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EDITORIAL

1. Visits to Malaya, Sarawak, Sierra Leone and Gambia

These four visits were made in the months of October and November, 1960. The Editor finds such visits to spheres of leprosy work an inestimable privilege and of the greatest value scientifically. Even on the humble level of the clinical appearance and evolution of leprosy in one country as compared to another, there is much to learn. Even in the difficult field of classification of leprosy, we would have less confusion and fruitless argument among leprologists, after organized visits. At present, each leprologist describes and classifies leprosy as he sees it in his country, and does it faithfully enough. But for solution of the problem of an *international classification* of leprosy, we consider it an essential first step that a team of leprologists of international provenance who should be good observers and not too proud to take notes should tour the leprosy countries to report on the leprosy found and its evolution, and its response to the modern drugs, and other matters of general interest to all countries who are trying to deal with leprosy. The human side must not be forgotten, for both leprosy workers as well as patients get great encouragement from visitors from abroad who are genuinely interested in their work and their cure, respectively, and in their problems as a whole.

(*a*) *Malaya.* The Federation of Malaya has now achieved independence. We only had 5 days there but these were crammed with interest. We were on our way to Sarawak in Borneo as the main purpose of our journey to Southeast Asia from London, but in Malaya there was much to see, and there was no sloth nor tardiness in seeing it. The main focus of the visit was Kuala Lumpur which is the Federated Malayan capital in the State of Selangor. Only 10 miles away is the large leprosarium of Sungei Buloh, and some 21 miles from Kuala Lumpur is Pulau Ketam which is the site of the careful long-term BCG trial as a prophylactic against leprosy. We also met in Kuala Lumpur the Hon. the Secretary for Health, Dr. Mohammed Din Bin Ahmed, and Mr. E. J. Lawrence, who is the publicity secretary of the Malayan Leprosy Relief Association (MALRA) which is newly formed but very active and likely to be a tower of strength to leprosy work in Malaya. Dr. M. Waters kindly took us many times to Sungei Buloh leprosarium and to his leprosy Research Centre there (which is under the guidance of the Medical Research Council of U.K.) and to the site of the BCG trial against leprosy amongst a static well-controlled population. Sungei is a large leprosarium of over 1000 patients which is very beautifully situated and built and was formerly under the charge of Dr. Gordon

Ryrie, then Dr. David Molesworth, and latterly Dr. P. K. Reddy. At present it has no medical superintendent, and the Hon. Dr. Mohammed Din Bin Ahmed, Secretary for Health, assured us that the post can be considered open and applications will be welcomed by him. Dr. Bhojwani is a medical officer still working in the leprosarium, and Dr. Waters of the Leprosy Research Unit has 2 wards under his charge. At Sungei Buloh no physiotherapy is available but the reconstructive and plastic surgery for repair of deformities and stigmata of leprosy has been undertaken by Dr. Reddy and Dr. Bhojwani. Dr. Waters kindly accompanied us to visit Pulau Ketam, where we found a well-planned, well-documented, and well-supervised trial of BCG as a prophylactic against leprosy. The population is static and well-recorded. A leprosy survey there was done at the very beginning and in 5 years or so some useful data about the value of BCG may emerge. This trial impressed us as so well planned and observed over the years that it can hardly fail to yield useful results, and we congratulate Malaya and the Medical Research Council on this trial. MCFADZEAN, J. A. and BHAGWAN SINGH, R. reported on this trial in *Leprosy Review*, **31**, 3, July 1960, pp. 145–158. In the island of Pulau Ketam on the West Coast of Malaya, 3,720 persons in the age group 0–25 years were examined and the incidence of leprosy found to be 19 per thousand. Then 3,649 persons apparently free of leprosy were tuberculin-tested. Of these 3,222 were eligible for vaccination with BCG and by randomization 1,648 were vaccinated and 1,574 left as controls. The expected incidence of leprosy in the unvaccinated group over 10 years would be enough to demonstrate a level of protection of the vaccine of 50% or more. The expected incidence of leprosy in the intake of the newborn is too low to give significant results and this part of the trial has been given up. The plan is to examine for leprosy at intervals over the next 10 years the present population of 0–25 years of age. It was found that the conversion rate after BCG vaccine was lower than expected almost certainly due to a fall in the viable count of the vaccine used, itself due to tropical conditions. The authors think that in future trials the viable counts of the vaccine should be checked before use in the tropics.

The present incidence of leprosy in Malaya as a whole is unknown. There is need of a leprosy survey. Seeking to make a guess, it might be between 30 and 50 per thousand. The type of leprosy is preponderately lepromatous, of one variety or other, perhaps 70% lepromatous, and Dr. Waters has studied some cases which resemble the Lucio phenomenon. Deformities may be 25%. The task in Malaya is not only huge but they have a grave type of leprosy. Nevertheless they have priceless assets in the shape of Sungei Buloh Leprosarium, with the Leprosy Research Centre in its grounds, and the Pulau Ketam trial. One feels that a build-up of staff will set the

whole campaign going again. There is another priceless asset in the shape of the Malayan Leprosy Relief Association (MALRA) which already exists with a powerful membership and is already engaged in a publicity campaign to explain the true nature of leprosy and is interested in all sorts of support and ideas to help forward the leprosy campaign.

One feels that the Malayan leprosy work is of good quality at the base, and could readily aim at complete victory over the disease. The next stages are opening up the campaign by organizing surveys and treatments in the rural areas, restoration of full staffing, training of nationals in leprosy recognition and care, the introduction of physiotherapy, and reconstructive surgery, the use of research to try out new drugs as they become available, as well as basic research, propaganda to explain the true nature of leprosy, that it is only a disease like any other and that patients can be medically cured and surgically restored to beauty and usefulness, so that very many can be returned to civic life as useful citizens.

(*b*) *Sarawak*. We spent 2 weeks there (10–24 October), and found it a most attractive and stimulating country. There are some countries in the world which envelop the visitor in happiness, and Sarawak is high in this select group, because of the niceness of the people and their goodwill for good causes, allied to a refreshing strain of practicality. The population is 175,000 and our guess at the leprosy incidence would be the existence of 15,000 active cases of leprosy (a leprosy survey has not yet been done). The Director of Medical Services, the Hon. D. A. Baird, O.B.E., is "well up" in the experience of and understanding of leprosy, and surely an unique feature of the present Sarawak is the possession of a Governor who has *taken part in a leprosy survey* and also understands leprosy. Sir Alexander Waddell helped us in an early leprosy survey in 1938 in Malaita Island of the British Solomon Islands in the Western Pacific, and was indispensable. It was a magnificent stimulus to hear at the outset something of Dr. Baird's plans for the improvement of district or "ulu" medical work, and for the training of nationals as medical assistants, which obviously would fit in splendidly with the opening-up or widening-out of any future leprosy campaign. We also met and stayed with Mr. and Mrs. Hamish MacGregor, M.B.E., who live in a staff house at Kuching leprosarium (Rajah Sir Charles Brooke Memorial Settlement) which is 13 miles from Kuching the capital. Mr. Hamish MacGregor has been Superintendent of the Kuching Leprosarium for 11 years, and our later daily examination of the work revealed its essential soundness and the faithful steady work of Mr. and Mrs. MacGregor, Generawi bin Mok, Lau Thian Seng, Edward Chia, and Chin Jin Fok reflecting the greatest credit on them and the Sarawak Medical Department and Government, who fostered such good work. In the Rajah Sir Charles Brooke

Memorial Leprosarium, some 300 to 380 patients are treated. We had the chance of examining all the patients in the ensuing days and found that most of the patients had become cured medically, but the great number awaiting discharge, but prevented by deformities, was striking. Naturally a patient does not consider himself cured if he has a claw hand or a perforating plantar ulcer, and the introduction of active physiotherapy and reconstructive surgery will soon be arranged. The great centre of these arts is Prof. Brand's work in Vellore, and volunteers will go from Sarawak to learn his techniques. We found that in Kuching they had made themselves familiar with the potentialities of the newer drugs, had tried them out, and apprehended their advantages. There is a heavy preponderance of the lepromatous type of leprosy, and of the diffuse lepromatous in particular, and examples of the Lucio Phenomenon were not wanting (a necrotizing diffuse lepromatous variety). The tuberculoid type of leprosy provided few cases, and the lepromatous rate in the leprosarium was 90%, and probably 70% in the country as a whole. Yaws is a frequent complicating disease, also tuberculosis of the lungs. The whole picture of the leprosy was of a grave infectious disease, with strong tendency to nerve involvement and to reactions. These reactions are, however, mild on the whole. The heavy incidence of the diffuse lepromatous type should be noted. This type in very early stages may be missed in diagnosis, which emphasizes the value in any future survey or leprosy control scheme of the importance of the laboratory for smears, histology, lepromin preparation and tests. Another thing notable in the Kuching patients was the infrequency of the Borderline types, almost as if in a recent invasion by leprosy of the country (1200 A.D. for Sarawak?), the complicated intermediary types of leprosy have not had time to appear in all their delectation for argumentative leprologists. The bacterial transmission and invasion seems to remain uncomplicated for a long time, producing in a people who have low resistance on the whole a general manifestation of leprosy of the lepromatous type, and in the few who *have* resistance scanty manifestations of tuberculoid leprosy which may become borderline or lepromatous if not rapidly "cured". Another point of great interest, in view of the *González theory of the beneficial influence of thyroid depression on leprosy*, was the fact that Sarawak has goitre valleys between limestone hills, in which valleys leprosy was thought to be minimal in incidence and clinically less grave than in non-goitrous areas. In the future leprosy survey needed in Sarawak, it would be most valuable to include a close epidemiological study of the goitre areas, with special reference to the incidence and morbidity of leprosy. We did see one case at Kuching of a boy of about 12 years who had a developing goitre and leprosy, and the leprosy was a mild *tuberculoid* type.

Sarawak is soon to attempt a country-wide leprosy campaign,

aiming at eradication. The good work already done augurs success, perhaps in 10 years. As we mentioned above, we detect a strain of practicality in Sarawak peoples, and certainly they are not rigidists nor obscurantists. The Medical Department under Dr. D. A. Baird, with a wealth of excellent personnel, has already planned the training of nationals as medical assistants, and this will include training of nationals in leprosy lore under Mr. Hamish MacGregor at Kuching Leprosarium (Rajah Sir Charles Brooke Memorial). Recognising leprosy as a human disease occurring frequently in the country, they are forward-looking and open-minded, and quite ready to try to use if of value every possible good means, *even if new*. They are quite ready to get away from the conception of the modern leprosy campaign as a ponderous military operation with counter-marching and marching of big-booted parties of soldiers, and accept a conception of a Commando operation containing continued frequent, lively, and widespread attacks, recruiting and training of more soldiers (national leprosy personnel), maintenance of laboratories and research (one cannot imagine commando soldiers not being interested in new weapons, and not making intelligent trials of promising new weapons, as well as not seeking new discoveries of their own to improve the campaign and basic discoveries which will help *all* commandos). A good Commando will also take prompt steps to eliminate possible obstructions, as for example a large accumulated backlog of untreated deformities and stigmata, which can be dealt with by volunteers especially trained for the task in physiotherapy and surgery, otherwise this obstacle would cause depression and loss of hope among the *people*, and bring the campaign to a halt. These pioneer volunteers can set up schools and courses to teach other commandos. Obtaining of officers for the commandos (medical officers supervising the campaign or parts of it) has not been forgotten by Sarawak. Finally, but not least, for it should come first, a good Commando group will certainly "case the joint" and keep on "casing the joint" which means sizing up the enemy and his territory by a leprosy survey, steadily repeated. It all comes down to personnel and good soldiers. We think Sarawak already has a fine nucleus of such, and because it proposes to recruit and train many others, and arm them with weapons and tactics which they have tried out and proved in their own conditions, success is very probable in a short period of time. The total leprosy problem is moderate in scope, say some 15,000 patients with active leprosy, and the task should be compassed successfully in perhaps 2 five-year periods.

(*c*) *Sierra Leone and Gambia.* We also had the privilege, in November 1960, of a visit to *Sierra Leone* and *Gambia*. In *Sierra Leone* the leprosy situation has been surveyed, the last survey being that by C. M. Ross and helpers in 1958, who indicate that probably there are 80,000 cases in Sierra Leone, with a lepromatous incidence

of the order of 20%. This means a far milder type of leprosy than in Sarawak and Malaya. Dr. Ross advised a countrywide campaign, with adequate trained personnel, and the opening of leprosy dispensaries and the use of mobile teams and domiciliary treatments if they could be staffed. Dr. Ross pointed out that it would be wise to build a new leprosarium to act as the focus or centre of the campaign, as a site of training of nationals as leprosy assistants, of records, of research, of physiotherapy and surgery, etc. There was no intention that this new leprosarium was to be based on the former idea of institutional segregation, but accommodation for 100 patients would be provided for those requiring special care and investigation. In leprosy campaigns the possession of at least one forward-looking leprosarium has enormous advantages, not the least as being a centre of training for leprosy workers. Of course leprosy workers need field training also, but their study of leprosy recognition and care best begins in an institution where there is time for reflective study and the learning of new techniques. This idea of Dr. Ross was obviously so sound that it appealed to the Medical Department, and finance was set aside and a site chosen at *Masanga*. BELRA helped by providing workers, first Mr. and Mrs. Alan Waudby, then Mr. and Mrs. J. Boyd and Mr. R. Lowes, and very recently Mr. Alex Munro. The Colonial Office provided a medical officer, Dr. W. Bowman, who was sent to Nigeria for the study of leprosy, and on this our recent visit it was a great pleasure to find that he had returned to Sierra Leone, and had been at work since August 1960. We met him later frequently up-country, and in Freetown also had the privilege of fruitful interviews with the Minister of Health, Hon. Taplimah Ngobeh, with the Chief Medical Officer, Dr. H. M. S. Boardman, with his Deputy, Dr. A. B. Cole, with the Epidemic Disease Control Officer Dr. Neville Campbell (who has been in charge of yaws work in Sierra Leone but well understands leprosy and has given great help where he can), with Mr. R. Lowes our BELRA worker, and with Dr. F. Marti, regional representative of UNICEF, who have always afforded great practical help in leprosy campaigns. Very soon we went up-country and were with Dr. Bowman at Magburaka, from whence we visited the Masanga site, and the active leprosy dispensaries of the EUB Mission at Rotifunk (Drs. Silver and Harris), at Moyamba Hospital (Dr. P. C. Kothari, F.R.C.S., who is interested in plastic and reconstructive surgery for leprosy patients), Mabonta Clinic (Dr. Campbell and Mr. Lowes and Mr. A. S. Conteh), the leprosy clinic at Magburaka Hospital, M.C.A. Mission Clinics at Yifin and Mayoso. I heard that there were 13 clinics or centres which give treatment with DDS. Mr. Alan Waudby of BELRA, before he left had opened 130 clinics or centres which give treatment with DDS. Dr. Bowman has begun training of leprosy assistants. We visited the Masanga site and found that the early stages had run into difficulties

and these had delayed progress, but it may be expected to go ahead now and soon achieve its full and crucial place in the antileprosy campaign. With approximately 80,000 cases of leprosy, Sierra Leone has a tidy task, but it could achieve success.

In Bathurst, *Gambia*, we spoke with the acting D.M.S. (Dr. D. W. Bringam) and found that things could go ahead there, but there was some delay in obtaining a medical officer for the leprosy campaign. BELRA has already sent a worker, Mr. Mead, and he and Mrs. Mead are housed at Bansang, which may later be the centre and focus of the Gambian leprosy campaign (8,000 to 10,000 patients, many with deformities).

2. The Theory of Hypothyroidism being Favourable to Leprosy and the Action of Thyroid-Depressant Drugs against Leprosy.

Dr. ARTURO O'BYRNE GONZÁLEZ of Cali, Colombia, is the originator of this theory and has long pondered and investigated it, and has tried out methimazole-Lilly (a propyl thiouracil type of thyroid-depressant drug) against active leprosy with reported good results (shortly to be published in the International Journal of Leprosy, we hear). Dr. González has recently sent us a *Letter to the Editor* which describes his main lines of thought. The original is in Spanish, and we reproduce it in English here, considering it of great interest and importance.

Letter to the Editor from DR. ARTURO O'BYRNE GONZÁLEZ:

In 1952 and 1953 I treated a female leprosy patient who also suffered from a thyrotoxicosis of Graves-Basedow. I started her treatment with propyl-thiouracil, thinking that the treatment of her thyroid condition was more urgent than that of the leprosy. Nine months later I noted two effects of the drug, an improvement in the endocrine state and the disappearance of the leprotic macules.

Seeking a reason for the effect of the propylthiouracil on the leprosy, I emerged with the first argument, as follows:

(*a*) Iodine is harmful to the leprosy patient;

(*b*) This harmfulness of iodine has been used as a therapeutic measure (Danielssen, Muir, Schujman, Ross Innes) through a stimulation of the antigenic processes;

(*c*) Iodine bound to protein (PBI) is a normal and necessary constituent of the human body, at a normal estimated level of 5 to 8 micrograms per 100 ml. of blood;

(*d*) It is known that thiouracil and its derivatives *decrease* the proteic iodine (PBI);

(*e*) It is probable that thiouracil and its derivatives, on decreasing the proteic iodine also decrease the vitality of *M. leprae*.

These 5 points above may be amplified with some secondary arguments.

Why does the vitality of M. leprae increase in the presence of iodine?

1. We should take into account that mycobacteria are thought to be derived from algae, modified and adapted to man. The *Encyclopaedia Britannica* says: "In many respects the bacteria resemble some of the simpler plants, particularly the blue-green algae and some of the moulds, and it is largely on the basis of

this resemblance that bacteria are considered to be *simple plants* rather than animals. They are placed with the fungi, a group which includes the chlorophyll-containing blue-green algae and the non-chlorophyll yeasts and moulds".

2. "As in the case of the other algae, diverse marine Chlorophyceae (Bryopsis, and to a lesser extent Ulvaceae, Cladeophora, etc.) store up considerable quantities of iodine, though it is not as definitely localised as in some Rhodophyceae (F. E. FRITSCH, Professor of Botany in the University of London, Queen Mary's College)".

3. "Iodine is present in sea water. It occurs most abundantly in seaweeds. For a long time iodine has been recovered on a commercial scale from seaweed".

4. Hence the "iodophilia" of the mycobacteria could have phylogenetic antecedents.

Could there be some etiological similarity in lepra reaction produced by the administration of iodine and natural lepra reaction?

1. Probably so. There are various epochs in human life in which the level of proteic iodine is higher, such as during pregnancy, menstruation, puberty, the menopause, psychic stress, etc. In the same way we note the frequent aggravation of leprosy during pregnancy and menstruation, the greater incidence of malignant forms during puberty, and the frequency of lepra reactions during the menopause and during periods of stress.

2. There exist other epochs in human life in which the proteic iodine and therefore the function of the thyroid gland are low, such as during the first months of life and during old age. In the same way we note that the child of leprosy parents does not have manifestations of the disease during the first year of life, and that the old man also has not a big incidence of malign forms of leprosy.

3. "Somewhere there must be an endocrine link, lepromatous leprosy being the masculine type and tuberculoid leprosy the feminine type, with a number of patients who are not definitely either, but are, at various stages, between. The same or a related endocrine influence may be associated with higher male and lepromatous ratios which exist at present time among races whose skins are less pigmented than the Africans". (J. A. KINNEAR BROWN, Internat. J. of Lep. **27**, 3, p. 250.)

Some biochemical studies by SISTER HILARY ROSS indicate that the proteic iodine in leprosy patients under treatment is *normal*. Various other studies show "that a diet too rich in either fats or proteins or both causes an increased rate of discharge of iodine from the thyroid gland and a resultant iron deficiency. Carbohydrate diets do not produce this condition". (MCCARRISON, R. Indian J. of Med. Res., Calcutta, **7**, 433–647, 1919–20.)

It is probable that this influence of carbohydrate diet on the peoples of India and of other leprosy endemic areas may explain some questions. The areas of the civilized world where the diet is rich in either fats or proteins have a low incidence of leprosy.

Antithyroid substances are those able to suppress the formation of thyroid hormone in the normal animal and thus to diminish the proteic iodine of the blood.

There are "antithyroid foods". Some of these have a considerable antithyroid activity. The chief foods of this class, in their order of potency, are the rape or rutabaga, carrots, lettuce, turnip, peas, peaches, grapefruit, kidney beans, pears, walnuts, beets, spinach, cabbage, filberts, string beans, celery, grapes, milk. A study of these foods in relation to leprosy in various countries of the world would be most interesting.

Derivatives of aniline and of mercaptan occur among the artificial antithyroid compounds. "It was concluded earlier that the aniline compounds owe their antithyroid activity to the presence of an appropriately substituted aminobenzene grouping: $NH_2C_6H_4$ (ASTWOOD, 1944–45; TAUROG, CHAIKOFF, and FRANKLIN, 1945). ANDERSON, 1949, notes that this concept must be expanded to include methylated aniline derivatives and amino-heterocycles (MCGAVACK, "The Thyroid", 1951, p. 177). This remark of MCGAVACK causes us to ask if diamino-diphenyl-sulphone, $NH_2C_6H_4SO_2C_6H_4NH_2$, which is the chief anti-leprosy drug, is one of the antithyroid substances? We could also ask the same about Ciba 1906 which is a thiourea derivative.

There is a fact of great importance for future investigations. The majority of the compounds used at present in the treatment of leprosy and of tuberculosis

have a certain degree of antithyroid activity (Streptomycin, INH, thiosemicarbazone, PAS).

A comparative study of biochemical analysis of blood in leprosy and in hyperthyroid states leads to analogous results, very encouraging worthy of a detailed study.

From 1953 to the present time I have treated 236 individual leprosy cases with antithyroid substances. I first used those associated with DDS, in small doses. Next, greater doses were used of antithyroid drugs of the type of propylthiouracil in assocation with small doses of sulphones. In the third stage I used antithyroid drugs alone in progressively increasing doses (Tapazole, propylthiouracil).

