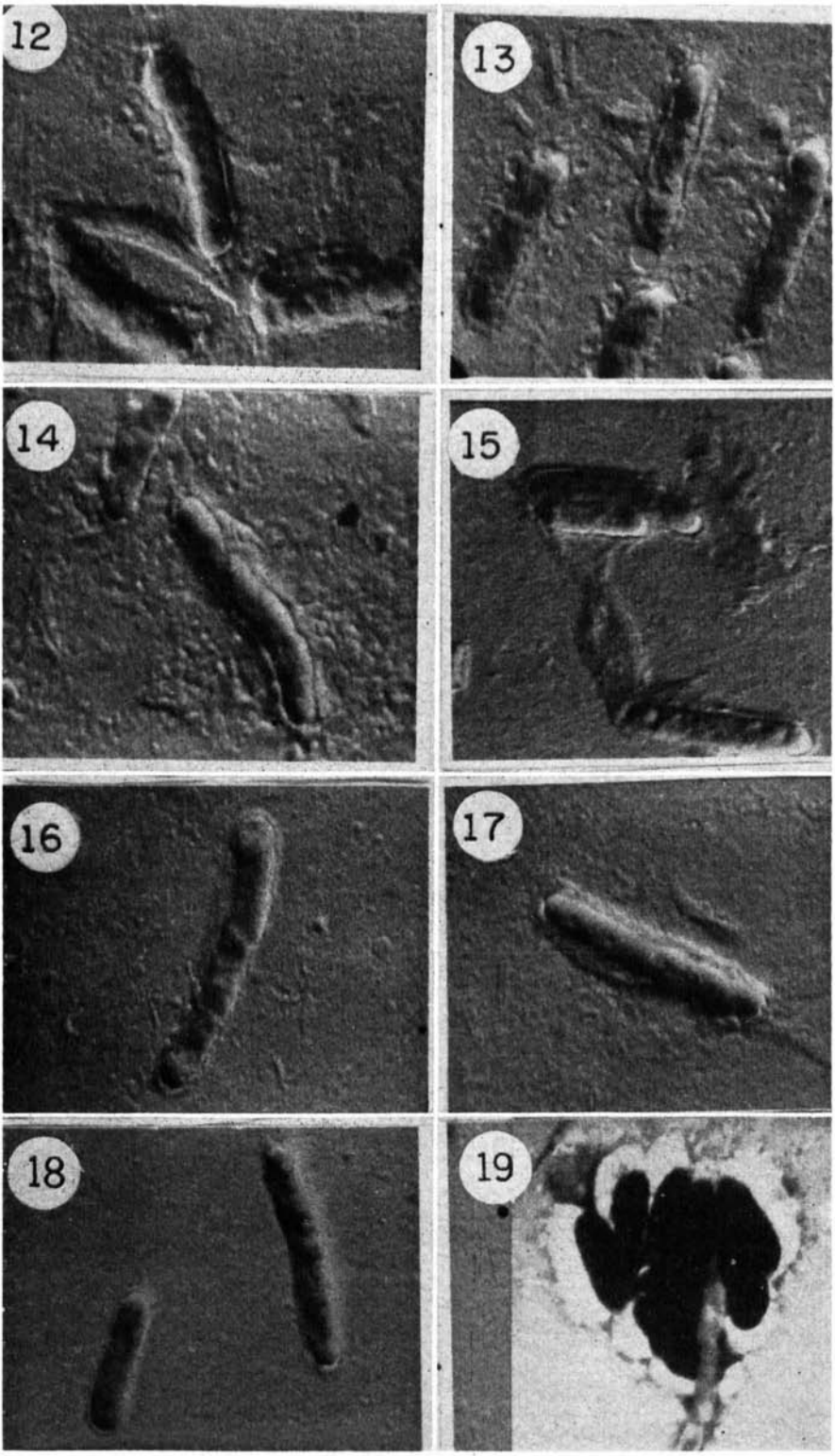


Plate 3

Stefansky

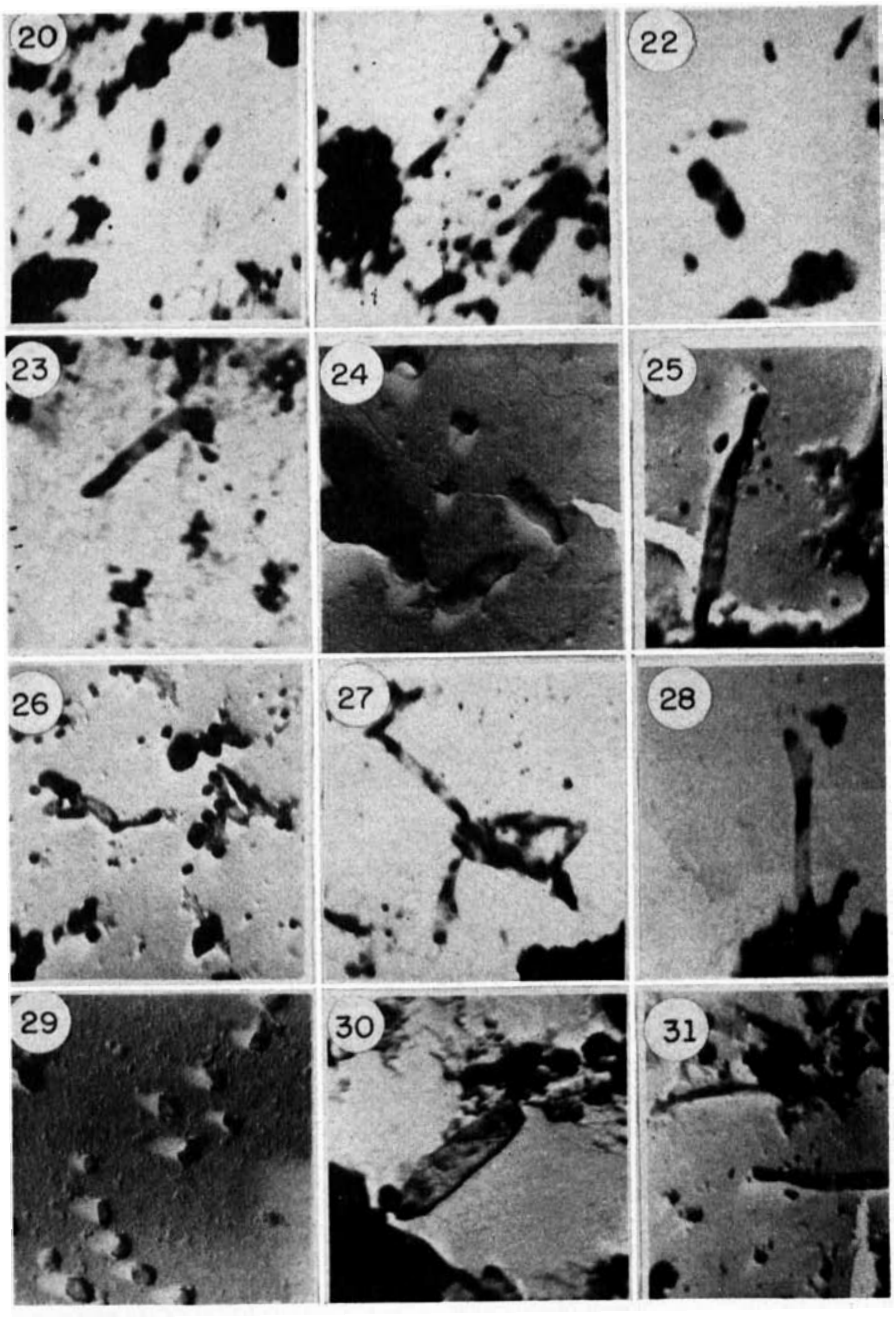


Plate 4

Human Lepromin

Magnification 3,900 to 4,720 x

PLATE 2

Nine electron-micrographs of 4,700 *to* 7,800 *x, of a fresh suspension of human leproma kept in* 40% *glycerin and water for ten days. After being put on collodium film on the stainless steel wire mesh the material was dried in incubation at* 40° *C. and shaded by jets of chromium vapour. All bacilli look damaged .The membrane of No.* 4 *appears well separated from the cytoplasm but fringed. The gloea belonging to Figs.* 8 *to* 11 *looks as if dissolved, and is irregularly spread. Figs.* 5 *and* 9 *look like a fusion. There are widespread granular particles (microspares?).*

Magnification 4,700 *to* 7,800 *x.*

PLATE 3

Seven electron micrographs of a suspension from an inguinal tumour of Mus musculus niger *at* 16 *days after inoculation with rat leprosy bacilli. The preparation was shaded with chromium and shows different aspects of the Stefansky bacillus, of which the morphology (Figs.* 12 *to* 18) *is similar to that of the Hansen bacillus. All bacilli show their membranes but none their gloea. For this suspension the Nadi Test was negative, as triphenol tetrazolium was not reduced, proving that the bacillus is pathogenic. Fig.* 19 *shows a compact mass of six or more bacilli from a leproma from a white rat (at magnification* 6,300 *x). These bacilli look black, unshadowed, with a surrounding white gloea as of the Hansen bacillus of Plate* 1.

Magnification 6,300 *x.*

PLATE 4

Twelve electron micrographs of fresh human lepromin prepared by the Mitsuda-Hayashi method (1933), *showing pleomorphic elements, most of them disintegrated by the heat of boiling and electronic bombardment, and without shadowing. Fig.* 20 *shows two normal bipolar bacilli, without gloea, destroyed by boiling. Fig.* 29 *shows twelve well-defined free granules at magnification* 4,780 *x. Most of the figs. show remnants of bacilli and granules. Such a lepromin, stained by Ziehl-Neelsen method and examined by ordinary microscope shows few normal bacilli, with disintegrated globi and acidfast filaments and granules of different sizes, fuchsinophil dust and dark-blue nuclear detritus.*

Magnification 3,900 *to* 4,780 *x.*

(*a*) *The Cell Membrane.* It is by phase contrast microscopy that that we see most clearly the cell membrane of *M. leprae*. In the bacillary form of *M. leprae* the membrane circumscribes the cytoplasm, which seems liquid, with granules in constant movement. In electron micrographs the aspect of the membrane changes according to whether the material was shadowed by chromium or not.

(*b*) *Gloea.* This vitrous mucous material described by Unna and Lutz in 1886 was considered by Jeanselme as characteristic of the bacillus of leprosy. It cannot be stained by the ordinary methods and by phase contrast appears as a clear halo around the human or murine leprosy bacilli. By electron micrography of unshadowed material the gloea appears as a white sheet enclosing the bacilli, whether isolated or in masses. Jeanselme says " . . . les substances grasses de la couche profonde de la glée sont des corps isotropes, homogènes, lipoides".[4]

(*c*) *Metachromatic granules.* Since 1953 the mycobacterial metachromatic granules are being called mitochondria (Mudd *et al.*), which means "thread granules" according to Stedman's medical dictionary, synonymous with "coccothrix", the name given by A. Lutz in 1886[5] for lepra and tuberculosis bacilli. The chemical constitution of the metachromatic granules is still undecided. F. Scanga[6] says that they represent a carbohydrate reserve and are

especially present in spore-bearing bacilli: from the biological point of view the glycogen granules are perhaps to be considered as a source of energy which the cell uses at special times. A. Paldrock[7] says " . . . l'acide nucléique libre (selon toute probabilité analogue à la volutive) se trouve dans les granulations, tandis que, dans les substances qui les enveloppent et qui constituent les bâtonnets, prédominent les nucléides et les nucléo-protéides". Max and Woith say that such granules are the reservoir of life energy and of the virulence of bacteria, and I myself think[8], as I said in 1943, that they are the original elements of mycobacteria, the cause of tuberculoid leprosy, and the cause of many relapses in patients who had reached clinical arrest of the disease. In tuberculoid leprosy, when we find granules in skin lesions, or later on masses or morulae of granules, there is a liability to the mutation into lepromatous leprosy.

(*d*) *M. leprae* by ordinary microscopy is best studied in the contents of the intracutaneous nodules of the ENL lesions rather than in the suspensions of lepromatous tissue, and the staining is by Ziehl-Neelsen or Fontes methods. The smear stained by Ziehl-Neelsen method shows a formidable quantity of acidfast bacilli lying in big masses, globi, and clubs intra- or extracellularly. The dense masses of bacilli stain well at the periphery and centrally there are pale rose filaments or detritus of bacilli. There are sometimes bacillary balls which are 10 to 15 times larger than the common globi, and have a dense peripheral sheet of bacilli, the centre being empty, or containing remnants of segmented bacilli. By the Fontes staining method the isolated bacilli show beautiful dark-stained granules of various size and position inside the bacilli. In general the central granules are larger than the terminal ones, and from these larger granules gemmules or branching may develop.

Repeated examinations by electron microscopy have confirmed for us what we described before[3], that *M. leprae* shows a membrane, and the halo of gloea which becomes more visible when it surrounds the globi or palisades of bacilli; there are also free granules of various sizes and external granules bound up with the membrane and sometimes forming branches or gemmules. In phase contrast microscopy at 400 X the leprosy bacillus shows free granules which have an intense rotatory movement, and there are granular bacilli which have a screwing, skipping, or stroke motion, which produces a slow progression. All the bacilli are surrounded by membrane and gloea, and the cytoplasm seems to be liquid or semi-liquid, because the internal granules change places, from one end to another. Sometimes the bacilli form into a ball. Sometimes the larger granule in a bacillus prolapses as a gemmule or branch, and finally detaches itself and progresses with a very rapid rotatory movement: later on it acquires a peduncle and grows until it takes the form of a comet or musical note and finally becomes a new bacillus. Not all the granules produce

new bacilli; most of them are sterile as are most of the seeds of any plant.

(*e*) *The Stefansky bacillus.* I have shown that the laboratory animal most sensitive to the Stefansky bacillus is the black mouse[9]. A suspension of nodular material or abscess from this mouse, taken a few weeks after the inoculation of the infection, and stained either by Ziehl-Neelsen or Fontes methods, shows that the Stefansky bacillus is thinner than *M. leprae* and its granules smaller and more regular. The globi are sometimes enormous.

Electron microscopy of fresh rat leproma shows their bacilli, a few homogeneous and the most granular, and the granules are smaller and more regular than those of *M. leprae.* The bacilli also show the membrane and the halo of gloea in unshadowed material. Owing to the electron bombardment both the Hansen and Stefansky bacilli are much altered in structure, so that centrally and terminally black bars or granules of chromatin condensation or carbonized globulin appear.

By phase contrast the Stefansky bacilli show as rods with one, two (bipolar), three, or more internal small granules, which show the same movements as the granules in *M. leprae.* The globi do not move, but the free bacilli around them indulge in normal movement. At 1000 X magnification the examination is less satisfactory than at 400 X. The addition of formol solution to the preparation suppresses all movements and the material becomes more suitable for the study of the static morphology.

Discussion

Electron and phase contrast microscopy have greatly advanced our knowledge of the morphology of *M. leprae* but we still have much to learn. More studies are needed of material from all types and groups of leprosy, and especially from dimorphous or borderline cases, and thin sections of florid lepromatous lesions, and lesions of ENL.

Summary

Both phase contrast and electron microscopy have been used by the author to study the bacillary morphology in human and rat leprosy. Phase contrast was best for revealing the cell membrane, the apparently liquid cytoplasmic contents, and the presence of granules in constant movement: also the gloea appears as a clear halo. The metachromatic granules are considered to be viable and the means of perpetuating the life history of the bacillus. By phase contrast also the granular bacilli were seen to have a slow progressive motion, and sometimes a larger granule prolapsed and extruded and progressed with a rapid rotatory movement, and acquired a peduncle and later a comet form and finally became a new bacillus.

Electron microscopy confirms the membrane, gloea, and granules, both internal and free, and in gemmule form. The Stefansky bacillus is thinner than *M. leprae* and its granules are smaller and more regular, and membrane and gloea are also clearly seen. By phase contrast the granules and the bacilli are also seen to have movements similar to *M. leprae*.

References

1. LÖHNIS, F. Studies upon life cycles of the bacteria. Nat. Acad. Sci. Vol. XVI. 2nd Memoir, Washington, 1922.
2. PALDROCK, A. Rapport III Conf. Internat, de la Lèpre, 1924, p. 138.
3. SOUZA-ARAUJO, H. C. DE. Morphology of *M. leprae hominis* and *M.l. muris*, based on electron and phase contrast microscopy. Memorias Inst. Osw. Cruz, Tomo 53, 1955, pp. 395/6.
4. JEANSELME, Ed. Le Lèpre, 1934, p. 123.
5. LUTZ. Ad. Zur Morphologie des Mikroorganismus der Lepra. Dermatologische Studien, Edited by P. G. Unna, 1886, No. 1.
6. SCANGA, FRANCO. La Cellula Batterica, Il Pensiero Scientifico, Roma, 1954.
7. PALDROCK, A. Les Microbes de la Lèpre contiennent des acides nucléiques libres et fixés. Rapport III Conf. Internat. de la Lèpre. 1924, p. 141.
8. SOUZA-ARAUJO, H. C. DE. A Lepra Tuberculoide, ou melhor, a Lesão Tuberculoide na Lepra, representa uma fase de transição desta Dermatose e não uma forma clínica autônoma.
   Novos achados bacterioscópicos na linfa subcutanea de leprosos. Memorias Inst. Osw. Cruz. T.39 (1) 1943. pp. 77-96.
9. SOUZA-ARAUJO, H. C. DE, Rat leprosy: Susceptibility of the Black Mouse (American Race) to the Stefansky Bacillus. Preliminary Report with 4 figures. International Journal of Leprosy, Vol. 18 (1). Jan. 1950. pp. 49-52.

