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LEPROSY REVIEW

VOL. XXXIII, No. 4 OCTOBER, 1962

CONTENTS

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A new hope in Leprosy

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EDITORIAL

I. Forthcoming 8th International Leprosy Congress

This is preliminary information. It is hoped that a fuller programme will be issued later. International Congresses of Leprology are usually held at intervals of 5 years, under the auspices of the International Leprosy Association (President Dr. H. W. Wade, Culion, Philippines; and General Secretary-Treasurer Dr. J. R. Innes, 8 Portman Street, London W.1, England), and usually a government or country offers to be host. In this case the country is Brazil, and the Congress will be held in Rio de Janeiro 12-20th September 1963, and a National Organizing Committee (COCIL) has been set up in Brazil, of which the President is Dr. Fausto Castelo Branco, Serviço Nacional de Lepra, Rua São Cristovão, 1298, Rio de Janeiro-Estado da Guanabara, Brasil. No doubt the Brazilian authorities will be issuing their official invitations to all countries, and in the meantime it should be noted that from the side of the International Leprosy Association we should like that everyone who is directly interested in leprosy should already consider himself or herself invited to the 8th Congress. We in ILA are most grateful to Brazil for their kind invitation to hold the 8th Congress in Brazil and for their invaluable collaboration, and it is obvious that all leprosy workers and all interested in leprosy can make the best return for their magnificent invitation to hold the Congress in Brazil by determining to attend this Congress. (If you are worried about who is going to pay your fare please do not expect Brazil or the ILA to do so, but approach your own governments and local organisations!) The scientific plan of the 8th Congress is already in process of organization. All that can be said now is that the subject has been sectioned into Round Tables and Panels. The chief difference between a Round Table and a Panel is that the members of the former will be expected to attend in Rio about a week before the date of the Congress, in order to discuss their subject "round the table". Both Panels and Round Tables will have to do a lot by correspondence. There is bound to be limitation on length and number of papers, proffered or called-for, and the Chairmen of Panels and Round Tables will have a great deal of influence on this, because after all they will be the "captains" of a particular ship of the whole navy. The sectional subjects chosen are:

Pathology and Experimental Transmission (Round Table)

Borderline and Indeterminate Leprosy (Round Table)

Leprosy Reaction (Panel)

Therapy (Panel)

Epidemiology and Control (Panel)

Bacteriology and Immunology (Panel)

Educational and Social Aspects (Panel)

Physical Medicine and Rehabilitation (including Surgery and Vocational Training) (Panel)

II. Report of a Trial of Etisul in Leprosy, by Russian scientists

We welcome very much a paper which we publish in this issue pp. 222–239 by TORSUYEV, BOGUN, TORSUYEVA, CHERNYAVSKAYA and SOKOLOV. In their paper, after a full study of the reports of previous authors, the present authors go on to describe the results of their own experience with Etisul in 10 patients at the Upper Kuban Leprosarium and 10 patients at the Rostov Leprosarium. The authors report data which convincingly indicate the therapeutic effectiveness of Etisul. They conclude that Etisul is an active and well tolerated anti-leprosy drug and that it is a valuable addition to therapy in lepromatous leprosy. The best effect is obtained in fresh or early leprosy. Inunctions of Etisul whether 3 times or 6 times a week are equally effective, and the bacilli disappear from the nasal mucosa much more quickly than from skin lesions. They suggest that the drug should be studied to assess its effectiveness in repeated courses of treatment.

This paper represents the first report in Leprosy Review, of a trial of this new drug, Etisul, in the USSR. We congratulate the authors on their careful work and only hope that reports of trials elsewhere in the Soviet Union will become available to us.

III. Lepra Reaction and the General Adaptation Syndrome

Another subject of very great interest and value at the present time is Lepra Reaction. Dr. ERNEST MUIR has made a study of it in relation to the general adaptation syndrome and his paper appears on pp. 240–251. He seeks to explain lepra reaction in its two forms of erythema nodosum leprosum and acute exacerbation, by the general adaptation syndrome of SELYE. He thinks that lepra reaction does not appear as a uniform response to one agent but as a response to a large number of widely differing agents. He thinks that in acute exacerbation as compared with erythema nodosum leprosum the difference lies in the success revealed by the latter in producing tolerance to certain causes of stress, whereas in acute exacerbation there is a failure to do so. He describes the cause of the appearance of erythema nodosum leprosum at the beginning of sulphone treatment and the effects of physical exercise, diet and complicating conditions. He describes the prevention and treatment of lepra reaction with special reference to physical training and cortisone therapy.

S. G. BROWNE and E. M. DAVIS: Also in this issue pp. 252–254 report on a related matter, namely Reaction in Leprosy precipitated by Smallpox Vaccination.

These authors found that patients suffering from lepromatous leprosy when exposed to smallpox, seem to be more susceptible to smallpox than those suffering from non-lepromatous leprosy, and those who succumb to smallpox tend to suffer from lepra reaction; also that lepromatous patients run a real risk of developing a reactional condition as the result of smallpox vaccination, especially if they have had reaction previously. This reaction is in general mild and transient, but patients who are already in reaction when they are vaccinated suffer a deterioration.

OBITUARY

Sir Leonard Rogers, K.C.S.I., C.I.E., F.R.S., M.D., F.R.C.S., F.R.C.P., LL.D., RET. MAJ. GEN. I.M.S.

Hon. Med. Adviser, British Leprosy Relief Association, Author of *Happy Toll; Fifty-five Years of Tropical Medicine* 1951.

Died 16 September, 1962, at Truro, Cornwall, at the age of 94.

All leprosy patients in India and the world, and all leprosy workers, mourn the passing of Sir Leonard Rogers and are grateful for his fruitful interest in the disease throughout his long life. His work for leprosy sufferers began in India in 1915 in the chaulmoogra oil days. In 1924 he founded (with Sir Frank Carter and Rev. F. Oldrieve) the British Leprosy Relief Association, and he wrote in 1925 a book on leprosy in conjunction with his friend and colleague Dr. E. Muir, C.M.G., C.I.E. (who to this day continues as a Medical Adviser, Chairman of the Medical Committee, and member of other committees of the British Leprosy Relief Association). Sir Leonard to the last continued his active interest in leprosy research, to which he gave much of his own financial resources. His marvellous scientific contributions to tropical medicine will be recalled elsewhere. That he included in these a long series of contributions to the understanding of leprosy and its relief will ever be remembered gratefully of this prince among men.

OUR EXPERIENCE IN THE TREATMENT OF LEPROSY WITH ETISUL:

A Preliminary Report.

By PROF. N. A. TORSUYEV, V. V. BOGUN, N. N. TORSUYEVA, G. YA. CHERNYAVSKAYA and V. V. SOKOLOV

In collaboration with Senior Doctor K. K. KHARABADZHAKHOV of the Rostov-on-Don Experimental-Clinical Leprosarium of the Russian Federation of Soviet Socialist Republics Ministry of Health; Senior Doctor L. N. KASPAROV of the Upper Kuban Leprosarium; and Rector and Professor A. M. GANICHKIN of the Donets Medical Institute named after Gorkiy.

(From the original Russian text, translated by Mr. D. M. Blakeley in collaboration with Dr. J. Ross Innes.)

In spite of the high therapeutic effectiveness of sulphone compounds they cannot be considered ideal for the treatment of leprosy and a pressing search for new, effective preparations continues.

In view of the impossibility of experimentation on animals, new preparations for the treatment of leprosy usually come into use after the degree of therapeutic effectiveness has been established in relation to experimental tuberculosis, and sometimes after clinical tests.

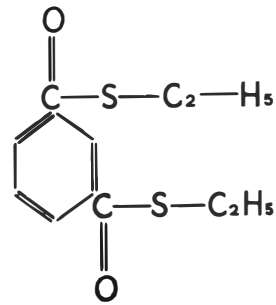
E. DEL PIANTO (1950) was the first to report that a mixture of two mercaptans—mercaptobenzothiazol-5- oxygen sulphate and ethylthiosulphonate retards the development of tuberculosis in porpoises. Later (in 1959) he indicated that as early as 1948 he had drawn attention to the antitubercular properties of oxygen ethylthiosulphate in experiments with the Koch's bacillus *in vitro*.

G. BERTACCINI (1955) beginning his work at the end of 1954, was the first to check the effectiveness of ethylthiosulphonate on leprosy, and in 1957 reported interesting results from the treatment of 31 lepromatous type subjects with this substance over a period of nine months, prescribing doses of from 0·8 to 1·6 g. every 24 hours.

J. G. ORBANEJA, F. CONTRERAS, M. SUCH, J. GUILLEN, A. GARCIA PEREZ, J. TARABINI, F. MORAN and J. TERENCIO (1957) treated 34 lepromatous type subjects with the compound "Leprosan Aue-3" with definite clinical and bacterial improvements. Chemically this compound is poliaryl polysulphide, a wax-like substance with an exceptionally unpleasant smell, probably explained by the presence of several aryls of mercaptan. There is no smell however, in capsules, in fat or in fine powder form. This preparation is known as Leprosan (Aue EL-3).

G. W. DRIVER (1959, 1957), making a study, as from 1951, of 400 different derivatives of ethyl mercaptan, focussed his attention on

diethyl dithiolizoftalene, a compound chemically very close to ethyl alcohol. This compound has the formula:



and is a light-yellow volatile oily liquid with a garlic smell. It was synthesized by the pharmaceutical division of the British firm Imperial Chemical Industries Ltd. and is sold under the trade name Etisul (synonyms: compound 15.688, ETIP, ET, Ditophal) in tubes, each containing 5·0 g. of pure preparation mixed with 2·0 g. of a neutral base (magnesium stereate). This preparation has the appearance and consistency of soft cream and should be kept in a cool place.

M. NAGUIB and J. M. ROBSON (1956) reported its high rate of efficacy; it retards the development of infection in mice infected in the eyes with the bacilli of rat leprosy. The mechanism of action of Etisul has not been explained. At present there is no chemical, biological nor clinical proof of its similarity in action, for example, to DDS or Ciba-1906, nor has its antagonistic influence on these preparations been established.

In experiments on tissue cultures G. E. DAVIES and G. W. DRIVER (1958) discovered that ethyl mercaptan affects the tuberculous bacilli to be found inside human monocytes and those of the porpoise. G. W. DRIVER (1960) confirmed the effectiveness of the preparation in relation to intracellular tuberculous bacilli even in the cultivation 10γ/ml. He considers that the preparation modifies the exchange of monocytic substances, depriving the bacilli of substance essential for their activity. According to E. L. ROSE (1958) ethyl mercaptan stimulates the natural defensive strength of the organism infected by the acid-fast mycobacteria and possibly strengthens the degree of antibacterial effectiveness of the macrophages.

T. F. DAVEY and L. M. HOGERZEIL (1958) consider that the preparation does not act directly on the mycobacteria of leprosy, and T. F. DAVEY (1959) thinks the mechanism of action more probably bacteriocidal rather than bacteriostatic.

Etisul is easily absorbed by the skin when rubbed in. J. S. LOWE (1960) with the aid of C-14 tracer substances, established that Etisul is dissolved in the lipids of the skin and calculated that the concentration of mercaptan in the blood, which separates from Etisul after inunction, is 1·5 mg.%, reaching a maximum on the second day. He

also discovered the preparation in the liver. The transformation of Etisul into ethylmercaptan takes place slowly, by means of the skin esterase.

Using the 35-S tracer substance, D. G. JAMISON and E. PALMER (1961) established that four hours after Etisul has been rubbed in particles of it are to be found in heavy concentration between the shaft of the hair and their outer root sheaths. It was also to be found in small quantities in the subepidermal region, a fact which shows the direct penetration of Etisul through the epidermis to the level of the hair follicles. After six hours radioactive particles were found in considerable quantities in the fatty cells and the connective tissue elements, forming an infiltrate. A concentration of radioactive particles is evidently always higher in those places where one can assume the existence of a great quantity of a large infiltration of cells. After 24 hours the marked particles penetrate into the circle of subepidermal nerve clusters and station themselves around the adventitial cells. The concentration of these particles increases around and inside the adventitial cells, in the granulomata, in the cells and lumina of the excretory sweat glands, this stage being particularly pronounced after 48 hours. Consequently Etisul is in fact secreted by the sweat glands, as M. LECHAT pointed out (1959), and after 24 hours penetrates into the blood stream and is concentrated mainly in the sites of the pathological process.

The firm recommends that Etisul should be applied by inunction. Several minutes after application the patient is conscious of a garlic smell on his breath. He may then clean his teeth regularly with a peppermint-flavoured toothpaste or eat peppermint lozenges or sweets. Etisul is most conveniently applied in the bathroom in order to avoid soiling the patient's clothing.

The actual inunction of Etisul (one tube) is done briskly over the whole of the body, except for the arms and the stomach, the head and neck, and the hairy parts of the body. Fifteen minutes after application the patient takes a hot shower (not a bath). After thoroughly cleansing himself of Etisul with soap, the patient dries himself, puts on his day clothes and goes to the ward. Treatment is given to inpatients either by fellow patients undergoing the same treatment or by a nursing sister wearing thick rubber gloves. Before application the patient should be laid on a rubber sheet and afterwards the body wiped down with a sponge and washed with water. The washing of soiled clothing is not effective; the alkali of the soap joins with the Etisul to produce a sulphide smell. The firm, free of charge, provides a special substance, "Lissapol", for washing soiled clothing in boiling water.

The firm's instructions, enclosed in each container with the preparation, advise that inunction should last 15-20 minutes and that on its completion there should be a period of 15-20 minutes to air the

skin before the patient dresses. Inunction should be carried out at any one time on a small part of the body. A. R. DAVISON (1961) prescribed washing one hour after inunction; T. F. DAVEY and L. M. HOGERZEIL (1959) three hours after inunction.

Following T. F. DAVEY's advice, M. LECHAT's patients (1959) were rubbed with Etisul only on the skin of the trunk, and treated each other. There followed a period of 2-3 hours after inunction and before washing during which the patients did not dress (these observations were made on the equator at Yonda leprosarium).

All the authors who have made a study of Etisul are unanimous in pointing out that it is well tolerated, also the absence of toxic complications whatever, even when the preparation is applied in doses of 5·0 g. every day (A. S. GARRETT 1959). In systematic clinical analyses of urine and blood, it has been impossible to detect any abnormalities (T. F. DAVEY and L. M. HOGERZEIL 1959).

According to the firm's prospectus, about 50% of patients during treatment with Etisul suffer slightly from erythema or dermatitis, but this quickly clears up when there is a temporary cessation in inunction. However, COBURN and MARSDEN (1960) reported that in some cases dermatitis was prolonged because of skin allergy. The authors consider that in these cases treatment can be continued, if at the same time as the inunction a dusting of 1% of hydrocortisone is applied. An allergic dermatitis of this kind is mainly to be found in people whose skin is deficient in pigmentation. Dermatitis usually appears after seven to ten days and, if the infection is particularly severe, treatment has to be stopped, but in less severe cases it can be continued. After three applications of Etisul on one patient, H. MCGREGOR (1961) observed that dermatitis, possibly allergic, was quickly developing but put this down not to Etisul treatment but to food which had contained a certain Saravakskiy plant from the Melanorrhoea group, of which the local name is "rengas".

Out of 86 patients receiving Etisul (inunctions two to five times a week) A. R. DAVISON (1961) observed six cases of dermatitis, which, in his opinion, were not connected with Etisul treatment but with the simultaneous dose of DDS; this is confirmed by two other cases of dermatitis (one severe, in the form of exfoliate erythrodermia), which developed in a control group of patients who had not received Etisul treatment.