The general results have been satisfactory in all stages of the investigation, but the order of therapeutic efficiency accords with the chronological order. The best results have been got with Tapazole-Lilly (methimazole) without combination with other antileprosy drugs. I have the impression that the addition of abundant milk to the diet improves the therapeutic effect still further.

The technique used in recent months with Tapazole was to push the dose to a maximum as soon as possible, which for an adult of average weight can be 40 to 50 mg. daily, divided into 3 or 4 doses. The possibility of intolerance must be watched, and white cell counts made whenever suitable.

I do not think that the optimum dose of Tapazole has been found yet. It must be remembered that (according to MCGAVACK) a patient of BASEDOW could become myxoedematous with a dose of 4 to 5 microcuries of radio-active iodine; on the other hand, a normal or mildly hyperthyroid subject reaches a myxoedematous state with a dose 10 *to* 15 *times greater.*

When the clinical and bacteriological improvement has been attained, the dose of Tapazole is reduced to an individual maintenance regime. In cases of febrile leprosy reaction, long in duration or strong, I have used Tapazole in very small doses (5 to 10 mg. daily), along with a moderate amount of dietary protein, with calcium gluconate, and some antimony compound. In some cases I combined Tapazole with prednisolone for a few days. Once the febrile reaction was controlled the Tapazole was continued alone, always in moderate doses.

In anergic non-reacting lepromatous cases without liver damage the dosage of Tapazole could reach the maximum in a few days. These cases yield the best results.

The most difficult leprosy cases are those in the stage of puberty. On the other hand, I think that lepromatous over 50 years of age are the easiest to treat. In general tuberculoid cases have excellent and rapid improvement.

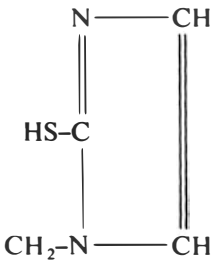
Special increase of dosage of Tapazole can be made during the time of menstruation, during pregnancy, the menopause, and periods of psychic stress.

In most of lepromatous patients treated with antithyroid preparations I note a strong pigmentation in the sites corresponding to the skin lesions of leprosy. I have tried to explain this pigmentation by the common origin of melanin and thyroxin.

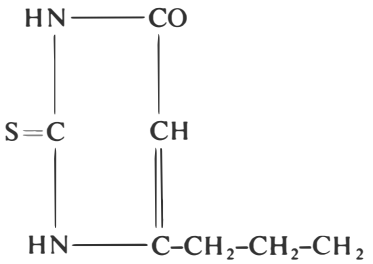
Drs. JORGE VERDAGUER and F. B. PECK, Jr., have collaborated fraternally with me in verifying this theory.

Dr. Arturo O'Byrne González,
Carrera 5a. No. 7–58,
Cali, Colombia.

Dr. JOSÉ VERDAGUER of the Lilly Research Laboratories has very kindly sent us information on the nature of Tapazole (methimazole-Lilly) and indicates that further reports on the trial of Tapazole in leprosy may be expected within the next 3 months. Tapazole has been used as an antithyroid drug for more than 10 years, and informative papers on it include that by J. CHEVALLEY, T. H. MCGAVACK, S. KENIGSBERG, and S. PEARSON, in the *J. of Clinical Endocrinology and Metabolism* 14, 8: Aug. 1954, pp. 948–960; also G. W. IRWIN, H. D. VAN VACTOR, and M. S. NORRIS, *J. of the Amer. M.A.*, **149**; 1637–40; Aug. 30, 1952. Tapazole (methimazole–Lilly) chemically is 1-methyl-2-mercapto-imidazole, and its structural formula and that of propythiouracil are as follows:—



"TAPAZOLE"



"PROPYLTHIOURACIL"

Tapazole was shown to be a potent antithyroid agent, and as little as 0.5 mg. was found to have a pronounced inhibitory effect on iodine accumulation in the normal human thyroid gland, and 5 mg. inhibited iodine uptake completely for nearly 24 hours. After dosage of 10 mg. Tapazole thrice daily the average protein-bound iodine level in the plasma fell to within normal limits and remained normal in hyperthyroid patients. The only absolute contra-indication to the use of Tapazole appears to be the presence of idiosyncracy in the form of agranulocytosis, severe leucopenia, drug fever, severe skin eruption, or other serious reaction. A history of such side-effects with antecedent use of drugs should contra-indicate Tapazole, though not necessarily if the previous drug has been an antithyroid one. The administration should be cautious, with close observation of the patient. The side effects typical of antithyroid drugs are skin rashes, urticaria, fever, granulocytopenia, and agranulocytosis.

Dosage with Tapazole is oral, and 10 to 15 mg. daily may be satisfactory for most patients as an antithyroid agent, but others may require 30 to 40 mg. daily to establish rapid and complete control. There seems to be no advantage in exceeding 60 mg. daily. A maintenance dosage may be 5 to 20 mg. daily.

Dr. O'Byrne González has very recently pointed out (Dec. 1960) that Dr. J. H. Hanks has already visualized the existence of factors which inhibit endogenous metabolic activity; and that Dr. C. T. Gray thinks that anaerobic conditions are definitely injurious to *M. leprae*; also that Dr. Pitt-Rivers in the Ciba Symposium on the thyroid gland presented some interesting data about oxygen metabolism and its variations under administration of antithyroid drugs.

This theory of antithyroid influence on leprosy is most interesting and surely should be explored more widely. We agree with O'Byrne González that a very useful part of further explorations of this question would be epidemiological studies in countries which have both endemic goitre and leprosy, of the relation between them. Such countries are Sarawak, Gambia, and Sierra Leone.

3. Transmission of the human leprosy bacillus to rats or mice placed on a special diet.

This work has been stimulated by Dr. MENY BERGEL who is Director of the Laboratory of Leprosy Research, Rosario, Argentina. This work is also of great interest and significance. Dr. Bergel informs us that in the Conference on Leprosy in the U.S. Public Health Service Hospital in Carville, La. Nov. 7–10, 1960, there were 5 papers delivered which related to this subject, namely "Inoculation of *M. leprae* in Mice on Severe Pro-oxidant diets" by MENY BERGEL; "Attempts to Infect Rats with *M. leprae*, the Rats being on a Pro-oxidant Diet" by S. S. BARKULIS, P. C. EISMAN, S. GEFTIC; "Intratesticular Inoculation of *M. leprae* in Different Species of Laboratory Animals under Special Dietary Conditions" by K. E. MASON; "A Method for the Investigation of Anti-leprotic Drugs using Pro-oxidant diets" by MENY BERGEL; "The Tocopherol-like Activity of Ciba-1906 and other Anti-leprosy Compounds in a Test System Involving Murine Trypanosomiasis" by F. C. GOBLE. Dr. Bergel says that Dr. Mason and colleagues confirm his work on the growth of *M. leprae* in rats on pro-oxidant dietary conditions.

The communications by MENY BERGEL at the recent Carville Conference on Leprosy are here summarized:—

We have shown in our laboratory that *M. leprae* grows in the testes of rats maintained on a pro-oxidant diet. We have also found that the incorporation of DDS, CIBA 6704, and CIBA 6600 into this diet at the time the animals are infected intratesticularly, suppresses the growth of the organism. These findings suggest the following method for the evaluation of compounds for anti-leprosy activity.

1. Male rats, 21 days old, are given a pro-oxidant diet which is deficient in vitamin E and contains 20% linseed oil. 0.5 parts $AgNO_3$ per 1,000 parts drinking water (distilled) is also given to the animals.

2. Thirty days later and while still receiving the pro-oxidant diet, the animals are injected in one testis with 0.1 ml. amounts of a suspension of *M. leprae* derived from a human source or from a testis of a rat previously infected and maintained on an unmedicated, pro-oxidant diet. Silver nitrate treatment is discontinued at the time of inoculation of the infection.

3. At the time of inoculation, the animals are divided into two groups: One group serves as a control group, receiving pro-oxidant diet. The other group receives the pro-oxidant diet plus the test compound. At the time of inoculation, 4 normal rats are also infected in the testis and the animals are sacrificed immediately and used as controls (starting count).

4. Four months after infection, all animals are sacrificed and the number of bacilli in the injected testes are counted.

5. Counts are also made of rats dying prior to the completion of the experiment.

6. Counts of the numbers of bacilli for each animal (in each group) are plotted. Comparison of these plottings will determine the effectiveness of the test compound in suppressing the growth of the *M. leprae*.

7. DDS, which markedly suppresses the growth of the bacillus in the testis, may be used as a reference drug.

PLANTAR ULCERS IN LEPROSY

Their Pathogenesis and Natural History, and their Therapy and Prevention

by JOHS G. ANDERSEN, Cand. Med. et Chir. (Hafn)

(*From the Hand Research Unit of Christian Medical College, Vellore under Prof. P. W. Brand; and the Schieffelin Leprosy Research Sanatorium, Karigiri under Dr. C. K. Job.*)

SECTION 1. PATHOGENESIS AND NATURAL HISTORY OF PLANTAR ULCERS.

Perforating trophic ulcers of the sole of the foot were called "plantar ulcers" by PRICE, and we approve of this useful short term for this special condition. Plantar ulcers in leprosy constitute a major problem. The patient is disabled and often ostracized socially. The community loses a working member, who either turns to begging or becomes dependent on relatives. Often plantar ulceration is the condition which first brings the patient to seek medical relief. Unless we devise a simple, safe, and efficient method of therapy the patient will continue to suffer and our therapeutic clinics will be congested.

The Normal Foot

The normal foot has a highly specialised plantar surface with a high degree of resistance to trauma. The construction of this plantar surface comprises (1) a thick epidermis with a particularly thick cornified layer functioning very much like a car tyre on an automobile wheel; (2) a thick layer of subcutaneous fat caught under pressure in a mesh of tough fibrous strands which bind the skin and deeper layers together in a three-dimensional net which has a very great resilience both to vertical forces (pressure) and to horizontal forces (shear); (3) the bony and ligamentous structural base of the foot, which is reinforced with long tendons much in the manner of reinforced concrete. The foot at rest, the *static foot*, and the foot during take-off in walking; the *kinetic foot*, form two natural sections for consideration of the forces at play in the foot. *In the static foot* the total body weight is distributed more or less equally on the two soles. The heel takes one-fourth of the total body weight, and another fourth is taken evenly (NAPIER) by the 4 lateral metatarsal heads and the 2 sesamoid bones at the head of the first metatarsal. It is a simple pressure taken up by the sole and carried from the pressure points to the whole of the structural base of the foot. When the foot shares in propulsion of the body, a complex mechanism operates. To absorb and modify the jar of propulsion small

movements take place in the skeletal structures from heel to metatarsal heads, and other adaptive changes in the structural base of the foot in relation to the subsurface from which the propulsion takes place. The pressure acts along the line from the heel to the metatarsal heads via the lateral border of the foot. At the moment of thrust the total body weight bears on each of the 2 sesamoid bones, one-fourth, and on each of the 4 lateral metatarsal heads, one-eighth. As the metatarso phalangeal joints dorsiflex, the sesamoids move forward with the phalanges, and the first metatarsal head (which projects towards the sole) is pressed against the taut plantar fascia, and the amount of underlying tissue is much reduced. A similar process takes place at the lateral metatarsal heads. The metatarsal heads are thus relatively unprotected when they meet the final thrust (HICKS).

The static foot meets pure pressure, the kinetic foot meets pressure plus shear. The amount of shear depends on the operation of a number of factors, namely the total body weight, the length of stride, the speed of propulsion, the nature and gradient of the ground surface, etc. The direction of the shear is longitudinal, transverse, and rotary, and the force is taken up and neutralised by the complex structure of the foot. It has been shown that the sites of choice of plantar ulcers correspond closely to the pressure points, more closely to the kinetic than the static (PRICE).

Deviations from Normal in the Foot of a Leprosy Patient

We shall consider these under the 3 main headings of anaesthesia, motor paralysis, and skeletal changes, and only in their relation to the natural history of plantar ulcers. *Anaesthesia* of the foot in leprosy may be due either to widespread destruction of the fine terminal nerve fibres, or to neurofibrosis at a particular point of a bigger nerve, notably the posterior tibial, resulting in anaesthesia to touch, to pinprick, to heat and cold, sometimes with loss of the sense of vibration and position. Deep analgesia is less common. The extent and intensity vary. The foot has lost its warning mechanism. The patient is unaware of where and how he places his foot. He does not preceive traumata. The foot is therefore frequently put to harder use, and may be used in spite of lesions that would have stopped a normal person from using his foot. Anaesthesia is the central factor in the pathogenesis of plantar ulcers. Even in the absence of other pathological findings plantar ulcers are likely to develop. An anaesthetic foot with no other damage to its tissue is exposed to the risk of ulceration; it is "ulcer-liable". The moment ulceration takes place, the foot will have a permanent, stronger tendency to plantar ulceration; it will be "ulcer-prone". Even in the absence of actual ulceration, a scarred foot is ulcer-prone.

The denervation of the foot in leprosy involves the sympathetic as well as sensory fibres. The area of anhydrosis is roughly the same as the area of anaesthesia. It is reasonable to suppose that the changes in vascular response might have some influence on the development of plantar ulceration. Experiments by FRITSCHI *et al.* and by CHATTERJEE, and recent observations of the digital arteries by JOB and ANDERSEN have not thrown any clear light on this problem.

Motor Paralysis. The motor paralysis in leprosy is selective and specific. In the vast majority only certain muscles are paralysed. This is in strict opposition to post-polio paralysis. Typically the ankle and toe dorsiflexors, the peronei and the intrinsic muscles are paralysed. The lack of the stabilising effect of the long tendons may have a bearing on the development of tarsal instability. The specific consequences are dropfoot and clawtoes. A claw toe is cocked up in dorsiflexion at the metatarsophalangeal joint with the consequent sharp flexion of the interphalangeal joints. This has a marked influence on the windlass mechanism at the metatarsophalangeal joints (HICKS). It also takes the braking effect off the pulps of the toes and transfers it to the tips (PRICE). In severe clawing the tips of the toes are protected, while the metatarsal heads are subjected to a higher risk. There is general agreement that severe degrees of clawing should be corrected. It seems that even milder degrees of clawing are worth correcting.

The dropfoot in leprosy is typically a paralytic equinovarus foot with either drooping or clawed toes. The drooping foot will tend to drag along the ground. It will hit the ground first with the antero-lateral border. It will not rest securely on the ground. The take-off thrust will tend to roll the foot over on the lateral metatarsal heads. An added ulcer risk is present at the antero-lateral border of the foot and at the tips of the dragging toes. The heel and the medial surface will be relatively protected.

Skeletal Changes. In the leprosy patient a number of skeletal changes of the foot are seen. Some are due to leprosy as a disease, others to incidental episodes (infection, scarring, loss of stability, etc.). The pathogenesis of these changes will not be discussed here. They will only be considered in their relation to development of plantar ulceration.

The stiff joints of a claw toe will have no particular effect except to make the claw deformity more vicious.

A stiff metatarsophalangeal joint, particularly at the first toe, will on the other hand seriously impair the take-off phase, leaving the foot either to take off in extremely high stepping or to place the final thrust on the very tips of the toes. This obviously adds considerably to the ulcer tisk at the tip of the toes.

In cases with phalangeal absorption the normal braking effect of

the toes is lost. This exposes the metatarsal heads to more severe thrust, and will endanger this region. Concentric absorption of the metatarsal shafts will often lead to complete separation of the metatarsal heads (the term "pathological fracture" is a misnomer), with subsequent plantar displacement. The presence of bone close to the skin will add greatly to the risk of development of ulcers in this region.

Whatever the cause, any shortening of the foot will add to the amount of force that is brought to bear on a particular point, both in the static and in the kinetic foot. Even in the absence of particularly marked scarring, the short foot is a serious problem in ulcer prevention.

The so-called "neuropathy" of bone and joints in leprosy is not very well understood. Apparently it can be caused both by leprosy as such, by denervation, by infection, by scarring, and by any incidental trauma. Without entering into the discussion of the pathogenesis of "neuropathy" of bone and joints it can be stated, that any lack of stability, any deformation of structure, and any decrease in tissue vitality, will play a role in the development of plantar ulcers. Once these changes are established they are notoriously difficult to treat. A moderately flat foot, either a true pes planus or a mild degree of eversion valgus deformity with tilting of the arch, is quite likely beneficial to the foot, since it tends to spread the weight bearing over a wider area. It also does away with the normal take-off thrust, the most dangerous part of the mechanism of the foot. In the more severe forms, especially the fully developed boat-shaped foot, the medial side of the foot is exposed to excessive danger, particularly at the navicular tuberosity, where very severe ulceration may develop.

The Natural History of the Primary Ulcer

It is the generally accepted impression in these two departments here that most plantar ulcers develop as what may be termed "closed ulcers" with only secondary breakdown into frank, open ulcers. It is well nigh impossible to obtain a reliable history of the ulcers. The basic pathology is the minimal necrosis blister or haematoma in the subcuticular or subcutaneous tissue, principally due to the shearing force of the kinetic foot. Many of these primary lesions undoubtedly heal up, but they leave behind them small stellate scars that will contract and jeopardize the blood supply. The general effect is creation of a vicious circle of haematoma–scar–haematoma. If unchecked the resilient weight bearing tissue will slowly be transformed into cicatricial, atrophic, ischaemic tissue with very little resistance to further traumata. A foot that presents its first open ulcer may very well have behind it a long history of a closed ulcer.

In certain cases the haematoma will spread, particularly if it gets infected. Since the skin of the sole is very thick and tough, the blister or abscess cannot point to the immediate surface, but will spread like a cold abscess. It may wrap round the border of the foot or through the interdigital webs, and will present a larger daughter blister on the dorsum of the foot, as a wrap-round abscess. Occasionally the penetration goes deep and may involve the structural base of the foot, especially joint cavities. This collar-stud abscess may be combined with the wrap-round abscess.

In comparatively few cases a frank breach of continuity is the beginning of the ulcer process. It may be due to a nail in the shoe, a thorn, or a stone, or maybe a shoe bite. It may be an insignificant and unnoticed trauma that would have no such deleterious effect on a normal foot with preserved sensation. Whatever the cause, once ulceration starts, the vicious circle begins. The ulcer-liable foot has entered the ulcer-prone state.

Many patients wear shoes, either as part of their social environment or because they want to protect their feet. It is an unfortunate fact that most shoes available to these patients are not only without any protective value, but are directly harmful. Ideas of what a smooth in-sole is, what a good fit it is, and what damage nails can do, vary considerably from cobbler to physiotherapist.

If a shoe is worn in the presence of an open ulcer, the discharge, even the insignificant amount from a "dry ulcer", will wet the in-sole. From dust and discharge a roughness is gradually built up, that will be a constant source of irritation to the ulcer. Not infrequently a veritable cement pyramid sticking right up into the ulcer can be seen. So it might be better to avoid shoes altogether if you are not prepared to look after them properly and if you cannot get special shoes made by a specially trained cobbler. Corns and callosities are particularly likely to occur on anaesthetic feet. They have the same effect as a stone in the shoe. They are extremely dangerous, and should be avoided. If they do occur, they must be removed under the direction of a trained physiotherapist or surgeon.

The early, primary ulcer only involves the superficial tissues in the vast majority of cases. Rarely will a thorn penetrate right into an overlying joint cavity and start a primary ulcer with joint involvement. A primary ulcer has a comparatively strong tendency towards spontaneous healing. The factors that work against healing are the constant traumatising of the ulcer, and the inevitable infection. Of these infection is of less importance. The relative absence of infection in these open lesions exposed to dust and dirt is remarkable. It might be taken as a negative proof of the traumatic origin of plantar ulceration.

The habit of sitting cross-legged is responsible for the development of lateral malleolus ulcers. In spite of the position outside the

plantar surface of the foot, their pathogenesis places them in the same group as the true plantar ulcers. They occur in an area with poor blood supply even in the normal individual. A major joint is very close. All in all they should be treated with due respect as potentially very dangerous ulcers. They have a poor response to therapy.

The Secondary Ulcer

The basic pathology is the change from ulcer-liable to ulcer-prone state with the first introduction of ulceration and scar. Their natural history revolves round the vicious circle of scar-ulcer-scar. The important thing to keep in mind is that they are much more difficult to treat than primary ulcers. This alone points to prevention as the real answer to ulcer therapy.

SECTION II. THERAPY AND PREVENTION OF PLANTAR ULCERS

This section will attempt to describe an approach to the problems of a simple effective therapy for these ulcers, and effective prevention of them. Basically, the patients must be led to understand the factors involved, and to co-operate, and the same applies to the general public. There is a widespread false notion that plantar ulcers are an indication of infectivity, and the need is not understood for traditional trades to be *adapted* so as to be suitable for these patients, and they should be encouraged to re-enter the economic and social life of the community. An important fact to get accepted is that *every anaesthetic foot is ulcer-liable*, further that ulcer prevention is easier than cure and within the reach of most of these patients. Extra precautions must be taught thoroughly to a patient with an ulcer-liable foot. Because he has lost the normal warning mechanism of his foot, he must be taught the importance of thinking about the use of his feet. It is essential for the doctor or responsible person to conduct a daily inspection of the feet to detect evidence of even minor traumata, and the patient himself can do the same. He must also be taught care of the early, apparently insignificant lesions. He must understand the importance of adapting his daily life to this added risk. As far as possible standing and walking should be minimised, even if it involves adjustments of his work. The protective footwear will be dealt with later.

If an ulcer does occur, it must be treated immediately. The patient and the therapist must understand the importance of the "closed ulcers". If closed blisters and haematomas are treated with respect they deserve, much of the gross, really disabling ulceration can be avoided.