EXPERIMENTAL INVESTIGATION OF THE ABSORPTION AND EXCRETION OF CIBA-1906 (DPT) [1]

BY DRS. K. SCHMID AND J. TRIPOD
Research Laboratories, CIBA Limited, Basle (Switzerland)

Experimental and clinical studies with CIBA-1906, hereafter referred to as DPT, had suggested that a large proportion of the administered dose was excreted unchanged in the faeces, since in urine and blood no measurable concentration or only a fraction of the quantity administered could be demonstrated. These results were obtained by colorimetric methods of estimation. In our laboratories we used the colour produced when DPT in alcoholic solution is allowed to react with bromine in carbon tetrachloride. Other authors employed the colour produced by the reaction of DPT with ferric chloride[2].

In view of the uncertainty of the findings obtained with colorimetric estimations and in view of the practical importance of knowing the exact degree of absorption of DPT under various conditions it was decided to undertake studies with radio-active labelled material. Only in this way did it seem possible to obtain quantitative values for the absorption and distribution of the substance in the organism and also an indication of the metabolic pathways in various species of animal.

The following is an account of the results of our experiments with C^{14}—and S^{35}—labelled—DPT in the rabbit and dog. However, it must be remembered these are only preliminary findings which need to be verified by further work.

Method

(*a*) *Synthesis and Estimation of Labelled DPT*

In principle DPT may be labelled with C^{14} in various ways. In the method chosen by us, as indicated in Fig. 1, we used as starting material the readily available barium-C^{14}-carbonate as a source of radio-active carbon. The carbon-dioxide liberated from this carbonate was allowed to react with propyl magnesium bromide to produce butyric acid. The latter was esterified and after reduction the butyl alcohol obtained was converted into butyl bromide. Reaction of the butyl bromide with acetamino-phenol and subsequent hydrolysis gave p-butoxyaniline, which on reaction with p-dimethyl-aminophenyl-iso-thiocyanate gave DPT (overall yield with respect to barium carbonate: 12%, specific activity ca. 0.2μC/-mg). The labelled DPT thus obtained bears now in the butoxy side-chain a radio-active carbon atom.

SYNTHESIS OF C^{14}-DPT

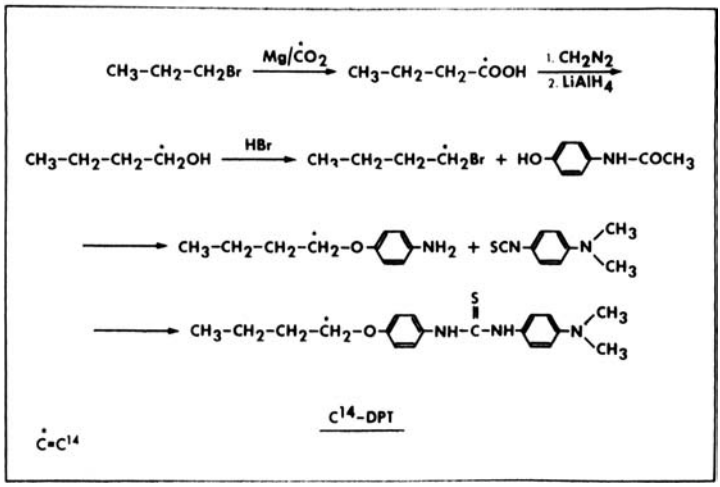


FIG. 1
Synthesis of C^{14}*-labelled DPT*

S^{35} labelled DPT was prepared as indicated in Fig. 2 according to the usual laboratory method, using radio-active carbon disulphide. S^{35}-carbon-disulphide was allowed to react with p-dimethylphenyl-aniline to give the corresponding isothiocyanate, which in turn reacts with p-butoxyaniline to give DPT in good yields (overall yield with respect to carbon disulphide: 78%, specific activity ca. 2.7 μC/mg).

SYNTHESIS OF S^{35}-DPT

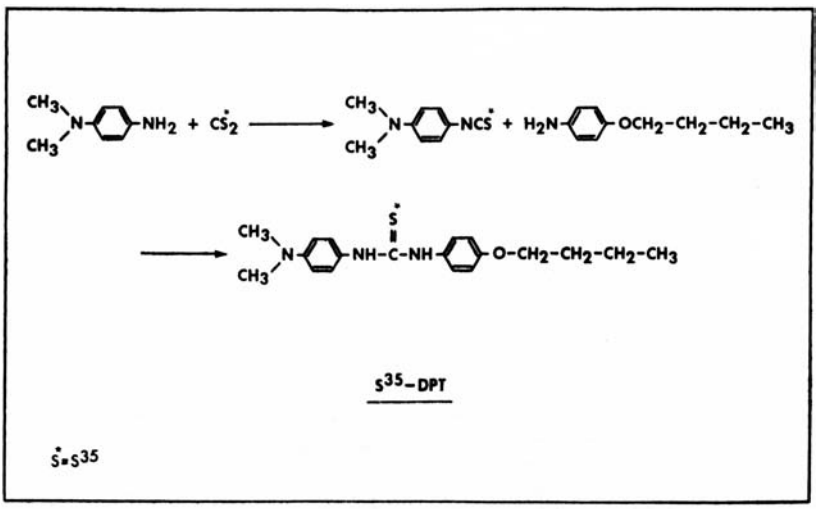


FIG. 2
Synthesis of S^{35}*-labelled DPT*

For the estimation of the radio-activity, known volumes of blood, urine, and bile or weighed portions of fresh faeces or tissue were first brought to dryness. In the case of the C^{14}-experiments the samples were converted to carbon dioxide by wet combustion, which after purification was measured in a gas counting tube. In the case of the S^{35}-experiments the samples were submitted to alkali fusion, and the sulphate obtained isolated as the barium-salt which when dried was used for counting in the solid state. These methods will be published in detail elsewhere. In the experiments described hereafter all values for DPT and its metabolites are expressed as DPT calculated on the basis of the measured radio-activity.

(*b*) *Studies in the Rabbit*

Rabbits of an average weight of 2 kilos received 0.03 g/kg DPT either by stomach tube in the form of a 1% suspension or intravenously as a 3% solution in polyethylene-glycol-400. For the determination of the blood concentration 1 ml. portions of blood were withdrawn at predetermined intervals from the ear vein. Urine and faeces were collected over 24 and 48 hour periods. Bile samples were collected through a cannula in the common bile duct simultaneously with the blood samples. In cases in which operative intervention was undertaken the rabbits were narcotised with urethane (0.8 g/kg s.c.). This dose of urethane is lower than that which is usually necessary to produce adequate anæsthesia (1.2 g/kg). This reduction in the dosage is possible because as a result of the intravenous injection of the solution of DPT in polyethyleneglycol-400, sedation and hypnosis is obtained which is evident even with a dose of 0.01 g/kg, and at a dose of 0.04-0.05 g/kg produces a state equivalent to narcosis. The solvent alone, at a dose of 1 ml/kg is without observable effect.

(*c*) *Studies in the Dog*

In these experiments DPT was administered orally at a dose of 0.03 g/kg as capsules of pure substance, or by the subcutaneous or intravenous route as a 3% solution in polyethyleneglycol-400. The amount of 2-3 ml. blood was taken for estimation at fixed intervals. Urine and faeces were collected during 24 and 48 hour periods. This dose of DPT (0.03 g/kg i.v.) produced in the dog only slight sedation of short duration, which was clearly less than that observed in the rabbit.

Results

(*a*) *Single Administration in Rabbits*

After the intravenous injection of 0.03 g/kg C^{14}-DPT the maximum blood concentration is reached shortly after the end of the injection and falls steeply up to the fifth hour, after which it slowly returns to zero (Fig. 3). With S^{35}-DPT the values in the non-narcotised animals are somewhat higher in the first hour than in

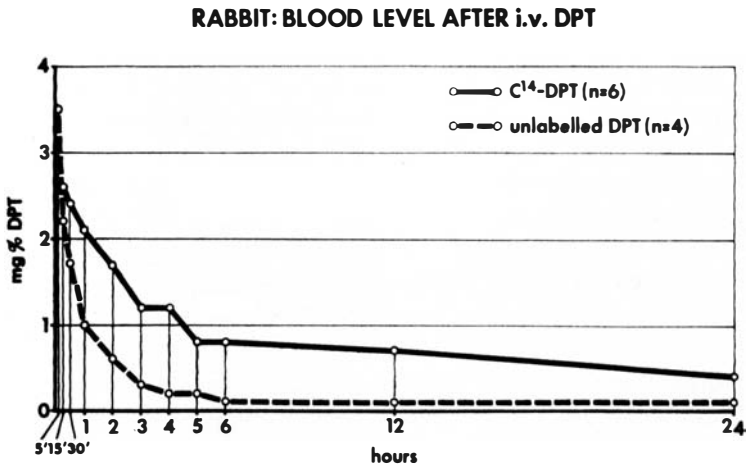


FIG. 3
Rabbit: Blood concentration after single i.v. dose (0.03 *g/kg*) *of DPT*

C^{14}-experiments after which time, however, the concentration curves approximate. With the exception of the first two, the values estimated colorimetrically are lower, the curve falling more steeply and reaching the baseline after six hours.

After oral administration of a suspension the blood concentration is considerably lower than after intravenous injection. The maximum reached is about 0.4 mg% and is only reached after about three to

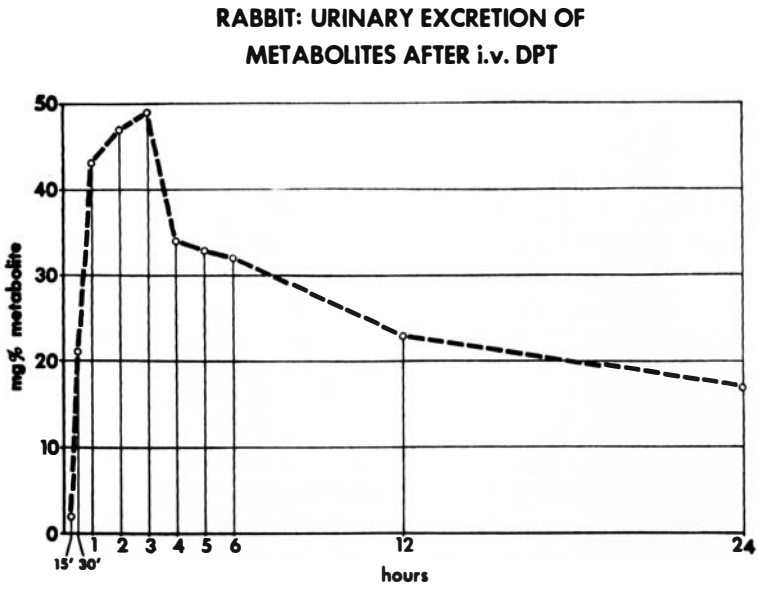


FIG. 4
Rabbit: Urinary excretion of DPT-metabolites after single i.v. dose (0.03 *g/kg of DPT* ($n = 4$).

six hours. After 12 to 24 hours the values have fallen below the detectable limits for the C^{14}-preparation employed (0.1 mg%).

After a single intravenous dose the maximum concentration in the urine is reached after three hours and up to this time about 20% of the administered radio-activity is demonstrable in the urine. Following this the urinary concentration slowly falls, but is still 17 mg% at 24 hours (Fig. 4).

Using the colorimetric method the maximum concentration found in the urine was 0.1 mg%, whereas using the radio-active method concentrations up to 50 mg% were demonstrated. *It is therefore clear that DPT is excreted in the urine substantially in the form of metabolites.*

The distribution of DPT in various organs was determined 4 and 24 hours after intravenous and 24 hours after oral administration (Table 1). It is remarkable that after intravenous injection, *radio-active material was demonstrable in the wall and also the lumen of the gastro-intestinal tract, so that it must be concluded that a part*

RABBIT: DISTRIBUTION OF DPT AND METABOLITES IN THE ORGANS AFTER SINGLE ADMINISTRATION (0,03g/kg)

	mg per organ		
	i. v.		p. o.
	4 hrs.	24 hrs.	24 hrs.
stomach cont.	5,0	5,5	7,1
" wall	1,1	0,1	0,04
small intest. cont.	2,2	3,8	0,6
" " wall	2,8	0,3	0,2
bile	0,03	0,02	0,01
large intest. cont.	3,8	11,3	11,0
" " wall	2,3	0,1	0,02
spleen	0,01	0,04	0,0
kidney	1,1	0,8	0,1
adrenal	0,0	0,0	0,0
liver	1,8	0,6	0,5
lung	0,02	0,09	0,04
heart	0,1	0,04	0,01
bones	18,1	1,3	0,0
muscle	13,3	2,1	0,4
skin	1,8	0,7	0,0
subcut. fat	0,3	0,0	0,0
brain	0,2	0,01	0,0

TABLE 1

Rabbit: Distribution of DPT and DPT-metabolites in the organs after single administration (0.03 *g/kg*) *of DPT.*

of the administered drug is excreted through the intestinal wall. Furthermore with the exception of the bones which show a relatively high concentration after four hours no especially marked concentration of radio-active material was observed in any of the other organs or tissues examined, in fact the distribution was approximately the same as is found with other drugs. Especially interesting with regard to leprosy is the fact that neither in the skin nor subcutaneous fat could any specially marked concentration of radio-active material be found. After 24 hours only traces of radio-active material were detectable in the tissues since at this time the majority of the administered dose has already been excreted in the urine.

Comparison of the concentration in the urine with that in the faeces confirms the supposition already made on the basis of the tissue analyses, that after intravenous administration radio-active material is excreted through the intestine (Table 2).

RABBIT: EXCRETION OF DPT AND METABOLITES AFTER i. v. AND p. o. DPT

	24 hrs. excretion in % of administered dose		
	i. v.		p. o.
	C^{14} (n=1)	S^{35} (n=3)	C^{14} (n=3)
stomach cont.	7,1	12,1	12,6
small intest. cont.	5,0	0,9	0,8
large intest. cont.	14,7	11,1	17,5
	26,8	24,1	30,9
urine	48,0	54,1	54,9
faeces	—	7,8	6,6

TABLE 2
Rabbit: Excretion of DPT and DPT-metabolites during 24 hours after single i.v. and p.o. administration (0.03 g/kg) of DPT.

The quantity demonstrable in the faeces after 24 hours is approximately the same when DPT is given by either route of administration. Similarly the excretion in the urine after intravenous injection is comparable with that obtained after oral administration and amounts to over 50% of the quantity given. Therefore it can be concluded that in the rabbit, DPT is well absorbed after oral administration and that no essential difference exists between the routes of excretion following the two methods of administration.

In order to clarify further the mode of excretion of DPT into the gastro-intestinal tract, the concentration of the substance in the bile was estimated (Fig. 5).

RABBIT: BILIARY EXCRETION OF METABOLITES AFTER i.v. DPT

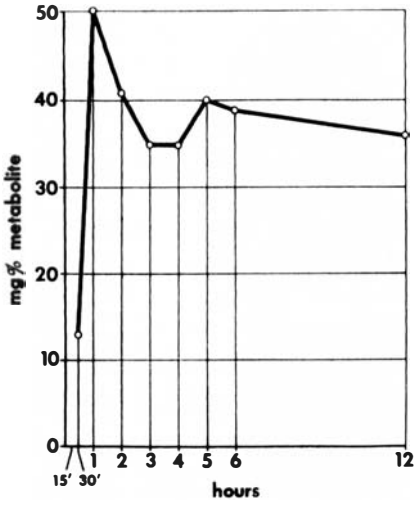


FIG. 5
Rabbit: Excretion of DPT-metabolites in the bile after single i.v. administration (0.03*g*/*kg*) *of DPT* ($n = 2$).

This demonstrated that after intravenous injection about 20% of the dose was excreted in the bile. The maximum concentration reached 50 mg% one hour after the injection and remained at approximately the same value during the following hours. Even after 12 hours 30 mg% was still present.

However, the biliary excretion does not represent the only source of the material demonstrable in the intestine after intravenous injection, since even with an occluded bile duct 20% of the total dose appeared in the intestinal wall and contents (Table 3). It may therefore be concluded that a proportion of the radio-active material is excreted directly through the intestinal mucosa.

