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LEPROSY REVIEW

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Contents

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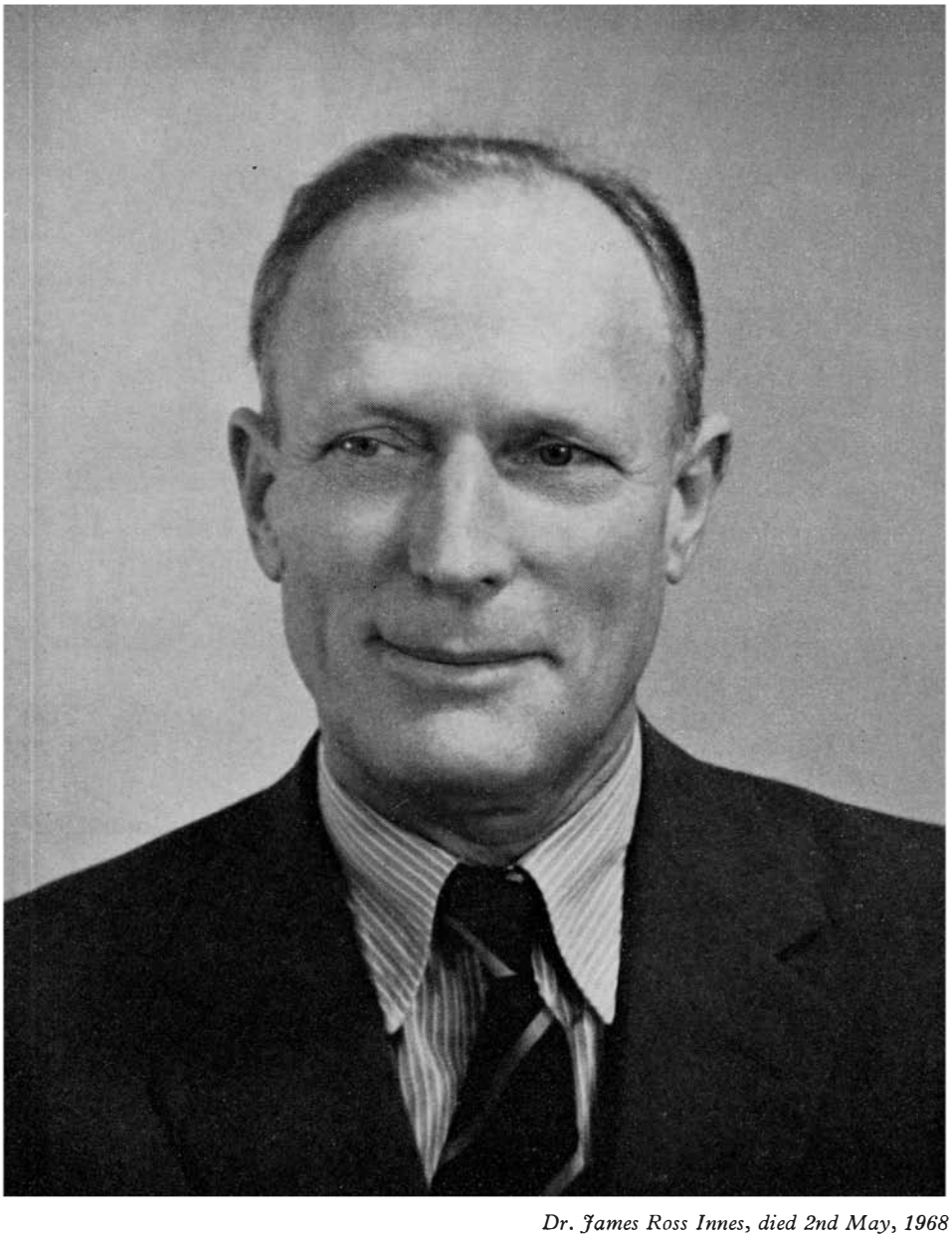

Dr. James Ross Innes, died 2nd May, 1968

James Ross Innes

M.D. (EDINBURGH), D.T.M. (LIVERPOOL)

Editor, *Leprosy Review*, 1957-1968

Medical Secretary, LEPRA, 1957-1966

With the passing of Dr. James Ross Innes on 2nd May, 1968, at the age of 65, *Leprosy Review* has lost a distinguished Editor and the cause of leprosy throughout the world is bereft of a wise counsellor and advocate. Our deep sympathy goes to his widow, who has herself for some years been most active and efficient in the conduct of the business side of the *Review*, and to his two daughters.

It was as Medical Secretary of LEPRA that he assumed the office of Editor, and after relinquishing the secretaryship in early 1966 because of failing health, he continued as Editor; in fact, he had just seen the second issue of 1968 off the press when the call came.

His connection with the British Leprosy Relief Association went back to the year 1957, when, retiring from his post as Leprologist to the East Africa High Commission, he was appointed Medical Secretary to the Association. His sage counsel, given without stint, was of great value to LEPRA throughout a decade of medical advance, of changing emphasis and of the inauguration of the Malawi Project. It was in connection with this Project that his organizing ability was put to the test as he faced the novel situation and its challenges. If he may be said to have acted as accoucheur for the Malawi Project, he had earlier gained experience as practising paediatrician of the Leprosy Research Centre at Alupe in Kenya, watching over its growth and development with expert and considerate care.

James Ross Innes was born in Brisbane, Australia, and received his early education at the Brisbane Grammar School. He came to Edinburgh, Scotland, to pursue his medical studies, which were crowned with the award of the degrees of M.B., CH.B. (with honours). His interest in leprosy was awakened by Dr. Ernest Muir, who happened to be his travelling companion on his voyage to India in 1928. As medical officer to the Khondwa Leper Asylum and the Wadia Hospital of the Church of Scotland Mission in Poona, India, he had every opportunity of seeing the sad ravages of leprosy in the pre-sulphone days.

During leave in England in 1934, Ross Innes took the course for the Diploma in Tropical Medicine at the Liverpool School. He gained the diploma, and also the Milne Medal as the most distinguished student of his year. Within months, his thesis (on leprosy) for the M.D. of Edinburgh University was accepted, 'with commendation'.

At the request of the (British) Colonial Office, he carried out a leprosy survey in the British Solomon Islands Protectorate in 1937-38. He then returned to India on a short contract, which was extended because of the war and his essential work at Cawnpore, till 1946. For 10 years from 1947, he was in East Africa as Leprologist under the East Africa High Commission, conducting leprosy surveys, advising on leprosy campaigns in the 3 territories and beyond in Nyasaland, the Rhodesias and Zanzibar, and publishing articles on his epidemiological and therapeutic researches. He wrote reports in the lucid, authoritative style he made his own, and had the satisfaction of seeing many of his recommendations acted on by the Governments concerned.

Dr. Ross Innes brought to his task as Editor of *Leprosy Review* a rich and varied experience of leprosy in India, the Pacific Islands and Africa, a cultured, questing mind, and a deep human sympathy. Under his firm guidance, *Leprosy Review* changed its format and extended its outreach. Many readers of these pages will have cause to remember with gratitude Ross

Innes' helpful criticisms of their draft papers and the despatch he showed when dealing with articles accepted for publication. His flair for words and his working knowledge of a score of languages could nowhere have been put to more productive use than in the editorial chair of such a publication as *Leprosy Review*.

Ross Innes had many interests beyond *Leprosy Review* and LEPRA. He became a member of the International Leprosy Association in 1931 soon after its inauguration, and was appointed its Honorary Secretary-Treasurer in 1957, succeeding Dr. Ernest Muir. He relinquished this task at the end of 1965. Meanwhile he had become known to a wide circle of friends, leprologists and others. He did much preparatory work behind the scenes for the International Leprosy Congresses in Tokyo (1958) and Rio de Janeiro (1963), and had been busily engaged in the preliminary steps for the London (1968) Congress, being a member of the Organizing Committee. He was elected a Life Fellow of the Royal Society of Tropical Medicine and Hygiene in 1934, and was an Honorary Member of the Indian Association of Leprologists.

A Memorial Service to Ross Innes was held in St. Columba's Church of Scotland in London's West End on 15th May, 1968. In the congregation were many of his friends and colleagues, representatives of those in many walks of life who knew him and respected him. Fitting tribute was paid to his memory by Rev. J. Fraser McLuskey, M.C., D.D., who referred to Ross Innes as a devout Christian, a fine medical missionary (ordained an elder of the Church of Scotland at the exceptionally young age of 25), a beloved physician, a good man.

He has gone, but his works remain. As was written of Christopher Wren, when we 'look around' we see them—in his publications, in the pages of *Leprosy Review*, in the victims of leprosy in the four corners of the earth touched by his scientific skill and innate kindliness, and in the mental pictures we retain of a man 'four square to all the winds that blew'.

S. G. BROWNE.

The Editors and Editorial Board of the *International Journal of Leprosy* wish to express their sense of loss in the passing of Dr. J. Ross Innes. Dr. Innes has contributed notably to the understanding and dissemination of knowledge of leprosy over a period of many years. His editorship of *Leprosy Review* and reviews of current literature in several abstract publications, for which his language facility was especially useful, have been of great value to leprosy workers in general. He will be hard to replace. We wish to express our condolences also to his family and friends.

ESMOND R. LONG,
Editor, IJL.
(MISS) DELTA DERROM,
Assistant Editor, IJL.

Dear Sir,

The workers of Gandhi Memorial Leprosy Foundation learnt with great grief of the demise of Dr. Ross Innes on 2 May, 1968.

Dr. Innes was a luminary amongst leprosy workers. With a sense of devotion and dedication he gave impetus to the leprosy control movement in the world. As editor of *Leprosy Review* he sought to establish a fraternity amongst the workers and encouraged scientific thought in the control programme.

We are sad that he is no more with us and pray that his soul rest in peace.

GANDHI MEMORIAL LEPROSY FOUNDATION AND STAFF.

May 30, 1968.

Editorial

For some time, the future of *Leprosy Review* had been a matter of interest and concern to both the Medical Committee and the Executive Committee of LEPRA (The British Leprosy Relief Association).

In these days of mergers and rising costs, of streamlining and rapid communication, it was inevitable that the usefulness and the viability of *Leprosy Review* had to be considered very seriously. Notwithstanding the existence of sister-organs in English (notably the *International Journal of Leprosy* and *Leprosy in India*), in French, in Spanish and in Japanese, and notwithstanding, furthermore, the welcome now being accorded by a variety of general and more specialized journals to articles embodying the results of research into some aspect of leprosy, it was considered that *Leprosy Review* was fulfilling an important and necessary function.

Leprosy Review will therefore continue to be published, with the backing and support of LEPRA, in the belief that it will, as in the past, serve the cause of leprosy by the prompt dissemination of information to its readers engaged in many branches of leprosy, thus stimulating good work in the field, the operating theatre and the wards, the laboratory, the workshop.

James Ross Innes has left his mark on *Leprosy Review*, and his untimely death (to which reference is made elsewhere in this issue) involves the bringing forward by some months of proposals that were intended to come into effect early next year. Although he continued to edit the *Review* after relinquishing the post of Medical Secretary of LEPRA, it had latterly become obvious that his failing health brought nearer the unwelcome but inevitable necessity for change. With the approval of the Executive Committee of LEPRA, therefore, the Medical Committee had already taken steps to ensure continuity of publication and continuity of editorial policy.

The Editor is replaced by an *Editorial Board*, constituted as follows:—

Drs. S. G. Browne (*Chairman*).
R. J. W. Rees (*Vice-Chairman*).
S. R. M. Bushby.
W. H. Jopling.
D. S. Ridley.

This Board will be responsible to the Medical Committee of LEPRA for the contents of *Leprosy Review*. It will, through its Chairman, receive articles submitted for publication and decide matters of policy.

The address of the Chairman of the Editorial Board, to whom all communications concerning the contents of *Leprosy Review* should in the future be directed, is:—

57A Wimpole Street,
London, W.1, England.

The Board will be assisted in its work by a part-time Sub-Editor, Dr. A. D. Duff, a medical man with considerable experience in medical journalism both in England and abroad. He will be responsible for the routine preparation for publication of accepted articles, illustrations, layout, etc.

Publishers of Leprosy Review

Leprosy Review has hitherto been published by The British Leprosy Relief Association, which has generously subsidized the costs of publication over the years. From the first number of the next volume (due to appear in January, 1969), The Academic Press Inc. (London) Ltd. will assume the duties and risks (and possible benefits) of publishing the *Review*, including the collection of subscriptions, sale of back numbers, etc. The implementation of this new arrangement will not need to be brought forward by reason of the lamented death of Dr. Ross Innes. As from 1 January, 1969, therefore, the whole of the business side of *Leprosy Review* will be handled by The Academic Press Inc. (London) Ltd., whose address is:—

Berkeley Square House,
Berkeley Square,
London, W.1, England.

A further and more detailed announcement will be made in the October, 1968, issue of *Leprosy Review*.

The procedure proposed is in keeping with that already adopted by many professional journals, and we look forward to a period of still greater efficiency and effectiveness in the dissemination of new knowledge about the diverse aspects of leprosy.

NOTE

Three titles of interest to readers of *Leprosy Review* have recently been added to the library of recorded talks on medical subjects sponsored by the Medical Recording Service and Sound Library of the Royal College of General Practitioners (Great Britain).

The author of the tapes is Dr. S. G. Browne, O.B.E., Medical Secretary of LEPRA.

No. 68/21 ('The recognition and management of leprosy in the tropics') is illustrated with 47 coloured transparencies. This should serve as a useful introduction to practitioners in the tropics who are not specializing in leprosy but who want to know more about this disease.

No. 68/22 ('Leprosy is here—in Great Britain'), illustrated with 23 transparencies, is intended for the general practitioner in countries like Britain where leprosy is but rarely met with, and is almost confined to the immigrant population. It tells the practitioner how to recognise leprosy and what to do if he suspects that a patient of his might have the disease.

68/23 ('Bringing you up to date with leprosy') is intended for general medical audiences desiring information on recent advances in leprosy research in the fields particularly of microbiology, animal transmission of *M. leprae* and therapeutics. This will supplement the recording made some years ago by Dr. J. Ross Innes which was sponsored by ICI Ltd., who have also contributed to the cost of the present recording.

The tapes are on 5 in. reels, and run at a speed of $3\frac{3}{4}$ i.p.s.

Tapes, with accompanying slides, may be borrowed from: Dr. John Graves, O.B.E., Kitts Croft, Writtle, Chelmsford, Essex, for 5 shillings each (plus postage) for 14 days' hire. Prices for purchase may be obtained from Dr. Graves.

ERRATUM

We wish to draw attention to a misprint in the April issue of *Leprosy Review* in the paper, 'Presence of *M. leprae* in the Nipple Secretion and Lumina of the Hypertrophied Mammary Gland' by Dr. J. C. Pedley.

p. 67, right-hand col., line 26-27

'. . . all of which were in good solid rod form'
should read
'. . . 11 (eleven) of which were in good solid rod form'.

S. G. BROWNE.
Chairman, Editorial Board,
Leprosy Review.

Ninth International Leprosy Congress LONDON

SEPTEMBER 16-21, 1968

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London, S.W.7

Lep. Rev. (1968) **39**, 3, 107-109

The Leprosy Problems in Taiwan

'What we do know is not being applied'

Y. F. CHAO, M.D.
Leprosy Clinic, Mackay Memorial Hospital, Taipei, Taiwan, Republic of China

Dr. Oliver W. Hasselblad, President of American Leprosy Missions Inc., has recently pointed out that the most optimistic appraisals fail to suggest that the incidence of leprosy is less today that it was 20 years ago[1]. Part of the problem, he feels, is that what knowledge we do possess of leprosy is not properly applied. These observations are entirely applicable to the present situation in Taiwan. We have advanced beyond the obstacles which were initially presented by lack of knowledge of the pathology and immunology of leprosy. Even though we now have more potent drugs and more knowledge of the disease, the number of leprosy patients seems to be increasing. This is, unfortunately, not entirely due to better case finding in the community.

The first regular surveys of leprosy prevalence in Taiwan were conducted through the police censuses between 1910 and 1939. In 1930, Dr. Y. Kamikawa, the superintendent of Losheng government leprosarium during the period of Japanese rule, reported a total of 1,080 leprosy patients in Taiwan—the largest number reported during these surveys[2]. There was no intensive leprosy survey during World War II, but in 1944 963 patients were found in a total population of some 6 million (including the Pescadores Islands). By 1948, there were still approximately 1,000 leprosy patients under treatment in the 2 leprosaria—Losheng Leprosarium and Happy Mount Leprosy Colony.

When J. A. Doull, M.D., Medical Director of the Leonard Wood Memorial (American Leprosy Foundation), visited Taiwan in late 1952, however, he cast doubt on the reliability of the previous studies[3]. He pointed out that the number of new patients admitted to the Losheng Leprosarium each year had varied greatly. In 1948, it was 124; in 1949, 56; in 1950, 79; in 1951, 112; and in the first 6 months of 1952, 76. These patients had had the disease for at least several years at the time of discovery, and there were, he estimated, at least 5 times as many in the general population. A police census made in 1939 had revealed 827 patients, but, from a study completed in 7 selected epidemic areas it was estimated that the true total number was 50% higher, or 1,241. Of the patients in the leprosaria in 1952, about 67% were Taiwan-born and 33% were mainland-born Chinese including military people who came to Taiwan after World War II. (The proportion of the Taiwan-born is now much lower, however.) The ratio of males to females, about 4 : 1 in 1952, was related to the influx of many young men from the mainland. Subsequent studies have indicated, however, that the true sex ratio of leprosy on Taiwan was 2 males for every female. In the institution at that time there were said to be only 2 or 3 under the age of 15 years, a fact that suggested the presence of a considerable reservoir of undiscovered patients.

Compulsory hospitalization of all leprosy patients was abolished in 1955, partly through the author's efforts to expand outpatient leprosy facilities, and partly because the leprosaria could not provide enough beds for the increasing number of patients seeking admission[4]. Between 1962 and 1967, the annual reports of all 'special skin clinics' and leprosaria on Taiwan were compiled by Dr. Kazuo Saikawa, WHO Medical Officer and Medical Adviser to the Taiwan Leprosy Relief Association. The information[4] thus derived is summarized in Table 1, and indicates a progressive increase in the number of leprosy patients attending outpatient facilities over this time.

TABLE 1

Number of patients treated during 1962 to 1967

Year	*In-patient*			*Out-patient*			*Total treated*		
	Adults	*Children*	*Total*	*Adults*	*Children*	*Total*	*Adults*	*Children*	*Total*
1962	1,081	10	1,091	1,958	103	2,061	3,039	113	3,152
1963	1,092	19	1,111	2,172	122	2,294	3,264	141	3,405
1964	1,098	16	1,11 4	2,370	146	2,516	3,468	162	3,630
1965	1,101	17	1,118	2,501	155	2,656	3,602	172	3,774
1966	1,133	11	1,144	2,726	184	2,910	3,859	195	4,054
1967	1,028	9	1,037	2,974	162	3,136	3,902	171	4,173

There has been a steady increase in the total number of leprosy patients reported since accurate statistics became available from 1962 onwards. As shown in Table 2, well over 250 new patients per year have been reported on average. The true figure, however, may be closer to 10,000 persons with leprosy, since case reporting from the special skin clinics may not be complete.

In 1968 the annual report of the Provincial Losheng Leprosarium showed that 4,204 leprosy patients were under treatment in a total population of 13,297,000—this is a prevalence of 3.18 per 10,000 population. The regional distribution of these patients was quite variable. Thus, there were 35.16 per 10,000 in Pheng-hu County (Pescadores Is. in the Taiwan Straits), the highest density in Taiwan, and the next, 6.86 in Kaohsiung city, 6.39 in Tainan city, and 4.51 in Taipei city, but only 0.78 per 10,000 in Nan-tou County in central Taiwan.

The shortage of trained leprologists and dermatologists on Taiwan greatly hinders control of the disease. Because patients with a variety of skin diseases visit the so-called 'skin' clinics, the non-specialist medical worker tends to miss any skin disease he does not recognize as leprosy. Thus, in the Department of Dermatology of Mackay Hospital in Taipei, the author has seen a great variety of skin disorders initially diagnosed as leprosy; such as seborrheic dermatitis, acne vulgaris, ringworm, burn scar, traumatic scar, chronic eczema, neuro-dermatitis, stasis dermatitis, leg ulcers, alopecia, leucoderma, erysipelas, psoriasis, syphilis, warts, new growths; and from such rarer diseases as cutaneous leishmaniasis, lupus erythematosus and acanthosis nigricans.

A major impediment to proper leprosy control on Taiwan is the frequent failure of local physicians to provide treatment for leprosy patients in the routine outpatient departments of general and mission hospitals. Fear of transmission is not a valid reason for this situation since the contagiousness of leprosy is less than that of tuberculosis, venereal disease, trachoma and measles—diseases for which outpatient treatment is readily available in urban areas in Taiwan.

TABLE 2

Number of new patients and incidence of treated patients, 1962 to 1967

Year	*New patients*			*Total treated*	*Number of treated per 10,000 population*
	Adults	*Children*	*Total*		
1962	357	22	379	3,152	2.74
1963	270	21	291	3,405	2.86
1964	238	19	257	3,630	2.96
1965	168	11	179	3,774	2.99
1966	189	24	213	4,054	3.05
1967	229	20	249	4,173	3.14

In order that maximal benefit may be derived by leprosy patients visiting outpatient clinics, such clinics should be located in urban areas where well trained medical personnel and adequate diagnostic and treatment facilities are available. In fact, we usually find more patients coming from urban areas than from rural areas. Despite this obvious necessity, leprosy clinics and leprosaria have been and are being located in rural areas by the governmental and volunteer agencies. Not only do such rural surroundings preclude adequate management of acutely ill or active patients, but also the patients are more exposed to the prejudices of the local population. Moreover, the sponsoring agency, governmental or volunteer, is burdened with a costly and static institution, and is unable to recruit adequate staff. As a result, important secondary programmes such as mobile clinics, home visitations and new case finding among relatives and contacts of known patients do not function properly.

Foreign missionary workers in clinics or leprosaria work under certain handicaps and restrictions due to problems in understanding the local language, customs and manners. We agree with Mr. James C. McGilvray of the World Council of Churches and the White House Advisory Staff who stated 'it is a tragedy that leprosy work in Taiwan has only attracted a few local Christian medical workers'[6]. This report was made with his 2 co-workers after a 4 weeks' medical survey of the islands in November, 1967.

Since the first outpatient clinic recommended by the author began in 1953 in the Losheng Leprosarium[4], and the second clinic in 1955 in the Provincial Pheng-hu General Hospital in Pescadores Islands, where the incidence of leprosy is the highest in Taiwan, there has been a definite increase in the utilization of such clinics[7]. At present three-quarters of the total number of known leprosy patients are treated as outpatients at the 12 skin clinics on Taiwan. Whether this type of treatment is the best remains to be seen.

In the author's opinion a broadened leprosy control programme is clearly needed in Taiwan. Such a programme should include:—

1. Education of the patients and the public regarding the true nature of leprosy.
2. Earlier detection of leprosy through home visiting of a patient's family and other close contacts, or through skin examination of all the students who are under compulsory education in middle schools.
3. Increased use of local medical personnel in the care of patients—both in institutions and in outpatient departments.
4. Provision of scholarships for training in leprosy, and the encouragement of leprosy research programmes.
5. Careful and complete documentation of each new leprosy patient (we still do not possess accurate data on the prevalence of leprosy on Taiwan).
6. Routine outpatient facilities in all hospitals should be open to leprosy patients as they are to patients suffering from other skin diseases.

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Lep. Rev. (1968) **39**, 3, 111-112

The presence of *M. Leprae* in the Breast Secretion of a Non-Lactating Woman with Lepromatous Leprosy

J. C. PEDLEY

Leprosy Department, United Mission Hospital, Tansen, Palpa, Nepal

It is generally known that secretion may be expressed from the breasts of a woman who has borne children but is not lactating.

In seeking further evidence of the presence of *M. leprae* in human milk[1], I decided to examine the breast secretion of a Nepali woman aged 60, with untreated lepromatous leprosy.

CASE REPORT

The patient, seen in November, 1967, complained that the skin of the face had become 'lumpy and swollen' during the past 4 months, and that for one year she had suffered with 'pins and needles' sensation in hands and feet. She had given birth to 7 children—the last 21 years previously.

Physical examination

The skin of the face is grossly infiltrated and covered with coalescing plaques of raised oedematous skin, and broad-based nodules. Both ear-lobes are greatly enlarged, pendulous, and swollen. The skin of the trunk, arms, thighs and legs appears to be diffusely infiltrated (although crinkly) and shiny. The skin over the breasts (which are atrophied) also appears to be diffusely infiltrated.

Investigations

1. *Skin slit scrapes:* from 6 sites—both ear-lobes, both brows, both breast areas, gave almost a maximum B.I. reading, and M.I. 11%.
2. *Nasal mucous smear:* showed maximum B.I. reading, and M.I. 90%.
3. *Breast secretion smears:* both nipples and surrounding skin were thoroughly cleansed with several swabs soaked in ether. By manipulation it was not difficult to express secretion from both nipples. Quite large beads of secretion were seen emerging from several points on the summit of each nipple. Examination of the smears revealed microscopic fields crowded with acid-fast bacilli, mostly in solid rod form, and numerous globi and globi-like accummulations of solid rod bacilli, one of which is seen in the accompanying photomicrographs.

DISCUSSION

Had this woman been of child-bearing age and lactating and in a similar state of untreated lepromatous leprosy, it is not difficult to believe, on the basis of the findings reported in this and the previous paper[1], that her child would have been ingesting active *M. leprae* in very large numbers.

In addition to the above patient, the writer has examined the breast secretion of 2 young non-lactating women who have borne children. Both were suffering with active and untreated lepromatous leprosy. Large beads of secretion were drawn off quite easily from the nipples with a breast pump, and in both of these women acid-fast bacilli in solid rod form were found in the secretion in scanty numbers, i.e., a few bacilli in some thousands of microscopic fields. Thus for this type of investigation it is *essential* to use a good binocular microscope with interior lighting, and an accurately moving stage on which a logging gauge is marked. By means of the latter, it has been possible to log the position of *each* bacillus or group of bacilli so that they could be checked by an independent witness.

SUMMARY

M. leprae have been discovered in great numbers in the breast secretion of a non-lactating woman suffering from highly active and untreated lepromatous leprosy. This finding provides further evidence that *M. leprae* may be present in human milk.

ACKNOWLEDGEMENT

I am greatly indebted to Dr. Douglas Harman of the Leprosy Study Centre, London, for the accompanying photomicrographs.

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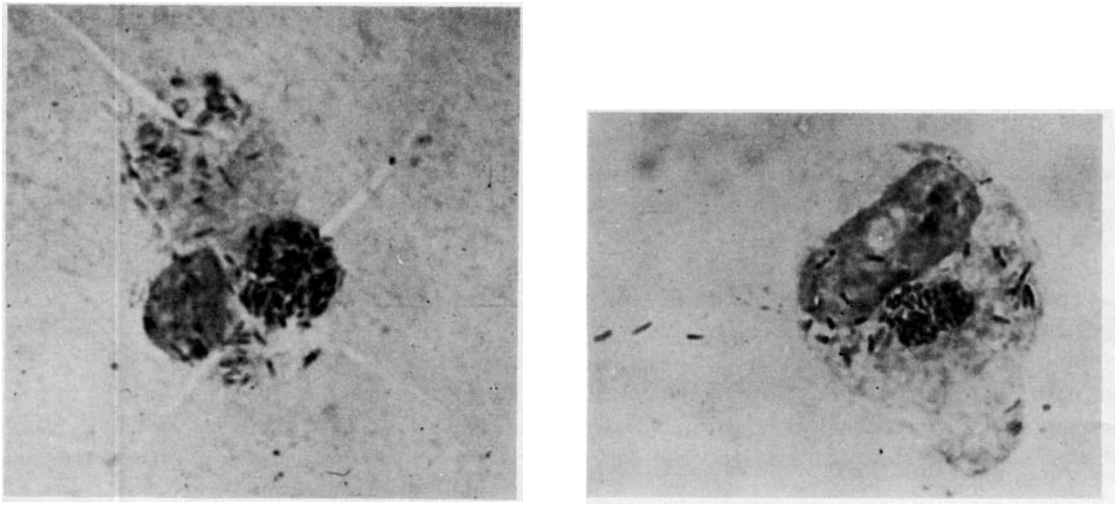

Macrophages containing *Myco. Leprae* in the breast secretion

Lep. Rev. (1968) **39**, 3, 113-117

Appearance of Resistance during Prolonged Treatment of Leprosy with Thiambutosine

J. M. B. GARROD, M.B., CH.B., D.T.M. & H.*

G. A. ELLARD, PH.D.†

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INTRODUCTION

Earlier reports have demonstrated the efficacy of oral thiambutosine (1-(p-Dimethylamino-phenyl)-3-(p-butoxyphenyl)-2-thiourea, CIBA 1906 or DPT) in the treatment of leprosy when administered for periods of between 2 and 2½ years (Davey *et al.*, 1958; Garrod, 1959). There is evidence, however, that if treatment is continued beyond this time, patients may suffer clinical and bacteriological relapse. Thus, while Davey *et al.* (1958) found no sign of drug resistance in 12 patients who had been treated for up to 32 months with thiambutosine, between the 36th and 44th month of treatment there was evidence that progress had halted in 6 patients with the reappearance in each patient of bacilli of normal morphology, and in 2 patients an eruption of fresh skin lesions (Davey, 1960).

This paper presents evidence of clinical and bacteriological relapse of 2 (1156/4 and 6203/36) of the 23 patients who had participated in the 24-month clinical trial of oral thiambutosine described earlier (Garrod, 1959) and who were then treated for a further 2 to 21 months with the drug. There was also evidence indicating the failure of another patient (6280/51) to respond normally during the first 2 years' treatment with thiambutosine.

While these clinical and bacteriological studies were being undertaken, the absorption and metabolism of thiambutosine were being investigated in the same group of patients. Neither the clinician nor the biochemist was aware of the details of each other's findings until the conclusion of these studies. By good fortune the absorption and metabolism of thiambutosine was studied in one of the patients (1156/4) at the very time that he was beginning to show signs of clinical and bacteriological relapse.

METHODS

Smears were taken on alternative months from 6 sites, their positivity graded as 0, 1, 2, 3 or 4 and the average calculated as a Bacillary Index (B.I.). The absorption of thiambutosine was estimated by measuring the urinary excretion of the drug and its metabolites, using the colorimetric and radioactive methods described previously (Ellard, 1961; Ellard and Naylor, 1961).