The Discharging Ulcer

A frankly active ulcer with discharge, slough, and undermined edges should be treated with strict bed-rest and elevation of the affected limb. Daily soaks in a solution of saturated magnesium sulphate or plain kitchen salt is the standard treatment. It should be followed by a simple dry dressing, mainly in order to keep flies off, but also for aesthetic reasons. Only rarely will one meet an ulcer with frank lymphangiitis and general symptoms of sepsis, that presents an indication for treatment with systemic sulphonamides or antibiotics. Generally they should be avoided, since the systemically administered drugs have very little chance of reaching the organisms, embedded as they are in the necrotic tissue, hidden behind a solid barrier of granulation tissue. The use of locally applied sulphonamides or antibiotics should be discouraged. They are not necessary. The chances of creating resistant strains of micro-organisms are very real. Plantar ulcers are not due to leprosy as such. There is no indication for the use of specific anti-leprosy drugs in the treatment of ulcers.

Under this regime most ulcers dry up, or even heal with surprising speed.

The Dry Ulcer

This comprises both the ulcer that presents this stage when first seen and the discharging ulcer that has dried up under treatment. The logical treatment is strict bed-rest and elevation as described above. A dry dressing can be applied for aesthetic reasons. The lack of bed space, and also economic considerations have led to the adoption of a compromise. *Application of a well fitting* below the knee *plaster of paris boot with a rocker device*, preferably a Bohler walking iron is an excellent therapy. It is very important that a correct plaster technique be adopted. Padding of prominent bony points and exposed nerves is even more necessary than in a normal foot, since the anaesthesia makes development of pressure ulcers a very real risk. We prefer to leave the toes open for inspection. A toe guard is a good protection against traumata to the toes.

Most ulcers heal under this therapy within six weeks. The main advantage is that a number of patients can leave the hospital, and even take part in some light occupation during this period. The chief disadvantage is that it is unsuitable in a really wet climate. The actual cost of a plaster of paris boot with rocker is approximately the same as the cost of daily dressings for six weeks.

Corns. Treatment of corns is an essential part of ulcer therapy. The method of choice has until recently been surgical, entering the plane of cleavage with the pointed end of a pair of strong scissors, and separating the corn from the skin. FRITSCHI now advocates

soaking the foot for thirty minutes in a solution of sodium carbonate (four heaped spoonfuls of ordinary washing soda to the litre), after which the corn can be scraped off bluntly. If a haematoma or a necrosis blister is found under the corn, it should be treated as an ulcer.

Cracks. Frequently the sole of an anaesthetic foot develops cracks. Their sites of predilection are the bases of the toes, the sides of the heel, and the mid-foot. Often they penetrate deeply into the subcutaneous tissue, laying bare tendons, bone, or articular structures. As far as therapy is concerned they should be considered ulcers. They are often surrounded by hyperkeratotic cuticle, that should be saucerised to allow the crack to heal from the bottom.

Protective Footwear. An essential part of prevention in any ulcer-liable or ulcer-prone foot is wearing of correct footwear. We have found that most of the shoes available to our patients are not only useless but directly harmful. Over several years work has been in progress to formulate the principles and practice of the correct footwear for anaesthetic feet. So far no reliable scientific method of assessing this problem has been developed. Recent experiments with pressure disc measurements (D. WARD and J. BAUMAN) seem to confirm the designs we have arrived at. In this paper the indications for the different types of shoe will be dealt with. A brief description of the principles of the shoes will be given.

Three principles are essential. (1) *Resilient insole* to replace the lost or jeopardised resiliency of the planta; (2) *Moulding* to ensure a broader distribution of pressure; and (3) *Rigidity* to prevent angulation deformity in unstable feet, and particularly to change the thrust on special points during the take-off phase with a large amount of shearing force to a simple pressure take-off from the whole sole.

For the ulcer-liable foot and for the foot with very little scarring at the front part alone a simple sandal with resilient insole and tough undersole to prevent thorns from entering the insole is sufficient.

For the foot with some damage to the front part, but with no heel or mid-foot ulceration and with no damage to deeper structures, *a metatarsal base bar* must be added to the shoe. This should be placed well behind the damaged area, and not further forward than the mid-point of the foot (not the shoe). Its height should be as the heel. The effect of the bar is to shift the thrust further back, thus giving relative protection to the metatarsal head area, and to help in the moulding of the instep.

For the foot with extensive scarring, with damage to the deeper structures, with heel ulcers, with mid-foot ulceration, and for the shortened foot we recommend *a rigid sole with resilient insole and a rocker*. This shoe must have a full heel-cap to protect the heel from the dangerous lateral shear. The rocker should be placed at or

slightly behind the mid-point of the foot. It should have the same height as the heel, or possibly slightly more. It causes the foot to take off from the rocker, distributing the total pressure over the whole area and diminishing the thrust on any one particular point. It is important that the tip of the shoe does not touch the ground during the take-off phase. When standing the patient must rest squarely on the rocker and the heel with no forward tilt of the shoe. The actual height of the rocker depends on the length of the stride and the length of the foot. An understanding patient who will take the trouble to educate himself to take short steps can get by with a much lower rocker. Moulding of the insole is a very tedious procedure. It is not very satisfactory under the rather poor conditions under which most of these shoes will have to be manufactured and worn. The adoption of *microcellular rubber preferably of shore 15° hardness*, has not only given us an almost ideal resilience of the insole but has also permitted us to let the resilient insole take care of the moulding except in very special cases. The upper shoe is important too. Lack of really well trained cobblers and paucity of funds have forced us to adopt a very simple upper, much of the same type as the ordinary Indian sandal. The popular big-toe strap however is decidedly unsuitable for feet with intrinsic paralysis.

It must be impressed upon the patient that *these shoes must be worn always*, also inside the house and at the bathroom. This may go against the local custom but it is very important. Apart from simplicity of design and cheapness, the appearance of the shoe plays an important role. If we shall have any chance of success in our attempts to persuade the patients to wear these shoes, they must be made in such designs that they conform to local fashion as far as possible, and so that they do not stigmatise the patient as a "leper".

It is important to impress upon the patient, cobbler, physiotherapist and medical officer alike that *shoes are preventive and not curative*.

Surgical Intervention in the Active Ulcer

Only rarely will the surgeon be called upon to perform such operations. If simple, straightforward therapeutic measures in the treatment of ulcers as described above be adopted, most ulcers heal with surprising speed. There does not seem to be much difference between superficial and deep ulcers, provided open drainage is ensured. Very occasionally a sequestrum is formed that will have to be removed for healing to take place. One should be careful when diagnosing dead bone, since obviously naked bone has been seen to heal up. The radiological evidence of dead bone is not so conclusive in leprosy as in other diseases. Deep sinuous tracks, especially if leading to joint cavities, may have to be opened. Ulcers with under-

mining edges and deep cracks may need the assistance of the surgeon. Simple procedures should be preferred, aiming at free drainage.

A heel ulcer may occasionally give rise to so widespread involvement of bone that surgical interference is indicated. DREISBACH advocates saucerising of offending bone through a fishmouth incision off the weight bearing surface. Occasionally it might be possible to combine this with excision of the ulcer and primary closure leaving the drainage to take place at the side of the heel.

Osteomyelitis of the sesamoid bones at the base of the first metatarsal bone is not infrequently an indication for surgical interference.

In all of these procedures it must be remembered that the operation is performed in actively infected tissue. Sufficient drainage is a *sine qua non*. The utmost conservatism should be the rule in the use of antibiotics and sulphonamides.

Surgical Intervention in the Quiescent Phase

When all ulceration and all residual heat and swelling have disappeared, the time has arrived for consideration of preventive surgery. As far as possible this should be done in an aseptic field. It is, however, well to remember that these operations will always have to be performed in potentially infected fields. The use of "antibiotic umbrellas" is strongly deprecated.

Operations Aiming at the Correction of Paralytic Deformities

Drop-foot and drop-toes should be corrected as soon as an aseptic field can be secured. It can be done in a single procedure without interfering with bone, which is a decided advantage. The method used by the author is recommended (circumtibial, subcutaneous transfer of the tibialis posterior tendon to the insertion of the tibialis anterior and subcutaneous transfer of the tendons of the extensor digitorum longus and extensor hallucis longus to the already transposed tibialis posterior tendon at the medial side of the leg.)

Claw toes can, if mobile, be corrected by a simple transfer of flexor tendon to the dorsal expansion. In cases of stiffness the offending joints should be resected. Occasionally claw toes are so bad that only amputation will do any good.

Operations Aiming at the Correction of Skeletal Deformities

The sequela of the deep ulcer, the adherent scar, is a menace to the foot. It is often an indication for removal of offending bone. The aim is to remove mechanically offending bone. The three

common localities for this procedure are the heel, at the metatrasal heads, and the base of the fifth metatarsal bone. The operations should be done through a fish-mouth incision off the weight-bearing surface (DREISBACH), Enough bone is sliced off or saucerised to give an even surface. The effect on the weight-bearing potential of the foot is often remarkable.

For extensive scarring of the fore-foot with a fairly well preserved hind-foot GASS recommended an amputation of the Lisfranc type with preservation of the largest amount of metatarsal shafts to allow a good flap from the plantar surface to be turned to the dorsum. This is undoubtedly a good procedure. Only it must be remembered that the field is almost certainly infected. Stiff, straight toes are frequently met with. They are highly offending and should either be amputated or "flailed" by resection of the offending joints.

Tarsal instability is an exceedingly troublesome condition. Its pathogenesis is not very well understood. Subtaloid arthrodeses have in many cases been attempted but with inconsistent results. The fixed tarsal deformities are equally important to correct. The methods employed here are modifications of Ryerson's, Dunn's and Lambrinudi's operations.

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Summary

In two papers an attempt has been made to present a concept of the natural history of plantar ulcers in leprosy with the main stress on factors dependent on anaesthesia of the foot. A rational therapy based on these findings has been described.

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IS LEPROSY TRANSMITTED BY ARTHROPODS?

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(*Paper delivered at a Symposium on Leprosy Research, London, June 10, under the auspices of the Acid-Fast Club of London and International Academy of Pathology*)

Introduction

About 1900 the distinguished Danish dermatologist EHLERS visited 3 different islands in which leprosy was endemic, namely *Iceland* with 181 known cases and an estimated number of 200, *St. Croix* in the Caribbean with 87, and *Crete* with about 600. Prof. Ehlers advised antileprosy measures for all three islands comprising the building of a leprosy hospital and the segregation of every new case. This was carried out, but the result was very variable. Thus in Iceland the leprosy hospital was built, and came into use in 1897, and leprosy decreased rapidly in the ensuing 20 years and had practically died out by 1940, and now there are only 4 patients left, i.e. 4 patients in a total population of 170,000 against 200 in 70,000 population in 1900. In St. Croix the results were very disappointing, and leprosy still remains a health problem. Knott in 1936 had occasion to deplore the inefficiency of the measures taken. The leprosarium was built in 1910 and since 1918 a total of 88 cases were found up to 1936, bringing the total known cases up to 99. In spite of good economic conditions and good nutrition the leprosy continued to spread.

In Crete, leprosy gradually decreased until in 1957 the leprosarium could be emptied.

In Norway, the course of the leprosy has been similar to that in Iceland, in that there has been segregation in the hospital at Bergen and from a fair incidence about 1900 it has declined to nil nowadays. But in the Philippines, after 40 years of segregation, leprosy has not declined. So segregation is successful in some countries but not in others. As long as we cannot point out the reasons for the discrepancy we are entitled to suspect that some factors operate which we do not know and do not understand.

CHAUSSINAND[2] thinks that tuberculosis and leprosy are competitive antagonists. This theory would explain much, but is difficult to prove, as we know too little about the dissemination of tuberculosis in Europe in the last two centuries, when leprosy was declining. Certainly in Iceland it is certain that the decline of leprosy had nothing to do with a spread of tuberculosis. Great numbers of adults were unaffected by tuberculosis. Magnusson[2] reports that in 1921–30 the percentage of non Pirquet positives at the age of 14 reached only 30%, and at age 20 only 50% were tuberculin positive when leprosy

in Iceland was dying out. Leprosy certainly does not inhibit the progress of tuberculosis as BJARNHEDINSSON[32] indicates from his study of autopsies on 111 leprosy patients, in whom 24 showed signs of healed tuberculosis and 20 had died of that disease. The cause of the decline and disappearance of leprosy must be sought elsewhere than in the idea of an immunization of the population against leprosy by a widespread dissemination of tuberculosis.

The main problem in the epidemiology of leprosy still remains, as 80 years ago, how do the bacilli enter the human body and produce leprosy?

CHAUSSINAND[2] and many others with him have incriminated the inhalation of nasal droplets of mucus from infective patients, as in tuberculosis. But if this were so leprosy should be much more widespread and should occur even in hospital staff, which does not occur. Leprosy is not a lung disease, nor are nasal lesions so common in many countries. In the Nauru epidemic, BRAY[3] found the nasal mucus free of acid-fast bacilli in nearly all cases, and Dr. Bjarnhedinsson, who was in charge of the leprosarium in Iceland, told me that nasal lesions were so seldom found there that he doubted their importance in the spread of the disease. Also in Iceland fresh cases were found at all ages and were not peculiar to infancy and childhood. FLOCH[4] found the same thing in Cayenne, where 81% of cases first showed the disease at ages 40 to 60.

It is generally maintained that there is little danger of infection unless the contact is long and close, such as found by BOENJAMIN.[5] Yet several cases are on record where the contact has been short and not very close. In Colombia there are certain "casas malditas", houses under a curse, where danger of contracting leprosy is believed to follow the spending of a night there. There are a few cases of *accidental* transfer of leprosy, as the case reported by MARCHOUX[6] of a surgical assistant having been infected by a needle prick; and the case of KLINGMÜLLER[4] of infection by a hypodermic needle previously used on a lepromatous case in reaction; also PORRETT and OLSEN[8] who reported the case of leprosy in a tattoo mark in two sailors in Australia in 1943. In Colombia[22] there is the case of a pinprick apparently having transferred the disease to a boy of 17, and even inoculation by scratching (FENNEL[12]) seems possible, as in a case of habitual scratching of the same place in the head by a contact, and later a leprotic granuloma developed in that site years later. Arning's well-known experiment to graft leprotic material and so infect a subject is of little value to our understanding as to how the disease is spread. DANIELSSEN[9] and MOURITZ[10] carried out unsuccessful inoculation experiments. It is surprising leprosy is not much more widespread in natural conditions, considering how many are the sources of infection. In a household, many will escape. AYCOCK and MCKINLEY[11] report that Gwyther found that only 4

of 178 women living with male leprosy subjects developed the disease, and conjugal leprosy occurred in 4.8% of women and 5.1% of men.

Unexplained Problems of Epidemiology

There are many cases where contact is unknown or cannot be recollected, and many cases where the transfer of the infection cannot be pinpointed. It may be easier to collect information in northern countries, and difficult to gain information in tropical countries densely populated, but KNOTT[1] from St. Croix reported several cases of leprosy in children who apparently never had contact with leprosy patients, except that there was a relative with leprosy who died before the children were born. This problem caused Knott to postulate a subclinical form of leprosy. Knott also reported cases of transient leprosy who made spontaneous recovery.

In Iceland the following cases are recorded:—

1. J.N., a male of 27 years with anaesthetic leprosy. At the age of 20 he slept one night in the same room as a leprosy patient, but not in the same bed, otherwise no history of contact with the disease. Two years later nerve pains began.
2. J.H., a male of 35 years with nodular leprosy who was a farm worker 10 years ago for 2 years. A year after he left the farmer's wife developed leprosy.
3. S.S., a male of 35 years with mixed nodular leprosy. About 7 to 8 years ago he slept in a large room where a leprosy patient slept in another bed. Then 2½ years later small nodules appeared on the dorsum of the right foot, and these later increased in size and multiplied.
4. T.S., a male of 36 years with nodular leprosy. He shared a bed 20 years ago with a man who later developed leprosy and there was no history of other contact with leprosy.
5. J.Th., a male of 32 years with nodular leprosy. At the age of 13 he shared a bed with a man who later developed leprosy and there was no history of other contact with leprosy.
6. P.J.H., a male of 53 years who gave no history of contact with leprosy, but who associated with a woman who developed leprosy after they parted.

FAGERHOLM[13] reports a striking problem of epidemiology. On a small island in the Baltic, off the coast of Finland, about 10 miles, a single family lived, with no other people on the island. This family left and was replaced by another family, this happening several times, and four housewives developed leprosy in succession, though all the families came from regions on the mainland where there was no leprosy. Dr. Fagerholm suggests a transmission through furniture or

household articles of a type mainly used by the women. Children are not mentioned in these families.

Insects as Possible Vectors

In 1911 EHLERS, BOURRET and WITH[14] wrote a paper on the possibility of propagation of leprosy by arthropods. They reared several kinds of arthropods and caused them to bite leprosy patients of lepromatous type, and dissected out and stained the stomachs for acid-fast bacilli. They found only 1 in 21 of *Pulex irritans* and 1 in 12 of *Stegomyia fasciata* were positive, and 53 bed bugs and 16 head lice were negative. They thought that leprosy was probably not transmitted by insects.

SANDES[15] starved certain insects and fed them on leprosy patients. He found acid-fast bacilli in 1 in 80 mosquitoes, in 20 of 60 fleas, and in 20 of 75 bed bugs. Later he found acid-fast bacilli in 30% of bed bugs, not only in their stomach contents, but also in other stomach fluids, and thought there were some signs of growth of the bacilli in the bed bugs. When bed bugs containing leprosy bacilli bit a patient with anaesthetic leprosy, a papule arose round the bite in which papule bacilli were absent but were found peripherally. It was impossible to decide whether these bacilli were inoculated or derived from the patient.

DE SOUZA-ARAUJO[16] found acid-fast bacilli in the blood-sucking garrapatas (*Amblyoma cajennense*) removed from leprosy patients and thinks they may transfer leprosy. BORREL[17] thought *Acarus scabiei* and *Demodex folliculorum* to be possible transmitters. Transmission of leprosy by insects is difficult to prove so long as we cannot cultivate the bacillus nor transmit it to experimental animals. We thought it worth while therefore to compare data from Iceland with the data of other countries. Possible insect vectors are few in Iceland but numerous in other countries, so we enquired of 62 leprosaria in other countries about their insect species, and whether few or abundant. From 42 countries we received replies which showed that *P. capitis* and *P. pubis* existed in all the countries, and *P. vestimentorum* was absent in 21, *Pulex irritans* and *Sarcoptes scabiei* were more or less frequent in 93 to 95% of leprosy countries. It seemed from the replies that no flying insect could be the sole vector of leprosy, nor is it likely that it transfers the disease at all. In Iceland the bed bug does not exist, which of course does not absolve it from being a possible vector elsewhere. The body louse probably does not transmit leprosy, for leprosy occurs in naked tribes, and naked tribes have no body lice, and leprosy was found in 9 out of 14 territories where the people go naked.

It is generally admitted that leprosy is a house-bound disease. The old idea that it is hereditary originates in its house and family incidence, though as a rule the spread of the disease is limited to the

household. TALWIK[19] reports of the island of Osel in the Baltic that leprosy concentrates on a small peninsula, tending to limit itself to small groups, mostly to single farms, and sharing a home seems of the greatest importance to the spread. "A house or farm in which a leprosy patient lives or stays becomes sooner or later a breeding place for new infections". The same was our experience in Iceland, certain houses and farms seeming to be breeding places of leprosy, and recalling the "malas habitaciones" or "casas malditas" of Colombia previously mentioned.

Housebound insect vectors might explain this close connection with houses, especially where infections seem to occur in a house which has been vacated by the previous occupants. Cockroaches, bed bugs, and houseflies are ubiquitous. The former two do not occur in Iceland, and the housefly is not a very likely vector, as it does not bite.

The biting insects are more likely as vectors, such as the flea, the louse, and *Acarus scabiei*.

The flea has long been suspected. CARRASQUILLA[23] in 1905 thought of it, but as no direct proof could be brought, in the course of time the charge was dropped, until in 1942 MUÑOS RIVAS of Colombia revived it. He had found that the incidence of leprosy in various parts of Colombia corresponded mainly with the humid regions where fleas abound in the primitive and dirty huts of the poor people. He examined fleas from leprosy environments and from those free of leprosy and found acid-fast bacilli in 11 to 16% of the former, and none in the latter.[21],[22] He found the bacilli in larvae developed from infected fleas in 2.36%, but none in the larvae from uncontaminated fleas. (Fleas can live up to 500 days.) OCKLAND[24] has pointed out how frequent fleas were in Norway during the time when leprosy was relatively prevalent, especially in the humid climate of the west coast, where leprosy was prevalent in dirty lodgings of the poor. Now in Norway housing conditions are good, fleas have disappeared, and leprosy is practically eradicated. In Iceland fleas were very frequent at the time leprosy was prevalent, but *Pulex irritans* seems now to have disappeared completely. In former times the use of sheepskins in the beds seems to have been associated with an abundance of fleas. Fleas are apt to be associated with dirty dwellings, with every animal having its own type of flea, except monkeys, on whom fleas do not thrive. Most initial lesions of leprosy occur on uncovered skin, and in tropical countries the initial lesions may be almost anywhere, whereas I find from the records in Iceland that initial lesions are in the face, feet, hands, and legs, but more rarely on the thighs and trunk. It may be a matter of more covering of clothes. In the case of sharing a bed, the initial lesions are anywhere.

Sometimes a flea may bite several times without being able to draw blood. SNODGRASS[25] and WENK[26] have made detailed studies,

from which it emerges that the biting apparatus not only can drill its way in very rapidly, and through the salivary tube saliva is pumped downwards during the bite without any admixture of blood. Bacilli from the host can easily stick to the lacinia and epipharynx. Any haemorrhage or exudate around the inoculated bacilli may inhibit the inoculation of the bacilli. MOURITZ[10] and WADE[27] described inoculation experiments with great numbers of bacteria, with negative results; it might be connected with the factor of the action of haemorrhage or exudate. The cases of the positive results from tattooing and accidental needle pricks might also be based on this factor, that a bloodless prick may be more effective. The flea can produce both bloodless and haemorrhagic pricks, and probably the pumping in of saliva has little influence. A simple dry prick into the dermis may be all that is necessary. Of all the biting parasites of man the flea lives longest, for weeks, months, or even a year. It may stay hungry for weeks waiting for a chance to draw blood, and if the flea were a transmitter of leprosy we can imagine the part it could play in the case of the sharing a bed with a leprosy subject. The flea may be the explanation why people can be infected in a house after the patients have left. The bacilli may remain attached to the piercing equipment of the flea and stay alive for weeks when the flea has nothing to bite. The bacilli may be able to keep alive for some time on the indented surface of the lacinia of the flea, in conditions of humidity and darkness.