RABBIT — BILIARY FISTULA OR OCCLUDED BILE DUCT: EXCRETION OF DPT AND METABOLITES AFTER i. v. DPT

	12 hrs. excretion in % of administered dose	
	biliary fistula (n=3)	occluded bile duct (n=1)
stomach cont.	16,1	9,9
small intest. cont.	1,7	5,0
large intest. cont.	4,5	5,7
	22,3	20,6
bile	20,1	—
urine	43,7	47,8
faeces	—	—

TABLE 3
Rabbit: Excretion of DPT and metabolites during 12 *hours by animals with biliary fistula or occluded bile duct after single i.v. administration* (0.03 *g*/*kg*) *of DPT.*

Furthermore, it is clear that excretion through the stomach wall also occurs since in the intact animal and also in the animal with a biliary fistula or occluded bile duct about 7-16% of the administered dose is found in the stomach contents (see Table 2).

After subcutaneous injection different excretion patterns occur depending on whether the preparation is given as a solution in polyethyleneglycol-400 or as a suspension. Neither in blood nor faeces did a measureable concentration appear, probably as a result of the slow absorption from the depot at the site of injection. On the other hand material appeared in the *urine* after subcutaneous injection of both forms. The higher concentration which was excreted after the injection of DPT in solution shows that absorption, as would be expected, is more rapid than after the injection of the suspension (Fig. 6).

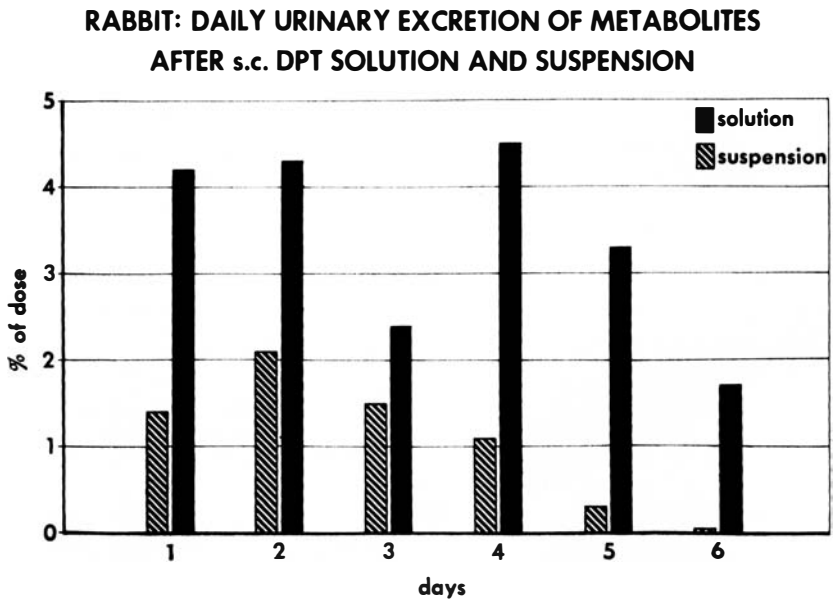


FIG. 6
Rabbit: Daily excretion of DPT and metabolites in the urine after single s.c. injection (0.03 *g/kg*) *of DPT in solution and suspension* ($n = 2$).

The incomplete absorption following subcutaneous injection is also manifest by the persistence of material at the site of injection after six days, which also occurs even when the preparation is injected in solution. It is probable that, as is also the case with other drugs in solution, the absorption of the solvent and the dissolved substance does not proceed at equal speed so that precipitation of the compound occurs at the site of injection. Thus it is clear that a depot effect must obtain after subcutaneous injection of DPT.

(*b*) *Single Administration in Dogs*

In order to clarify the specificity of the excretion pattern for

various animal species experiments analogous to those carried out in rabbits were also undertaken in the dog. Intravenous injection gave, in general, blood concentrations comparable to those found in the rabbit (Fig. 7). For technical reasons the C^{14} values could only be estimated up to two hours after the injection, whereas with S^{35} labelled material observations were carried out for 48 hours.

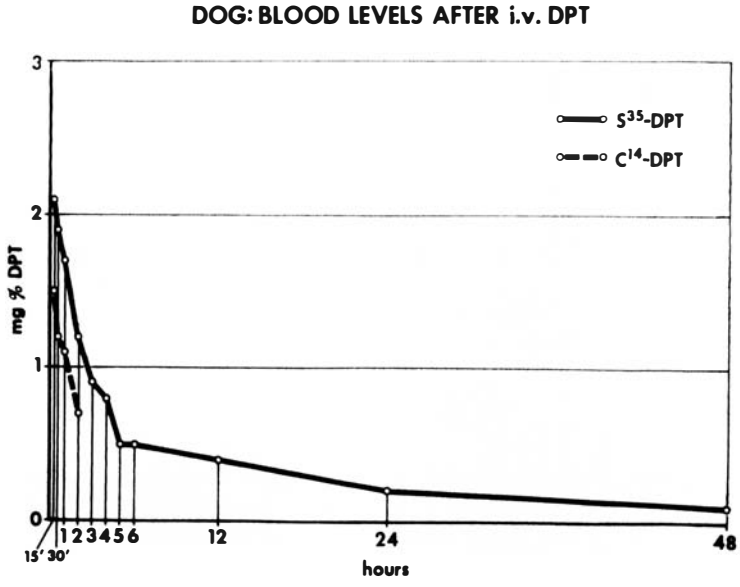


FIG. 7

Dog: Blood concentration after single i.v. injection (0.03 *g/kg*) *of DPT* ($n = 2$).

The tissue concentrations in the dog were not measured. After subcutaneous and oral administration no measurable blood concentration was detected.

The urinary excretion after oral S^{35}-labelled substance and especially after C^{14}-material was much less than in the rabbit over the first 48 hours (Table 4). Similarly the faecal levels were higher. Clearly the absorption after oral administration is less complete in the dog than in the rabbit.

After subcutaneous injection of DPT dissolved in polyethyleneglycol-400, 39.2% was excreted in the urine and 36.9% in the faeces. The ratio is about the same as after intravenous injection but with the difference that after subcutaneous administration the excretion was more prolonged (Fig. 8). In this respect the findings are similar to those in the rabbit experiments, the urinary excretion being significantly delayed, probably as a result of the retarded absorption of the subcutaneous depot. The quantity of material eliminated in the urine, however, is less in the dog than in the rabbit which is also the case after intravenous injection. The cause of this species difference is not known.

DOG: EXCRETION OF DPT AND METABOLITES AFTER i. v. AND p. o. DPT

	48 hrs. excretion in % of administered dose			
	i. v.		p. o.	
	C^{14} (n=2)	S^{35} (n=2)	C^{14} (n=1)	S^{35} (n=3)
urine	31,5	38,0	11,4	27,2
faeces	39,1	28,2	57,1	57,0

TABLE 4
Dog: Excretion of DPT and metabolites in urine and faeces after single i.v. and p.o. administration (0.03 *g/kg*) *of DPT.*

DOG: DAILY EXCRETION OF DPT AND METABOLITES IN FAECES AND URINE AFTER s. c. DPT

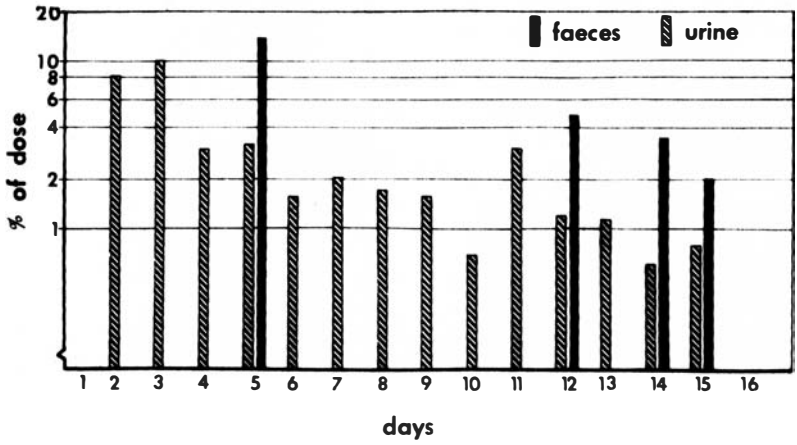


FIG. 8
Dog: Daily excretion of DPT and metabolites in urine and faeces after single s.c. administration (0.03 *g/kg*) *of DPT* ($n = 1$).

(*c*) *Repeated Administration in the Rabbit*

In order to determine whether accumulation of DPT occurs in particular organs 0.03 g/kg labelled-DPT was administered to rabbits daily for one week. One day after the last dose the animals were

killed and the radio-activity in various tissues measured. As after the single oral administration the blood concentration, estimated once daily remained below 0.1 mg% during repeated daily dosage. In the tissues studied, higher concentrations were not obtained than 24 hours after a single dose (see Table 1). There is therefore no evidence of a cumulative effect in the tissues. In contrast the majority of the daily intake was excreted in the urine and faeces within a short time (Fig. 9). Of the total dose given over seven days 61 % was found in the urine, 14% in the faeces and 14% in the intestinal tract of the sacrificed animals.

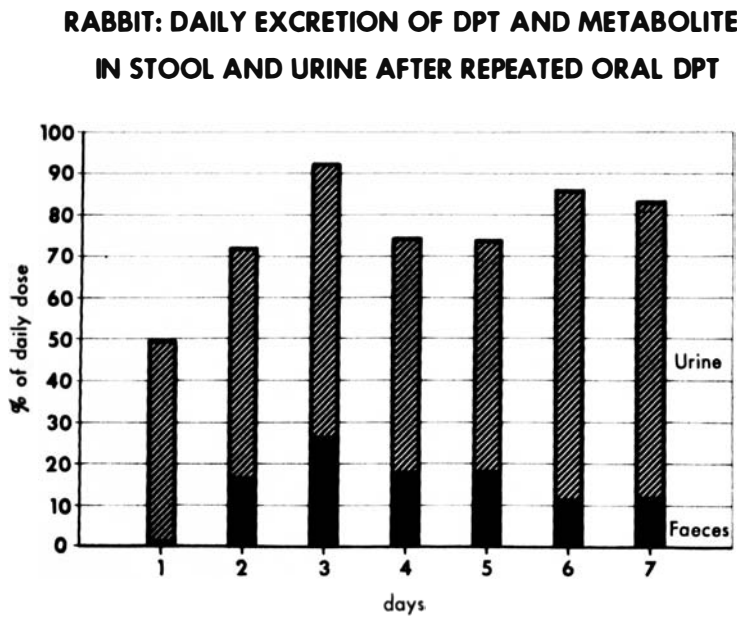


FIG. 9
Rabbit: Daily excretion of DPT and metabolites in urine and faeces after repeated p.o. administration (0.03 *g/kg*) *of DPT* ($n = 2$).

(*d*) *Experiments on the Isolation and Identification of Metabolites of DPT in Urine*

The studies on the isolation and identification of degradation products of DPT and the determination of their biological activity are incomplete and do not yet allow any definite conclusions regarding the metabolism of the drug to be drawn.

In one preliminary experiment about 100 ml urine was collected from one rabbit which had received intravenous C^{14}-DPT. On the basis of its radio-activity this urine contained about 20 mg DPT-metabolites from which by extraction with benzol-butanol, 4 mg of extract, containing 75-80% of the radio-active components, was isolated. The *in vitro* tuberculostatic activity of this fraction was found to be 100 times less than that of DPT[3]. This activity can either

be attributed to traces of unchanged DPT or to metabolites with weaker tuberculostatic activity than the parent compound. Which of these two possibilities is valid will be decided in further experiments.

Using different methods of extraction, the pooled urine of several rabbits yielded only about 50% of the available radio-active metabolites. Only after hydrolysis of the urine by boiling with acid was it possible to extract further quantities of radio-active material. This finding shows that part of the excretion products are in bound form. Paper chromatographic analysis showed that the extract is composed of at least two different metabolites. In further purification experiments these have been found to be rather unstable, so that up to now it has not been possible to isolate either of them in pure form, and therefore their nature can only be guessed at. However, all the indications are that they are probably carboxylated or hydroxylated derivatives of DPT, which are excreted partly in the free and partly in the conjugated form.

Discussion

The most important conclusions to be drawn from the experiments which have been described are the clear demonstration that absorption does occur after oral administration in the dog and the rabbit and secondly the fact that DPT is excreted unchanged in the urine only to a very small degree. For these reasons all the earlier results obtained using the characteristic color reactions for DPT were misleading.

It is not yet possible to deduce where and how the degradation of DPT is accomplished in the organism, since definite metabolites have not yet been identified in urine, bile or blood. For the same reasons also it is not possible to give any information regarding the tuberculostatic or anti-leprotic activity of these metabolites. Furthermore it is not yet possible to ascertain whether the degradation pathways in various animal species and in man are the same nor whether the resulting intermediate and end products are identical.

An important new finding is the demonstration of the excretion of DPT-metabolites in the bile and through the intestinal wall, so that the liver must be regarded as being involved in metabolism and excretion. Whether a true "enterohepatic circulation" exists so that the material excreted in the bile is again re-absorbed through the intestinal wall is not yet verified. However, it seems probable that the greater part of the substance secreted in the bile is also eliminated in the faeces. Therefore all the material demonstrable in the faeces has not failed to be absorbed but in contrast some of it has passed through the liver suffered degradation or modification and returned to the intestine. In a few preliminary experiments in the dog in which the faeces were extracted after oral administration, unchanged DPT was identified, so that it must be concluded that in this species a

proportion of the oral dose is not absorbed but passes through the intestinal tract unchanged.

On the basis of the failure to demonstrate DPT in the blood or urine of patients after oral administration using colorimetric methods it was concluded that absorption from the gastro-intestinal tract was minimal. Assuming that the mode of absorption in man is not entirely different from that in the dog and rabbit, the above conclusion is not tenable. On the contrary it seems more likely that even after oral administration the majority of the drug enters the organism. However, the question whether DPT itself possess tuberculostatic or anti-leprotic activity or if the effects are due to a metabolite cannot yet be definitely answered. *What is clear is that DPT is rapidly and completely metabolized after absorption*, and whether the products of this degradation possess antibacterial activity or not must be clarified by further experiments.

References

1. Presented in part at the 7th International Congress on Leprology in Tokyo (November 12th—19th November 1958).
2. J. ROSS INNES, M. SMITH and W. HARDEN SMITH, East African Medical J. **34**, 395 (1957).
3. F. KRADOLFER, private communication.

STUDIES ON PLANTAR ULCERS IN LEPROSY

E. W. PRICE, F.R.C.S.
Orthopaedic Surgeon to Leprosy Service, Eastern Nigeria

1 General

Introduction

Plantar ulcers are a major obstacle to the present-day rehabilitation of leprosy patients. We know that they occur in anaesthetic feet, and have an obvious relation to weight-bearing, and a possible relation to trauma, but do not know the full story of their causation, nor why they are so chronic, nor why they relapse so easily. There must be some other factors.

We use the term "plantar ulcer" instead of the usual names "perforating", "trophic", or "pressure ulcer", because these latter terms are not always truly descriptive. In using the term "plantar ulcer" we exclude ulcers due to infection, trauma, or fungus infection (as in clefts of the toes) and define it as a chronic ulceration of the anaesthetic sole of the foot, situated in well-defined areas overlying a bony prominence, resistant to local or systemic therapy, and characterised by a marked tendency to recurrence.

Survey of Plantar Ulcers

We undertook two surveys of plantar ulcers in the leprosaria of Eastern Nigeria. In the first survey we examined the plantar ulcers found in about 2,400 patients under leprosy treatment, and noted the position and character of the ulcer. In the second survey we treated and observed closely the ulcers in 100 patients. In addition and at the same time, we examined weekly every patient without ulcers in one leprosarium, in order to detect the earliest signs of impending plantar ulceration: this has turned out to be very valuable as a preventive measure.

Our initial investigation suggested a new approach to the study of plantar ulcers under the following heads; their distribution in leprosy; the mechanics of the foot in relation to them; their cause and the cause of their chronicity; their natural history; their early detection and prevention and treatment; and their complications.

The Distribution of Plantar Ulcers

From the literature we find that there is a general recognition that they occur in certain common sites, e.g., under the metatarsal heads, but there has been no study which relates the distribution to stresses undergone by the feet in standing and walking. We studied this matter in 2,395 patients in four leprosaria, and found 561 plantar ulcers representing 11.7 ulcers per 100 feet. There was a higher incidence in feet of males than females (12.7 as to 9.5), but no

difference between right and left feet. There was a difference in incidence in different leprosaria, varying between 6 and 16 per 100 feet. This is partly related to the predominant type of leprosy in the area, and partly to the method of dealing with ulcer patients; some leprosaria admit ulcer patients from outlying clinics more readily. Part of the difference is related to the actual method of treatment adopted for ulcers. The leprosarium with the least incidence has used treatment by plaster casts for the past few years.

