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CONTENTS

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

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EDITORIALS

Corticosteroids in Leprosy

Cortisone and corticotrophin have a place in the treatment of the acute phases of leprosy, as recently studied by Shuttleworth,[1] and Jopling and Cochrane,[2] and earlier reported by Dharmendra[3] and others. The great benefit of these compounds in the distressing and therapy-obstructing complications of leprosy is becoming clear, as well as in toxic drug dermatitis arising occasionally in the course of sulphone treatment. There seems no question that the use of a corticosteroid can quite transform the picture, as for example in a persistently reactive lepromatous case, or a very painful main nerve reaction, and the specific therapy can be continued throughout. All authors agree that the corticosteroids must be used with care and understanding, seeing that there are certain dangers inherent in their use, but they are being used with more and more confidence and with good results. In addition to short-term use of corticosteroids, there are some cases where they have been given for periods as long as two years.

More recently the literature contains several reports which serve to emphasize the care needed in the use of these products. Kellock and Sclare[4] report how prednisone had been given for 2 months for a case of multiple myeloma, and a virtually symptomless acute duodenal ulcer developed, with fatal perforation. Baar and Wolff[5] describe how pancreatic necrosis followed corticoid therapy in two children and they think it was probably due to this therapy. They believe that cortisone has an effect on pancreatic secretion and that in the presence of an unknown constitutional factor, there is stagnation of the secretion and pancreatic necrosis by a "reflux" mechanism. Allanby[6] reports on 18 deaths associated with corticosteroid therapy in the experience of Guy's Hospital. Infection was the cause of death in 7 cases, gastro-intestinal haemorrhage and perforation of 3 each. The cortisone, corticotrophin, or prednisolone therapy was given for periods varying from 5 days to 18 months, and was considered directly responsible for 11 of the deaths, and probably to have hastened the death in 3 more. Those patients who encounter added stress during steroid therapy seem to run a serious risk of adrenal failure, and at such times doses should be increased and antibiotics given in large amounts. Regular and careful observation is essential for all patients under steroid therapy.

Slaney and Brooke[7] report that the stress of surgical operation can lead to collapse in those who have previously received cortisone

therapy, and say that there is evidence that the cortisone causes atrophic changes in the adrenal cortex which lead to adrenal insufficiency, from whence comes the state of shock after operation. In three of the authors' cases death occurred, and could only be explained on these grounds. In four other patients the state of shock was treated successfully by the further administration of cortisone, though one died later. The authors think that cortisone should be given as preventive cover to any patient who is to undergo operation and who has had corticosteroid therapy within the year, and possibly the two years preceding operation. This cortisone cover should include the operation period and be withdrawn gradually during convalescence, and they give a practical scheme of dosage using corticotrophin, cortisone, and hydrocortisone. Since this scheme of dosage was followed, 8 patients have been treated without collapse in any. They think that there is no question that operative risks are increased by antecedent administration of cortisone, and the chance of an operation being needed should be considered carefully for any patient to whom corticosteroid therapy is about to be applied.

* * * *

Is there a place for Hypnotherapy in Leprosy?

Professor Kennedy[1] recounts his experience in conditions not including leprosy, with this mode of therapy over more than 20 years. Conditions in which hypnosis is often the treatment of choice are states of recent onset in which there is an alteration or dissociation of consciousness which has something in common with hypnosis itself, such as hysterical amnesia and fugue and hysterical stupor, and similar psychiatric conditions. There are also conditions in which hypnosis is one of the methods which can be used, such as for the replacement of drugs by hypnosis in abreaction techniques applied to anxiety states, hypertension and peptic ulcer, and nocturnal enuresis. Then there are conditions in which hypnosis is occasionally strikingly successful and its use is worthy of further investigation. Such are the smoking habit, obesity, psychomatic disorders, and intractable pain, and in normal subjects, in childbirth, anaesthesia for surgical operations, stammering, and as an aid to recall of memory. Kennedy thinks that " there seems to be a case for a treatment that can remove the symptoms of which the patient complains, even if it is unsatisfactory to the therapist in terms of insight and psychopathology ".

Stewart[2] presents the matter from the general practitioner's point of view, as also Fry,[3] the first reporting on 41 and the second

on 120 cases. The method used was of fixed gazing and verbal suggestion. Leaving aside the psychoneurotic and psychosomatic cases, it is of interest to leprosy workers that they treated dermatological cases, given as eczema, psoriasis, rosacea, warts, pruritus. Most of these were associated with underlying emotional states, but not all cases. Hypnosis seemed very useful in the relief of anxiety-tension complicating an organic disease, and to replace hypnotic, analgesic, and anticholinergic drugs.

An annotation in the British Medical Journal which contained the above papers reminds us that most patients are fairly good subjects for hypnotism and most doctors could probably acquire a competent facility. Hypnotism apparently produces its results mainly by suggestion, yet the results of it are apt to be much better than those obtained by ordinary suggestion.

Many of us who are in clinical charge of leprosy patients might care to reflect on the applicability of hypnosis to the neuro-dermatosis that is leprosy. No only are there emotional states to be dealt with but there are the states of severe pain and paraesthesiae, and perhaps even the dermatosis itself might be amenable. Certainly the use of hypnosis would impel us to a closer understanding of our patients, and the surmounting of any barriers of race and language.

There is a Russian report of the actual use of hypnotherapy in leprosy patients, by Ilarshe.[4] From 5 to 12 sessions of hypnotherapy were given to 15 patients, using the method of fixed gazing and a monotonous stream of verbal suggestion, and a session lasted 40 to 50 minutes. The therapeutic suggestions were of the cessation of pain, of better sleep, and of a cheerful state of mind. Of these patients 6 suffered from severe ulnar neuritis with pain in the course of the nerve. Of these, 3 lost their pain entirely and recovered the ability to sleep. There were 6 other patients who complained of distal lower limb paraesthesiae, and after hypnotherapy were relieved, but 2 patients had recurrences after 14-17 days though to a weaker degree. In them it was considered that the number of hypnotic sessions had been too few. Finally there were 3 other patients who had diverse subjective sensations of indefinite type, such as oppression over the praecordium, feelings of suffocation, and unpleasant sensations in the bladder region. Of these patients, 2 had a good result which was maintained over a period of observation of one month, and the remaining patient had subjective improvement for only a few days, after which came relapse.

The author concludes, " Hypnotherapy may be used with success in leprosaria as a useful auxiliary method of treatment.

This is shown not only in cases of neuritic pains and paraesthesiae, but to an even greater degree when the psychic state of the patient is more or less strongly depressed in connection with the existence of the leprosy. In such patients suggestions of cheerfulness certainly have a favourable effect on the general background for the specific treatment, and bring best results."

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SECONDARY INFECTIONS AND NEOPLASMS IN LEPROSY PATIENTS

DR. FELIX CONTRERAS

Medical Director, Colony-Sanatorium of San Francisco de Borja, Fontilles, Alicante, Spain.

It is not often that the same patient suffers different diseases at the same time, and even less often does the same organ or tissue show coexisting pathological processes. It can happen more easily in the skin than in other organs because the skin is the chief defensive barrier against most pathogenic agents. Many skin diseases turn up in leprosy patients, much in the same proportion as non-leprosy patients, and they should be diagnosed early, in order to avoid the spread of infections and parasitic conditions to the other patients, to cure those which are amenable to cure, and more easily to achieve our basic aim of curing the leprosy infection. The treatment of leprosy is always more difficult when the body has to defend itself against the attack of different simultaneous pathogenic processes.

Even when the patients come already diagnosed to the dispensaries and sanatoria, one must think always of the following possibilities: (a) leprophilia, when individuals who do not suffer from leprosy try to simulate it; (b) errors of diagnosis, due to dermatoses similar to leprosy; and (c) leprosy patients having another disease at the same time, which easily can pass unnoticed.

It seems to us of interest to compile a list of such problems, though not a complete one, confining ourselves to those connected with dermatology and which we think are the most frequent.

When 15 years ago we took charge of the medical work at Fontilles, among 258 patients there were 4 who did not suffer from leprosy. In the course of the 15 years, 645 patients were admitted, and of these 11 did not suffer from leprosy. We may classify 4 of these 15 individuals in the leprophilic group and 11 as errors in diagnosis.