The louse. Much of what has been said about the flea also applies to the louse. However, the louse has to live all its life on the host, and bites its host at least once or twice a day, and the crab louse may suck blood for hours. Lice die if they have to live without blood for a few days. The piercing and bloodsucking apparatus resembles that of the flea, with the difference that the louse has only one pump which sucks blood, and it has no pressure pump for saliva, as the flea has. I think it is doubtful if lice transmit leprosy, as it is short-lived, and would not survive in deserted houses, wherein we know leprosy has sometimes apparently originated. FAGERLUND[28] reports an interesting case, where a leprosarium nurse, who had to comb the hair of female louse-infected patients, developed in 1½ years an anaesthetic spot on the left little finger and later macules in various parts of the body. There were no bacilli and the lesions later regressed, leaving anaesthesia.

Doubts about the louse as a vector also extend to the crab louse.

Sarcoptes scabiei. This is certainly one of the insects under suspicion, especially as leprosy and scabies are often associated. INNES[29] found leprosy and scabies so closely connected in certain parts of East Africa that he came "to accept the amount of scabies in a group as a rough indicator of the incidence of leprosy. Where there is much gross untreated scabies, there is liable to be much

leprosy in the community, and instances are numerous of the two diseases being coincident in the same person". If the shallow pricks of the tattoo needle transferred leprosy, as in the case reported from Australia and previously mentioned, it would not be surprising if the scabies mites, which operate to a similar depth in the skin, could convey leprosy bacilli.

Cimex lectularius has long been suspected. It does not exist in Iceland, so must be ruled out as a vector there, but it could be so in other countries, for it is a household insect, can live a long time without drawing blood, and frequently attacks people in bed, piercing right into the dermis. SANDES[15] from his experiments incriminates the bed bug as a possible vector. Cockroaches are non-biting and therefore much less likely to be vectors. They have not been found in Iceland.

Comments

Leprosy is first and foremost a housebound disease. Infection in a modern leprosarium never occurs, if the hygienic standard is high and ectoparasites absent. Infections could occur in a leprosarium of lower standards in these things. Cases of purely domiciliary infection, where the patients have moved out, are puzzling but could be explained if arthropods, especially fleas, were vectors. In cases of apparent transmission from person to person by sharing a bed, the case may have been one of latent leprosy, as suggested by FIGUEREDO and DESAI[30] who found acid-fast bacilli in 10% of apparently sound contacts of leprosy patients. Some latent cases may be expected to develop into recognisable leprosy, some never develop frank lesions.

Conclusion

In the absence of success in human and animal inoculation experiments, another approach to the problem of the transmission of leprosy is called for. I suggest that choice be made of a limited area or island relatively isolated, with a fair incidence of leprosy. In this area or island a thorough planned effort should be made to eradicate all skin arthropods, particularly in houses occupied or formerly occupied by leprosy subjects. It may have to include the extermination of fleas on cats and dogs and perhaps other animals. Efficient insecticides are now available and the task is not insuperable. Such an experiment would of course include the choice of a control area or island, careful preliminary surveys for leprosy and ectoparasites, and adequate recording and supervision over a long period, say 5 to 10 years or more.

Summary

The author points out the unsatisfactory state of knowledge of the mode of transmission of leprosy, and thinks that insects cannot

be ruled out. He reviews work which makes it possible that some of them are at least worth considering, and discusses in this respect fleas and body lice and scabies. He suggests the advisability of planning a field experiment based on the extermination of ecto-parasites by modern insecticides.

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A PRELIMINARY TRIAL OF ETISUL IN TREATMENT OF LEPROSY PATIENTS

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Introduction

The object of this trial was to gain first experience with Etisul as a practical drug in the treatment of patients in Sarawak. The patients chosen were 29 as follows: 6 Ibans, 9 Chinese, and 14 Malays; their ages were 18, 18, 20, 21, 22, 23, 23, 25, 25, 25, 26, 30, 32, 34, 35, 37, 38, 38, 39, 39, 40, 44, 45, 47, 49, 50, 53, 61 and 64. There were 19 males and 10 females. The type of leprosy in all was some variation of lepromatous leprosy and secondary neural complications of a mild type occurred in 5 cases. Smears for acid-fast bacilli were taken at the beginning of treatment and continued being taken at 2-weekly intervals until the end of the course, which was at the end of 12 weeks. We used Etisul in the standard pack of 5 grammes of the cream containing the active drug. The drug was applied over a wide area of the body surface, usually the broad of the back, by gentle persistent inunction, preceded by the morning bath. After the inunction patients were required to rest for 2 hours before having another bath. The inunction was carried out by medical assistants under my supervision or that of responsible members of staff.

Reaction of the Patients

I think it is always worthwhile noting the personal reaction of patients to a new drug. Until recently the drug treatment of leprosy was slow and hence somewhat disappointing in results. In the days of the coming of DDS it was found almost everywhere in the world that patients reported that this drug had an effect on the disease which they felt in themselves. In the case of this present trial of Etisul our patients reported that they felt the new drug (Etisul) was having a good effect. They said they had a feeling of wellbeing and felt stronger. As regards the supposed bad odour of the drug they had no real objection perhaps because the garlic odour is a familiar thing in their environment. One patient objected to the rubbing which at the time to him was perhaps excessively vigorous, a point which assisted us to establish the rule of gentle and persistent inunction over a wide area rather than an inunction with perhaps too much vigour. There was one case which ceased treatment after 3 inunctions of Etisul owing to a sudden dermatitis, which however may well have been an allergic phenomenon due to a certain tree

which is familiar in these parts. This tree is of the Mellanorrhoea group, known here as Rengas, and is sometimes inadvertently used as firewood. There was one other case who had to cease treatment after 10 inunctions after suddenly developing a severe reaction of the ENL type. Even at this point of stopping Etisul treatment her Bacillary Index had fallen from 0.5 to 0.33, and subsequently she resumed treatment on DPT and has continued satisfactory progress so that 5 months after the cessation of Etisul and the occurrence of her reactional episode and adoption of treatment by DPT she has attained bacterial negativity. There was no other case of lepra reaction during the Etisul course.

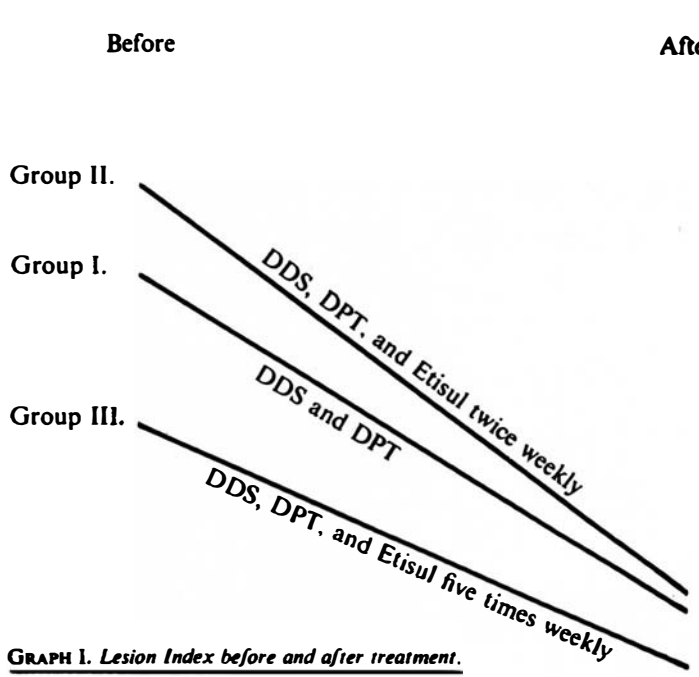
Previous or Concurrent Treatment

Of the 29 patients treated with Etisul all had had previous treatment with DDS (in 3 cases with DPT) which was ceased at the time of the beginning of the Etisul course, so that Etisul was given alone for a period of 12 weeks. The average duration of treatment on standard drugs before applying Etisul was 9 months, during which time a certain amount of progress had been made. The Bacillary Index of an average of 1.18 fell to an average of 0.83 on the previous treatment by standard drugs.

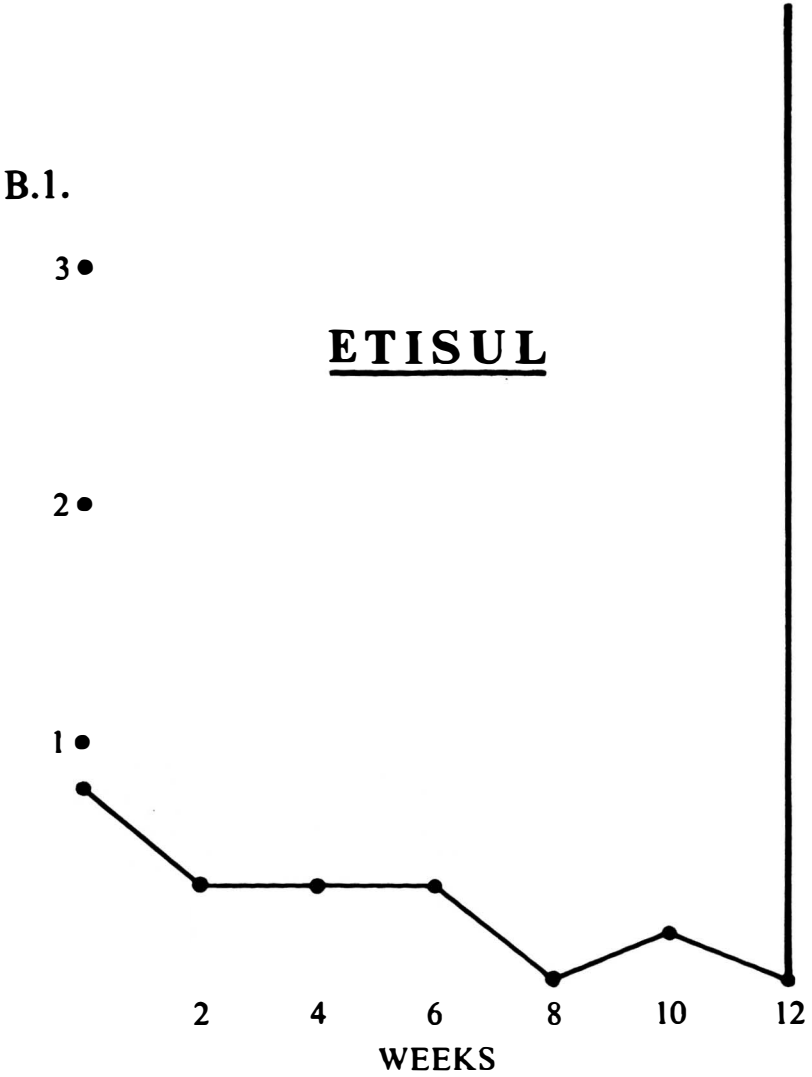
Results

In all the 27 cases who completed the Etisul course we observed a moderate to marked clinical improvement. As regards the Bacillary Index the average of the groups at the beginning was 0.83 and, 12 weeks later, at the end of the course, was 0.34. In effect there was no case which failed to achieve a good result in the end, and 62% achieved a satisfactory result in the 12 weeks. Of these cases only 3 are still positive, the Bacillary Indices being 0.4, 0.2 and 0.2 respectively.

(*a*) Clinical improvement was judged by the flattening of macules and nodules, and subsidence of diffuse thickening, and generally speaking this took place toward the end of the course. The patients themselves reported and indicated such improvement much earlier in the course, approximately at the end of the first 3 weeks. The decline of infiltration of the skin could be detected by changes in the reflection of light in the skin, so that it looked less turgid, and also by the appearance of fine wrinkling. This wrinkling also can be detected in the early stages of subsidence of infiltration by examination in a good light but becomes obvious in the later stages. No patient during the course, or in fact after it, showed any sign of acute leprotic neuritis. A marked feature of all the patients in the trial was the considerable improvement in bearing and fitness to outward observation. The patients looked well and it was noticeable that they carried themselves as if they were normal beings in the best



GRAPH I. *Lesion Index before and after treatment.*



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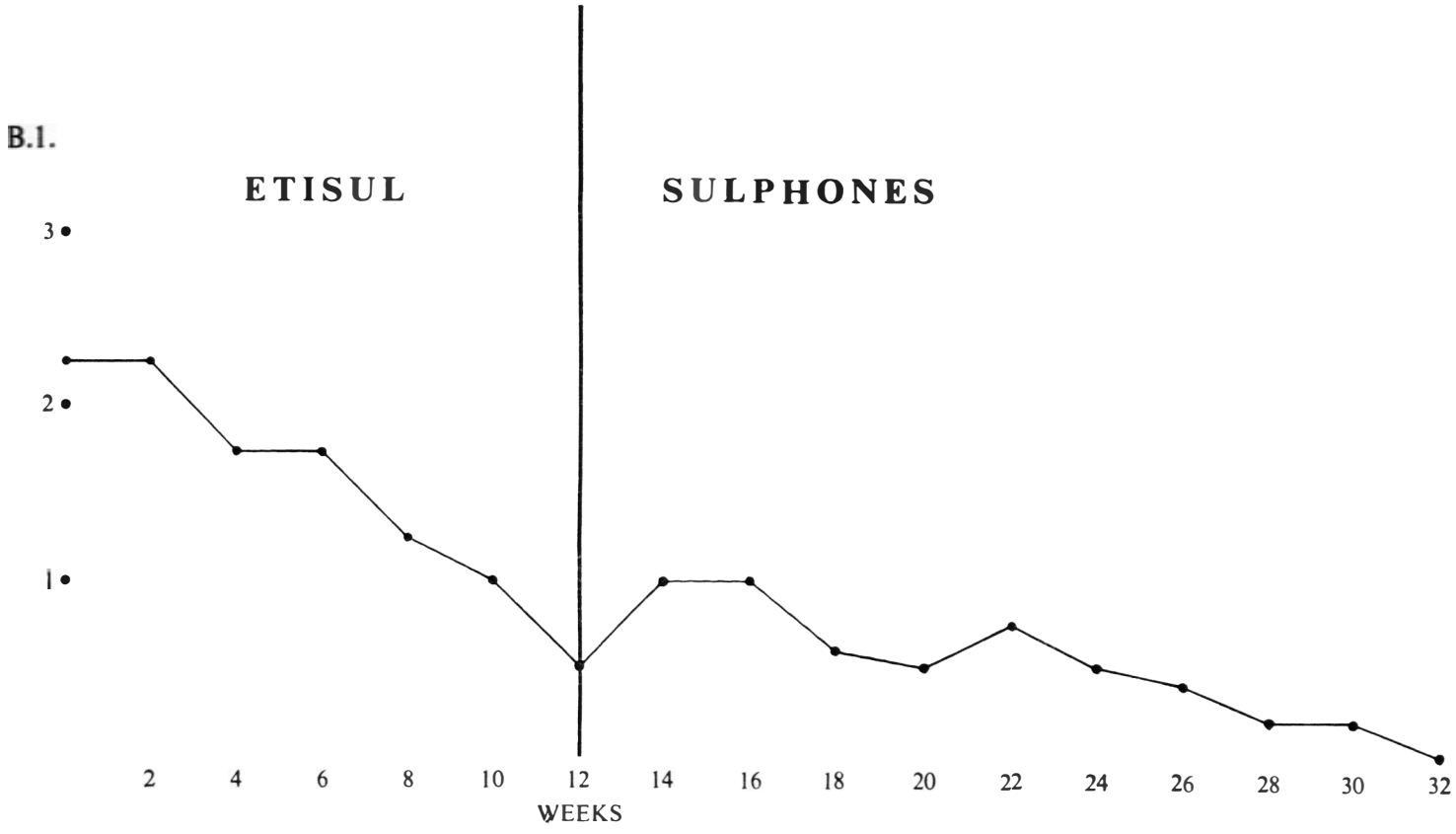
ETISUL
SULPHONES
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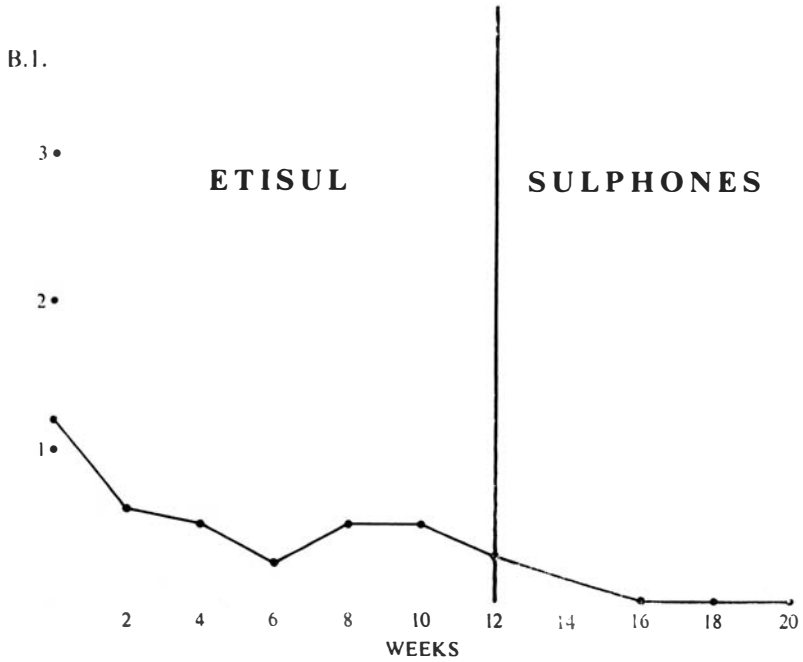
WEEKS



of health. To our observation this finding has not been seen under any previous leprosy treatment in such a short time. It may of course in part be a psychological impact, but the physical signs which formed part of it were very definite. Of the patients concerned 13 were employed in jobs round and about the leprosarium and continued their work satisfactorily, and the remainder continued their normal work in the daily life of the Settlement. We can confirm the report of Ross, Telfer and Hilton (Leprosy Review of October 1960) that there was an improvement in the oedema of hands and feet which often accompanies lepromatous leprosy, but our cases were mild and few.

We were fortunate in having a visit from Dr. James Ross Innes, Medical Secretary of the British Leprosy Relief Association and Secretary-General of the International Leprosy Association (10th to 26th October 1960), and were able to show the patients to him. He allows me to state that, in his opinion, this group of patients showed unmistakeable evidence of a drug active in leprosy in a relatively short time for anti-leprosy drugs. He has suggested to us that we proceed to a controlled trial of the drug and this we hope to do.

Summary

Patients, 29 in number, subjects of lepromatous leprosy who had previously been treated with standard drugs were subjected to a

trial of Etisul for a duration of 12 weeks. The results have been encouraging, showing a clinical and bacteriological improvement in the period well beyond the level of our experience of other drugs. We found no difficulties in obtaining the co-operation of the patients and have found that a widespread, gentle, and persistent body inunction for 20 minutes or more is practical and efficient. The odour caused no difficulty. There is much more difficulty following crude and rough inunction. We hope to proceed to a controlled trial as the next step. We found that certain cases who apparently had poor results at the end of the trial went on to a satisfactory result when placed on DDS or DPT. It appears from this that the association of Etisul with one or more of the standard drugs is important. We think that Etisul can readily be used not only in hospital conditions but also in district work.

Acknowledgments

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A CLINICAL EVALUATION OF ETISUL

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In July 1959 we chose 60 male and 26 female leprosy patients for a controlled trial of Etisul. These patients were all lepromatous, except for 6 borderline cases, and were all strongly positive in skin smears.

Each case was given 100 mg. daily of DDS by mouth for 6 days per week, a single dose daily, also diphenylthiourea (DPT or Ciba–1906) by mouth in a dose of 2 g. daily for 6 days per week, the daily dose being divided into three. Two groups were formed in which Etisul inunction (5 g.) was given, either on two days per week or five days per week. The patients rubbed in the Etisul for 20 minutes and then sat in the sun for 1 hour before taking a bath. Nearly all the cases had had previous medication with DDS. The control group was given no Etisul.

Smears were taken and examined *monthly*. The method was Wade's scraped skin incision, and the sites of the body from which they were taken were the ear, forehead, cheek, and from a lesion on the body. Each smear was graded for bacterial content, as is customary, from 0–4, and the *total* of the 4 smears taken as the smear index or bacterial index of the patient. We took no note of any distiction between whole and disintegrating bacilli, as we had found in a previous investigation of thiosemicarbazone that the bacillary morphology was of no practical importance.[1]

We recorded the body weights of the patients monthly, as also blood examinations, and found no significance in these findings. Every month we noted and recorded the presence or absence of infiltrations, nodules, plaques or macules (maculae). The extent of the lesions was estimated and graded on an arbitrary scale from 0–3, and the total of this for all the lesions was called the *lesion index*. From the male patients we formed 3 almost equal groups by age, weight, bacterial and lesion indices, and we divided the females similarly. The treatment of each group was then allocated by the spin of a coin, and the following groups emerged: *Group* 1 of 20 males and 13 females, placed on DDS and Ciba–1906; *Group* 2 of 20 males and 13 females on DDS and Ciba–1906, plus Etisul by inunction twice weekly; *Group* 3 of 20 males on DDS and Ciba–1906 plus Etisul by inunction five times weekly. The treatments were given under supervision, and absenteeism was rare. The trial continued for 12 months.