C. M. ROSS, J. F. TELFER and D. D. HILTON (1960) reported two cases of dermatitis, accompanied by an aggravation of specific eruptions, which quickly passed after Etisul inunctions had stopped. The authors emphasise, moreover, that amongst those patients who had taken DDS treatment rather badly the tolerance of sulphones became considerably better when Etisul was applied simultaneously; severe leprosy reactions ceased and the symptoms of erythema nodosum leprosum became markedly weaker.

B. D. MOLESWORTH (1961) reported that out of 29 patients treated with Etisul, dermatitis developed in one patient but quickly disappeared, although treatment was not stopped; apart from this, eruptions of mild erythema nodosum leprosum appeared only infrequently.

E. DEL PIANTO (1959) indicates that while Etisul is being given in combination with DDS, any existing leprosy reactions cease but usually reappear in weaker form after the course of inunction has finished. D. J. JAMISON, E. PALMER and R. L. VOLLUM (1961), however, observed that children sometimes had leprosy reactions during combined treatment if the dose of Etisul were large. After a temporary cessation of inunctions, the reaction swiftly disappeared. Out of 133 patients treated with Etisul T. F. DAVEY saw only two with weakly-marked leprosy reactions and M. LECHAT (1961) only two out of 28.

H. MCGREGOR (1961) observed that not a single case of severe nephritis developed during Etisul treatment. Out of 29 patients one, after 10 inunctions, developed severe erythema nodosum leprosum. By that time his bacterial index had fallen from 0·5 to 0·33, but five months later, with the continuation of DDS treatment, the patient became bacterially negative.

According to A. R. DAVISON (1961), the percentage of people with erythema nodosum leprosum in a group treated solely with DDS was 37%; in a group treated with DDS, Ciba-1906 and Etisul twice a week it was 33% and amongst those treated with DDS, Ciba-1906 and Etisul five times a week it was 50%.

Given the excellent tolerance of the preparation and the absence of unpleasant collateral effects, many authors think that Etisul could be widely used in outpatient treatment. (H. MCGREGOR 1961; C. M. ROSS, J. F. TELFER and D. D. HILTON 1960; M. LECHAT 1959 and others).

As far as the unpleasant garlic smell of Etisul is concerned, it is not very strong and is, in any case, less unpleasant than chaulmoogra preparations. According to M. LECHAT (1959) and H. MCGREGOR (1961) the smell elicited complaints neither from other patients in the same wards not being treated with Etisul, nor from the patient's family in the case of outpatients. M. LECHAT (1959) points out that after each application the patient's perspiration acquires a definite smell of garlic. In the light of the above information it is a little surprising to see T. F. DAVEY's statement (1960) that because of the strong and unpleasant smell of ethyl mercaptan he was obliged to stop his first trials of Etisul on 18 patients.

Although COBURN and MARSDEN (1960) consider that the *Mycobacterium leprae* does not develop resistance to Etisul, the majority of authors do not share their opinion.

T. F. DAVEY (1959), backed by very great experience in the use of

Etisul, maintains that if treatment is given with Etisul alone its therapeutic effect ceases after 2-3 months. It is not yet clear if Etisul can again become effective after a break in treatment, during a second course. If Etisul treatment is begun at the same time as dosing with DDS the effect mentioned above is usually absent. On the other hand, when a patient begins by taking DDS internally over a period of several weeks and Etisul treatment is then begun, in addition, when the daily dose has reached 200 mg., no resistance develops to the preparation by the end of the third month.

T. F. DAVEY and L. M. HOGERZEIL (1959) maintain that without any doubt there is in fact resistance to Etisul from leprosy bacilli. The first indication of resistance is the recurrence of the typical *Mycobacterium leprae* in smears where only granular forms had appeared before. At the same time there is a definite increase in the activity of eruptions. This is usually to be observed three or four months after the beginning of treatment with Etisul alone. These developments are always absent if treatment is first begun with DDS, augmented with Etisul for about three months, and the treatment then continued with sulphone preparations.

A year later, T. F. DAVEY (1960) reported that out of 15 patients treated solely with Etisul, 6·0 g. each, twice a week, there were signs of resistance in six. Such indications were completely absent from patients subjected to the combined treatment during seven months of observation.

In the beginning dosages and methods in the use of Etisul differed very widely.

Thus, E. DEL PIANTO prescribed for his 33 patients for one year ethyl sulphate daily, 1·2 g. each, in one group and in combination with DDS in the other group. The preparations were taken six days a week; the daily dose was divided into three and taken three times a day, and it was found that the second method was the more effective.

T. F. DAVEY (1960) tried out several methods. One group of patients was treated solely with Etisul—6·0 g. each a week; five out of 15 lepromatous patients showed clinical improvement. In a group treated simultaneously with DDS and Etisul results were significantly better during the first 8-12 weeks than in the following three months. Etisul alone, applied over a period of three months, also gave good results.

However, the best results were achieved with patients who were first put on a course of DDS, orally, 100-400 mg. each, over a period of several weeks after which the treatment was augmented by Etisul inunctions. The author considers it most satisfactory to prescribe Etisul when the preliminary initial DDS treatment reaches its maximum dosage. H. MCGREGOR (1961) treated 27 patients with Etisul over a period of 12 weeks and found clinical improvement in

all of them. M. LECHAT (1959) treated 28 patients, of whom 20 had previously taken DDS. They were all prescribed DDS orally in increasing doses, from 400 to 600 mg. each day, taken three times a day, and Etisul was rubbed in for 12-14 weeks, up to a dosage of 32·0 g. for adults and about 15·0 g. for children. All achieved good results, except two who left observation and two who had severe leprosy reactions.

A. R. DAVISON (1961) made a year's observation of 86 patients, divided into three groups: in the first (33 people) the patients took DDS orally and Ciba-1906; in the second (33 people)—DDS, Ciba-1906 and Etisul, 5·0 g. twice a week; and in the third group (20 people)—DDS, Ciba-1906 and Etisul, 5·0-6 g. once a week. In all groups there was a definite clinical improvement: the "lesion index" in group 1 fell from 6·6 to 4·8, in group 2 from 7·1 to 4·9 and in group 3 from 5·9 to 4·5.

T. F. DAVEY (1960) came to the conclusion that it was most sensible to use Etisul in conjunction with doses of DDS and, better still DDS and Ciba-1906 at the same time. Initially treatment should be given with DDS alone, and when the dose reaches 200 mg. should be augmented by Etisul; this combined treatment should continue for three months, after which sulphones should be used to carry on the treatment.

This principle is now generally accepted and even ICI Ltd. itself recommends users to observe it. At present it is becoming clear which method of treatment is the more advantageous; the 24-week one (application three times a week) or the twelve-week one (six times a week).

Only N. MUKERJEE and S. GHOSH (1960) have been unsuccessful in using Etisul in isolation, in the treatment of 3 lepromatous patients over a period of six months; A. R. DAVISON (1961) reported that the effectiveness of combined treatment was no greater than the usual treatment with sulphone preparations. Everyone else, however, affirms that this form of treatment is in fact more effective. True, T. F. DAVEY and L. M. HOGERZEIL (1959) note that although in the majority of cases there is an exceptional clinical and bacteriological effect, this effect is very weak in some cases. In this connection, the writers remark, the nature of the patients' diet and the length of the illness may play a definite part.

Clinical improvement following treatment by ethylthiosulphate alone was observed by E. DEL PIANTO (1959) in two months; after 3-4 months with Etisul and DDS by T. F. DAVEY and L. M. HOGERZEIL and in even in 3 weeks by H. MCGREGOR (1961).

T. F. DAVEY concludes (1959) that Etisul is "satisfactory" in the treatment of fresh cases of leprosy; in old cases, however, previously treated over a number of years with many other substances, for patients with few bacilli, the results obtained by Etisul treatment are

not marked. M. LECHAT (1959) describes the success of Etisul treatment as "exceptional", and in any case much greater than that achieved by sulphone treatment. In some cases he has been able to observe the disappearance of the leproma and the abundant lepromatous infiltrations literally in the space of two months.

According to ICI information, Etisul treatment obtains its best results, from a clinical and bacteriological point of view, in completely fresh lepromatous and dimorphous cases, which have previously not been treated at all.

D. J. JAMISON, E. PALMER and R. L. VOLLUM (1961) consider an intensive combined course of treatment with Etisul and DDS to be the "optimum".

An improvement in the general condition and well-being of patients is noted by E. DEL PIANTO (1959), D. G. JAMISON, E. PALMER and R. L. VOLLUM (1961), H. MCGREGOR (1961) and many others.

C. M. ROSS, J. F. TELFER and D. D. HILTON (1960), like other writers, point to the resolution of the lepromatous infiltrates and isolated leproma, the loosening of contractures, an easing of pain arising in thickened nerve trunks, and improvement in finger movement and also the comparatively swift disappearance of oedema in the dorsal surfaces of hands and feet. This last phenomenon is particularly emphasised by H. MCGREGOR (1961). Apart from this, he draws attention to the exceptionally rapid resolution of leproma in several cases. D. G. JAMISON, E. PALMER and R. L. VOLLUM (1961) write that in one case of severe lepromatous infection the disease had completely disappeared after three weeks of combined treatment with DDS and Etisul.

B. D. MOLESWORTH (1961) relates that two of his patients were treated with DDS over five years and were constantly suffering from erythema nodosum leprosum eruptions and very severe nephritis. After Etisul began to be added to their treatment the trouble stopped and their bacterial index fell from 2·5 to 0·75 and from 2·1 to 1·3. By the electrophetic method on paper, E. DEL PIANTO (1959) established that in patients with increased globulin content in the blood serum there was a rapid fall which went parallel with the clinical improvement.

E. DEL PIANTO (1959), in observations carried out over a period of one year on patients treated with Etisul alone, noted an improvement in the bacterial index, beginning as from the third month, and remarked that the typical bacilli disappear but that the granular forms of them remain.

According to M. LECHAT (1959), even after two months the bacterial index falls considerably and several patients become negative, although clinically not all eruptions had then resolved.

T. F. DAVEY (1959) carried out observations on several groups of patients. In the first group patients received DDS orally and were also

rubbed with Etisul, 3·0 g. each every two days, over a period of three months, and then took DDS; and even during the first 2-3 months there was an abrupt fall in the index. Under this method of treatment the index continued to improve even after nine months, which does not happen in the case of treatment by DDS alone. In the second group, over a long period of Etisul treatment (from three to 6 months), when the inunction was carried out in limited areas absorption was obviously inadequate and the index fell less than in the case of the patients of the first group. In all the patients of the third group, who had undergone a short course of Etisul treatment following chemotherapy by DDS orally, the bacilli became granular and in some cases disappeared altogether. The treatment of the fourth group was begun simultaneously with Etisul and DDS or Ciba-1906. During the first two months the fall in the bacterial index was more marked than in those patients treated with DDS alone, but in the fourth and fifth months the fall slowed down. In the first month of combined treatment of this kind the quantity of normal bacilli in five of the ten patients decreased by half. In scraped slitskin smears they had disappeared in nine patients, but in scrapings of the nasal mucus they were there as before. Some lepromatous patients were first given DDS orally (twice a week in doses of 100 mg., then of 200 mg, and finally of 300 mg.) after which treatment was augmented by Etisul. During the first two months the results were entirely satisfactory, but then there was a slowing down in the pace of the index fall. In the fifth group 15 patients with severe lepromatous leprosy, who had not previously been treated, received full doses of Ciba-1906 (2·0 g. each), DDS at the ordinary dosage and Etisul (6·0 g.) twice a week. After a month, in the case of 11 patients, the number of normal bacilli had decreased by half and by the end of the fourth month they had in all cases vanished completely in scraped slitskin incisions, but were to be found in the nose. The best bacteriological result was reached in this group.

T. F. DAVEY (1959) emphasises that signs of degeneration of *Mycobacterium leprae*, in the form of pronounced granularity, appear as early as three weeks after the beginning of Etisul treatment.

According to T. F. DAVEY (1959), in lepromatous patients, treated first with DDS and subsequently with Etisul, the bacterial index fell after eight weeks from 3·0 to 1·5, whereas in the case of treatment with DDS alone it was three months before there was any bacterial improvement: Ciba-1906 has the greatest effect in the first three months but to a lesser extent than DDS and Etisul in combination. The best results occur in cases where the illness is recently contracted. There was no effect observed in old cases, previously treated over many years, cases with a great number of bacilli. Treatment with Etisul alone over a 2-3 month period is unsuccessful.

Six months after the initiation of combined treatment in several

leprosaria, C. M. ROSS, J. F. TELFER and D. D. HILTON (1960) observed a fall in the bacterial index in one group of patients from 1·6 to 0·6, in a second from 2·0 to 0·8 and in a third from 3·5 to 0·8. According to their observation, there are morphological changes in the bacilli in skin smears.

The bacilli from the lobe of the ear and the resolved lepromata disappear comparatively slowly. The best results in terms of bacterial negativisation are obtained by regular and combined treatment with DDS and Etisul.

T. F. DAVEY (1960) again reported that there was a bacterial improvement in all 15 lepromatous patients treated by Etisul inunctions twice a week in 6·0 g. doses. It is particularly noticeable that Etisul acts on leprosy bacilli of normal morphology; its influence is weaker on the granular forms.

In 29 lepromatous cases, treated initially over a nine-month period with DDS alone, the bacterial index fell from 1·8 to 0·83; and in the subsequent twelve days of combined treatment from 0·83 to 0·34—a fall of 62%.

According to B. D. MOLESWORTH's observations (1961), out of 22 patients treated with Etisul and DDS, the average fall in the bacterial index was 40%. Typical bacilli, which before treatment amounted to 90%, disappeared during the first month and only reappeared periodically (over a 3-month period) in the cases of two patients and then disappeared again.

Thus, all the writers are in complete agreement in recording the rapid and beneficial effect of Etisul on the bacterial index. Unfortunately, this effect continues when Etisul is used alone for 3-4 months but weakens when combined treatment is employed.

Only A. R. DAVISON (1961), in a comparative study, was unable to record a noticeable difference. Thus, amongst his patients receiving combined DDS and Ciba-1906 treatment, the index fell during a period of one year's observation from 19·9 to 16·2 on average; DDS and Ciba-1906 treatment in conjunction with Etisul inunctions twice a week—from 21·8 to 18·3; similar treatment to above but with Etisul applications five times a week—from 20·5 to 16·8.

All writers agree that Etisul has a much stronger effect on normal leprosy bacilli and a much weaker one, if indeed it exists at all, on the granular forms. Carrying out treatment on four lepromatous patients, previously treated for 2-3 years with sulphones, W. H. JOPLING (1960) was unable to record any clinical bacterial improvement. He supposes that this is because of the absence in such patients of live normal staining bacilli; he assumes that their granular forms are already incapable of living.

There are very few data on the histological changes which take place under the influence of Etisul treatment. In most published work—as, for example, in T. F. DAVEY's article (1959)—there is the

terse statement that after 3-4 months, together with a clinical improvement, "a histological improvement is also observed".

Only D. G. JAMISON and E. PALMER (1960) have reported in greater detail: after Etisul treatment a comparatively rapid cellular change occurs (as early as after three weeks) and considerable decrease of infiltrate takes place in lesions of dimorphous leprosy, and particularly of perivascular infiltrate, and the bacilli gradually disappear; in tuberculoid cases the density of the infiltration diminishes, the number of epithelioid cells diminishes and the peripheral fibrosis is more marked; in lepromatous cases there is a sudden decrease in the density of the infiltrate, the gradual disappearance of bacilli in the infiltrate itself, but the bacilli remain in the nerve fibres of the skin.