Leprophilia

Miranda used this designation of leprophilia ("friend of leprosy") for those cases who for different reasons tried to have themselves taken for leprosy patients and be admitted to the sanatoria. These cases are exceptional, but not so much that some cannot be seen in well-established sanatoria where every care is given to the patients. We can add 5 more cases to the case published by Miranda, and our 5 were seen over 15 years in our

sanatorium of about 300 patients. Of these cases, 4 were admitted while simulating leprosy under family circumstances of some justification, such as a mother with two children and her husband having leprosy; she had no signs of the disease but feigned to have areas of anaesthesia, in order to avoid separation from her family. We think that in such cases we ought to fall in with her wishes without forcing them to have recourse to the simulation of the disease. Besides the four cases who came into the sanatorium in these conditions, in conjunction with Gay Prieto we published the case of a patient who with great tenacity tried to inoculate himself with leprosy, but without success.

Diagnostic Errors

In 15 years we have seen 11 cases of mistaken diagnosis in 803 patients. Six of these had different diseases accompanied by pigmentary dermatoses; one was a female patient with glandular and genital tuberculosis, and marked chloasma; two had vitiligo, two poikilodermia and one scleroderma. The most frequent cause of confusion has been cancer of the face, with extensive and repulsive ulcerations, and we have seen four such cases. Photograph No. 1 is of a patient with the most unpleasant appearance that we have seen in our sanatorium; the nose was completely gone, destroyed by wide ulceration in the form of a triangle, with red, ragged, undermined margins, and a dirty purulent base. On cleaning this base of the mixture of mucus and pus which covered it the remnant of the nasal septum could be seen in the middle line, and the entrances to the nasal fossae, all covered with tortuous swellings which entirely changed the local anatomy. On the forehead and in the vicinity of the ulcer small semi-soft swellings stood out, discharging a yellow pus. Scattered over almost the whole skin were numerous rose-coloured papular lesions of the size of a lentil and some of them hyperkeratotic, and some becoming confluent, more especially in the lower parts of the limbs. The skin surrounding the tumours and papules was completely normal, and repeated clinical and laboratory investigations for leprosy were entirely negative. Histological study showed that the destructive process in the nose was due to an epithelioma which was based on a precancerous dermatosis, the epidermodysplasia verruciforme of Lewandowsky and Lutz. Photographs Nos. 2 and 3 are of two other cases of skin cancer who came in under the diagnosis of leprosy, and like the earlier case looked worse than the rest of the patients at Fontilles. Besides these three cases there was one of the same sort of whom we did not keep photographs. Finally, another

diagnositic mistake was due to another wide ulceration caused by tuberculous lupus.

We think these cases are not exceptional; in other Spanish and foreign leprosaria we have seen cases of epithelioma, tuberculous lupus, and tinea which have been confused with leprosy. About 10 years ago in one Central African leprosarium it was found that 20 per cent of the patients were suffering from other skin diseases. Recently, in December, 1956, Prof. Gay Prieto, when studying the present state of the leprosy problem in Turkey, was able to show that in the Elazig leprosarium, in which there still survives an examination room in which the doctors see their patients through a window glass, and there is a small opening to allow of the passage of the hand to distribute the medication, among the 173 patients submitted to such rigorous isolation there were some completely free of leprosy. Two of these had very advanced cancer of the skin. In the Bakirkoy leprosarium which is joined to a mental asylum containing 4,000 patients, he showed the presence of one case of ulcerating tuberculosis of the face.

These fundamental diagnostic errors occur less and less often, and we think they are a natural consequence of those times when many other diseases were massed together under the name of leprosy.

Another condition which can cause error in diagnosis, but of which we have no experience, is that called the disease of Bairnsdale, caused by an acid-alcohol-resistant organism, *Mycobacterium ulcerans*, discovered in Austria in 1948 by MacCallum and colleagues, and which Levaditi, Vaisman and Levy considered a *Para-mycobacterium tuberculosis*. This condition is characterized by indolent ulcers which respond badly to the usual treatments. MacCallum, Oye and Ballion, Pardo Castello and co-workers, Meleney and Johnson, Middlebrook and Gardner and Lavalle and co-workers, have all published cases of it.

Dermatoses coexisting with Leprosy

At the present time, when leprosy is better understood, these diagnostic errors are not justifiable, but we think more excusable are the mistakes in those cases, where besides the skin manifestations of leprosy there are lesions of other concomitant conditions which pass unnoticed, due to superadded infections of malignant neoplasms; such can occur in leprosy, as in tuberculosis, lupus, etc. The well-known pleomorphism of leprosy manifestations justifies the attributing of some skin symptoms to it; but because they are not characteristic of leprosy they should be analysed with great care.

Parasitic dermatoses. Taking into account the low social level of a great number of leprosy patients, it is to be expected that they will suffer from all varieties of these parasitic conditions. Carruccio, Ramsay, Brug, Haga, Joost, Vergunt, Moriya, and Neves published papers on scabies and Norwegian scabies in relation to leprosy, and we think it will be rare for a leprologist not to have confirmed this association more or less frequently. We could say the same about pediculi and other blood-sucking insects. Ehlers, Leboeuf, Marchoux, Leger, Asami, Markianos, and others have reported this association and discussed the part these insects could play as propagators of the infection. We should bear all these parasitic infections in mind, especially at the time of admission of patients, so as to avoid regrettable spread of them.

The other parasitic skin conditions can occur occasionally. Cases of filariasis along with leprosy have been reported by Jeanselme and Horowitz, Chatterji, Muir, Floch and others: in our climate far from the tropics we consider them rare. Infestation with threadworms and round worms is more common, as mentioned by many authors. Sant Anna suggested that these parasites also could transmit leprosy.

The fungoid infections are more common still than those caused by animal parasites, and the lesions resulting by their appearance and outline, can easily be confused with tuberculoid and indeterminate macules. It is just this type of skin condition which predominated in some regions of Central Africa and caused mistakes in diagnosis when occurring in relations of leprosy patients. Weidman found filaments and mycelia in giant cells in leprosy, Muir described fungus infections in leprosy patients. We have seen some of our patients with mycosis and epidermomycosis. Ringworm is apt to turn up more among the children. Some years ago, in San Lazaro Sanatorium of Santiago de Compostela, children suffering from different kinds of ringworm lived in the same building as leprosy patients, but without any known case of cross-infection in either direction. Ferreira described 4 cases of tinea tonsurans in the San Tarcisio preventorium, and Dauden one in Chapineria preventorium. Muir thinks that the different kinds of tinea form the most troublesome complications of leprosy.

Sporotrichosis and mycetoma and actinomycosis can occur, though we have not seen a case and only know of the case of sporotrichosis published by Caballero.

Pyogenic dermatoses. Skin infections with staphylococci and streptocci are common in leprosy, and occur about as often as in

the general population, but we are dealing with easily identifiable lesions which do not change the identity of the specific leprosy lesions, and do not constitute any problem.

Skin tuberculosis. Leaving aside the connections and coincidences of leprosy with pulmonary and generalized tuberculosis, I confine myself to those skin manifestations of tuberculous nature which can be similar to leprosy and sometimes occur at the same time, as Petrone, Babes, Strempel, Silva, etc., have shown in their papers which try to clarify the diagnostic points. Lie, Pavlov, Oberdorffer and Collier and Cornbleet have reported cases of common or tuberculous lupus occurring with leprosy. We have not seen any case of the same. We recall 2 cases, a male and a female, who were clearly cases of leprosy, but both had facial lesions which were exactly like those of lupus, and even the vitropressure test was positive; but both cases responded to the sulphone treatment, parallel with the other typical leprosy lesions. Photograph No. 4 belongs to one of these cases, which we think are only lupomas by analogy, as Ramos y Silva pointed out some time ago. The patient seen by Gay Prieto in the Bakirkoy leprosarium, of ulcerating facial tuberculosis and enlarged cervical glands, cannot be included in this group because he was not suffering from leprosy. Bechelli and Godoy de Araujo published a case of concomitant leprosy and tuberculosis in a huge glandular tumour of the crural region.

Often some skin lesions of leprosy also resemble atypical skin tuberculosis. Not to take this matter too far, we confine ourselves to recalling the papers of Rabello, Jaque and Fisher, dealing with the relation of sarcoidosis to leprosy.