Complications

ENL was present in all groups before the start of the project, and at the end of a year had increased. This finding was to be expected as the incidence of ENL increases with the length of therapy. *The percentage increase of ENL* in each group was 37% in Group 1, 17% in Group 2, and 33% in Group 3. The fact that Group 2 had 50% less increase than the other groups I do not think important, as the other groups started with a higher index and consequently fewer individuals were at risk. One patient in Group 1 developed exfoliative dermatitis and was off treatment for 1 month. An itchy papular dermatitis occurred twice in Group 1 and in Group 3, and five times in Group 2. It was trivial and only one case (in Group 3) was put off treatment for 1 week. As this dermatitis also occurred in Group 1 it cannot be blamed on the Etisul.

Results

In all groups there was a slight improvement clinically. The *Lesion Index* before and after treatment was 6.6 to 4.8 in Group 1, 7.1 to 4.9 in Group 2, and 5.8 to 4.5 in Group 3. *Graph* 1 illustrates the parallel improvement in all groups. A feature difficult to explain were remarkable monthly fluctuations in the bacterial index. The smears were examined by two medical officers on each occasion. In an attempt to obviate the fluctuations we calculated for each group the combined results of the first two and the last two smears as follows: the *combined first* 2 *smears* were 19.9 in Group 1, 21.8 in Group 2, and 20.5 in Group 3, and *the combined last* 2 *smears* were 16.2, 18.3, and 16.8 respectively.

Discussion

It may cause surprise that our results differ so widely from those of DAVEY.[2] In our opinion, we differ in the interpretation of the same results, rather than in the results themselves. Davey lays great stress on the changed morphology of the bacilli, whereas we think this is unimportant, a conclusion to which we were forced during our trial of thiosemicarbazone, of which the end results supported our conclusions. In the thiosemicarbazone trial 2 patients took 3 years to become negative and 11 took 4 years, 8 took 7 years, and 1 took 6 years, and half of the patients had previously been on sulphones for 1 or 2 years. The bacillary morphology was so markedly altered during that trial that I stated in my report[1] "We were able to say from the smears alone whether the patient was receiving thiosemicarbazone or not". Despite the change in bacillary morphology 9 patients remained bacterially positive for 4 or more years after the end of the trial. We do agree with Davey that the patients on Etisul

showed disintegrated bacilli as well as whole ones; but so did the control group.

The interpretation of the bacterial index is also a matter of individual interpretation. Most workers make an average of their findings over a certain number of fields and call this the bacillary index. We search the slide for the highest reading in any one field and call this the index for that slide, trying thus to indicate how sick the patient is rather than how well the patient is.

Conclusions

We carried out a controlled trial of Etisul in combination with oral DDS and Ciba–1906 and think that we have shown that when Etisul is inuncted twice or five times a week it does not produce results that are better than DDS combined with Ciba–1906, without Etisul.

Summary

A trial of Etisul was arranged of groups in which 33 patients were given DDS and DPT, a parallel number of 33 patients were given DDS, DPT, and Etisul inuncted twice a week; and 20 patients DDS, DPT, and Etisul inuncted 5 times a week. The trial was carried on for 12 months and at the end of that time we thought that there was no evidence that Etisul treatment had a greater effect, clinically or bacteriologically, than standard treatment. During the trial of Etisul we noted marked monthly fluctuations in the bacterial index, for which we have no explanation. In calculating the bacterial index, we aggregate the data and do not strike an average as others do. We think that disintegration of bacilli under therapy has no significance. We use a lesion index for assessing clinical results, which is based on the extent of the lesions.

Acknowledgments

We thank Dr. J. M. Mungavin of Imperial Chemical Industries Ltd. for the free supplies of Etisul and the Secretary for Health, Union Government, for authority to publish.

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CLASSIFICATION OF BORDERLINE LEPROSY

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The object of any classification of leprosy is to promote the understanding of the processes which are taking place in the individual. This will naturally entail the prognosis in the particular case. The classification must be made when the patient is first seen but the accuracy and value of the classification can only be tested by observing the subsequent history of the case.

We have accepted the Madrid classification, except that we do not agree that "conspicuous asymmetry" is a feature of Borderline leprosy. To the list of lesions we also add macules that are flat, infiltrated, and positive for *M. leprae*. We also insist that lesions must arise out of normal skin, and we test for the presence of normal skin by taking skin smears at a short distance away from the lesion. I see that PERIASWAMY[3] also uses this technique. These "normal skin" smears must be negative. We also lay great stress on the finding of an "immune area". Such immune areas are the centres of old tuberculoid lesions, and even if lepromatous changes have occurred around them, their presence indicates a previous degree of immunity, and we think this degree of immunity is never lost, and incidates a good i.e. short prognosis.

Our idea of the prognosis of the various classifications hinges on what we have come to expect under our present lines of treatment. I have described[1,2] the action of DDS combined with Stibophen and Atebrin in Tuberculoid lesions. This we call the "triple treatment". It is also effective on the external lesions of borderline leprosy, but we no longer use it in lepromatous leprosy as we do not think it affects the bacilli. Our experience of indeterminate leprosy is too little to be of value, but very few of our cases have retrogressed, so we have adopted the "triple treatment" as a routine.

We expect therefore:

1. Tuberculoid macules to have resolved in an average of 5 months, and in reactional tuberculoid lesions we expect the bacteria of leprosy to have disappeared in less than 5 months.
2. Borderline lesions should resolve in 12 to 15 months and should be bacterially negative in under 2 years. Failures in this group lose their external lesions but diffuse infiltration persists in those who remain positive, as they regress to lepromatous.

Most of the cases reported here were treated before we adopted the "triple treatment" and their lesions took longer to revolve.

3. Lepromatous plaques subside to lepromatous pale macules in under two years. Nodules may become "crushed tissue paper" scars in the same time or may leave dusky skin blemishes. Bacilli begin to fade away after the third year.

Our greatest difficulty is to distinguish between Borderline and Tuberculoid in reactional cases. To some extent we have now obviated this by searching for the following criteria in Borderline cases.

(*a*) Infiltrated lesions, positive for *M. leprae*, must be surrounded by skin which shows no *M. leprae*. The centre of the lesion is usually more elevated than the margin. The margins merge diffusely into the surrounding skin, except where the case was originally tuberculoid.

(*b*) The finding of flat "immune areas".

(*c*) A negative lepromin.

(*d*) The histology to be lepromatous or non-specific.

(*e*) Neurological signs not always present.

Description of Lesions with Illustrative Cases

Bands of Infiltration

Zones of infiltration may occur on any part of the face, trunk or limbs. They differ from plaques in that they have no circumscribed shape. The margins are sometimes clearcut but more commonly diffuse into the surrounding skin. Smears are positive in the lesion but the surrounding skin is negative. They may be acute in their onset and sudden in their disappearance.

Case No. 12418. Admitted in March, 1955, with "plaque-like" macules with elevated centres and indefinite margins on buttocks and limbs. Mitsuda 2 mm. Five months later a zone of infiltration appeared on his forearm and took 4 months to disappear. *Plate* 1.

Infiltrations

Infiltrations which arise out of normal skin occur in Borderline leprosy.

Case No. 12383. This case was admitted with infiltration of the ears, malars and supraorbital ridges. (*Plate* 2.) Smears from the ridge were 2 + but only scanty from the other sides. Smears from the forehead and cheek were negative. Patient also had slightly raised plaques on the arms and legs. Smears were 2 + and 4 + respectively. Mitsuda 2 mm. All smears were negative after 7 months. The lesions were gone in the 9th month, but plaques recurred 2 months later and remained active but negative for a further 4 months after which they faded away.

Granular Infiltration

Granular (or pebbly) infiltration is usually generalised over the whole face and is a sign of lepromatous leprosy. It can occur in borderline leprosy.

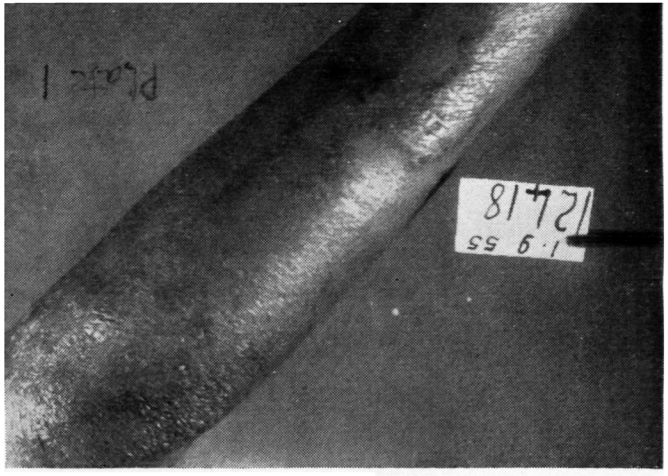
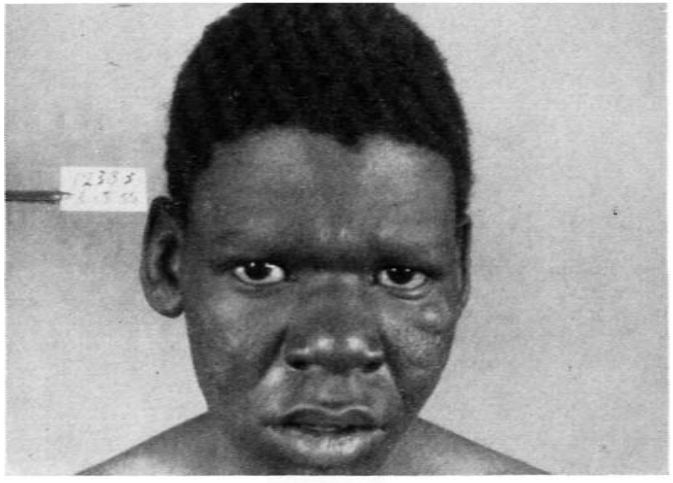


PLATE 1



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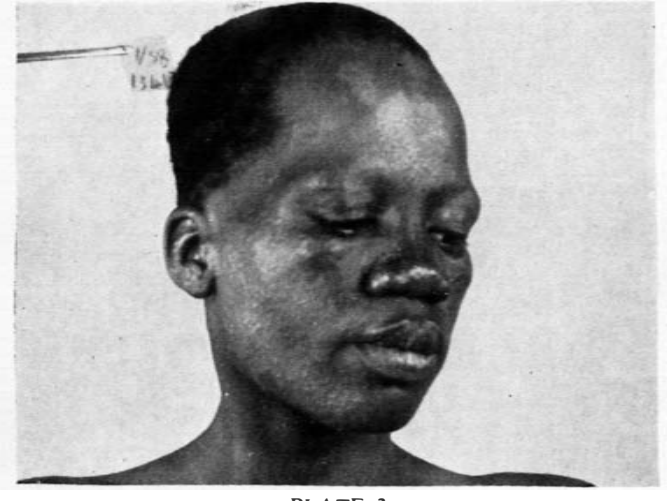

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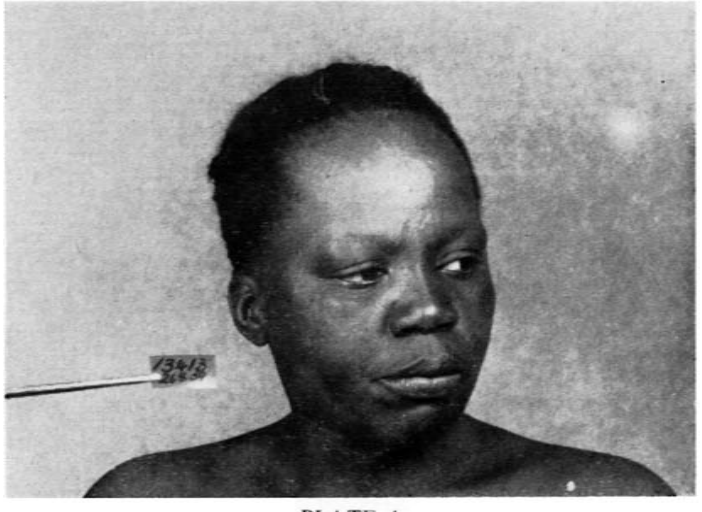

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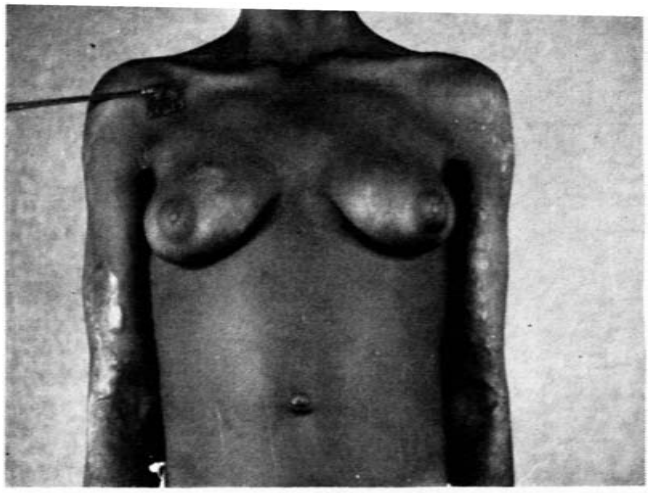

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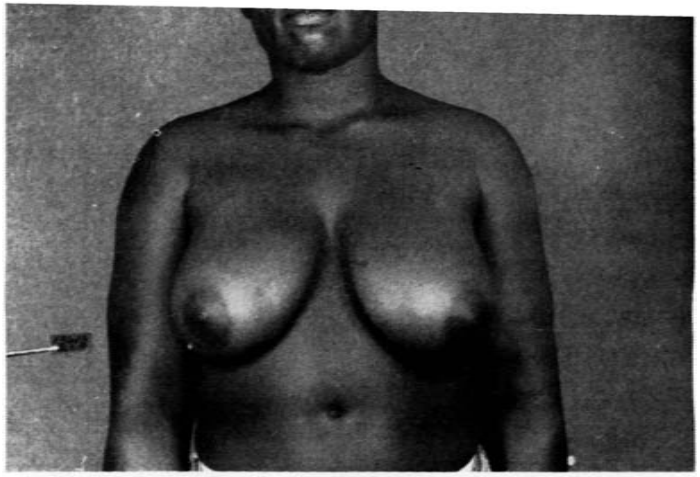

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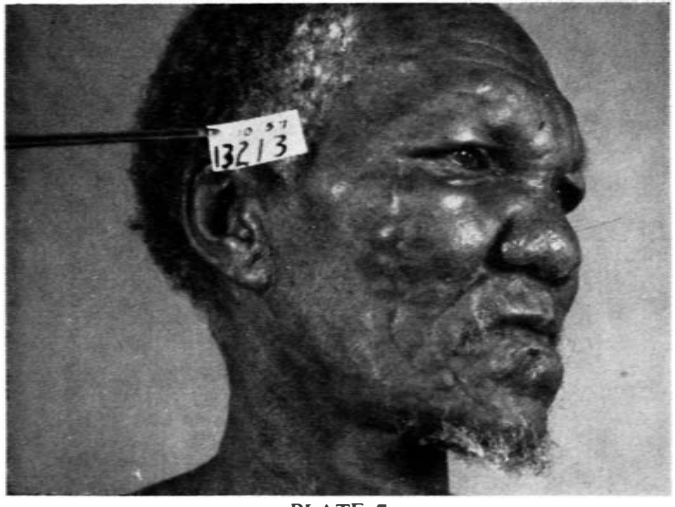

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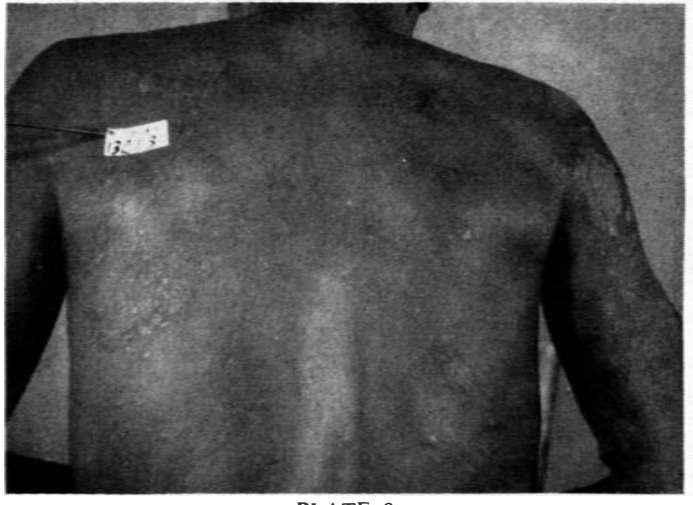

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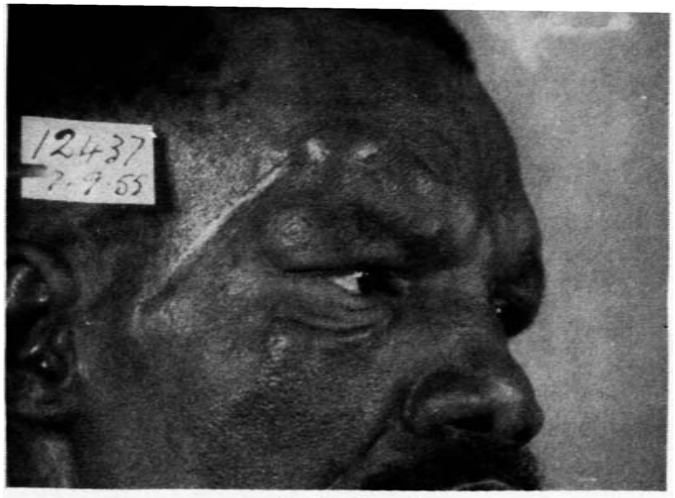

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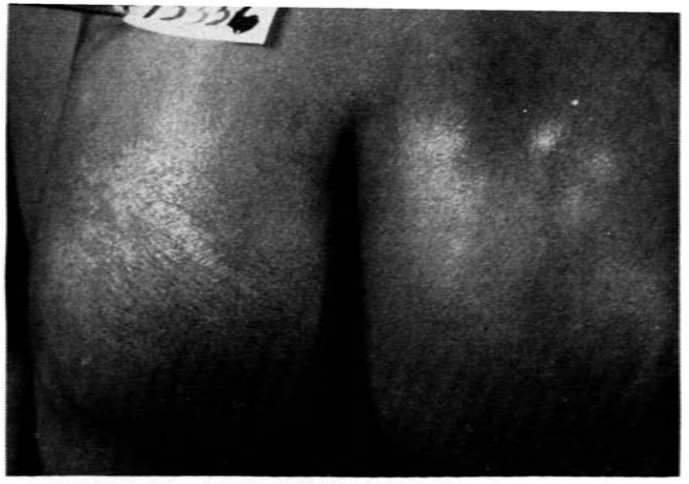

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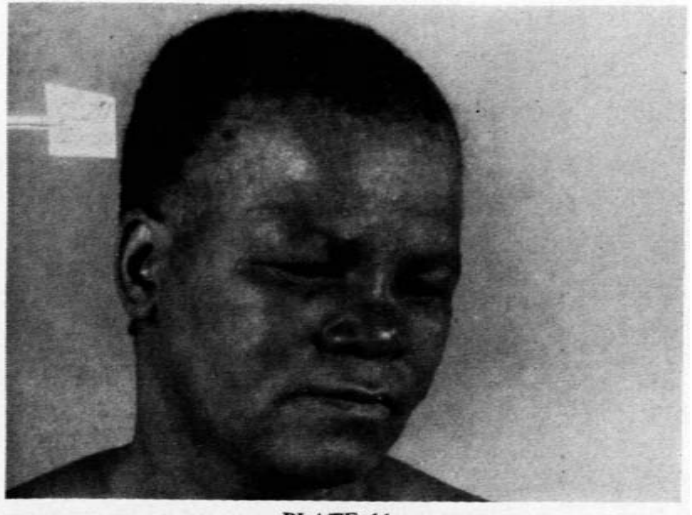

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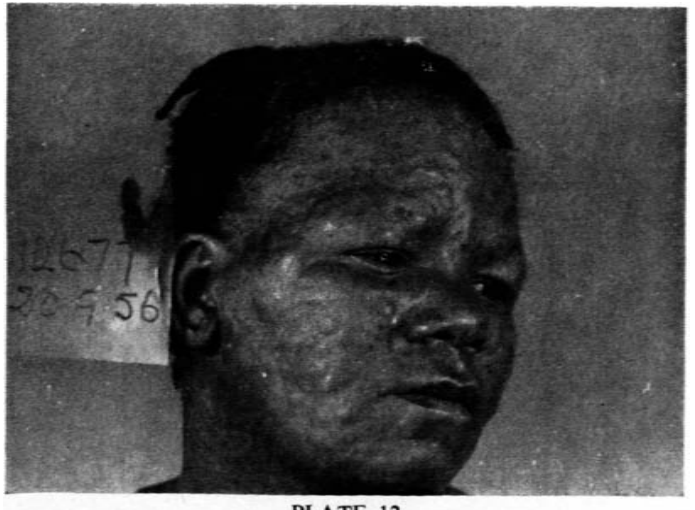

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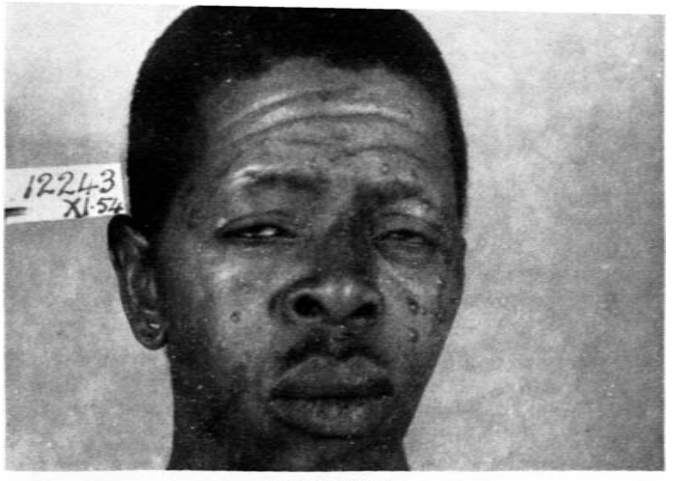
PLATE 13