RESULTS

Clinical and Bacteriological

Patient 1156/4, a male aged about 35 years, had a history of nodular lepromatous leprosy of 7 years duration. He had proved intolerant to treatment with DDS. His B.I. at the commencement of treatment with thiambutosine was 1.7 and his Mitsuda reaction negative. A skin biopsy confirmed the clinical diagnosis. A daily dose of 3 gm. thiambutosine was administered for 15 months when persistent erythema nodosum leprosum with arthritis occurred. This was relieved with prednisone and by reducing the daily dose of thaimbutosine to 1 gm. for 2 weeks. The dose of thiambutosine was increased over the next 5 months to 3 gm. a day according to the patient's response and maintained at this level for a further 24 months, making a total of 45 months' treatment with thiambutosine. By the 19th month the B.I. had fallen to 0.3, by the 23rd to 0.17 and it was negative during the 28th and 29th months. At this time the only visible evidence of leprosy was a

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coppery appearance to his back. All nodules had disappeared from his face and forehead and except for some looseness of the skin his face was apparently normal. By the 32nd month even the coppery tinge on his back had disappeared but the B.I. had risen to 1.0, although few intact bacilli were visible. His B.I. fluctuated between 1.0 and 0.5 until the 43rd month when it rose to 1.16 and in the 44th month to 1.3. By the 34th month the possibility of resistance to thiambutosine was considered as, in addition to the rise in the B.I., his face had become slightly puffy and the skin infiltrated. By the 45th month the infiltration could no longer be disregarded. At this time a nodule on his forehead, slightly to the right of the centre line, had definitely reappeared, together with another on his right mid-finger. Skin biopsies taken during the 11th, 20th and 33rd months had indicated that he was responding satisfactorily to treatment with thiambutosine. The third biopsy was almost normal, with insufficient infiltration present to enable Ridley's Biopsy Index to be estimated (Ridley, 1958). However, by the 46th month bacilli were again very plentiful and the Biopsy Index had risen to 6 (1.0×6).

It was therefore concluded that relapse had occurred in this patient due to the appearance of strains of *M. leprae* resistant to thiambutosine. His treatment was therefore changed to DDS (dapsone).

The second patient (6203/36) was a young female in her teens with untreated lepromatous leprosy believed to have started 5 years previously Her initial B.I. was 3.7 and her Mitsuda reaction negative. Treatment with thiambutosine was commenced at a dose of 1.5 gm. daily. After 6 months the daily dose was raised to 2 gm. until the 25th month when the dose was reduced to 1.5 gm. a day as it was suspected that she was starting a lepra reaction. By the 28th month new lesions were appearing and it was apparent that she was no longer responding to treatment. By the 18th month her B.I. had fallen to 2.16 and it remained at this level until the 25th month when it had risen to 2.5. The initial diagnosis of lepromatous leprosy had been supported by a skin biopsy showing a Ridley's Index of 2.75 (0.5×5.5). By the 9th month her Biopsy Index had fallen to 0.5, and by the 17th month to 0.05. However, it was 0.1 at the 23rd month and had risen to 0.4 (0.1×4) by the 30th month. This last biopsy confirmed the reappearance of bacilli in large numbers. It was therefore concluded that this patient had relapsed during continued treatment with thiambutosine, and she was accordingly transferred to treatment with DDS without mishap.

The third patient (6280/51), a male aged 22 years, absorbed thiambutosine particularly poorly. He had received no previous treatment. His initial B.I. was 3.7 and his Mitsuda reaction was negative. He received 2.5 gm. oral thiambutosine daily for 33 months. By the 12th month his B.I. had only fallen to 3.0 and by the 26th month to 2.8. Progress was slower than for the other lepromatous patients treated with thiambutosine (average B.I's initially 3.2, after 12 months 2.0, and after 24 months 1.6 (Garrod, 1959)). Although clinical progress was slow it was significant. However, by the 33rd month progress had definitely stopped and the infiltration of his face appeared to be more marked. An old lesion on the trunk was also becoming more obvious. The initial assessment and diagnosis was supported by a skin biopsy and further biopsies carried out in the 11th, 13th and 25th months confirmed his slow response to treatment. Although in this case the initial response was very poor, the clinical evidence did suggest that this patient could also have relapsed after prolonged treatment with the drug.

As it had been established that this patient was absorbing unusually small amounts of thiambutosine, he was accordingly transferred for a short period to treatment with injectable thiambutosine, and eventually to treatment with oral DDS.

TABLE

Excretion 'Total Diphenyl Thioureas' (mg.)

	1.5 gm. or more thiambutosine in a single daily dose		*1.5 gm. thiambutosine twice daily*	
	Mean excretion ± Standard Deviation	*(Range)*	*Mean excretion ± Standard Deviation*	*(Range)*
Patients in this study excluding 6280/51	116±37 (n*=31)	(73-185)	288±75 (n=17)	(168-385)
1156/54	119 (n=2)		239 (n=1)	
6280/51	7 (n=2)		25 (n=1)	
Previously† published data from all patients at the research centre ..	127±53 (n=54)	(57-191)	266±88 (n=21)	(126-412)

* n= total number of determinations † Ellard (1961)

Biochemical

The results obtained using the colorimetric method are shown in the Table. The absorption of thiambutosine was measured in 15 of the 22 patients who responded satisfactorily during the first 24 months' treatment with oral thiambutosine. In these patients the absorption of thiambutosine was normal. These findings were confirmed in 3 patients by radioactive studies using ^{35}S-labelled thiambutosine (Subjects 1-3 in Experiment 1 of Ellard and Naylor, 1961).

Of the 2 patients described here, who initially responded to treatment in a satisfactory manner but on prolonged treatment subsequently relapsed, one (1156/4) was in the group studied and shown to absorb the drug normally (see Table) and this was also confirmed by radioactive technique (Subject 2, Experiment 1 of Ellard and Naylor, 1961). Hence there is definite proof that the relapse of this patient, while undergoing treatment with thiambutosine, could not have been due to unusually low absorption of the drug. The other patient who relapsed (6203/36) also excreted normal amounts of thiambutosine and its metabolites in the urine after oral dosage. However, a detailed study of her absorption of the drug was not undertaken.

The absorption of oral thiambutosine by the third patient (6280/51) was, however, abnormally low. The excretion of thiambutosine and its metabolites was about a tenth of the normal amount, indicating that only about 1% of the dose was being absorbed (see Table). These investigations were repeated 3 times during a period of a year with similar results and were confirmed by radioactive studies using ^{35}S-labelled thiambutosine. He was then treated by intramuscular injection with an aqueous suspension of thiambutosine and normal amounts of the drug and its metabolites were excreted in the urine (Patient 3, Table 1 in Ellard, 1966). This demonstrated that thiambutosine was being metabolised normally. After subsequent transfer to treatment with oral DDS, it was shown that he absorbed DDS normally.

DISCUSSION

Definite clinical and bacteriological evidence of relapse was obtained in 2 patients and there were indications of resistance to thiambutosine in the poor absorber of the drug (Patient 6280/51). From evidence not presented here, there was also some suggestion of the emergence of resistance in at least 2 of the other 20 patients who had been treated for over 2 years with thiambutosine. These clinical and bacteriological results confirm the previous findings of Davey (1960). Since our studies were concluded, Rees (1965, 1967a, 1967b) has inoculated mice with strains of *M. leprae* from patients who had been treated with thiambutosine for 2 or more years, and from patients who had relapsed while taking thiambutosine. He reported that a much lower proportion of the resultant foot-pad infections were inhibited by thiambutosine than were infections from untreated patients. The appearance of resistance to thiacetazone in *M. leprae* was suggested by Lowe (1954). He concluded that despite the initial effectiveness of thiacetazone, after 2 or more years treatment a considerable proportion of patients reached a stage where the drug seemed to lose its action and further progress was not seen. Moreover, in several patients there was definite clinical and bacteriological regression.

A chronic infection where the limitations of treatment with a single drug are well documented is pulmonary tuberculosis. The emergence of resistant strains of *M. tuberculosis* can readily be demonstrated by sensitivity tests on sputum cultures. The fundamental bacteriological reasons for the successful treatment of tuberculosis with combinations of 2 or 3 drugs and the comparative failure of 'mono-therapy' have recently been discussed by Mitchison (1965). In tuberculosis, the large population of bacilli in an untreated patient infected with a 'sensitive' strain of *M. tuberculosis* contains a small number of mutants of varying degrees of resistance to the drugs employed in chemotherapy. Presumably a similar situation occurs in leprosy. Mutants with high degrees of resistance are probably rarer than those with low degrees of resistance. When tuberculosis is

treated with isoniazid alone, raising the dose of isoniazid from 100 through 200 to 400 mgm. resulted in increased inhibition of the growth of mutants of low degrees of isoniazid resistance (Selkon *et al.*, 1964) and at the same time improved therapeutic effectiveness (Tuberculosis Chemotherapy Centre, Madras, 1960).

In contrast, DDS has been used very successfully without other drugs for the treatment of leprosy, and the appearance of strains of *M. leprae* resistant to the concentrations of DDS obtained in the body after dosage with 300 mgm. DDS twice weekly, is very rare (Pettit and Rees, 1964; Pettit, Rees and Ridley, 1966). The reason for this somewhat surprising finding appears to be that *M. leprae* is inhibited by very low concentrations of DDS. The concentrations of DDS obtained in the body, when doses of the order of 100 mgm. a day are given, are probably 100 or even 1,000 times greater than the concentration of DDS required to inhibit the growth of *M. leprae* (Shepard, McRae and Habas, 1966; Rees, 1967a, 1967b). Mutants of *M. leprae* capable of growing at the DDS concentrations in the body are likely to be very rare and may even be absent in many patients.

Nothing is known concerning the concentration of thiambutosine (and/or its metabolites) necessary to inhibit the growth of *M. leprae*. An increase in the dose of thiambutosine does not increase the amount of drug absorbed (Ellard, 1961), and so could not be expected to reduce or delay the appearance of resistance to thiambutosine. There is some evidence, however, suggesting that twice daily treatment with thiambutosine, which doubles the amount of drug absorbed each day (Ellard, 1961), may delay the emergence of resistance (East African Leprosy Research Centre, 1960).

Adams and Waters (1966) have demonstrated the cross-resistance of a DDS-resistant strain of *M. leprae* to a long-acting sulphonamide, but not to thiacetazone or thiambutosine; and Rees (1967a) has demonstrated the cross-resistance of thiambutosine-resistant strains of *M. leprae* to thiacetazone. It is therefore anticipated that just as patients with DDS-resistant leprosy responded satisfactorily to treatment with the rimino-phenazine derivative B663 (Pettit and Rees, 1966), so patients who have relapsed during prolonged treatment with thiambutosine should respond satisfactorily to treatment with DDS or B663. In our studies patients were transferred to treatment with DDS and appeared to respond normally.

It was concluded that the poor response of one of the patients (6280/51) to treatment with thiambutosine was probably due to his absorbing an unusually small amount of the drug. The reasons behind this rather uncommon phenomenon are not understood.

SUMMARY

1. Clinical and bacteriological evidence is presented suggesting the appearance of resistance to thiambutosine in 3 patients from a group of 23 patients who had been treated with the drug for between 24 and 45 months.

2. Biochemical studies showed that 2 of these 3 patients absorbed the drug normally, but that the other patient absorbed an unusually small proportion of the dose.

3. Resistance to thiambutosine developed after 28 and 44 months, respectively, in the 2 patients who absorbed the drug normally.

4. It is therefore concluded that although thiambutosine has a useful role to play in the treatment of leprosy it would seem unwise to continue treatment with the drug for more than 2 years.

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A Treatment of Corticosteroid-Dependent Lepromatous Patients in Persistent Erythema Nodosum Leprosum

A Clinical Evaluation of G.30320 (B663)

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Attention to the anti-inflammatory effect of B663 was first drawn by Browne[3 4]. In 2 patients receiving 600 mgm. B663 daily, Williams *et al.*[10] observed that the drug apparently controlled the signs of erythema nodosum leprosum (ENL).

Pettit[7] on the other hand, reported that B663 in a dosage of 100 mgm. daily had no dramatic effect in patients with very severe ENL (grades 3 and 4). He did, however, show that B663 had an anti-bacterial action in leprosy, thus confirming the early reports of Browne and Hogerzeil[5], Barry and Conalty[2] and Pettit *et al.*[8]

It is of great importance to find a drug that is effective in the control of ENL, which, when severe, is most distressing to the patient and very difficult to treat. Jopling[6] advocates the use of ACTH (cortico-trophin) or corticosteroids, with due regard to their limitations and serious side effects.

Because of the conflicting reports concerning the value of B663 in patients suffering from lepromatous leprosy with severe and long-standing ENL, we decided to put the drug to the test.

THE PATIENTS

Eighteen lepromatous patients (10 of them males) were selected for study.

Their ages ranged from 20-54 years when the B663 treatment was begun. In all of them the lepromin test (Mitsuda) was completely negative. All had suffered long periods of chronic severe ENL, classified 3+ to 4+ (Waters[9]), before the trial started. They were corticosteroid dependent, and some could be considered as being addicted to the drug. They had received corticosteroids continuously for from 9 months to 4 years and 5 months, the average being 2 years 7 months. All the patients had previously been receiving anti-leprosy drugs, 16 of them DDS; all had also received thiambutosine, and 13 had had isoniazid. A number of drugs had been used on occasion, including thiacetazone, streptomycin, sulphorthormidine and ditophal. Each patient had his own pattern of ENL which recurred when attempts were made to reduce—even slightly—the dose of corticosteroids. All were bedridden, wasted and in very poor condition.

METHOD OF INVESTIGATION AND FOLLOW-UP

Chest X-ray examination was made of all patients at the beginning of the trial to exclude pulmonary tuberculosis. Regular urine tests were carried out for albumin, sugar and urobilinogen; haemoglobin levels and the white cell count were estimated every 2 months during the period of the trial; the differential white cell count was done at the beginning of the trial and after 12 months.

LEPROSY INVESTIGATION

Smears (Wade's technique) were taken from 7 sites every 2 months for calculation of the bacterial index (B.I.), and the morphological index (M.I.).

TABLE I

Patient Number and Sex	Age when B663 started years	Date of Admission to Liteta	Length of time on Prednisolone for ENL and maximum dose	Date when B663 started and daily dose	Length of time on Prednisolone or ACTH after B663 started	Time to control ENL	Time to suppress ENL	Effect of increased dose of B663 on relapse and max. daily dosage	Comments
1 Male	41	6.61	4 years 3 months 50 mgm.	8.66 200 mgm. 1/12 100 mgm. 1/52 200 mgm. 1/52 then 100 mgm.	4 months	2 months	4 months	Very good 200 mgm.	Continuous ENL since 1962, extensive nodulation with breakdown, lymphadenopathy, abscess, fever, generalised neuritis, systemic upset together with large bed sores and emaciation, orchitis, insomnia. Now employed as full-time clerical officer.
2 Male	32	8.64	4 years 1 month 50 mgm.	8.66 100 mgm.	None	Few days	Few days	No relapse	Generalised nodular eruption, malaise, high fever, punched out ulceration on arms and legs. August, 1967, lepromata resolved, ulcers closed. Now leading normal life in leprosarium.
3 Male	28	1.62	3 years 6 months 50 mgm.	7.66 100 mgm. 6/12 200 mgm. 2/52 then 100 mgm.	None	Few days	6½ months	Very good 200 mgm.	Large painful nodules and ulnar neuritis. Now working in leprosarium as ward attendant.
4 Male	31	8.62	2 years 10 months 50 mgm.	2.66 100 mgm.	None	1 week	2 weeks	No relapse	Initially extremely ill with severe deep bone pain, painful intracutaneous nodules, ulnar neuritis. Now leading normal life in leprosarium.
5 Male	30	2.63	2 years 10 months 50 mgm.	7.66 100 mgm. 2/12 200 mgm. 2/52 then 100 mgm.	6 weeks	1 month	2 months	Very good 200 mgm.	Multiple painful nodules with extensive ulceration, ulnar neuritis, attacks of orchitis. Now working as bricklayer in leprosarium.
6 Male	35	4.64	2 years 2 months 50 mgm.	9.66 100 mgm.	None	Few days	Few days	No relapse	Extensive painful nodules and neuritis, arthritis, general malaise, deep bone pain and insomnia. Now leading normal life in leprosarium.
7 Male	44	3.64	2 years 2 months 50 mgm.	6.66 100 mgm. 2/12 200 mgm. 10 days 300 mgm. 11 days 200 mgm. 6/52 then 100 mgm.	7 weeks	10 weeks	3 months	Very good 300 mgm.	Generalised swelling and painful nodules, iridocyclitis, median and ulnar neuritis, oedema of legs, feet, deep pain, fever. Now leading normal life in leprosarium.
8 Male	44	7.64	2 years 1 month 50 mgm.	8.66 100 mgm.	8 days	2 weeks	1 month	No relapse	Generalised nodular eruption, left ulnar neuritis, lymphadenopathy, orchitis, fever. Now leading normal life in leprosarium.
9 Male	54	5.64	1 year 9 months 50 mgm.	3.66 100 mgm. 10/12 200 mgm. 3/52 then 100 mgm.	3 months. Stopped 3/52 Short course 3/52	6 months	10 months	Very good 200 mgm.	Painful extensive lesions with ulcerations, epididymitis, neuritis, recurrent fever, extensive weight loss. Now employed as assistant store keeper in leprosarium.
10 Male	25	9.64	10 months 50 mgm.	7.66 100 mgm. 200 mgm. 300 mgm. 400 mgm. varied Finally 100mgm.	1 month Stopped 2/52 Short course 2/52	1 month	1 year	Excellent 400 mgm.	Very severe neuritie pain in ulnar and median nerves, ulcerated skin lesions and fever. Now ambulant patient in wards requiring daily physiotherapy for contractures of hands.
11 Female	43	10.61	4 years 5 months 50 mgm.	6.66 100 mgm.	1 week	Few days	1 week	No relapse	Extensive panniculitis and persistent, painful lepromata with pain in arms and legs and fever. Now performing normal domestic duties in leprosarium.
12 Female	26	6.61	4 years 2 months 75 mgm.	8.66 100 mgm. 2/52 200 mgm. 10/52 then 100 mgm.	1 week	1 week	3 months	Very good 200 mgm.	Extensive nodular lesions, swelling of hands and feet, fever, general malaise. Now performing normal domestic duties in leprosarium.
13 Female	31	8.61	3 years 6 months 50 mgm.	9.65 100 mgm. 11/12 200 mgm. 7/52 then 100 mgm.	11 months*	3 weeks	2 months	Very good 200 mgm.	*(For the first 11 months no attempt was made to withdraw steroids completely, as this was before the trial started.) Extensive painful lesions with fever, headache and all peripheral nerves painful. Arthritic ankles and knees, swelling of hands and feet, general malaise. Now performing normal domestic tasks in leprosarium.
14 Female	20	12.62	2 years 6 months 50 mgm.	8.66 100 mgm. 6/52 200 mgm. 1/52 300 mgm. 6/52 200 mgm. 2/52 then 100 mgm.	6-day course 9 days after starting B663	12 weeks	15 weeks	Very good 300 mgm.	Extensive painful nodules, laryngeal oedema, polyarthritis, neuritis, lymphadenopathy, fever. Now performing usual domestic duties in leprosarium.

TABLE I (cont.)

Patient Number and Sex	Age when B663 started years	Date of Admission to Liteta	Length of time on Prednisolone for ENL and maximum dose	Date when B663 started and daily dose	Length of time on Prednisolone or ACTH after B663 started	Time to control ENL	Time to suppress ENL	Effect of increased dose of B663 on relapse and max. daily dosage	Comments
15 Female	32	10.63	1 year 10 months 50 mgm.	9.66 100 mgm. 4/12 200 mgm. 1/12 then 100 mgm.	None	Few days	5 months	Very good 200 mgm.	Extensive nodular painful eruption, ulnar and popliteal neuritis. General body pain. Discharged to leprosarium and became pregnant in August, 1967.
16 Female	42	11.63	1 year 6 months 50 mgm.	7.66 100 mgm. 2/12 200 mgm. 2/12 100 mgm. 5/12 200 mgm. 4/12 300 mgm. maintenance dose	3 days	2 months	13 months	Good 300 mgm. maintenance	Continuous nodular eruption of large areas, fever, insomnia, extensive neuritis. Now performing normal domestic duties in leprosarium.
17 Female	40	4.64	1 year 5 months 50 mgm.	7.66 100 mgm. 3/12 200 mgm. 1/52 then 100 mgm.	None	2 months	3½ months	Very good 200 mgm.	Repeated attacks of generalised nodular eruptions, arthritis pains, bone pain in arms and legs. Now performing normal domestic duties in leprosarium.
18 Female	36	8.66	9 months 50 mgm.	8.66 100 mgm.	None	Few days	Few days	No relapse	Extensive nodular eruptions with suppurating ulcers, fever, swelling of feet, neuritis. Now performing usual domestic duties in leprosarium.

Biopsies were taken at the beginning, after 3 months and then at 6-monthly intervals (except the initial biopsy from patients who were too ill even for a biopsy). These were examined and reported on by the Leprosy Study Centre, London.

ASSESSMENT OF RESPONSE

Pettit[7] used the dose of ACTH required as a measure of assessing the progress of the patients. We concur that the amount of corticosteroids withdrawn, coupled with the clinical picture and biopsy reports, provides a reasonable method of assessing the anti-inflammatory action of a drug under investigation.

ADMINISTRATION OF B663

The absorption of B663 has been said to be enhanced when administered in olive oil (Barry[1]), and Browne[4] used 5 ml. of edible oil to facilitate absorption from the intestine. However, the addition of oil is now considered unnecessary (Vischer[11]); this was a great advantage since it would have been most difficult to persuade these critically ill patients to take a dose of oil by the mouth.

In the following case histories, our personal observations started in February, 1966; the previous facts and clinical data were summarised from clinical notes made before the writer assumed the medical care of the patients in the Liteta Leprosarium.

RESULTS

Table 1 gives a summary of the clinical findings and results of treatment. All the patients had been having repeated courses of prednisolone, starting with a dose of 50 mgm. (except Patient No. 12, whose maximum dose was 75 mgm.) and gradually reducing, but in all patients reduction of prednisolone precipitated a recurrence of ENL. When B663 treatment was begun, the patients were either on a maintenance dose of prednisolone or were just completing a course.

The starting dose of B663 was 100 mgm. per day without oil (except Patient No. 1, who began with 200 mgm. daily). Corticosteroids were discontinued at once in 7 patients, and discontinued gradually in from 1-28 days in 6 patients, and in from 1-2 months in 2 patients, and over 2 months in the other patients.

In the 7 patients (Nos. 2, 3, 4, 6, 15, 17 and 18) in whom corticosteroids were discontinued at the same time as B663 was started, ENL was rapidly controlled in all patients. Three of these patients (Nos. 3, 15 and 17) had a mild recurrence, which responded rapidly to an increase in dose of B663 to 200 mgm. per day.

Of the 6 patients (Nos. 8, 10, 11, 12, 14 and 16) whose corticosteroids were continued for from 1-28 days, 4 had recurrences of ENL. These occurred within a few days of stopping the drug in 3 patients (Nos. 10, 12 and 14), and after 6 weeks in Patient No. 16. All but one (No. 10)

responded rapidly to an increase of B663 to 200 or 300 mgm. per day (without prednisolone). Patient No. 10 had severe ulnar neuritis, was emotionally unbalanced and addicted to prednisolone; he was given a 2 weeks' course of prednisolone while B663 was continued at a dose of 100 mgm. daily. Patient No. 14 was given a 6-day course of prednisolone 9 days after beginning treatment with B663. Three of this group had further recurrences of ENL (Patient No. 14 after 6 weeks, and Patients Nos. 10 and 16 at 9 months after the start of B663). All 3 responded very well to a temporary increase dose of B663 alone.

The 2 patients (Nos. 5 and 7) in whom the corticosteroids were continued for 2 months, had a recurrence of ENL within one month of stopping the drug, but responded very well to an increase of B663 alone, for a short period.

Three patients (Nos. 1, 9 and 13) continued taking corticosteroids for a long period together with B663. In Patients Nos. 1 and 9, very gradual reduction was particularly necessary in these very ill, corticosteroid dependent and emaciated patients. Patient No. 1, who started with 200 mgm. B663 daily while the dose of prednisolone was being gradually reduced, had a recurrence of ENL when the B663 daily was reduced to 100 mgm daily while he was still having 3 mgm. prednisolone daily. This recurrence was rapidly controlled when B663 was again increased to 200 mgm. daily, for one week. No further ENL occurred when the prednisolone was eventually stopped, and the dose of B663 remained at 100 mgm. daily.

In Patient No. 9, a recurrence of ENL 16 days after steroids were stopped, necessitated a further 3 weeks' course of steroids. After 4 months on 100 mgm. B663 daily alone, the patient had a further recurrence of ENL, which responded to an increase in dose of B663 200 mgm. daily for 3 weeks, and no prednisolone. The patient is now well controlled on 100 mgm. B663 daily. As this patient was already on B663 before the trial started, he was included in the study.

In Patient No. 13, no attempt was made to stop steroids when B663 was given (Sept., 1965), as this was before the trial started. Two weeks after steroids were stopped, the patient had a recurrence of ENL, which responded to an increase dose of B663, 200 mgm. daily, alone.

WEIGHT GAIN AND LOSSES

In a few patients, weight loss was observed at the beginning of the trial. This was attributed to loss of oedema following withdrawal of corticosteroids. (Patients Nos. 2, 4, 15 and 18 losing 4, 5, 3 and 10 lbs. respectively, this weight being regained in all cases, except No. 2 whose nett loss was 2 lbs.) Of far greater significance is the increase in weight of the patients who had been seriously ill and emaciated. This can only be appreciated by seeing the individual figures, shown in Table 2. Nine of the 18 patients gained more than 10 lbs., and 5 of these gained 17 lbs. or more. This was all true weight gain, since none of the patients had any sign of oedema while on B663 treatment.

TABLE 2
Weight Gains

Patient		*Patient*	
No. 1	99 lbs.	No. 11	17 lbs
No. 3	Constant	No. 12	6 lbs.
No. 5	11 lbs.	No. 13	2 lbs.
No. 6	12 lbs.	No. 14	18 lbs.
No. 7	3 lbs.	No. 16	11 lbs.
No. 8	8 lbs.	No. 17	5 lbs.
No. 9	27 lbs.	No. 18	29 lbs.
No. 10	12 lbs.		

EFFECT ON *M. leprae*

Table 3 shows the Bacteriological Index (B.I.) and the Morphological Index (M.I.) at the outset of the trial in 1966 and at the end of 1967. An earlier figure is given for Patients Nos. 4 and 9, in whom B663 was given before the trial period. No earlier figure is given for Patient No. 13, although she also began taking B663 before the trial.

In 5 patients (Nos. 2, 3, 7, 11 and 14), the initial M.I. is higher than would be expected in patients who had been on anti-leprosy treatment for a considerable time; this may suggest that although cortico-steroids control ENL, their use may in some way have affected the action of anti-leprosy drugs.

TABLE 3
B.I. and M.I. at the start of B663 to the end of 1967

Patient No.	*B.I. mid-1966*	*M.I. mid-1966*	*B.I. end 1967*	*M.I. end 1967*
1	3.1	0%	1.0	0%
2	4.7	3.8%	3.8	0%
3	4.7	15.0%	4.2	0.2%
4	31.3.66 4.2	6.4%	3.2	0%
5	2.0	0.4%	1.1	0%
6	2.7	0%	1.1	0%
7	4.2	6.2%	3.4	0.5%
8	3.8	0.1%	1.5	0%
9	29.3.66 4.8	2.0%	4.8	1.0%
10	3.8	1.7%	3.1	0%
11	4.1	3.7%	4.1	0.2%
12	4.5	0.7%	3.0	0%
13	1.8	0%	0	0%
14	4.7	4.1%	2.5	0.1%
15	4.8	1.4%	3.2	0%
16	2.4	0%	0.1	0%
17	4.1	2.1%	3.5	0.5%
18	5.0	2.5%	4.1	0.2%

The overall picture of the smears taken every 2 months during the trial, shows a fall in the B.I. in all but 2 patients. The M.I. fell in all patients. All smears were examined by the same experienced laboratory technician throughout the trial. There was no evidence of the development of resistance to B663 in any patient.

DOSAGE OF B663

In most patients, 100 mgm. per day proved an adequate maintenance dose. Twelve patients at some time required an increased dose, which controlled a recurrence of ENL. This was either 200 or 300 mgm. per day, except in one patient who needed 400 mgm. per day. The dose used depended on the response to the initial increase.

The dose was subsequently reduced to 100 mgm. per day, with complete control in all patients except one, who required a daily dose of 300 mgm. This patient's weight being 178 lbs., it is considered that the body weight may be related to the dosage required.

SIDE EFFECTS OF B663

Gastro-intestinal

Patients Nos. 1, 10 and 12 had diarrhoea. All were taking 200 mgm. per day at that time. Patient No. 1 had been on treatment for 3 weeks and Patient No. 12 for 7 weeks. In all patients, the diarrhoea cleared rapidly when treatment was stopped for a few days. Patient No. 1 had a recurrence of diarrhoea at 8 weeks while taking 100 mgm. B663 daily. After 11 months, Patient No. 10 developed diarrhoea while on 200 mgm. per day. This patient also had some vomiting when on 100 mgm. per day, early in the investigation. At that time he was suffering from considerable emotional upset and was very reluctant to take B663 and demanded corticosteroids. This probably aggravated the vomiting. He did not vomit or have diarrhoea later when on a course of increased dosage of B663, even though at one time this reached 400 mgm. per day.

Pigmentation

All patients were told at the beginning of the trial that their skin would become darker. None of the patients objected, for at that time the majority were too ill to care, and later they regarded it as a sign that the medicine was 'doing good'.

There appeared to be no difference in the density of pigmentation between those patients who have received 100 mgm. daily and those who received a higher dosage. The parts of the body exposed to light were darker than the covered parts. This was especially noticeable in the men wearing short trousers and short-sleeved shirts. Darker pigmentation in the women was seen above the neckline of the dresses and on the forearms.

Eyes

The eyes of all patients were subjected to slit-lamp examination at the end of the trial. There was no evidence of active ocular disease or abnormal pigmentation of the conjuctival or corneal epithelium. One patient showed signs of cataracts (which had been noted before the treatment with B663 had been started).

Pregnancy

One patient (No. 15) had been on treatment with B663 from September, 1966, at a daily

dose of 100 mgm., apart from one month when she received 200 mgm. per day. In November, 1967, she delivered a normal healthy female child, weighing 7 lbs. 12½ ozs. Her pregnancy was normal and there was no increase in M.I. during pregnancy. The skin of the baby was thought to be slightly darker than is usual in this part of the world.

Laboratory Results

During the trial no abnormalities were reported in the blood or urine tests performed.