Four months after the beginning of combined Etisul and DDS treatment, according to D. G. JAMISON, E. PALMER and R. L. VOLLUM (1961), the characteristic lepromatous infiltrate is replaced by a great quantity of fibroblasts, the number of bacilli diminishes and they take on a granular form.

The report of R. RHODES-JONES (1960) is worthy of great attention in connection with bacteriological research; if microscopic sections of skin for drying, stained according to Ziehl-Neelsen, are put in a thermostat at 37 deg. C. it is frequently impossible to observe the bacilli during subsequent days. In patients treated not with Etisul but with other preparations this phenomenon is absent. Checking his observations, the author established that the "disappearance" of the bacilli in such microscopic sections takes place in periods from 6 to 24 hours. He therefore recommends that stained microscopic sections from patients treated by Etisul should be looked over immediately after staining. It should be recalled that according to D. S. RIDLEY (1960) in ordinary preparations kept at room temperature the stained bacilli continue to be observable at least up to a period of six months. Recently ICI produced a new preparation—Etisul Formulation F-565—analogous to ordinary Etisul, but in liquid form. This preparation is cheaper, and is easier and quicker to apply and has less smell. In literature so far received by us there are two reports by S. G. BROWNE (1961): for three months he treated 17 lepromatous patients, at first giving them dapsone or thiambutosine (Ciba-1906) and then, in addition, EF-565 in doses of 5 ml. each twice a week in the form of inunction; he notes that the therapeutic effect of this substance is higher than that of Etisul. B. D. MOLESWORTH (1961) records that it is well tolerated by the patient and that its therapeutic effect is an improvement in the clinical picture and a rapid fall in the bacterial index.

Our Experience in Russia

In the Upper Kuban leprosarium a course of Etisul treatment was

begun on 10 patients; but of these one left the leprosarium after 10 days; the treatment of another was stopped after one week becauseof the development of universal toxic dermatitis from DDS; and, finally, the treatment of a third patient was curtailed because of an aggravation of chronic nephritis. Thus, seven patients (5 men and 2 women) underwent the full course of treatment. Their ages varied from 23 to 53. They were treated for three months, receiving DRT (sodium hydnocarpate) in the usual doses and Etisul applications six times a week. All patients were of the lepromatous type; four of them were in the progressive stage, two in the quiescent and one in the regressive stage of the disease. All except two had severe and widespread infection. Six patients, apart from skin lesions, had specific nephritis with contractures, atrophy of the hand muscles etc. The duration of the disease varied from three to 19 years (one patient three years; one 9 years; one 11 years; one 16 years; one 17 years; one 18 years; and one 19 years).

Only one patient had not previously been treated at all. The rest, over periods varying from one to six years, had been treated with various sulphone preparations (DDS, sulphetrone, sulphatin); the majority had had intradermal localised infiltrations of moogrol or other chaulmoogra preparations.

Mycobacterium leprae was present in scrapings of nasal mucus in two patients; in scraped slitskin smears from infected parts of the skin it was present in large quantities in five patients and in moderate quantities in two.

As a rule the treatment was well tolerated; there were no complications nor accompanying upsets. The following developments were recorded: an aggravation of neuritic pains during the first two weeks of treatment in two cases; a feeling of sickness, also during the first two weeks, in two cases; erythema nodosum leprosum in one case (before Etisul treatment the patient suffered from this repeatedly), erythematous spots on the chest (quickly disappeared) in one case and, again in one case, a mild papular itching rash on the skin of the stomach, which disappeared without trace after two weeks, in spite of continued treatment by inunction. As far as red and white corpuscles were concerned, there were no changes in haemoglobin content. In the case of three patients the erythrocyte sedimentation rate remained as before (within the range 5-10 mm. an hour), in one case it rose from 8 to 15 and in the case of three patients it fell from 23-43 mm. an hour to 3-8. The maximum arterial blood pressure in one patient fell from 150 to 105 mm. of the mercury column; there were no changes in the rest. No pathological changes were to be observed in urine.

We have no grounds for connecting the development of universal toxic dermatitis in one patient with Etisul treatment. To judge from the clinical picture, it was most probably caused by sulphone preparations (DDS), with which the patient had previously been

treated. The origin of the aggravation of chronic nephritis is not fully clear. In any case, as is mentioned above, special anti-leprosy treatment was temporarily stopped in both these cases.

In all patients treated with Etisul there was, to a greater or lesser degree, a marked clinical improvement and this comparatively rapidly (after 3-4 weeks)—certainly more rapid than in the case of treatment by any other preparation. By the end of the course of treatment all patients had shown good regression of the leproma and lepromatous infiltrates. Down hair, previously absent, appeared on the extremities in the case of one patient. In a second case there was a noticeable loosening of contractures of the hands, and in a third an improvement in high-steppage gait.

Towards the end of the course of treatment, traces of *Mycobacterium leprae*, found in the two patients in scrapings of nose mucus, had completely disappeared and were not observable during the most thorough search. In one patient bacilli were completely absent in the serum from infected places on the skin; they remained in the case of six patients but in greatly reduced quantities, being granular in the majority of cases.

We determined the bacterial index according to the method suggested by M. E. ORLOVA. The index of homogenous forms of *Mycobacterium leprae* is recorded in the numerator and the granular forms in the denominator; the presence of amorphous fuchsinophil granularity is recorded by crosses. If the numerator diminishes regularly and progressively when the treatment is proceeding successfully, the denominator, proportionately with the disintegration of the bacilli, first increases and then diminishes too. The quantity of amorphous fuchsinophil dust, initially absent, gradually increases and then slowly begins to decrease.

The dynamics of the lowering of the bacterial index in individual patients can be judged from the following data:

Patient No. 1	2·0	0·2	0·17		
	0·07	2·2	2·3		
Patient No. 2	1·2	0·3	0	0·3	
	1·5	0·5	0·5	0·5	
Patient No. 3	0·25	0	0		
	0·45	0·08	0		
Patient No. 4	0·17	0	0·5	0	0
	1·2	0·5	0·5	0·25	0
Patient No. 5	0·7	0·5	0	0·2	
	0·8	0·5	0·1	0·2	
Patient No. 6	0·3	0·5	0·17	0·6	
	0·7	0·9	0·6	0·6	
Patient No. 7	0	0·5	0·3	0·5	
	0·3	0·2	0·5	0·5	

In one patient (No. 6) the quantity of normal leprosy bacilli increased from 0·3 to 0·6, and in another (No. 7) the bacterial index of homogenous bacilli rose from 0 to 0·5.

For these seven patients the average index decreased from 0·53 before treatment to 0·21 by the end of the course, i.e. it was more than halved.

At the RSFSR Ministry of Health's experimental-clinical leprosarium at Rostov 10 lepromatous patients including three relapsed patients were given Etisul treatment. The age of these patients—six men and four women—ranged from 15 to 78: one was 15; two were between 31 and 40; two between 41 and 50; one between 51 and 60; two between 61 and 70; and two between 71 and 78. Duration of the disease varied in length from one to twenty years: four patients had had the disease for periods up to five years; one for a period between 6 and 10, and five for periods between 11 and 20 years.

Eight patients were in the progressive stage of the disease, one in the quiescent stage and one in the regressive. All patients, without exception, had previously received different sorts of leprosy treatment, mainly by sulphone preparations, intradermal injections of moogrol, and also Ciba-1906 over more or less lengthy periods of time. Before Etisul treatment *Mycobacterium leprae* was to be found in the case of all patients in scrapings of the nasal mucus and in the serum from skin lesions.

It can therefore be seen from the above that the group of patients receiving Etisul treatment consisted for the most part of severely affected patients with long case histories, half of whom were older than 50. This group of patients was treated by another method. The valid dose of Etisul (5·0 g.) was well rubbed into different parts of the integument, with the exception of hairy parts and the large flexures. After 40-60 minutes the patient took a hot shower and washed himself thoroughly using soap. The inunctions took place three times a week. The course of treatment lasted 24 weeks, during which time each patient rubbed in a total of 360·0 g. of Etisul.

Simultaneously the patients were being treated with DDS according to the standard dosage (maximum dose 0·1 g. twice a day) and were also receiving vitamins, and iron preparations. During the course of treatment it was found necessary in two cases to replace DDS by intramuscular injections of a 50% aqueous solution of soluble sulphone (in saline) and in one case by Ciba–1906, in view of the low tolerance to 4,4, diaminodiphenyl sulphone; in two cases the course of Etisul treatment was not completed, being interrupted before time because of severe true leprosy reaction and eruptions of erythema nodosum leprosum, together with a bad general condition.

As a rule, Etisul was well tolerated by the patients. Only in three cases were there dyspeptic disturbances (loss of appetite, sickness, vomiting), together with weakness and indisposition. One of these

patients, in addition, had a subfebrile temperature. The complete disappearance of these symptoms was achieved by the substitution for DDS of soluble saline sulphone injections with continued and uninterrupted Etisul treatment. Before the course of Etisul treatment, one patient had constant albuminuria, sometimes reaching 0·33 albumen, together with white cells and, at times, slightly modified red cells. There was no worsening in the condition to be observed during the whole course of treatment.

One 40-year old patient suffering from a regressive, strongly marked lepromatous type of leprosy, after one month of combined treatment (DDS and Etisul) developed a severe leprosy reaction with lesions or nodes of the erythema nodosum leprosum type, fever reaching 38 deg. C. oedema of the hands and feet and bad general condition, leucocyte count reaching 23,450, muffled heart tones, a lowering of haemoglobin to 39 % (76 % initially); the red cell sedimentation rate quickened from 33 mm. per hour to 66-70 mm. DDS and Etisul treatment was discontinued and replaced by anti-anaemic and desensitizing preparations. Although, in all probability, the leprosy reaction had nothing at all to do with the Etisul inunctions and was most probably caused by DDS, further treatment on this patient, who had received 180·0 g .of Etisul, was stopped.

The second patient was 15 years old with severe lepromatous leprosy, had been ill for three years and continually had albumen in his urine (up to 0·66 %), erythrocytes and from time to time hyaline casts. He had continual eruptions of erythema nodosum leprosum and the lepromata became aggravated. He was not, therefore, treated regularly but with interruptions of varying length, and, having received 210·0 g. of Etisul, was withdrawn from the tests. This was the only patient who did not derive some benefit from the combined treatment.

Only in the case of one patient—78 years of age—were Turk cells, 1:200 and 1:100, discovered, twice, in the blood, and these disappeared with continued treatment.

Only in the case of two patients, who did not finish the combined treatment because of leprosy reactions, did the erythrocyte sedimentation rate increase—from 33 to 51 and from 54 to 70 mm. an hour. In all other cases it decreased to a greater or lesser but quite marked extent: from 52 to 43, from 41 to 17, from 50 to 35, from 17 to 5 and from 39 to 16. In three cases the erythrocyte sedimentation rate did not change.

After 24 weeks of combined treatment the body weight of three patients had shown no change; one patient lost 2·5 kg. in the middle of the treatment but then regained it. Four patients lost 1-4·5 kg. and three gained weight in the range 3·0-4·5 kg.

No transition from the Mitsuda negative reaction to positive was observed. It should be mentioned that in the case of one 49-year old patient with the progressive lepromatous type of the disease, the

serological reactions (Kahn and Sachs-Witebsky) became negative two weeks after Etisul treatment had begun.

Except for the 15 year old patient mentioned above, who was withdrawn from treatment before the end of the course, all patients to a greater or lesser degree showed a very marked improvement clinically; spots disappeared, the lepromatous infiltrates resolved, and sometimes there was a complete modification of lepromata which became noticeably softer and flatter, some, the fresh ones particularly, resolving completely. Resolution of lepromata was sometimes observed in patients having a disease history of about 20 years. According to our observations, the lepromata and lepromatous infiltrates which yielded best to treatment were those in the upper part of the body and on the upper extremities, rather than those in the lower parts.

The combined treatment was particularly effective in the case of one 53 year old patient, suffering from very widespread and severe lepromatous type leprosy; apart from a very marked regression of infiltrates and lepromata on the integument, numerous lepromata had improved on the tongue and decreased in volume, and fibrous subcuticular lepromata on the dorsal surface of the hand, where they had formed a thick immovable conglomerate sharply decreased in number. There was a hardly noticeable lessening in the thickness of the massive infiltrate on the shins (chronic fibrous panniculitis). *Mycobacterium leprae* disappeared completely. In the case of another patient with a comparatively recent disease history, the skin was almost entirely cleared of lepromatous lesions and the bacilli in the skin serum disappeared entirely three months after the course of Etisul treatment had begun. It can be assumed that Etisul has a continuing effect for some time after the inunctions have come to an end.

After the end of the course of combined therapy, bacilli in the scrapings from the nasal mucus remained in only two patients (one of them did not finish the full treatment). After two weeks of Etisul treatment they had disappeared in the case of one patient; after one month in another; after 1·5-2 months in two others; after 2·5-3 in three cases and after 3·5 months in one case—data which, of course, show the very positive effect of Etisul.

The data presented are convincing proof of the therapeutic effectiveness of Etisul; in all cases, without exception, the index of the homogenous forms of the bacilli fell, sometimes very considerably, as for example in the case of Patient No. 8 from 3·42 to 0·21. The increase in the number of granular forms also proceeded regularly in all patients, reaching a maximum in the middle of the course of treatment, and had fallen in all cases without exception at the end of treatment, being lower than at the outset. The quantity of fuchsinophil dust in the large majority of cases had increased several times by the end of the course of treatment. A biopsy of infected

parts of the skin was carried out on five patients both before Etisul treatment and at the end of the course. Histological study shows that under combined treatment by DDS and Etisul the lepromatous infiltrate resolves, and the contours of the lepra cell become indistinct, while the quantity of bacilli decreases considerably at the expense of an increase in the granular forms and disintegration, and a transformation into fuchsinophil dust.

The dynamics of the bacterial index in the case of each separate patient can be judged from the following chart:

Patient No. 1	0·142+	0·28+			0 +		
	0·428	0·46			0		
Patient No. 2	1·142++	1·14+			0·78+	0·24++	
	1·142	1·39			0·88	0·64	
Patient No. 3	1·42+	1·5	0·32+		0·2+	0·08	0·01+
	0·71	1·35	0·55		0·59	0·35	0·07
Patient No. 4	3·0+	0·85	1·14	1·65+++++		0·48++++	
	2·64	2·14	2·14	2·58		1·2	
Patient No. 5	1·71+	1·48	1·42+++	1·0++++			
	2·14	2·071	1·63	2·52			
Patient No. 6	0·285+	0 +	0·21+	0 +		0	
	0·428	1·75	0·25	0·12		0	
Patient No. 7	1·71+	4·42+	0·67++++	0·07++			
	1·42	6·95	1·0	0·99			
Patient No. 8	3·42	1·81	0·21+++	0·11++			
	2·71	2·1	1·42	0·58			
Patient No. 9	1·285++	1·21+	0·07+++++	0·21++++			
	1·285	1·64	0·85	0·85			

Patient No. 10 was not treated systematically and did not finish the course. In this group of patients there was not one single case of rise in the bacterial index of homogenous bacilli, and on average it fell by almost a third—from 1·568 to 0·606.

The albumen fractions in the blood, which we determind by the paper electrophoretic method, it is not possible to record with definite regularities. At the end of the treatment the albumen content had increased in 8 patients and decreased in two: α1—globulin increased in 4 and decreased in 6, α2—globulin increased in 7 and decreased in 3; the content of γ-globulin increased in 3 and decreased in 7 patients.

On the basis of published data and our own material one may draw the following conclusions:

1. Etisul is an active, well tolerated, anti-leprosy substance and is a valuable addition to the arsenal of medicines for the treatment of lepromatous leprosy.