Syphilis. The frequency of the coincidence of syphilis and leprosy is well known, but it is not often that skin lesions of both appear at the same time, such as in the published observations of Krishewitsch on simultaneous lepromatous leprosy and gummatous syphilis; also of Gaujoux and Bourret on two cases of leprosy in congenital syphilitics, with lesions of both diseases; of Balina and Basombrio, on a recent cutaneous leprosy with muco-cutaneous secondary syphilides; of Muir and Chatterji, on the co-existence of syphilitic and leprotic lesions; of Greco, on a syphilitic gumma in a leprosy patient; of Mariano, on a florid secondary syphilis in a leprosy patient. Galvao Peixoto published a case of a negress with tuberculoid leprosy and active syphilis, in which the symptomatology of leprosy predominated and the histology showed a sarcoid structure but with some modifications attributed to the syphilitic infection. Souza Campos and Alayon describe lesions which they

call "syphiloid leprides", and 'leproid syphilides", and analyse all these questions.

In Fontilles we have always studied all the patients serologically, with a view to the possible association of syphilis and leprosy, but in fact up to a short time ago it was very difficult to be definite, because the serum of the leprosy patients is polyvalent and none of the reactions helped in clearing up diagnostic difficulties between syphilis and leprosy, not even after the introduction of more modern antigens, such as cardiolipin.

The Treponema Immobilization Test has been tried in leprosy, with similar results, but better than before, though different according to different workers, and false positives continue to appear in the results. We tried this test in 300 patients, sending the sera to the University Clinic of Prof. Flarer (Padua) and to the Laboratory of the Chair of Dermatology of Prof. Gay Prieto (Madrid). Of these 300, 61 had some previous syphilis. The results of the two laboratories agreed exactly. There were only 4 positives and 1 doubtful, in one of the laboratories. One of the 4 positive cases had no history of syphilis when questioned, but showed elephantiasis of both legs, with numerous nodular lesions which looked gummatous, and some ulcers. All investigations of his bacteriology gave negative results, and histology carried out by Prof. Llombart showed a granuloma, probably syphilitic. Another of the positives is probably a congenital syphilis, which had not been treated. The other two had begun treatment for syphilis which had been early interrupted. We shall continue these studies hopefully, relying on the Nelson test as the test of greatest value in this matter.

We have not had experience of any case of simultaneous lesions of leprosy and syphilis, and we think that the first case mentioned is one of gummatous syphilides in both legs coinciding with active lepromatous leprosy, a case very difficult in its differential diagnosis.

Lupus erythematosus. We have not seen any typical case of this syndrome along with leprosy. The first report was due to Kerl, Director of the leprosarium at Surinam (Dutch Guiana), and concerned a fixed lupus, with nasal and preauricular plaques. A similar case, also fixed and with several plaques on the face, is reported by Rodriguez Sousa. A case of subacute lupus erythematosus was published by Nudemberg, Rechter and Bizzi. Fiol and Blanco in the Sanatorium General Rodriguez saw a generalized atypical case along with lepromatous leprosy, with pharyngeal

lesions and the peculiarity of presenting lupus in the scars of biopsies and in some burn scars. Geny published another case, but later showed that it was tuberculoid leprosy. This confusion is really easy, especially in the fixed lupus erythematosus, for we have seen several very similar cases, but in the hyperkeratotic lesions of the leprosy the horny spicules typical of lupus erythematosus are not produced, at least in the patients whom we have observed.

Erysipelas. We often see reactions similar to erysipelas in leprosy patients, especially in the lepromatous. Sometimes accompanying the most genuine leprosy reactions, besides the appearance of new lesions typical of leprosy, in some areas we see true erysipeloid plaques which recede at the proper time with the lepra reaction, but leave us in doubt about their cause. At other times we see true erysipelas or erysipeloid reactions, but now it should be possible to distinguish them as treatment progresses, as we can see them yield to the action of some sulphonamides and antibiotics which have no effect on the lepra reactions proper. The similarity of the two conditions justifies the numerous publications on the question, such as those of Campana, Leonardi, Milache, Abe, Namba, Patron, Miranda, Cassiano, Contreras, and others.

Leishmaniasis. Different kinds of leishmania infections occur in leprosy patients. Muir, Klingmuller, Miranda and others have described kala azar in leprosy patients. Probably sometimes both infections will coincide in tropical countries where leishmaniasis americana exists. From our own experience we refer particularly to the coexistence of leprosy and oriental sore, which has also been described by Napier, Henderson, Muir, Zetina, Lowe, Dharmendra, and others.

Fontilles is sited in an endemic area of oriental sore and has helped materially in the diagnosis and treatment of the cases which occurred in the sanatorium and surrounding towns. We found 33 cases of oriental sore from 1946 to 1956, and we have data on 22 other antecedent cases. Of these 55 cases diagnosed in the Fontilles laboratory, none occurred in leprosy patients, but in recent years we have found two such. The first was in a nun (Photograph No. 5) of 58 years of age, who had entered the sanatorium in March, 1948, with abundant lepromas, which regressed under sulphone treatment, so that she reached clinical and bacteriological arrest of the disease from December, 1952. The scars of the face had not resolved completely when a small red nodule appeared on the right cheek in 1953. In a few months the erythematous infiltration extended over the whole cheek, and besides the chief

nodule other smaller sized tiny nodules appeared on the cheek, giving rise to the fear of a reactivation of the leprosy. These lesions were not typical of leprosy, and were bacteriologically negative; on the other hand a due parasitological examination detected the existence of *Leishmania tropica*, with a great number of intracellular and extracellular protozoa in the chief nodule and scanty extracellular ones in the tiny nodules. Suitable treatment cured all the lesions and the patient continued as an arrested leprosy.

In October, 1951, a mentally retarded female patient entered the sanatorium with indeterminate leprosy, and positive bacteriologically. Although her treatment was irregular and insufficient on account of her refusal of the prescribed medication, she improved rapidly and the bacteriology was negative at the end of 1952. She was still negative in August, 1953, when she was seen to have on the right superciliary arch a small infiltrated papule covered with a scab, surrounded by a zone of erythema of some 3 cm. in size, which also was lightly infiltrated. We thought that it might be an oriental sore, and on raising the scab saw the horny spicule (the rake sign or Montpellier sign), and in the base of the lesion we also found the pearl sign (Rodriguez Puchol) and the presence of some leishmania, histiocytic cells, lymphocytes, and a few plasma cells. Thus was proved the second case of coexistence of leprosy with oriental sore in our sanatorium.

Other Infections. All the dermatoses due to pathogenic agents can coincide with leprosy, and in addition to the more frequent ones which we have mentioned we cite as curiosities; an epidemic of measles in a leprosarium described by Noronha Miranda; some cases of Chagas disease published by Diniz, Porto, and others; and, finally, an interesting case of tetanus discovered by our ear, nose and throat specialist, Chover, in his private clinic. A male patient attended with intense and progressive dysphagia, which was difficult to explain, and by exclusion tetanus was thought of. He had no history of wound or trauma, but had a trophic ulcer as part of indeterminate leprosy. After the tetanus infection was confirmed it was thought that the portal of entry could have been the ulcer. Response to specific treatment was more rapid than usual. The course was extraordinarily favourable and Chover thinks that possibly the leprotic neuritis influenced it, by obstructing the conduction paths for the toxin.

Cancer. Different opinions have been expressed on the possible relation between cancer and leprosy. The leading idea is that of those who think that the impregnation of the body by the Hansen

bacillus and its toxins interferes with the development of the cancerous cells. In support of this approach, Munch-Soegaard in 1910 brought forward the data of a Norwegian leprosarium, in which out of 2,269 deaths only 19, or 8.5 per cent were for cancer. The same author pointed out that in the general population during more than 40 years, the cancer mortality was 5.1 per cent for males and 8.5 per cent for females, whereas in leprosy patients the figures descended to 1.2 and 1.8 per cent respectively. In 1911 Bjarnhjedinsson, after enquiry by correspondence of leprologists all over the world, ratified this opinion and maintained that the coexistence of cancer and leprosy was extraordinarily rare. In 1912 Lie cast doubts on the assertions as not having enough foundation. In 1913 Biehler compared the autopsy figures from the general hospital and the leprosarium of Riga, and the deaths from cancer were in the same proportion. In contrast Kobayashi in 1930 agreed with the ideas of Munch-Soegaard. In 1932 Feil said that neither he nor his chief Beurmann had ever observed the association of leprosy and cancer: he made a search of the literature and enquiry of different co-workers, among them Rost and the director of the Bombay laboratory, and obtained no information of the association of the two diseases. In 1937 Martins de Castro, father and son, described 44 cases of carcinoma in leprosy patients, and thought there was no reason to postulate that leprosy can protect from cancer. In 1945 Rubio recalled the opinion of Hueck, that the pathological influence of epithelioma on leprosy may be analogous to that of epithelioma on lupus, being favourable in both cases, because of the sclerohyperplastic proliferations of the epidermis which by chance acquire malignant infiltrative characters. This theory seemed logical and well founded histologically to Rubio, but without rejecting it neither did he decide to accept it, considering that leprosy is less sclerogenic than tuberculosis. On the other hand and in agreement with Vilanova it must be taken into account that therapeutic factors such as caustics and radiation are apt to influence the genesis of epitheliomas, and these are used more often in lupus than in leprosy, influencing the greater prominence of cancer in lupus; so would it be in leprosy if we used some of these harsh treatments. In 1954 Waaler agreed with this opinion, and added that the patients in leprosaria should have a lower incidence of cancer because they are less exposed to carcinogenic influences, such as actinic rays, etc., than the rest of the population.