Biopsies

All biopsy reports confirmed the clinical diagnosis of lepromatous leprosy—and the last report of every patient stated: no evidence of any bacillary activity.

DISCUSSION

All the 18 patients in this investigation had been on a high dosage of prednisolone for periods varying from 9 months to 4 years and 5 months, an average of 2 years and 7 months.

They had been given frequent courses of high dosage, the usual regime being to give 50 mgm. per day at the onset of acute ENL and gradually reducing till the lowest maintenance dose was attained. In all patients, repeated attempts at withdrawal had been followed by recurrence of ENL. Four patients had developed moon-face, and another had osteoporosis and collapsed vertebrae, together with bilateral posterior capsular cataracts. All the patients were seriously ill, and so addicted to prenisolone that they demanded an increased dose at the first symptoms of recurrence of ENL. The anxiety they experienced on the withdrawal of prednisolone when B663 was begun, was quite genuine, and required high dosages of tranquillisers, a situation which persisted until the patients became aware that the ENL could be controlled by B663 alone.

After cessation of steroids, the ENL in 6 patients (Nos. 2, 4, 6, 8, 11 and 18) was completely controlled by B663, 100 mgm. daily. In a further 7 patients (Nos. 1, 3, 12, 13, 15, 16 and 17) the ENL was controlled by a temporary increase of dose to 200 or 300 mgm. a day. (Patient No. 1 was still on a reducing scale of prednisolone.) None of these 13 required further courses of prednisolone.

Five patients (Nos. 5, 7, 9, 10 and 14) were given further prednisolone together with 100 mgm. B663 daily when ENL recurred in the early stages of the trial. At this time, a cautious procedure was thought to be necessary in view of the patients' serious condition. In retrospect, it seems likely that the doses of steroids had been reduced too rapidly. Later recurrences were controlled by B663 alone, at daily dosages from 200 mgm. to 400 mgm. All could be reduced again and were controlled by 100 mgm. per day.

It is important to point out that the dose necessary to control ENL or a recurrence of ENL varies from patient to patient. If all other patients had been maintained on 100 mgm. per day, in only 6 out of the 17 (Patient No. 1 started on 200 mgm. per day) would the ENL have been controlled. This different dose regime may well explain the discrepancies apparent between Pettit's[7] findings and ours.

As described previously, effective antibacterial action was attained and sustained in all patients. One patient (No. 13) showed complete resolution of all signs and symptoms of active leprosy, with complete clearance of B.I. and M.I.

Side-effects were minimal, and there were no toxic effects. Patients improved greatly in general condition, as shown by weight gain, and all are leading a normal life; a number are employed in the leprosarium. There has been no adverse effect on pregnancy or on the foetus.

SUMMARY

A series consisting of 18 lepromatous patients is reported; all had severe ENL, which was just controllable only with large doses of corticosteroids. They were all initially bedridden, severely ill and steroid-dependent. After an average period of 2 years and 7 months of corticosteroid treatment, they began treatment with G30320 (B663) at a dose of 100 mgm. per day, except Patient No. 1, who began with 200 mgm. daily. It was then possible to stop or

withdraw steroids in all patients. Six patients had no recurrence of ENL, 7 patients had some recurrences which were controlled by a temporary increase of B663. Five patients were given prednisolone together with 100 mgm. B.663 daily, for relapses early in the trial, but subsequent relapses were controlled by an increase of B663 dosage alone. Seventeen patients were ultimately controlled with a maintenance dose of 100 mgm. of B663 per day, and one patient (No. 16) required 300 mgm. per day as a maintenance dose.

Over a period of from 14-18 months, all patients showed a steady improvement in B.I. and M.I. (except for 2 whose B.I. remained stationary). The patients showed marked clinical improvement, all are now leading a normal life, and some are employed in the leprosarium.

Side-effects were minimal, and the hyperpigmentation that developed was cheerfully accepted. All patients are most enthusiastic about B663 treatment.

It is considered that this drug represents a real advance in the treatment of ENL in that it will control persistent recurrence of such a degree as otherwise to require high dosages of corticosteroids, at the same time providing active chemotherapy.

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The Anti-Inflammatory Effect of Indomethacin in Lepromatous Leprosy

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There is growing evidence that the anti-inflammatory effect of indomethacin originally described in the inflammatory phases of rheumatoid disease, gout, psoriatic arthritis and the inflammatory complications of degenerative joint disease is widely distributed in the body. Thus indomethacin causes a moderate reduction in the size of the lymph nodes in Hodgkin's disease (Begemann *et al.*, 1966) and benefits subacute and chronic recurrent inflammation of the uterine adnexa (Mehring *et al.*, 1966). It prevents post-operative facial oedema after extraction of teeth (Mathis and Kempfle, 1966), and post-operative oedema following fractures of and operation on limbs (Penners, 1966). In animal experiments it has been found to have a favourable effect on the regenerative wound healing phase (Struck, 1966).

Equally interesting are the results obtained with indomethacin in skin diseases. Successful results have been obtained in herpes zoster, herpes simplex, varicella, parapemphigus and chronic benign familial pemphigus. A useful anti-inflammatory effect has also been noted in chronic lupus erythematosus discoides, Boeck's disease, pemphigus vulgaris and cicatrizing mucosal pemphigus. Erythema multiforme exudativum bullosum and occasionally vesiculation in lichen ruber, erysipelas and mycosis fungoides have been favourably affected (Herzberg and Heyl, 1966).

Therefore, in a planned trial we led ourselves to assess (1) whether indomethacin has an anti-inflammatory effect in lepromatous leprosy, and (2) if so, whether indomethacin would hasten the rate of bacterial clearance by anti-leprotic drugs. The results of the first phase of the trial are reported in this paper.

MATERIALS AND METHOD

The patients were 20 Indians, all males, service personnel, 23 to 40 years old. The duration of lepromatous leprosy was 1 to 10 months in 19 of the patients and 18 months in the twentieth. They were all bacteriologically positive.

An initial estimate of the clinical condition of each patient comprising the type and extent of lesions found, bacteriological state, lepra reactions, haemoglobin, total and differential leucocyte count, erythrocyte sedimentation rate, and urine examination was made. The skin smears for lepra bacilli were obtained by Wade's scraped incision procedure from several sites and the drop obtained was deposited on a clean slide, dried and stained with Ziehl-Neelson's stain. Nasal scrapings were made over the nasal septum and treated the same way.

The trial, which was controlled but not blind, then commenced. As far as possible all comparable patients were paired by randomization. One in each pair received Treatment A, the other Treatment A plus Treatment B. Treatment A consisted of Dapsone with an initial test dose of

TABLE 1

Details of individual results in 10 patients after 4, 8 and 12 weeks of Treatment A plus Treatment B

Sl. No.	*Age (yrs.)*	*Duration (months)*	*Lesions*	*Distribution*	*Response to treatment after*		
					4 weeks	*8 weeks*	*12 weeks*
	2	3	4	5	6	7	8
1	23	8	Papular				
			Erythema	Face, forehead and	50%	70%	90%
			Infiltration	hands	50%	70%	90%
			Nodular				
			Infiltration	Ear	50%	70%	80%
			Well-defined margins	lobules	No change	50%	100%
			Hypesthesia	Papular and nodular patches	No change	No change	No change
			Loss of eyebrows	Outer third	No change	50%	100%
			Thickended and tender nerves	Great auricular and ulnar both sides	No change	No change	No change
			Lepra bacilli	Positive	Negative	Negative	Positive
2	27	6	Papular				
			Erythema		40%	40%	40%
			Infiltration	Both arms, thighs and	No change	40%	50%
			Well-defined margins	trunk	No change	30%	50%
			Hypopigmentation		No change	No change	No change
			Anaesthesia	Patches, hands and feet	No change	No change	No change
			Thickened and tender nerves	Ulnar and lateral popliteal of both sides	No change	No change	No change
			Lepra bacilli	Positive	Negative	Positive	Positive
3	25	7	Papular				
			Erythema	Face, forehead, ear lobules,	50%	70%	90%
			Infiltration	hands and feet	50%	70%	90%
			Oedema	Hands and feet	50%	100%	100%
			Anaesthesia	Hands and feet	No change	No change	Return of touch sensation over feet
			Trophic ulcer	Right, middle and ring fingers both second and third toes	No change	30%	60%
			Lepra reaction	Present	50%	100%	100%
			Loss of eyebrows	Outer half	No change	50%	70%
			Thickened and tender nerves	Both ulnar and lateral popliteal	No change	No change	No change
			Lepra bacilli	Positive	Positive	Negative	Negative
4	25	4	Papular				
			Erythema	Left arm and left	No change	50%	80%
			Infiltration	leg	No change	50%	80%
			Well-defined margins		No change	No change	30%
			Hypesthesia	Over patches	No change	No change	No change
			Anaesthesia	Hands and left foot	No change	No change	Return of pain sensation
			Oedema	Both hands, both legs and feet	50%	100%	100%
			Lepra reaction		Occurred on ninth day	100%	100%
			Thickened and tender nerves	Left ulnar and lateral popliteal	No change	No change	No change
			Lepra bacilli	Positive	Negative	Negative	Negative

Sl. No.	Age (yrs.)	Duration (months)	Lesions	Distribution	Response to treatment after		
					4 weeks	8 weeks	12 weeks
1	2	3	4	5	6	7	8
5	37	6	Papular				
			Erythema	Face, trunk and both	30%	70%	80%
			Infiltration	upper and lower	30%	70%	80%
			Well-defined margins	extremities	No change	20%	50%
			Nodular	Face, trunk and extremities	30%	70%	90%
			Trophic ulcer	Left knee, right foot	30%	50%	80%
			Anaesthesia	Both hands, legs and feet	No change	No change	No change
			Thickened and tender nerves	Both ulnar and lateral popliteal	No change	No change	No change
			Lepra bacilli	Positive	Positive	Positive	Positive
6	25	1	Papular				
			Erythema	All over the	30%	50%	70%
			Infiltration	body	30%	50%	70%
			Erythema marginatum	Over chest and extremities	30%	50%	70%
			Anaesthesia	Patch over left leg	No change	30%	60%
			Thickened and tender nerves	Both ulnar and lateral popliteal	No change	No change	No change
			Lepra bacilli	Positive	Positive	Positive	Positive
7	40	1	Papular				
			Erythema	All over the	No change	30%	60%
			Infiltration	body	No change	30%	60%
			Nodular	Ear lobules	No change	30%	60%
			Anaesthesia	Patch on left arm	No change	30%	50%
			Thickened and tender nerves	Great auricular, ulnar and lateral popliteal of both sides	No change	No change	No change
			Lepra bacilli	Positive	Negative	Negative	Negative
8	30	6	Papular				
			Erythema	All over the	30%	50%	50%
			Infiltration	body	40%	50%	50%
			Nodular				
			Infiltration	Ear	No change	50%	60%
			Well-defined margins	lobules	No change	30%	50%
			Anaesthesia	Both upper and lower extremities	No change	No change	No change
			Trophic ulcers	Back	50%	100%	100%
			Thickened and tender nerves	Great auricular, ulnar and lateral popliteal of both sides	No change	Ulnar 50%	ulnar 100%
			Lepra bacilli	Positive	Positive	Negative	Positive
9	27	10	Papular				
			Erythema	Face, forehead and ear	30%	50%	50%
			Infiltration	lobules	30%	50%	50%
			Macular				
			Erythema	Back and	30%	50%	50%
			Well-defined margins	forearms	No change	No change	No change
			Thickened and tender nerves	Great auricular and lateral popliteal of both sides	No change	No change	No change
			Lepra bacilli	Positive	Positive	Negative	Negative
10	37	18	Papular				
			Erythema	All over the	20%	30%	40%
			Infiltration	body	20%	30%	40%
			Nodular				
			Infiltration	Trunk and extremities	30%	30%	50%
			Anaesthesia	Both extremities	No change	30%	No change
			Trophic ulcer	Thigh	20%	30%	40%
			Loss of eyebrows	Outer third	No change	No change	No change
			Thickened and tender nerves	Great auricular and lateral popliteal of both sides	No change	No change	No change
			Lepra bacilli	Positive	Positive	Positive	Positive

TABLE 2

Details of individual results in 10 patients after 4, 8 and 12 weeks of Treatment A

Sl. No.	*Age (yrs.)*	*Duration (months)*	*Lesions*	*Distribution*	*Response to treatment after*		
					4 weeks	*8 weeks*	*12 weeks*
2	3		4	5	6	7	8
	27	3	Papular				
			Erythema	Face, trunk and	No change	No change	No change
			Infiltration	extremities	No change	No change	No change
			Anaesthesia	Over patches	No change	No change	30%
			Thickened and tender nerves	Great auricular and lateral popliteal of both sides	No change	No change	No change
			Lepra bacilli	Positive	Positive	Positive	Positive
2	40	1	Macular				
			Erythema	Face, trunk and extremities	No change	30%	40%
			Anaesthesia	Lateral aspect of legs and feet and patches	No change	No change	No change
			Thickened and tender nerves	Lateral popliteal both sides	No change	No change	No change
			Lepra bacilli	Positive	Positive	Positive	Positive
3	25	1	Papular				
			Erythema	Face, back and both upper	No change	No change	No change
			Infiltration	extremities	No change	No change	No change
			Nodular infiltration	Ear lobules	No change	No change	No change
			Thickened and tender nerves	Ulnar and lateral popliteal of both sides	No change	No change	No change
			Lepra bacilli	Positive	Positive	Positive	Positive
4	29	4	Papular				
			Erythema	Left elbow and arm, chest	No change	No change	40%
			Infiltration	and back	No change	No change	40%
			Oedema	Left arm	No change	70%	90%
			Anaesthesia	Over the patches	No change	No change	No change
			Thickened and tender nerves	Great auricular, ulnar and lateral popliteal both sides	No change	No change	No change
			Lepra bacilli	Positive	Positive	Positive	Positive
5	23	6	Papular				
			Erythema	Face, neck, chest and both	No change	No change	No change
			Infiltration	upper extremities	No change	No change	No change
			Anaesthesia	Over the patches	No change	No change	No change
			Thickened and tender nerves	Great auricular and ulnar of both sides	No change	No change	No change
			Lepra bacilli	Positive	Positive	Positive	Positive
6	24	2	Papular				
			Erythema	Ear lobules, extremities and	No change	No change	No change
			Infiltration	trunk	No change	No change	No change
			Anaesthesia	Forearms and legs	No change	No change	No change
			Thickened and tender nerves	Great auricular, ulnar and lateral popliteal both sides	No change	No change	No change
			Loss of eyebrows	Outer third	No change	No change	No change
			Lepra reaction			Occurred on fortieth day	No change
			Lepra bacilli	Positive	Positive	Positive	Positive

Sl. No.	Age (yrs.)	Duration (months)	Lesions	Distribution	Response to treatment after		
					4 weeks	8 weeks	12 weeks
1	2	3	4	5	6	7	8
7	25	3	Papular				
			Erythema	Left arm and	No change	No change	No change
			Infiltration	left leg	No change	No change	No change
			Anaesthesia	Over the patches	No change	No change	No change
			Thickened and tender nerves	Left ulnar and lateral popliteal	No change	No change	No change
			Lepra bacilli	Positive	Positive	Positive	Positive
8	27	5	Papular				
			Erythema	Both upper and lower	No change	No change	No change
			Infiltration	extremities and trunk	No change	No change	No change
			Anaesthesia	Over the patches	No change	No change	No change
			Thickened and tender nerves	Ulnar and lateral popliteal both sides	No change	No change	No change
			Lepra bacilli	Positive	Positive	Positive	Positive
9	25	5	Papular				
			Erythema	Face and ear	No change	No change	No change
			Infiltration	lobules	No change	No change	No change
			Trophic ulcer	Left second and third toes	No change	No change	No change
			Anaesthesia	Hands and feet	No change	No change	No change
			Thickened and tender nerves	Ulnar and lateral popliteal of both sides	No change	No change	No change
			Lepra reaction			Occurred on fifty-sixth day	No change
			Lepra bacilli	Positive	Positive	Positive	Positive
10	23	8	Papular				
			Erythema	Face	No change	No change	40%
			Infiltration		No change	No change	No change
			Nodular	Ear lobules	No change	No change	No change
			Anaesthesia	Over the patches	No change	No change	No change
			Thickened and tender nerves	Great auricular and ulnar both sides	No change	No change	No change
			Loss of eyebrows	Outer third	No change	No change	No change
			Lepra bacilli	Positive	Positive	Positive	Positive

10 mgm., followed by 25 mgm. daily for 6 days in the first week, 50 mgm. daily for 6 days in the second week, 75 mgm. daily for 6 days in the third week, and 100 mgm. daily for 6 days in a week indefinitely. Treatment B consisted of indomethacin 50 mgm. in capsules 3 times a day. The dosage of indomethacin was increased gradually over 3 to 6 days to avoid intolerance.

During treatment an estimate of the clinical condition was made every 4 weeks for 12 weeks. It was felt that whereas this was a reasonable period for assessment of any worthwhile anti-inflammatory effect of indomethacin, it was not too long to influence the results by itself.

The recession, if any, of various lesions including lepra reaction was recorded as maximum 71 to 90%, moderate 51 to 70%, minimum 31 to 50%, and none less than 30%. Bacteriological clearance was recorded as maximum if both nasal and skin smears were repeatedly negative, and none if continuously or intermittently positive.

The number of patients that would be required for a significant result remained a problem as facilities for work were limited by shortage of beds. We felt, however, that since we were testing primarily the anti-inflammatory effect of indomethacin, in spite of variations in

TABLE 3

Summary of the results in 10 patients of each pair after 12 weeks of Treatment A plus Treatment B and Treatment A respectively

Lesions	*Treatment A plus Treatment B*					*Treatment A*				
	Total No.	*Maximum* 71-90%	*Moderate* 51-70%	*Minimum* 31-50%	*None Less than* 30%	*Total No.*	*Maximum* 71-90%	*Moderate* 51-70%	*Minimum* 31-50%	*None Less than* 30%
Macular	1	Nil	Nil	1	Nil	1	Nil	Nil	1	Nil
Papular	10	4	2	4	Nil	10	Nil	Nil	1	9
Erythematous	10	4	2	4	Nil	10	Nil	Nil	2	8
Nodular	5	2	2	1	Nil	2	Nil	Nil	Nil	2
Oedema	2	2	Nil	Nil	Nil	1	1	Nil	Nil	Nil
Trophic ulcer	4	2	1	1	Nil	1	Nil	Nil	Nil	1
Anaesthesia	9	Nil	1	2	6	9	Nil	Nil	Nil	9
Thickened and tender nerves	10	Nil	Nil	1	9	10	Nil	Nil	Nil	10
Loss of eyebrows	3	1	1	Nil	1	2	Nil	Nil	Nil	2
Lepra reaction	1	1	Nil	Nil	Nil	2	Nil	Nil	Nil	2
Lepra bacilli positive	10	4	Nil	Nil	6	10	Nil	Nil	Nil	10

type, extent, and severity of lesions in the paired groups, any obvious difference between patients on Treatment A and those on Treatment A plus Treatment B would emerge. Since both groups received Treatment A the difference in favour of Treatment B would be the result of its indomethacin component.

RESULTS

Table 1 gives details of individual patients, the type and extent of their lesions and the response after 4, 8 and 12 weeks of Treatment A plus Treatment B.

Table 2 gives details of individual patients, the type and extent of their lesions and the response after 4, 8 and 12 weeks of Treatment A.

Table 3 summarises the results obtained in all 10 patients of each group after 12 weeks of Treatment A plus Treatment B and Treatment A respectively according to the criteria of assessment defined above.

There is striking improvement with Treatment A plus Treatment B in respect of skin lesions, oedema, healing of ulceration, and regrowth of eyebrows. Anaesthesia and nerve involvement have shown negligible improvement but there is some indication that improvement in these parameters may have occurred in time with further treatment. Bacteriological positivity has been favourably affected in 4 out of 10 patients which is considered significant for the period under observation.

One patient (Serial No. 4) under Treatment A plus Treatment B had a severe lepra reaction on the 9th day of treatment. It was associated with fever, joint pains, swelling of both legs and arms, appearance of fresh erythematous patches over forearms, hands and legs, with thickening and tenderness of both ulnar nerves followed by wasting of small muscles of the hands. The treatment was continued without alteration of dosage. The effects of reaction subsided completely in 7 weeks.

Two patients (Serial Nos. 6 and 9) under Treatment A had lepra reactions. Serial No. 6 had a comparatively mild reaction with fever and appearance of new patches all over the body on the 40th day of treatment. Serial No. 9 had a more severe reaction with swelling of hands and feet and fresh patches all over the body, mainly the trunks, on the 56th day of treatment. The treatment was continued without alteration of dosage. The effects of the reactions were unaffected during the remaining period of observation.

DISCUSSION

In lepromatous leprosy the dense granulomatous inflammatory reaction which occurs at the site of the infection fails to destroy the bacilli or to anchor the infection. Infection spreads to other parts of the skin via the tissue fluids and the lymph, to the peripheral nerves via their axonal pathways, and to distant organs via the lymph and the blood vessels. Resolution is by fibrosis and local blood vessels may be occluded by the process of obliterative endarteritis. The inflammatory reaction is therefore passive and useless. We feel, by its very nature, the inflammation is possibly responsible for the slow action of anti-leprotic drugs. The results which we have obtained so far in the trial seem to indicate that this is really so.

The granulomatous inflammatory reaction in the skin in lepromatous leprosy consists mostly of mononuclear cells and a few lymphocytes and plasma cells. To what extent this is reversed will become evident only in the histological studies which we are now carrying out.

Although axonal filaments are invaded by lepra bacilli there is no cellular infiltration within them. Hence they do not suffer from structural damage. The loss of hair and sensation apparently results from their involvement in the surrounding skin inflammation and have shown signs of return under indomethacin treatment.

Oedema of hands and feet which may be due to inflammatory reaction within the lymphatics, or their involvement in the skin inflammation, and affection of the autonomic nerves also subsides during indomethacin treatment.

The acute inflammatory manifestations in reactional states involving skin lesions and nerves with or without oedema of the hands and feet seem to be benefited but not altogether prevented by indomethacin.

SUMMARY

In a controlled (but not blind) trial in 10 patients with bacteriologically positive lepromatous lepsory, within 12 weeks indomethacin produced striking improvement in respect of skin lesions, oedema of limbs, healing of ulcers, and regrowth of eyebrows. Anaesthesia and nerve involvement showed negligible response, although comparison of the 2 groups of patients indicates that improvement in these parameters may occur in time with further indomethacin treatment. Four of the 10 patients on indomethacin became bacteriologically negative which is considered significant for the period of treatment. The effects of a severe lepra reaction which occurred within 10 days of indomethacin treatment subsided completely within 7 weeks under continued treatment with the drug.

ACKNOWLEDGEMENT

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Deformity in the Reactive Phases in Leprosy

Aetiology and Physiotherapeutic Management

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Various authors have reported on some of the deformities that occur in the reactive phases of leprosy, and have stressed the value of physiotherapy in the prevention and correction of these deformities. Muir (1962) considered the use of suitable, graded physical exercise together with proper nutrition in the prevention of lepra reaction. Cochrane (1964) emphasised the necessity for adequate physiotherapeutic care during the reactive phases of the disease. Ramanujam *et al.* (1964) pointed out the importance of physical treatments for severe, acute neuritis, acute nerve palsies and 'reaction hands'. Brand (1964) and Namasivayan (1965) described the damage to hands during lepra reaction and suggested physiotherapeutic measures of prevention. Furness *et al.* (1967) studied the mechanism of deformity in the upper extremity during the reactive phases and outlined the rationale of physical therapy for its prevention and correction. Karat *et al.* (1967) in describing a rheumatoid-arthritis-like syndrome in association with erythema nodosum leprosum (ENL) have briefly mentioned the physical measures used.

This paper attempts to study the aetiology of deformity occurring during the reactive phases of lepromatous leprosy. It also presents the comprehensive physiotherapeutic management used to prevent, minimise and correct deformity in this period.

MATERIAL AND METHODS

Forty-two consecutive patients with lepromatous leprosy who were admitted to the Schieffelin Leprosy Research Sanatorium for treatment during the reactive phases of the disease are reviewed in this study: 36 of these patients had from 2 to 10 episodes of reaction and 6 patients from 10 to 20 episodes.

Four-hourly temperature records were made. X-rays of the hands and feet were taken during and after each reactive phase. Manual muscle tests and strength-duration curves and sensory maps were used to assess peripheral nerve integrity. Oedema was recorded by water displacement tests.

COMPLICATIONS

The reactive phase in lepromatous leprosy may disappear in a few days or may recur on and off for years. The damage may be extensive, involving skin, nerve, muscle, bone, joints and lymph nodes. Table 1 shows the complications

TABLE 1

Complications observed in 42 patients during reactive phases

Complications	*No. of Patients*	%
Erythema Nodosum Leprosum (ENL)	42	100
Raised temperature	42	100
Peripheral oedema	41	97
Lymphadenitis	40	95
Nerve involvement	28	67
Joint involvement	21	50
Muscle involvement	20	48
Bone involvement	18	43

relevant to this study. All patients in this group were ill, with a high temperature and general malaise.

Among the complications occurring in the skin are the characteristic ENL lesions, the necrotising forms of ENL, subcutaneous nodules and an acute inflammaton of the skin and subcutaneous ti sue, '*en plaque*', down to the deep fascia known as leprous panniculitis. Tables 2 and 3 show the distribution of the necrotising forms of ENL and leprous panniculitis in these patients.

TABLE 2

Distribution of necrotising forms of ENL in 42 patients

Sites involved	*No. of Patients*	%
Face	15	36
Trunk	14	33
Upper extremity	17	40
Lower extremity	15	36

TABLE 3

Distribution of Leprous Panniculitis in 42 patients

Sites involved	*No. of Patients*	%
Face	2	5
Trunk	3	7
Upper extremity	11	26
Lower extremity	11	26

Peripheral oedema (97%) was a common complication among these patients (Table 1). Table 4 shows the distribution of oedema in the limbs. Oedema of the feet was present in 41 patients (97%), and oedema of the hands in 32 patients (76%).

TABLE 4

Distribution of oedema in 42 patients

Sites involved	*No. of Patients*	%
Hands	32	76
Feet	41	97
Forearm	10	24
Leg	22	52

Table 5 records painful neuritis. Twenty-seven patients (64%) showed involvement of the ulnar nerve, and 10 patients (24%) had neuritis of the lateral popliteal and posterior tibial nerves. Only in 9 patients (21%) was a median neuritis recorded, and in one patient (2%) a radial neuritis.

TABLE 5

Nerve involvement (neuritis) in 42 patients

Nerves involved	*No. of Patients*	%
Ulnar	27	64
Median	9	21
Radial	1	2
Lateral popliteal	10	24
Posterior tibial	10	24

The complications found in bone were osteoporosis and periosteitis. Periosteitis occurred most frequently in the tibia (26%) while osteoporosis was recorded in 43% of hands and 33% of the feet studied (Table 6).

TABLE 6

Bones involved	*Osteoporosis* No.	%	*Periosteitis* No.	%
Small bones of the hand	18	43		2
Small bones of the feet ..	14	33	1	2
Tibia	1	2	11	26

Pain, effusion and limitation of movement were the 3 complications studied in the joints. All the joints of the upper and lower extremeties were included in the study. The results are shown in Table 7.

TABLE 7

Joint involvement in 42 patients

Joint involved	*Pain* No.	%	*Effusion* No.	%	*Limitatin of Movement* No.	%
Shoulder	9	21	—	—	5	12
Elbow	22	52	1	2	11	26
Wrist	25	60	5	12	9	21
Proximal inter-phalangeal joint	25	60	10	24	13	31
Hips	8	19	—	—	2	5
Knees	24	51	9	21	5	12
Ankle	28	67	12	29	8	19

Table 8 records the muscle involvement in the upper and lower extremities in this group of patients. Atrophy of muscles was the most common complication observed. Pain and an occasional myositis were also found to occur.

TABLE 8
Muscle involvement in 42 patients

Sites involved	*Atrophy*		*Pain*		*Myositis*	
	No.	%	*No.*	%	*No.*	%
Arm	24	57	9	21	3	7
Forearm	23	55	10	23	4	10
Hand	14	33	4	10	2	5
Thigh	20	48	8	19	3	7
Leg	17	40	4	10	—	—
Foot	2	5	2	5	—	—

OBSERVATIONS

In the course of a reactive phase, the patient may experience a combination of pain in the joints, the nerves and the bones, together with muscle spasm, and usually assumes an immobile posture in the flexed position (Furness *et al.*, 1967). The bones of such a patient tend to become osteoporotic. Leprous panniculitis and the necrotising forms of ENL when occurring over the limbs heal with scar tissue, which forms adhesions between skin, tendons and muscles, resulting in limitation of movements (Tables 2 and 3). Panniculitis was observed in the upper and lower extremities of 11 patients (26%) and necrotising ENL in the upper extremities of 17 patients (40%) and the lower extremities of 15 patients (36%). An occasional myositis was found to occur over the triceps, the origins of the flexor and extensor muscles of the forearm, the abductor digiti minimi and the first dorsal interosseous muscle in the hand. Myositis in the lower extremity was noted occasionally in the quadriceps and near the region of the iliotibial band (Table 8). There seems to be a relation between the appearance of panniculitis in an area and the presence of underlying myositis, both being distributed over similar regions of the body. Effusion of the joints, especially of the knees (21%), ankles (29%) and wrists (12%) caused stiffness and limitation of movement (Table 7). Oedema due to venous and lymph stasis contributed to considerable damage in the hands and feet (Table 4). Painful neuritis caused considerable discomfort, and repeated bouts of reaction sometimes resulted in paralysis. A generalised muscular atrophy occurred occasionally (Table 8). This atrophy resulted from various causes, such as general debility, prolonged periods of inactivity in bed, and muscle spasm due to pain in the joints.

Specific deformities were noticed in the joints of the upper and lower extremities. An adduction deformity was sometimes seen in the shoulder joint due either to panniculitis and necrotising ENL over the scapula and shoulder region, or painful axillary lymphadenitis, or to faulty posture during the acute phase. A flexion contracture of the elbow tended to occur in the presence of oedema, panniculitis or necrotising ENL. The elbow was also sometimes held in a flexed position because of a painful ulnar neuritis. Both the 'intrinsic plus' (swan neck) and 'intrinsic minus' (claw) deformities were seen in the 'stasis hand' without intrinsic paralysis. However, a true ulnar or median paralysis was sometimes recorded.