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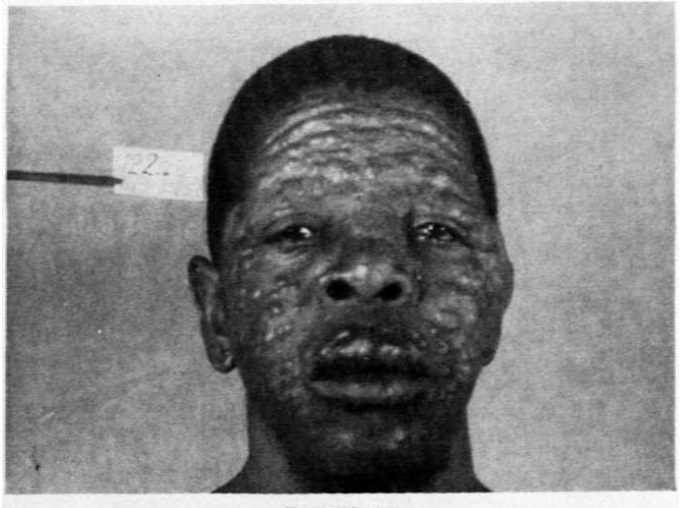

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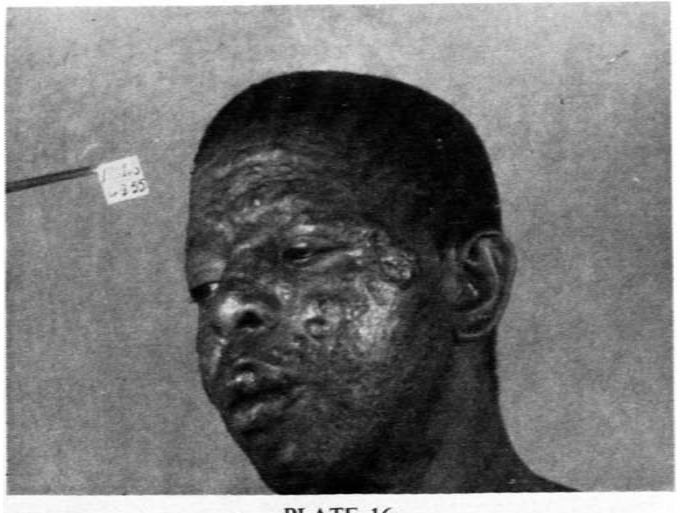

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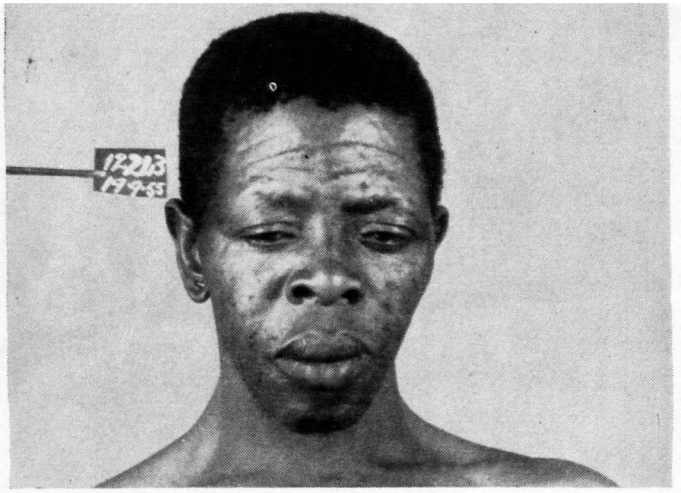

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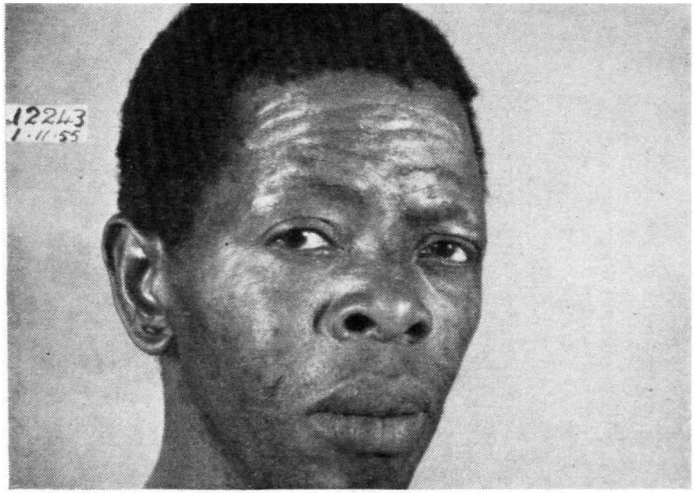

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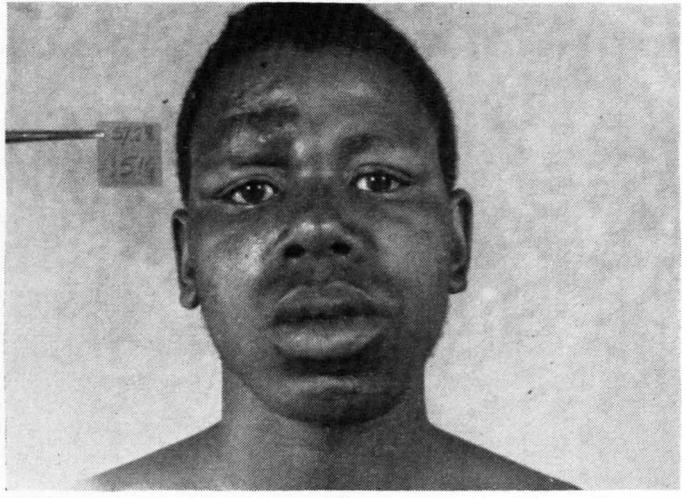

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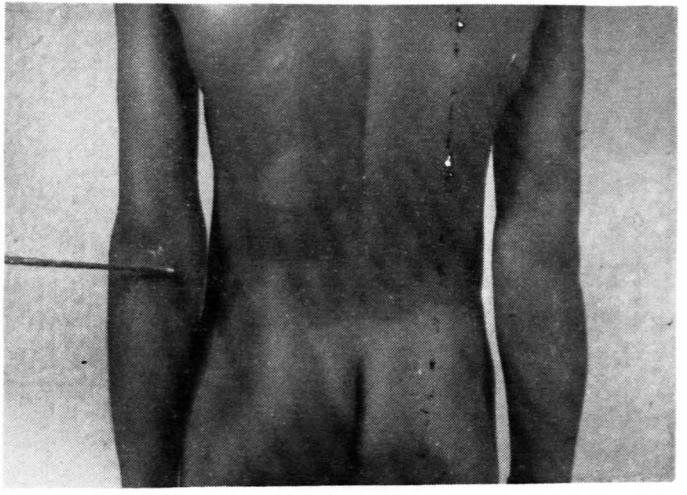

PLATE 20

Case No. 13413. Admitted January 1958, with grey granular infiltration of the face and ears with well marked margins and well defined normal skin on forehead. (*Plates* 3 *and* 4.) There were zones of infiltration on limbs arising out of normal skin. Macules with lepromatous margins but flat "immune area" centres on shoulders and right biceps region. (*Plate* 5.) Mitsuda 0. Smears 2 +. (*Plate* 6.) shows resolution of lesions on 26–8–59. Gain in weight of 54 lbs.

This case is important in that it emphasizes the importance of finding "normal skin" and "immune zones".

In July we noted "No evidence of infiltration. Macules on face and arms have serpiginous margins". Smears from all involved areas were 2 or 3 +. The last positive smear was in April 1959. In this month she first developed ENL and had four attacks of ENL during next 8 months.

It is unusual for an infiltrated area to become a macular area and this suggested that she may have been a tuberculoid case. This is ruled out by the length of time she took to become negative and more particularly by the development of ENL.

Macules and Immune Areas

The macules in borderline leprosy may be elevated over their whole extent but with clear-cut margins. We give the name "spongy maculae" to such lesions. They may show healed centres and infiltrated margins or they may be identical with lepromatous maculae, being infiltrated and flat. They must arise out of skin which appears normal and which shows no *M. leprae*.

Case No. 13213. (*Plate* 7.) This patient had infiltration over the forehead, nose and malar regions. Smears were 3 +. Yet around the mouth were spongy maculae arising out of normal skin. On the trunk (*Plate* 8) the macules were plaque-like, with margins fading into the surrounding skin. Some of these lesions, as seen over the left scapula, had flattened centres. This evidence of the "immune area" clinched the diagnosis of Borderline. This classification was borne out by the subsequent history as the lesions were gone in 12 months and the smears were negative in 16 months. Treatment was by DDS, Atebrin and Stibophen. (For details see Ref. 2.)

Plaques

Plaques are isolated infiltrated lesions, which are more raised in the centres than in the margins. The margins are indefinite and blend diffusely into the surrounding skin. The skin surrounding a plaque shows no *M. leprae*. The plaque is usually strongly positive on bacterial examination.

Case No. 12437. This case (*Plate* 9) was admitted with "erythematous plaques arising from normal skin". There are hypopigmented macules on the trunk and buttocks. The normal skin may be seen in front of the ear in the photograph reproduced. Smears from the ear, the forehead and the malar regions were 3 +. Mitsuda was 1 mm. Smears remained positive for 16 months and the lesions had faded in 18 months.

Plaques Reverting to Lepromatous Macules

Case No. 13354. This case was admitted with "raised, slightly erythematous plaques with indefinite margins on face, buttocks, and thighs. These plaques arise out of normal skin". The earlobes appeared infiltrated. Smears of the normal skin were negative. The treatment was DDS, Atebrin, and Stibophen. Within five months the raised plaques resolved to flat lepromatous maculae. See (*Plate* 10).

The margins were indefinite but the centres were hypopigmented and appeared infiltrated. They faded away completely in the next two months. Smears were negative after the 19th month. The Mitsuda was slightly positive, i.e. 3 mm.

Reactional Borderline

1. Multiple Plaques

The resistence of a patient may break down completely but temporarily. In such instances there is a "shower of bacilli" throughout the body and the development of multiple, raised, erythematous, nodular-like plaques. These are invariably positive for *M. leprae.*

Case No. 12677 (*Plate* 11). This case was admitted in November 1955, with "Suggestion of infiltration of face. A shower of bacilli on forehead, trunk, and limbs has caused plaques of the diameter of a pea. A tuberculoid macule with central area of immunity had undergone lepromatous change in the margins". A classification of Borderline was made because of this immune area. Mitsuda result was 1 mm. positive. A biopsy of the margin of the macule showed lepromatous histology. Smears of earlobe were negative but eight other sites were from 1 to 3 +. Smears became suddenly negative and remained so until the 6th month when the reaction recurred and smears became positive. The clinical condition became worse (see *Plate* 12 dated 20.9.56) and then suddenly subsided. One scanty positive was found in January 1957, since when patient has been clinically and bacteriologically arrested. *Plate* 13 dated 3.12.56.

2. Multiple Plaques and the Immune Area

It is often difficult to distinguish, on clinical appearance alone, between multiple plaques and spongy, reactional, tuberculoid lesions.

Case No. 12243. This patient in September 1954 showed "raised, spongy, erythematous maculae or nodules on face. Margins over nose and elbow have become lepromatous or Borderline. A similar lesion on the right elbow shows a central immune area. Mitsuda 3 mm." (*Plate* 14 November 1954). Histology was "lepromatous leprosy". These plaques faded away and the biopsy in November showed "the histological features are not typical of either lepromatous or tuberculoid leprosy". In January 1955 he had a reaction and nodular-like lesions appeared on the face and below the knees. (*Plates* 15 + 16.) These lesions showed no *M. leprae.* In fact the patient was never positive except on the day of admission when three lesions were 1, 3 and 4 + respectively. In October 1955 he showed "slight dusky staining in the site of old lesions". He was declared a clinical cure. (*Plate* 17.) This staining gradually faded (*Plate* 18, November 1955).

In view of the slightly positive Mitsuda and the short bacteriological history the classification of tuberculoid must be considered, but the lepromatous histology points to our final conclusion, i.e. borderline.

Classification Open to Doubt

Plaques and Papules

Plaques and papules may occur together in Borderline cases. The lesions called papules are under 3 mm. in diameter. Larger than this they are called nodules, and nodules are unusual in Borderline cases.

Case No. 13519. This patient had plaques and papules on the right side of his face and plaques on his trunk. Asymmetry was marked, though we do not find this in most cases. Mitsuda was 2 +. (*Plates* 19 *and* 20.) Smears from lesions were 2 +. The papules disappeared in 7 months. The plaques on the trunk faded to pale blemishes in 14 months. The plaque on the forehead took 2 years and 4 months to become negative. In this month, too, the patient developed ENL,

which recurred again the next month. Histology was not done in this patient. In view of the long history before negativity was achieved, and the fact that ENL occurred, this case may really belong to the lepromatous group.

Summary

1. It is stated that classification entails prognosis.
2. Borderline lesions must arise out of apparently normal skin in which no *M. leprae* can be found.
3. The centres of old tuberculoid lesions do not become involved when a borderline or lepromatous change take place. These centres are called "immune areas" and are of favourable prognosis.
4. The lesions found in borderline leprosy are:
   (*a*) Zones of infiltration.
   (*b*) Diffuse infiltration.
   (*c*) Granular infiltration.
   (*d*) Maculae.
   (*e*) Plaques.
5. Borderline cases may go into reactional phases.

Acknowledgments

I have to thank the Secretary for Health, Union Government South Africa, for permission to publish this article.

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A THREE YEAR CLINICAL EVALUATION OF DALACIN IN THE TREATMENT OF LEPROMATOUS LEPROSY

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The Research Laboratories of the Upjohn Company, Kalamazoo, Michigan, U.S.A., have isolated a new antimicrobic complex produced under conditions of submerged fermentation by *Streptomyces spectabilis*, an Actinomycete isolated from a sample of soil from Dallas, Texas, U.S.A. The laboratory designation of Antibiotic 10la bears the generic name Streptovaricin and has subsequently been marketed under the trade name of Dalacin.

Streptovaricin has been demonstrated to have a high degree of activity against *Mycobacterium tuberculosis*, both *in vitro* and *in vivo*, and it has also proved active in *in vitro* against a number of gram-positive, gram-negative and saprophytic acid-fast bacteria.

Under the same conditions of *in vitro* tests, Streptovaricin proved approximately 10 times as active as Streptomycin, 100 times as active as para-amino-salicylic acid, and half as active as isonzaiid.

Streptovaricin proved highly effective in treating mice infected with *M. tuberculosis* (c37Rv). When the microbic enumeration technique was employed, Streptovaricin and isoniazid given together produced an anti-tuberculosis effect that was considerably greater than was achieved with either drug alone.[1, 2, 3, 4]

Streptovaricin resulted in regression and healing of tuberculosis lesions in guinea pigs infected with tubercle bacilli resistant to Streptomycin and to P.A.S.[6] It was also shown to exert a suppressive action against murine leprosy in mice.

Studies on the biological distribution of Streptovaricin revealed that it was well absorbed from all parts of the digestive tract except possibly the stomach.[7]

In view of the encouraging preliminary laboratory investigation, the clinical evaluation of Streptovaricin in human mycobacterial infection was undertaken. There have been rather extensive studies of the therapeutic effect of Streptovaricin in human pulmonary tuberculosis. For the most part, these have all been discouraging. Nathan makes the following observations:[8]

1. Streptovaricin does not delay the emergence of tubercle bacilli resistant to Isoniazid.
2. Streptovaricin (3 gms./day orally) along with Isoniazid provides no more in therapeutic efficiency than might be achieved in Isoniazid alone.
3. Toxicity due to Streptovaricin in the dosage levels used was severe enough to warrant withdrawal of the drug in 1/5 of the cases. Nausea, vomiting and diarrhoea were the most commonly encountered symptoms.

Similar conclusions have been reached by other investigators.[9, 10] In another study of the emergence of bacillary resistance to Streptovaricin in 10 patients it was shown that varying degrees of resistance developed in all cases.[11]

The purpose of this paper is to report the findings of a three year clinical evaluation of the therapeutic effect of Streptovaricin in a small series of cases of Lepromatous leprosy treated at the Kano Leprosarium of the Sudan Interior Mission in Northern Nigeria.

Method

The patients chosen for this study were all far advanced cases of lepromatous leprosy. With the exception of the first case all were previously untreated. Preliminary studies included C.B.C., urine, stool, sedimentation rate, skin smear, biopsy and photograph. The C.B.C., urine, stool and skin smear were repeated monthly during the course of this study, and repeat biopsies and photographs were taken approximately every 6 months.

Procedure

Streptovaricin was supplied in 200 mgm. capsules. The drug was given daily, with the exception of Sunday, up to 3 gms. at which level it was maintained. The study was instituted in January, 1957.

Case Reports

1. SA'A KANKASA. No. 2316. 20-year-old Fulani female.

This patient was first admitted in 1949, as a 12-year-old girl. At that time she had 2 years of Diasone treatment and then left against medical advice.

She was re-admitted in January, 1957, having had no treatment in the intervening more than 6 years. She was in very poor condition with marked progression of the disease, being a far advanced case of lepromatous leprosy. There were marked mucosal lesions, nasal septal ulceration, perforation and collapse of the nasal arch. There were buccal and laryngeal nodules, and diffuse infiltrative lesions with ulceration. There was widespread heavy diffuse infiltration of the whole body, the heaviest being on the face.

She was started on Streptovaricin in February, 1957. The drug was very well tolerated. At no time were any toxic manifestations noted. She did experience two very mild ENL reactions at the 6th and 15th months. Neither of these reactions was severe enough to warrant interruption of the treatment.

It was noted that there was a tendency to a chronic dermamycosis during the course of this sutdy. A total of 34 months' treatment have been completed at the time of this report. Total dose: 2128,6 grams.

We noted that there was a definite clinical improvement as seen in the moderate resolution of the heavy diffuse infiltrative lesions. There remained, however, definite clinical infiltrative lesions, particularly of the extremities. The nasal septal mucosal ulceration persisted. The buccal and laryngeal involvement has shown some improvement. The bacteriological index (Ridley) (12) came from a high of 5.6 in April, 1957, to a low of 2.8 at the time of this report.

Histopathological Reports on biopsy material sent for examination:

1*st Biopsy* (26/1/57), 525 (Lab. No. 2495)

H. E. SECTION: There is a massive infiltration occupying the whole of the dermis up to the epidermis, but leaving a narrow quite clear sub-epidermal zone. The infiltrate consists almost entirely of macrophages, many of which have undergone commencing foamy cell change. Amidst the infiltration there are round cells and a significant number of plasma cells. The nerves, however, are quite unrecognisable, owing to the intensity of the granulomatous tissue. This may indicate, however, that the patient may have passed through the dimorphous phase.
F. F. STAIN: Very numerous bacilli seen all through the granulomatous area showing no morphological change, and there are no characteristic globi.
DIAGNOSIS: A very active, moderately advanced lepromatous case.

2*nd Biopsy* (19/2/58), 555 (Lab. No. 3014)

H. E. SECTION: The whole of the corium is occupied by a gross infiltration not extending up to the epidermis, but leaving a relatively clear sub-epidermal zone. The infiltrate is seen to be chiefly round cells in the background of foamy cell change. In addition there are fairly numerous plasma cells. In this gross infiltration nerves are almost impossible to recognise.
F. F. STAIN: Large numbers of acid-fast bacilli seen throughout the section, showing some morphological change.
DIAGNOSIS: This is a moderately advanced lepromatous case showing considerable activity, and is probably under the influence of therapy.

3*rd Biopsy* (22/1/59), 572 (Lab. No. 3357)

H. E. SECTION: There is a moderately gross infiltration underneath the epidermis leaving a broad free sub-epidermal zone. The infiltrate is a more or less continuous mass going down to, but not extending deep into the subcutaneous fatty tissue. The infiltrating mass consists almost entirely of macrophages which have undergone gross foamy cell change. In between the foamy cells there is some round-celled infiltration, but this is not significant. Plasma cells are easily recognisable and show some increase. Nerves do not seem to have been included in the section, except for one which is distinctly recognisable.
F. F. STAIN: Numerous acid-fast bacilli showing marked morphological change. One nerve was recognised in the longitudinal section with proliferation of Schwann cells, some of which contain a number of bacilli.
DIAGNOSIS: Moderately advanced active leproma, not in reaction, and with some evidence of being under the influence of therapy.

4*th Biopsy* (26/11/59), 576 (Lab. No. 3741)

H. E. SECTION: The whole of the superficial part of the corium underneath the epidermis is occupied by a continuous sheet of foamy cell change. The infiltration does not go up to the epidermis and leaves a relatively free, broad sub-epidermal zone. The infiltrate consists almost entirely of foamy cells. Interspersed between the foamy cells are round cells and there seems to be quite an increase in plasma cells. An occasional nerve is seen, recognised chiefly by the fact that the histiocytes have the shape of Schwann cells. Otherwise, nerves are unrecognisable.
F. F. STAIN: Numerous acid-fast bacilli seen throughout the section showing little or no morphological change.
DIAGNOSIS: Moderately advanced lepromatous case, showing considerable activity, but not in reaction.

Conclusions

There has been very definite clinical and bacteriological improvement, but we feel it is slightly less than what we could have expected on Sulphetrone; there is no corresponding histological evidence

indicating any improvement, in fact the last biopsy from this case showed definite deterioration in the patient's condition.

2. YAHAYA ZAKARA. No. 4612. 17-year-old Fulani male.

This patient was first admitted in December 1956. He was a well advanced case of lepromatous leprosy. There were nodular and diffuse infiltrative lesions, widespread, but heaviest on face and thighs. Some of the nodules had become necrotic with superficial ulceration.