It was found that the sites of the ulcers tended to be the clearly defined areas overlying a bony prominence. Thus 71% of the ulcers are under the forefoot, in sites which closely follow the operation of dynamic pressures on the walking foot. The heel bears only 12.5% of ulcers and therefore is the least common area for plantar ulcers. The middle of the outer border of the foot bears 16.5%. It will be noted that the heel bears more standing pressure, yet is the least common area. Ulcers involving the mid metatarsal area have been spread over more than the one metatarsal head and make it difficult to decide which was the primary lesion.

The photograph in Fig. 1 illustrates the typical sites of plantar ulcers in leprosy. This case is unusual in showing four of the commonest sites of plantar ulcers, namely under the first and second metatarsal head, under the tubercle on the base of the fifth metatarsal and on the heel.

Feet which have been deformed by previous gross infection or from surgical intervention on the metatarsal bones may show ulcers in other sites, according to the deformity.

The limitation of ulcers to certain special sites makes it possible to advise a system of recording which relates the ulcer to the underlying bony prominence and uses the initial letters of the bone. Thus MH_1—MH_5 would mean an ulcer over the metatarsal head as numbered; mid-MH would mean mid-metatarsal; mid-lat. would mean an ulcer over the base of the fifth metatarsal; PPH means the plantar ulcer seen quite often over the proximal phalangeal head of the first toe. Except for the second toe, the other toes rarely have it.

Ulcers at the tips of the toes are frequently multiple in any given case and can be considered as a single ulcer spread over the tips of more than one toe. With this reservation, we find that of 100 plantar ulcers, 61 are single, with one on each of 61 feet; 30 are double, with 2 on each of 15 feet; 9 are triple, with 3 on each of 3 feet. We also find that of 100 patients with plantar ulcers, 58 have a single ulcer on 1 foot; 22 have two ulcers on 1 foot only; 4 have 3 ulcers on 1 foot only; 15 have 1 ulcer on each foot; 1 has a single ulcer on 1 foot and 2 ulcers on the other.

Excluding 2 tip ulcers, the greatest number of ulcers was 7, with 4 on 1 foot and 3 on the other.

In the few cases of multiple ulcers there were all possible combinations of sites. The commonest combination was that of heel and mid-metatarsal ulceration on the same foot.

Discussion and Summary

The most striking feature of the distribution of plantar ulcers is the predominance in the forefeet, where 70% of ulcers occur. In the forefoot itself most ulcers are on the medial side. The heel is the least common of the usual sites. If one relates pressure diagrams of the standing and the walking foot to the distribution of plantar ulcers, it is obvious that the distribution of pressures on the walking foot is much the more important. The distribution of ulcers and all dynamic pressures on the walking foot correspond closely, except for the occurence of mid-lateral ulceration, and a slightly lateral displacement in the forefoot of the position of maximum incidence of ulcers. These two differences may be related to the weakness of the pronators of the foot which is a feature of the damaged foot in leprosy. A review of the mechanics of the walking foot appears in the next section of this study.

A brief summary of our observations follows:

1. Plantar ulcers were observed in 11 of every 100 feet of patients under treatment for leprosy in Eastern Nigeria.
2. Seven of every ten plantar ulcers occur in the forefoot.
3. The commonest single site is under the second metatarsal head.
4. The commonest area is that of the big toe and associated metatarsal pad.
5. The heel is the least common of the usual areas of ulceration.
6. The plantar ulcer is commonly a single ulcer on one foot of a patient, but one in six ulcer patients have one on each foot, and one in five have two ulcers on one foot. Triple ulcers are uncommon and quadruple ulcers rare.
7. The typical plantar ulcer occurs in clearly defined areas in the following order of frequency:
   i. under the second metatarsal head.
   ii. under the first metatarsal head.
   iii. under the lateral metatarsal heads.
   iv. under the tubercle on the base of the fifth metatarsal.
   v. at the heel.
8. Ulcers of similar type were observed under the head of the proximal phalanx of the big toe, and on the tips of the toes.
9. Ulcers are commonly associated with, or preceded by, callosities.

II The Mechanics of the Foot in Relation to Plantar Ulcers

In the first part of this study we reached the point of emphasising

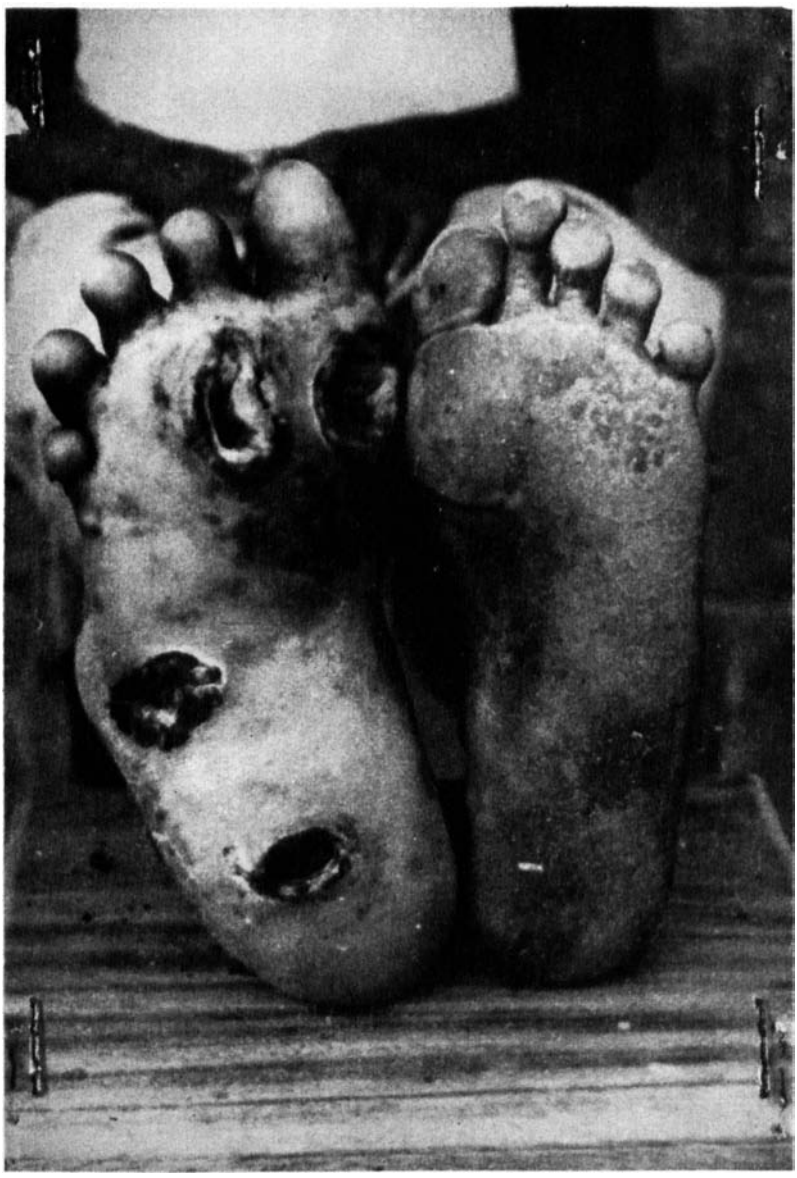


Fig. 1 The typical sites of Plantar Ulceration in Leprosy.

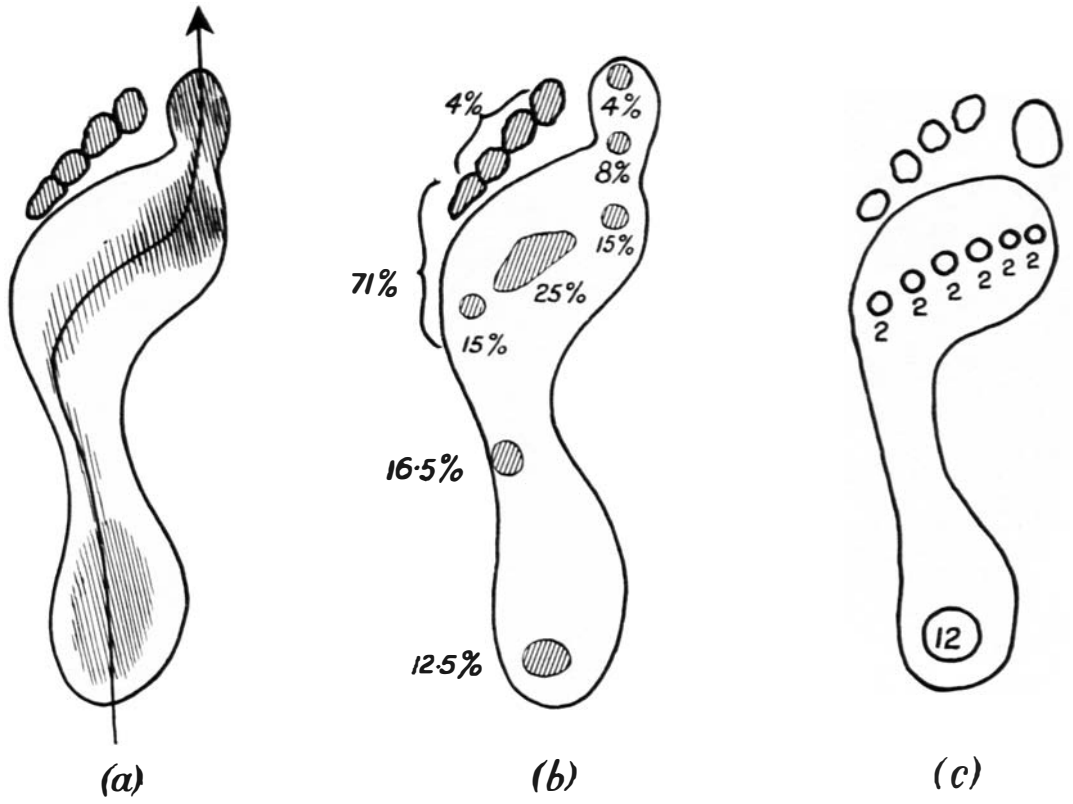


FIG. 2

(a) The footprint of the walking sole. (after Morton)

The shading represents the degree of walking pressures. Note that these pressures pass across the sole in succession from heel to toe-tips following the direction of the arrow, and that the toe-tips play a definite part in the sequence.

(b) The distribution of plantar ulcers in leprosy.

Note that the distribution is far closer to those of the walking pressures than to the standing pressures. The tendency for maximal pressures to be displaced laterally, and the particular ulcer at the base of the 5th metatarsal, are related to the pronator weakness characteristic of the neuropathic foot of leprosy.

(c) The footprint of the standing sole. (after Morton)

The figures represent kilogram pressures on each area for a man of total weight 48 kg—24 on each foot. These pressures exist simultaneously on all areas so long as the patient stands on the foot. Note that the toes play no part in supporting the standing pressure.

the importance of walking pressures, and now wish to proceed to a study of the mechanism of walking as concerns the sole of the foot, especially the region of the metatarsal pads of the big toe.

The walking cycle involves almost the whole of the skeletal musculature and most of the joints. It depends on the integrity of sensory circuits concerned with balance and the avoidance of slipping on the ground. This mechanism was first studied in detail by Carlet 90 years ago, but he lacked the technical facilities for a full understanding. Recent workers (Morton 1935) have greatly increased our knowledge and this has been applied to clinical problems by Lake (1952) and others. Recent techniques, notably of high-speed cinephotography, have thrown more light on the details (Barnett, 1956) and it can be said that the mechanics of walking are fairly well understood.

The walking cycle, with special reference to the sole of the foot is examined as follows:

1. The walking "roll" and sole pressures.
2. The "angle of gait".
3. Sole dorsiflexion during the walking roll.
4. The function of the big toe in walking.
5. The intrinsic musculature of the foot in walking.
6. The role of sole sensation.
7. Types of gait.

1. *The Walking "Roll" and Sole Pressures*

Each step of walking involves a roll of the body across the sole of each foot in succession from heel to toe tips. The line of the roll begins at the point of heel-contact, and passes rapidly round the under-surface of the heel, up along the lateral border of the sole to the region of the head of the fifth metatarsal bone; thence it passes across the metatarsal heads to the first, and finally turns forward along the big toe to its tip (Fig. 2a). The speed at which this roll takes place depends on the rate of walking, but at a brisk pace each roll is completed in about $\frac{3}{4}$ of a second.

The pressure associated with this cycle also pass rapidly across the sole, and follow in sequence so that no portion of the sole is compressed for longer than half a second. The pressure is moderate at the heel, then falls rapidly as it passes along the lateral border of the foot; turning medially across the sole, the pressure builds up to a maximum over the sesamoid bones of the first metatarsal head, and continues forward at a high level till the final push-off in which all the toe tips co-operate.

These pressures have been measured and may reach as much as 20 kg (45 lbs.) more than half the body-weight, which is the standing pressure on one foot. The remainder of the body-weight is meanwhile transferred by the momentum of the body.

It will be noted that, on *standing*, the pressures on each sole are simultaneous all over the pressure-bearing area of the sole (Fig. 2c). This pressure is distributed so that half the amount is on the heel and half on the forefoot (Morton 1935). The forefoot pressure is itself equally distributed between the four lateral metatarsal heads. It will be seen that each head or sesamoid bears one-sixth of the pressure on the forefoot, which is one-twelfth of the total pressure on the sole—or one-twentyfourth of the total body-weight.

For a man of 50 kg (115 lbs.) this is about 2 kg (4½ lbs.).

The heel, which is the least common area for plantar ulcers, bears six times the standing pressure of any bony prominence in the forefoot. The importance of the walking pressures as opposed to the standing pressures is reflected in the relative strength of the metatarsals. The first, which bears only twice the standing weight of each of the other digits, has much more than twice their bulk and strength.

The distribution of plantar ulcers in leprosy is reproduced in Fig. 2b, so that the relation to walking pressures may be evident. The slight differences that exist can be related to the pronator weakness which is characteristic of the neuropathic foot of leprosy.

2. *The "angle of gait"*

Most people out-toe slightly in walking, and the degree of external rotation relative to the direction of walking is known as the angle of gait. The effects of this angle are described in detail by Napier (1957). In the study of plantar ulcers, it should be noted that an alteration of the angle of gait modifies the site of maximal sole-pressure and the function of the big toe in the push-off. A wide angle transfers the pressures medially, while a narrow or negative angle displaces the pressures and the push-off towards the lateral toes.

This difference must be kept in mind in noting the distribution of plantar ulcers among patients of different areas, and between the sexes. In the survey described, it was noted that among the women, in particular, the position of maximal plantar ulceration tended to vary from region to region; and it was observed that the carrying of heavy loads, which often included babies, was associated with a tendency to walk with a wide base and some in-toeing, or lessening of the angle of gait.

3. *Sole-dorsiflexion during the walking roll*

The roll of the walking step occurs, not across a rigid sole, but across a flexible structure which dorsiflexes so as to present a type of rocker. This is illustrated diagrammatically in Fig. 3, which is compiled from data given in the series of cinephotographic exposures at high speed reproduced by Lake (1952) from Elmslie's work.

The importance of this mechanism is emphasised by observing the artificial foot which gives the best imitation of the natural gait. This is illustrated in Fig. 3, where the three points round which the

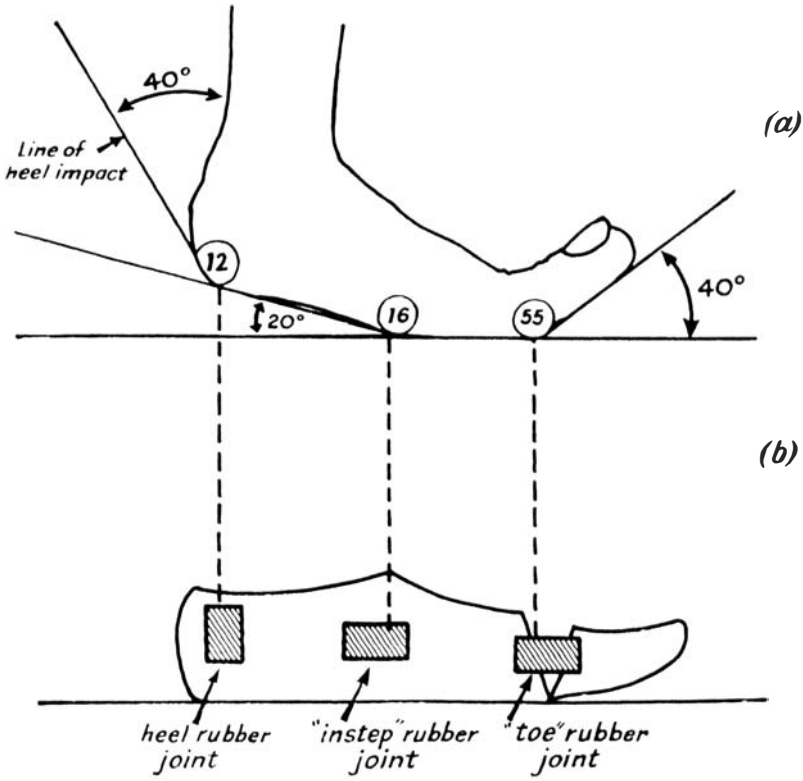


FIG. 3

The points of Rotation-pressure on the sole

(a) A composite diagram summarising the three points of rotation-pressure and indicating, in degrees, the amount of rotation occurring in the walking "roll" during a brisk step. The foot is shown at the middle of the cycle, and the big toe is dorsiflexed to the extent to which the metatarsals dorsiflex on the big toe at the final push-off. The degree of heel rotation on heel-contact is also indicated. The encircled figures indicate the percentage of plantar ulcers occurring at each site. (b) A tracing of a wooden artificial foot, showing the rubber joints normally placed to obtain a suitable gait; these are at the points of rotation under discussion.