In the lower extremity, deformity of the knees resulted from hamstring contracture and/or effusion into the joint (Karat *et al.*, 1967). Mobility of the patella was reduced, and extension of the knee was thereby made more difficult especially when the quadriceps muscle was atrophied. Marked atrophy of the quadriceps resulted not only from scarring of a panniculitis or myositis, but also from disuse following pain and consequential inhibition of movement. Ankle deformities commonly developed during the acute phase when the ill patient allowed the feet to drop. This resulted in a tendo Achillis contracture and limitation of dorsiflexion. Other foot deformities included stasis foot with hammer toes, and claw toes due to paralysis of the posterior tibial nerve. Varying degrees of contracture of the flexor hallucis longus and, to a lesser extent of the flexor digitorum longus, observed in 9 patients, were considered to be due to scarring and contracture of these muscles following the

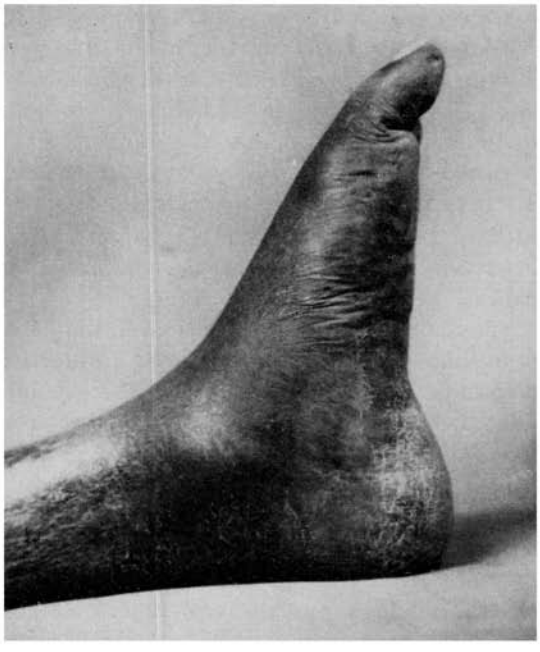

FIG. 1

Foot where oedema had subsided. Shows flexion deformity of great toe due probably to contracture of flexor hallucis longus.

localisation of oedematous fluid behind the ankle, in the vicinity of the lowest fibres of these muscles (Fig. 1). The tendency to contracture increased when the feet were allowed to drop.

MANAGEMENT

Acute phase: The aim of treatment in the acute phase is threefold—the relief of symptoms, the improvement of the patient's general health, and the prevention of deformity. Since there is usually an associated constitutional disturbance, systemic measures are important. The patients at the Schieffelin Leprosy Research Sanatorium are put to bed rest, and specific anti-leprosy treatment is stopped. Adequate intake of fluids is ensured. Mild sedatives are given together with appropriate anti-inflammatory drugs. Antimonials are the sheet anchor of treatment in most patients. Steroids are not given except in very severe and refractory cases.

Bed rest should not be continued any longer than necessary and detailed attention must be given to the posture of the patient while in bed. To combat venous stasis the foot of the bed is raised (about 9 inches). The shoulder is held in semi-abduction, the elbow in 100 degrees flexion, the forearm midway between pronation and supination, and the hand in a functional position. The whole arm is raised on pillows. In the lower extremity, the hip is held in a position of 20 degrees of flexion, slight abduction and without rotation, the knee in almost complete extension and the ankle is flexed at a right angle. A padded board may be used at the end of the bed to prevent dropping of the feet. When necrotising ENL is present, a cradle is placed over the legs and feet.

Splints are used at this stage for patients who, because of extreme pain, are unable to maintain correct posture in bed. These splints should be comfortable and allow for increased swelling yet prevent movement. Their function is to protect and immobilise the inflamed tissues and to preserve a movable and functionally useful joint. Splints also help to rest the inflamed nerves and minimise nerve damage. Gutter splints made of plaster of Paris or alkathene are used, being cuffed at intervals. In the lower extremity, they extend from below the gluteal fold to the toes and keep the limb in a functional position (Fig. 2). In the upper extremity they extend from below the axilla to the tips of the fingers, all joints being held in a functional position. Special care is taken to maintain the metacarpophalangeal joints of the fingers in flexion.

Once the acute phase is passed, mobilisation is immediately encouraged. The anti-inflammatory drug is gradually withdrawn over a period of 2 to 6 weeks and (depending on the clinical state) an appropriate anti-leprosy drug is introduced.

When the patient is comfortable and the limbs are adequately splinted, attention may be turned to the restoration of joint function. Function is maintained during the acute stage of the disease by gentle local joint movements for a short period each day. These movements are

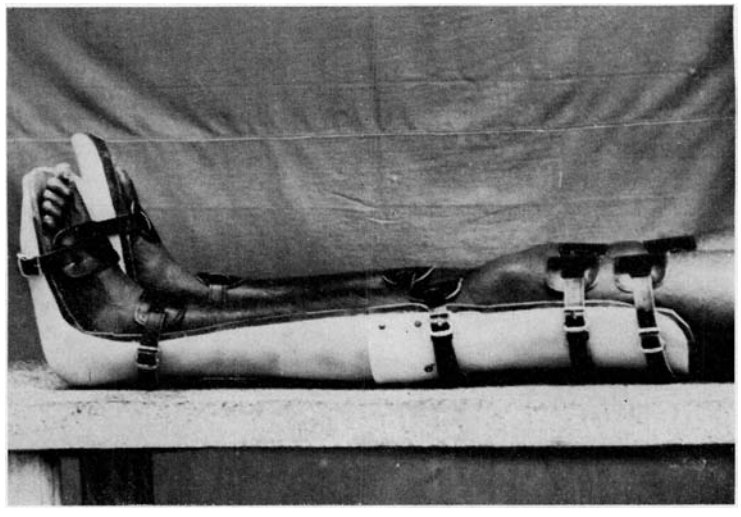

FIG. 2

Padded alkathene splint cuffed to the limb to maintain functional position.

done so as not to cause pain. The most effective approach to daily movements is the 'assisted active' exercise for the large joints, which eliminates the risk of strain for the patient. Movements of the hands and feet help to clear the oedema; this clearance was recorded by water displacement measurements whenever possible. When the daily range of movement is completed the limb is returned to the splint. Isometric contraction of muscles may also be employed while the limbs are splinted, to reduce oedema and prevent muscle atrophy. Whatever method is employed, the patient's exercise tolerance is noted. Any increase in pain or spasm for more than an hour after the session indicates an excessive amount of exercise, which is reduced at the next treatment period.

Phase of recovery: When the acute phase has subsided (as shown by the subsidence of ENL and a superficial desquamation of the skin) active measures of rehabilitation are instituted.

The 3 main aims of treatment in this stage are: the maintenance of general health, the prevention of renewed exacerbation, and the correction of residual deformity. This is the transition period between recumbency and gentle cautious movement, progressive weight-bearing and active exercises. If splints were used, they may now be discontinued during the day and worn only at night. Walking with manual assistance or between parallel bars is instituted as early as possible. Particular attention is paid to strengthening the postural muscles. Group exercises may be conducted in the wards every day. In this series proprioceptive neuromuscular facilitation techniques were usefully employed to increase the range of movement in the joints and to increase muscular power.

LOCAL PHYSIOTHERAPEUTIC MEASURES

Stiff joints: When there is residual stiffness in the large joints such as the shoulder, elbow, wrist, knee and ankle, the 'hold-relax' technique of proprioceptive neuromuscular facilitation may be used. The joint is taken to the point where further movement is limited by tension or pain. Having made sure that the position is pain-free, the physiotherapist asks the patient to 'hold' while he applies maximal resistance to the antagonistic muscles. The isometric contraction is held in order to obtain build-up of excitation, then the patient is told to relax. Time is allowed for relaxation to take place, and then an attempt is made to move in the direction of limitation to gain an increase in range. The technique is used as often as possible, and is followed by 'repeated

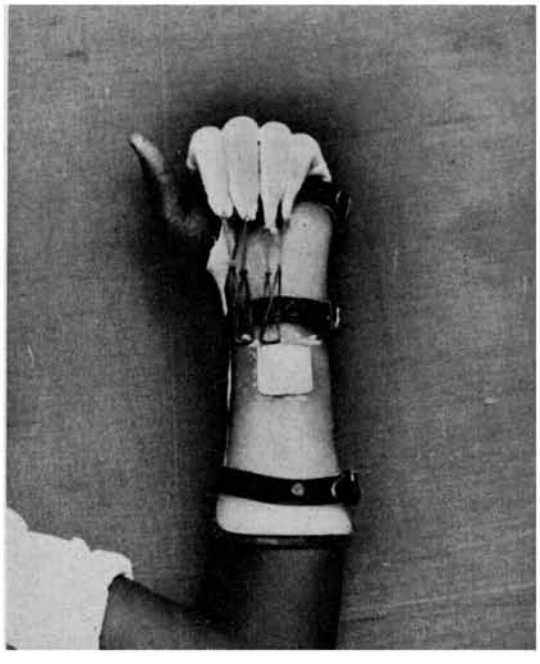

FIG. 3

'Stasis hand.' Mild traction through use of glove prevents hyperextension of metacarpophalangeal joints. Alkathene slab maintains wrist in extension.

contractions' to consolidate any increase in range. Heat treatment is usually given before these exercises, wax baths being used to reduce pain and muscle spasm.

'Stasis hand' and 'Stasis foot': When oedema is present over the dorsum of the hand and fingers, gentle traction may be given through a glove to prevent hyperextension of the metacarpophalangeal joints and contracture of the collateral ligaments (Fig. 3). A plaster of Paris or alkathene anterior slab extending to the mid-palm may be used to prevent flexion contracture of the wrist. If the intrinsics are in spasm and show a tendency to flex at the metacarpophalangeal joint level, the plaster of Paris anterior slab may be extended to just below the level of the proximal interphalangeal joint so that, with the metacarpophalangeal joints held in extension, traction may be applied gently through a glove to flex the proximal interphalangeal joint and to stretch the intrinsics. The glove may be removed twice daily for wax baths and exercises, given with the hand held in elevation. These exercises must be directed at maintaining full range of movements in all the small joints of the fingers, particularly the metacarpophalangeal joints. When there is oedema in the region of the thumb web contracture of the soft tissues occurs in this area; this contracture may interfere with abduction and rotation movements needed for normal function of the thumb. Active exercises to maintain full range of movement in the thumb are therefore encouraged. When subcutaneous nodules or panniculitis is present over the dorsum of the hand and there is a tendency for adhesions to form with the underlying extensors, massage is given to the scarred area with oil, using circular, transverse and longitudinal frictions to mobilise the scarred structures. Ultrasound therapy may also be employed for this purpose, the dose being 0.5 to 1 watt per square centimetre for 5 to 6 minutes daily until the area is mobilised.

The 'stasis foot' is maintained in a plaster of Paris or alkathene back slab and elevated to prevent tendo Achillis contracture and to reduce oedema. The back slab also prevents the great toe and the other toes from developing flexion contractures. Wax baths are used for the feet, followed by active exercises for the toes and ankles.

Neuritis: Where there is evidence of a painful neuritis either in the upper or lower extremities a well-padded plaster is applied to rest the nerve. The plaster is maintained over a period of 5 to 6 weeks, during which time isometric exercises are encouraged within the plaster to prevent muscle atrophy. At the end of this period, the plaster may be removed and re-education started to restore muscle strength. Lively splints are used when indicated by muscle weakness.

Ulcerations: Particular attention should be paid to the ulcerations occurring from the necrotising forms of ENL, over either the extensor or the flexor surface of the fingers. When these ulcerations occur over the dorsum of a finger, they tend to damage the delicate dorsal apparatus. When occurring near the flexor crease of a finger, they heal with scar

tissue which tends to contract. The hand should be carefully immobilised in a functional position until the ulcers are well healed. The scarred areas may then be gently massaged with oil and the fingers actively exercised to restore function.

Osteoporosis: Osteoporosis due to disuse becomes completely reversible when active movements are instituted over a period of time or when the patient returns to work. Osteoporosis due to diffuse lepromatous involvement of the bones takes many months, or years, to heal. These bones are vulnerable to damage, and the patient must be warned not to use his hands for strenuous activities and hard manual labour.

CONCLUSION

If competent physiotherapeutic care is given both in the acute phase and during the phase of recovery deformity is prevented and function restored. The accumulated effect of repeated episodes of reaction is tissue damage and diminished function, especially in the small joints of the fingers, and peripheral nerve damage. Complete correction of residual deformity should be attempted during quiescent periods in those patients who suffer from recurrent bouts of reaction.

SUMMARY

The complications arising in 42 consecutive patients with lepromatous leprosy during reactive phases of the disease are reviewed. Damage to skin, nerve, muscle, bone and joints is recorded, and an attempt made to study the aetiology of deformity relative to these complications. Physiotherapeutic care of the patient during the acute phase and the phase of recovery is described. Specific physiotherapeutic management of stiff joints, 'stasis hand' and 'stasis foot', ulcerations, neuritis and osteoporosis have also been detailed.

Although imperceptibly progressive damage and reduced function in muscles and nerves may occur with repeated episodes of reaction, careful comprehensive physiotherapeutic care will minimise the functional loss.

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Decompression of the Ulnar and Median Nerves in Leprous Neuritis*

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This study was undertaken to assess the value of partial decompression of the ulnar and median nerves in leprosy to relieve pain due to neuritis and to improve muscle function.

Muir (1948) was of the opinion that a painful swelling of nerves following progressive paralysis was suitable for decompression. 'Splitting of the nerve sheath will give relief and conserve function in the most severe cases.' Cochrane (1964) pointed out that the operation on all nerves should be replaced by a much more cautious approach; however, if a nerve abscess is suspected the nerve should be explored forthwith, for if, under these conditions, surgical interference is not initiated, gross damage may result—a damage far more crippling than that caused by any operative interference. Gramberg (1955) has reported that after decompression pain and paraesthesia disappear in nearly all cases.

MATERIAL AND METHODS

Thirteen leprosy patients (10 males and 3 females) of ages ranging from 16 to 57 years attending the out-patient clinic of the Acworth Leprosy Hospital, Wadala, Bombay, were selected for the study.

The duration of the disease as given by the patients ranged from 6 months to 16 years. The type of leprosy in these patients was as follows:—

TABLE 1

Type of Leprosy	*No. of Patients*
Tuberculoid	10
Borderline	1
Lepromatous	2
Total	13

All the patients were suffering from severe ulnar neuritis with or without involvement of median nerves, resulting in severe pain along the course of the nerves not responding to oral analgesics and perineural injections of hydrocortisone or intradermal 'Hydnocreol' along the course of the nerve or local ethyl chloride spray, etc.

Table 2 shows the types of disease and site of nerve lesions.

* Paper read at the Xth All India Conference of the Indian Association of Dermatologists and Venereologists held at Cuttack in January, 1968.

TABLE 2

	No. of Patients	*Rt. Ulnar alone*	*Rt. Median and Ulnar*	*Lt. Ulnar alone*	*Lt. Median and Ulnar*	*Abscess*
Tuberculoid	10	3	3		Nil	8*
Borderline		Nil	Nil	Nil	1	Nil
Lepromatous	2	2	Nil	Nil	Nil	Nil
Total	13		3			8

* One patient showed calcification inside the nerve sheath (Fig 1) (detected during operation). Another patient had an abscess in the median cutaneous nerve of the forearm as well as ulnar.

Detailed clinical examination with special emphasis on the severity of the pain and paraesthesia was done. The gradation of the muscular weakness was assessed both clinically and with the help of the electric stimulator, before and after surgical operations as shown below:—

The muscle is stimulated at its motorpoint (neuromuscular junction) by the galvanic units and later by the faradic unit.

Findings. The normal muscle responses are brisk both to the galvanic and faradic units. The completely denervated muscle responds sluggishly to the galvanic unit but does not respond to faradic unit. The partially denervated muscle responds briskly to the galvanic unit and only with a very high output to the faradic unit. The difference between the galvanic and faradic units is noted and muscle weakness is graded accordingly.

The technique of nerve decompression:

Premedication used: Chlorpromazine hydrochloride (Largactil) 25 mgm. and pethidine 50 mg. injection I.M.

Anaesthesia: Brachial plexus block using 20 c.c. of 1% xylocaine with or without adrenaline (1 : 1000 aqueous solution). A tourniquet is applied to the upper arm.

The ulnar nerve is exposed from the middle of the arm to the upper quarter of the forearm. The superficial and deep fascia and medial intermuscular septum are incised exposing the nerve in the arm. The nerve is followed distally up to the upper quarter of forearm by slitting the fibrous origin of the flexor carpi ulnaris over the ulnar groove. No attempt is made to mobilise the nerve or to incise the epineurium or to transpose the nerve anteriorly. A caseous nerve abscess in relation to the ulnar nerve generally took the form of a well encapsulated almond-shaped swelling (Fig 2). No pedicle was seen, the swelling projecting out from the interior of the nerve. The contents were almost solid or semi-solid and hence could not be 'drained' away in the conventional sense. Its roots were in the interior of the nerve from where the caseous material was picked or scooped off, taking care not to damage normal looking fibres. At times, however, the entire nerve was converted into a caseous cone with an epineural shell (Fig 3).

Median nerve: This nerve is exposed in the lower third of the forearm and followed into the hand by incising the flexor retinaculum and palmar aponeurosis. The maximal thickening and induration was generally seen and felt to be proximal to the wrist just distal to the sublimus belly.

The criteria of improvement were (1) relief from pain and (2) improvement in the muscle functions as judged clinically and by electrical assessment.

The period of follow-up after surgery ranged from 10 months to $2\frac{1}{2}$ years (except in one patient where the follow-up period was only 3 months).

As a result of surgical decompression, pain of a moderate to severe extent was relieved in all patients except 3. Persistent excruciating pain, often experienced by patients in spite of oral and parenteral analgesic treatment or perineural and antiphlogistic therapy should therefore be taken as an indication for surgery. The relief obtained by nearly 77% of the patients would by itself justfy the surgical intervention.

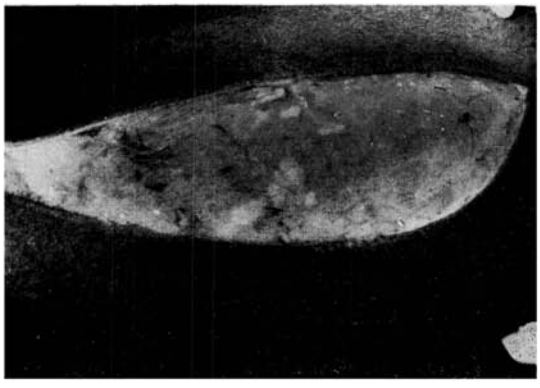

FIG. 1
Calcification inside the nerve sheath.

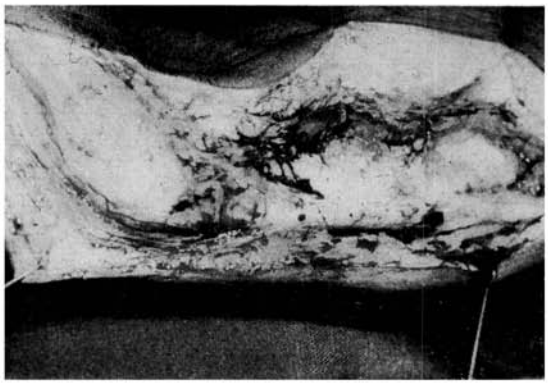

FIG. 2
Encapsulated almond-shaped swelling.

FIG. 3
Caseous cone with an epineural shell.

TABLE 3

Type	No. of Patients	PAIN						MUSCLE FUNCTION					
		Before operation			After operation			Before operation			After operation		
		Severe	Moderate	No pain	Severe	Moderate	No pain	Complete paralysis	Moderate paralysis	No paralysis	Complete paralysis	Moderate paralysis	No paralysis
Tuberculoid	10	8	1	1	1	—	9	3**	3*	4**	5	—	5
Borderline	1	1		—	1			1	—	—	1		—
Lepromatous	2	2		—	1		1	1	1	—	2		—
Total	13	11	1	1	3	—	10	5	4	4	8	—	5

* Of the 3 patients who had moderate paralysis, one had an abscess.

** All these patients had an abscess of ulnar nerve.

Assessment of muscle function has shown that 4 patients who did not have any paralysis preoperatively were not adversely affected as a result of the operation. One patient who had moderate paralysis showed some improvement after surgery, while in 3 moderate patients the progressive paralysis was unchecked by decompression, since only the external pressure on the individual nerve was relieved and the nerve fibres themselves were not subjected to any interference during surgery. The progressive paralysis observed in these patients may be the result of degeneration of the nerve due to the disease process itself.

SUMMARY

Follow-up study of 13 surgically decompressed patients with severe leprous ulnar and median neuritis who did not respond to medical measures is presented. In all patients except 3, pain was completely relieved; improvement in muscle function was seen in only one patient and 4 patients who had visible caseation remained unchanged. Three patients with progressive nerve lesions became progressively worse after surgery.

ACKNOWLEDGEMENTS

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Radiological Changes in Bones of the Limbs in Leprosy

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The radiological changes in bones of the limbs in leprosy show a variety of lesions. It is often difficult to classify them into definite groups. Widely varying aetiological and pathological factors may be involved in their production. A single aetiological and pathological factor may produce widely dissimilar radiological appearances. The aetiology can be classified under 3 major groups. First, those changes that are directly attributable to the disease process; secondly, those changes that are secondary to paralytic deformities; and thirdly, those that are secondary to anaesthesia of the limbs and consequent trauma. In a single patient all these factors may exist together. One factor may aggravate the deleterious effect of another, as in the case of plantar ulcer under the metatarsal heads which is made worse by claw toes due to posterior tibial paralysis (Fig. 20 *a* to *c*).

Various authors have described some of the patterns of involvement such as leprous dactylitis[1], concentric absorption[2] and tarsal disintegration[3]. Mœller-Christensen[4] has described the various bony changes found in the skeletons of leprosy patients, though without directly relating them to clinical conditions.

This paper describes the various radiological appearances of bones in leprosy and attempts to relate these changes to possible aetiological factors.

PRIMARY INVOLVEMENT

Primary involvement of the bone in leprosy may present as generalised osteoporosis or as localised area of destruction.

Generalised Osteoporosis

Generalised osteoporosis is often found in patients with lepromatous leprosy who have a high bacillary load (Fig. 1 *a* and *b*). There is no definite correlation between the clinical appearance of the hands and feet and the osteoporotic changes seen radiologically. For example, lepromatous nodules or swelling of the fingers may not be present. Biopsy from areas of osteoporosis invariably shows lepromatous granuloma. The bone is soft, and a drill biopsy is easily obtained with manual pressure. The phalanges are fragile and may fracture with moderate trauma. Concurrently with the control of the disease and the reduction in the Bacterial Index, the osteoporosis improves.

Generalised osteoporosis may also occur as a transient phenomenon during reactive episodes in both lepromatous and non-lepromatous leprosy. Among non-lepromatous patients, it is more often present when an active lesion overlies the fingers or toes (Fig. 2 *a* and *b*), and in these, histopathological examination shows no evidence of a specific lesion due to leprosy.

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Localised Osteoporosis

Localised osteoporosis occurs as circumscribed, well-defined, osteolytic lesions in patients with lepromatous leprosy, or in those with near-lepromatous borderline leprosy (Fig. 3 *a*). Most of the patients with clinically recognisable disease have a high Bacterial Index. Contrary to previous reports, these are not necessarily associated with nodular lesions or gross infiltration of the overlying skin or subcutaneous tissue or swelling of the fingers[5]. The bones involved are very fragile and may fracture with minimal stress, especially when the subarticular osteolytic areas extend into the surrounding bone. Such pathological fractures are common, and result in angular deformities or fore-shortening of the phalanges (Fig. 3 *b*). However, with effective anti-leprosy therapy, these areas heal with formation of thick, dense trabeculae. Deformities due to bony displacement at the fracture site persist after healing of the fractures.

Localised osteoporosis may also occur in patients with non-lepromatous leprosy in the bones underlying an active localised skin lesion passing through a phase of acute exacerbation (Fig. 5 *a* and *b*). Histopathological examination shows no specific lesion in this area. With the resolution of the skin lesion, the radiological appearance of the bone returns to normal.

Periostitis

Periostitis is often noticed clinically during the phase of reaction, the patient presenting with intractable pain and tenderness over subcutaneously placed bones. The tibial crest is the most common site (Fig. 5 *a* and *b*). Occasionally the subcutaneous border of the ulna may be involved. X-ray examination of these bones reveals thickening of the cortex, and histological examination shows lepromatous infiltration of the periosteal layer of the bone.

BONE CHANGES DUE TO SECONDARY CAUSES

The chief cause of secondary bone changes in leprosy is anaesthesia. The pattern of their occurrence and progression is very similar to that found in other 'neuropathic' conditions in which similar patterns of sensory involvement are present. For example, peripheral neuropathy in diabetes mellitus, syringomyelia, familial sensory neuropathy and meningomyelocele associated with spina bifida all present similar radiological patterns. The Charcot type of disintegration of the joints is conspicuous by its rarity. Joint involvement in the anaesthetic limbs of leprosy demonstrable radiographically is almost always associated with adjacent ulceration and subsequent destruction of the joint.

Some of the less common features of bony changes in anaesthetic limbs occurring in the course of acute and chronic inflammation, and the mode of occurrence and pattern of repair of traumatic lesions are worth describing.

Acute inflammation associated with trophic ulceration results in severe osteoporosis (Figs. 6 and 10 *b*). Sometimes the bone seems to disappear, leaving soft tissue unsupported (Fig. 10 *c*). The bones involved are invariably in communication with a sinus from an adjoining trophic ulcer, and small fragments of osteoporotic bone are frequently extruded through the sinus. However, there is usually no periosteal reaction, nor are large dense sequestra found. Destruction is usually more extensive than repair. Osteomyelitis in anaesthetic bones thus usually results in loss of part of the bone or the entire bone.

In the case of concentric absorption, the endostium attempts to lay down bone while the outer layer of bony cortex is uniformly eroded. The total diameter of the shaft is reduced at the expense of the medullary cavity while the thickness of the cortex itself is maintained (Fig. 18 *a* and *b*). Often, these bones are very hard and much more difficult to operate on, than normal bones.

Progressive shortening of the phalanges and metatarsals may also be observed over a period of years. Once an osteomyelitis in an anaesthetic limb heals, destruction of bone does not recur in the absence of another episode of infection. Recurrent infections can arise either as a direct extension of trophic ulceration or as a primary osteomyelitis following a penetrating

injury or a deep avascular pressure necrosis. The prevention of such infection and injury will obviate further loss of bony substance.

The importance of the relation of the soft tissue to the bony architecture is often not fully recognised. Deformities may occur because of muscle imbalance following paralysis, or because of destruction of flexor or extensor tendons at sites of trophic ulceration. These deformities result in abnormal sites of stress, which in turn lead to trophic ulceration and destruction of soft tissue and underlying bone.

On the other hand, loss of supporting bony structure results in contraction of the soft tissues. The soft tissue of the finger may thus be contracted to a third of its original length, with loss of the bony phalanges. The nail and pulp lie at the level of the proximal phalanx, and there is no redundant soft tissue to indicate its original length. The same sequence occurs in the dorsal skin and soft tissues of the feet. Total loss of metatarsals and the adjoining phalanges may result in the remnant of the toes being withdrawn proximally to the level of the tarsals. Ulceration on the plantar surface may account, in part, for the shortening of the plantar soft tissues, but the dorsal skin and subcutaneous tissue (which, as a rule, is not involved in the ulcerative process) is reduced to half its original length without having undergone any obvious destructive process. It is this tendency of the soft tissue to contract in the absence of bony support which has given an air of mystery to the process of shortening of the limbs in leprosy.

On the other hand, loss of support to the soft tissues may result in gross distortion and deformity of the foot (Fig. 18 *c*). Stretching or even rupture of the soft tissues by abnormal stress may proceed uninhibited in the absence of pain. The same is true of fractures, which may occur from repeated and unappreciated micro-traumata to anaesthetic bones (Figs. 21 to 26). For example, the posterior tuberosity of the calcaneum undergoes avulsion fracture from the pull of the tendo Achillis (Fig. 16 *a*). This is not an uncommon finding in radiographs of anaesthetic feet. The majority of patients are unaware of having sustained such an injury.

PATTERNS OF BONY CHANGES IN THE LIMBS DUE TO INFECTION

Infection in the anaesthetic limbs includes trophic ulceration initiated by injury, infection or deep aseptic necrosis.

Infection in the hand

Severe osteolytic lesions due to acute inflammation are common in the fingers (Fig. 6). Recurrences are directly related to the number of injuries sustained. The site of the lesion is determined by the site of injury and has no fixed pattern. However, occupational injuries occur at specific sites due to pressure from unadapted tools. Shortening of the soft tissues follows the destruction in the bony support.

Progressive shortening of the fingers is due to recurrent ulceration and macroscopic and microscopic sequestration of bone (Fig. 8 *a* to *d*). Pathological fractures of the diseased bone contribute both to the shortening and to the angular deformities of the fingers (Fig. 7).

Infections of the foot

The basic pathology of the progress of infection in the foot is similar to that of the hand (Fig. 10 *a* to *c*), but the distribution of plantar ulcers follows a definite pattern. In a foot that is not distorted and which retains the normal mechanics of gait, ulcers occur along the areas of maximum stress which corresponds to the walking roll[6]. However, when the areas of stress are altered during walking, owing either to muscle imbalance or to destruction of the bony support, the areas of trophic ulceration are correspondingly altered.

The radiological appearance of bone changes due to plantar ulceration has no consistent pattern (Fig. 9). Uniform concentric absorption, or irregular absorption, or widely varying distortions following irregular loss of bone and joints, gives a bizarre appearance, that may defy description (Figs. 9 and 19 *b*). Individual bones may be dense and sclerotic, or they may show severe osteoporosis or osteolysis. The joints may

become arthritic, or develop fibrous ankylosis or bony union. Often, the adjoining bony components of a joint are destroyed, leaving a large gap between the two ends. Soon the soft tissue contracts and pulls the bony ends together (Figs. 11 *c* and 17 *b* and *c*). Such distortion is often associated with destruction of some of the tendons acting on the joint. The resulting imbalance of muscle action produces a postural deformity of the part, distal to the joint. Thus, destruction of the flexor tendons under the metatarsal heads results in unopposed hyperextension, and dorsal and proximal subluxation of the toes is commonly found following deep plantar ulceration (Fig. 20 *c*).

PATTERNS OF DESTRUCTION DUE TO PLANTAR ULCERATION

Individual bones or toes

Fig. 10 *a* to *c* shows a series of radiographs from different patients, that demonstrate the pattern of progressive destruction of a toe until it is totally lost. This may occur rather rapidly during an acute episode, followed by chronic ulceration if the patient remains untreated, or it may take many years of recurrent ulceration. Each such episode results in a small amount of bony destruction. The foot that has lost its big toe develops new areas of stress. Such an area may be the distal end of the first metatarsal head, unprotected by the big toe, and overlying a scarred avascular area, or it may be the adjoining toes, which deviate without the support of the hallux (Fig. 10 *c*), or it may be another metatarsal head which has come to bear the maximum stress during the 'kick-off phase' of walking. Footprints show the changing pattern of stress. Without protective footwear, these new areas of stress are likely to become the seat of plantar ulcers.