There were advanced mucosal lesions, nasal septal ulceration, perforation and early collapse of the nasal arch. There were labial, buccal and laryngeal mucosal infiltrations with labial ulceration.

He had had no previous treatment. Treatment with Streptovaricin was started in January, 1957. The drug was well tolerated. At no time was any toxic manifestations noted. He did experience a number of mild ENL reactions.

At the 11th, 17th, 28th and 32nd months there were mild ENL reactions, at which times the dose was reduced for a short period, but with no interruption of treatment. At the 13th and 20th months the ENL reactions were moderate in severity and short rest periods were given.

A total of 35 months of treatment has been completed at the time of this report. Total dose: 1214.8 grams.

We note at the time of this report that there has been definite clinical improvement. There has been moderate resolution of the nodular and diffuse infiltrative lesions. He still shows, nonetheless, moderate cutaneous and subcutaneous infiltrations, particularly of the lateral aspect of the thighs.

The nasal mucosal lesions persist with ulceration and progress in the degree of collapse of the nasal arch. There has been moderate improvement of the labial, buccal and laryngeal lesions. The bacteriological index went from a high of 5.9 at onset of treatment to a low of 3.5 at the termination of the study.

Histopathological Reports on biopsy material sent for examination:

1*st Biopsy* (21/12/56), 490 (Lab. No. 2478)

H. E. SECTION: This shows a massive infiltration throughout the corium leaving a relatively clear sub-epidermal zone; this is somewhat vascular. The granoloma consists almost entirely of macrophages, the majority of which show foamy cell change. There is also considerable round cell infiltration and some increase in plasma cells. The nerves are very interesting; there is a very great deal of proliferation of the perineurium seen as the characteristic onion-peel appearance which is so typical of lepromatous leprosy, and in some nerves this proliferation of the perineurium results in a general constriction of the nerve tissue. The cellular invasion is mostly around the nerve rather than in the nerve, although there is some increase of the cells of Schwann.

F. F. STAIN: Very numerous acid-fast bacilli seen throughout the granulomatous infiltrate and in the nerve.

DIAGNOSIS: Moderately advanced lepromatous case.

2*nd Biopsy* (19/2/58), 548 (Lab. No. 3007)

H. E. SECTION: About 80% of the corium is occupied by a massive infiltration consisting of numerous foamy cells. The infiltrate does not go up to the epidermis, but leaves a relatively clear sub-epidermal zone. In the midst of the foamy cells there is a considerable round-celled infiltration with moderately numerous plasma cells. A number of nerves were seen in which there was proliferation of the perineurium and some increase of the Schwann cells. One nerve was difficult to recognise, but I think there was an increase in the cellular infiltrate consisting chiefly of Schwann cells and some round-celled infiltration.

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

DIAGNOSIS: This is a moderately advanced lepromatous case, with indications of considerable activity. There is a little evidence that it is under the influence of therapy.

3*rd Biopsy* (22/1/59), 571 (Lab. No. 3356)

H. E. SECTION: There is a diffuse infiltration scattered throughout the dermis leaving a broad, clear sub-epidermal zone. The infiltrate is seen in masses chiefly associated with the appendages of the skin, particularly the hair follicles and the sebaceous glands. The biopsy has probably been taken from the face. The infiltration cannot be said to be focalised. The infiltrating cells

are chiefly large histiocytes (macrophages) all of which have undergone gross foamy-cell change. In one area immediately underneath the epidermis there is what appears to be an epitheloid cell focus; macrophages look like epithelioid cells and are associated with marked round celled infiltration. On closer examination some of the epithelioid cells appear to have undergone foamy cell change, but there are a number of macrophages which could be described as epithelioid cells. The section is rich in nerves which are completely uninvaded.

F. F. STAIN: Very numerous acid-fast bacilli scattered throughout the dermis and in nerves showing some morphological change.

DIAGNOSIS: An active, moderately advanced lepromatous case. There is some evidence that there may still be some dimorphous features clinically.

4th Biopsy (20/11/59), 577 (Lab. No. 3742)

H. E. SECTION: This shows a moderate infiltration scattered throughout the dermis leaving a fairly broad sub-epidermal zone. The infiltrate is not continuous but is mostly around the skin appendages, the sweat glands, the sebaceous cysts and the neuro-vascular strands. The infiltrate consists almost entirely of well developed foamy cells. There are collections of foamy cells; here and there, between the foamy cells there are also some plasma cells. Several nerves are very clearly seen and cut longitudinally showing no invasion whatever.

F. F. STAIN: Moderate numbers of acid-fast bacilli seen scattered through every field of the microscope. They show some, but not marked morphological change.

DIAGNOSIS: This is a moderately early lepromatous case showing some activity, but not in reaction.

Conclusions

Although there was definite clinical and bacteriological improvement, we feel that it was no more, if as much, as we could have expected on Sulphone. This opinion is supported by the fact that from a study of the histopathological sections there is no indication of any definite improvement in the patient's condition.

3. AMINA DABI. No. 4629. 30-year-old Fulani female.

This patient was first admitted in January, 1957. At that time she was a far advanced case of lepromatous leprosy. There were widespread heavy nodular and diffuse infiltrative lesions. Face, arms, and trunk posteriorly were the heaviest areas affected. There was marked nasal septal mucosal ulceration. Marked labial and moderate buccal and laryngeal mucosal infiltration.

She had had no previous treatment. Streptovaricin was started in February, 1957. The drug was very well tolerated. At no time were any toxic manifestations noted. She did show two mild ENL reactions. At the 17th month, one week rest. At the 30th month, the dose was reduced but treatment was not interrupted.

A total of 34 months' treatment has been completed. Total dose: 2426,2 grams.

At this time we can make the following observations. There has been very definite clinical improvement as seen in the resolution of the very heavy nodular and diffuse infiltrative lesions. There does remain moderate infiltrative lesions, particularly in the areas of heaviest involvement mentioned above.

The nasal septal mucosal ulceration persists with progression to the point that there is now a large septal perforation. The other mucosal lesions have shown resolution and healing.

The bacteriological index went from a high of 6.0 at the onset of treatment to a low of 4.0 at the time of reporting.

Histopathological reports on biopsy material sent for examination:

1st Biopsy ($26\frac{11}{2}57$), 526 (Lab. No. 2496)

H. E. SECTION: The whole corium is occupied by a mass of infiltrate extending up to the epidermis, but leaving a narrow, relatively free sub-epidermal zone. The infiltrate occupies the whole of the corium as a broad and continuous band. The infiltrating cells are round cells, macrophages and a fair number of plasma cells. Some of the macrophages have the appearance, but not the distribution of epithelioid cells; others show quite definite foamy

cell degeneration. Nerves, by and large, are not recognisable, although one or two can be seen with some increase in the cellular infiltrate.
F. F. STAIN: Fairly numerous bacilli seen throughout the section and all the macrophages contain bacilli. Nerves can be recognised and there is an increase in the Schwann cells, but the nerves show little evidence of infiltration. Bacilli, by and large, show themselves as acid-fast rods but there are many beaded and granular forms.
DIAGNOSIS: Active, moderately advanced lepromatous leprosy. It is difficult to say whether the bacilli are under the influence of therapy or not; there are too many well-stained acid-fast rods to be certain of this.

2nd Biopsy ($191_2 2_2 158$), 563 (Lab. No. 3022)

H. E. SECTION: There is a fairly marked and diffuse round celled infiltration scattered throughout the dermis leaving a clear sub-epidermal zone. In addition there are fairly numerous plasma cells. The lymphocytic response in this section is seen in the background of well marked foamy cell change. No nerves were actually seen in the section, except one in the Fite section in which there was no involvement.
F. F. STAIN: Very numerous, very granular, rather poorly stained acid-fast bacilli.
DIAGNOSIS: This is probably a lepromatous case resolving under therapy, passing through a phase of marked activity. There are too many bacilli in the section to suggest that it is an erythema nodosum lesion, but I would certainly surmise that this was a very active lesion.

3rd Biopsy ($22_2 1_2 59$), 570 (Lab. No. 3355)

H. E. SECTION: There is a moderately gross infiltration throughout the dermis and under the epidermis leaving a relatively clear sub-epidermal zone. The infiltrate tends to show itself in a continuous band. There is no evidence of focalisation. The infiltrating cells consist of large histiocytes (macrophages) all of which have undergone foamy cell change. In one area there is a giant cell in the middle of the foamy cell infiltrate but there is no evidence of epithelioid cells. Curiously enough there is no nerve tissue recognisable. In addition to the gross foamy cell change there is interspersed between the foamy cells a considerable amount of round celled infiltration and I should think a definite increase in plasma cells.
F. F. STAIN: Large numbers of acid-fast bacilli showing some morphological change. In this section an occasional nerve is seen cut longitudinally, in which there is an increase in Schwann cells.
DIAGNOSIS: Apart from the presence of one solitary giant cell I would diagnose this as a moderately advanced and active lepromatous lesion.

4th Biopsy ($201_2 111_2 59$), 578 (Lab. No. 3743)

H. E. SECTION: Most of the corium is occupied by a relatively gross infiltration; this does not extend up to the epidermis and leaves a relatively free sub-epidermal zone. The infiltration in the corium is practically continuous throughout, except towards one end, where the infiltrate thins out. The infiltrating cells consist almost entirely of macrophages which have undergone gross foamy cell change. In fact, the whole infiltrate looks as if a considerable number of plasma cells and some round cells are infiltrating in-between the foamy cells.
F. F. STAIN: Fairly numerous acid-fast bacilli in almost every field. Many of the acid-fast bacilli are short, stumpy rods and some appear to be somewhat granular.
DIAGNOSIS: Active, moderate lepromatous case showing some influence under therapy.

Conclusions

The clinical and bacteriological improvement, we feel, is comparable to that which we might have expected under sulphones, but there is no evidence that there is commensurate histological improvement.

4. SHALAIBU GURGIYA. No. 4631. 30-year-old Hausa male.

This patient was first admitted in January, 1957. At that time he was a very far advanced case of lepromatous leprosy. There were heavy nodules and diffuse infiltrative lesions seen over the entire body, being the heaviest on the face and

ear lobes. The right eye showed a scleral nodule. There were rather advanced mucosal lesions and nasal septal ulceration. There was buccal and laryngeal mucosal infiltration.

Treatment with Streptovaricin was started in January, 1957. He had had no previous treatment. The drug was tolerated and at no time were any toxic manifestations noted. He did, however, show a number of mild ENL reactions. At the 11th and 23rd months brief rest was given. At the 14th 21st and 26th months the dose was reduced but treatment was not interrupted.

He has now completed 35 months of treatment. Total dose: 2104.4 grams.

Histopathological Reports on biopsy material sent for examination:

1st Biopsy (18/1/57), 510 (Lab. No. 2494)

H. E. SECTION: There is a massive and gross infiltration throughout the corium leaving a narrow, free sub-epidermal zone. The infiltrate occupies the whole of the dermis and is very dense. The infiltrating cells are round cells and macrophages. Many of the macrophages have the appearance of epithelioid cells. Here and there, there seems to be some foamy cell degeneration. The nerves are so involved in the granulomatous tissue that only an occasional one is recognised, but in these nerve tissue is recognisable. The infiltrate presses up around the nerve and one would consider that when there is organisation of this infiltrate there will be considerable fibrosis. The skin appendages are also involved in the gross infiltrate and these are reduced in number.

F. F. STAIN: Very large numbers of acid-fast bacilli seen throughout this section with numerous globi. The acid-fast bacilli show little morphological change. Nerves are recognisable, and there appears to be a considerable increase in Schwann cells. Most of the macrophages show large numbers of bacilli within the cells.

DIAGNOSIS: Advanced infiltrated lepromatous leprosy.

2nd Biopsy (26/1/57), 524 (Lab. No. 2565)

H. E. SECTION: A massive infiltration is seen throughout the corium leaving a narrow clear sub-epidermal zone extending deep into the corium. The granulomatous infiltrate shows marked foamy cell change with interspersed round cells, but plasma cells are not conspicuous. Granulomatous infiltrate is so massive that all the skin elements are obliterated and nerves are not recognisable.

F. F. STAIN: Acid-fast bacilli in very large numbers seen throughout the section and in rod forms and clusters. There are no characteristic globi seen.

DIAGNOSIS: Active, advanced lepromatous case, not in reaction. I do not think that the fact that nerves are not seen is necessarily significant, because they are probably unrecognisable among the gross foamy cell change.

3rd Biopsy (19/2/58), 556 (Lab. No. 3015)

H. E. SECTION: Diffuse infiltration underneath the epidermis of moderate intensity, leaving a relatively clear sub-epidermal zone. The infiltrate is scattered diffusely throughout the corium of the skin with some relationship to the skin appendates, but with no evidence of any focalisation. The infiltration consists very largely of histiocytes. On one area there is quite definite foamy cell change, and in another area in the vicinity of a hair follicle and near to the epidermis there is a small collection of round cells. Nevres, when seen, are quite uninvolved.

F. F. STAIN: Very numerous acid-fast bacilli seen throughout the section which are undergoing considerable morphological change.

DIAGNOSIS: Moderate lepromatous leprosy, showing considerable influence of sulphone therapy. It is possibly a lesion which is responding to therapy fairly well.

4th Biopsy (22/1/59), 569 (Lab. No. 3354)

H. E. SECTION: There is a moderate infiltration underneath the epidermis and throughout the corium with a clear sub-epidermal zone. Immediately under the epidermis the infiltrate is seen as a continuous band. In the deeper layers of the corium the infiltrate, generally speaking, is around the appendages of the skin, but there is no evidence of focalisation. The infiltrate consists almost entirely of histiocytes (macrophages) practically all of which have undergone foamy cell change. In addition there is interspersed between the foamy cells considerable round celled infiltration and a definite increase in plasma cells. Nerves are not easily recognised.

F. F. STAIN: Several nerves were seen; they were seen to be uninvaded and

show increase in Schwann cells. Very numerous acid-fast bacilli seen throughout the section showing little or no morphological change.
DIAGNOSIS: A very active, moderately advanced lepromatous case.

5th Biopsy (20/11/59), 579 (Lab. No. 3744)

H. E. SECTION: Practically all the corium is occupied by a mass of infiltration consisting almost entirely of foamy cells. Interspersed between the foamy cells are round cells and an occasional plasma cell. The infiltrate does not go up to the epidermis and leaves a very clear and well defined free sub-epidermal zone. The infiltrate is so gross that nerves are quite unrecognisable among the mass of foamy cells.
F. F. STAIN: Acid-fast bacilli seen in scanty numbers in most microscopic fields. In addition, I think I can make out some nerve tissue and there does not seem to be any evidence of nerves being involved in the infiltrating process.
DIAGNOSIS: This is a moderately early, somewhat active lepromatous case.

Conclusion

We note at this time that there has been very marked clinical improvement as seen in the resolution of the nodules and diffuse infiltrative lesions. There remains, however, widespread moderately heavy nodular and diffuse infiltrative lesions. The feet and hands show brawny oedema.

The nasal septal mucosal ulceration persists. The scleral nodule is resolving. The other mucosal lesions are showing resolution.

The bacteriological index went from a high of 5.2 early in the study to 2.6 at the present.

There would appear to be very significant clinical and bacteriological response to treatment, but we feel that the response is comparable to that which we could have expected on sulphones. The histological reports on this case show quite definite improvement. The last biopsy shows a decrease in the number of bacilli in the section and the 3rd biopsy shows that these bacilli are undergoing gross morphological change, but whether this improvement will be maintained is difficult to say.

Summary and Conclusions

In our experience we have found Streptovaricin to be a well tolerated non-toxic drug. The only complaint we heard from the patients was that 15 capsules at one time was a little difficult to take.

We note that in all cases there were mild Erythema Nodosum Leprosum reactions which we feel is an indication of some effectiveness of the drug in dealing with the *M. leprae*. It should be noted that in all cases there was definite and significant clinical and bacteriological improvement.

One aspect of the study was the discouraging failure of the nasal mucosal lesions to respond to treatment. Similar lesions in patients treated with sulphones and Streptohydrazid would have shown rapid healing.[13]

Results of the biopsy examinations were not commensurate with the clinical improvement, and, on the whole, the biopsy results were disappointing.

Therefore, we have to conclude that there is little evidence that Streptovaricin has any appreciable effect on the *M. leprae* as administered.

This series of cases is, admittedly, small; but in view of the fact that Streptovaricin alone has little or no effect on the *M. leprae* we would be prepared to undertake a trial of Streptovaricin used in connection with one of the sulphones. The expense of its manufacture, the necessity of high daily dosage, the lack of any superiority to existing drugs makes it questionable whether it is worthwhile to continue a further trial of Streptovaricin along with sulphones. These preliminary trials do not fulfill conditions which would justify further expense in experimental usage of these drugs.

Acknowledgments

We wish to express our thanks to the Upjohn Co. for the supply of the Streptovaricin used in this study and for their close cooperation in keeping us abreast with current findings in other fields of research.

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LETTERS TO THE EDITOR

1. From Dr. R. E. PFALTZGRAFF, of Garkida, Yola, Nigeria, on *A Practical Method of Mailing Small Biopsies:* "Dr. Cochrane has suggested I report this new simple economical way of sending small biopsy specimens. *Method:* The biopsy is fixed by placing in a relatively large amount of whatever fixative solution is chosen, e.g. a small specimen less than 1 cm. in size, is placed in 30 ml. of fixative for 24 hours or more. If passed through several solutions the tissue should remain in the ultimate solution for 24 hours. Cut a finger off a discarded rubber glove, and house the piece of tissue in that, and add 2 to 3 ml. of the fixative solution. Squeeze out all air and fix a rubber band round the neck of the glove finger, in order to seal off the package. Round the constricting rubber band wind 2" to 3" (5 to 7.5 cm.) of "Scotch tape" (equivalent to "sticking plaster" in English usage). The little package is then affixed by sticking plaster to a suitable light card, and inserted with the covering letter into a regular air mail envelope. If the card fits the envelope, there will be less chance of destructive movement inside the envelope during its travels. By keeping the weight of biopsy specimens in their envelopes less than ½ oz. (about 15 gm.), the use of air mail becomes a practical method of sending them about the world to desired laboratory destinations".

2. From R. RHODES-JONES, ESQ., F.I.M.L.T., of the East African Leprosy Research Centre, on the *Technique of Staining Leprosy Bacilli in Smears.* He refers to the article by A. R. DAVISON on this subject in LEPROSY REVIEW **31**, 4. He states that Dr. Davison in that article quoted from a letter from him and that Dr. Davison had failed in that article to notice that slides 1–3 had faded, and it was for that reason Mr. Rhodes-Jones had to restain them. Slides 4 to 6 had *not* faded, so were not restained, though it would seem from Dr. Davison's article that they were. In all the slides the bacilli had stained blue, which masked the pale pink diphtheroids. This is the meaning of the term "masked".

[In this question of fading of stained specimens, we think a possible explanation is the effect of excess of light. In East Africa the intensity of natural radiation of ultraviolet light is 12 times that in Switzerland. To put it another way, places in East Africa *in one month* may have the ultraviolet radiation of a whole year in Switzerland. In a laboratory with plenty of windows, specimens placed even for 1 hour or 2 hours not too far away from a window, and perchance not covered, might well get into trouble even before staining? *Editor.*]

Anonymous or Unclassified Mycobacteria

3. From H. C. DE SOUZA-ARAUJO, M.D., DR. P. H., of Instituto Oswaldo Cruz, Laboratory of Leprology, Rio de Janeiro, on the subject of Mycobacteria:

Ten years ago the NEWS LETTER of the Society of American Bacteriologists (Vol. XVI, N.1, Jan. 1950, p. 6) published that Dr. Frederick Eberson, M.D., Chief, Clinical Pathology, Assistant Chief, Laboratory Service, Kennedy Veterans Administration Hospital, Memphis, Tennessee, U.S.A., was "seeking cultures of chromogenic strains of *Mycobacterium tuberculosis* or similar unclassified acid-fast bacteria" for studies.

By letter of 25th February 1950 to Dr. Eberson I offered to furnish him "more than 30 trains of acid-fast bacteria isolated by myself from leprous patients, directly or with the 'help' of various hematophagi; from leprous patients with pulmonary tuberculosis, under Streptomycin treatment; from rats and mice inoculated with Stefansky bacillus (Strain of the Institut Pasteur of Paris); from ticks (*Amblyomma rotundatum*) captured in cold-blooded animals (*Bufo marinus*, *Bufo crucifer* and *Constrictor constrictor*), in various occasions; and from effluent sewage of OMS tank of two leprosaria, one in this city and another in São Paulo. If you want a set of these cultures and promise me to help in their classification, I will be glad to send you a sample of each one, by air-mail, as soon as you answer this letter", etc.

Dr. Eberson answered me by air-mail letter of March 6, 1950, telling: "Dear Dr. Araujo: Your response in reply to my note in the S.A.B. News Letter is most gracious. I appreciate your generous offer and shall be pleased to have a set of the cultures for inclusion in a study of chromogenic 'variants' of *Mycobacterium tuberculosis*. If it is not too much trouble, can you let me have certain data pertaining to the history of these cultures, particularly, the human strains . . . etc". He added: "P.S. It has occurred to me to ask if you have available any serums from patients or animals, snakes, etc. corresponding to the cultures of chromogenic organisms or other T.B. strains. I propose to do serologic studies as an aid in attempting to classify these cultures", etc.

On 31st March 1950 I sent to Dr. Eberson, by air-mail registered, 51 tubes with cultures and 13 tubes with sera of patients, accompanied with a full explanatory list, which will be transcribed in the following page. In the same day I sent him also one confirmatory letter. On 28th April I wrote again to Dr. Eberson confirming the above remittance and sending him, in separate, another sub-strain "Chaves" recovered from experimental lesion produced in rhesus monkey and the serum of patient Emilia, corresponding to strain n.14 of the list.