Before dealing with the question of skin cancer, we think it would be of interest to state our data on the incidence of cancer in

the leprosy patients, comparing it with that in the general population. In the general population the percentage rate of deaths from cancer from 1943 to 1953 has progressively increased, with small variations only and similar figures for both sexes, from 4 per cent to 9.5 per cent. In Fontilles necropsies are carried out on most of those who die and on all where the cause of death is unknown. From 1946 to 1956, 171 males and 2 females; cancer was the cause of death in 4 males and 2 females, or a rate of 2.3 per cent and 1.7 per cent respectively. This is very much lower than in the general population of Spain and similar to the result found in the Norwegian leprosarium by Munch-Soegaard.

As for skin cancer, which especially interests us, we think that the first case published was that of Blaschko in 1897, at the First International Leprosy Conference of Berlin. In 1913 Toyama published a paper called " Leprosy and Cancer of the Skin ", but we do not know if he reported cases observed by him. In 1929 Portugal reported 9 more cases at an Argentinian conference. In 1930 Puente and Quiroga reported 2 others, one basocellular and the other spinocellular. Feil in 1932 described another basocellular case. Roldan in 1936 described 3 new cases. In 1937 Martins de Castro (father and son) greatly increased the study with 25 more cases. In 1945 first Rubio and later Vilanova published 2 cases in Fontilles patients. In 1949 Vilanova, Ribas and Alvarado added another new case. In 1954 Waaler reported another, making 45 altogether which we have been able to compile.

In October, 1956, a female patient with diffuse lepromatous leprosy entered the sanatorium. She had extensive generalized infiltrations and a massive tumour which affected the whole central part of the face. The patient (Photograph No. 6) had had leprosy for more than 30 years and the tumour had begun 2 years ago, and the diagnosis was of leprosy solely. When she was admitted recently we had the idea that the tumour was malignant, and histological study confirmed this (mirco-photographs Nos. 7 and 8). It was a spinocellular epithelioma in which some horny masses could be seen. The neoplasm infiltrated the dermis very considerably, and in the dermis Virchow cells were seen, and an abundant lymphoplasmatic infiltrate.

This is the fourth case published in Spain of cutaneous cancer on top of leprosy, and if we take into account that the first two reported by Rubio and Vilanova were also Fontilles patients, three cases have been seen among 800 patients. Skin cancer is rare in leprosy patients and as far as Fontilles is concerned it is worth

while pointing out that we use electrocoagulation and cauterization of resistant lesions in some cases, and of the margins of ulcers; also the excellent situation of the sanatorium very near to the Mediterranean coast provides a fine sunny climate for the patients. These are factors which could favour the increase of these new growths.

We think that this slight compilation may serve to emphasize the importance of a meticulous study of all patients and their relations; even when the diagnosis of leprosy is confirmed one must always remember the possibility of the coexistence of other diseases. Leprosy patients suffer other dermatoses with similar frequency to that of healthy individuals. Infections and parasitic affections are probably more frequent among our patients than in the general population, and on the contrary malignant tumours seldom coincide with leprosy; but we should always think of the possibility in order to bring timely aid, and to contribute to clearing up the causes which influence this lesser incidence.

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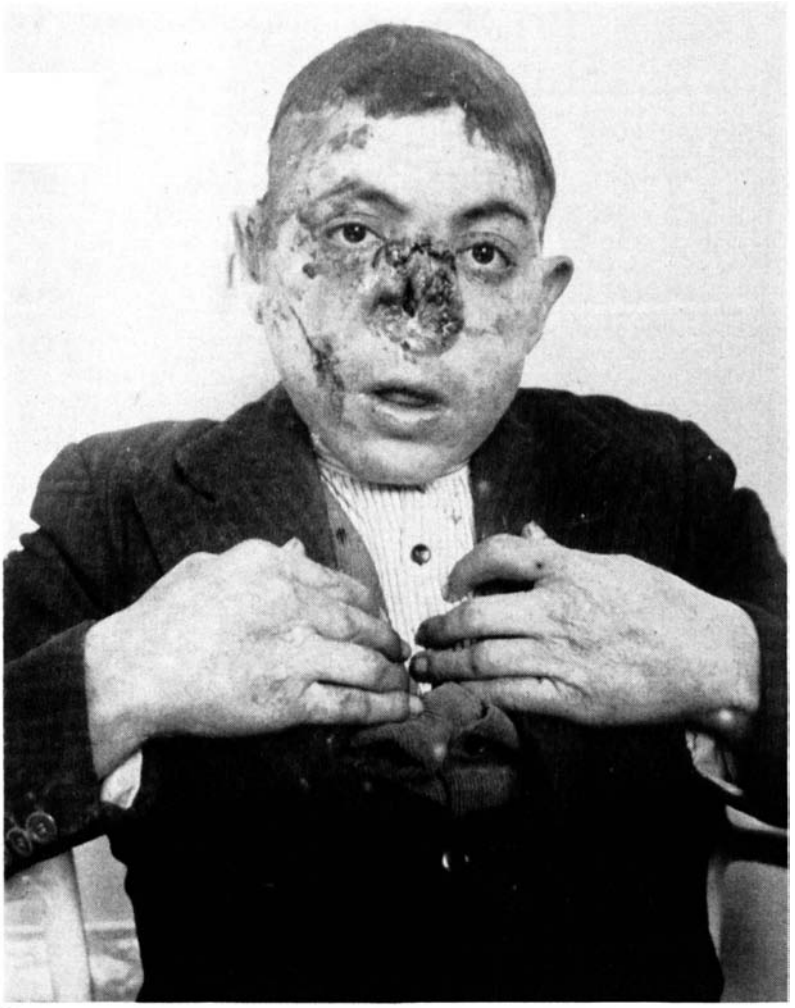
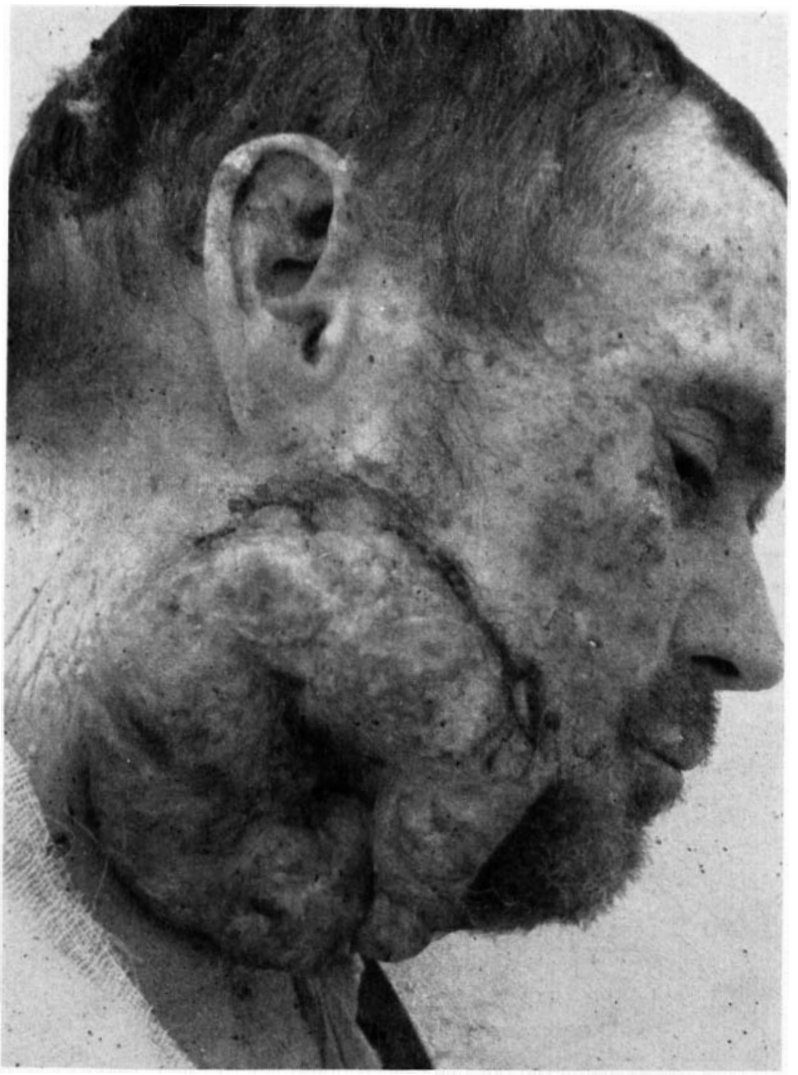
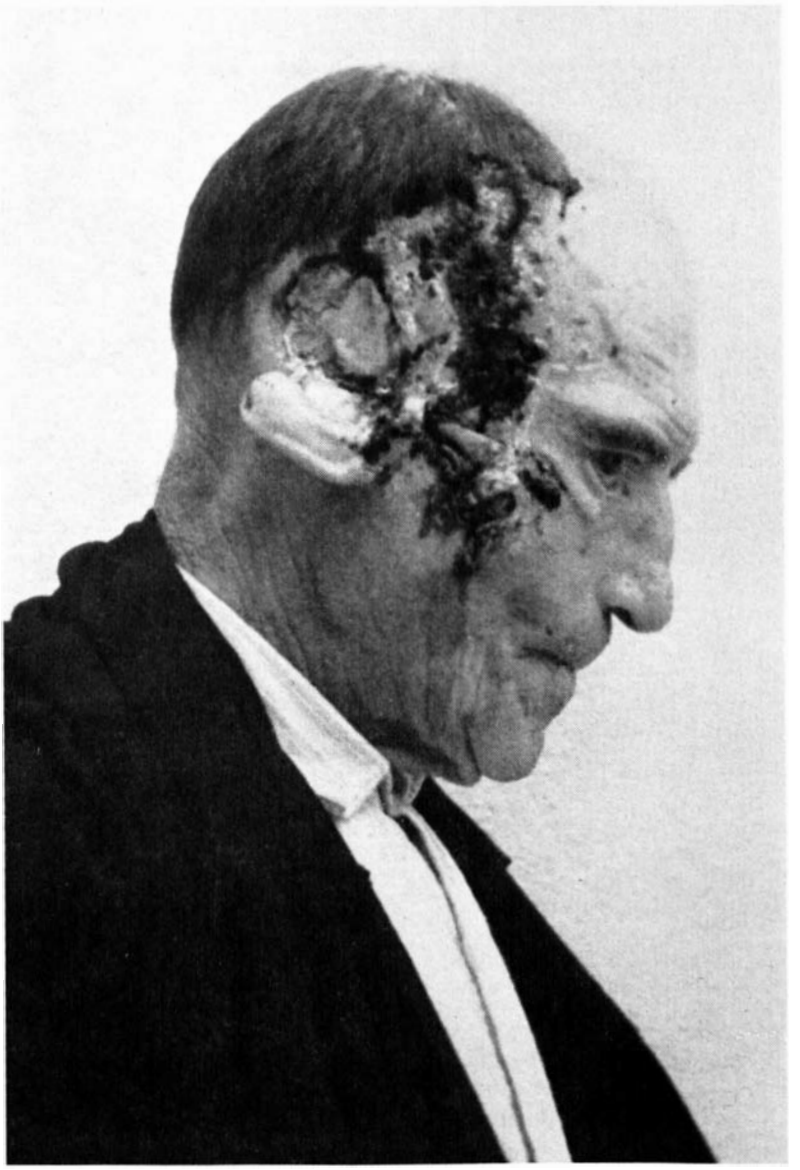