When loss of bony support is more extensive than is represented by a single toe, the remaining part of the foot suffers a marked reduction in the total weight-bearing surface, and consequently shows a greater predilection to trophic ulceration. In such cases, the outlook for long-term trouble-free survival of an active anaesthetic foot is poor. When such destruction involves the major components of the foot, the resulting functional imbalance during weight-bearing aggravates the tendency to plantar ulceration in the new areas of stress.

The major components of the foot are the medial ray, the lateral ray, forefoot and hind foot.

Medial Ray

The highest incidence of plantar ulcer occurs on the medial side of the forefoot: 27% of all plantar ulcers occur under the big toe and the first metatarsal head[6]. Recurrent ulceration results in the destruction of the big toe and the first metatarsal head (Fig. 11 *a* to *c*). The forefoot loses a third of its weight-bearing surface, and this results in excessive pressure under the adjoining metatarsal heads.

Lateral Ray

The incidence of plantar ulceration under the fifth metatarsal head is 15%, but in cases of lateral popliteal paralysis the fifth metatarsal head shows peak pressure at the onset of the 'stance' phase, when the foot hits the ground in a slightly inverted and plantar-flexed position. Thus, lateral ray destruction is common in lateral popliteal paralysis (Fig. 12 *a* and *b*).

Forefoot Ulceration

Ulceration and destruction of the metatarsal heads in the forefoot is commonly seen. As already pointed out, loss of one metatarsal head predisposes to ulceration in the skin overlying the remaining metatarsals. Footdrop, tendo Achillis contracture, or equinus deformity due to any other cause aggravates the tendency for forefoot destruction. Fig. 14 *a* to *d*, a series of radiographs from different patients, show progressive shortening of the forefoot. The final result is severe reduction in the weight-bearing area.

Hind Foot

Heel ulcers are often chronic. Once the calcaneum is involved, osteomyelitis extends deep into the bone meeting with very little resistance, and the shell of the calcaneal cortex

becomes fragile and vulnerable to trauma. Avulsion of the posterior tuberosity by the pull of the tendo Achillis or fracture of the calcaneum itself is a common occurrence (Fig. 15 *a* to *c* and Fig. 16 *a* and *b*). The posterior fragment of the calcaneum is pulled backwards by the tendo Achillis, and as the ulcer heals the calcaneum assumes the shape of an elongated boat (Fig. 16 *b*).

The infection in the soft tissue may spread anteriorly to involve the calcaneo-cuboid and calcaneo-navicular joints. Once these joints are destroyed, the head of talus is in direct contact with the plantar ulcer and soon becomes involved. The process of mid-foot destruction is thus initiated.

THE IMPORTANCE OF MAINTAINING THE ARCHITECTURAL INTEGRITY OF THE FOOT

A balanced foot, in which the bones support each other and the mechanics of weight-bearing follow a normal pattern, is considered necessary if the anaesthetic foot is to maintain its integrity. Fig. 17 *a* to *c* illustrate the need for maintaining architectural integrity, so that balanced distribution of pressure in the foot may not be altered. Fig. 18 *a* to *c* illustrate the severe disintegration that may result from destruction of the soft tissue components that help to maintain the normal alignment of the bones of the foot.

PARALYTIC DEFORMITIES

Paralytic deformities may result in fixed deformities and secondary bony changes (Fig. 19).

Abnormal position of bones and joints, combined with imbalance of the muscle action on the joint, may result in alterations in the distribution of pressure in the foot. Ulcers over the metatarsal heads occur as a result of abnormal pressures from claw toes (which are themselves the result of paralysis) (Fig. 20 *a* to *c*), and from lateral ray destruction from lateral popliteal paralysis.

FRACTURE IN ANAESTHETIC BONES (FIG. 21 TO 26)

Fractures in anaesthetic feet are often unrecognised by the clinician. These fractures occur most commonly as a result of unappreciated repeated micro-traumata and are similar to march fractures in their causation[3]. Osteoporosis, abnormal posture of the foot while walking, and infection are the common predisposing factors[7].

Osteoporosis

Osteoporosis may be due to prolonged immobilisation (Figs. 21 *a* to *b*, 23, 24 *a* and *b* and 25), or it may be due to long-continued steroid therapy (Fig. 22). Sometimes it is due to primary lepromatous granuloma in the bones (Fig. 3 *b*).

Abnormal posture of the foot

The common clinical example is walking on a dorsiflexed foot. A tight 'foot-drop spring', or a foot immobilised in a walking cast with the ankle held at extreme dorsiflexion, are common causes of such abnormal postures (Figs. 23 and 14). The trabeculae of the bone are normally arranged according to the lines of stress, along which the body weight is transmitted. When the foot is held in dorsiflexion and the patient is made to walk, the line of transmission of body weight is altered. This results in fractures along the line of maximum stress.

Infection

Bony destruction due to osteomyelitis is a common cause of fractures in anaesthetic limbs. The bones may be so fragile that minimal force produces a fracture (Fig. 26).

SUMMARY

An illustrated outline of radiological changes observed in the limbs of leprosy patients is presented. These are broadly classified as primary and secondary changes. Primary changes are seen in patients with either lepromatous or non-lepromatous leprosy. Secondary changes, the result of anaesthesia and/or paralysis, are outlined. Changes in individual bones due to trophic ulceration, as well as general patterns of destruction due to plantar ulcers in the foot, are described. The effect of paralytic deformities in anaesthetic limbs is

pointed out. The need for maintaining architectural integrity of the foot is emphasised, and illustrated with examples. Fractures and their aetiology in anaesthetic limbs are outlined and illustrated. An attempt is made to correlate radiological changes with the clinical course.

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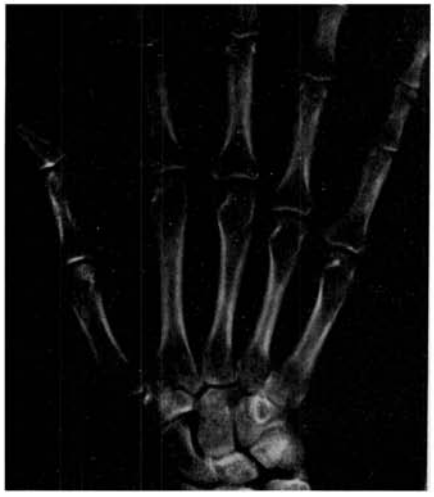

FIG. 1 (*a*)

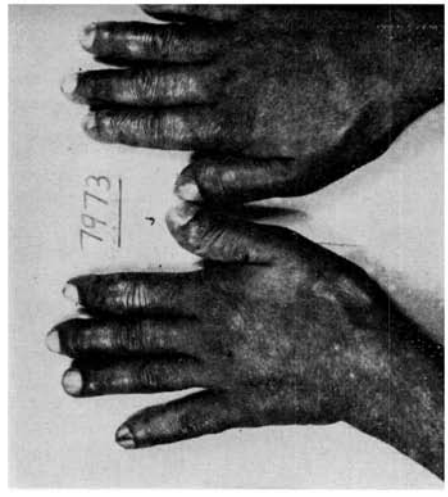

FIG. 1 (*b*)

FIG. 1 (*a*) and (*b*)

Case History: Name: N.R. Age: 35. Sex: Male. SLRS No. 7973. X No. 4289. Lepromatous leprosy of 7 years' duration. Was admitted with infiltrated lesions over the face and back. Fingers were swollen and spindle-shaped, but not tender.

X-ray: X-ray taken on 31.VI.1966 shows marked sub-articular osteoporosis of all the phalanges with severe osteolysis of the adjoining surfaces of the proximal inter-phalangeal joint of the index finger. Biopsy taken on 15.IV.1966, from the left little finger, head of the middle phalanx, shows lepromatous granuloma of the bone.

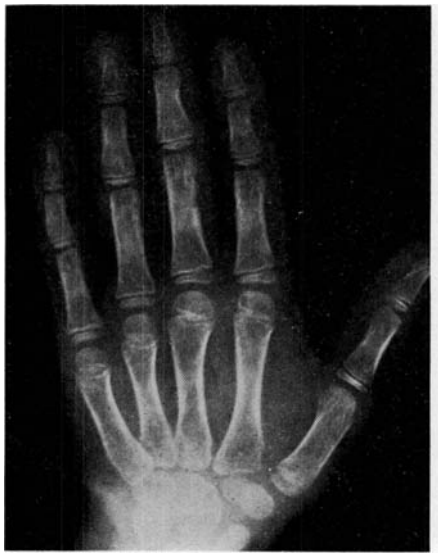

FIG. 2 (*a*)

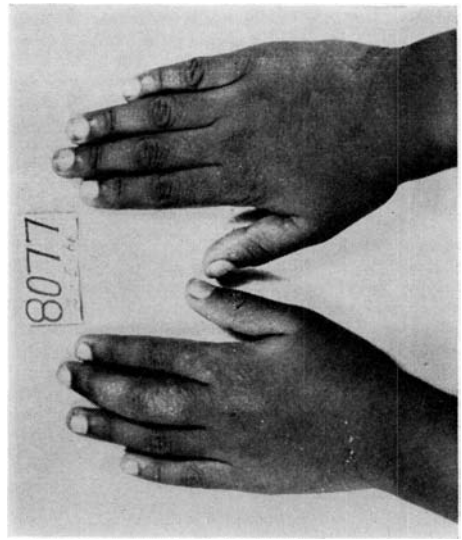

FIG. 2 (*b*)

FIG. 2 (*a*) and (*b*)

Case History: Name: A.R. Age: 9. Sex: Male. H. No. 8077. X. No. 2571. Admitted with a history of multiple patches over the body of 1 year's duration.

On examination: A number of well-defined, hypo-pigmented infiltrated lesions with raised edges and resolving centres, most of which are anaesthetic. There was a lesion over the left middle finger with fusiform swelling of the entire finger and pebbling along the edges, with satellite lesions. X-ray showed osteoporosis of the phalanges. Skin smear for acid-fast bacilli was negative. Skin biopsy taken on 31.III.1966 from a patch on the left leg showed typical tuberculoid leprosy. Bone biopsy was taken from the proximal phalanx of the middle finger on 25.III.1966. Histology showed bone and fibrous tissue with no evidence of inflammation due to leprosy.

X-ray: X-ray shows generalised osteoporosis. Patient was treated with steroid and anti-leprosy drugs. X-ray taken 3 months later showed no osteoporosis. The swelling and erythema in the finger subsided, and the patient had no further symptoms.

Summary: Generalised osteoporosis of bones of hand under a tuberculoid leprosy patch. Negative skin smears; bone biopsy—negative.

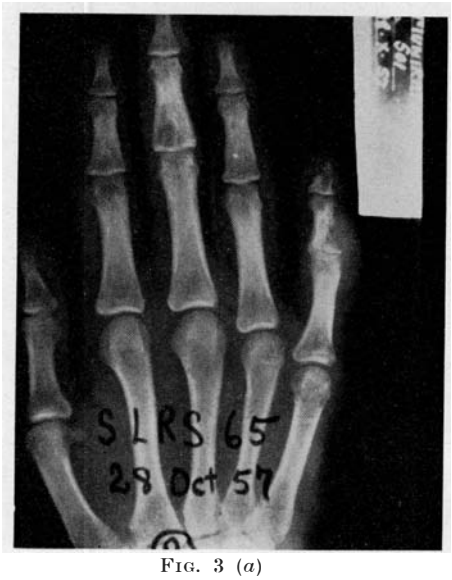

FIG. 3 (*a*)

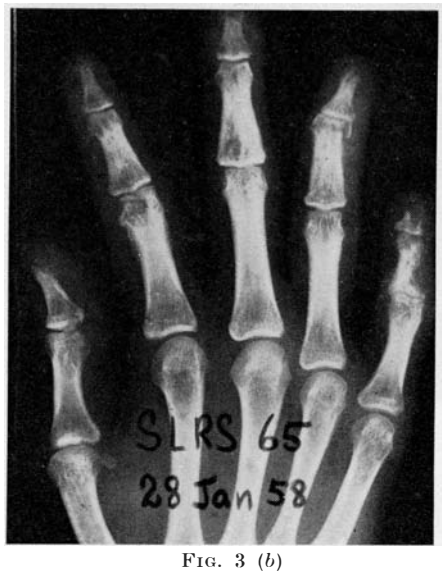

FIG. 3 (*b*)

FIG. 3 (*a*) to (*c*)

Case History: Name: M.R. Age: 30. Sex: Male. H. No. 501. X. No. 65. Lepromatous leprosy of 12 years' duration, with history of repeated reaction; treatment with anti-leprosy drugs for one year, with repeated interruptions due to reactionary episodes. Ulcerative nodules all over the extremeties and buttocks. Right hand showed diffuse swelling of all the phalanges, slightly more around the proximal interphalangeal joints of index, long and little fingers. Nodules over the dorsum of the hand with ulceration. No gross deformity at that time.

FIG. 3 (*a*)

X-ray taken 28.X.1957, showed osteolytic lesions, fairly localised, at the base of the middle phalanx of the index finger, head of the proximal phalanx of the index finger, terminal tufts of index, long and little fingers, base of the middle phalanx of the middle finger and base and lateral surface of the middle phalanx of of the little finger with soft tissue shadow around it. Biopsy taken from the index finger proximal phalanx on 12.XI.1957, showed dense inflammation, mainly foamy cells and macrophages, with small islands of dead bone. Acid stain for acid-fast bacilli shows cells loaded with leprosy bacilli.

FIG. 3 (*b*)

X-ray dated 28.I.1958, after one year anti-leprosy treatment, bacillary index 2.6. Patient had no reaction in this interval. X-ray shows more definite osteolytic areas in all the fingers, and more osteolytic changes in the tufts of all the fingers. In addition, there is a sub-articular fracture at the head of the middle phalanx of the ring finger with ulnar angulation of the distal fragment.

FIG. 3 (*c*)

X-ray dated 5.VIII.1960. Patient has had 3 more years of treatment, interrupted repeatedly because of re-current reactions. Smear taken 30.XII.1960 showed bacterial index of 2.12. Skin biopsy done 22.II.1963 shows typical lepromatous leprosy. X-ray now shows

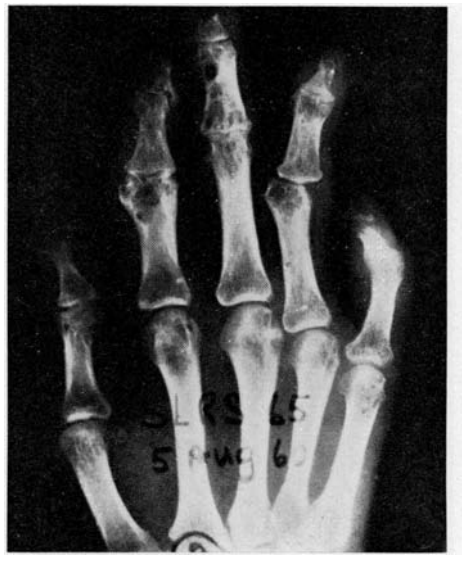

FIG. 3 (*c*)

increase in the size of sub-articular osteolytic areas with some broadening of the proximal phalanx of the middle finger. The fracture at the distal sub-articular area of the middle phalanx of the ring finger (seen in the earlier X-ray) has healed with good continuous trabeculae formation. Angular deformities of proximal interphalangeal joint of ring and little fingers are seen. Some early changes in the head of the index finger metacarpal is present.

Summary: Hand X-ray shows localised areas of lysis of bone showing early changes, moderate changes 3 months later and marked changes 33 months later. Bone biopsy shows lepromatous granuloma.

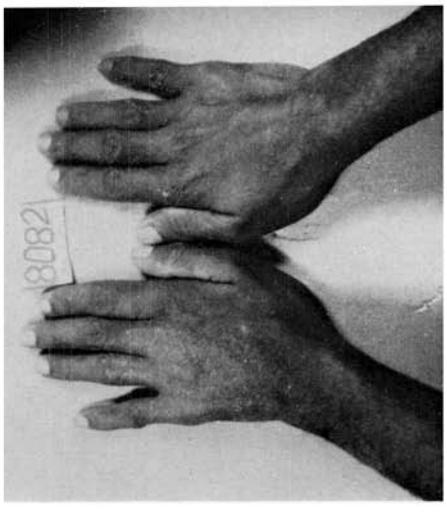

FIG. 4 (*a*)

Case History: Name: M. Age: 29. Sex: Male. H. No. 8082. X. No. 252. Diagnosis: Tuberculoid leprosy. 30.III.1966, patient gave a history of hypopigmented patches over the forehead and limbs of 8 months' duration, and exacerbation of these lesions for 2 months. *On examination:* There were large numbers of well-defined infiltrated hypopigmented lesions with clear-cut edges, a number of them showing central resolution. Large plaque-like lesions over the left hand, with maximum infiltration in the centre. Infiltrated erythematous left ear and enlarged greater auricular nerve were present. There was considerable oedema of both lower limbs, but no swelling of the hands. Skin biopsy from the left shoulder and left forearm showed typical tuberculoid leprosy. Lepromin test was positive.

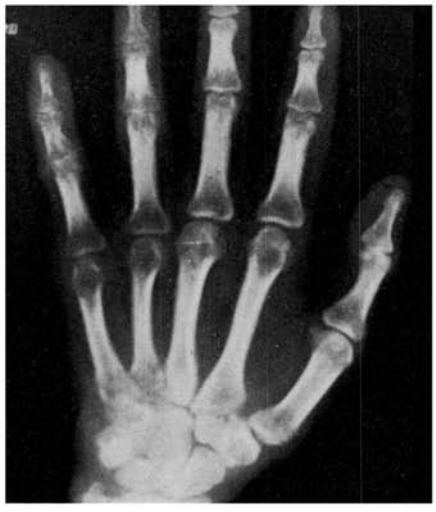

FIG. 4 (*b*)

Histological section of lepromin test site showed changes characteristic of tuberculoid leprosy. Radial cutaneous nerve biopsy also showed tuberculoid leprosy. Skin smears for acid-fast bacilli were negative.

FIG. 4 (*b*)

X-ray taken on 30.III.1966 shows sub-articular osteoporosis of all the phalanges of little and ring fingers. Biopsy taken from the base of the middle finger proximal phalanx shows fibrous tissue and bone with no leprosy lesions.

Summary: Localised severe osteoporosis with no significant microscopic lesions in tuberculoid leprosy during a phase of exacerbation.

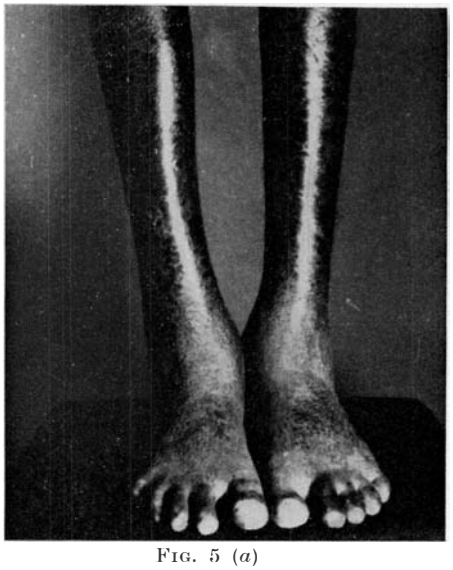

FIG. 5 (*a*)

Case History: Name V.N. Age: 17. SLRS No. 4455. X. No. 683. Lepromatous leprosy. Bacillary index for acid-fast bacilli in the skin smear was 0.62. Duration of disease: 6 years. Generalised fine lepromatous infiltration of trunks and limbs, and nodular infiltration of face, ears and eyebrows. History of repeated reactions, with erythema nodosum leprosum. Swelling

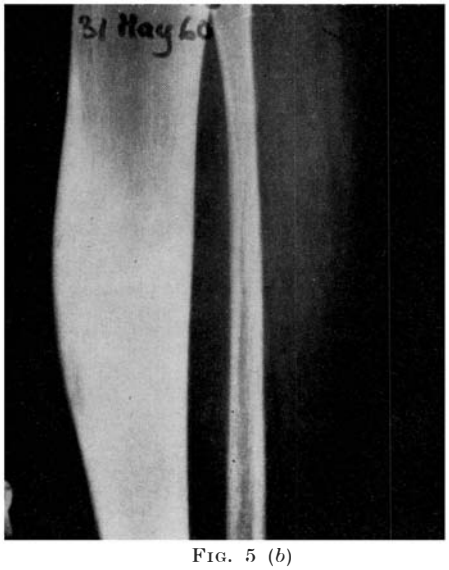

FIG. 5 (*b*)

along the tibial crest, with pain and tenderness. Pain worse at night.

FIG. 5 (*b*)

X-ray No. 683. X-ray taken on 31.V.1960 shows periostitis. Biopsy taken on 6.VI.1960 shows periostitis, due to lepromatous leprosy.

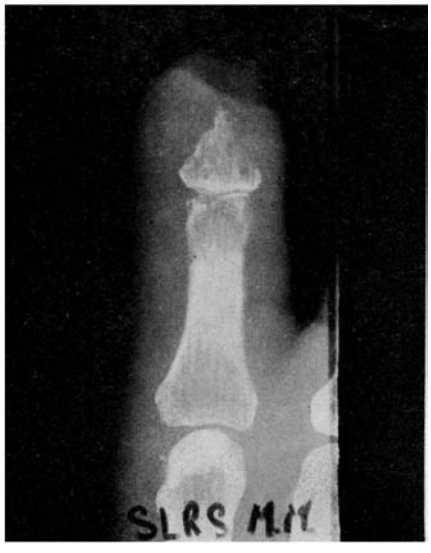

FIG. 6

X-ray of bone changes of the adjoining surfaces of the proximal interphalangeal joint of an index finger following injury and infection in an anaesthetic hand with chronic ulceration and bone changes.

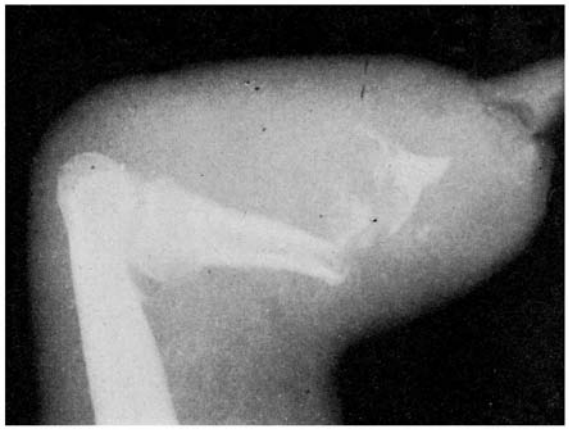

FIG. 7

Example of bony destruction in the hand due to infection and chronic ulceration in anaesthetic fingers, with marked osteolysis, destruction and subluxation at the terminal interphalangeal joint and pathological fracture of the neck of the middle phalanx. There is very little evidence of periosteal reaction in the adjoining bones. Note the soft tissue shortening due to internal derangement and destruction of the architecture of the finger.

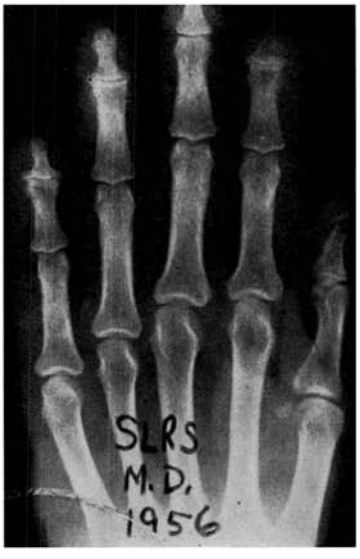

FIG. 8 (*a*)

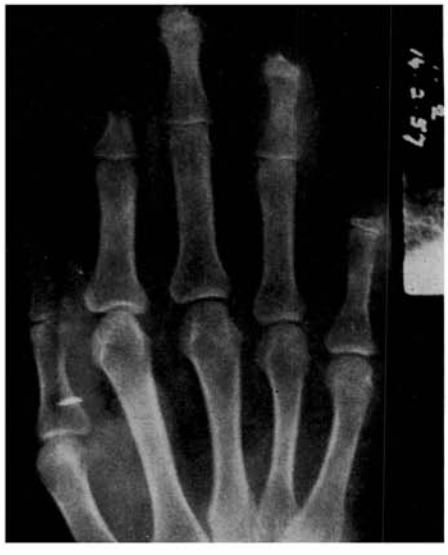

FIG. 8 (*b*)

FIG. 8 (*a*) to (*d*)

Series of X-rays showing the pattern of shortening of the fingers to the level of the metacarpals due to chronic repeated ulceration of the fingers of the anaesthetic hand.

FIG. 8 (*a*)

X-ray shows various degrees of early destruction of the terminal phalanges of anaesthetic finger due to injury and infection. Thumb shows destruction of the terminal tuft, with a loose piece of bone. Index finger: soft tissues of the terminal phalanx are destroyed and shortened up to the level of the base of the terminal phalanx, with the joint line still intact. Note some soft tissue destruction of the radial side of the pulp of the ring finger.

FIG. 8 (*b*)

More advanced destruction due to recurrent episodes of injury and infection with loss of major part of terminal phalanx of long and ring fingers and destruction up to the base of middle phalanx of index and little fingers. Dense soft tissue shadow and mottling of the ring finger indicates presence of infection and osteomyelitis. Note the absence of periosteal reaction.

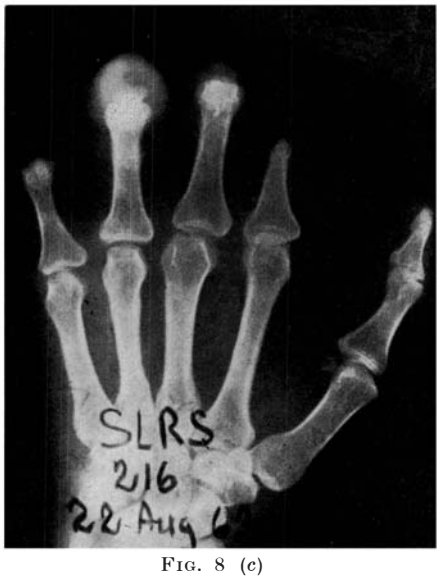

FIG. 8 (*c*)

Gross destruction of the hand, leaving stumps of proximal phalanges from index to little finger. Evidence of infection and soft tissue swelling in the ring finger stump.

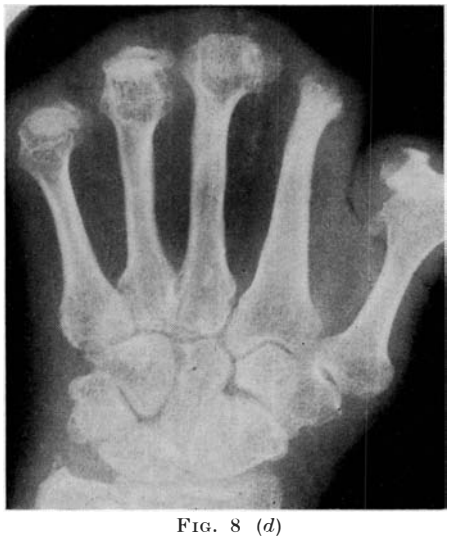

FIG. 8 (*d*)

Complete destruction of the fingers with only metacarpals and bony remnants of proximal phalanges left. (Corn picker's hand.)

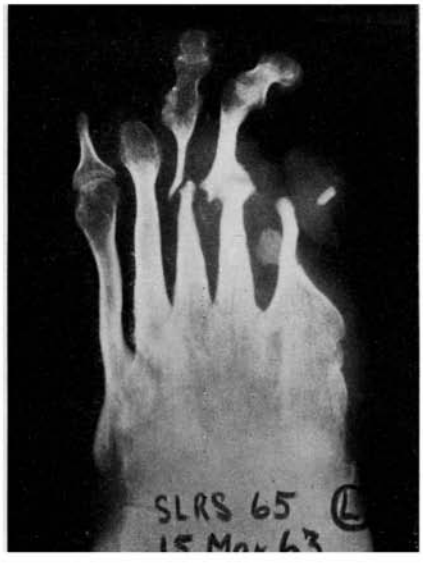

FIG. 9

An example of a foot showing result of trophic ulcerations of all the toes and metatarsal heads resulting in varying patterns of healing in each bone.

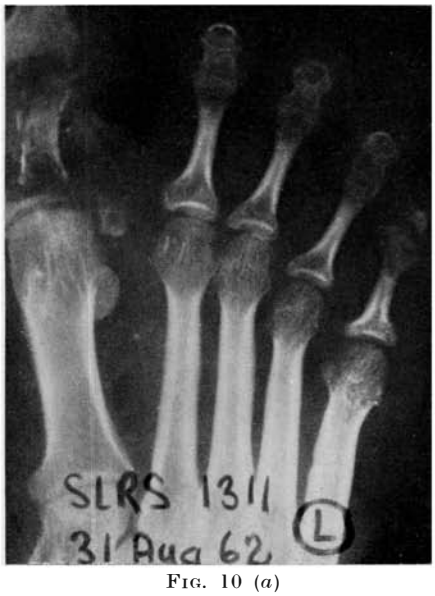

FIG. 10 (*a*)

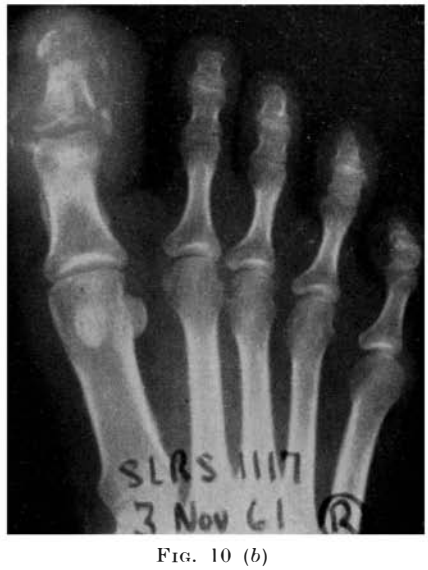

FIG. 10 (*b*)

FIG. 10 (*a*) to (*e*)

Series of X-rays showing pattern of progressive destruction and loss of big toe due to repeated ulceration.

FIG. 10 (*a*)

Acute inflammation due to 'trophic' ulceration under the interphalangeal joint of big toe with early destruction of the adjoining surfaces of bones of the interphalangeal joints. There is gross soft tissue swelling and some periosteal reaction of the proximal phalanx.