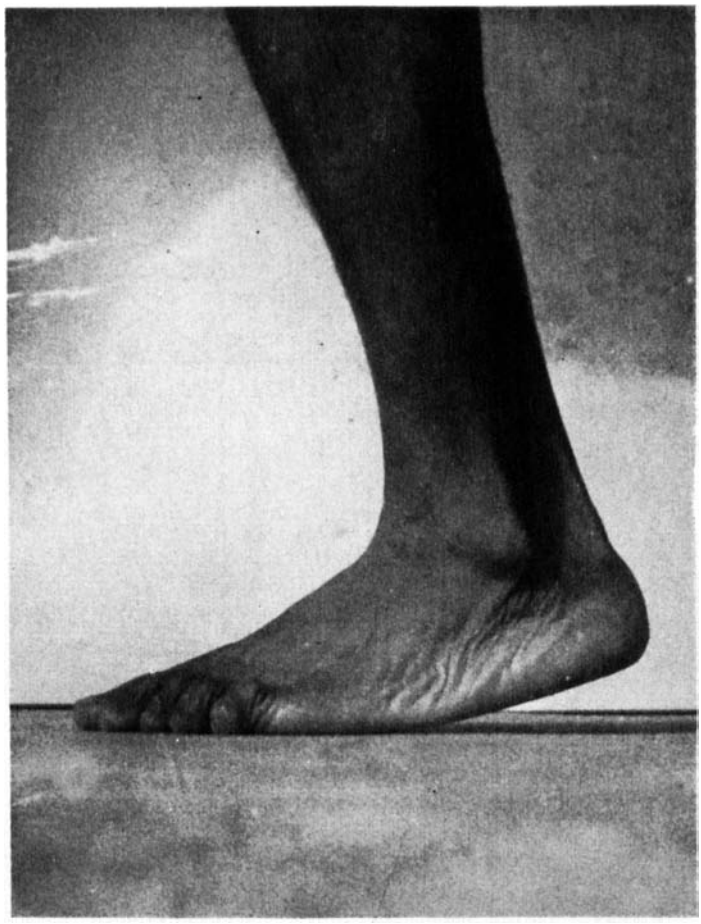
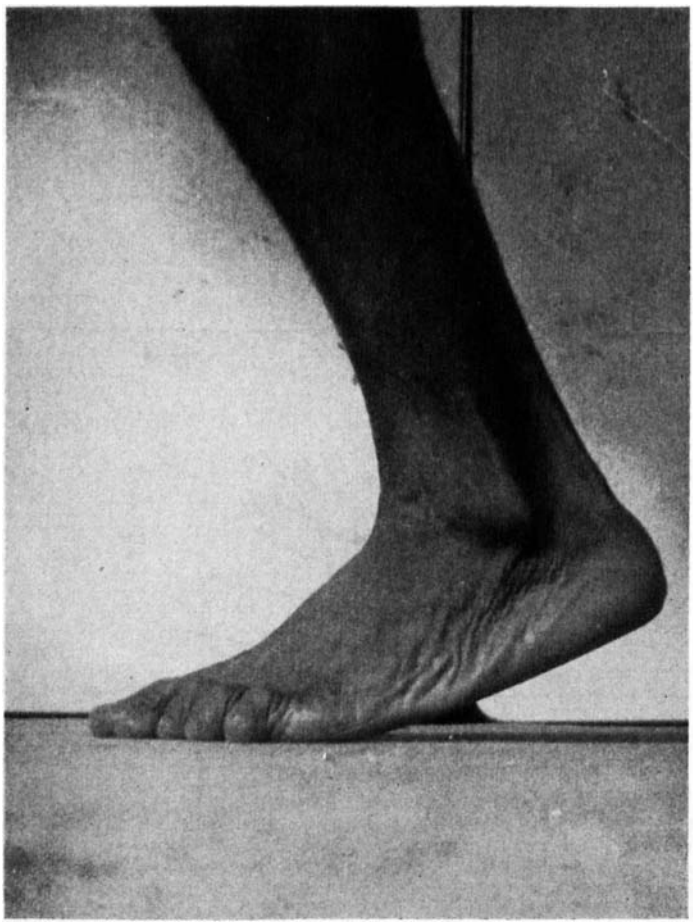


FIG. 4

The Walking Foot

Photographs taken during walking at 1/500*th of a second.*
(*a*) *Dorsiflexion at the mid-lateral joint. Dorsiflexion up to* 20° *takes place in the region of the base of the* 5*th metatarsal during the walking roll. A sesamoid not infrequently protects the tissue from friction damage. In failure of the protective mechanism, plantar ulcer is not uncommon* (16.5%) *at this point.*



(*b*) *Dorsiflexion at the metatarso-phalangeal joints. Dorsiflexion at the M-P joints reaches as much as* 45° *and the walking pressures are at their maximum. The metatarsal pads are the commonest sites of plantar ulcers.*

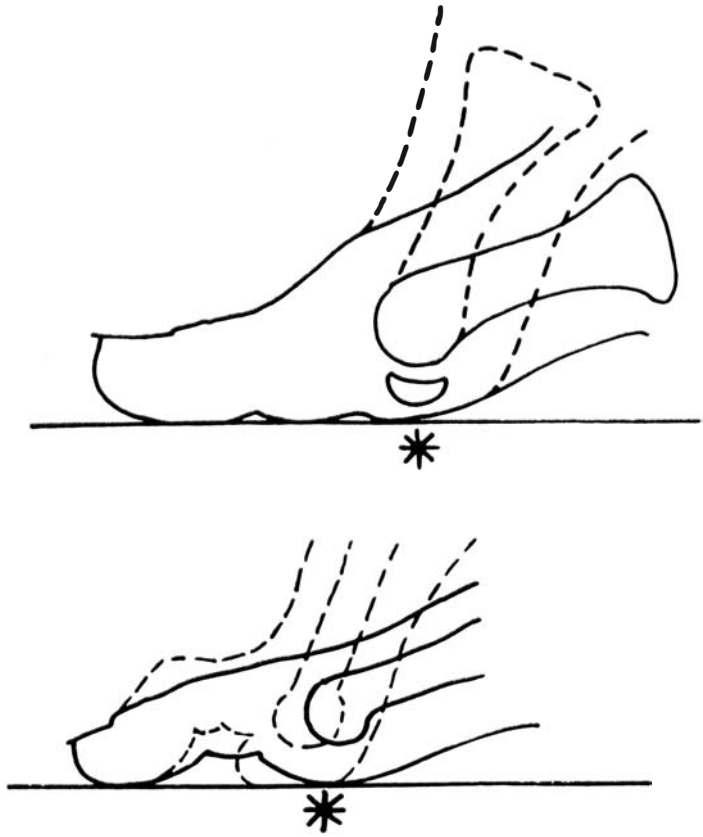


FIG. 5

Method of absorption of friction-pressures during dorsiflexion of metatarsals with each step

(*a*) *The big toe. Tracings of X-rays of beginning and end of metatarsal rise. Here damage to tissues is avoided by rotation of the metatarsal head in situ, on an underlying cartilage buffer (the sesamoids). The big toe does not move.*

(*b*) *The lateral toes.*

In these cases, the damage is avoided by a rolling-forward of the metatarsal head, with the underlying pad of tissues, much as a garden roller does on a lawn. The corresponding toe slowly brakes the roll to a standstill at the moment of push-off, by firm contact at its tip.

The asterisk indicates the point of maximum incidence of sole-ulcers in leprosy.

roll occurs are cushioned by three rubber "springs". These are named, by limb-makers, the heel, instep and toe rubbers, though in fact the "toe" rubber is placed at the site of the metatarso-phalangeal joints. A "foot" without these rubbers is very clumsy in action.

The degree of rotation and the percentage of plantar ulcers occurring at each site of rotation are indicated in the diagram.

Mid-foot rotation occurs between the cubo-calcaneal and cubo-metatarsal joints, but the latter is better constructed than the former for dorsiflexion, and is the commoner of the two sites for plantar ulcers.

The foot in action is shown in Figure 4, taken by high-speed photography during the act of walking.

Rotation, under pressure, of the degree that occurs in walking must be associated with considerable friction in areas of the sole where rotations take place. It should be noted that these are the site of 91% of plantar ulcers, if the tips of the toes are included.

There must evidently be some method by which these frictions are controlled or dissipated so that they do not damage normal tissues on the numerous occasions that they take place every day. That there are two distinct mechanisms for avoiding damage in the forefoot is evident by the observation of the sesamoids under the first metatarsal head, and their absence under the others. The occasional presence of a sesamoid under the mid-lateral joint is significant in this connection.

Radiographs of the bony and soft tissues during the actual step clarify these mechanisms as follows:

(*i*) *Rotation mechanisms at the first metatarsal head* (*Fig. 5a*)

The first metatarsal head rotates in *situ* during the walking step, somewhat as the femur does on the tibial plateau. It is prevented from slipping forward by the big toe, which remains rigid and in full contact with the ground until the end of the metatarsal rise.

The plantar skin of this area does not move during this time, but it can be seen that any point on the under-surface of the metatarsal head rotates backward through an angle of 40° or more. The considerable friction thus engendered is absorbed, as at the knee, by a cartilage buffer, cartilage being the only tissue in the body capable of absorbing, without damage, repeated pressure-frictions.

The sesamoids present a cartilage surface to that of the overlying head, and so absorb the friction that would otherwise damage unprotected tissues.

It can be seen that tissue-protection is afforded at the first metatarso-phalangeal joint (*a*) by the stability of the sesamoids, which are kept in contact with the head during the motion, and (*b*) by the rigidity of the big toe. If either or both of these are compromised, tissue-protection is in jeopardy.

(*ii*) *Rotation mechanism at the lateral metatarsal heads* (*Fig. 5b*)

At the lateral metatarsal heads, a different mechanism is involved. The pressures are a good deal less and a simpler protection suffices. It will be seen that the metatarsal head, as it rises, rolls forward with the underlying pad of tissues much as a garden-roller rolls forward across the lawn.

The stresses are gradually reduced to zero by the action of the corresponding toe, which remains in contact with the ground only at its tip, and which produces a gradual braking effect by slowly and actively yielding to the advancing forefoot. The downward pressure on the ground exerted by the tip of the toe reflects this action; it increases steadily to a maximum at the final moment of push-off.

As in the case of the big toe, it can be seen that a toe that failed to stop the forward roll of the metatarsal bone and pad exposes the tissues to damage.

4. *The Function of the Big Toe in Walking*

The big toe is a common site of plantar ulcer, especially at its base, and the role of the big toe in walking is important. Attention has been drawn to the fact that the walking roll, as it passes across the sole of the foot, ends by turning forward along the big toe for the final push-off. The thrust is larger the faster the gait, and in such circumstances as walking up-hill or in sandy soil.

The pressure on the big toe at push-off is little less than that occuring elsewhere in the foot. When the loss of stability is taken into account (following weakness of the flexor hallucis brevis and other intrinsics of the foot), it is not surprising that plantar ulcers occur here for similar reasons to those responsible for ulcers on the sole proper. In fact, the big toe can be considered as a miniature sole from the point of view of walking.

In cases where the big toe is lost, or fails to function, or where the patient habitually in-toes, the second toe can partially take over big toe function. In such cases in leprosy, the plantar lesions typical of the big toe are seen on the second toe.

5. *The Intrinsic Musculature of the Foot in Walking*

While the intrinsic musculature of the hand is largely concerned with the grasp and other finer movements of the hand, that of the foot is mainly concerned with the act of walking—though barefooted people can and do pick up objects from the ground with their toes.

The importance of stability of the toes in protecting the sole from damage during the friction-pressures of walking has been stressed. It should be recalled that the muscle controlling flexion of the proximal inter-phalangeal joints of the lateral toes is an intrinsic muscle in the foot, while in the case of the hand it is a forearm muscle, and so largely spared in leprosy.

This means that the foot is more crippled than the hand by weakness of its intrinsic musculature.

6. *The Role of Plantar Sensation*

The tendency to slip during the walking step is considerable if ground friction is inadequate, as a walk on ice will confirm. The friction necessary to prevent slipping is therefore important to the walking mechanism and depends on the character of the ground. The actual friction-force on the sole is increased either by an increase in the roughness of the ground, or by an increase in the proportion of total body-weight put on the foot as the step is taken. If the ground is smooth or unstable, extra weight must be thrown on to the stepping foot, as the gait of the sailor testifies.

Sensation of the sole is an important factor in informing the brain of the amount of weight that must be transferred to the sole to prevent a fall.

In the absence of this information, the only solution is to put excessive weight on each step, so as to be sure that friction is adequate to prevent a slip. Without sensory control, the brain can only add weight blindly and so this is always much greater than would suffice if sensation were normal. Thus lack of plantar sensation automatically involves increased pressure on the sole during walking.

7. *Types of Gait*

The types of gait have been adequately described by Lake (1952) and are significant in the treatment of the damaged foot in leprosy. Lake describes a "springy" gait, seen in its most obvious form in the walking race, and the "rigid" gait, which is the traditional gait of the soldier wearing thick-soled rigid boots. Either gait can be employed at will, but individuals vary in their use of them.

Although the rigid gait appears ungainly, it is found to give maximum protection to the sole of the foot and is used by the armies of the world, where foot-protection is particularly desirable. It will be recalled that wooden clogs—which induce a rigid gait—are standard footwear in many parts of the world. Advantage is taken of the rigid gait in the development of the treatment and prophylaxis of sole-ulcers described in a later chapter.

Summary

1. Attention is drawn to the high incidence of plantar ulcers in leprosy on the parts of the foot where walking pressures are maximal, and the importance of the walking mechanism is stressed.

2. Details of this mechanism are discussed in relation to the occurrence of plantar ulcers.

Acknowledgements

I am indebted to the Director of Medical Services, Eastern Nigeria, for permission to publish.

References

BARNETT, 1956 "The Phases of Human Gait" *Lancet* 2 : 617.
LAKE, N. C., 1952, The Foot. Ballière, Tindal and Cox, 4th Edition.
MORTON, D. J., 1935, The Human Foot, quoted by Lake, see Fig. 57 of Lake's book.
NAPIER, J. R., 1957, Physiotherapy, 43 : 65.

CAMOQUIN IN THE TREATMENT OF ACUTE LEPRA REACTION

R. H. THANGARAJ, M.B., B.S.

Medical Officer, Purulia Leprosy Home and Hospital, Purulia, West Bengal

When I was medical officer at Schieffelin Sanatorium, Karagiri, I treated 45 lepromatous patients for acute lepra reaction in three groups of 15 patients. One group was kept as a control, and the others were put on potassium antimony tartrate or camoquin, each patient being placed in one of the three groups by drawing lots. Only cases with fever, erythema nodosum, or subcutaneous nodules were selected for the study. All cases had been under treatment with DDS, sulphetrone, or thiosemicarbazone, and the blood had been examined for malaria.

Thus in the potassium antimony tartrate group, 13 were on DDS, one on thiosemicarbazone, one on sulphetrone. In the camoquin group, eleven were on DDS, two on thiosemicarbazone, and two on sulphetrone. In the control group, 14 were on DDS and one on thiosemicarbazone.

In the potassium antimony tartrate group, this drug was given intravenously on alternate days, with an initial dose of 0.02 gm. gradually increasing to 0.05 gm. In the camoquin group the initial dose was three tablets, then one tablet twice a day for four days. Camoquin of Parke Davis & Co., Ltd. contains 0.25 gm. per tablet of amodiaquine hydrochloride.

Results

In the potassium antimony tartrate group the reaction subsided in five patients after four days, in six patients after six to eight days, in three patients after nine to twelve days, in one patient only after cortisone was used.

In the camoquin group, four cases had subsidence of the reaction on the second day after camoquin was begun, four cases after the third day of camoquin, three cases after the fourth day, two cases after the fifth, and the remaining two cases did not respond to the camoquin after six days of it and potassium antimony tartrate was then used and the reaction subsided after four days more.