2. Its therapeutic effect is most clearly pronounced in patients with fresh manifestations of leprosy.

3. Both methods of application (inunctions 3 times and 6 times a week) are equally effective.

4. The disappearance of bacilli in scrapings from the nasal mucus takes place considerably more quickly than in the infected parts of the skin.

5. Further study of the preparation is necessary, in particular to discover its effectiveness during repeated courses.

We tender our thanks to DR. J. M. MUNGAVIN (Medical Division, ICI Ltd.) who kindly made available to us the supply of the preparation necessary for us to carry out our tests.

References

BERTACCINI, G. *L'etil-thiosolfato di sodio nella cura della lebra. Min. Dermatol.* 1955, **32,** 22.

COBURN, J. G. and MARSDEN, C. W. *The Treatment of Cutaneous Tuberculosis with Diethyl-Dithiolisophthalate. Brit. J. Dermat.* 1960, **72,** 192.

DAVISON, A. R. *A Clinical Evaluation of Etisul. Lep. Rev.* 1961, **32,** 40.

DAVEY, T. F. and HOGERZEIL, L. M. *Diethyl Dithiolisophthalate in the Treatment of Leprosy. Lep. Rev.* 1959, **30,** 61.

DAVEY, T. F. *Diethyl Dithiolisophthalate in the Treatment of Leprosy.* A Second Progress Report. *Lep. Rev.* 1959, **30,** 141.

DAVEY, T. F. *Some Recent Chemotherapeutic Work in Leprosy. Trans. Roy. Soc. Trop. Med. Hyg.* 1960, **54,** 199.

DAVIES, G. E. and DRIVER, G. W. *Inhibitory Action of Ethyl Mercaptan on Intracellular Tubercle Bacilli. Nature* 1958, 182, 664.

DAVIES, G. E. and DRIVER, G. W. *The Antituberculous Activity of Ethyl Thiolesters, with Particular Reference to Diethyl Dithiolisophthalate. Brit. J. Dermatol.* 1957, **12,** 434.

DAVIES, G. E. and DRIVER, G. W. *Action of Two Ethyl Thiol Esters against Experimental Tuberculosis in the Guinea-Pig. Brit. J. Pharmacol.* 1960, **15,** 122.

GARRETT, A. S. *Etisul Work in Progress in West and East Africa. Col. Res. Rep.* 1958/59, 1959, pp. 250–2.

JAMISON, D. G., PALMER, E. and VOLLUM, R. L. *Preliminary Trial with Etisul in Northern Nigeria. Trans. Roy. Soc. Trop. Med. Hyg.* 1961, **55,** 142.

JAMISON, D. G. and PALMER, E. *The Distribution of ^{35}S-labelled Etisul in the Skin as Indicated by Autoradiography. Lep. Rev.* 1961, **32,** 135.

JOPLING, W. H. *The Treatment of Leprosy. Postgrad. Med. J.* 1960, **36,** 634.

LECHAT, M. F. *L'Utilisation pratique de l'Etisul (diethyl-dithiolisophthalate) pour le traitement de la lèpre chez l'Africain. Lep. Rev.* 1960, **31,** 265.

LOWE, J. S. *Metabolism of Compounds Related to Ethyl Mercaptan. Biochem. Pharmacol.* 1960, **3,** 163.

MCGREGOR, H. *A Preliminary Trial of Etisul in the Treatment of Leprosy Patients. Lep. Rev.* 1961, **32,** 36.

MOLESWORTH, B. D. *Preliminary Note on a Series of Cases of Lepromatous Leprosy Treated with Etisul. Lep. Rev.* 1961, **32,** 150.

MUKERJEE, M., and GHOSH, S. *Preliminary Trial of Etisul in the Treatment of Leprosy. Lep. Rev.* 1960, **31,** 275.

NAGUIB, M., and ROBSON, J. M. *The Activity of Diethyl-dithiolisophthalate alone and Combined with Isoniazid in the Treatment of Murine Leprosy in the Mouse Cornea. Lancet i,* 1956, 411.

ORBANEJA, J. G. et al. *Primeros resultados del tratamiento de la lepra con un nuevo preparado: "Leprosan". Rev. Fontilles, Valencia,* 1957, **4,** 97.

DEL PIANTO, E. *Chemotherapy of Tuberculosis with 2-mercapto benzthiazole and its Derivatives together with Salts of Sesters of Thiosulfuric Acid. Ricerca. Sc.* 1950, **20,** 83.

DEL PIANTO, E. *The Thioethyl Compounds in the Therapy of Leprosy. Lep. Rev.* 1959, **30,** 23.

RHODES-JONES, R. *Preliminary Report on the Rapid Fading of M. Leprae in Sections from Patients Treated with Diethyl Dithiolisophthalate. Lep. Rev.* 1960, **31,** 200.

ROSE, F. L. *Ethyl Mercaptan*-15,688. *Pharm. J.* 1958, **181,** 235.

ROSS, C. M., TELFER, J. F. and HILTON, D. D. *An Account of the Use of Etisul in the Treatment of Leprosy in the Northern Region of Nigeria. Lep. Rev.* 1960, **31,** 260.

LEPRA REACTION AND THE GENERAL ADAPTATION SYNDROME

By E. MUIR, M.D., F.R.C.S.E., C.M.G., C.I.E.

Introduction

Lepra reaction, in its various forms and symptoms, is one of the most distressing complications of leprosy. Little is known about its direct cause, but it is generally agreed that a reliable method of prevention or control would considerably simplify and shorten the period of treatment, save much suffering, and remove an important cause of deformity.

The objects of this paper are: (1) without dogmatizing to suggest a hypothesis which seems to the writer to harmonize to a certain extent with the principal known facts about lepra reaction, and (2) to indicate lines of investigation which might gather evidence in favour of or against that hypothesis. A list of suggested objects for further study is given at the end of the paper.

The General Adaptation Syndrome, as set forth by Professor Hans SELYE, in his book on *Stress**, seems to throw light on some of the problems connected with leprosy, and particularly on the nature and treatment of lepra reaction† in its two forms: erythema nodosum leprosum‡ (ENL) and acute exacerbation (AE).

ENL is recognised by the sudden appearance of raised, erythematous patches or nodules on the skin of patients with the lepromatous or dimorphous form of leprosy. These patches or nodules generally appear on the sites of already visible skin lesions, but may become visible on apparently healthy skin. Histologically they show oedema, dilatation of cutaneous vessels, infiltration with lymphocytes and mononuclear phagocytes. There is also permeation of polymorphs in direct proportion to the severity of the reaction.

ENL can occur spontaneously without an apparent cause, but it is most commonly associated with chemotherapy and the administration of sulphones, particularly when these are given in excess of the tolerance of the patient and without careful grading of initial dosage. When sulphone therapy is the cause, temporary suspension of the

* SELYE, H. (1955) *Stress*, Montreal.

† It is acknowledged that there are valid objections to the term "lepra reaction" since all the manifestations of leprosy are reactions to *Myco. leprae*. But I have employed it for want of a more suitable generic term, and because it is in general use and is generally understood.

‡ *Erythema nodosum leprosum*, as originally described by M. MURATA (Lep. Rev. April 1958, 116) obviously included both forms of lepra reaction. But in recent years it has generally been restricted to the milder form of reaction, chiefly though not exclusively associated with chemotherapy. Some writers consider the term inappropriate as the lesion in leprosy does not show identical pathological features with classical *erythema nodosum*, but it is used here as the term generally applied and understood.

drug or lowered dosage generally results in the disappearance of the inflammatory signs, but sometimes ENL continues or passes on into AE.

AE is similar in nature to ENL, but much more severe in degree. It affects not only the skin but also the buccal and respiratory mucous membranes, the peripheral nerves, the eyes, and in fact any or all of the regions where lepra bacilli are present. Biopsy shows severe oedema, infiltration and destruction of tissue, with large numbers of polymorphs present. Nodules may suppurate and discharge pus laden with lepra bacilli. There is rise of temperature with general febrile symptoms, and there may be considerable pain and swelling in affected peripheral nerves. There is less tendency than in ENL towards self-healing, and a greater inclination towards repeated relapse. ENL may be aggravated into AE if the cause is not removed in time.

The General Adaptation Syndrome (GAS)

This is described by SELYE as the manifestation of "the sum of all specific systemic reactions of the body which ensue upon long-continued exposure to systemic stress." He divides the syndrome into three stages:

1. *The Alarm Reaction:* This may be called forth by 'alarming stimuli' or 'stressors' and lasts until adaptation has begun to take place. The Alarm Reaction has two phases: shock and counter-shock. During shock there are such manifestations as hypothermia, hypotension, blood concentration, deranged capillary and cell-membrane permeability, and generalised tissue breakdown. There is a discharge of adrenaline, corticotrophin and corticoids, which are early defense reactions. During the phase of counter-shock the phenomena of defense develop. There is enlargement of the adrenal cortex, with signs of increased activity. The phase of counter-shock passes into the second stage, that of resistance.

2. *The Stage of Resistance:* According to SELYE this "represents the sum of all the non-specific reactions elicited by prolonged exposure to stimuli to which the organism has acquired adaptation. It is mainly characterised by an increased resistance to the particular stress or agent to which the body has been exposed, and a decreased resistance to other stimuli. Thus the impression is gained that during the stage of Resistance adaptation to one agent is acquired at the expense of resistance to other agents", whereas during the Alarm Reaction Stage there is loss of lipids from the adrenal cortex, there is deposition of lipids into this gland during the Stage of Resistance.

3. *The Stage of Exhaustion* "represents the sum of all non-specific systemic reactions which ultimately develops as a result of prolonged over-exposure to stimuli to which adaptation has been developed, but could no longer be maintained".

GAS and Specific Adaptive Reactions

"The GAS must be distinguished from the specific adaptive reactions, such as the hypertrophy of the musculature after prolonged exercise, the allergic or immunologic phenomena elicited by certain foreign proteins or microorganisms, etc. These latter responses are not evoked by systemic stress. They usually endow the body with a great deal of resistance against one particular agent (that to which it had previously been exposed), but both the manifestations of such specific adaptive reactions and the resistance which they confer upon the organism are limited to the agent which elicited them".

It has been held by some leprologists that lepra reaction (ENL and AE) is of an allergic nature, but two facts suggest that it is more related to GAS, as described above, than to allergy. These two facts are: (1) lepra reaction appears not as a uniform response to one agent, but as a response to a large number of widely differing agents; (2) it appears most commonly (as will be shown below) in subjects with low general resistance.

The tissue changes described under the Alarm Reaction of GAS (blood concentration, deranged capillary and cell-membrane permeability, and generalised tissue breakdown) correspond with those found in lepra reaction, and it seems reasonable to expect that these changes should be most readily produced and most marked in tissues already weakened and damaged by leprosy infection.

Stressor Agents

SELYE mentions a large number of stressor agents whose manifestations are "so preponderantly due to abnormal adaptive reactions that the direct consequences of the eliciting pathogenic agent assume a secondary position". He compares the convulsions of tetanus toxin in which abnormal adaptive processes are relatively unimportant, with such diseases as hypertension and gastric ulcer in which "the abnormal adaptive response to the agent is the major cause of disease". This is especially obvious since "the same pathogenic stimulus, which produces such changes in one person, elicits no significant disturbances in others whose adaptive mechanism functions normally".

From among the many stressor agents and groups of stressor agents discussed by SELYE I have selected four as having particular relevance to leprosy and lepra reaction. These are (1) sulphur derivative, (2) muscular exercise (excessive or deficient), (3) diet (deficient, excessive or unbalanced), and (4) complicating diseases. It will be noticeable that in all of these power of adaptation is closely connected with the endocrine system, and more particularly with the efficient functioning or failure of the adrenal cortex.

1. *Sulphur Derivatives.* SELYE writes that considerable attention has been given in recent years to adrenal changes caused by various

organic sulphur derivatives, and especially by the thioureas. "It was found in the rat that addition of 1% thiourea to drinking water produced atrophy, simultaneously with signs of hypothyroidism. After 3 or 4 months of treatment with thiouracil all 3 layers of the adrenal cortex showed considerably involution with lipid deposition in the fasciculata; occasionally there were haemorrhages and cysts in the reticularis. Simultaneously there is a progressive decrease in the size of the adrenal medulla. The cortical involution may be regarded in a large measure as an extreme attempt of compensation, probably due to depression of the adrenocorticotrophic factor, since the cortex of such animals promptly responds to infections with hypertrophy. "The production of adreno-cortical atrophy with thioureas has been repeatedly confirmed in the rat, cat, mouse and guinea-pig. It can be counteracted by simultaneous thyroxine administration and, since this atrophy is essentially similar to that produced by thyroidectomy, it is probably due to the resulting hypothyroidism. In the rat occasionally the cortical involution is sufficiently severe to produce a functional hypocorticoidism in which NaCl or cortical extract treatment appear to be beneficial.

"In patients with fatal sulphathiazole intoxication the adrenals often show foci within the inner fasciculata and reticularis, the medulla is apparently not involved.

"Experimental observations suggest that certain sulphur-containing compounds such as sulphonal or sulphocyanate are concentrated in the adrenal cortex following oral administration, especially when free elimination is prevented".

I am not aware whether or not the effect of sulphone administration on the adrenal cortex of experimental animals has been studied but, if the effects are similar to those described above as produced by other sulphur compounds, this would suggest an explanation of lepra reaction in both its ENL and AE forms.

It is a well known clinical experience in sulphone therapy of leprosy that patients are intolerant of full doses at the beginning of treatment. The most common sign of intolerance is lepra reaction, in either its ENL or AE form. Tolerance can however generally be induced by grading the dosage over a period of weeks or months till the patient can stand the most effective amounts.

On the supposition that sulphone acts as a 'stressor agent', this gradual acquisition of tolerance appears to correspond with the General Adaptation Syndrome. Each successive 'alarm-reaction' dose is followed by a higher Stage of Resistance until the patient becomes inured to the most beneficial dosage.

The GAS may also explain the difference between ENL and AE. If sulphone is pressed still further beyond the tolerance of the patient, AE results. This would correspond with the Stage of Exhaustion in which, as mentioned above, "adaptation to

prolonged over-exposure to stimuli can no longer be maintained".

We are justified in considering that this Stage of Exhaustion resulting in AE is caused by hypocorticoidaemia, consequent on the failure of the adrenal cortex to function normally, since AE is promptly relieved by oral administration of corticoids.

2. *Muscular Exercise and Inactivity*. SELYE states that intense muscular exercise in rats, especially in those sensitised by fasting, elicits loss of chromaffin granules of the adrenal, and occasionally extensive necrosis of medullary tissue, as well as cortical enlargement with lipid discharge. He says that his investigations "revealed that in the rat the adrenal becomes extremely hyperaemic during the first hours of muscular exercise, that is at a time corresponding to the Alarm Reaction." Experiments on guinea-pigs showed that, as a result of long-continued training, both the number of cortical sinusoids and their blood content increase, especially in the fasciculate region. Those vascular changes are also similar to those observed upon exposure to alarming stimuli. "Numerous experimental observations in various animals show that sudden intense muscular fatigue causes depletion in cortical sudanophil lipids, while during subsequent rest an inverse reaction takes place". He mentions that a similar depletion of cortical lipids was often reported in prolonged motor agitation due to various diseases. He quotes one investigator as reporting an absolute loss of adrenal weight in rats exposed to brief anorexia, and concluding that this is probably due to loss of cortex tissue, since the water content is actually increased, and histological examination reveals areas of necrosis, exhaustion, atrophy and oedema, SELYE remarks that "since cytolytic phenomena are quite characteristic of very intense alarm-reactions, these observations are not in contradiction with the generally accepted view that the response of the adrenal to anorexia is essentially the same as to any other stressor".