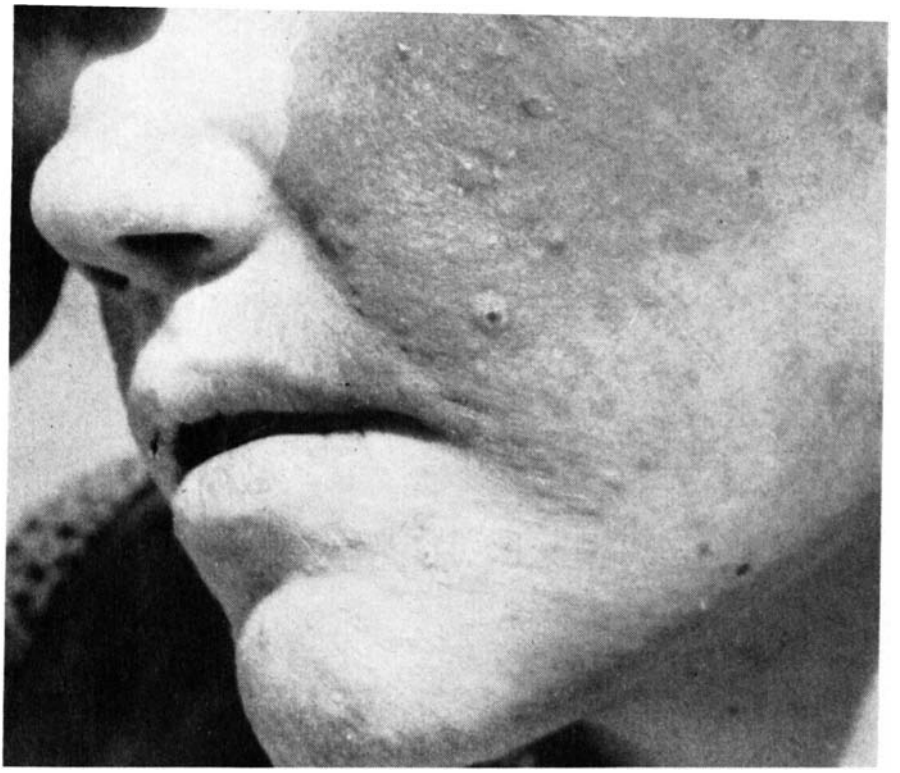
PHOTOGRAPH 1. Epithelioma and epidermodysplasia verruciforme, diagnosed mistakenly as leprosy.



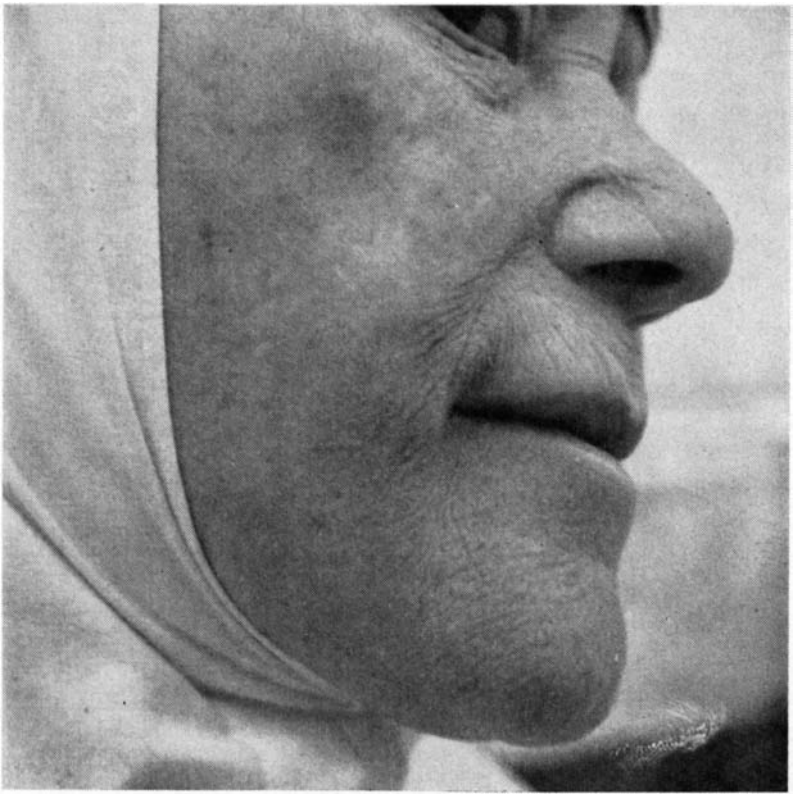
PHOTOGRAPH 2. Epithelioma and xeroderma pigmentosa, diagnosed mistakenly as leprosy.