In the control group, in three patients the reaction subsided after four days, in six patients after five to eight days, and in the remaining six cases potassium antimony tartrate or cortisone had eventually to be used to control the reaction.

Summary

Camoquin is effective in the control of acute lepra reaction in lepromatous leprosy at an initial dosage of three tablets by mouth, followed by two tablets daily for four days. In one case only the camoquin was given for six days and in that case it failed. In this and in one other case in which camoquin failed, subsequent use of potassium antimony tartrate was successful.

Compared with a group on potassium antimony tartrate, camoquin achieves its effect in less time. In an untreated group, nine out of fifteen cases became free of the reaction spontaneously in four to eight days.

References

SUSMAN, I. A., Clinical Observations on Erythema Nodosum Leprosum. *Leprosy Review* **29**, 4: Oct. 1958, pp. 227-228.

CASALS, D. A. Camoquin in Acute Lepra Reaction. Revista de Sifil. Leprol. y Dermatol. Cuba 13th year, No. 1, 1957, pp. 19-21.

LEPROSY CONTROL IN UGANDA DURATION OF TREATMENT OF INPATIENTS AND OUTPATIENTS

by J. A. KINNEAR BROWN, B.SC, M.D., M.R.C.S., D.T.M.
Specialist Leprologist, Uganda
and W. M. BLENSKA, M.B., B.S., D.T.M. & H.
Medical Officer, Buluba and Nyenga Leprosaria

The Buluba and Nyenga Leprosaria are in Southern Uganda close to the shores of Lake Victoria and within 25 miles of each other. They are under the same administration so that the methods of treatment and the criteria adopted before discharge are identical. The majority of patients are of the Baganda or Basoga peoples, but there is a sprinkling of related tribes from adjacent territories. Together the two settlements accommodate between 500 and 600 inpatients. They have each a very large outpatient clinic. Treatment is mainly by oral diaminodiphenylsulphone.

Since January 1957, 410 patients have been discharged free from symptoms and all signs of active disease. They had all been bacteriologically negative to repeated examinations for at least one year. Table I shows the duration of treatment in years before discharge. The numbers are classified under the various disease types and arranged under inpatients and outpatients.

TABLE I

Duration of Treatment of Discharged Patients—In Years
(*Number of patients*)

Type	2-3	3-4	4-5	More than 5	TOTAL
TUBERCULOID					
Inpatients	9	9	22	15	55
Outpatients	9	26	55	56	146
INDETERMINATE					
Inpatients	13	12	7	7	39
Outpatients	7	21	37	43	108
DIMORPHOUS					
Inpatients	0	1	0	1	2
Outpatients	1	6	1	6	14
LEPROMATOUS					
Inpatients		2	2	11	15
Outpatients	3	5	6	17	31
TOTAL					
Inpatients	22	24	31	34	111
Outpatients	20	58	99	122	299
	42	82	130	156	410

Table II expresses the results of Table I in percentages to make comparison easier. As the lepromatous and dimorphous groups are small they have been put together.

TABLE II

Duration of Treatment of Discharged Patients—In Years
(*Percentages of total*)

Type	2-3	3-4	4-5	More than 5
TUBERCULOID				
Inpatients	**16**	**16**	**40**	**27**
Outpatients	**6**	**18**	**38**	**38**
INDETERMINATE				
Inpatients	**33**	**31**	**18**	**18**
Outpatients	**6**	**19**	**34**	**40**
DIMORPHOUS and LEPROMATOUS				
Inpatients	**0**	**18**	**12**	**71**
Outpatients	**9**	**24**	**16**	**51**
ALL TYPES				
Inpatients	**20**	**22**	**28**	**31**
Outpatients	**7**	**19**	**33**	**41**

The percentages of discharges among the lepromatous and dimorphous groups in the first four years almost suggest that for them outpatient treatment is the method of choice, but it has to be remembered that besides being disproportionately smaller than the other groups those who are allowed to attend as outpatients are the early and mild cases. The difference between these inpatients and outpatients is therefore due to the manner of selection.

Patients with the tuberculoid and indeterminate types of leprosy formed seven-eights of the total discharges. Despite the fact that inpatients are drawn from the more advanced or more seriously ill cases *their discharge rate under four years was significantly higher than that for those attending as outpatients.* Regularity and continuity of treatment cuts down the period of treatment.

The introduction of drugs that can be administered more easily than the traditional hydnocarpus oil and that are more effective has tended towards an oversimplification of some of the issues involved. It is a great temptation to open clinics for those who can attend and sit back and feel that that is the end of the problem. In the conditions of East Africa it matters little whether the treatment is oral once or twice weekly or parenteral once each fortnight, the ability of patients to travel in all kinds of weather decides whether their treatment will be irregular or continuous. A fluctuating blood level of circulating sulphone means a longer period before cure, a longer period before the patient is uninfectious and a better chance for the bacillus to become drug resistant.

The figures in this report are not put forward as an argument for the extension or multiplication of leprosaria, but to emphasise the importance of treatment villages built by the community to enable the more infectious and those who live at a distance to obtain adequate treatment.

THE DEPOT LEPROMIN TEST AND BCG VACCINATION

J. A. KINNEAR BROWN, M.D., B.SC., D.T.M.
Specialist Leprologist, Uganda
and M. M. STONE, S.R.N., S.C.M.

Kumi Ongino Leprosy Settlement, Uganda

Investigations reported recently suggest that for purposes of preventive medicine weak reactors to normal lepromin could be identified if they can be considered to be those who would fail to respond to a multi-puncture test with 1 : 100 depot lepromin. This test has none of the drawbacks of the ordinary Mitsuda, it is simple to apply, economical of material and would have advantages in field work. (Kinnear Brown 1958). The depot medium used consisted of one part of anhydrous lanoline and eight parts of light liquid paraffin. 0.25 gramme of autoclaved bacteriologically positive lepromatous tissue was ground into 4 ml. of medium and 1 ml. of isotonic saline to form a suspension in a concentration of 1 : 20. A dilution of 1 : 100 was made by adding medium and saline in similar proportions.

Fourteen healthy children about one year old, whose mothers had leprosy were now tested with both concentrations. One child was positive to both, the others negative. Five weeks later 12 of the 14 were tuberculin tested. They were all negative. Ten were then vaccinated with BCG and retested with 1 : 20 depot lepromin.

The child who was lepromin positive at the beginning remained positive. The nine who were negative became positive. The signs of conversion appeared first in the final lepromin test, in one child in three weeks, in the others after four. The maximum response was reached in four to six weeks. Conversion signs in the original lepromin tests were later by two weeks, when seven of the nine children showed positive in both concentrations; there was some slight alteration at the sites in the other two children but the signs were less definite. In these seven therefore the depot lepromin had remained in the skin long enough to act as an indicator and the final test might have been avoided. It is possible this would have happened in all if the interval between the original tests and the vaccination had been three weeks instead of five; the longer interval was deliberate.

Conversion was not demonstrated by the original lepromin tests for 11 weeks, i.e., six weeks after the BCG vaccination. Had there been any significant sensitisation by the dose of lepromin injected in those tests one would have expected conversion in them not later than in the final tests. Lepromin is a comparatively weak antigen and in the dosage given by the multi-puncture route it is difficult

to imagine it could have any profound effect except in a very small minority. The order of events suggests that in these children the BCG vaccination was responsible for the conversion.

The work was repeated on a further 13 children who were negative to both lepromin and tuberculin. Nine of the 13 showed conversion at the end of six weeks. It was not possible to follow up the other four, as they went home to relatives, this being the reason why only ten of 14 children in the first series completed the schedule.

By contrast there was no change to positive in 22 lepromin negative patients who were tested and BCG vaccinated, which confirms the impression that the effect of BCG on patients and non-patients is different.

Conclusion

1. Depot lepromin injected by the multi-puncture route remained in the skin long enough to act as an indicator.

2. The considerable economy of material that is possible and the saving of time both to the examiner and the individual examined make it desirable that the method should be further investigated with a view to its use in the field and in control campaigns.

Acknowledgements

Our thanks are due to Dr. J. M. Lea, Medical Superintendent of the Kumi Ongino Leprosy Settlement, for his assistance and giving access to his patients.

References

BROWN, J. A. KINNEAR, *Leprosy Review*, **19,** 4: Oct. 1958, pp. 184-196

ERYTHEMA NODOSUM LEPROSUM

DR. A. R. DAVISON
Westfort Institution, Pretoria

Erythema nodosum leprosum, hereinafter called ENL, was studied in its relation to duration of treatment and the bacterial index. This paper carries the study further on cases originally reviewed by Davison and Kooij, 1957[1], and also by Doull and others[2-3] in 1954 and 1957.

1. An analysis was made by grouping the first series of 201 patients according to the occurence of ENL or not, high or low bacterial index (B.I.), and the period in months required to attain bacterial negativity. There were 101 patients with *high B.I.*, with values varying between 3½ and 18, and an average of 8. Those who escaped ENL were 20, and they took 64 months to reach negativity; whereas the 81 who had ENL took 75 months and more to attain negativity, and there were five still positive at 83, 83, 87, 120, and 80 months respectively. There were 100 patients with *low B.I.*, with values ranging between ½ and 3½, and an average of 1½. Of these, 24 who had no ENL took 57 months to attain negativity, whereas 76 who had ENL took 65 months or more, and one of them took 110 months.

The above analysis took place in June, 1958, on patients who had begun treatment under the Clinical Evaluation Project in February, 1952[2], but many had been on DDS for various periods before this.

The longer period before positivity and the persistent negativity stand out in patients who had ENL in the high B.I. group. There were four deaths in the ENL group and none in the other group. The time taken to reach negativity between low and high B.I. groups (57 and 64 months respectively) suggests that the initial degree of positivity is important in prognosis. The general conclusion is that ENL is of bad prognostic significance, and more time is taken in the high B.I. group than the low.

2. An analysis was made by grouping cases according to *long or short duration of treatment.*

In 98 patients with a long duration of treatment (average of 79 months) there were 85 with ENL and 13 without it. In the former, 79 months were required to reach negativity, and in the latter, 77 months. Of the 98 patients, 49 had an average high B.I. of nine, and 49 had an average low B.I. of three.

In 97 patients with a short duration of treatment (average of 56 months), there were 66 who had ENL and 31 who did not. The former took 58 months to become negative, and the latter 53. The average group B.I. was 3.3, varying from 1 to 5½.

The analysis showed that long duration of treatment does increase the number developing ENL, and patients with lower B.I. developed less ENL and required shorter treatment.

3. An analysis was now made of a second series of 103 patients as at June, 1958, who had been included in the evaluation project[3])

in September, 1953, but most of them had been under DDS for various periods before this.

There were 53 patients of *high B.I.*, with values varying between 8 and 25, and an average of 15. There were 14 who escaped ENL and 39 with it. In the former, the period before negativity was 54 months, but five remained positive at 61, 72, 68, 59, and 66 months respectively. For 39 with ENL, the period before negativity was also 54 months, but 15 remained positive at 61, 72, 64, 59, 66, 70, 59, 76, 59, 65, 65, 73, 74, 77, and 73 months respectively. There were 50 patients with a *low B.I.*, with values ranging from ½ to 7½, and an average of three. Of these there were 19 without ENL and 31 with it. The former took 41 months to attain negativity, and there was one case still positive at 73 months: the latter took 63 months, and one was still positive at 60 months.

The bad significance of ENL is again shown. There is a prolongation of the time needed to reach negativity, and in one section there is a striking preponderance of cases who still remain positive after 54 months. Whether the initial B.I. is high or low does not seem of much significance.

4. Another analysis of ENL was made on the basis of long treatment or short.

In 40 patients with *long treatment*, namely an average of 70 months, there were 33 who had ENL and seven who did not. The 33 who had ENL took 70 months to attain negativity and the seven took 69 months. The initial B.I. was between 2 and 10½, with an average of six for the group.

In 41 patients with *short treatment* of an average of 43 months, there were 21 who had ENL and 20 who did not. The former took 45 months to attain negativity and the latter took 40 months. The initial B.I. was between 3 and 13, with an average of seven for the group.

It seems that long duration of treatment does increase the number developing ENL. There was no significance in the initial B.I.

Summary

From analyses of the records of patients who had been used in clinical evaluation studies with J. A. Doull, it appears that ENL is of bad prognostic significance so far as length of treatment is concerned. There were two series of patients. From the first it is clear that the longer the treatment the more ENL develops, and the lower the initial B.I. the less ENL develops and the shorter the treatment required. From both series it appears that ENL does not depend on the degree of positivity but does depend on the duration of treatment.

References

1. DAVISON, A. R. and KOOIJ, R. Is Erythema Nodosum Leprosum a Favourable Occurrence? Internat. J. of Leprosy, **25,** 1957, 91-98.
2. DOULL, J. A. Clinical Evaluation Studies in Lepromatous Leprosy, First Series. Internat. J. of Leprosy, **22,** 1954, 377-402.
3. DOULL, J. A. Clinical Evaluation Studies in Leprosy, Second Series. Internat. J. of Leprosy, **25,** 1957, 173-192.

NOTES ON LEPROSY IN ADEN

by A. L. FAWDRY, M.A., M.D., (CANTAB.)
Pathologist, Aden

The visit of Dr. R. G. Cochrane to Aden in 1955 stimulated an attempt to see whether more could be done for sufferers from leprosy in Aden Colony. There had been before the last war a small leprosy hospital managed by the Church of Scotland Mission Hospital, holding about 30 men and half a dozen women: but in the early war years it had been taken over for more urgent medical needs and never restarted. Regular outpatient treatment has been given recently at the Mission Hospital itself—24 men and 6 women patients recorded in 1957-58. No regular treatment with sulphones was being given in the government hospitals and dispensaries, the general impression being that the disease was uncommon. The other acid-fast bacillus claimed a great deal of attention: rightly so as tuberculosis was and is by far the most important endemic disease of Aden Colony, whether viewed from the angle of personal suffering, economic loss, or contribution to the Colony's death and morbidity rates.

All medical officers of the department were asked to refer cases of leprosy or suspected leprosy to the laboratory of the Civil Hospital where details of history and physical examination were noted and examination of scrapings from the most likely-looking lesions made. The patients were then started on the standard course of DDS ("Avlosulphone") and told to attend twice a week as outpatients.

The majority came from the large outpatient department of the Civil Hospital (total new attendances per annum c. 20,000): a few from the Colony's other four dispensaries: a few sent by colleagues for medical, dermatological, or laboratory consultation: and a few spotted in the streets of the town and urged to attend hospital.

The resultant "Leprosy Clinic" has now been in action (April 1958) for 26½ months and 126 persons have been seen and offered treatment. However, for 11½ months, other duties and the interruption of a leave reduced the clinic's activities to a minimum, only 15 cases being recorded. The other 111 were seen within 15 months, making an average of seven new cases of leprosy presented per month.

Distribution of cases: the places of origin of the patients and the presumed origins of their infections were as follows:

Yemen	76	60%
Western Protectorate ..	33	26%
Eastern Protectorate ..	5	4%
Aden Colony	5	4%
Unrecorded	5	4%

Of the above only eight were women (four Yemen, two W.A.P., two Colony).

It is impossible to disentangle from the circumstances which determine attendance, such as transport facilities, the factor of the local incidence of the disease. Nevertheless, it is clear that the vast majority of those with leprosy come from outside the Colony and most of them from the neighbouring country for the health of the subjects of which we in Aden have no responsibility and over which we have no control whatever. Of the 33 seen from the Western Aden Protectorate, 11 came from the close-by sultanate of Lahej, where there is an accessible focus of disease which should and could be eradicated.

It is doubtful whether all seven of the persons with leprosy now permanently resident in the Colony did acquire the disease here.

The small proportion of women and children is partly due to the reluctance of the women to come to hospital, but mostly because the immigrant labourers from the Yemen leave their families at home when they come down to Aden, either for work or medical attention.

Types of Leprosy

Tuberculoid	69
Intermediate	24
Lepromatous	19
Unrecorded	14

There was no noticeable relationship between place of origin and type of leprosy. What was remarkable was that there were no completely incapacitated patients, and none with gross ulceration. It may be that such advanced cases never succeed in reaching Aden, but advanced cases of all other varieties of chronic disease, e.g., tuberculosis and cirrhosis of liver, arrive here in small numbers continually. One concludes that the resistance of the Arab to the disease is high and that in a large proportion of cases the defences of the body arrest its extension and the disease burns itself out. However, in Yemen, advanced cases do exist in plenty according to Hayyat (1958).

Examination for M. leprae

M. leprae found	62
M. leprae not found ..	39
Not examined	25

Acid-fast bacilli were sought in scrapings taken from the nose and from the two other most likely-looking sites: nodules, edges of leprides, ear-lobes, etc. Some were omitted owing to pressure of other work and sometimes patients who had been examined clinically failed to return to the laboratory for examination of scrapings.