Later, SELYE writes: "The changes accompanying severe muscular fatigue have been ascribed to a relative corticoid deficiency comparable to that produced by infections, irradiations, trauma, etc. This is in accord with our concept of derangements due to hypoadaptation. In some respects, however, the systemic consequence of exercise differ from those produced by other alarming stimuli. Exercise produces remarkably little shock and very pronounced counter-shock phenomena. There is an especially intense and prolonged hyperchloraemia, and, after an initial fall in blood sugar, there follows a marked hyperglycaemia".

SELYE also mentions that the wild Norway rat has much larger adrenals than the inbred albino laboratory rat, and that this is mainly a difference in the development of the cortex. He suggests that more frequent exposure to stress in the case of the wild rat may be respon-

sible for this difference, interpreting the phenomenon in terms of the General Adaptation Syndrome.

In contrast with muscular exercise, SELYE describes the effects of excessive *rest*. "Bed-rest alone can cause marked losses of nitrogen and potassium, a decrease in blood volume, and considerable vasomotor disturbances. The resemblance of these manifestations to those seen in various spontaneous diseases has been emphasised and the delay of recovery from disease caused by extensive 'therapeutic' bed-rest has been illustrated by many examples. Lack of exercise itself requires adaptive adjustments and, since it represents a pronounced deviation from normalcy, it may perhaps act as an 'alarming stimulus'. The possibility has not yet been adequately studied, but observations on the rat suggest that forced restraint can produce General Adaptation Syndrome changes".

There is thus evidence that both excessive muscular exercise, and excessive rest, act as stressor agents, and that at least the former and probably also the latter may help to lead the subject to a state of exhaustion in which adaptation can no longer be maintained, this stage coinciding with damage to and exhaustion of the adrenals.

On the other hand, if stressors are applied moderately in the form of muscular exercise graded according to the tolerance of the subject, resistance can be built up enabling the subject to tolerate not only more strenuous muscular exercise but also other stressors which may offer challenge. Of all stressors muscular exercise is the most suitable for building up general resistance because, as mentioned above, exercise produces remarkably little shock and very pronounced counter-shock phenomena. I shall attempt to show below how muscular exercise in the form of physical training is important in the treatment of leprosy, and particularly in the prevention and cure of lepra reaction.

3. *Deficient, Excessive and Unbalanced Diet.* Reference has been made above to the effects on the adrenals when rats sensitized by fasting are subjected to intense muscular exercise. SELYE states that "various types of unbalanced diets, which cause stress, have been shown to produce typical GAS changes in the adrenals of animals and man. The total fat content of the cortex increases while the birefringent lipid granules tend to disappear from the cortex during prolonged starvation in birds. This is accompanied by an increase in the size of the cortex". Also in the fasting dog the adrenal cholesterol falls below normal. "In the guinea-pig the principal changes observed during starvation are: hypertrophy of the cortex with an increase in total fat and a decrease in birefringent lipid and ascorbic acid content". There are also similar changes in the mouse, rabbit and rat. "Perusal of the literature suggests that complete acute starvation acts as an alarming stimulus and causes an increase in cortical size with loss of lipids, while chronic underfeeding can elicit a stage of resis-

tance with an increase in the lipid content and size of the cortex, presumably due to inhibition of ACTH production. Thus, if the composition of the diet is kept in mind, it appears that partial starvation acts like any other stressor in that it elicits ACTH discharge, but the effects of this response can be modified by conditioning factors". SELYE also mentions that "in man observations concerning the effects of hunger on the adrenals have often been made on a large scale in times of famine. Most investigators agree that the lipid content of the cortical cells can remain high even after most of the fat disappeared from other tissues. Only in very grave acute starvation is there considerable hydropic degeneration, haemorrhage and cytolysis in the adrenal cortex. All these data are consonant with the view that in man, as in animals, chronic undernutrition tends to cause resistant stage manifestations with lipid storage in the adrenlas, while acute complete starvation imitates the alarm reaction with a predominance of cytolytic phenomena and lipid discharge".

Overfeeding likewise causes adrenal enlargement, for instance in the rat. Such an enlargement is produced not only by acute 'food shock' but also by chronic overfeeding. "The possibility has been considered that this again may merely be a manifestation of the GAS. Presumably adaptation both to lack and to excess of food elicits GAS changes in the adrenal".

Various *qualitatively inadequate diets* cause GAS responses in the suprarenals. To quote SELYE: "Protein-rich diets greatly facilitate the production of corticotrophin in animals under stress. On the other hand, in animals not exposed to alarming stimuli, the concentration of protein in the food exerts no significant action upon the adrenal cortex, unless the protein concentration is so high (70 to 90%) that the diet itself becomes a stressor". Again to quote the same author: "In connection with GAS it is of particular interest that muscular exercise causes especially marked adrenal enlargement in rats having insufficient stores of thiamine, and that exogenous administration of yeast prevents this hypertrophy".

"The adrenal lesions in thiamin deficient animals are generally accompanied by thymus involution and other GAS manifestations, and have hence been interpreted as part of this syndrome". This view received further support by histochemical studies.

Ascorbic acid deficiency causes especially pronounced adrenal lesions in the guinea-pig which is notoriously sensitive to scurvy. There is marked enlargement and hyperaemia of the cortex; at the same time haemorrhages are particularly common, especially along the cortico-medullary junction line.

It is difficult to pinpoint the connection between diet and leprosy or lepra reaction, but on the whole there is a correlation between the experimental findings above and the writer's experience of leprosy in India. Throughout that country malnutrition is widespread, but it has

been found that leprosy is most common in areas which are subject to periodic famine following failure of the monsoons, or destruction of crops by floods, thus causing occasional severe starvation.

Physical exercise is important in the treatment of leprosy, but it must be backed by adequate nourishment. Yet it is remarkable how leprosy patients, inured to hard physical work on a diet of little more than a scanty ration of rice or other cereal, along with some form of lentils and a few vegetables, make satisfactory improvement towards recovery.

On the other hand, rich feeding without sufficient exercise is positively harmful, as may be shown by one example typical of many known to the writer. The son of a rich Indian landowner, while his father was still alive, led a physically strenuous life as an engineer. His history showed that for years he had been infected with leprosy, but the symptoms had not been sufficient to attract his attention and lead to a diagnosis. On his father's death, however, he inherited wealth and took up a more sedentary selfindulgent life. Within six months the signs of leprosy appeared in an acute exacerbated form.

The commonest food deficiency among leprosy patients in India is that of vitamins, especially vitamin B; and yeast is found to be beneficial, especially in children. A common indigenous remedy is found in various forms of home-made beer.

4. *Accompanying and Complicating Conditions.* These have an important bearing on lepra reaction, but the effects they produce vary considerably according to the condition of the patient, the type and advancement of the leprosy infection, and the acuteness, chronicity and nature of the complicating disease.

Vaccination for smallpox in a leprosy institution is well known to give rise to lepra reaction in a number of the patients. So is influenza or any acute virus epidemic. Chronic conditions, such as ankylostomiasis and subclinical malaria or filaria, are often found in India to underlie persistent or relapsing lepra reaction. Those complications may be interpreted according to the GAS as affecting the adrenal cortex and causing lepra reaction through hypocorticoidaemia over a shorter or more prolonged period. In leprosy one of the most damaging accompanying conditions is mental distress induced by the social stigma associated with the disease, which often affects the patient and his reactions and involves loss of employment and worries regarding means of livelihood.

Climatic changes such as excessive heat or cold are often responsible for inducing lepra reaction.

Summary of Relationship of Leprosy to the GAS

1. The General Adaptation Syndrome in its true stages of Alarm Reaction, Resistance and Exhaustion is evoked not as a uniform response to a single agent but as a response to many varied agents.

In this it corresponds with and offers an explanation of the nature of lepra reaction which is also evoked by many varied agents.

2. GAS also explains the difference between ENL and acute exacerbation. In the former tolerance is gained during the stage of resistance; while in the latter, stressors too strong or too prolonged lead to exhaustion.

3. Lepra reaction is represented as a result of hypocorticoidaemia. This hypothesis is supported by the fact that the oral administration of corticoids rapidly relieves, at least for a short period, the symptoms of the more severe form of lepra reaction.

4. The tissue changes described by SELYE as those elicited by the Alarm Reaction of GAS (blood concentration, deranged capillary and cell membrane permeability, and generalised tissue breakdown) correspond largely with those found in lepra reaction.

5. Out of many stressor agents mentioned by Selye four are chosen as particularly relevant to the causation of lepra reaction, viz. sulphur derivatives, muscular exercise, defective diet, and accompanying conditions.

6. The stressor effects of certain sulphur derivatives on experimental animals, and particularly on the adrenal cortex, are discussed, and it is suggested that similar effects may be caused by sulphones, thus accounting for ENL so frequently occurring in the beginning of treatment.

7. It is shown how graded muscular exercise in animals strengthens the adrenal cortex, and increases general adaptation to other stresses, while excessive exercise has an opposite effect through damage to the adrenal cortex.

8. Similarly in leprosy patients muscular training may be used to prevent and remedy lepra reaction. The adverse effects of excessive rest and sedentary habits are mentioned.

9. In the treatment of leprosy physical training must be supported by suitable diet. Both unbalanced diet and excessive indulgence are apt to give unfavourable results.

10. Acute and chronic accompanying diseases, and other unfavourable conditions such as mental distress and climatic changes may underlie lepra reaction, and their diagnosis and treatment are of importance.

The Prevention of Lepra Reaction

The milder form, ENL, when caused by excessive initial chemotherapy, can be prevented as a rule by grading the early doses according to the tolerance of the patient. When careful examination shows that the general resistance of the patient is low, sulphone treatment should be preceded by remedying the general condition. Accompanying diseases should be diagnosed and treated, and weakening conditions such as mental anxiety and deficient nutrition

rectified as far as possible. This does not mean that sulphone or other specific treatment is to be completely withheld until all deficiencies have been entirely adjusted, but their presence should be kept in mind when grading the early dosage, and weak patients should be kept under frequent and careful inspection.

The importance of getting into, and remaining in 'training' by means of suitable, graded physical exercise backed by good nutrition has already been emphasised. The patient should be taught that he has to walk towards recovery on two limbs—physical training and chemotherapy, and that neglect of or interference with either will delay or imperil his ultimate cure. It has been repeatedly found by clinicians with wide experience of leprosy treatment that lepra reaction, especially in its severe AE form, is most common among educated 'better class' patients with sedentary habits, and comparatively rare among those whose livelihood is by the 'sweat of the brow'; also that, while defective nutrition is harmful, excessive indulgence in eating and drinking is even more likely to be accompanied by a tendency to lepra reaction. Explained in the light of the general Adaptation Syndrome, those 'in training' are strongly conditioned and adapted to resist the stresses of leprosy itself, of sulphone or other specific treatment, and of adverse complicating conditions. We may consider that in these patients the endocrine system, and particularly the adrenal cortex, is healthy and functioning strongly, and can enable them to stand up to intercurrent adverse circumstances.

Treatment of Lepra Reaction

The milder type of reaction (ENL), when induced by specific treatment with sulphone or other drugs, requires as a rule only temporary suspension or lowering of the dosage.

Acute exacerbation with inflammation, febrile symptoms, neuritis, and pain in the affected parts requires not only suspension of sulphones or other specific treatment but also bed-rest, laxatives, diaphoretics, alkalis and analgesics.

It is important to bear in mind the possibility of some underlying condition which must be diagnosed and treated if the symptoms continue; recourse should be had to some of the well-known forms of treatment of AE, chief among which is the intravenous injection of antimony compounds (potassium antimony tartrate, fuadin, etc.). Only when these fail to bring the condition under control, or when symptoms are particularly acute or urgent (severe nerve pain, inflammatory eye conditions, for example), should corticoids be used. Also in a disease like leprosy where there is a tendency toward osteoporosis and neuropathy, these conditions are apt to be aggravated by large or long-continued dosage with corticoids or by their sudden suppression.

Two methods of corticoid treatment of AE have been practiced in recent years.

1. Large doses of prednisone are given (10 to 20 mgm. daily) with gradual reduction of the dose as the symptoms subside. After this sulphone or other form of specific treatment is continued, its reaction-producing effects being countered with an adequate quantity of prednisone. The objection to this procedure is that fairly large quantities of corticoid have often to be continued over a long period, which implies the danger of producing atrophy of the adrenal cortex, with addiction to corticoids and production of the Cushing syndrome.

2. The other method of procedure, recommended by the writer, is to suspend all specific treatment until the general resistance of the patient has been built up. Begin with minimal doses of prednisone (1½ to 3 mgm. daily), and increase the amount slowly only if improvement fails to appear within 1 or 2 days. As soon as the AE has been brought under control, begin graded physical exercises. These may have at first to be of passive nature if the strength of the patient is much reduced or there is residual pain or stiffness. Certain parts may have at first to be kept at rest (such as an arm or leg by means of bandage, sling, cast or special footwear), but the patient should be encouraged as soon as possible to take active exercise, carefully regulated to his capacity. Further corticoid treatment should be held in reserve, and only given (in minimal doses) if there are signs of relapse of reaction. In the writer's experience it is possible in most cases to built up the physical strength of the patient till at last he gets 'into training'. Only when the resistance of the patient is restored should specific treatment be continued, beginning with carefully graded amounts. The greatest dangers in AE consists in the patient becoming accustomed to bed-rest, and habituated to corticoid medication.

A special note is necessary regarding the prevention and treatment of irido-cyclitis. In any form of lepra reaction the eyes should always be examined, and any sign of ocular pain or inflammation, sluggish, fixed or irregularly shaped pupil should be an indication for dilatation of the pupil with mydriatics.

Further Study

This paper suggests certain questions which require further study.

1. What are the effects of sulphones on the adrenal cortex of animals?
2. What are the effects of iodides on the adrenal cortex in animals? Iodides are well known to have a powerful effect in producing lepra reaction. Is this due to indirect action on the adrenal cortex via the thyroid?

3. What is the effect of thyroxine administration in leprosy and in lepra reaction?
4. What is the effect of NaCl administration in lepra reaction?
5. Could *M. leprae* be successfully inoculated in animals after suppression or partial suppression of the adrenals?

Summary

1. It is sought to explain lepra reaction in its two forms of Erythema nodosum leprosum (ENL) and acute exacerbation (AE) by means of the General Adaptation Syndrome (GAS) of SELYE.

2. Lepra reaction appears not as in allergy as a uniform response to one agent, but as a response to a large number of widely differing agents.

3. It is suggested that the difference between ENL and AE lies in success in producing tolerance to certain stressors in the former, and failure to do so in the latter.

4. An explanation is offered for the appearance of ENL at the beginning of sulphone treatment.

5. The effects of physical exercise, diet and complicating conditions are discussed in the light of the GAS.

6. The prevention and treatment of lepra reaction are discussed with special reference to physical training and cortisone therapy.

7. Certain questions are raised by this paper which require further investigation.

REACTION IN LEPROSY PRECIPITATED BY SMALLPOX VACCINATION

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Smallpox vaccination, it has long been recognized, may precipitate erythema nodosum leprosum and lepra reaction in a proportion of lepromatous patients, and the risk of developing such a reaction must sometimes be weighed nicely against the risk of contracting smallpox. The observations recorded in this paper, drawn from a recent experience of smallpox, may help doctors whose leprosy patients are faced with the threat of the disease.

The outbreak of smallpox.

After a fortnight's visit to his village, a patient under treatment for tuberculoid leprosy returned to the Ekpene Obom Leprosy Settlement, Eastern Nigeria, suffering from mild smallpox. Although he remained in the settlement for only a few hours, within a fortnight 4 patients (1 lepromatous, 1 borderline and 2 tuberculoid), who had been in contact with him, succumbed to the disease.