FIG. 10 (*b*)

Shows further destruction of the bone with more marked destruction of the proximal phalanx and early destruction of the distal phalanx.

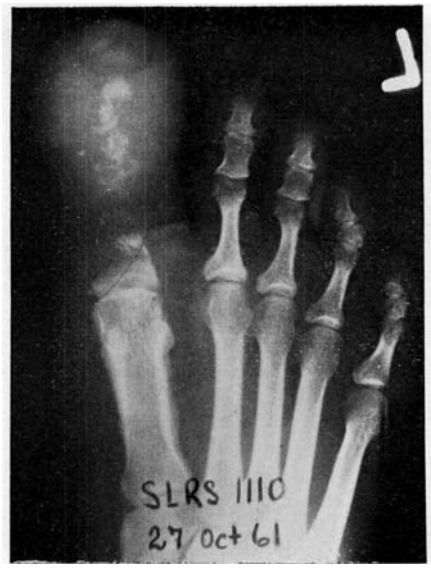

FIG. 10 (*c*)

Shows gross soft tissue swelling and extreme osteolysis of the proximal phalanx. Remnants of pieces of distal phalanx lying in the soft tissue. There is periosteal reaction along the shaft of the proximal phalanx.

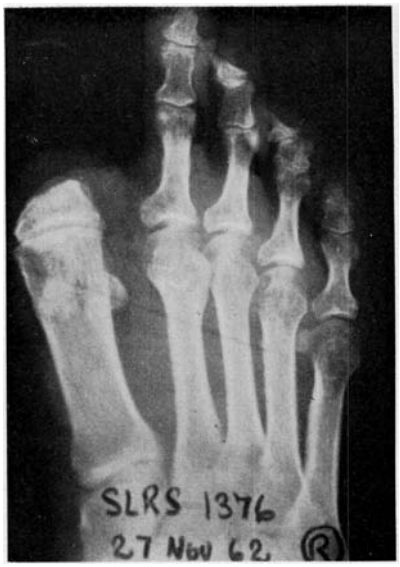

FIG. 10 (*d*)

Shows destruction of the entire big toe up to the base of proximal phalanx, with complete disappearance of the soft tissue. Some uniform thickening of the proximal phalanx, due to increased weight-bearing on this surface.

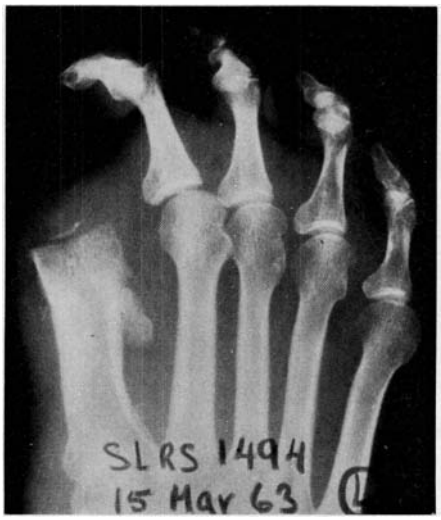

FIG. 10 (*e*)

Shows disappearance of the entire proximal phalanx, including the base of the big toe, due to repeated chronic ulceration on the distal-medial surface. Early changes in the head of the first metatarsal with some changes of the sesamoid bone. Note the deformity of the second and third toes, inclining towards the area of the big toe in the absence of its support.

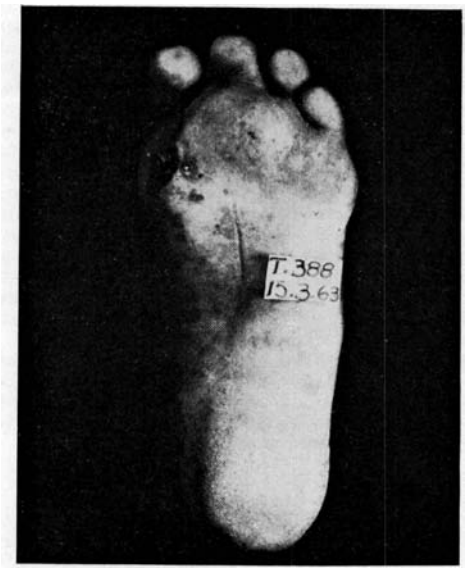

FIG. 10 (*f*)

Clinical pictures of a foot which has lost its big toe due to progressive destruction following chronic ulceration.

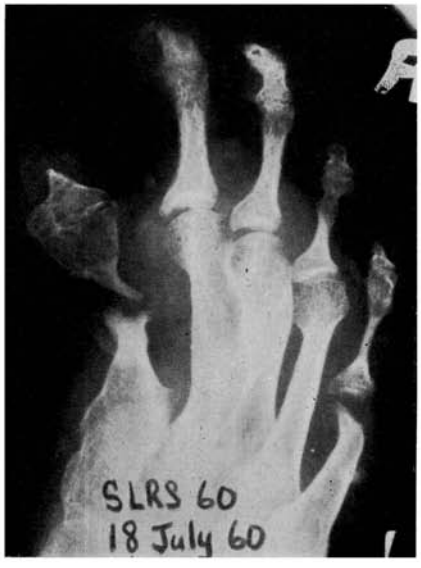

FIG. 11 (*a*)

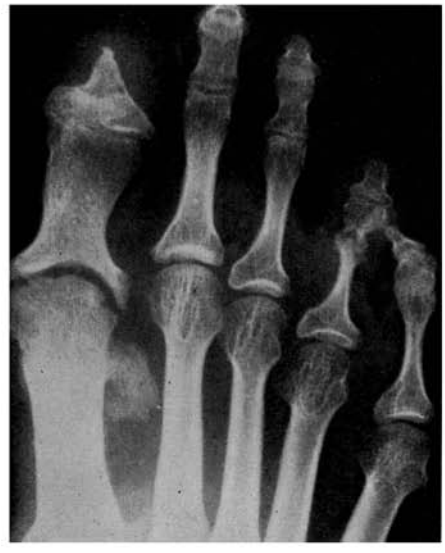

FIG. 11 (*b*)

FIG. 11 (*a*) *to* (*c*)

Case History: Name: M. Age: 35. Sex: Male. SLRS No. 60. Patient with arrested lepromatous leprosy, had anaesthetic feet and bilateral ulnar-median nerve paralysis and glove type of anaesthesia of the upper limb. When seen he gave a history of 5 months' duration of ulceration under the first metatarsal head and tip of big toe (July, 1955). Ulcer was healed with bed rest and rest in plaster cast and special footwear. However, patient reported every few months with recurrent ulceration in the same area. The ulcer later led to bone. Bone could be felt at the end of a probe and occasionally glairy synovial fluid discharged profusely from the ulcer on probing. There were about 5 recurrences a year, and at each recurrence further shortening of the big toe was noted. Patient was seen in November, 1959, again with gross swelling and a deep large ulcer under the first metatarsal, exposing three-fourths of the length of the bone. This sequestrated, and was removed, after which the ulcer healed.
Summary: Three X-rays taken over a 5-year period documented progressive destruction of great toe and first metatarsal associated with recurrent 'trophic' ulceration in a patient with arrested lepromatous leprosy having residual anaesthesia of feet.

FIG. 11 (*a*)

X-ray taken on 25.VII.1955, shows narrowing of joint space and irregularity of margins of metatarso-phalangeal joint of great toe. There are changes in the bit toe sesamoids and in the terminal phalanx of the great toe.

FIG. 11 (*b*)

Eighteen months later, base of proximal phalanx of great toe more sclerotic; narrowing of adjacent metaphysis more marked. In this view, the great toe sesamoid appears fused to the metaphysis of the metatarsal.

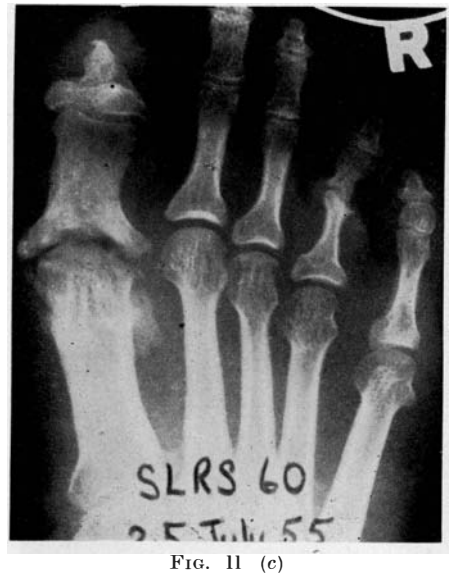

FIG. 11 (*c*)

FIG. 11 (*c*)

Five years later, X-ray shows gross shortening of the great toe with destruction of most of the proximal phalanx and first metatarsal head. Note the new ulcer under the fourth and fifth metatarsal heads and under the pulp of the other toes, resulting in early destruction in these areas.

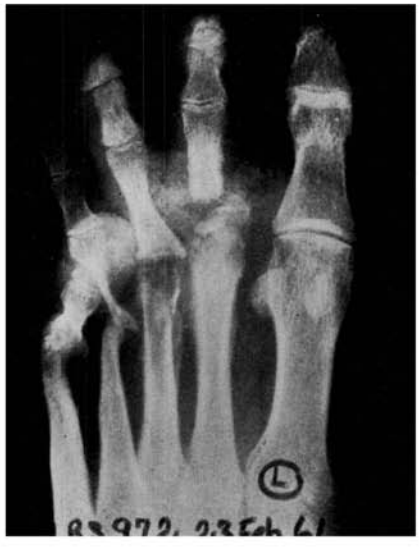

FIG. 12 (*a*)

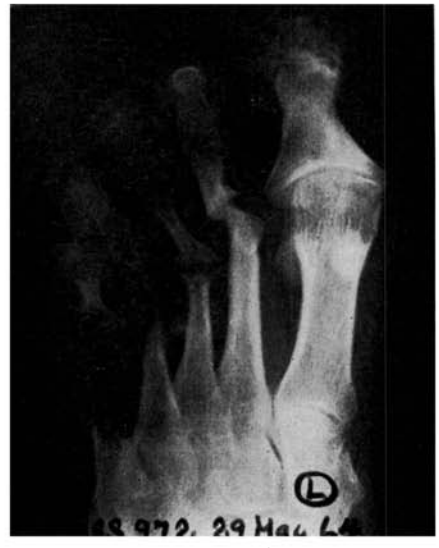

FIG. 12 (*b*)

FIG. 12 (*a*) and (*b*)

Case History: Name: M.A. Age: 39. Sex: Male. SLRS No. 5044. X. No. 972. Patient with arrested lepromatous leprosy and negative skin smears. Disease 5 years' duration. Onset with fissures in left sole. Patient was admitted 31.I.1961 with swollen left foot and plantar ulceration over the lateral metatarsal heads which was initially treated with antibiotics, bed rest and elevation and later in plaster immobilisation. These ulcers took 11 months to heal (November, 1961). Frequent recurrences during the next 3 years. The second X-ray was taken dated 29.V.1964.

FIG. 12 (*a*)

X-ray on 23.II.1961, shows destruction of the second, third, fourth and fifth metatarsal heads, resulting in loss of alignment of corresponding toes and destruction of metatarso-phalangeal joints.

FIG. 12 (*b*)

X-ray taken on 29.V.1964, after a 3-year interval, shows gross shortening of the metatarsals of the lateral foot with shortening of the toes. Note the different patterns of healing after ulceration. At the second metatarso-phalangeal joint level there is fusion. At the third toe there is fibrous ankylosis with deformity. Fourth toe shows extreme concentric absorption with probably fibrous connection between the narrowed metatarsal base and the proximal phalanx. The fifth metatarso-phalangeal joint shows a large gap between the remnants of the fifth toe and the fifth metatarsal with broadening of both the edges.

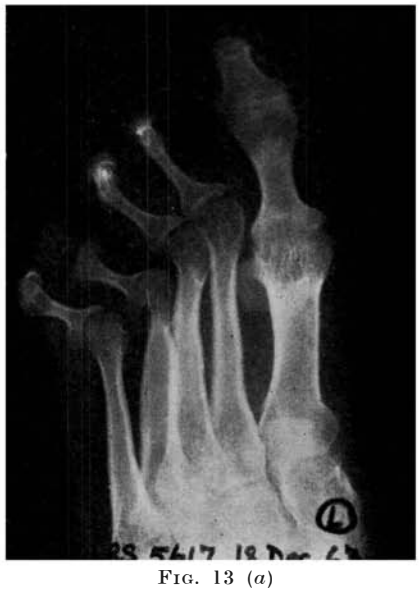

FIG. 13 (*a*)

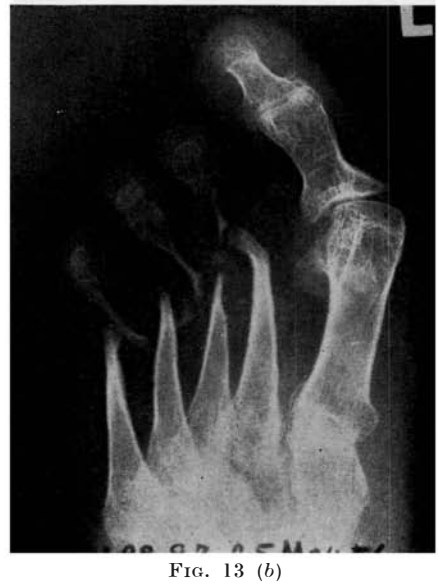

FIG. 13 (*b*)

X-ray of a patient with ulceration of the metatarsal heads and destruction of the inferior capsule and deformity of the metatarso-phalangeal joint.

Late result of chronic ulceration of the metatarsal head and severe concentric absorption of the adjoining bones.

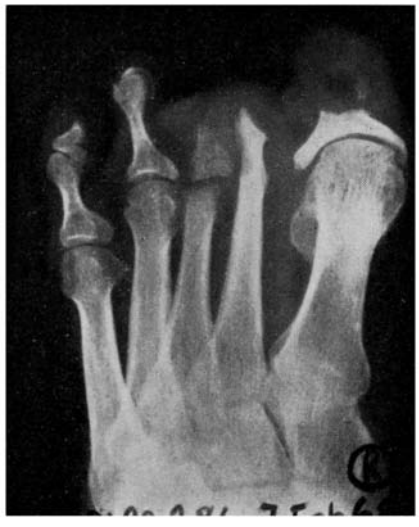

FIG. 14 (*a*)

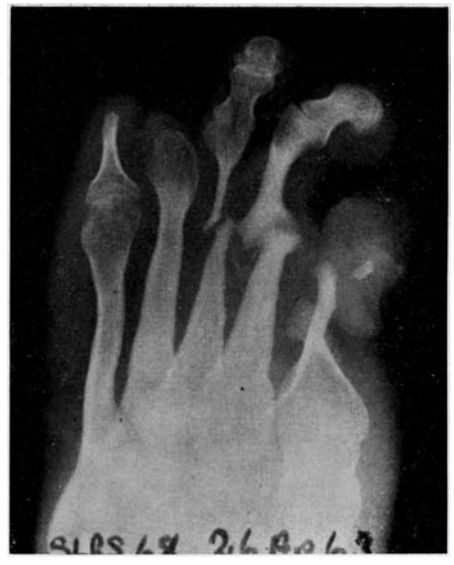

FIG. 14 (*b*)

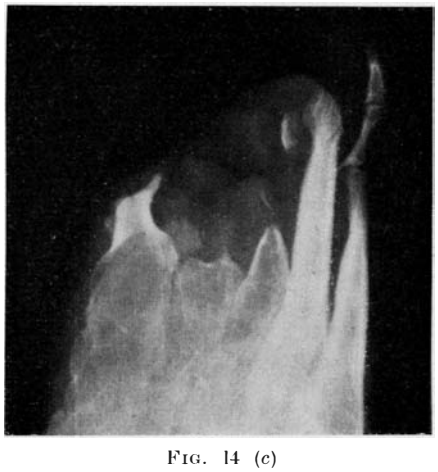

FIG. 14 (*c*)

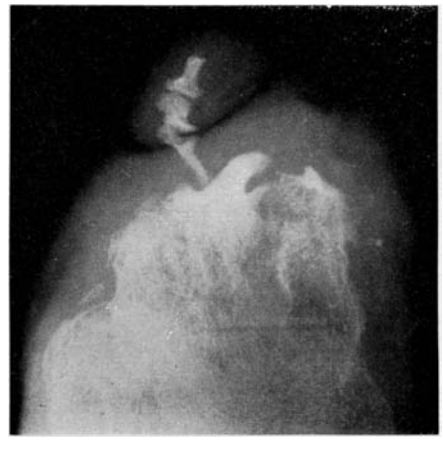

FIG. 14 (*d*)

FIG. 14 (*a*) to (*d*)

FOREFOOT

X-rays of a foot from 4 different patients demonstrate a pattern of progressive destruction and gross shortening of the forefoot. Scattered areas of destruction in the forefoot due to multiple areas of trophic ulcerations progressing to destruction and shortening of the entire forefoot. Finally, only the tarsals are left for weight-bearing. These changes are most commonly associated with an uncorrected foot-drop of long duration. In a shortened foot, the present of foot-drop may not be appreciated by the casual observer.

FIG. 14 (*a*)

X-ray shows that all the metatarsals are full length. The second metatarsal head is fused to the base of the proximal phalanx. The great toe sesamoids appear to be fusing with the head of the first metatarsal. The great toe metatarso-phalangeal joint is narrowed, with gross changes in the remnant of the proximal phalanx.

FIG. 14 (*b*)

First, second and third metatarsals show varying degrees of shortening and concentric absorption. There is progressive shortening of the forefoot.

FIG. 14 (*c*)

Severe shortening of the forefoot. Only the fourth metatarsal is nearly full length.

FIG. 14 (*d*)

Complete destruction of forefoot. Remaining toe is probably fourth. Remaining bones are mid-foot tarsals and fused remnants of bases of metatarsals.

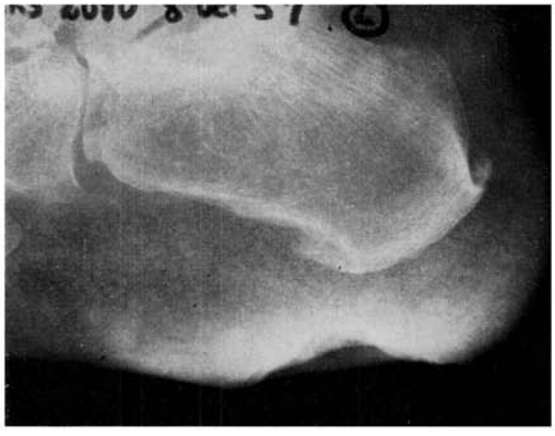

FIG. 15 (*a*)

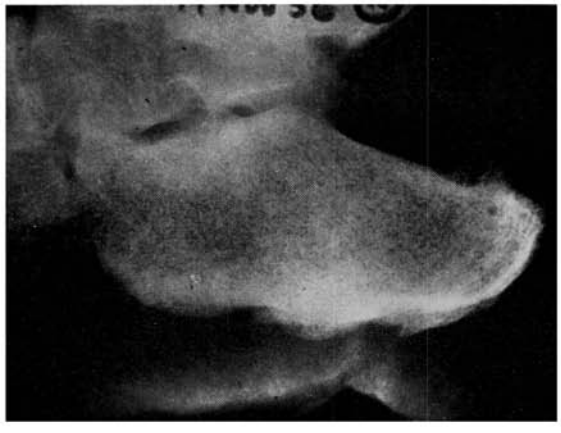

FIG. 15 (*b*)

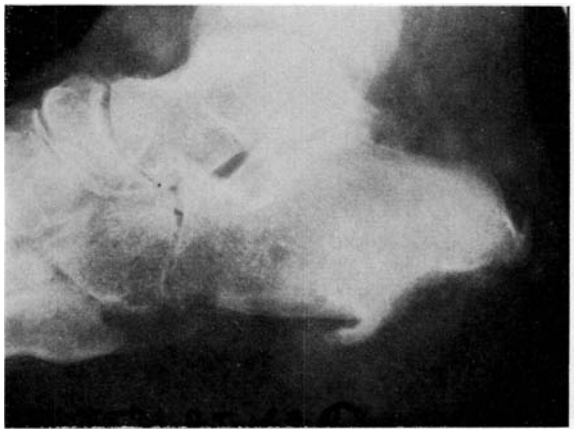

FIG. 15 (*c*)

FIG. 15 (*a*) to (*c*)
Demonstrates destruction of the calcaneum caused by progressive hind-foot ulcer.

FIG. 15 (*a*)
Showing calcaneal ulcer under the tuberosity (inferior) of the calcaneum, with mainly soft tissue destruction.

FIG. 15 (*b*)
Showing soft tissue destruction and scarring leading to the bone, with extensive destruction of the inferior surface of the calcaneum and loss of a quarter of the height of the calcaneum.

FIG. 15 (*c*)
Showing destruction of the posterior-inferior part of the calcaneum, with involvement of the adjacent bone—sclerosis and loss of trabecular pattern.

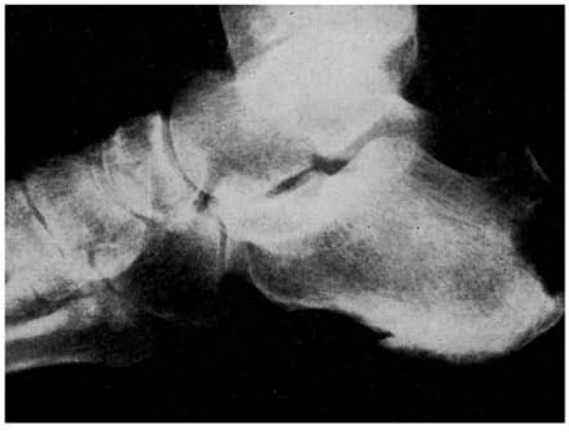

FIG. 16 (*a*)

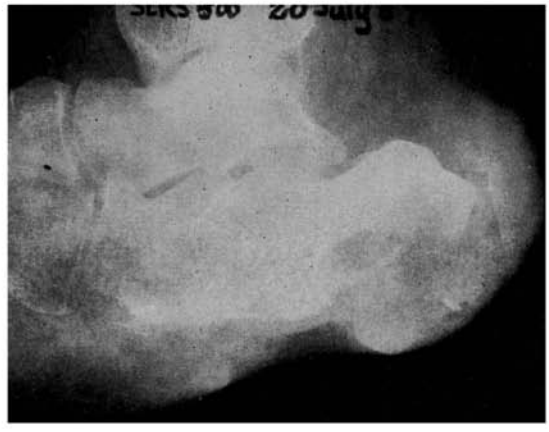

FIG. 16 (*b*)

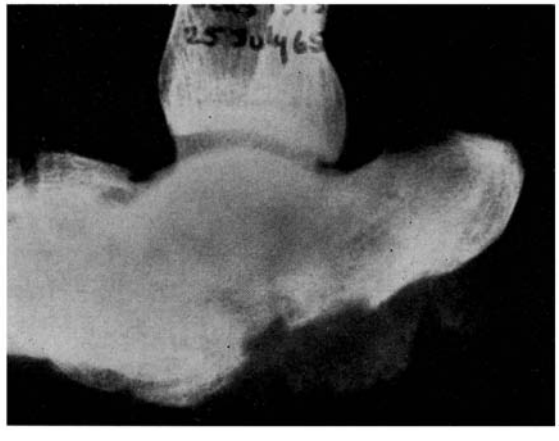

FIG. 16 (*c*)

FIG. 16 (*a*) to (*c*)

COMPLICATIONS OF HIND-FOOT ULCERATION

FIG. 16 (*a*)

Showing avulsion of the posterior tubercle at the tendo achillis' insertion following chronic calcaneal ulcer.

FIG. 16 (*b*)

Showing gross destruction of the soft tissues with deep involvement of the calcaneum, extending almost to its superior cortex. Pathological fracture, now healed, producing equinus deformity of the posterior half of the calcaneum, resulting in a lengthened and abnormally shaped calcaneum. Note the ulcer extending up to the bone, with very little soft tissue intervening.

FIG. 16 (*c*)

Showing mid-foot collapse due to an anterior calcaneal ulcer destroying the short spring ligament, sustentaculum tali and other supporting structures for the head of the talus between the calcaneum and the navicular. The calcaneum is displaced posteriorly and upwards and the unsupported head of the talus tilts downwards towards the ulcer. Part of the talo-calcaneal joint is destroyed.

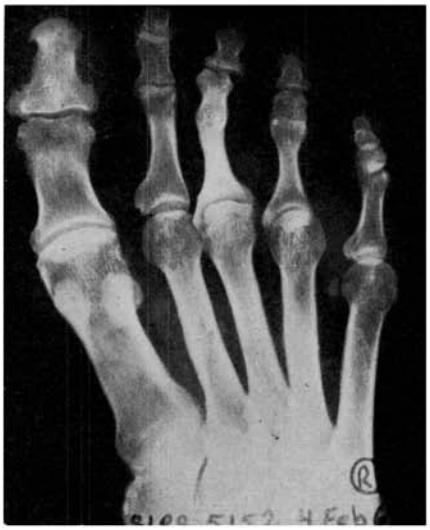

FIG. 17 (*a*)

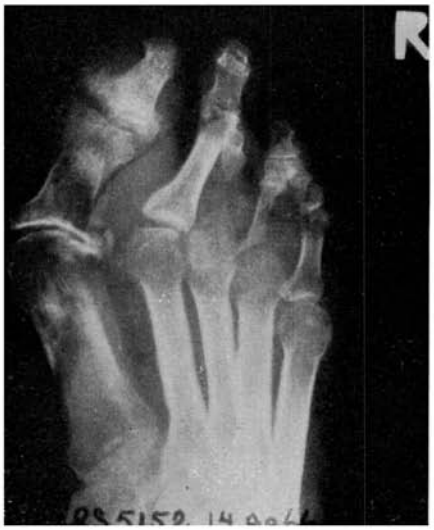

FIG. 17 (*b*)

FIG. 17 (*a*) to (*c*)

Demonstrates need for maintaining the *architectural balance* in anaesthetic feet. Removal of even a small part of an essential component of the architecture of the foot results in the production of new areas of stress and pressure. These become vulnerable to ulceration, which results in a gross pattern of deformity.

Case History: Name: R.N. Age: 30. Sex: Male. SLRS No. 5152. Tuberculoid leprosy, with anaesthetic foot; presented during April, 1961, with deep fissure under right third toe. Duration: 2 months. Healed after plaster of Paris immobilisation. Third toe was clawed.

FIG. 17 (*a*)

February, 1963, again presented with an ulcer under the third toe. Foot immobilised in a plaster slab and later in a plaster of Paris walking cast. Ulcer healed and patient discharged. X-ray taken on 4.II.1963 shows sclerosis of the proximal phalanx and involvement of proximal interphalangeal joint of the right third toe. Patient presented again with an acute episode of swelling and infection of the third toe with purulent discharge. Bare bone felt through a sinus. Sloughed tendon was visible. One week later, sequestrectomy was performed, the proximal phalanx and most of middle phalanx being removed. Ulcer healed and patient discharged.

FIG. 17 (*b*)

Patient was admitted with a large gangrenous ulcer on the medial side of right fore-foot. The remnant of the third toe was a shrunken, flail appendage withdrawn proximally and displaced dorsally. The second and great toes had fallen into the gap left by the third toe, which resulted in marked valgus deformity. Patient wore a sandal with tight broad straps which pressed on the medial surface of the metatarso-phalangeal joint of the hallux valgus, which gave rise to a large area of necrosis. Soon the gangrenous area separated, exposing large areas of the underlying bones. X-ray taken on 14.IV.1966 shows valgus deformity of great and second toes, with large area of dead bone on either side of the metatarso-phalangeal joint of the great toe. The ulcer took 3 months to heal in a posterior slab, during which time most of the fragments of dead bone were extruded.

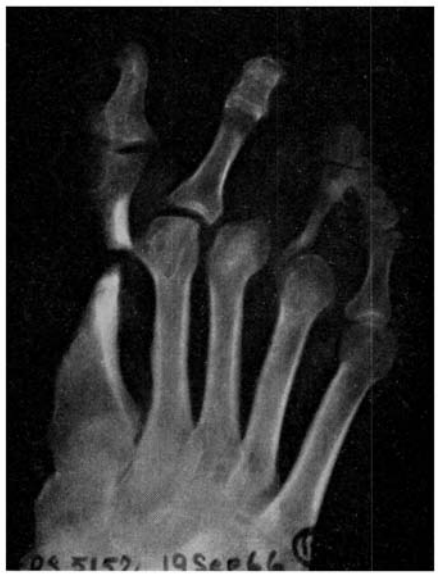

FIG. 17 (*c*)

FIG. 17 (*c*)

X-ray of the same patient taken 19.IV.1966 shows total loss of adjoining surface of the first metatarso-phalangeal joint, resulting in the loss of large area of weight-bearing surface of the medial ray of the foot. The middle of the proximal phalanx now lies at the level of the neck of the second metatarsal. It is difficult to believe that the gross deformity of the foot is a consequence of the loss of proximal part of the third toe.

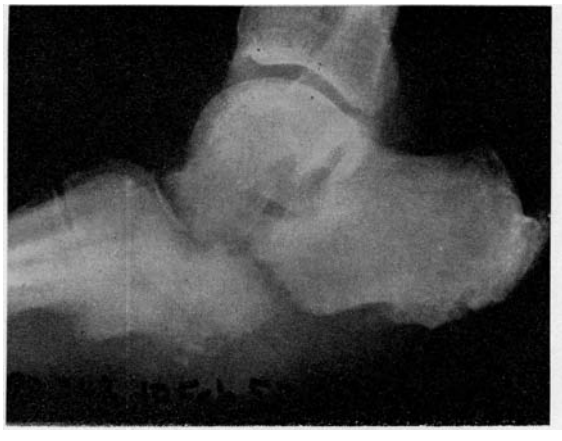

FIG. 18 (*a*)

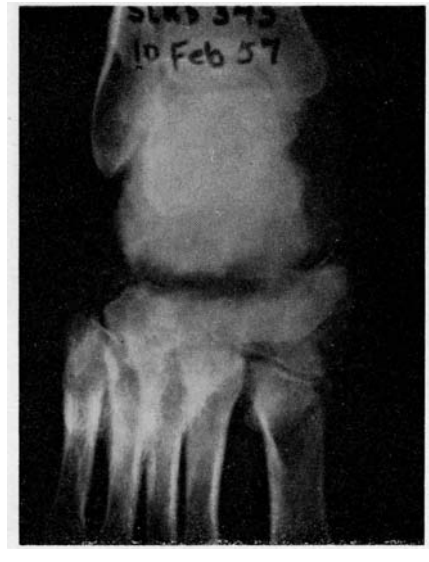

FIG. 18 (*b*)

FIG. 18 (*a*) to (*c*)

Progressive destruction of the mid-foot, due chiefly to loss of soft tissue support, which assists the maintenance of mid-foot architecture.