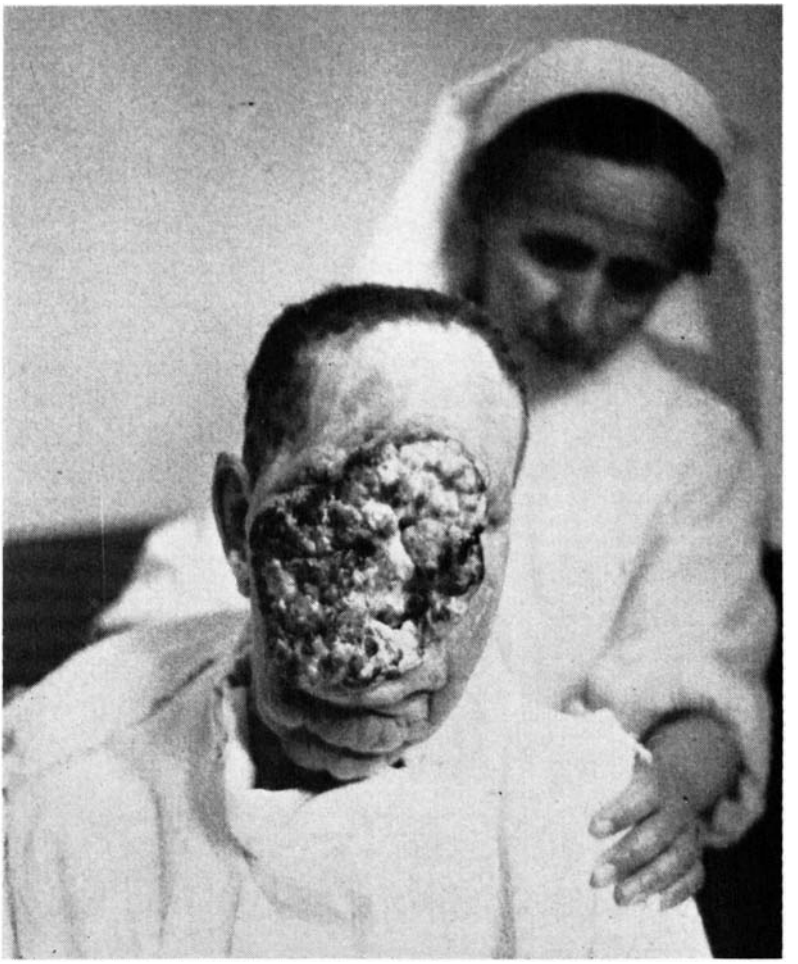
PHOTOGRAPH 3. Epithelioma diagnosed mistakenly as leprosy.



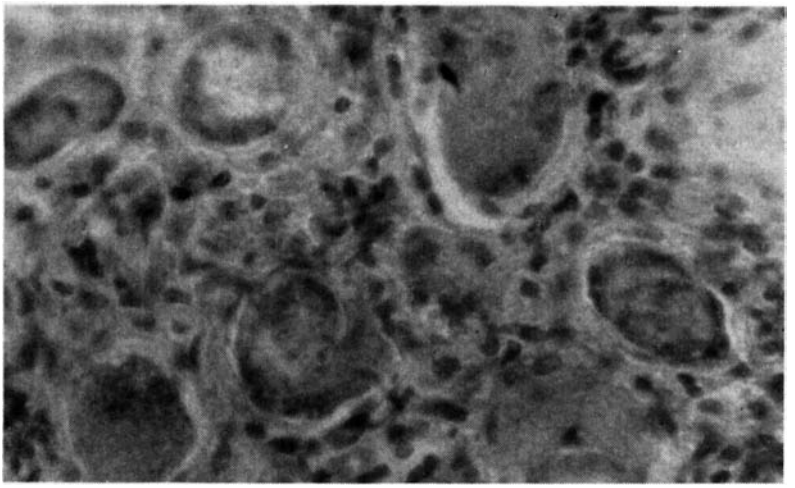
PHOTOGRAPH 4. Lepromas similar to lupomas even to positive vitropressure test.



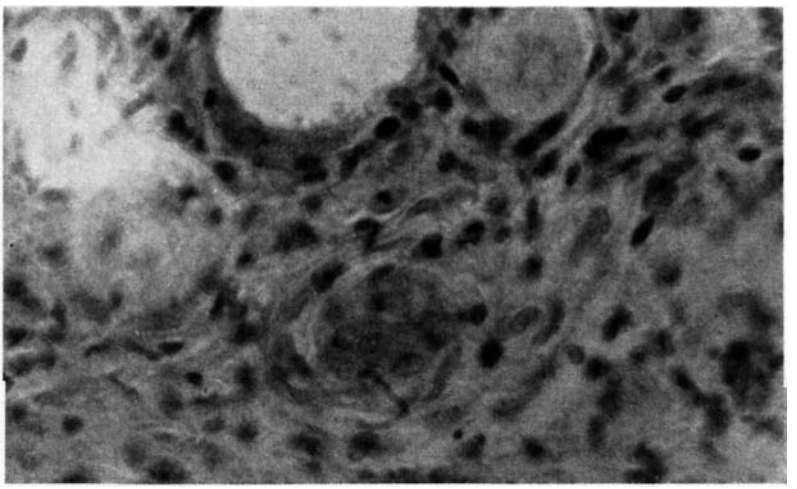
PHOTOGRAPH 5. Oriental Sore in a lepromatous female patient.



PHOTOGRAPH 6. Epithelioma in a male leprosy patient.
(Microphotographs 7 and 8 are of this same patient)



MICROPHOTOGRAPH 7. Epithelioma and lepromatous leprosy: belongs to the patient in Photograph 6.



MICROPHOTOGRAPH 8. Epithelioma and lepromatous leprosy: belongs to the patient in Photograph 6.

LEPROSY OF THE EYE

WILLIAM JOHN HOLMES, M.D.

Honolulu, Hawaii

General Considerations

The eyes are subject to a great variety of infectious diseases. Of these the disturbances caused by the Mycobacterium leprae were, until recently, responsible for more ocular and adnexal damage and more blindness than the microorganisms and toxins of any other infectious disease. This led Boshoff to urge, " Always examine the eyes in leprosy."

The spread to the eye is most likely by the hematogenous route. However, an ascending infection from the nose by way of the nasolacrimal duct or a direct extension from macules and nodules of the face has been suggested. Mycobacterium leprae also enter the fine cutaneous twigs of the peripheral nerve of the face and forehead. From there they spread upwards into larger branches affecting both the motor and sensory axones. Involvement of the eyes and the extent of ultimate visual impairment are influenced by geographic and racial factors, the type and duration of the infection, the patients' general health, the adequacy of therapy, and other variables.

In Japan, Korea, Okinawa, Formosa, and Hong Kong, I found ocular involvement in approximately 10% of the patients. In India, I noted an even lower percentage of eye involvement. From Israel, Landau and Gabboy reported involvement of the eyes in over 90% of the cases. In Havana, Lopes found " some lesion of the eye or of its appendages in every single case of leprosy."

In Prendergast's series, at the United States Public Health Hospital in Carville, Louisiana, Mexicans developed fewer eye lesions than patients of other races. According to Cochrane, King, and Clemmy, dark-skinned natives of Asia and Africa also exhibit fewer ocular manifestations than lighter-skinned patients, such as Anglo-Indians.

In a recent survey amongst the multi-racial population of Hawaii, Chung-Hoon and Hedgcock found a smaller incidence of the disease among lighter-skinned, "diluted " part-Hawaiians than among other ethnic groups, such as the darker-skinned pure Hawaiians and Filipinos.

Defective nutritional status, vitamin ,iron, other mineral and protein deficiencies, notably those of lysin and methionine, are capable of rendering susceptible individuals more prone to ocular complications and retard the healing of existing eye lesions.