All the settlement patients were thereupon vaccinated (on 4th and 5th February, 1962), but 6 of these (all with lepromatous disease) developed smallpox in mid-February: 4 of them had adequate scars of primary vaccination, and 2 had been successfully vaccinated for the first time. A fortnight later, a further 3 patients fell ill with smallpox (1 lepromatous, 1 borderline and 1 tuberculoid); 2 of these had been revaccinated and the other had been primarily vaccinated with success, in February.

Except in one fatal case (whose vaccinal state was not known), the disease was generally mild, whether the victims had been revaccinated (10) or vaccinated for the first time when the risk of smallpox was apparent (3). To judge from the symptoms and the low mortality, the severity of the disease was probably attenuated by the vaccination.

Susceptibility to smallpox infection

Although the vaccinal state of patients suffering from the different forms of leprosy was similar and the exposure to smallpox infection was probably uniform, susceptibility to the disease appears to have varied roughly with the numbers of *M. leprae* in skin and nasal mucosa, as the accompanying table indicates.

Form of leprosy	*No.*	*%*	*Vaccinations, February, 1962*				*Smallpox*	
			Total	*Revaccinations*		*Primary vaccinations*	*No.*	*Attack rate*
				No.	*%*			*%*
Lepromatous	64	25	63	38	60	25	8	13
Borderline	36	14	34	18	53	16	2	6
Tuberculoid	140	54	138	90	65	48	4	3
Indeterminate	19	7	19	11	58	8	0	0
	259	100	254	157	62	97	14	5

Lepra reaction in the vaccinated

No patient suffering from non-lepromatous leprosy developed any local or focal reactional condition following vaccination. Of the 63 lepromatous patients vaccinated or revaccinated in February, 1962, 12 developed reaction of some degree: 5 of them were among the 14 patients (including 8 lepromatous) who developed smallpox, the remaining 7 being among the 56 lepromatous patients who did not develop smallpox. Two of the 12 patients (who were suffering from persistent severe reaction when vaccinated), developed smallpox and became worse.

To complete the picture, it should be added that 3 patients with tuberculoid leprosy and 3 with borderline leprosy who had had recurrent attacks of neuritis in the past, with swelling of the skin lesions, experienced no recrudescence after vaccination. A lepromatous patient who had suffered from psychosis four years previously had no recurrence after being vaccinated.

Susceptibility to reaction following vaccination

Of 16 patients with lepromatous leprosy who had previously had one or more reactional episodes, 9 experienced no reaction after being vaccinated, but vaccination precipitated a recurrence of reaction in the remaining 7.

The appearance of reaction seemed to bear no relation to the clinical severity of the vaccinia as judged by the size of the vesicle and the systemic disturbance, nor to the precise level of the Bacterial Index (either on admission or before vaccination), except that only 3 patients experiencing reaction had an index below 1·0.

Clinical features

There were no remarkable features in the clinical varieties of reaction observed, and nothing to differentiate them from reaction as it occurs in this district in lepromatous patients either in the course of treatment or spontaneously. In most of the 12 patients affected, the temperature was raised for a variable period and generalized malaise was marked: 6 had erythema nodosum leprosum; 4 had acute

polyneuritis; in 3, new lepromatous lesions appeared in the skin; 1 had epistaxis.

In 9 cases, the reaction was mild, and seemed to respond to rest, suppression of anti-leprosy treatment and sedatives, though spontaneous resolution cannot be ruled out.

In the remaining 3 patients, however, 2 of them being in reaction when smallpox showed itself, the reactions failed to respond to these non-specific measures and were sufficiently severe to require corticosteroid therapy.

Subsequent progress

Ten of the 12 patients who experienced reaction in some form recovered completely from the episode within a short time, and no clinical deterioration of the leprosy condition occurred. Bacteriological examination of skin smears revealed no interruption in the progressive fall of the Bacterial Index, no difference being discerned between them and the patients who had no reaction.

The condition of the two patients already under treatment for severe reaction when vaccinated continued to be serious. My mid-May one of them was well enough to be discharged from hospital, prednisolone having controlled the symptoms. He, however, died a month later of an intercurrent disease unconnected with leprosy or with lepra reaction. The other patient who had experienced recurrent severe reactions since 1960, was admitted to hospital early in March, 1962, with high temperature, acute purulent degeneration of many recent nodules, and severe polyneuritis. He lapsed into sudden unconsciousness after four weeks of corticosteroid and supporting therapy, and died in a few minutes.

Summary

When exposed to smallpox, patients suffering from lepromatous leprosy seem to be more susceptible to smallpox than those suffering from non-lepromatous leprosy, and those who succumb to smallpox tend to suffer from lepra reaction.

Lepromatous patients run a real risk of developing a reactional condition as the result of smallpox vaccination, especially if they have had reaction previously. This reaction is in general mild and transient, leaving no sequelae and not interrupting clinical or bacteriological progress, but patients already in reaction when vaccinated undergo a deterioration.

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A SURVEY OF DEFORMITIES IN LEPROSY

(with special reference to face)

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Introduction

One of the important reasons why leprosy patients cannot be rehabilitated into society is because of their deformities. With the increasing scope of reconstructive surgery, it is important at this stage to have a better understanding of the incidence of the various deformities of the disease, particularly those which are permanent in nature and which will need surgery in some form or other for their correction. With this object a survey as detailed below was undertaken.

Selection of the Material

In order to assess the true incidence of deformities it is necessary to examine a random and unselected group of persons suffering from leprosy. At Acworth Leprosy Home, Wadala, Bombay, both inpatients and outpatients are available. Inpatients naturally form a selected group and the incidence of deformities in them will be much higher than average, because of accumulation of the deformed cases. This also will be the case with the old outpatients who attend the clinic.

Therefore all persons were screened who visited the clinic for the first time either for diagnosis, confirmation of diagnosis and/or for the treatment of their disease. Out of these people 200 consecutive patients who were confirmed as suffering from leprosy were included in the survey. These patients were examined for the type of disease and deformities as they came to the outpatients' department, there being no selection of any kind. This survey was conducted from December 1961 to February 1962.

Examination of the Patients

The patients were examined clinically and bacteriologically; clinically for the detection of skin lesions, anaesthesia, any obvious deformity of the body, and for the type of the disease; bacteriologically for *M. leprae* in the lesions. The examination was concentrated mainly on the obvious deformities of the body and finding the incidence of deformity such as both affects function and/or appearance of the individual to make him sufficiently distinguishable to a layman as a subject of leprosy and which would hinder his rehabilitation.

Criteria of the Deformity

A. Face.

1. *General facial skin:*
   (a) Nodularity or lepromatous infiltration of the skin sufficient to cause visible stigma.
   (b) Gross wrinkling and laxity of the skin.
2. *Eyebrows:*
   Visible loss of hair sufficient to comprise a stigma.
3. *Nose:*
   (a) Depression or irregularity in its contour sufficient to cause visible deformity. (The interior of the nose was examined by anterior rhinoscopy to detect lesions of mucous membrane cartilage and bone. The sense of smell was also tested but in the analysis only visible deformities are included.)
4. *Ears:*
   (a) Wrinkling and elongation of lobules.
   (b) Loss of helix.
5. *Lagophthalmos: Partial or total*
   (Ophthalmic complications without lagophthalmos such as watering, corneal ulcers or opacities, iritis, etc. are not included.)
6. *Paralysis of other branches of the facial nerve.*

B. Upper extremity

(a) Ulnar, median or combined ulnar and median paralysis.
(b) Absorption of fingers.
(c) Contractures of the fingers and thumb
(d) Ulcers.

C. Lower extremity

(a) Foot drop
(b) Absorption of toes.
(c) Plantar ulcers.

(Anaesthesia, nerve thickening, skin patches have been excluded, though the patients were examined for them, because anaesthesia and nerve thickening do not by themselves constitute visible deformity and later will regress with treatment, and none of them will require surgical correction.)

D. Sex organs

(a) Gynaecomastia
(b) Atrophy of testes.

Classification and Typing of the Disease

The disease was typed first clinically and this later was supported by bacteriological findings, into Tuberculoid, Intermediate and

Lepromatous. Subtyping in these three main types was done according to the extent and number of skin lesions, anaesthetic patches, and nerve lesions, as is given below.

Tuberculoid or Non-lepromatous			*Intermediate or Indeterminate*	*Lepromatous*
A	B	C		
TM1 MA1 P1	TM2 MA2 P2	P3	I B (Border line) RT (Reactionary Tuberculoid)	L1 L2 L3

TM—Tuberculoid major
MA—Maculoanesthetic
P—Polyneuritic (affecting the nerves)
I—Indeterminate

Thus TM1 is a Tuberculoid major case with a small or single patch somewhere on the body and TM2 is a similar case with multiple and/or extensive tuberculoid lesions, all over the body. P1 is a case of nerve involvement with little paralysis or anaesthesia and P3 is a case of multiple nerve lesions and with extensive anaesthetic patches over the limbs and/or gross paralysis of groups of muscles in limb or limbs. The Intermediate group includes borderline cases and reactionary tuberculoid varieties. All sorts of combinations of polyneuritic and other sub-types are possible, e.g. TM1, MA2P3, L1P1, etc.

Sex Incidence and Distribution of Deformity

Males comprise 79% of the cases examined, 63·92% of whom had obvious deformity; while the percentage in female patients examined was 57·14%. Out of 200 cases, 125 had showed visible deformity and 76 cases of these (i.e. 60% app.) required some form of surgery. The number of operations required for these 76 cases, for one or more deformities was calculated as 180 operations.

A few deformities, e.g. absorption of fingers and toes, cannot be corrected by surgery. Some of the deformities recover without any operation, e.g. skin patches, ulcers and many of the lepromatous skin lesions. Thus of the 76 cases with the deformities, the average number of surgical operations required per patient was 2·36.

TABLE 1

Sex	*Number of cases*	*% in* 200	*No. of cases with deformity*	*% in total sex cases*	*% in* 200
Male	158	79%	101	63·92%	50·5%
Female	42	21%	24	57·14%	12%

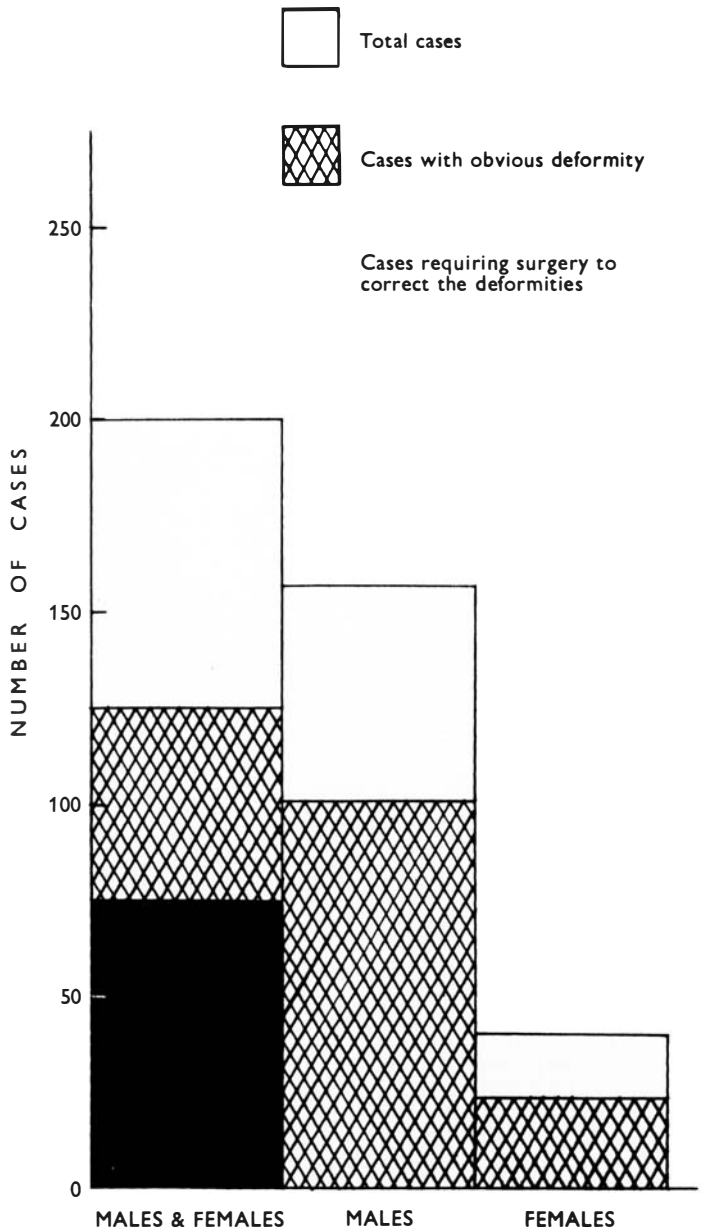


DIAGRAM 1
SEX INCIDENCE AND DISTRIBUTION OF DEFORMITY

Age Incidence and Deformity

The maximum incidence of disease was in the 20 to 29 age group. The number of deformed cases was also maximum in the same age-group. In terms of percentages there is a steep rise from 8·33% at 0 to 9 years to 54·54% at 10 to 19 years. This rise continues with the

TABLE 2

Particulars	0–9	10–19	20–29	30–39	40 & up
	age group in years				
Total cases in each group	12	22	66	54	46
% of age group cases in 200	6	11	33	27	23
No. of deformed cases	1	12	40	38	34
% of deformed cases in total age group cases	8·33	54·54	60·60	70·47	74
No of cases requiring surgery	0	7	19	25	25

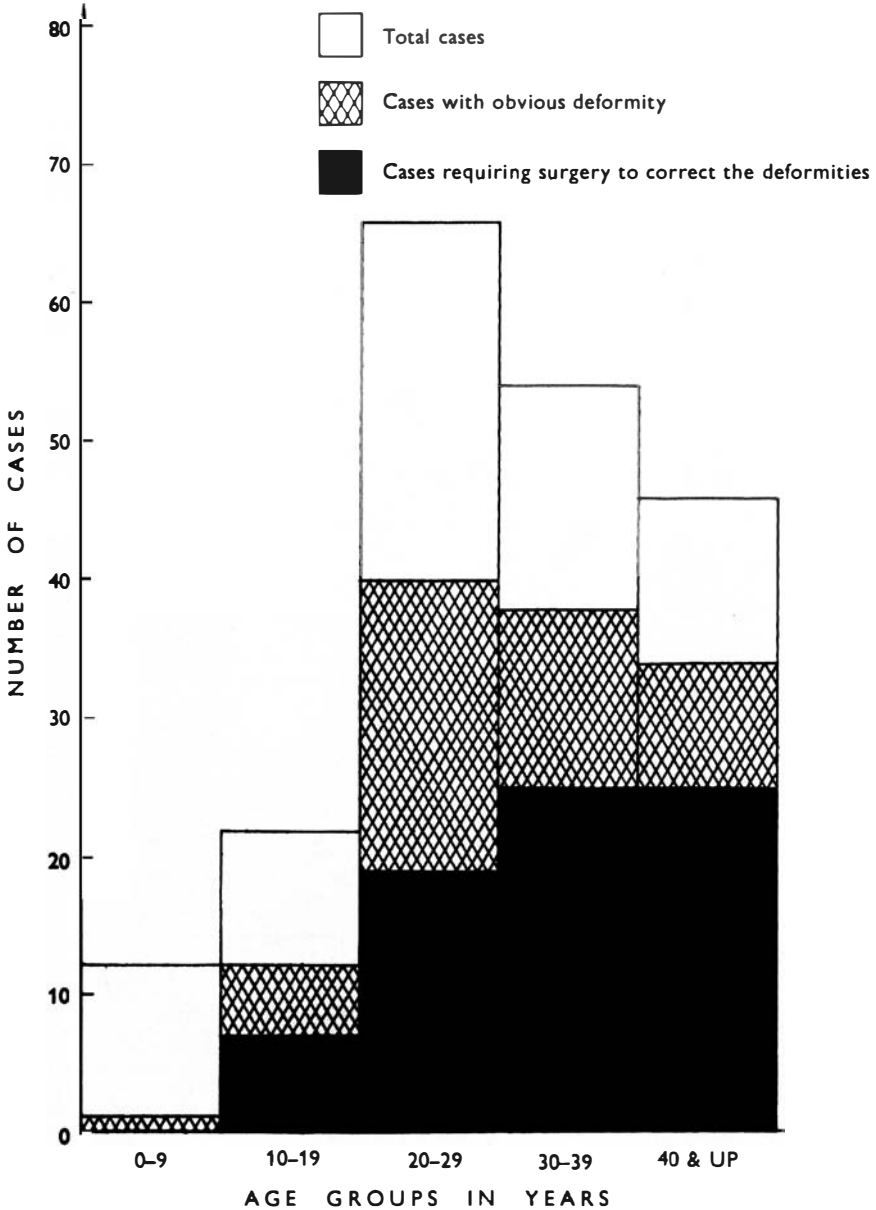


DIAGRAM 2
AGE INCIDENCE AND DISTRIBUTION OF DEFORMITY

age and attains 74% at 40 years and above. The number of cases requiring surgery in each age group also increases with the age, being zero in 0 to 9 years age group and 25 in 5th age group. In 20 to 29 age group the number of cases requiring surgery out of the total deformed cases is 19, which as compared to later age group is less.