Case History: Name: R. Age: 45. Sex: Male. SLRS No. 343. Tuberculoid leprosy of 10 years' duration, beginning with numbness of left heel. Early in the course of the disease, an ulcer developed on the left heel, which became chronic. The ulcer became chronically infected, and the infection eventually destroyed the mid-foot bony arch and left the foot clinically unstable.

FIG. 18 (*a*) and (*b*)

Shows a heel ulcer which had extended forward to involve calcaneo-cuboid and calcaneo-navicular joints, with the loss of the short spring ligament. The sustentaculum tali of the calcaneum is detached from the forefoot and ceases to support the head of talus. The head of talus is pushed downwards into the gap, because of the transmission of the body weight through this line of force. The calcaneum, having lost its anterior attachments, is pulled backwards and upwards by the unopposed action of the tendo achillis. The medial arch of the foot is reversed, and the mid-foot becomes the maximum weight-bearing area. The boat-shaped foot renders the tarsals vulnerable to 'trophic' ulceration.

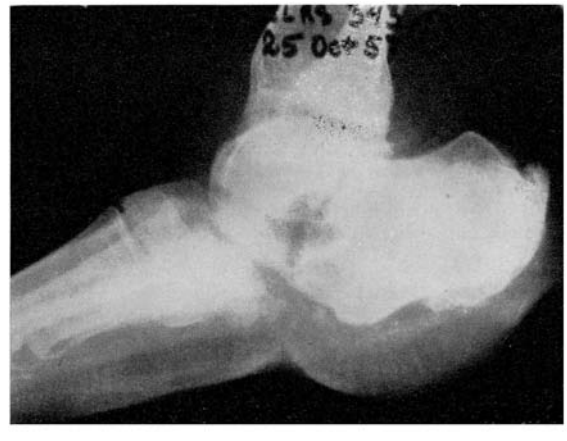

FIG. 18 (*c*)

X-ray taken 25.X.1957, shows loss of the head of the talus, navicular and most of cuboid, due to 'trophic' ulceration at the mid-foot. Calcaneum shows equinus deformity. The soft tissue shadow shows deformity of the contour of the sole.

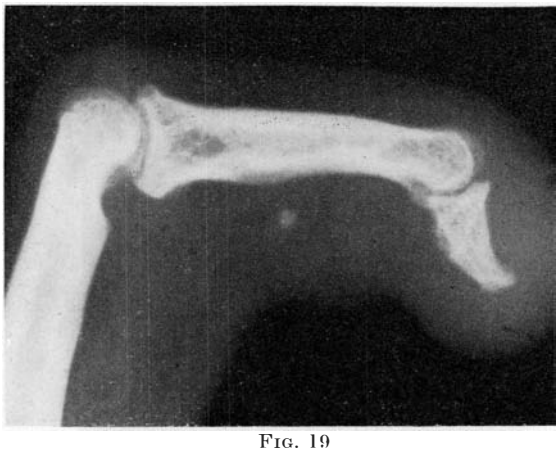

FIG. 19

FIG. 19

Case of ulnar paralysis resulting from nerve destruction above the elbow, resulting in a long period of clawing, with contracture of soft tissue and some capsular contracture of the anterior part of the proximal inter-phalangeal joint. X-ray shows early subluxation of the base of the middle phalanx with 'ditching' of the anterior surface of the neck of the proximal phalanx due to pressure atrophy from the contiguous surface of the base of the middle phalanx.

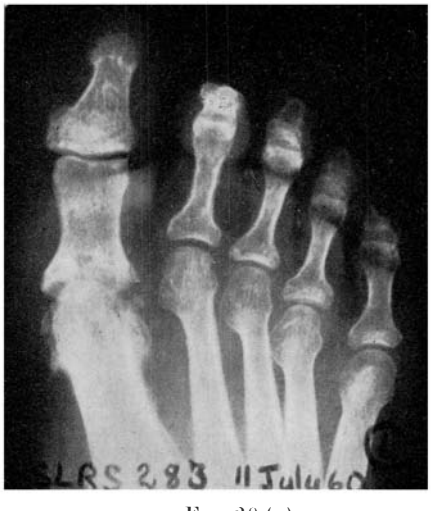

FIG. 20 (*a*)

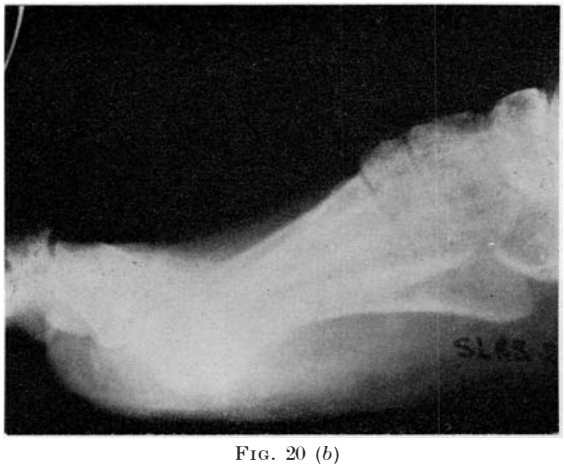

FIG. 20 (*b*)

FIG. 20 (*a*) to (*c*)

Anaesthetic feet with posterior tibial nerve paralysis and early clawing.

FIG. 20 (*a*) and (*b*)

Antero-posterior and lateral view of a foot (SLRS No. 283) shows clawing of toes with hyperextension and dorsal subluxation of the proximal phalanges. Note soft tissue shadow of 'trophic' ulceration under the first metatarsal head with early bone changes on the inferior surface of the first metatarsal head in the lateral view. Antero-posterior view show X-ray changes of the adjacent sides of the first metatarso-phalangeal joint with some early destruction and fragmentation of the articular surface of these 2 bones.

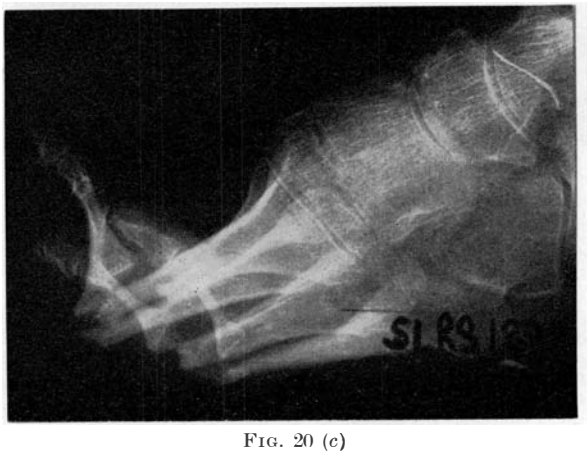

FIG. 20 (*c*)

FIG. 20 (*c*)

Late result of 'trophic' ulceration over the metatarsal heads with posterior tibial nerve paralysis and claw toes. X-ray shows complete destruction of all the metatarsal heads with dorsiflexion and subluxation of the proximal phalanges of all the claw toes. The neck of the metatarsals is now the most prominent weight-bearing surface.

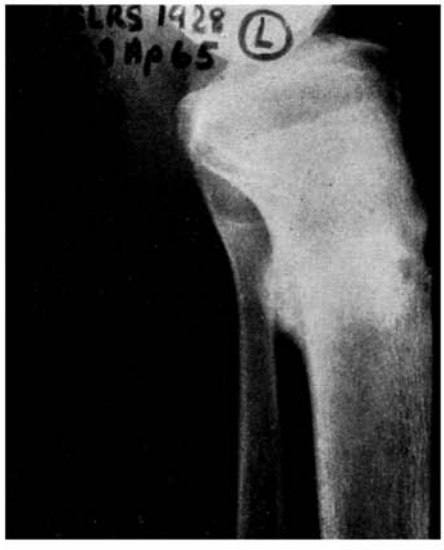

FIG. 21 (*a*)

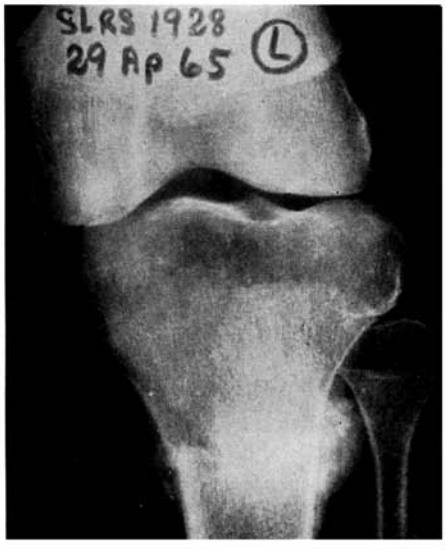

FIG. 21 (*b*)

FIG. 21 (*a*) and (*b*)

Case History: Name: B. Age: 21. Sex: Male. H. No. 1928. Dimorphous leprosy, with chronic deep calcaneal ulceration of the left foot and complete loss of soft tissue under the calcaneum following accidental burn. Had 4 months' strict bed rest, followed by cross-leg flap for the heel, for which both legs were completely immobilised in a plaster cast for 3 weeks. Patient had a further period of 6 weeks' rest before being allowed to walk. Had a total of 6 months of bed rest and/or immobilisation. On starting ambulatory treatment, patient complained of insidious onset of pain at the upper end of tibia; after the first 7 days, X-ray showed typical picture of march fracture with periosteal reaction in a fairly osteoporotic bone.

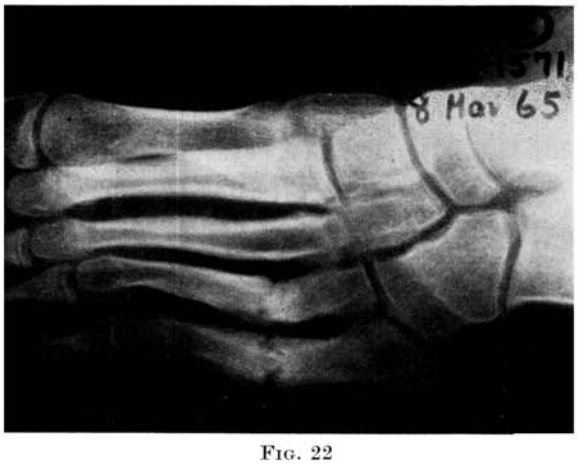

FIG. 22

FRACTURE METATARSAL

Case History: Name: K. Age: 18. Sex: Male. H. No. 3908. X. No. 1571. Dimorphous leprosy, with negative skin smears. Disease complicated by peripheral neuritis, treated with long-term steroids. Left foot-drop was partially supported with an above-ankle boot. Patient gives no history of a fall, injury, swelling or discomfort at any time during the past one year. X-ray: Routine pre-operative X-ray 8.III.1965, prior to tibialis posterior transfer, showed old healing fractures of fourth and fifth metatarsals. Previous X-ray taken 11 months earlier shows no evidence of fractures.

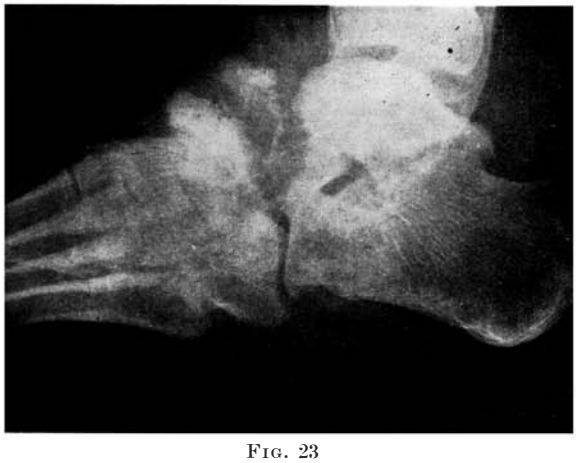

FIG. 23

Case History: Name: M. Age: 36. Sex: Male. H. No. 2544. X. No. 311. Lepromatous leprosy. Negative skin smear 6.I.1959. History of left foot-drop with plantar ulceration, for which he was treated by repeated plaster immobilisation. Had tibialis posterior transfer on 30.III.1959. The foot was immobilised in maximum dorsiflexion post-operatively. Patient walked on this dorsiflexed plaster and complained of severe pain, following which plaster was removed. This X-ray taken 7 months later, shows fracture proximal neck of talus followed by avascular necrosis and destruction of the body of the talus.

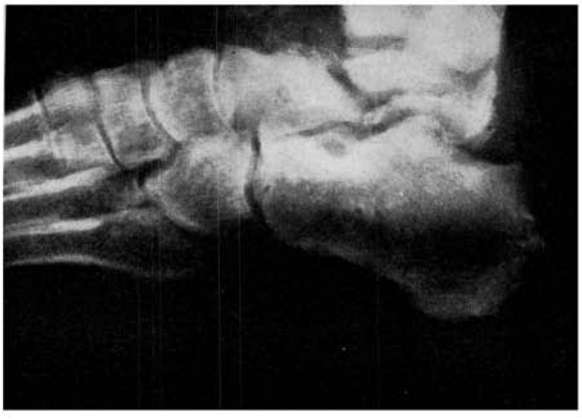

FIG. 24 (*a*)

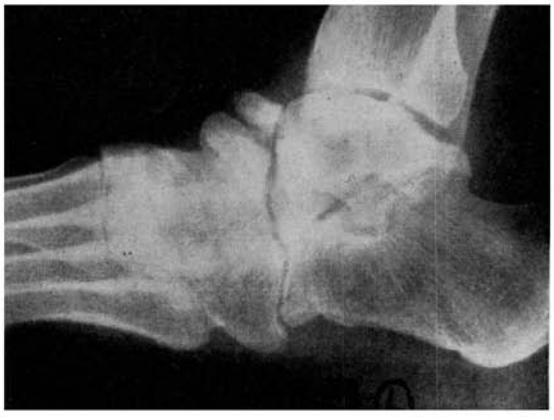

FIG. 24 (*b*)

FIG. 24 (*a*) and (*b*)

Case History: Name: P. Age: 22. Sex: Male. H. No. 2028. Admitted on 2.VIII.1957 with bilateral foot-drop and anaesthesia of lower extremities. Was treated by repeated plaster immobilisation for plantar ulceration, followed by tibialis posterior transfer and immobilisation of the foot in maximum dorsiflexion. Post-operatively, patient complained of marked swelling and some discomfort of the left foot after walking on dorsiflexed walking cast.

X-ray: X-ray shows destruction of the head of the talus and navicular. Treated by immobilisation for a period of 6 months, following which the adjoining parts of the bone showed healing. Patient later had an abnormal flail sub-talar joint which needed arthrodesis.
Summary: Fracture neck of talus and crush fracture of navicular, due to repetitive micro-traumata acting on osteoporotic bones: i.e., walking on an abnormally postured foot.

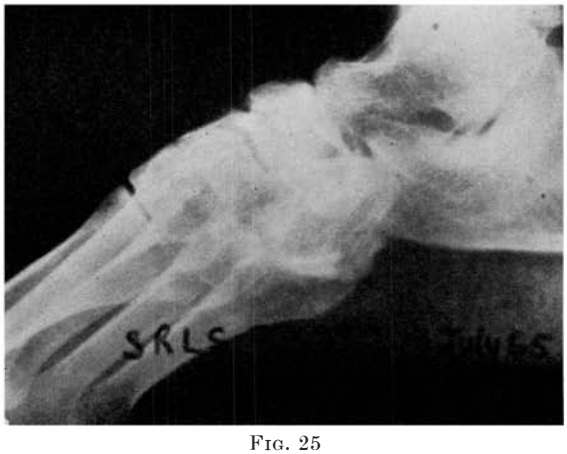

FIG. 25

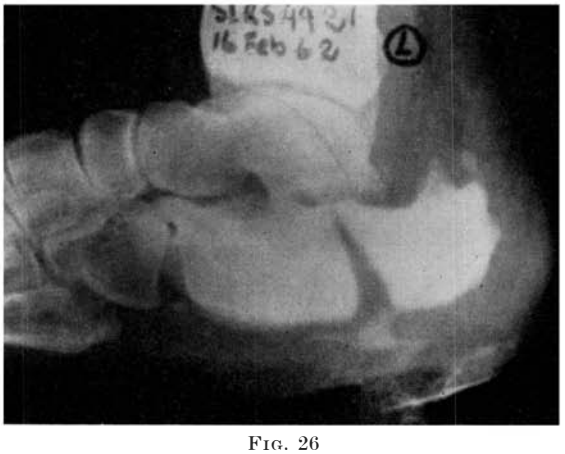

FIG. 26

Case History: Name: R. Age: 26. Sex: Male. No. 5898. Dimorphous leprosy (with negative skin smears), bilateral anaesthetic feet. Patient had foot-drop, for which tibialis posterior transfer was performed, giving a good result. Had a period of post-operative immobilisation, and a later period because of ulceration of the tip of the second toe. Subsequently he had a a minor twist and fall, following which he complained of slight discomfort on walking long distances.
On examination: There was localised warmth and slight swelling over the talo-navicular area, which subsided on complete bed rest in a posterior slab over a period of 48 hours. Though initial X-rays did not reveal the fracture, it was clinically assumed to exist, and treated with a non-weight-bearing ischeal-bearing caliper.
X-ray shows crack fracture across the navicular. This X-ray, which was taken 7 months after the occurrence of fracture, shows the fracture line still present with no evidence of healing. Subsequently, the patient was allowed to weight-bear for a period of 4 weeks, after which the navicular collapsed into half its width (not shown).

FIG. 26

Case History: Name: A.K. Age: 30. Sex: Female. H. No. 4921. Arrested lepromatous leprosy, with negative skin smears. Patient was treated for a chronic heel ulceration for 1½ years with repeated plaster of Paris immobilisation. Admitted on 26.I.1962 with an ulcer on the heel 1cm. × 1 cm. with gross swelling, and redness of few days' duration. No history of trauma. X-ray shows a fracture across the calcaneum The calcaneum is sclerosed and shows loss of normal trabecular pattern. The posterior half of the calcaneum is pulled upwards by the tendo achillis. The site of insertion of the tendo achillis is already deformed. A loose sequestrum lies inferiorly in the soft tissue. There is also evidence of underlying soft tissue involvement, due to 'trophic' ulceration.
Summary: Pathological fracture of the calcaneum in an ulcerated anaesthetic foot. The patient was unaware of the fracture.

Lep. Rev. (1968) **39**, 3, 171

An Injection Solution of Dapsone

T. M. FRENCH, B.PHARM.
Pharmaceutical Department, University College Hospital, London

Dapsone is normally administered orally but occasionally oral therapy cannot be tolerated and a preparation suitable for injection is required. Until recently a preparation for intramuscular injection was available under the name of Avlosulfon Soluble but it is no longer marketed. Avlosulfon Soluble consisted of a water soluble derivative of Dapsone which is not easy to prepare in the hospital pharmacy. Dapsone itself has a very low solubility in water and the only official formulation, which was contained in the British National Formulary 1963, consisted of a suspension of Dapsone in arachis oil. Oily injections are however inconvenient to use and may irritate the tissues.

The following formulation contains Dapsone dissolved in a water-miscible vehicle.

Dapsone	5 g. (100 mgm. in 2 ml.)
Absolute Alcohol	40 ml.
Benzyl Alcohol	5 ml.
Propylene Glycol to	100 ml.

The Dapsone is dissolved in the absolute alcohol, benzyl alcohol added and then propylene glycol to volume. The solution, after filtration and filling into 2 ml. ampoules, is sterilised by autoclaving. Because the efficiency of autoclaving is much reduced in the absence of water the ampoules are sterility tested before use. Work is in progress to determine whether water can be introduced into the formulation without affecting stability, thus increasing the efficiency of the sterilisation process.

This solution is suitable for intramuscular injection, the benzyl alcohol being incorporated to reduce pain on injection. After storage for 9 months in the dark, analysis of the solution shows no significant loss of potency, though slight darkening occurs; the therapeutic activity is also unimpaired after this time.

ACKNOWLEDGEMENT

My thanks are due to Dr. W. H. Jopling, Consultant Leprologist, Hospital for Tropical Diseases, who originally encouraged this work, and has commented on its therapeutic efficacy.

Letters to the Editor

Dear Sir,

In leprosy patients with a 'triple nerve' paralysis of the hand (i.e., a high radial nerve paralysis plus a high ulnar and low median nerve paralysis) one of the great problems in any reconstructive surgical procedure is to overcome the persistent tendency of the hand to go into ulnar deviation. This tendency is hard to understand because the flexor and extensor carpi ulnaris muscles are paralysed, leaving the flexor carpi radialis unopposed in its action, so that one would anticipate, as more likely, a tendency to go into radial deviation. The following case is of interest in that it offers an explanation of this problem.

A female patient, aged 23, had been doing some extra cooking involving a lot of stirring. Following this, she developed pain in the forearm, and found it difficult to straighten the 2nd, 3rd and 4th fingers. There was tenderness over the corresponding forearm flexor muscles. The patient was much more comfortable if the wrist was in ulnar deviation. The long flexor tendons of the 2nd, 3rd and 4th fingers were in spasm and on attempting to straighten the fingers, the ulnar deviation would increase, without any contraction of the flexor carpi ulnaris. This suggests that the direction of the long flexors to these fingers is such that when acting by themselves they not only flex the fingers, but also pull the wrist into ulnar deviation.

In 'triple paralysis' of the hand in leprosy as described above, these three long flexors, supplemented by the flexors to the 5th finger, would almost certainly overpower the lone flexor carpi radialis with the resulting ulnar deviation, which is so troublesome. This tendency would also be increased when the flexor carpi radialis is transferred, for instance, as a motor to the extensor tendons.

FRANK I. TOVEY

Holdsworth Memorial Hospital,

Mysore.

9th April, 1968.

Dear Sir,

What Effects have Oral Contraceptives on Lepromatous Leprosy?

It is known that the administration of iodine to leprosy patients may induce erythema nodosum (ENL) and exacerbation of the disease within a few days. On the other hand, corticosteroids improve the condition during its active phase within a short period of time.

During the bacterio-positive stage of leprosy, contraception is strongly indicated because of danger of infection for the child through postnatal contact. Oral contraception is a most reliable and convenient contraceptive method. However, as the hormonal balance of lepromatous patients is known to be unstable owing to the involvement of the suprarenals, the administration of oral contraceptives, which have more or less pituitary-inhibiting and other endocrine effects, might have adverse effects on the disease. In order to clarify this point, we have performed a trial with norethisterone acetate ethinyl oestradiol* (N.A.E.O.) in a series of 20 lepromatous women, and a control group of 10 of about the same average age and the same stage of the disease.

Simple laboratory tests (such as erythrocyte sedimentation rate (E.S.R.), leucocyte count, haemoglobin estimation, urinary albumin) which could easily be repeated under field-conditions, were performed before, during and after the 3 months' trial in all patients. The E.S.R. is a useful test in this connection because it indicates exacerbation of the condition, particularly in patients with a history of ENL (which is generally preceded by an accelerated E.S.R.).

Before the trial, both groups discontinued standard treatment with DDS or Promine for one month. The test group was then put on N.A.E.O. for one month. No difference in frequency of E.N.L. in either group could be observed. DDS or Promine (one patient) was then continued for a further 2 months. Fre-

quency of reaction (ENL) and bacteriological results showed no significant difference between the two groups.

In summary, N.A.E.O. seems to exert neither adverse nor beneficial effects on lepromatous leprosy and, hence, seems to be a safe drug in women with lepromatous leprosy. Further studies on a large scale appear to be called for.

J. WALTER.
Ministry of Public Health,
Devavesem Palace,
29*th April*, 1968 Bangkok, Thailand.

* ANOVLAR (Schering A.G.)

Abstracts

The following 16 abstracts are reprinted, with permission from *Trop. Dis. Bull.*, 1968, **65**, 3:

1. **Health education in leprosy—Kerala's efforts in the field,** by T. N. N. BHATTATHIRIPAD. *Lepr. India*, 1967, **39**, 3, 110-17.

This paper gives a factual account of the success achieved in overcoming prejudice, inertia and fear in relation to leprosy in the state of Kerala, South India. Thanks to a leadership that combined imagination and enthusiasm, knowledge and a practical outlook, and thanks also to a wise use of all possible methods of mass education, long-standing prejudice against the leprosy patient was broken down and much misunderstanding about leprosy was removed. Doctors and paramedical workers were given special courses of instruction in leprosy. Leprosy figured in school textbooks, in dramatic performances, in cinema films, in newspaper articles and radio talks; special pamphlets written in the vernacular were distributed widely; camps for social workers were organized, and essay competitions for schoolchildren arranged.

Much of the success of the campaign is attributed to the work of local Leprosy Welfare Committees, which ensured the informed co-operation of people of goodwill in even the most outlying districts.

By means of educating the patient and his family and the general public, the attendance rate of patients under treatment for leprosy has shown a gratifying increase and a high degree of confidence has been gained.

S. G. Browne.

2. **Análisis epidemiológico de la lepra en Costa Rica** (The epidemiology of leprosy in Costa Rica), by R. JIMÉNEZ MÓNGE and E. RAMÍREZ CASTRO. *Acta Méd. Costarric*, 1967, **10**, 1, 59-70. English summary.

The authors have made an epidemiological analysis of leprosy in Costa Rica and found that the disease is prevalent in all parts of the country. The incidence and prevalence rates remained constant during the quinquennium under survey—1961-1965—and the provinces of Limón and Puntarenas had the highest incidence while Heredia had the lowest. 38 new cases were notified in Costa Rica in 1965, an incidence of 2.6 per 100,000. The disease predominates in males and most of the patients are aged over 50. In all the Latin American countries the control of leprosy contacts is inadequate but in Costa Rica it is better than in the other Central American countries as general practitioners are sufficiently interested to report suspected cases. However, more opportunities for training in the early diagnosis of leprosy are necessary.

There are 6 tables of figures, 5 of them relating to Costa Rica. The first table gives a useful summary of the cases, by age and clinical type, and the number of contacts, in 18 countries in Central and South America, and in the West Indies in 1963.

J. R. Innes.

Studies on *Mycobacterium leprae* in media enriched by mycobacterial extracts, by A. L. OLITZKI and D. GODINGER. *Int. J. Lepr.*, 1967, **35**, 2, Pt. 1, 154-65

Mycobacterium leprae was subcultured *in vitro* 8 times on a modified Eagle's medium enriched by extracts obtained from saprophytic mycobacteria and from human foreskin. It was not proved that multiplication took place, but since the sub-culturing techniques involved the making of 8 successive 10-fold dilutions, and there were still large masses of organisms in the final culture, it is thought that the result cannot be otherwise explained, unless conceivably it was due to an agglutinating factor in the medium. The growth or maintenance of the organisms depended not on a single factor but on a multiplicity of factors of bacterial and human origin.

D. S. Ridley.

4. **Microscopic, cultural and serologic studies on *Mycobacterium leprae* and other mycobacteria isolated from leprosy patients,** by A. L. OLITZKI, D. GODINGER, Z. OLITZKI and M. L. DORFMAN. *Int. J. Lepr.*, 1967, **35**, 2, Pt. 1, 166-74.

Cultures or prolonged maintenance on enriched Eagle's medium of organisms thought to be *Mycobacterium leprae* (see above) were successful in 13 out of 17 cases, when the material from ear lobes was used, and in 7 of material from nasal mucosa. The patients from whom these organisms were derived came from Asia, Africa and South America, 11 countries in all. Antigens were prepared from the second and third subcultures and used for complement-fixation tests with the sera of the patients, but the results did not definitely indicate

whether the various strains were antigenically identical. It is postulated that some of the atypical mycobacteria isolated from leprosy lesions may act as growth promoters for bacteria-dependent leprosy bacilli.

D. S. Ridley.

5. **La lépre borderline et la lèpre tuberculoïde reactionelle. Leur réunion dans un groupe interpolaire** (Borderline and reactional tuberculoid leprosy: their juxtaposition in the interpolar group), by J. Languillon. *Méd. Trop.*, 1967, **27**, 2, 183-92, 8 figs. on 2 pls.

After a brief historical résumé of borderline leprosy, the author advances the thesis that reactional tuberculoid leprosy has more affinities—clinical, immunological and bacteriological—with borderline leprosy than with tuberculoid leprosy, and should therefore be considered as falling into the broad intermediate or interpolar group. While this suggestion is unexceptionable rather than novel, the article provides a useful summary of the clinical and pathological features of this unstable form of leprosy, which is characterized by a variable immunological pattern and an unpredictable prognosis.

S. G. Browne.

6. **Inoculación accidental de la lepra por transfusión sanguinea en gemelos univitelinos** (Accidental inoculation of leprosy by blood transfusion in identical twins), by J. Terencio De Las Aguas. *Revta Leprol. Fontilles*, 1967, **6**, 7, 603-11, 3 pls.

The author gives a list of references to instances of accidental inoculation with the leprosy bacillus. He then reports the history of a pair of twins who developed leprosy as a result of blood transfusions.

A pair of identical twins with no family history of leprosy or contact with the disease were given blood transfusions at the age of 20 months because of gastroenteritis with dehydration. The blood donor was later diagnosed as suffering from lepromatous leprosy. When aged 2 years both children developed cutaneous lesions simultaneously and infantile nodular tuberculoid leprosy was diagnosed in the first and tuberculoid leprosy in the second. The case notes in this interesting report show the temporary lowering of resistance at the time of transfusion, the factor of infancy in favouring the development of the disease and the genetic factor, in that the children were identical twins.

J. R. Innes.

7. **Estudios de immuno-precipitación en la lepra** (An immuno-precipitation test in leprosy), by M. Salazar Mallén, E. Amezcua Chavarría and A. Escobar Gutiérrez. *Revta Invest. Salud. Publ.*, 1967, **27**, 1, 3-14. English summary.

The authors used an immunologically active polysaccharide named Poly I Nb which occurs in *Nocardia brasiliensis*, *Mycobacterium tuberculosis*, *Myco. lepraemurium* and *Myco. leprae*. Their present sample was prepared from *N. brasiliensis* (*Trop. Dis. Bull.*, 1967, **64**, 375). This was tested by Ouchterlony plates and by paper chromatography against sera of patients with leprosy and other infections. Of 71 sera from patients with lepromatous leprosy, 6 were positive by the agar method, 35 by paper; of 13 patients with tuberculoid leprosy, 6 were positive by paper; 1 patient with dimorphic leprosy was positive; of 9 patients with the indeterminate form, 3 were positive by paper; with the exception of 6 of the patients with lepromatous leprosy, all were negative by agar plates. 69 healthy control subjects were negative by both tests. The amount of antibody in the lepromatous sera was higher than that in tuberculoid sera (not statistically significant). In 2 cured patients the reaction was negative. 6 positive sera were treated with 2-mercaptoethanol, and the titre of precipitation was much diminished; from this it is concluded that the antibody in the serum belongs to the IgM class. With sera from patients with pulmonary tuberculosis, 4 out of 18 were positive by paper chromatography, and so were 3 out of 6 from persons with *N. brasiliensis* infection.