Treatment

The standard course recommended by the manufacturers of "Avlosulphone" was used. Patients were told to come twice a week

to get their tablets, and when they showed that they could be relied on to come regularly, they were given supplies for a month at a time, and warned to return at any sign of reaction. The scheme was on the whole not a success, as can be seen from the following table:

Referred elsewhere, i.e., to Protectorate Health Services or other Colony dispensaries ..	23
Did not return for any treatment	36
Attended for less than one month	31
Attended for one to six months only	24
Attended for more than six months	10
Completed course of 1½ to 2 years	2

Two patients developed severe reactions to the drug, with anaemia, and fever during the treatment: both recovered, though slowly, when admitted to hospital and deprived of the medicine. They were able to continue on a reduced dose.

Social Circumstances

Most of these patients are very poor indeed and while in Aden exist by begging; they are illiterate labourers from the Yemen or the Aden Protectorates, living on a diet barely sufficient in calories or protein, and subject to other diseases too, such as malaria and schistosomiasis. A fair proportion might be able to do light manual labour in their own villages but the progress of the disease has driven them to seek medical aid in Aden where they cannot compete with their fitter countrymen. The doctor's offer of a two year course of treatment with tablets is of very little use to them: they try the unimpressive bi-weekly doses for a short time and then finding no noticeable relief, give up attending the clinic. There is no way of following up such defaulters, even if we had the staff, as they have no permanent addresses in the Colony and sleep in the streets. A very few decide to make a real job of mendicancy in Aden—probably an income of a shilling a day is enough to keep body and soul together (3/- a day provides a nutritionally adequate diet in Aden, and I have lived on it for a month myself). They can then continue treatment, and one cheerful mild lepromatous lad of 16 or so has persisted long enough to feel and know the improvement in his health. A few continue begging without returning for the tablets, but most—it is impossible to say how many—go home disappointed.

There have been, however, a dozen or so attending regularly or irregularly who were in reasonable economic circumstances from the start: these are the ones who will also probably persist in the future with treatment. A broker, a merchant, a clerk, a student, a housewife living near the hospital—they have done well and the disease has been arrested at least: with the assistance of a health visitor, they could probably all be persuaded to continue for the full period of time desirable—but they need "chasing".

There seems to be no rejection of the case of leprosy by society as a whole whether in the town or in the villages of the Protectorates or the Yemen: no attempt is made to isolate them and there is little or no "leprophobia".

Western Protectorate

Patients from this area were sent back to their villages and arrangements for their treatment left in the hands of the Protectorate Health Service, through their Health Units. These are staffed by trained orderlies who can issue the DDS tablets regularly, and 63 patients were registered in 1956.

Eastern Protectorate

A similar arrangement exists but there is also a small leprosarium in Mukalla housing about 50 sufferers, at public expense.

The Yemen

Sulphone treatment was instituted a few years ago at Sana and Taiz hospitals but there must be far more leprosy than can be dealt with by these two centres in the rest of the country.

Conclusions

Leprosy is not a major public health problem in the Colony, but there are at any one time probably between 30 and 60 cases at large, most of them infectious. With the assistance of a health visitor it would not be difficult to get adequate treatment for any who live permanently in the Colony: and as these are living in houses and are likely to be in close contact with children, this is important not only for themselves but for the prevention of spread. As the rest live and sleep for the most part in the open air and are unlikely to be in close contact with children, the danger of spread is slight: the problem here is one of the tragedy of the individual—cure is available but cannot be used so long as there is a lack of supervisory health personnel. The patient makes the long journey from a remote village to the hospital in hope, but is apt to go back in despair when he finds that prolonged treatment is necessary.

Summary

A description is given of an attempt to assess the problem of leprosy in Aden Colony, and initiate treatment.

My thanks are due to the Director of Medical Services, Aden, for permission to publish this paper.

Reference

HAYYAT, M. U. Late WHO Adviser in Public Health to the Government of the Yemen. Personal communication.

OJI RIVER,
ONITSHA AREA,
NIGERIA LEPROSY SERVICE.
15th November, 1958.

The Editor,
Leprosy Review
Dear Sir,

Vadrine "131" in the Treatment of Leprosy

I was interested to see that Vadrine had been tried by Drs. W. H. Jopling and D. S. Ridley in human leprosy and that Dr. H. Brodhage reported on its effect in experimental murine leprosy (*Leprosy Review*, **29**, 3; July, 1958, pp. 143 and 148).

At Oji River, we also tried it and found it of no value, and I have written to the manufacturers to this effect. The reports in *Leprosy Review* make it necessary to publish our findings. We are grateful to Messrs. Geistlich for the generous supply of this drug for trial.

The experiment was carried out by Dr. K. M. Ellis and myself, and at the beginning and the end of the trial Dr. T. F. Davey saw the patients and checked results, and has confirmed our findings.

The manufactuers advised a daily dose of 20 to 40 mg./kg. We chose four untreated lepromatous patients, and two borderline who had shown slow progress on DDS and thiacetazone.

Results:

i. A nodular lepromatous patient became noticeably worse with ulceration of nodules.
ii. One became worse by showing an increase in the skin thickening and the nerve pain; this was not a case of erythema nodosum leprosum.
iii. The bacterial index of two cases became higher than at the beginning.
iv. Patients who had received previous treatment remained unchanged.
v. Only one showed any improvement. This was a grossly anaemic and undernourished patient, who improved in general health as a result of receiving a good diet, but the leprosy showed no improvement.
vi. We transferred all the lepromatous patients to DDSO and they subsequently showed the usual expected improvement over six months, and slight bacteriological improvement.

On this evidence we have discontinued the use of Vadrine, having found a marked contrast to the consistent good results from DDS, DDSO and DPT.

Yours sincerely,
A. S. GARRETT,
Area Superintendent.

HOSPITAL FOR TROPICAL DISEASES,
4 ST. PANCRAS WAY,
LONDON, N.W.1.
23rd January, 1959.

The Editor,
Leprosy Review,
8 Portman Street, W.1.

Sir,

We were interested to see the report by Drs. Garrett and Ellis on their trial of Vadrine. Their results have caused us some surprise for our findings with this compound, during the first year of treatment, were comparable with those to be expected from sulphone except that there was more individual variation in the responses. However, further observations on those patients who showed an early improvement have been disappointing, for they have either ceased to improve after 12 months or more of treatment or have actually deteriorated.

It would seem therefore that Vadrine, used alone, has no place in the treatment of leprosy, but we are at present trying it in conjunction with sulphone in view of the very good initial response made by a few patients in our trial.

We are, Sir,
Yours faithfully,
W. H. JOPLING
D. S. RIDLEY

The Editor,
Leprosy Review,

Dear Sir,

Dr. J. T. Worsfold's results for Rhodesia resemble those of the extensive surveys in Uganda which I have published at various times, namely a child rate of between 18% and 19% and an equal sex distribution. In some respects, however, his interpretations differ from my own.

The extremely low conjugal rate, which is the usual experience, suggests that something other than prolonged intimate contact is necessary for infection, and the fact that so many cases show their first clinical signs in later life may have a significance other than that of a prolonged latent period, although the lengthening of this period is probably a feature of a decline in an endemic. In East Africa there is a fall in the incidence between the ages of 15 and 20, which may also be traced in the figures published from other countries. It suggests that in this five year period the losses by death are not replaced by new cases and that there is an intrafamilial risk in childhood followed by an extrafamilial risk in adolescent and adult life.

The relative proportions at risk in each period will naturally vary with the opportunities for contact that society provides. This has an important implication for schemes of control, especially those which concentrate primarily on children, for apparently susceptibility does not necessarily decline with age.

The sex distribution and the lepromatous and non-lepromatous rates often appear to be related. Where the lepromatous rate is high males are principally affected, with a ratio as high as 2 : 1; where the tuberculoid rate is greater, the sex ratio approaches equality. This latter is true in Uganda and may be inferred from survey reports elsewhere. The fact that some institutional figures differ from Dr. Worsfold's findings in the field should not lead him to doubt his observations. In Uganda where the ratio is 1 : 1, the proportion in settlements often approximates 2 : 1. This relationship is seen in figures from general hospitals for ordinary diseases and indicates the customs of the people rather than the incidence of the disease. In under-developed countries there are many reasons why women attend hospitals less often, just as there are reasons why there are fewer girls at school than boys. In fact I judge the efficiency of the Uganda scheme of control by comparing the sex and child ratios in settlements, treatment villages and clinics with those I have found in surveys of whole population groups in the field.

There are many very interesting conclusions to be drawn from such epidemiological studies of leprosy which compensate to some extent for the impossibility so far of obtaining answers by a direct approach through the culture of the organism and the use of an experimental animal. I hope Dr. Worsfold will accept my congratulations on his work with the comments I have briefly offered.

Yours faithfully,

J. A. KINNEAR BROWN,
Medical Headquarters, Uganda.

OBITUARY—DR. A. FILIPEANU

Prof. Dr. Scarlat Longhin of the Societatea Stiintelor Medicale din R.P.R., Bucaresti, Str. Progresulin, No. 8, has had the kindness and courtesy to send the following obituary notice of a Rumanian leprologist, Dr. Alexander Filipeanu.

Dr. Alexander Filipeanu, director of the Tichiliesti State Leprosarium died on 24th December, 1957. Born in 1889 at Cocuisca village in the Dorohoi department, he studied in the Faculty of Medicine at Iassy, obtaining the M.D. degree in 1920. He successively occupied the posts of externe, interne, and secondary doctor at St. Spiridon Hospital in Iassy. After obtaining his degree, he occupied the post of assistant at the Neurological Clinic, Iassy, and then that of Dozent at the same clinic, up to 1924. From 1922 to 1923 he studied at the Dermatological Clinic of the Faculty of Medicine in Leipzig, directed by Prof. Richle. From 1924 to 1939 he was a chief dermatologist at the Central Hospital in Chisinau.

In June, 1939, he was appointed chief doctor at the State Leprosarium, Tichilesti. Subsequently, Dr. Alexander Filipeanu dedicated himself, until the end of his life, to the care of the leprosy patients. Far from any medical centre, at 50 km. from the nearest town, he showed a special self-sacrifice in the care of these patients separated from their families, leading the same lonely life. His work in the leprosarium was a shining example of self-abnegation. Even after reaching 60 years of age, he continued on duty, in spite of the fact that he was rather ill.

Dr. Alexander Filipeanu also contributed to many scientific works on leprosy in its clinical, epidemiological and therapeutic aspects.

By the death of Dr. Alexander Filipeanu, Rumanian Dermatology loses a valued specialist, chiefly in leprology.

OBITUARY

DR. CYRIL F. A. WALLACE, M.B.E., M.B.CH.B. (ABERD.)

Dr. Cyril Wallace was born at Montego Bay, Jamaica, on 19th July, 1900, and died at Tanga in Tanganyika on 11th May, 1958. He graduated in 1922 and in 1924 went to the Mission Field at Lebombo in Portuguese East Africa. In July, 1929, he offered his services to Bishop G. A. Chambers, of Central Tanganyika and began work there as the only doctor in the C.M.S. mission field in that area, and, when he was centred on Kilimatinde, he discovered at Makutapora a neglected small leprosarium which had been established by the German colonial authorities. This place was revived and reconstructed by the Mission, and continues to the present time. In 1936 Dr. Wallace was ordained at the Cathedral in Dodoma and in 1937

he went to India to study leprosy at the School of Tropical Medicine, Calcutta. Dr. Wallace spent 16 years in the Mission, mostly in charge of Kilimatinde hospital and Makutapora Leprosarium. In February, 1945, he joined government service, and continued in leprosy work for 13½ years. He took over the Chazi Leprosarium in 1945. It was then in its infancy and he watched over its development. In 1948 he was transferred to the Makete Leprosarium where again he pioneered its development into one of the best institutions in Tanganyika. In both places he was the pioneer of modern therapy in leprosy. He knew the importance also of diet and hygiene and left magnificent citrus orchards in both institutions. In 1952 he was transferred to Muheza in Tanga Province and developed a large scale scheme of outpatient treatment which eventually embraced a large part of the Tanga Province and cared for about 4,000 patients. Dr. H. W. Wheate, who has furnished some of the above details, writes: "It was my privilege to visit this project after the death of Dr. Wallace. In the course of six weeks, I travelled 3,000 miles by Land Rover and saw about 50% of the registered patients. I found that Dr. Wallace was held in high esteem by these patients and that he had succeeded in obtaining a reasonable attendance rate and in extending adequate supervision and care by constant travel in rough conditions. His clinical judgment was unerring." Dr. A. G. Farr, Provincial Medical Officer of the Tanga area, writes: "He made a deep impression on the people of this area, both by his character and his devotion to his work, and his loss is greatly mourned by many people, and particularly by his patients. This also applies to the people and his former patients of Chazi and Makete. Tanganyika has lost one of its beloved physicians who long will be remembered with admiration and affection."

(We also had the privilege of knowing Dr. Wallace and his work in Tanganyika from 1947 to 1953, and record our abiding impression of a calm and faithful service as a leprosy medical officer. His work was crowned by the highly successful outpatient work from Muheza. In all his work he had the comradeship and support of his gallant wife, who survives him. *Editor*).

ABSTRACTS

Progressive Experimental Infection with M. leprae in a Chimpanzee: Preliminary Report. A. E. GUNDERS, Journ. of Trop. Med. & Hyg., **61,** 9, Sept. 1958, pp. 228-230

Human lepromatous material was inoculated into a female chimpanzee of six to seven months of age. The sites of the inoculation were sub-arachnoid, round the left ulnar nerve, and intravenously and intraperitoneally. At 11 months the chimpanzee developed signs of acute and progressive leprosy, with many nodules on the limbs and some depigmentation. Sections from skin biopsies showed a granulomatous process of epithelioid cells and smaller cells, and bacilli were found in all sections. Regression of nodules began at the 14th month after inoculation. Another chimpanzee aged 2½ years was similarly inoculated, but has shown no lesions to date.

Haemagglutination and Haemolytic Reaction of Red Cells Sensitized with Extracts of Murine Leprosy Bacilli. N. YAMADA, La Lepro, **27,** 2, March 1958, pp. 126-135.

The findings appeared to verify the idea that a common antigen between *M. tuberculosis*, *M. leprae*, and *M. lepraemurium* exists. Also the hæmolytic reaction occurring on addition of complement to the haemagglutination reaction system using murine leprosy bacilli was more specific and sensitive than haemagglutination similar to old tuberculin antigen. Leprous involvements of the internal organs in murine leprosy seemed closely to influence the reaction: this has also been reported by Kawaguchi. With the haemolytic reaction using old tuberculin about one half of the sera of leprosy patients showed prozone but it is thought that this is a pattern occurring in the optimal relation between antigen and antibody, and is not due to anti-complement action of the serum. The haemagglutination and haemolytic reaction of tuberculosis serum and murine leprosy antigen are closely interrelated and coincide with the results obtained with old tuberculin antigen.

Studies on the Lepromin Test: Sensitization Experiments with Trypsin Isolated Bacilli. K. YANAGISAWA and N. ASAMI. La Lepro, **27,** 2, Mar. 1958, pp. 107-113.

After 5.2 g. of lepromatous tissue had been homogenized, trypsin was added and it was left for three days at 30° C. then centrifuged for thirty minutes at 10,000 r.p.m., yielding a sediment of 180 mgm. of bacteria, almost free of tissue fragments. Using this sediment and also the purified wax of tubercle bacilli, sensitivity tests were carried out in guinea pigs, by inoculation of 3 mgm. and 15 mgm. of the leprosy bacilli. There was a third group in which 2 mgm. of the purified wax of tubercle bacilli was given in addition to 3 mgm. of leprosy bacilli. The fourth group had 2 mgm. of

purified wax of tubercle bacilli as the sole inoculum, and the fifth group was an untreated control. After the inoculations, spaced tests were given with Dharmendra lepromin and with tuberculin. Enhancement of allergy was noted in both the lepromin and tuberculin tests: in the first two groups where leprosy bacilli had been inoculated both the lepromin and tuberculin tests became positive three weeks after inoculation and the lepromin reaction was retained up to 24 weeks and was stronger than the tuberculin. Both reactions, especially the tuberculin, were stronger in group 3 where purified wax of tubercle bacilli had been given in addition to leprosy bacilli. The Dharmendra antigen does not enhance allergy whereas the bacilli collected by the trypsin method do so. It appears that the Dharmendra method removes the wax substance of the bacteria because of the use of chloroform.

Sensitization of the Dog with Lepromin and BCG, and Evidence of Cross Sensitization: Persistence of the Sensitization and Cross-Sensitization. (2 papers). N. O. CASTRO and P. A. ARCURI, Internat. J. of Leprosy, **25,** 3, July-Sept. 1957, pp. 231-242.