Regional Incidence

TABLE 3

	Face	*Upper extremity*	*Lower extremity*	*Sex Organs*
No. of cases with deformity	85	51	40	4
% in 200	42·5	25·5	20	2
No. of cases requiring surgery	48	39	12	4
% in total regional cases	56·46	77 app.	30	100
No. of operations required to correct deformities	101	56	17	6

Of all the regional deformities, those of the face form the largest group and also require the largest number of operations.

Regional Deformities and the Type of the Disease

TABLE 4

	Total cases of each type of the disease and its % in 200	*Face*	*Upper extremity*	*Lower extremity*
Total cases of deformity in each region	→	85	51	40
Tuberculoid	126 or 63%	23	31	24
Intermediate	25 or 12·5%	14	6	5
Lepromatous	49 or 24·5%	48	14	11

The tuberculoid variety constituted 63% of the total cases, then came the lepromatous 24·5% and least were the intermediate with 12·5%. In the lepromatous variety, out of 49 cases, 48 were with visible face lesions and 14, i.e. 28% were suffering from some lesions of the extremities. It is commonly believed that in the lepromatous variety the extremities are not much affected, but in this survey 28% of the cases were found to have some deformity of the extremities. More than 60% of deformities of the extremities belonged to the tuberculoid variety (see table 4A.).

From the table it is seen that more than half of the cases of face lesions belonged to the lepromatous type and about $\frac{1}{3}$ to the tuberculoid variety. In extremities 60% belonged to the tuberculoid and

TABLE 4A

Particulars	*Approximate Percentage in each Group*		
	Tuberculoid	*Lepromatous*	*Intermediate*
Face	27	56	17
Upper extremity	61	28	11
Lower extremity	60	28	12

28% to the lepromatous variety. The cases of deformity of different regions, belonging to the intermediate type varied from 11% to 17%.

Details of Facial Deformities

From Table 3 it is observed that cases with visible facial lesions were 85, i.e. 42·5%. Of these, 48 cases required surgery to correct these lesions. Hence nearly 24% of the total leprosy cases needed some type of facial reconstruction. The total number of operations to correct these deformities was 101.

TABLE 5

Particulars	*General facial skin*	*Ears*	*Nose*	*Eyebrows*	*Lagophthalmos*	*Paralysis of other facial branches*
1. Deformed cases	70	57	36	33	5	2
2. % in total face cases	82·33	67·05	42·33	38·83	5·88	2·35
3. Number of cases requiring surgery to correct the deformity	8	33	22	30	5	2
4. % of total cases requiring surgery to the total in each column	11·42	57·9	61·11	90·90	100	100
5. % of 3 to total face cases	9·41	38·82	25·88	35·29	5·88	2·35

Maximum cases of deformity were in general in the facial skin and constituted 82%. Many of these were lepromatous infiltrations which would regress on treatment but cases with paralysis of facial nerve branches which were very few would need operations in all the cases. In the nose, lesions of the mucous membrane, cartilage, or bone did not always produce visible deformity. Silent perforations of the septum without visible external deformity were present in 4 cases in the series. It was also observed that unless there was complete destruction of the nasal lining the sense of smell did not disappear.

Summary

200 unselected cases of confirmed leprosy attending the out-patient's department at The Acworth Leprosy Home, Wadala, Bombay, were surveyed for deformities and the results analysed in terms of age, sex and regional distribution. The sex distribution of

deformities showed predominance of males to females in the approximate ratio of 4 : 1. The incidence of deformities with age showed a steep rise in 2nd decade (55%) and by the age 40, 70% of all cases examined showed visible deformities which could be classified as stigmata of leprosy. The regional distribution of deformities showed preponderance of facial deformities. The estimated total number of operations per patient with deformity was 2·36. The relation of various deformities to the type of leprosy have also been discussed.

It is hoped that this survey will be of help to the planning of a reconstructive surgery programme in any area where the percentage incidence of leprosy per population is known.

Acknowledgement

I am greatly indebted to my teacher Mr. N. H. Antia, M.B.F.R.C.S. (ENG)., Hon. Plastic Surgeon, J.J. Group of Hospitals, Bombay, for his kind help and guidance in this study. I am also thankful to the Superintendent, The Acworth Leprosy Home, Wadala, Bombay, for his permission to examine the cases in his institution and for help and advice. Also to Miss K. B. Kothare, Occupational Therapist, A.L. Home, Wadala, Bombay, who has helped me at every stage of this study.

AN UNUSUAL CASE OF ACNE KELOID

H. W. WHEATE, M.B.B.S., D.T.M. & H.
Chazi Leprosarium, Morogoro, Tanganyika.

A police constable, aged 20 years, was referred to this leprosarium for diagnosis in May 1962. He gave a history of bilateral swelling of the ears of about three months' duration, not associated with pains or irritation.

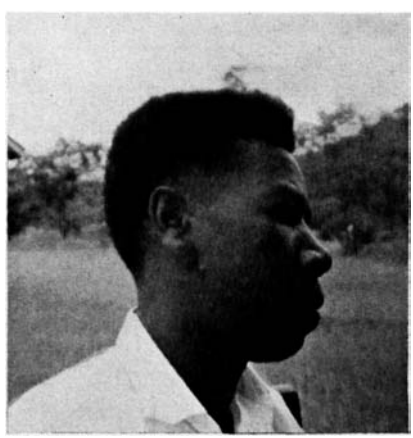
The findings on examination were:

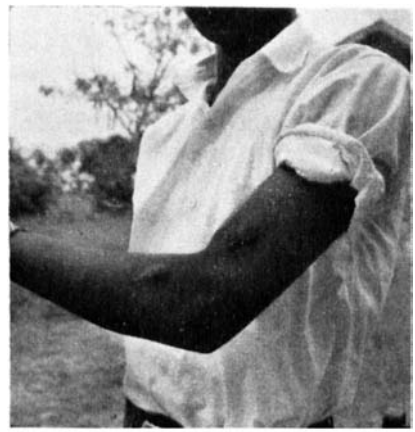
1. Acne Vulgaris of the face, with keloid scarring over the jaws.
2. Very hard nodular swellings of both ear lobes similar in size and shape.
3. Two keloid scars of the left arm, which the patient stated were the result of injury some years ago.
4. Skin scrapings were negative for *M. leprae.*

Acne Keloid, as seen in African dermatological practice, is usually situated on the neck (CLARKE, 1959) but SIMONS (1952) illustrates a case with a keloid, due to acne vulgaris, on the nose.

Other conditions considered were:

1. Sporotrichosis, to which the lesions of the jaw bore a superficial resemblance. No fungal elements were found and there was no history of exposure to infection (A. GONZALEZ OCHOA, 1953).
2. Chondroma, excluded on the history and the nature of the swellings.
3. Lepromatous Leprosy was, of course, excluded by the absence of any typical lesions and negative skin scrapings.





It may be of interest to record that, although one frequently sees keloid scarring in patients with tuberculoid and near tuberculoid leprosy, particularly following the local application of indigenous remedies (usually vegetable caustics) I cannot recall seeing keloid in a lepromatous case. This is perhaps not surprising when one considers the absence of foreign body reaction in lepromatous leprosy.

Acknowledgement

My thanks are due to the Chief Medical Officer, Tanganyika for permission to publish this case.

References

CLARKE, G. H. V. (1959). *Skin Diseases in the African*, p. 39.
OCHOA, A. GONZALES (1953). *Handbook of Tropical Dermatology and Medical Mycology, Vol. II*, p. 1329. (Edited by R. D. G. Ph. Simons).
SIMONS, R. D. G. PH. (1952). *Ibid., Vol. I, Fig.* 23, p. 40.

ARTIFICIAL LIMB MAKING

By HAMISH MACGREGOR, M.B.E.
Superintendent, Rajah Sir Charles Brooke Memorial Hospital, Kuching, Sarawak.

One of our patients with a completely disorganised foot and ankle and with chronic ulceration was eventually persuaded to undergo below the knee amputation. Although a Sea-Dayak he is a singer of Malay songs and was the recognised soloist with our orchestra but, due to the ulceration, he had to give this up. Amputation was advised but he was most reluctant to agree until members of the orchestra prevailed upon him to have it done and thus be able to take part in their various activities. Following the amputation he was as miserable as could be for he was still unable to join with them during the Christmas entertainments but, thanks to two members of our staff, he was fitted with a home-made artificial limb and joined in the celebrations of both Chinese New Year and Hari Raya.

The artificial limb is made of materials which are readily available here and in most places:

A. Stump-holder made of strong leather with a soft leather lining or cork-latex cast to the actual stump; the holder can be made to lace up or to fit the actual stump—whichever is desired.

B. Metal strips (two) which are rivetted to the stump-holder and screwed to the wooden leg—one to each side.

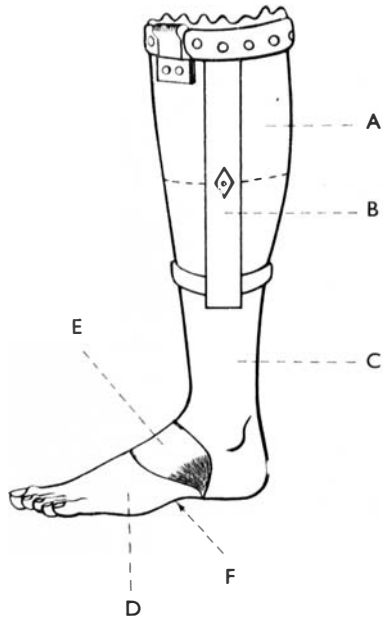
C. Wooden leg—local timber and shaped as required.

D. Wooden foot—local timber and shaped as required; a thin metal rod is passed into the wooden foot and screwed into the wooden leg to prevent any swivelling of the foot.

E. Leather flap which helps to hold the foot and leg in position.

F. Metal strip (thin springy metal preferably) inset into foot and base of leg—which acts to hold both foot and leg together and as a spring when walking.

The great merit of this limb is not only that the patient can and does walk but that it can be made up wherever there is a handyman available and it is relatively cheap to make. When Dr J. Ross Innes, the Medical Secretary of the British Leprosy Relief Association, visited us in 1960 he advocated surgery for a number of patients and stated that the first operation, whatever it might be, must be successful for then other patients would readily come forward. This has been proved by the fact that since this limb was successfully fitted a number of patients, with equally useless feet, have requested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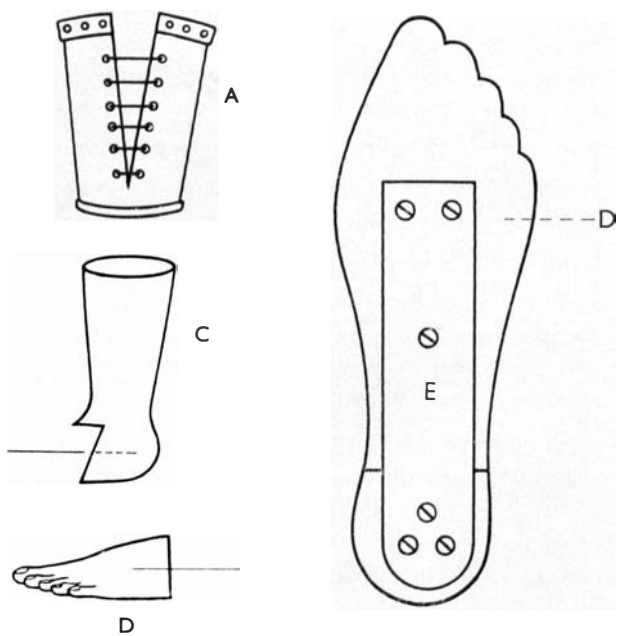
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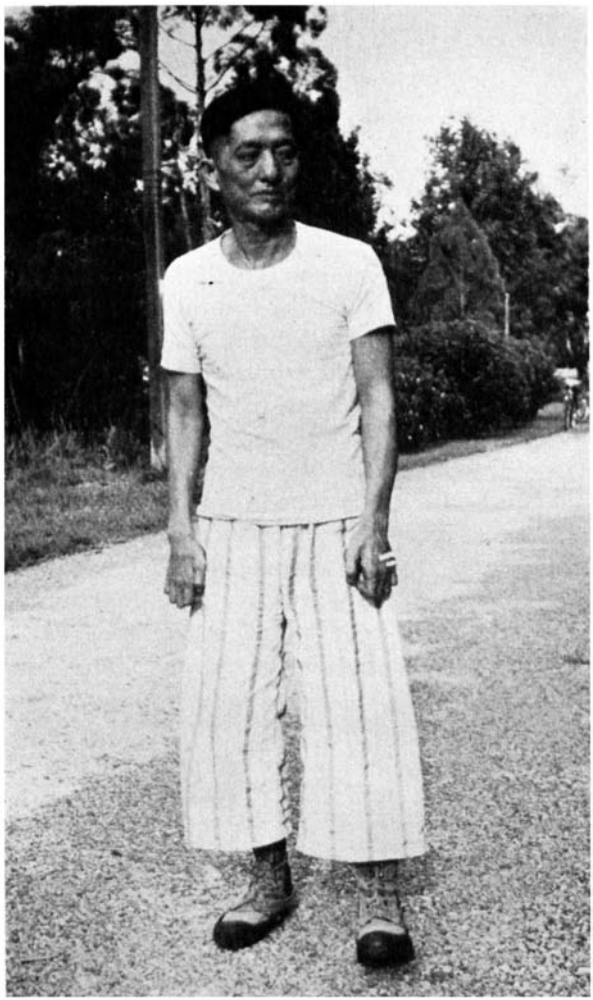

amputation—knowing now that they can be fitted with artificial limbs and will be able to walk around.

Great credit is due to the two members of staff who worked on this project and whilst it is still subject to adaptation, as and when experience indicates, the fact remains that it works, is cheap to make, the patients concerned are happily walking about and no longer occupying hospital beds.

Thanks are due to the Director of Medical and Health Services, Sarawak, for permission to publish.

LETTER TO THE EDITOR

INST. OSWALDO CRUZ,
RIO DE JANEIRO.