F. Hawking.

8. **Patterns of radial paralysis in leprosy in Papua-New Guinea,** by J. K. A. Clezy. *Int. J. Lepr.*, 1967, **35**, 3, 345-7.

'A high incidence of radial paralysis has been encountered in leprosy patients in Papua-New Guinea. The commonest single pattern involving this nerve is radial/ulnar paralysis, sparing the median nerve. The surgical management of hands suffering from radial paralysis due to leprosy is outlined.'

9. **Acute exudative arthritis in leprosy — rheumatoid-arthritis-like syndrome in association with erythema nodosum leprosum,** by A. B. A. Karat, S. Karat, C. K. Job and M. A. Furness. *Br. Med. J.*, 1967, Sept. 23, 770-72.

The authors report that, in the past 2 years at Schieffelin Leprosy Research Sanatorium, Karigiri, South India, they have seen 10 patients with lepromatous leprosy who developed painful exudative polyarthritis simulating acute rheumatoid arthritis during the course of erythema nodosum leprosum (ENL). They give the history and results of treatment for 2 of the patients and they suggest that these two conditions occurring in conjunction may be aetiologically determined by an immunological phenomenon. Histological study of synovial membranes showed that the acute inflammatory reaction was similar to that seen in the ENL lesions elsewhere in the body and differed from the lesions characteristic of rheumatoid arthritis. The joint manifestations cleared after the subsidence of ENL which responded to the usual measures.

J. R. Innes.

10. **Chemotherapeutic trials in leprosy. 4. Dapsone (DDS) in low dosage in the treatment of lepromatous leprosy. A demonstration pilot study,** by J. H. S. Pettit and R. J. W. Rees. *Int. J. Lepr.*, 1967, **35**, 2, Pt. 1, 140-48.

There is much experimental evidence that leprosy bacilli which stain solidly are alive and those which stain irregularly are dead. Accordingly the present

authors suggest that the percnetage of solidly staining bacilli (the Morphological Index, MI) can be used to assess the value of a treatment in selected patients with lepromatous leprosy in a period of 6 months. They illustrate this test by a trial on 6 previously untreated patients in Malaya, with lepromatous leprosy, each of whom was given 50 mgm. dapsone twice weekly by mouth. Full case histories are given. Briefly the average Morphological Index (in biopsies) at the start was 34 (25-42) and after four and a half months it was only 0.75 (0-1). The conventional Bacterial Index was not much changed (3.9 became 4.2). Clinically, there was only slight to moderate improvement in these patients as might have been expected in this short period. The mean blood concentration of dapsone was 0.09 μgm./ml. before each dose and 0.75 μgm./ml. 6 hours after a dose. There was no progressive build-up in blood concentration. It is concluded that this method affords a relatively quick way of testing new treatments and that 50 mgm. of dapsone twice weekly is probably as effective therapeutically as the conventional 600 mgm. per week, while being less toxic.

F. Hawking.

11. **Attempt at treating leprosy with a sulfone in conjunction with iodine,** by R. N. Miranda, L. C. Perera, A. Sao Marcus and S. F. Tarlé. *Publções Cent. Estud. Leprol.*, 1966, **6**, 1/2, 18-19. (Also in Portuguese and French.)

The authors, who are from the Federal University of Parana, Brazil, tested the value of a combination of dapsone and potassium iodide (KI) in 11 patients with leprosy. The drugs were used in the following dosage: tablets of dapsone 100 mgm.; KI 50% solution, each drop of the solution containing 0.03 gm. KI. The drugs were given orally in doses of 0.025 gm. dapsone and 0.03 gm. KI per week; the dose was increased slowly to 300 mgm. dapsone and 1.2 gm. KI by the 15th week. 11 patients who had never received any anti-leprosy treatment were selected; 8 had the lepromatous form of leprosy, 2 the tuberculoid and 1 the indeterminate form. All tolerated the treatment well and showed definite clinical improvement during the first 5 months. Later 4 of the patients with lepromatous leprosy showed reactivation and acute manifestations of symptoms. The condition of one patient with lepromatous leprosy deteriorated and that of another showed no improvement. The remainder of the patients showed clinical, bacteriological and histological improvement.

The authors state that although only a few patients were treated the scheme seemed to be effective when the doses were small, i.e., not more than 200 mgm. dapsone and 300 mgm. KI per week.

W. K. Dunscombe.

12. **Sulforthomidine (Ro 4-4393) in the treatment of lepromatous leprosy,** by K. Ramanujam. *Lepr. India*, 1967, **39**, 3, 95-9.

After reviewing the literature on long-acting sulphonamides in the treatment of leprosy, the author describes his experience with Sulforthomidine—better known as sulphormethoxine or Fanasil—given in a single oral dose once a week to 17 patients, and concludes that it is not as effective as standard DDS (dapsone) treatment. Two-thirds of the patients underwent reactional episodes.

W. H. Jopping.

13. **Evaluation of B663 in human leprosy,** by A. J. Atkinson, Jr., J. N. Sheagren, J. Barba Rubio and V. Knight. *Int. J. Lepr.*, 1967, **35**, 2, Pt. 1, 119-27.

Although this paper is based on the case-history of only a single patient treated with B.663, it records useful details of clinical observations and laboratory investigations, and confirms earlier work on this interesting phenazine derivative. (*Trop. Dis. Bull.*, 1965, **62**, 422; 1966, **63**, 1344.)

From previous experience and from the results in this patient, the following conclusions are drawn: B663 is therapeutically effective in lepromatous leprosy, causing a progressive reduction in both the Bacterial and the Morphological Indexes and a corresponding clinical improvement; when given in adequate doses, B663 is able to control even severe erythema nodosum leprosum; in high doses (600 mgm. daily), it may provoke gastro-intestinal disturbance and consequent loss of weight, symptoms which, in the present patient, ceased when the drug was stopped. Radiographic evidence of small bowel irritation was accompanied by the deposit of crystals of B663 in the lamina propria of the intestinal wall. Apart from these signs of drug intolerance, and the pigmentary changes in the skin already reported (*ibid.*, 1965, **62**, 422 *bis*), no evidence of toxicity (renal, hepatic, or haematological) was obtained in this patient after almost 2 years of treatment with high doses of B663.

S. G. Browne.

(Long-term observation on the development of experimental mouse leprosy), by Y. Kawaguchi and Y. Takahashi. *Lepro*, 1967, **36**, 1, 13-18. (In Japanese.) English summary.

(Effects of BCG on the development of visceral lesions in CF 1 mice with subcutaneous murine leprosy infection), by Y. Kawaguchi and Y. Takahashi. *Ibid.*, 19-24. (In Japanese.) English summary.

(i) Mice of 4 strains were infected with murine leprosy bacilli and observed for periods of up to 80 weeks.

Mice of the C3H strain died within 50 weeks with extensive disease of the visceral organs. In the C57BL and ddY strains the infection was of a more benign type. In CF 1 mice the lepromata at the inoculation sites were of the benign type, but the visceral lesions were severe, comparable with those of C3H mice.

(ii) The second paper reports the effect of vaccination on the course of a subsequent infection with murine leprosy in mice of the CF 1 strain. BCG and a killed murine leprosy bacillus vaccine both gave partial protection, but the former was the more effective.

D. S. Ridley.

15. **Activity of repository sulfones against** *Mycobacterium leprae* **in mice,** by C. C. Shepard. *Proc. Soc. Exp. Biol. Med.*, 1967, **124**, 2, 430-33.

The finding that minute doses of DDS (dapsone) were sufficient to suppress the growth of *Mycobacterium leprae* in mice (*Trop. Dis. Bull.*, 1967, **64**, 53) suggested the possibility that repository sulphones might be effective in leprosy. A number of repository sulphones were therefore tested against footpad infections in mice in the same manner as before, and all were found to suppress completely the growth of *Myco. leprae* when injected at intervals of 2 months. Dapsone by contrast had to be given every 2 weeks to achieve comparable suppression. In the case of 4,4-diacetyldiaminodiphenylsulphone (DADDS) the lowest dose which gave nearly complete suppression was 6 mgm. per kgm. at intervals of 2 months.

D. S. Ridley.

16. **Histobacteriologia de la almohadilla plantar del raton inoculado con** *M. leprae* (Histological and bacteriological study of the footpads of mice inoculated with *M. leprae*), by M. Bergel. *Publções Cent. Estud. Leprol.*, 1966, **6**, 1 2, 5-12, 7 figs. on 4 pls. English summary.

The following is a free translation of the author's summary:—

The author made a histological and bacteriological study of the footpads of mice which had been inoculated with 0.03 to 0.05 cc. of recent leproma suspension taken from patients with untreated lepromatous or borderline leprosy. The animals were divided into 2 groups, one of which had normal food and the other a pro-oxidant diet; it was found that the experimental leprosy developed much better in the footpads of the animals who had been fed on the pro-oxidant diet. Two types of granulomata were found. In one type the granuloma was large and found in a deep part of the skin with damage to vascular and nerve elements and even muscular tissue. The bacilli in these granulomata were either 'globi' or isolated and were large and acid-fast, which indicated a state of great vitality. In the other type, the granuloma was found in the dermis and was small and contained only isolated bacilli. This confirms the findings of Palmer *et al.* (*Trop. Dis. Bull.*, 1965, **62**, 879) concerning the presence of bacillary groups in striated muscular tissue in the footpads of mice with the bacilli showing characteristics which indicated a great degree of vitality.

J. R. Innes.

The following 9 abstracts are reprinted, with permission, *Trop. Dis. Bull.*, 1968, **65**, 4:

17. **Leprosy rehabilitation in Japan,** by S. Takashima. *Lepro*, 1967, **36**, 2, 63-7.

For nearly 60 years, patients with leprosy in Japan were subject to legally enforced segregation, and the old attitudes and superstitions of patients, public and the profession towards leprosy persist despite recent enlightened legislation.

In this study, the author analyses the factors that underlie the reluctance of these patients to leave the national leprosarium in Aiseien, Japan, and return to life outside.

In Aiseien, the 1,489 patients were examined and assessed according to their degree of physical disability. Most of thr 41% who had no deformities, and who were bacteriologically negative, worked in the sanatorium at jobs of various kinds (as medical orderlies, or in stock-raising, farming, shop-keeping, light industries and so forth). The 37% with slight or moderate degrees of disability were candidates for the recently-introduced facilities for reconstructive surgery (orthopaedic and plastic), physical therapy and education in the use and protection of their anaesthetic and deformed extremities. The 16% with severe deformities (blindness, serious physical defect, psychosis, etc.) would continue to need institutional care. Determined efforts are made to rehabilitate all patients, whatever their degree of disability. (It is gratifying to note the informed enthusiasm of this paper, typifying the new outlook that augurs well for the future.)

S. G. Browne.

18. **La lèpre en Polynésie française. Esquisse épidémiologique** (Leprosy in French Polynesia: epidemiological sketch), by G. Schollhammer and P. Aubry. *Bull. Soc. Path. Exot.*, 1966, **59**, 6, 939-43.

Introduced apparently by Chinese immigrants round about 1870, leprosy has not assumed epidemic proportions in the islands of French Polynesia (mainly Tahiti, Tuamutu and the Marquesas). The known number of patients at present under treatment is under 400, giving a prevalence rate of under 4 per 1,000. The proportion of patients with lepromatous leprosy is 40%, and the male/female ratio is about 2/1.

The authors consider that in view principally of the recent (slight) fall in the lepromatous rate and in the total prevalence rate of leprosy, the present time is opportune for the successful application of standard measures of control and eradication.

S. G. Browne.

19. **Human macrophage culture. The leprosy prognostic test (LPT),** by T. A. Barbieri and W. M. Correa. *Int. J. Lepr.*, 1967, **35**, 3, 377-81

The authors have attempted to establish a new and reliable test for determining the resistance of man to leprosy based on observations of the ability of cultured human blood macrophages to lyse heat-killed *Mycobacterium leprae*.

The blood macrophages were cultured by the method of G. Cameron (Tissue culture technique, 2nd edition, 1950, New York: Academic Press) in Leighton tubes. The medium, which was replaced every 3rd day, was composed of Hanks's balanced salt solution plus antibiotics and 10% human serum. The bacilli, from lepromin, were added to the culture on the 6th day and, although in the early investigations the cells were observed daily, the day of examination was finally fixed as the 10th day of infection. Examination was made on Ziehl-Neelsen stained preparations and lysis and non-

lysis of the ingested bacilli was scored as LPT-positive and LPT-negative, respectively. Cultures were studied from 35 patients with tuberculoid leprosy, 40 with lepromatous leprosy and 50 healthy persons.

The sequence of events after infection was as follows: after 24 hours, the cytoplasma of the macrophages enveloped the bacilli; after 48 hours, almost all the bacilli were ingested: from the 3rd to the 10th day, in the non-losing macrophages the bacilli were present as intact rods or globi, but in the lysing cells were thinner, broken or completely hyalinized: and on the 16th day, the bacilli were still intact in the non-lysing cells but were completely lysed in the lysing cells.

The results showed complete agreement between the lepromin status of the donors and their macrophage test, the cells from lepromin-positive persons being invariably LPT positive and those from lepromin-negative persons being invariably LPT negative. The authors consider that this test is an advance over the lepromin test because it is carried out at the cellular level of resistance and not at the level of complex organism reaction.

S. R. M. Bushby.

20. **Contribución al estudio de las formas de transición de la lepra** (Study of the transition forms of leprosy, by G. HERRERA. *Revta Dominicana Derm.*, 1967, **1**, 2, 111-14. English summary.

The author, from the Dominican Republic, reports a case of combined lepromatous, tuberculoid and indeterminate forms of leprosy. The patient was a man aged 37 years who was seen at the Dermatological Clinic in Santo Domingo. He had had a lesion in the skin of the left buttock for 5 years; 1 year later leprotic foci in the eybrows, gluteal and lumbar regions appeared, and subsequently nodules on the lobe of the left ear and on the left cheek. Large numbers of *Mycobacterium leprae* were seen in histological sections which showed appearances characteristic of all 3 forms of leprosy.

W. K. Dunscombe.

21. **The lepra reaction with necrotizing skin lesions. A report of six cases,** by S. L. MOSCHELLA. *Arch. Derm.*, 1967, **95**, 6, 565-75.

The author gives the case histories of 6 patients with lepra reaction and necrotizing skin lesions and discusses their clinical features. He was disturbed by the slow response of these patients with the Lucio phenomenon to sulphone therapy and the necessity of using systemic corticosteroids for long periods to control this reaction.

He concludes that: 'The primary diffuse (the pure and primitive) lepromatous leprosy has sufficient clinical characteristics to be classified as a subtype of lepromatous leprosy.

'The cutaneous expression of the lepra reaction depends upon the subtype of lepromatous leprosy, the location and degree of the involvement of the cutaneous vessels, the duration of the reaction, and the degree to which the reaction has been modified by therapy.

'Patients with the grossly infiltrative and nodose lepromatous leprosy usually react with erythema nodosum leprosum. The Lucio phenomenon which occurs in patients with diffuse lepromatous leprosy is seen most frequently in Mexico and Costa Rica.

'Necrtotizing skin lesions which are the typical lesions of the Lucio phenomenon are seen infrequently in erythema nodosum leprosum and in an eruption which resembles the cutaneous allergic vasculitis of Ruiter and rarely appears as part of the lepra reaction. The erythema nodosum leprosum with necrosis and the lepra eruption resembling the cutaneous allergic vasculitis of Ruiter can be loosely described as expressions of the Lucio phenomenon. It is preferred (by the author) to limit the use of the Lucio phenomenon to describe the distinctive lepra reaction which occurs in diffuse lepromatous leprosy and is characterized by the presence of only erythema necroticans. All the other lepra reactions with reactive necrotic skin lesions can be classified clinically as variants of erythema nodosum leprosum.'

J. R. Innes.

Poststeroid nodular panniculitis and the erythema nodosum of leprosy, by S. G. BROWNE. *Derm. Int.*, 1965, **4**, 4, 215-18.

Precipitate reduction in the dose of corticosteroid drugs being given to patients with rheumatism may cause a form of panniculitis which resolves on increasing the dose of the steroid. The author sees close parallels between poststeroid nodular panniculitis and the erythema nodosum of leprosy, e.g., the typical symptomatology, especially polymorphism, the typical histological picture and the recurrence of symptoms on the over-rapid reduction of the dose of steroids. (This would, of course, be true of other forms of erythema nodosum which, as the author is aware, is a reaction due to a wide variety of infections and drugs, sometimes associated with a demonstrable change in immunity, e.g., the development of tuberculin sensitivity in primary tuberculosis. Presumably poststeroid panniculitis is due to the abrupt withdrawal of the cushioning effect of steroids in cases of continued antigenic stimulation.)

P. J. Hare.

23. **Chemotherapeutic trials in leprosy. 5. A study of methods used in clinical trials in lepromatous leprosy,** by M. F. R. WATERS, R. J. W. REES and I. SUTHERLAND. *Inter. J. Lepr.*, 1967, **35**, 3, 311-35.

The authors write with the authority of experience and give a detailed description of the controlled chemotherapeutic trial in leprosy. They stress the importance of ensuring that patients in the trial belong to one carefully defined, homogeneous group, and recommend untreated patients suffering from pure lepromatous leprosy who are temperamentally suitable and who have a predominance of solid-staining bacilli in skin smears. The various methods of assessing progress—clinical, bacteriological and histological—are described. Only drugs which have shown promise in pilot trials should be considered for the much more elaborate controlled trials. The design of pilot trials is next considered, and it is suggested that evidence of therapeutic activity may be gained within 4½-6 months by

studying the effect of the trial drug on the morphological characteristics of the bacilli as seen in skin smears. Finally, the question of erythema nodosum leprosum (lepra reaction) is discussed with reference the effect of drugs on its initiation and treatment.

W. H. Jopling.

24. **Effect of X-irradiation and thymectomy on the development of *Mycobacterium leprae* infection in mice,** by J. M. GAUGAS. *Br. J. Exp. Path*, 1967, **48**, 4, 417-22.

This report confirms the recent findings of REES (*Trop. Dis. Bull.*, 1966, 63, 1346) that the multiplication of *Mycobacterium leprae* in mouse footpads is enhanced by previous thymectomy and irradiation of the mouse. 3 experiments, with albino mice, were undertaken to determine the effects of irradiation and thymectomy both separately and in combination. The technical details are fully described.

The increase of organisms in either irradiated or thymectomized animals was little greater than in control animals, the enhancement being about two-fold. By far the greatest increase was obtained in mice that had been thymectomized and also irradiated with a single dose of 900r, the multiplication of bacilli then being 16,800 times, which was 29 times greater than in control mice. 900r is a lethal dose, and injection of homologous marrow cells is necessary for survival. But sub-lethal doses of 420r, though they were repeated several times, were less successful in conjunction with thymectomy in enhancing multiplication. Although the footpad infections were enhaced they were not progressive beyond a certain point. Cellular infiltration at the site of infection was diminished.

D. S. Ridley.

25. **Effect of immunosuppressive drugs on infection in mice by *M. marinum* (*balnei*), *M. tuberculosis* and *M leprae***, by C. C. SHEPARD and M. A. REDUS. *Int. J. Lepr.*, 1967, **35**, 3, 348-54.

The authors have studied the effect of immunosuppressive drugs on infections in mice produced by *Mycobacterium marinum* (*balnei*), *Myco. tuberculosis* and *Myco. leprae*, and, although the ultimate aim of increasing growth of *Myco. leprae* in footpads was not achieved, some useful information was gathered.

The drugs were administered subcutaneously at their highest sub-lethal doses; amethopterin at 6 mgm./kgm. thrice weekly, 6-mercaptopurine at 75-150 mgm./kgm. thrice weekly and cyclophosphamide at 300, 200 or 150 mgm./kgm. at various intervals.

The infection with *Myco. marinum* was in the footpad and the drug was injected 2 days before inoculation. Direct visual inspection of the feet and viable counts of the bacteria present at the 13th and 35th day showed that the chief effect of the treatments was a marked persistence in the viability of the bacteria during the plateau phase of the infection, and because cyclophosphamide had the most pronounced effect, it was the only drug used in the other infections.

The tubercle bacilli were injected intravenously in doses that caused death between the 20th and 90th day and the effect of treatment with the phosphamide was assessed by changes in mortality and the number of viable bacilli in the tissues. In the first experiment, in which the drug was given in doses of 300 gm./kgm. 5 days before and 2 and 9 days after infection, no effects were observed on the number of bacilli, although the mice died earlier. Similarly, results were obtained in 2 other experiments in which the doses of the drug and the bacteria were varied.

The effect of the phosphamide on the rate of multiplication of *Myco. leprae* was examined in 4 experiments. The bacilli were injected into the footpads. In the first 3 experiments, treatment was delayed until multiplication had reached countable levels; in the fourth experiment it was started 3 days before infection and given at approximately 2-week intervals in doses of 150 mgm./kgm. Little, if any, effect was observed on the rate of multiplication.

S. R. M. Bushby.

Reports

A.L.E.R.T., Addis Ababa

Another step forward in the work of the All-Africa Leprosy and Rehabilitation Training Centre was taken on 4 April, 1968, when Emperor Haile Selassie I laid the foundation stone of the new buildings adjacent to the Princess Zenebeworq Leprosy Hospital, Addis Ababa. The Project came into being as the result of discussions by the Leprosy Committee of the International Society for Rehabilitation of the Disabled. The Leprosy Mission and the American Leprosy Missions Inc. early evinced interest, and in 1966 the Imperial Ethiopian Government (through the Ministry of Public Health) and the Haile Selassie I University (Addis Ababa) gave the proposals official and academic support.

The teething troubles and growing pains inseparable from a scheme as broadly based as this, with so many interests involved, now seem to be passing. The problem of priorities still has to be faced, since leprosy is only one of the crippling diseases that calls for rehabilitation of the individual patient, and African countries would be well advised to tackle the problem of leprosy deformity at its source by attempting to

control the disease itself.

However, staff already on the job are providing an augmented service for leprosy patients in Addis Ababa, and are engaged in the preliminary preparations needed for the provision of courses of instruction in all aspects of the rehabilitation of leprosy patients and the control of the disease. In accordance with hopes expressed in many African countries, courses are being provided for physiotherapists, leprosy field workers (especially supervisory staff) and medical officers wishing to learn surgical techniques. A rural area will furnish good facilities for realistically demonstrating the possibilities of leprosy control in circumstances far from ideal—where communications are difficult, basic medical services almost non-existent, and the population diffusely scattered. The making of protective footwear with materials and skills locally available in African countries will be another feature of the training programme.

The Centre should produce real practical help for African countries facing comparable leprosy problems. It should also shed welcome and much-needed light on such questions as the transmission of leprosy, the natural history of nerve damage, the frequency of bacilliferous leprosy lesions in Ethiopia, and the occurrence of diseases with which leprosy has in the past often been compared, such as cutaneous leishmaniasis.

ELEP

The Co-ordinating Committee of the European Leprosy Associations (ELEP), representing some 14 organisations that raise funds in Europe for leprosy work overseas, met in London, 19-21 April, 1968. Some of the organisations draw their support from Christian sources, Protestant or Roman Catholic, while others are non-sectarian. In addition to the founder-members, observers were present from Denmark, Holland, Spain and Turkey, and also from Canada. The importance of their contribution to the world-wide campaign against leprosy may be judged by the fact that in Europe alone, through the activities of these voluntary organisations, an annual amount of over 3½ million dollars U.S. is made available for work on behalf of leprosy patients. This help is given to 463 centres in 69 countries.

Thanks to the work of the Medical Commission, guiding principles and priorities in the distribution of funds are now being applied, to the enhancement of the co-ordinared efforts of the diversely-orientated members of ELEP.

International Leprosy Congress, 1968. The travel expenses of 28 participants to the Congress are being covered by ELEP members. In addition, a generous contribution to the overhead expenses of the Congress has been promised.

The International Journal of Leprosy. Members of ELEP learned with concern of the serious financial state of the International Journal of Leprosy, and resolved to make a sum available annually that would go far towards meeting the considerable gap between income and expenditure, a deficit that has hitherto been covered by the Leonard Wood Memorial. Members of ELEP have already been encouraged to devote a proportion of their funds towards leprosy research, and it has been suggested that some of this money could appropriately be diverted to the publication, in the *Journal*, of the results of this research. Needless to say, this welcome gesture is much appreciated.

The LEPRA Leprosy Control and Eradication Project, Malawi

In his capacity as Medical Secretary of LEPRA, Dr. S. G. Browne recently visited Malawi. Well over 6,000 leprosy patients have already been registered for treatment. The mobile teams have already proved their worth, both in case-finding and treatment. The wards erected adjacent to the Queen Elizabeth Hospital, Blantyre, serve for patients in temporary need of closer medical supervision. The 'President's Appeal' for funds to build a Rehabilitation Unit has been almost fully subscribed. The British Government is presenting to Malawi the equipment and apparatus to be installed in the new building. Dr. David Molesworth and his team are to be

congratulated on their practical outlook and adherence to commendable priorities in leprosy control.

Armauer Hansen Research Institute, Addis Ababa

Professor Morten Harboe, of Oslo, outlined the present plans and future hopes of the Institute. The expatriate staff will consist of a Director and Sub-director, 2 research associates and 2 technicians. Local Ethiopian staff will be recruited for the routine laboratory technology, and it is hoped that the full facilities for training to be offered will be taken up by Africans. Sustained efforts will be made to interest students of the Medical Faculty of the Haile Selassie I University, Addis Ababa, in leprosy generally and in the research work of the Institute, and the training of technical associates will be an integral part of its work. In this the work of the Institute should dovetail into that of the A.L.E.R.T. project, and make a valuable scientific contribution to the control of leprosy both in Ethiopia and throughout Africa.

In accordance with the interests and experience of Professor Harboe, the emphasis of the research work contemplated at the Institute will, at least initially, be on the diverse immunological aspects of leprosy, particular those impinging on aetiology, pathogenesis and the phenomena of acute exacerbation in lepromatous leprosy. These aims will probably exclude the experimental culture of *M. leprae* in special biological systems like the mouse food-pad and the sophisticated preparation of the thymectomised and irradiated mouse—investigations better left to laboratories in the West with their excellent facilities for animal work. With so many untreated leprosy patients within a short radius of the Centre, there will be no lack of material for such studies as the composition of the gamma-globulins in the different varieties of leprosy, in acute exacerbation or not, the occurrence in the plasma proteins of antigens to other mycobacteria and naturally-occurring antigens. By means of the fluorescent antibody technique, it should be possible to demonstrate the existence of antibody in relation to individual *M. leprae*, and to determine the actual site of antigen-antibody reaction during phases of acute exacerbation.

It is hoped that by encouraging the simultaneous development of research and teaching, the Institute will worthily perpetuate the memory of Armauer Hansen and stimulate not only the continent-wide attack on leprosy but also the elucidation of many of the puzzling and intriguing scientific enigmas of this disease.

The British Leprosy Relief Association (LEPRA)—44th Annual Report (1967)

The Annual Report of LEPRA is dominated by the Leprosy Control Project in Malawi, though supported work in other countries finds brief mention therein.

Dr. David Molesworth, the Field Director of the Project, whose photograph adorns the cover, has reason to express himself as highly satisfied with the progress achieved, and the firmly laid foundations for future work. The Project is, in short, a practical demonstration of leprosy control within a circumscribed area in which the terrain, the difficulties of communication and dispersion of the population and the social attitudes of the people are perhaps typical of much of Africa and of many of the developing countries where leprosy remains an endemic problem.

By means of case-finding surveys and the provision of regular treatment by mobile clinics manned by trained Malawian auxiliaries, it is hoped that all leprosy patients within the Project area will eventually be under treatment. The small central hospital, in the grounds of the Government Hospital in Blantyre, was opened during the year, and very shortly an adjacent Rehabilitation Centre will be in use.

With the emphasis on early diagnosis and the utilisation of mass treatment methods, the problem of leprosy should be tackled successfully, and the decrease in the annual incidence of new leprosy patients should become evident within a few years.

Partners. The Story of the Year 1967
The Leprosy Mission, London. Price: 1s.
The popular Annual Reports of The Leprosy Mission are always excellently reproduced and more than adequately illustrated. They give a very readable account of the many fields in which the Mission aids the leprosy work of almost a hundred protestant missionary societies, as well as sponsoring special projects and centres of its own. From inauspicious beginnings in the historic year 1874, the Mission—with its auxiliaries in the countries of the Commonwealth and beyond—has grown into a vast organisation for the channelling of help to leprosy sufferers in many lands.

Several matters in the report call for mention.

Firstly, the change of emphasis from custodial care for the few to domiciliary treatment of the early disease in the many, is reflected in reports from India and Korea, from Papua and Zambia. Having faced opposition in the early days in the care of leprosy patients, the Mission workers—aided or sponsored—are more and more tackling leprosy where it should be tackled, that is before deformity has occurred.

In the second place, it is gratifying to note that the spirit of early pioneers is by no means dead today. New work is reported in Nepal and Bhutan, in Pakistan and in Ethiopia.

Thirdly, it is not only geographically that the work of The Leprosy Mission is showing evidence of the pioneering spirit. In the development of a microcellular rubber plant at Karigiri, South India, the provision of protective footwear in Papua, in the 'new look' shown by co-operative ventures in various countries, in the infusion of new blood and new ideas into many long-established institutions, the workers of The Leprosy Mission are showing commendable vision and initiative.

The extending influence of several of the Mission's activities is of importance in the world of leprosy. The Medical Consultant conducts seminars in various countries. A surgeon from the East travels widely, demonstrating the techniques of reconstructive surgery to interested and appreciative audiences. A physiotherapist trains others in many lands, and enlists the help of auxiliary workers.

The Leprosy Mission is a partner in well-known co-operative undertakings, e.g., the ALERT project in Addis Ababa, and the Schieffelin Leprosy Research Sanatorium. The results of research into many aspects of leprosy find their way into this *Review* and into other specialised and general medical publications.

We wish The Leprosy Mission another year of fruitful service on behalf of leprosy sufferers in many lands.

The Leprosy Mission. Annual Report of the work in Southern Asia, 1966-1967

This 50-page Report maintains the style of previous reports from the pen of Dr. Victor Das, the well-known and much-travelled Secretary of the Leprosy Mission for Southern Asia.

Graphic pen-pictures are supplied of the work in many of the aided homes and hospitals, and the statistics reveal a surprisingly wide coverage: nearly 120,000 out-patients under treatment, nearly 20,000 in-patients cared for in the course of the year; an impressive record of reconstructive operations performed, laboratory investigations undertaken, farm projects developed, rural health schemes inaugurated, new work developed.

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