Only in May 8, 1950 Dr. Frederick Eberson wrote me: "In confirmation of your letter dated April 28th, referring to the shipment of cultures, I received on Saturday May 6th, 51 tubes of cultures and 13 specimens of serum. *The package arrived in excellent condition.* Upon removing the wrappers and sorting the cultures, I

found 13 which have no visible surface growth and 6 which were grossly contaminated with a black or greyish white mold. Transplants are being made on all the strains and I *anticipate very interesting findings*. Thank you again for your very generous contributions and your courtesy", etc. Dr. Eberson says that he had received the culture and the serum sent to him on 28th April.

I do not understand why was spent 38 days to be open my package. The tubes being flat so long time (38 days) explains the wetting of the cotton-cover with condensed water of the medium and germination of the spores of *Aspergillus niger* existing in the same. My cultures of mycobacteria preserved in standing position in general last 2 to 3 years without mold contamination.

In his letter of November 30th, 1950, Dr. Eberson informed me: ". . . It may interest you to know that the culture N.24, *Mycobact. lutzi*, appears to be a Nocardia strain with inhibitory properties for tubercle bacilli", etc.

On 19th December 1950 I sent to Dr. Eberson 17 tubes of cultures, of which nine new strains or sub-strains and the other to replace those arrived contaminated. The new strains or sub-strains were included in the general list below.

List of Cultures of Mycobacteria furnished in 1950 to Dr. Frederick Eberson, Chief Pathologist of the Kennedy Veterans Administration Hospital, Memphis 15, Tennessee, U.S.A.

No. of Tubes; Origin of the Cultures; Other data.

1—Strain "José", 1941. Isolated in October and November from closed skin leprous lesions of a 7-year boy. Case L2, son of leprous parents, from Piauhy.
2—Strain "Alcebiades", 1942. Isolated from *Amblyomma cajennense* experimentally infected in skin lesion of A.P., aet.32, L3–N1 case, Paraná.
3—Strain "Ramtun", 1942. Isolated from *Boophilus microplus* experimentally infected in skin lesion of J.R., aet.45, L3–N1 case, from Paraná.
4—Strain "Rudan", 1942. Isolated from *Boophilus microplus* experimentally infected in skin lesion of P.R., aet.26, L3–N1 leprosy case, from Paraná.
5—Strain "J. Carlos", 1943. Isolated from *Triatoma infestans* experimentally infected in skin lesion of J.C., aet.23, L3 leprosy case, from S. Paulo.
6—Strain "Chaves", 1949. Isolated from skin lesion of right thigh of J.C., aet.30, L2–N1 leprosy case, aviator, 7th biopsy.
7—Sub-strain "Chaves", 1950. Recovered from experimental lesion in mouse.
8—Sub-strain "Chaves", 1950. Recovered experimental lesion in the same part
9—Sub-strain "Chaves", 1950. Recovered from experimental lesion produced in his wife Maria D., aet.18, she being a tuberculoid incipient case.
10—Strain "Hecke", 1949. Isolated from leprous skin lesion of Agronomist Hecke, aet.26. Case L2–N1, biopsy of right buttock. From Paraná State.
11—Sub-strain "Hecke", 1949. 3rd recovery from experimental lesion in mouse.
12—Sub-strain "Hecke", 1949. Recovered from experimental lesion in Chaves.
13—Sub-strain "Hecke", 1949. Recovered from infection of guinea-pig: 6 days.
14—Strain "Emilia", 1950. Isolated from leprous skin lesion of E.P., aet.53.
15—Strain "A. Alho", chromog., 1948. Isolated from sputum of this leper with pulmonary TB, under treatment with Streptomycin. Gave another strain.
16—Strain "JP Souza", chromog., 1948. Isolated from sputum of this leper with pulmonary TB, under treatment with Streptomycin. Gave another "R" strain.
17—Strain "Santos", chromog., 1948. Isolated from sputum of this leper with pulmonary TB, under treatment with Streptomycin. Gave another "R" strain.
18—Strain "Stefansky I", 1948. Isolated from experimental infection of rat.

19—Strain "Stref. II", 1948. Isolated from white rat. Pasteur Inst. strain.
20—Sub-strain "Stef. II", 1949. Recovered from black mouse infected with same.
21—Strain "Stef. III", 1949. Isolated from black mouse infected with leproma.
22—Sub-strain "Stef. III", 1949. Recovered from black mouse infected with same.
23—Strain "Stef. IV", 1949. Isolated from black mouse infected with leproma.
24—Strain *Mycobacterium lutzi*, 1947. Isolated from *Amblyomma rotundatum* parasiting of *Bufo marinus*, from Rio City. New species.
25—Strain *Mycob. sp.* 1949. Isolated from same tick above of same toad.
26—Strain *Mycob. sp.* 1949. Isolated from same tick from same toad. Nat. museum.
27—Strain *Mycob. sp.* 1950. Isolated from same tick from same toad. State Rio.
28—Strain *Mycob. sp.* 1950. Isolated from same tick from same toad. State Rio.
29—Strain *Mycob. sp.* 1949. Isolated from same tick from *Bufo crucifer* of Rio.
30—Strain *Mycob. sp.* 1949. Isolated from same tick captured in *Constrictor constrictor* of the garden of the Nat. Museum, of Rio de Janeiro.
31—Strain "Geraldo V.", 1948. Isolated from pus of cervical lymphnode of this leper with ganglioar TB. Died 2 days later.
32—Strain "A. Alho II", 1948. Isolated from sputum of this leper with pulmonary TB, separated from strain 15, chomogenic.
33—Strain "JP Souaz II", 1948. Isolated from sputum of this leper with pulmonary TB, separated from strain 16, chromogenic.
34—Strain "M. Rodrigues", 1948. Isolated from sputum of this leper with pulmonary TB, like the other, under treatment with Strepromycin.
35—Strain "A. Simoes", 1948. Isolated from sputum of this leper with pulmonary TB, under treatment with Streptomycin.
36—Strain "Raymundo T.", 1948. Isolated from sputum of this leper with pulmonary TB, under treatment with Streptomycin.
37—Strain "Dinorah", 1948. Isolated from sputum of this leper woman suffering with pulmonary TB, under treatment with Streptomycin.
38—Strain "G. Silva", 1948. Isolated from sputum of this leper with pulmonary TB, under treatment with Streptomycin.
39—Strain "A. Lopes", 1948. Isolated from sputum of this leper with pulmonary TB, under treatment with Streptomycin.
40—Strain "Waldivia C.", 1948. Isolated from sputum of this woman leper suffering from pulmonary TB, under treatment with Streptomycin.
41—Strain "Minervina F.", 1948. Isolated from sputum of this woman leper suffering from pulmonary TB, under treatment with Streptomycin.
42—Strain "Geraldo R.", 1948. Isolated from suptum of this leper with pulmonary TB, under treatment with Streptomycin.
43—Strain "Alcides G.", 1948. Isolated from sputum of this leper with pulmonary TB, under treatment with Streptomycin.
44—Strain "Clovis S.", 1948. Isolated from sputum of this leper with pulmonary TB, under treatment with Strepromycin. Gave another chromog. strain.
45—Strain "Adauto P.", 1948. Isolated from sputum of this pulmonary tubercle patient. No leprosy. TB alone.
46—Strain "FF. Goulart", 1948. Isolated from sputum of this leper with pulmonary TB, under treatment with Streptomycin.
47—Strain "C. Amorim", 1948. Isolated from sputum of this leper with ulmonary TB, under treatment with Streptomycin.
48—Strain *Mycob. sp.* 1948. 1948. Isolated from effluent water of sewage biological OMS tank from Leper Hospital Curupaity, Rio de Janeiro.
49—Strain recovered from tuberculosis lesion of guinea-pig infected with the above 48 strain.
50—Strain *Mycob. sp.* 1946. Isolated from effluent water of sewage biological OMS tank of Padre Bento Leper Hospital of Sao Paulo. 1st strain.
51—Strain *Mycob. sp.* 1946. Isolated from the same effluent water above. 2nd strain.

NB. At the occasion the Author obtained 4 other pure strains from sewage water of OMS purifying tank, all with the characteristic of TB bacillus.

Second remittance:

52—Strain *Mycob. sp.* 1950. Isolated from *Amblyomma rotundatum* parasite of snake *Drimachon bifossatus*. No. 1.
53—Strain *Mycob. sp.* 1950. Isolated from same tick above from same snake.
54—Strain *Mycob. sp.* 1950. As above. No. 3.

These three strains are similar to *Mycobaterium lutzi*.

55—Sttain "Chaves II", new strain, 1950. Isolated from residual skin lesion of the left knee of that patient. 14th biopsy. Identical to "Chaves I."
56—Sub-strain "Hecke", 1950. Recovered from experimental lesion produced in the leprous patient Chaves.

57—Sub-strain "Hecke", 1950. Recovered from experimental lesion produced in the leprous patient N.14 of Recife, Pernambuco.
58—Sub-strain "Emilea", 1950. Recovered from white rat experimental lesion.
59—Sub-strain "Emilia", 1950. Recovered from experimental lesion produced in the face of rhesus N.2. (*Maccaca mulatta.*)
60—Sub-strain "Emilia", 1950. Recovered from experimental lesion produced in leprous patient N.21, of Recife, Pernambuco.

1. *Technique of the Cultures.* The above cultures were obtained from skin lesions, subcutaneous lymph, lymphnodes or sputa of leprosy patients, and from triturates of ticks and triatomas, and biopsies of experimental lesions produced in men, murines, and monkeys. After trituration and suspension in saline solution, the materials were treated by 10% solution of NaOH (Petroff method) or 5% solution of H2SO4 (Loewenstein Method), kept in the incubator at 37·C during 30 minutes, then washed by 2 or 3 centrifugations and the sediments sown in series of 9 tubes of Loewenstein medium and 1 tube of 5% glycerin broth as control. Incubation at 37C° for 30 days, because we know that pathogenic mycobacteria germinate from 14 to 29 days. Those growing in a few days are, in general, symbiotic bacteria. All 15 advanced leprous cases, suffering from pulmonary tuberculosis, confirmed by X-ray, No. 32 to 47 (excepted No. 45 who had no leprosy), after having taken the maximum dosage of Streptomycin then used gave, from their sputa, pure cultures of *Mycobacterium tuberculosis*, and died within a few days or months later.

2. *Staining Properties.* All the above 60 cultures were permanently acid-alcohol fast, staining by classic Ziehl-Neelson method, and granulated, coccothrix form stained by Fontes method. Dr. L. M. de Andrade, using auramine, proved that 49 out of the first 51 samples sent to Dr. Eberson, were fluoroscent, being 2–plus 34, 1–plus 15 and 2 negative (Technic of Emil Bogen: American Rev. of Tuberculosis, 44 (3), Sept. 1941, p. 367). Such results were confirmed, in other transplants of the same cultures, by Prof. Joao Christovao Cardoso, now President, Conselho Nacional de Pesquisas.

3. *Dubos Test for Virulence.* Testing the 51 cultures first sent to Dr. Eberson, Dr. L. M. de Andrade, then chief of the Laboratory of Mycobacteria of the Instituto Oswaldo Cruz, proved that 25 gave 2–plus, 7 1–plus, 18 negative and 1 unsufficient material. (Technic of Dubos and Middlebrook: Amer. Rev. of Tuberculosis, 58, Dec. 1948, p. 698). Professor Pierre Hauduroy, Director, International Centre of Cultures, Lausanne, Suisse, confirmed such results in a few strains sent to him. Some leprosy-strains being too pigmented, gave doubtful results (Dr. Andrade). All the 15 strains, from sputa of leprosy patients with TB gave 2–plus fluoroscence and 2–plus Dubos test.

4. *Phage Typing.* From the above list I selected 20 strains and sub-strains and sent on 20th December, 1950, to Professor Giuseppe

Penso, Director, Istituto Superiore di Sanitã, of Rome for study, as he asked for when he was in Rio in August 1950. Such cultures were passed to the hands of Dr. Vittorio Ortali, who, on 26th December 1950 wrote to me: "The 20 strains of Mycobacteria to be typed with the available phages were received". By letter of May 29, 1951 said Dr. Ortali: "Now we are working with strains of Mycobacteria isolated from leprosy. I have received some new phages from Canada, and I hope to find some one active". Later on (Sept. 24, 1951) Dr. Ortali informed me: "I tried yours strains with all my phages, and I did not get any reaction. A technician who works with me now tries to find new phages active on some strains of Mycobacteria, among which there are also your strains. If you can send me other strains I will be very grateful. If some phage exist, it would be easier to find in leprosy material . . . ."

As it is very, very difficult to get an acid-fast culture from leprotic skin, and I got twice identical and pathogenic cultures from patients "Chaves" and "Emilia", then I consulted to Dr. Eberson if I could classify the same as *Mycobacterium leprae hominis*. Dr. Eberson answered me by letter of January 23, 1951, as follows: ". . . In regard to your 'Chaves' and 'Emilia' strains, do you not agree that identity of these warrants the name of *Mycobacterium leprae hominis* similar to others belonging to the International Collection? However, the naming of such cultures need not carry the implication that they are in fact etiologic agents in the disease mentioned. I have not had the opportunity to work with the new cultures 52, 53, 54, aside from making necessary transplants. Presumably these strains will conform to varieties known to exist in cold-blooded species of animals. The research problem is, as you see, one of such magnitude that I wish it were possible to devote more attention to the study. . . . In connection with the study of certain chromogens, another important phase of biological interest has been occupying my attention, that of the antibiotic properties. I hope to have some of this ready for publication in the near future", etc.

In answer to my letter of February 28, 1952, Dr. Eberson wrote to me on 6th of March 1952: ". . . Unfortunately my studies with all our acid-fast chromogenic Mycobacteria, including your strains from leprous lesions, have been interrupted during the past few months. In the near future our bacteriological research laboratories will be fully staffed and I hope to continue the studies on an intensive sacle. As I wrote you some time ago, perhaps, it has seemed to me important to classify the entire group of chomogenic acid-fast mycobacteria. This is a gigantic undertaking, aside the many problems introduced by antibiotic therapy, variation and mutation of strains, and so on", etc. This was the last letter I received from Dr. Frederick Eberson.

In 1959 the Veterans Administration and the National Tubercu-

losis Association sent out a questionnaire and requested co-operation of the specialists to resume and intensify the research upon which is now called "unclassified" mycobacteria. I offered immediately to collaborate with both institutions, informing them about my previous co-operation with VA. By letter of March 29, 1960 Dr. Ernest H. Runyon, Ph.D., Microbiology Research Chief, Veterans Administration Hospital, Salt Lake City, Utah, U.S.A., informed me: "About 10 years ago I received from Dr. Eberson transfers of some cultures which were from South America—presumably the ones you sent to him. We have been concerned with strains of mycobacteria which are known to be closely associated with human diseases. Since information concerning the relationship of the South American strains to disease was lacking we did not retain these cultures. . . ." By letter of June 23, 1960 informes Dr. Runyon: "Dr. Floyd Feldmann has kindly sent me the transcription of your correspondence with Dr. Eberson concerning mycobacterial cultures. You are to be congratulated on having isolated so many interesting organisms", etc. In this letter he asked me for transplants of five of my mycobacteria cultures. I sent him ten, to start new co-operation and promised him, for September, new strains from cold-blooded animals.

The anonymous mycobacteria were the theme of the XVth Conference of the International Union against Tuberculosis, held in Istanbul, September, 1959, and will be also of the XVIth Conference to be held in Toronto, in 1961.

The subject is of great importance and merits international co-operation for its study.

Instituto Oswaldo Cruz, Rio de Janeiro,
September 8, 1960 H. C. DE SOUZA-ARAUJO

ABSTRACTS

Phenylbutazone in the Treatment of Some Reactive and Painful Complications of Leprosy. R. H. THANGARAJ and S. THANGARAJ. J. of the Indian Med. Assoc., **35**, 9; Nov. 1, 1960, pp. 395–397.

The authors, working at Purulia, tried in 52 patients of whom 46 were lepromatous, the drug Butazolidin (phenylbutazone GEIGY) for the following occurring in leprosy patients: acute and chronic arthritis, erythema nodosum leprosum, neuritis, thrombophlebitis, and burning sensation. The dosage was 800 mgm. by mouth daily for 3 days in 4 divided doses, then 400 mgm. per day for a further 1 or 2 days, with as alternative method 600 mgm. per day by injection for 3 days and then 300 mgm. per day for another 1 or 2 days. In chronic cases a maintenance dose of 200 mgm. per day by mouth can be given. Only 7 cases failed to show improvement, and 31 cases had "excellent" improvement, 9 "good". and 5 "fair". In erythema nodosum 1 case had a "fair" result and 3 "poor". Mild side reactions were seen in 4 cases, which disappeared when the drug was stopped. The side reactions were salt retention oedema (2 cases), mild jaundice (1 case), and giddiness (1 case).

Action of Two Ethyl Thiol Esters Against Experimental Tuberculosis in the Guinea Pig. G. E. DAVIES and G. W. DRIVER. Brit. J. of Pharmacology and Chemotherapy, Mar. 1960, **15**, 1: p. 122.

The compounds tested were ethyl dithiolterephthalate and ethyl dithiolisophthalate (Etisul, or ditophal). Both showed a therapeutic effect against a subcutaneous infection even when that was well established as an infection, but both were less effective than streptomycin. The two thiol esters and streptomycin had no effect on the development of the tuberculin reaction, or on the time of appearance and subsequent course of inoculation abscesses, or on enlargement of axillary lymph glands. The results from INH contrast with this, as with INH a small abscess appeared in only 1 guinea pig and axillary lymph nodes did not enlarge. Ditophal had a definite effect against an intracerebral infection of *M. tuberculosis* in guinea pigs, when given twice daily orally at 100 mg/kg. and 200 mg/kg., the effect being comparable with that of streptomycin subcutaneously at 40 mg/kg. In contrast, ethyl dithiolterephalate had no effect against the intracerebral infection. The positive Ditophal effect was, however, inferior to that from INH given twice daily at 5 mg/kg., and Ditophal was without therapeutic effect with intracerebral twice weekly doses at 100 mg/kg., or when given once daily subcutaneously at 100 and 200 mg/kg. The striking anti-tuberculosis effect obtained

with ditophal in mice was not achieved in guinea pigs, probably because the maximum dose tolerated in the latter was limited by the ulceration which occurred at the site of injection with doses greater than 50 mg/kg. The results however do indicate that the two thiol esters possess definite activity against tuberculosis in the guinea pig.

BOOK REVIEW

Notes on Leprosy, by DHARMENDRA. Dr. Dharmendra of the Central Leprosy Research Institute, Chingleput, South India, will inform us later from whom it can be obtained at Rs. 8/– per copy (sh. 12/– stg.). Those who wish to reserve copies might write to Dr. Dharmendra direct. Pages 200, figures and plates 283, many in colour.

Dr. Dharmendra explains that these Notes on Leprosy are based on lecture material used for the classes at the Calcutta School of Tropical Medicine, and that a book on leprosy was also contemplated, but because of delays he decided to issue the Notes instead.

The *Notes* are written in English and are intensely practical and will be of great value to all those who wish to learn about leprosy without becoming confused by discussions and controversies on the intermediary types of leprosy (e.g. borderline) and on the classification of the clinical types of leprosy. The description given by Dharmendra will readily be understood. Lepromatous, Tuberculoid, and Maculoanaesthetic are thought to include the vast majority of cases met with in India, with 3 other secondary forms, Borderline, Indeterminate, and Polyneuritic. There is a very helpful chapter (p. 57) on Differential Diagnosis. Treatment of leprosy is dealt with perhaps too much bias to the past. Treatment with Hydnocarpus Oil is fully described, in which the description of intradermal injections still has practical value, the rest being of academic value. The sulphones are dealt with fully. For the rest, one gets the impression that leprosy treatment in India stops with the sulphones: there is small mention of the many exciting drugs which have been tried out in the rest of the world, e.g. the thioureas and thiol compounds.

Physiotherapy and reconstructive and plastic surgery are described (p. 126) and there is a useful discussion of prevention of leprosy (p. 130) and of leprosy surveys (p. 134) and of the mass campaign (p. 144). We owe a great debt to India for the demonstration of what preventive and curative physiotherapy and reconstructive surgery can do for leprosy patients. It remains true that anyone wishing to learn these valuable techniques should go to India in person and study them.

Dr. Dharmendra's *Notes on Leprosy* will be welcomed everywhere and be of greatest value to anyone who makes careful study of them. They will be a great help in teaching in those countries which are hoping to build their own indigenous leprosy services.

REVIEWS

Uchyeniye Zapiski; Instituta po Izuchyeniyu Lepri (*Study Reports: Institute for Study of Leprosy*), Astrakhan, 1959, No. 1.

These study notes of 47 pages in the first issue are of great interest as will appear from the following list of subjects and of the authors:

Leprosy and Children, pp. 3–9, E. I. CHEKALINA.

Clinical Changes in the Eyes in Leprosy, pp. 10–14, K. I. NAZAROV.

Humidity of the Skin in Leprosy, pp. 15–17, A. M. LETICHEVSKAYA.

Data on Histopathological Investigations in the Early Diagnosis of Leprosy, pp. 18–20, N. A. IVANOVA.

Methods of Experimental Therapy in Model Rat Leprosy, pp. 21–24, N. M. BALUYEV and E. A. MAGIDSON.

Treatment of Exacerbation of Lepromatous Leprosy by Blood Transfusion, pp. 25–27, V. N. STRUCHKOVA and V. A. MLASHYENKOVA.

The Application of Novocain Ionophoresis in Leprotic Neuritis, pp. 28–29, A. D. TIMOFEEVA and V. M. KOZELSKII.

Wassermann Reaction and Precipitation Reactions in Leprosy Patients, pp. 30–34, K. A. KOLESON and L. S. REZNIKOVA.

The History of Leprosy in Latvia, pp. 35–39, I. D. SISOEV.

Leprosy in Kamchatka, pp. 40–44, V. M. KOZELISKII.

Researches in Leprosy of V. K. Stefanskii, pp. 45–47, V. N. POGORELOV.