Their experiments show that whole lepromin can sensitize dogs, confirming the observations of Wade, similar to the effect of BCG in causing sensitization to BCG. There is further a cross-sensitization between BCG and lepromin. The cross-sensitization to lepromin induced in the dog by BCG appears to be a transitory phenomenon which may disappear within nine months. The non-specific sensitization to BCG induced by lepromin is more stable. The specific sensitization to either lepromin or BCG is equally stable.

Studies on the Immunology of Murine Leprosy, T. TANIMURA, S. NISHIMURA, Y. TANIMURA. Internat. J. of Leprosy, **25,** 3, July-Sept. 1957, pp. 247-256.

Young white rats of a mixed strain were used as the experimental animals, and the material was derived from lepromas of the Kumamoto strain of murine leprosy. Injection of a saline vaccine of heat-killed *M. lepraemurium* into such rats some time before inoculating them with live bacilli, caused inhibition of the onset of the infection to a high degree, though not completely. There is a lesser degree of inhibition with the simultaneous inoculation of dead and live bacilli. By adding liquid paraffin to the vaccine of dead bacilli there was also strong inhibition of the onset of an infection to live bacilli, more so than with the saline vaccine of dead bacilli. There was only a slight degree of inhibition when a vaccine was used of non-pathogenic acid-fast bacilli with liquid paraffin added. When a secondary infection was tried in rats already infected with murine leprosy there was seen to be a greater resistance than anything the paraffin murine leprosy vaccine could induce, and complete prevention was noted to a challenge inoculum of 0.5 cc. of 10^4 leproma suspension. There was no kind of Koch phenomenon as in tuberculosis, in

the shape of an acute reaction of the skin over the reinoculation site. The size of the primary lesion did not influence the results of the secondary inoculation, nor did the latter influence the progress of the primary lesion.

Chemotherapy of Murine Leprosy. The Effect of Cycloserine (Seromycin) on Mouse Leprosy. Y. T. CHANG. Inter at. J. of Leprosy, **25,** 3, July-Sept. 1957. pp. 257-261.

Cycloserine was given against mouse leprosy induced by intraperitoneal infection. It was found to be moderately effective in supressing the infection, similar to streptomycin but less than INH. Cycloserine was reported beneficial in human tuberculosis though without effect in experimental tuberculosis of mice and guinea pigs. As it has now been found that it is effective against murine leprosy, this and other forms of mycobacterial infections should be included in the screening tests for more active anti-tuberculous agents.

Réaction de la Peau des Lépreux aux Injections Intradermiques d'Acides Gras Provenant du Bacille Tuberculeux (Reactions in the Skin of Leprosy Patients to Intradermal Injections of Fatty Acids from Tubercle Bacilli) N. P. BUU-HOI and T. V. BANG. Revue Française D'Etudes Cliniques et Biologiques, **3,** 7: Sept. 1958, pp. 770-773.

The bacilli of tuberculosis and leprosy are very similar in their content of lipids. Fernández and Chaussinand have pointed out the phenomena of allergy and para-allergy between these bacilli, which suggest a similar chemical composition. Anderson has shown for the tubercle bacillus that the lipids are made up in great part by branch chain fatty acids of high molecular weight, one of the most interesting being phthienoic acid (C 27), which is especially abundant in the virulent strains. Buu-Hoi has tried the effect of fatty acids from tubercle bacillus in similar conditions to those of the Mitsuda. He obtained fractions with more than 20 atoms of carbon and by intradermal injection obtained skin reactions in lepromatous cases, both papules and nodules of varying intensity. These reactions are non-specific, as they also occur in non-leprous subjects.

Le Traitement de la Lèpre par Injections Mensuelles de DDS (Treatment of Leprosy by Monthly Injections of DDS). P. LAVIRON, L. LAURET, P. KERBASTARD, and C. JARDIN. Médicine Tropicale, **17,** 6: Nov.-Dec. 1957, pp. 795-808.

The authors treated 107 patients for periods varying from 8 to 40 months by different suspensions of DDS, using one injection a month. The suspensions were (*a*) 2.50 g. DDS in hydnocarpus oil, (*b*) 2 g. in water containing gelose and saccharose, (*c*) 1.50 g. in saline containing gelose. The results are less rapid than from dosage at shorter intervals but are quite satisfactory and the method is useful for induction of treatment or as maintenance after the disappearance of the lesions.

Le Traitement de la Réaction Lépreuse (*Treatment of the Lepra Reaction*). M. F. LECHAT. Bulletin d'information sur la lèpre, No. 5, Foreami, Brussels. 1958, pp. 1-56: also Maroc Médical, **36,** 390: Nov. 1957, pp. 1039-1062.

This paper is a comprehensive review of the subject, with 159 references, and deals with the classic lepra reactions (lepra fever and the erythema nodosum type) and excludes the transitional phases, namely the tuberculoid reaction, the pseudo-tuberculoid exacerbation, and borderline cases. The author describes the many treatments that have been tried and mentions the contradictory results from chlorpromazine and the excellent results from ACTH and cortisone. He thinks zinc-ACTH is worth trying in borderline cases and tuberculoid reactions. He advocates more small hospital wards being made available everywhere for the bed treatment of reaction cases.

Consideraciones sobre Quimioterapia de la Lepra (*Thoughts on the Chemotherapy of Leprosy*). M. BERGEL Leprología, Buenos Aires, **2,** 2: 1957, pp. 107-110.

Drugs of which the therapeutic activity has already been demonstrated should serve to help us in further search. We do not know the mechanism of action of hydnocarpus oil. We only know it is an oil and that in patients who have had intense treatment with it there is a deposit of it in the fatty tissues. All the sulphones seem to act by the liberation of DDS in the tissues. DDS has a primary direct anti-oxidant action, e.g., it prolongs the induction period of the oxidation of methyl oleate (Lips). The sulphones can act as metallic inactivators: they form insoluble and inabsorbable complexes in the digestive tract, especially with iron (Brownlee). The thiosemicarbazones inactivate heavy metals such as iron, copper, and cobalt (Liebermeister). *In vivo* they diminish the level of copper in the body (Carl). They stabilize organic substances by means of their inactivation of metallic pro-oxygens (Clarkson). INH inactivates heavy metals, such as copper and iron (Albert), and has a primary direct anti-oxidant activity. In certain concentrations INH is up to ten times more active as an anti-oxidant than alpha-tocopherol (Hasselstron).

Because of its bacteriological, immunological, and histo-pathological connexions with tuberculosis, every drug active in tuberculosis is worth trying in leprosy. Similarly, because of the bacteriological connections every drug active in murine leprosy is worth trying in human leprosy, but there is a certain lack of parallelism between them and hence Domagk does not think that the chemotherapy of murine leprosy is a good index for the human. Because of the relations between actinomycetes and mycobacteria, fungostatic drugs might be worth while trying in human leprosy. Buu-Hoi thinks we should try any anti-tuberculous or fungostatic drug, especially if there is also a certain degree of liposolubility.

The lepromatous-like picture provoked in animals by the lack of anti-oxidants, when they are on a pro-oxidant diet, suggests that we should try in leprosy every drug which *in vivo* prevents the deposition of acid-resistant pigment. Methylene blue and nor-dihydroguayaretic acid can do this. Acid resistance is connected with a good bacillary oxygenation and the loss of acid resistence is thought to depend on an insufficient supply of oxygen (Gran Triana). The failure of inoculation and culture of *M. leprae* is related to its dependence on oxygen. Hanks in his study of the oxidative metabolism of the mycobacteria throughout their range from the saphrophytic to the pathogenic noted less and less capacity *in vitro:* the oxidative capacity was lowest in *M. lepraemurium* and *M. leprae* which could not increase their respiration in the presence of many different substrates. Hanks thinks that conditions which favour a more rapid and continuous oxidation of lipids tends to preserve the infectivity of these mycobacteria and that in our studies of pathogenesis and chemotherapy we should not miss the chance of creating an oxygen deficiency in certain stages of leprosy or the chance of augmenting it if it exists. In connexion with this, it may be recalled that the lepromatous state does not progress in patients at high altitudes, where there is an environmental deficiency of oxygen. Referring to the conditions necessary to create this deficiency of oxygen, Hanks pointed out that the reducers as well as the toxins of the process of oxido-reduction and the anti-oxidants act in the same way, limiting the oxidations and creating what might be called "a system of negative oxygen" which we should seek to use to oppose *M. leprae*. The bacillus is favoured in its development by "a system of positive oxygen" (Bergel). In order to obtain the pro-oxidant action of diet in leprosy, there should be intake of crude fats and green vegetables as supply of tocopherols, and even of supplementary tocopherols by mouth.

The lipo-solubility of hydnocarpus oil seems to indicate that this may be a favourable condition in chemotherapy of leprosy. Buu-Hoi points out that of all the anti-tuberculous drugs, only those which also have lipo-solubility have activity against leprosy. The fact that hydnocarpus oil is deposited in the fatty tissues of the patients seems to indicate an active compound against leprosy should have this property: this is closely bound up with lipo-solubility. Hopeful compounds would also be those which are able to decrease oxidation at the tissue level, to inhibit respiratory enzymes, to form catalytically-inactive stable complexes with the pro-oxidant metals and to prevent the auto-oxidation of the lipids. So it would be worth while trying in leprosy every metallic and anti-oxidant inactivator which has low toxicity and can be absorbed by mouth and which has good conditions of distribution in the tissues and of elimination: if possible, it should be lipo-soluble and able to be deposited in the fatty tissues,

and better still have a degree of anti-tuberculous and anti-mycotic activity. Among the vast group of organic compounds patented for industrial use as preservers of organic substances, as anti-oxidants, and as metallic inactivators there should be some with a strong action against leprosy. We could benefit also from the industrial knowledge of the solubility and synergism and other practical details of these compounds.

Familial Leprosy. N. MUKERJEE and S. GHOSH. Journ. of the Indian Med. Assoc. **31,** 3: Aug. 1958, pp. 129-131.

A Hindu female aet. eight years, belonging to a family in which the mother and three sisters were cases of leprosy, developed flat hypopigmented macules over the face, and later on the limbs and back. There was no disturbance of sensation and no thickening of nerves, and the smears were negative. After three months of observation there was slight increase in size and a biopsy was taken from a lesion. This showed a moderate infiltration of round cells with a few epithelioid cells and the subepidermal zone was invaded in places. A few bacilli were seen in the infiltration and inside a nerve. Hence the diagnosis of leprosy was made. Of the family, the father was dead, the mother was lepromatous, the three sisters tuberculoid, and the brother was found free of leprosy.

Acupuncture and Galvanic Current in the Treatment of Lepra Reaction. KAO HUAI-AN and colleagues; Chinese Journal of Dermatology, **6,** 4; 1958, p. 298 (reported in Chinese Medical Journal, **77,** 3, Sept. 1958, p. 287).

Nerve and joint pains and erythema nodosum in leprosy patients were treated by the typical techniques of Chinese acupuncture. Apparently the needle is inserted into the nerve trunk considered to govern the area, and galvanic current from a 1.5 volt storage cell is allowed to run for 30 to 50 minutes. This treatment is given every alternate day until 15 treatments have been given, and then a rest of one to two weeks is given. In 72 cases of severe arthralgia and neuralgia and in 21 cases with erythema nodosum the results were very good. Thus in 18 cases of erythema nodosum the lesions subsided rapidly in 15 and improved greatly in 3.

O Emprego da D-Cycloserina no Tratamento da Lepra: Resultados Preliminares. (The Use of D-Cycloserine in the Treatment of Leprosy: Preliminary Results) E. DE ALMEIDA NETO and J. P. REVELLES. Revista Brasileira de Leprologia. **26,** 2, Apr.-June 1958, pp. 63-91.

A full report, with details of bacterioscopy and haematology, and 28 clinical photographs, is given of a trial of D-cycloserine in 20 leprosy cases. This drug is a new antibiotic obtained from *Streptomyces orquidaceus*, and is given by mouth six-hourly in tablets of 250 mg. daily for the first seven days, increasing by one tablet per week up to four tablets daily. In one case only they tried six tablets

daily but on perceiving signs of intolerance, returned to four tablets daily. Treatment has lasted six months in most of the 20 cases. In four cases the drug was combined with DDS and in one with thiosemicarbazone.

There has not been time for full clinical cure, but the influence of the drug on clinical signs was early and considerable. There have been no cases of exacerbation, nor of drug resistance. Bacteriological results have been good and the histology shows a favourable modification. Tolerance has been good: central nervous system intolerance has been of the slightest and was easily avoidable. There were focal reactions of good prognosis noted at the beginning of treatment. Lepra reactions were moderate. The drug seems to act directly on *M. leprae*. The combination with the sulphones seemed particularly advantageous, and the drug seemed very useful in cases which had reactivated after being resistant to the sulphones. The trial will continue.

Nossas Observacoes Sobre a Difenil-Tiourea no Tratamento da Lepra (Our Observations on Diphenyl-Thiourea in the Treatment of Leprosy). A. M. ALONSO. Boletim do Servico Nacional da Lepra, Rio de Janeiro, **17,** 1: March 1958, pp. 5-11.

This is a report on 16 months of trial of DPT (Ciba 1906) on seven patients, of whom six were lepromatous and one tuberculoid. Clinical improvement was marked, and the new drug seemed superior to DDS in this regard. There was one case who had had a gastrectomy and was intolerant to thiosemicarbazone and DDS. This case tolerated DPT very well and had excellent clinical improvement. There was another case which had an abnormal resistance to the action of all anti-leprosy drugs: this case showed partial improvement in bacterial indices and histology but it is too early to expect much change in these.

An Experimental Study on the Action Exerted by Certain Synthetic Anti-malarial Drugs upon the Endocrine System. C. I. PARHON, V. SAHLEANU, and L. IANCU. Rumanian Medical Review, Bucarest: April-June 1958, **2,** pp. 56-61.

The authors gave a daily oral dosage, with controls, of quinine sulphate, atebrine, chloroquine sulphate, and paludrine in different groups of rats, and studied the effect on the endocrine glands and liver. They found that these drugs in non-toxic doses caused no depression of the endocrine system. Chloroquine and paludrine stimulated the adrenals, as shown histologically, histochemically, and in the weight of the organs. They think that this action is similar to ACTH, probably due to a stimulation of the release of this hormone. The general cortisone-like action of these drugs is not, they think, exclusively due to the stimulation of the adrenals. It is possible that there is a peripheral action upon the fundamental substance of the connective tissue and upon inflammatory phenomena, as well as

a central adrenal stimulation. The adrenal hypertrophy they obtained in their experiments was more insignificant with the most toxic substances (quinine, atebrine), so they do not think that it was merely part of the general adaptation syndrome of Selye. Liver histology showed the probable stimulation of the reticulo-histocytic system. It is well known that the adrenal hormones stimulate this system. The authors advance the hypothesis that the synthetic anti-malarials may influence the causal factors of a disease and stimulate the non-specific defence reactions of the body. They point out that their experimental results showed that paludrine can be introduced into dermatological therapy for the same purposes as those for which chloroquine is now being used.

Tratamiento Local de las Ulceras Neurovasculares de los Miembros Inferiores. (Local Treatment of Neurovascular Ulcers of the Lower Limbs). O. RAMIREZ. Boletin de la Sociedad Cubana de Dermatologia y Sifilografia. **15,** 2, 1958, pp. 59-64.

In four cases of neurovascular ulcers of the lower limbs, which had failed to heal after long periods of treatment, the author applied *dehydrated coffee powder* of the "instant coffee" type, in a simple dressing covered by gauze, and changed at intervals of eight days for a similar dressing. There was healing of the ulcer in three or four weeks in three cases and in two weeks in one case. There have been no relapses, and this treatment was tolerated perfectly.

Outstanding Achievements in Health Work in 1958. Chinese Medical Journal, Dec. 1958, **77,** pp. 582-586.

In an enthusiastic article describing the stimulating influence of the political approach on the health campaign, rats, sparrows, flies and mosquitoes are said to have been slaughtered in huge quantities and 960 counties of China to have been made pest-free. One impressive item was that 62.7 million public latrines were built. Traditional Chinese medicine has been revived, including acupuncture, and is used alongside modern medicine. "Traditional medicine has given remarkable results in the treatment of hypertension, apoplexia, arthritis, joint sprains, pulmonary tuberculosis, *leprosy*, syphilis, *Taenia solium*, infantile paralysis, Japanese B encephalitis, chronic nephritis, liver cirrhosis, tetanus, whooping cough, scarlet fever, and diphtheria. Its successes in treating silicosis, malignant tumours, aplastic anaemia, and leukaemia are unprecedented in world medicine."

There is a further reference to leprosy on p. 583. "In leprosy prevention, Shantung has completed a thorough survey of this disease and has isolated all sufferers for care and treatment. In Kwangtung province, during the past six months, over one half the cases of leprosy of the lepromatous type have been concentrated in leper villages, and 1,104 patients have already been cured and discharged".