General debility, diabetes, chronic liver or kidney disease, hypertension, amyloidosis, venereal disease, tuberculosis, chronic dysentery, malaria and parasitic infections may per se be responsible for ocular complications. When these conditions co-exist with leprosy they often predispose to the ocular manifestations of this disease. Foci of infection such as carious teeth, infected sinuses, infected or draining ulcers, areas of infected bone necrosis may aggravate lesions of the cornea and uveal tract or precipitate and prolong endogenous uveitis, episcleritis and scleritis.

Eye injuries among patients with leprosy are potentially more serious than those among a corresponding group of healthy population. It is therefore essential that patients' eyes be protected with goggles, case-hardened lenses, or at least with regular glasses or sunglasses when they are exposed to hazardous occupations. It is also highly desirable that patients wear glasses or goggles when they are out of doors, exposed to flying particles of dust and dirt. Trivial injuries in patients with anaesthetic cornea are capable of producing corneal abrasions and ulcers that pass unnoticed but may go on to perforation, uveal prolapse, and possible purulent endophthalmitis.

Acute or chronic alcolism and drug addiction are also of considerable importance in leprosy. They render patients less aware of foreign particles and injuries to their eyes and predispose them to potentially grave and permanent ocular damage.

Duration of Infection

Kirwan called attention to the relative scarcity of eye complications during the first five years of the disease. Chance stated, " The incidence of ocular symptoms bears no relation to the duration of the general disease, but may come on at any time in its course; although it is not usually found till several years have passed." Morrow and Lee, on the other hand, in commenting on the frequency with which the eye is involved, said that such involvement occasionally occurs quite early in the disease. Elliott reported perineural beading along the course of corneal nerves together with early degenerative changes of the iris in a child four years old! He drew up an " ocular manifestation time scale," and postulated that the duration of infection bears a distinct relationship to the appearance of various ocular lesions.

Type of Infection

In lepromatous leprosy, ocular lesions are due to destruction and replacement of the normal cellular structure by an overgrowth of granulomatous tissue. This process is accompanied by inflammatory and ultimately degenerative changes within the eye. Bacilli in this type of leprosy are usually present in large numbers with a tendency to aggregate to form " globi " and typical foamy " lepra cells."

The eye lesions are for the most part confined to the anterior segment. However, they do invade the posterior segment as well, though less frequently.

In tuberculoid leprosy, epithelioid cells predominate. The Mycobacterium leprae are rarely found in smears. Invasion occurs in the sheath of the nerves, producing a chronic interstitial neuritis with ultimate destruction of nerve fibres and thickening of fibrous tissue. The ocular lesions and mask-like expression which are often associated with tuberculoid leprosy are secondary to an extension of the inflammation along the source of the fifth and seventh cranial nerves.

In the indeterminate forms of leprosy, skin lesions show few bacilli and do not have a tuberculoid histologic structure. The severity and nature of ocular involvement run a parallel course with the systemic manifestations.

Actue Leprous Reaction and Erythema Nodosum

According to Muir, they are one of the most distressing conditions of leprosy, as they may bring on " irreparable damage to the eyes in a few days." From an ophthamologic standpoint, acute lepra reactions may be accompanied by severe pain, lachrymation, photophobia, circumcorneal injection, cells in the anterior chamber, K.P.s, pigment deposits on the anterior lens capsule, posterior synechiae, and occasionally exudation into the vitreous body. In addition to severe uveal inflammation, episcleritis and nodular scleritis may also occur during these reactions. Erythema nodosum leprosum causes similar ocular complications.

Treatment of the eyes during these reactions depends upon the extent and severity of the involvement. If signs of iridocyclitis or other ocular complications supervene, they should be treated in accordance with standard accepted methods of therapy.

The advent of steroids such as cortisone, ACTH, prednisone, prednisolone, and others have replaced many of the older forms of therapy. These hormones are especially valuable, as they permit

continuation of sulfone therapy without interruption. In Wade's opinion, " cortisone does not cure iritis but changes the process from one of acute, increasing inflammation to a low-grade, easily controlled, subsiding one." It is very likely that as the physiologic and biochemical action of pituitary and cortical hormones becomes better understood, our concepts regarding them will undergo further modifications in the future. For the present, from the clinical standpoint, we are fortunate to have available substances that dramatically supress the symptoms of inflammation. Long-term, individualized steroid therapy as advocated by Steffensen often produces great improvement or even clinicial remission in chronic cases that heretofore have been relatively unresponsive to shorter and less intensive treatment.

If cortisone is used, Jopling and Cochrane recommend five-day courses, beginning with 100 mg. on the first day, 75 mg. the second day, 50 mg. the third day, 25 mg. the fourth day, and 12.5 mg. the fifth, as long as the reaction is being controlled. They feel that these courses may be repeated as the need for them arises.

If ACTH is used, Jopling and Cochrane recommend five-day courses, beginning with 40 mg. of long-acting ACTH gel on the first day, reducing it to 30 mg., 20 mg., 10 mg., and 5 mg. over a five-day period. We have used higher beginning dosages than these—40 mg. long-acting ACTH gel twice a day—for the first two to three days and then gradually reducing the dosage. We also use ACTH gel at the beginning of therapy and follow it with meticortone, 5 mg. three times a day.

Improvement of chronic cases can be maintained by the administration of prednisone or prednisolone. These drugs have been used continuouously for ten months or longer. The dosage schedule for relief of patients varies from an initial dose of 10 to 30 milligrams daily for the first three or four days followed by a maintenance dose of 2.5 to 5.0 milligrams daily and later on alternate days.

When long-term steroid therapy is used, the intake of sodium should be limited, and 1 to 3 grams of potassium chloride by mouth daily should be prescribed. Antacids have been recommended to prevent gastrointestinal disturbances.

The long-term systemic administration of any of the steroids calls for thorough and repeated careful physical examinations and laboratory tests.

Therapy

The introduction of sulfone drugs has resulted in greatly improved prognosis for both the systemic and the ocular manifestation of leprosy.

Lowe believed that the serious eye problems in leprosy were preventable by early diagnosis and thorough general treatment. Cochrane felt that blindness may be prevented if treatment is commenced at an early stage. However, he called attention to the danger of complacency of assuming "all is well" because these drugs are being administered. He felt that active lepromatous eye lesions may become aggravated and blindness may be hastened if the drugs are administered by untrained personnel and the eyes are not carefully watched to prevent damage from iridocyclitic complicating acute lepra reactions. Choyce observed that sulfones prevent, mitigate, and delay ocular complication. In his series, as a result of adequate therapy, the ocular signs became arrested in several patients, while in others regression took place. Yet, he noted that no patient had a "complete cure" of his eye lesion.

Once a lepromatous eye lesion develops, sulfone therapy alone as a rule will not arrest its progress. Nor will sulfone drugs restore the vision of patients whose eyes have undergone irreversible damage. However, if chemotherapy is administered early in the course of the disease, at regular intervals, over a sufficiently long period of time and in adequate doses, it appears to have a beneficial effect on eye lesions in many, though by no means in all, patients. Unfortunately, even under the most ideal conditions, eye complications continue to occur both among patients admitted previous to and since the discovery of sulfone drugs.

Elective, intraocular surgery should not be undertaken unless the patient's eyes have been in a quiescent stage for at least three to six months. If it is decided upon, preliminary slit lamp examination of the eyes should be done. If this reveals evidence of active uveitis, the operation should be postponed. The nasolacrimal passages should be tested for their patency and should be free from discharge. The patient should be able to recognize light and be able to tell the direction from which it comes. For four to seven days preceding surgery, as a prophylactic measure, he should be given eye drops containing a sulfa drug (e.g. 30% sulfacetamide) or a topical antibiotic (e.g. 1.5% chloromycetin solution) for instillation into both eyes several times a day. His general health should be checked over. Regarding surgical treatment itself, only those operations should be chosen which combine the greatest safety with the best results; the operative technique

applied should be best suited to the type of surgery that is being planned; a great deal of experience should be acquired in the method of one's own personal preference; meticulous, aseptic surgical surgical technique should be observed. The postoperative use of steroids, enzymes, antibiotics, analgesics, and hypnotics should be prescribed as need for them arises. Adequate electrolyte balance should be maintained. With these precautions, some degree of useful vision may often be restored to patients who were previously considered hopelessly blind.