Dear Sir,

In answer to the remarks of Prof. R. Chaussinand (Leprosy Review, 31 No. 4, October 1960, p. 308) I beg you the kindness to publish the following information. On 12th September, 1947, Dr. Chaussinand kindly gave me at the Institut Pasteur, Paris, two rat lepromas for my studies. From September 1947 to December 1948 I inoculated suspension of said lepromas in two batches of white rats in which the classical lesions appeared from six to twelve months. With the new lepromas, after various unsuccesses, I obtained in November and December 1948 two strains (I and II) of chromogenic cultures in Loewenstein medium, of pure a-f bacilli, which I passed to other rats, recovering retrocultures pathogenic for murines.

On 15th March, 1949, I inoculated suspension of Stefansky lepromas in ten black mice (Mus musculus, C-57 Rockland Farms, New City, N.Y., U.S.A.) which from 22 to 48 days incubation showed plaques of alopecia, musculocutaneous lesions and enlarged lymph-nodes. From these black mice I obtained two non-chromogenic eugonic cultures of a-f bacilli (Strain III) from tumor of mice killed on 22nd day incubation and Strain IV from enlarged lymphnode of the last mouse died on 12th July (118th day incubation. These four a-f strains I presented at the 5th International Congress for Microbiology (meeting of 23rd August, 1950, presided over by the late Professor Sir Alexander Fleming), telling that all four were permanent acid-alcohol fast, fluorescent 2 plus, but the chromogenic negative to Dubos test for virulence and the non-chromogenic (III and IV) positive 2 plus. This fact was kindly confirmed by Professor P. Hauduroy. Dr. Chaussinand present at the meeting of 23rd August in Petropolis, gave a look to the cultures and said that they were "Para-tuberculous bacilli" (sic!). After the Congress I sent to Dr. Chaussinand samples of all four above strains, with the hope that he could confirm or not his suspicion. But he never wrote me any word on the subject. Now, in October 1960, after ten years, he says: "I have not changed my mind since then".

Dr. W. K. Stefansky published in 1903 as "Eine lepraaenlich Erkrankung der Haut und der Lymphdruesen bei Wanderratten" (Centralb. f.Bakteriologie etc., Bd. 33, No. 7, 1903. Orig. Abt.) the disease of rats he discovered in Odessa, Russia, and confirmed in the same year in Germany and in England, and later on described all over the World as "Rat Leprosy". In 1948, being elapsed 45 years of the important discovery, Professor Chaussinand presented a paper at the National Academy of Medicine of Paris, telling that the

infection described by Stefansky was not leprosy, but paratuberculosis (Bull, A.N.M., Année 112, Tome 132, 1948, pp. 486-488).

If the strain of rat infection of Chaussinand's Laboratory is really "paratuberculosis", I should be congratulated for having got the above strains of a.a. fast bacilli. The great speciálists in mycobacteria, Professor P. Hauduroy and Professor G. Penso affirm that it is very easy to isolate and cultivate acid-fast bacilli from such type of infection. Why then Dr. Chaussinand failed after ". . . the very numerous attempts at culture of the Stefansky bacillus . . . strain have never up to now resulted in the appearance of a culture of acid-alcohol-fast bacilli of any type"?

In July 1951, in the Van Deinse's Laboratory, Professor Hauduroy said to me that the name para-tuberculosis bacillus has no significancy, what should be taken into consideration is the pathogenicity of the strain in cause.

Also Professor Giuseppe Penso says: ". . . la division des mycobactéries, en bacilles tuberculeux et en bacilles paratuberculeux, est une distinction fictive qui peut servir à de simples fins empiriques et conventionelles, mais que n'a pas use base rationellement scientifique". (In P. Hauduroy—Bacilles Tuberculeux et Paratuberculeux, Masson, 1950, p. 101).

The following characteristics of my a-f strains differentiate them from the so-called paratuberculous: All four cultures are permanent a.a. fast; show coccothrix form when strained by Fontes method; are fluorescent 2-plus; (the chromogenic I and II), "S" type are negative to cyto-chemical Dubos test for virulence; the non-chromogenic "R" type (III and IV) gave positive Dubos 2-plus. All four strains gave negative reaction with all nine phagi from the Instituto Superiore di Sanitá of Rome, according to Dr. Vittorio Ortali, some of which do react with paratuberculous bacilli. The strain III used as antigen in Bordet-Gengou test carried out with bloods of 38 leprosy patients gave 69, 2% positivity.

Higher positivity (92%) was obtained with such bloods using as antigen the suspension of Stefansky leproma, the same strain obtained with Dr. Chaussinand. The subject merits larger scale of researches.

DR. H. C. DE SOUZA-ARAUJO

(Note: We regret to report the sad news of the death of Dr. de Souza-Araujo this year in Brazil. This news was brought by Dr. E. Muir who visited Rio in August this year).

ABSTRACTS

Early Diagnosis of Leprosy by Study of the Sweat Response to Ionophoresis with Parasympathomimetics. V. MARTINEZ DOMINGUEZ. Bull. World Health Organization, **26,** 1962, pp. 227-231.

The early diagnosis of leprosy is essential to the success of a leprosy control scheme. Simple clinical examination does not always lead to early diagnosis, and skin tests using pilocarpine and histamine employ a complicated technique, and there is a degree of difficulty in interpreting the results. At the 7th International Leprosy Congress in Tokyo in 1958 Prof. Gay Prieto suggested a new technique which utilises the sweat response to the ionophoresis of parasympathomimetic substances. The present article describes in detail the apparatus and how to use it, and how to read the results. Some Tables give the results in healthy skin and in skin of the lesions. In Katsina in Northern Nigeria the consultative team in leprology of WHO tried out the new method, using acetylcholine for ionophoresis. The author reports of 45 skin lesions. In 40 cases sweating was modified. Some cases gave a response of doubtful value, possibly because of an organic defect in the physiological processes of sweating in the people of that part of the world. Total anhydrosis was met with often in the tuberculoid form, and not so much in the indeterminate form. In 5 cases of the 45 the test did not cause any modification in the lesions of macular leprosy. The test on the whole was found to be useful. It is easy to use and previous sterilisation is not needed, which is a great advantage in field work, especially with children. Further trials of the method are now called for.

Isolation of Diphtheroid-like Organisms from Human Leprous Nodules; J. K. SARKAR. Journ. Indian Med. Assoc. **38,** 8, April 16, 1962, pp. 387-388.

On a culture medium prepared from human foetal nerve extract two strains of diphtheroid-like organisms have been isolated from human leprosy lesions. One of these organisms injected into a lepromin-negative guinea pig converted it to lepromin-positive. This organism or its filtrate may therefore possibly be used as antigen in place of lepromin.

Neurological, psychological and psychopathological aspects of leprosy. A clinico-nosographic contribution concerning 75 cases. G. ARGENTA. Monograph of 118 pages, with many illustrations and references, Editrice Calia, Napoli, 1961. (Original in Italian.)

The findings can be summed up as follows:

1. Practically all the patients presented neurological symptoms: in only 8% did the neurological examination give a negative result.

2. In 56% of the cases (42 patients) the onset of the disease was characterized by non neurological symptoms; subsequently, however, 36 of these patients developed neurological signs, many of them in an early stage. In 44% (33 cases) the onset of the disease was marked by neurological symptoms.

3. Most of the patients in whom the disease commenced with non-neurological manifestations were between 10 and 35 years old; patients in whom the nervous symptoms were already present at the onset were of all ages at that time.

4. In 60% of the cases the disease was of familial nature. The criteria of familial character and of geographical origin are of great importance in connection with an early diagnosis of the disease.

5. The beginning of the nervous manifestations was characterized by the following manifestations (in order of decreasing frequency):

hypo-aesthesia to heat and pain (accidental burning etc.)
pains, sometimes of truncal, sometimes of pseudo-rheumatic type
fatigue, depressions, insomnia
paraesthesia (not painful)
disturbances of trophism: torpid ulcer, painless whitlow, etc.
earlier trauma
psychic disturbances.

6. The objective symptomatology was characterized by:

peripheral paralysis, with very evident atrophy; the deep reflexes decreased parallel with the atrophy, but they were rarely completely abolished. Sometimes they were lively but without pathological pyramidal phenomena. The atrophy showed a predilection for the musculature of the hands and to a lesser degree of the arms, legs and feet;

in 10 cases (approximately 13%) without clinically demonstrable atrophy, the hands showed a loss of the capacity to make certain movements connected with the intrinsic musculature; 7 of them proved incapable of opposing the first and fifth fingers; the author ascribes to this phenomenon the significance of early symptom of neurological involvement in leprosy;

superficial tactile anaesthesia (76%), heat and pain anaesthesia (85%), vibration anaesthesia (20%) and deficiency of the sense of position and movement (4%);

enlargement of the nerve trunks: the ulnar nerve was palpable on one side in 15% and on both sides in 25% of the cases; the median nerve was palpable in 6% of the cases, the branches of the superficial cervical plexus were palpable in 3% of the cases;

disturbances of osseous and cutaneous trophism (24% of the cases);

ocular symptoms: corneal opacification (17%), cataract (3%), disturbances of accommodation (2%), disturbances of the pupil reflex, anisocoria, anisocyclia (9% of the cases);
parkinsonian syndrome (1 case), ataxic syndrome (1 case), their relations with the leprosy infection are doubtful;
psychic disturbances (15%).

7. The topography of the peripheral nervous lesions was studied according to the distribution of the anaesthesia.

The distribution of the anaesthesia in the truncal innervation territories is to be regarded as the most frequent form; the distribution in very large territories (stocking type, glove type, etc.), entering only partially into the truncal territories is the less frequent form, while the form with irregular areas is a little more frequent than the second type mentioned but much less frequent than the first mentioned type; in 4 cases, the possibility of a localisation of the lesion at the radicular level was to be considered.

8. The author comes to a conclusion that according to his own clinical experience "leprosy psychosis" is not be to reputed to exist.

In 2 cases of confusional syndrome with excitement, a specific toxi-infectious mechanism was likely to exist. In the remaining cases (2 depressions, 2 morphine toximanias, 1 case of hysteria, 1 case of delusional reaction, 1 hypochondric syndrome, 1 case with dysphoric crises, leprosy has got only a pathogenic value through only a psychogenic mechanism. The psychologic silouhette sprang from the clinical research and mental tests (Rorschach, Wechsler Bellevue Intelligence-test) and is characterized by mental poverty. (We are dealing though with people at a very low standard of education), a pretty balanced affectivity, a rather dysphoric temper.

REVIEWS

A new Journal "Rovisco Pais", a Portuguese Review of Leprosy, has just issued its first number of its first volume January to April *1962*. We give a warm welcome to this new leprosy journal, and give some account of it. It is produced by an editorial committee at the Hospital-Colonia Rovisco Pais, Tocha, Portugal. The first number is well produced and printed and contains 109 pages with many illustrations. The work of the Technical Committee on Leprology is first described and the following original articles given:

1. The Lepromin Reaction of the Staff and Officials of the Hospital—Colonia, by P. DE. MAGALHAES BASTO and H. SEABRA SANTOS, pp. 24–30.
2. A Trial of Ciba-1906 in hospital inpatients of Rovisco Pais, by A. JOSE DE FIGUEIREDO BARBOSA, pp. 31–59, and
3. The Residual Aspect of Chronic Pyodermatitis in Childhood, considered in the Differential Diagnosis of Leprosy, by J. OWEN PINTO, pp. 62–68.
4. The Decompression of the Cubital Nerve in Leprosy, by J. VEIGA VIEIRA, pp. 71–81. There are 13 illustrations to this paper.

The Journal "Rovisco Pais" also contains many interesting notes and short articles, such as "The Politics of Leprosy in Portugal", Bibliography of the Activities of the Institute of Assistance to Leprosy Patients and of the Hospital—Colonia Rovisco Pais, Activity of the Services, and the Movement of Patients.

Collected Papers of Prof. Tanimura of Osaka University.

Volume of 636 pages issued by the Alumni Union of the Department of Dermatology and Urology of the University of Osaka School of Medicine, and dedicated to Prof. Tanimura in celebration of his 70th birthday. This great Japanese scientist was born in 1891 and retired in 1955 and is now an Honorary Professor of Osaka University. His main interests have been in dermatology, dermato-urology, microbiology, and he has given a lot of attention to leprosy and murine leprosy. The volume is beautifully produced and printed, and it is extremely valuable to have all his scientific papers in one book, and printed in English, and some in German. There are 12 papers on tuberculosis (9 in German and 3 in English) and 11 on leprosy and murine leprosy (all in English). There are also 16 papers on miscellaneous subjects (3 in German and 13 in English), and 10 papers contributed by members of the Alumni Union (all in English).

The papers on leprosy are:

1. TANIMURA, T. and NISHIMURA, S. *Studies on the pathology of murine leprosy.*

2. TANIMURA, T. and NISHIMURA, S. *A Review of recent animal inoculation studies with human and murine leprosy.*
3. TANIMURA, T., NISHIMURA, S., and TANIMURA, Y. *Studies on the immunology of murine leprosy.*
4. TANIMURA, T. and NISHIMURA, S. *Experimental study on the chemotherapy of leprosy. Efficacy of drugs on murine leprosy.*
5. TANIMURA, T., NISHIMURA, S., and KONO, M. *Experimental study on the chemotherapy of leprosy.*
6. TANIMURA, T., NISHIMURA, S., and IWASA, K. *The screening test for chemotherapeutic agents for leprosy.*
7. TANIMURA, T., NISHIMURA, S., NAKAO, M., and KOSAKA, K. *Susceptibility of hamsters and wild rodents to murine leprosy bacillus.*
8. TANIMURA, T., NISHIMURA, S., YASUKAWA, T., and KOSAKA, K. *Immunological relationship between leprosy and murine leprosy.*
9. TANIMURA, T., ITO, T., and SONODA, R. *The enzyme activities of murine leprosy bacillus.*
10. TANIMURA, T., HONDA, H., and OSIMA, T. *Studies on the serology of leprosy.*
11. TANIMURA, T., FUJINAMI, T., and HONDA, H. *Studies on the serologic test for leprosy: serum reaction using Wax D.*

"*De Diffuse Lepra Van Lucio en Latapi*" (Diffuse Leprosy of Lucio and Latapí) is a valuable monograph of 250 pages by J. H. FRENKEN of Rotterdam. There are many illustrations. The main text is in the Dutch language but a summary is given in English on pp. 234–239. An excellent bibliography is given on pp. 240–248. This monograph carefully systematizes and records the present knowledge and opinions on the Lucio phenomenon and is so important that we hope an English and a Spanish version can be issued.

MØLLER-CHRISTENSEN, V. *Bone Changes in Leprosy*. 51 pp., 9 figs. and 16 pls. (32 refs.) 1961. Copenhagen: Munksgaard, Denmark. (from Tropical Diseases Bulletin).

This is in effect an extremely well illustrated thesis which establishes the diagnostic point in leprosy that atrophy of the anterior nasal spine and loosening of the upper central incisors are typical of leprosy. This has been shown to apply not only to the 358 skeletons of mediaeval leprosy patients at Naestved in Denmark, but also to modern leprosy all over the world, where the changes in the nasal bones and teeth can be clinically detected, and furthermore are detectable at an early stage. The author also describes the accepted bony changes in the limbs and small bones of the limbs. In the plates I to IV the changes in the maxillary alveolar process, the anterior

nasal spine and the palate, are convincingly demonstrated in contrast with normal bones. There is no doubt that Dr. Møller-Christensen provides a means of making an early diagnosis in modern leprosy, because the nasal-dental changes can be seen everywhere in early lepromatous leprosy. This thesis should be in everyone's hands.