Bony Orbit

Deep-seated orbital pain may be encountered. When it is associated with a blind eye, retrobulbar injection of 1 to 2% novocain followed by 1 to 2 c.c. 75% ethyl alcohol usually effects relief for several months or permanently. Enucleation is an alternative form of treatment. Supraorbital, infraorbital, and frontal neuritis, like neuritis elsewhere in the body, may also give rise to severe subjective discomfort. It may be treated with analgesics, salicylates, the administration of vitamins B and K, discontinuation of sulfone drugs and diathermy over the affected area. Intraneural injection of equal parts of 1 to 2 c.c. of 2% novocain and a suspension of 25 mg. per c.c. of hydrocortisone has been recommended to relieve the edema responsible for the pain. If these measures are ineffective, injection of 1 to 2% novocain followed by 75% ethyl alcohol or 25% magnesium sulphate may effect symptomatic relief. As a last resort, splitting the nerve sheath or avulsion of the nerve must be considered.

Lacrimal Apparatus

Fuchs noted that Japanese investigators found lepra bacilli in the tears of 66 per cent of patients whose eyeballs were normal.

Leprotic dacryoadenitis has been described by King, Cochrane, and Sloan. Amendola, prior to the discovery of sulfone drugs, recommended surgical excision of the lacrimal gland as the treatment of choice for acute eye complications. In his experience, "this procedure never failed. It completely relieved pain and stopped other acute ocular manifestations."

Leprotic dacryocystitis is often secondary to advanced nasal disease. It may be treated by intubation of the nasolacrimal duct, dacryocystectomy, or if the condition of the nose permits, with dacryocystorhinostomy.

Epiphora occurs occasionally. It may be attributed to lagophthalmos or to eversion of the lacrimal punctum. Both conditions are amenable to surgical repair.

Diminished secretion of tears—dry eyes—associated with facial palsy and inability to close the eyes in tuberculoid leprosy, is more frequently encountered than excessive tearing. For this condition, the local instillation of 1% methyl cellulose is an especially valuable artificial tear substitute, as it does not support bacterial growth.

Eyeball

Shrunken, deformed, phthisical blind eyes are still encountered among patients in the older age groups. Large, bulging, unsightly staphyloma, and corneal leproma are not infrequent accompaniments of the disease. At times the globe is so large that it protrudes between the lids; the upper lid is drawn up and the lower lid sags down in lagophthalmos. However, as long as light perception remains and the eye is free from pain, it is best to leave it alone. If light perception is lost or if the eye becomes red and painful, its removal for both therapeutic and cosmetic reasons is indicated. Contracted sockets may need surgical reconstruction to permit the wearing of an artificial eye. In this regard, it should be kept in mind that patients who have lost several fingers find it difficult or impossible to insert and remove artificial eyes. In these cases, dark glasses or merely an eye patch worn over the affected eye may be sufficient to conceal the cosmetic deformity and is preferable to a major surgical procedure such as reconstruction of the conjuctival cul de sac.

Brows and Lids

The disease affects the eyebrows and lids with great frequency. Simple hypertrophy of the lids and brows is common. Lepromas appear on the brows and upper lids, but do not invade the lower lids. These lesions often resolve in time on systemic treatment with sulfone drugs. Blepharochalasis of the upper lids is seen in late cases. It is due to stretching of the skin and relaxation of the tissues, by previous lepromatous nodules. If it impairs vision in the upper isopters of the peripheral visual field, it can be corrected by operative interference.

Anaestheic areas on the face, upper and lower lids occur in tuberculoid leprosy. The blinking reflex is frequently absent. In this type of the disease abnormalities of the lids and lashes are primarily responsible for the ocular damage and ultimate visual impairment. Paralysis of the orbicularis with facial paralysis is noted in about ten per cent of the cases. Atrophy of the involved muscles usually follows. The lid margins are almost invariably involved. Entropion of the upper and lower lids causes subjective

discomfort and objective cosmetic deformity. When the lashes are present, they may de misdirected, causing trichiasis, conjunctival or corneal irritation, corneal ulcers and scars. Widening of the palpebral fissures with sagging of the lower lids is frequently observed. In early cases, this causes only slight cosmetic disfigurement. As the condition progresses, paralytic ectropion and lagophthalmos result. Loss of sensation, loss of protection by the lids, and loss of diminuation of tearing may result of chronic conjunctivitis, exposure keratitis, corneal ulceration and perforation of the globe.

Entropion of the upper lid can be corrected by using Gleyze's technique or other similar operations.

Entropion of the lower lid may be corrected by resection of the tarsus and orbicularis, or by a Hughes type of tarso-conjunctival graft.

Trichiasis may be very annoying and may cause corneal damage. It is treated by periodic epilation or electrolysis of the misdirected lashes. If severe, the condition may be surgically repaired with a tarso-conjunctival graft from the opposite lid sutured into an incision at the muco-cutaneous junction.

Ectropion of the lower lid may be paralytic or cicatrical. If it is paralytic, it is usually associated with lagophthalmos. A transparent, plastic cup worn over the affected eye will protect the eyes, especially during sleep. The instillation of 1% methyl cellulose with or without 0.5% cortisone or mild antiseptic or antibiotic ointments also affords some degree of protection to partially exposed globes. However, the ideal treatment for ectropion and lagophthalmos is surgical repair. Lateral tarsorrhaphy, Minsky's figure " 8 " suture, the Kuhnt-Szymanowski operation, or repair by a fascia lata sling are all suitable and may be used, depending upon the severity of the defect and the discretion of the surgeon.

In paralytic lagophthalmos involving the upper lid, recession of the levator as recommended by Goldstein is a valuable approach.

In all operations involving flaccid lid tissue, it should be kept in mind that the underlying muscles lack tonus and are usually atrophic. To obtain an adequate functional and cosmetic result, it is advisable to correct these conditions fully or even slightly overcorrect them. Transplantation of the temporalis muscle according to Ferris Smith's technique has also been recommended to improve the appearance of patients and to lend tonus to paralytic lids.

Uni- or bilateral loss of hair follicles from the eyebrows with loss of lashes may appear early in the course of the disease. The

loss of brows commonly begins on the temporal side and may involve the entire brow. In countries where eyebrow pencils are available, female patients are often content to use them as cosmetic beauty aids. Intradermal artificial pigmentation—tattooing—to the area of the brows has been successfully performed at the United States Public Health Hospital in Carville, Louisiana. Transplantation of individual hair folicles to create eyebrows was first suggested by Fujita. At the present it is commonly and successfully practiced in Japan. We prefer hair-bearing grafts from the scalp or from the opposite brow if they are available.

Ocular Muscles

Leprosy seldom causes oculomotor disturbances. Mitsuda reported that he has not seen paralytic squints arising from the disease nor was he able to find the bacillus in the oculomotor nerve. However, Viallefont and Fuentes and King did find paralytic strabismus due to involvement of the third nerve. Divergent strabismus secondary to amblyopia of one eye is not uncommon. Paralysis of the intrinsic muscles of the eye involving paralytic mydriasis or accommodative palsy occur periodically. They occur more frequently in patients with lepromatous leprosy who have undergone erythema nodosum type of reactions. Prescription of eye glasses with suitable presbyopic reading addition is usually sufficient to enable patients with such defects to read, sew, and do close work.

Conjunctiva

Leprosy bacilli as a rule do not invade the conjunctiva. However, the bacillus has been recovered from the conjunctival secretions in large numbers, even in eyes showing no leprous stigmata.

Acute superimposed infectious conjunctivitis usually responds to topical applications of 30% sulfacetamide or ophthalmic aureomycin drops. If these drugs fail, a smear, culture and antibiotic sensitivity test from the conjunctival sac frequently help determine the antibiotic to which the bacilli are most sensitive and which is most likely to control the infection. Coexisting trachoma occurs frequently, especially in the tropics. According to Professor Ida Mann, the sulfones used in the treatment of leprosy " can entirely kill the trachoma virus." Professor Mann confirmed this observation by successfully treating with DDS a group of children who had trachoma, but did not have leprosy.

Chronic conjunctivitis is common. It is believed to be due to exposure and secondary bacterial infection rather than leprous

infiltration. The treatment of chronic conjunctivitis depends upon the bacterial flora of the conjunctival sac. It usually responds to antiseptic or antibiotic collyria or to the local application of 0.15 to 0.25% zinc sulfate drops, 1% methyl cellulose, etc. We have no experience with the topical instillation of sulfone drugs in the treatment of leprous eye lesions. Due to the granulomatous nature and chronicity of the disease as well as the slow action of sulfone drugs, we feel that this method of administration is of doubtful value. However, Tsukahara, Ishihara, and Tajira advocated topical applications of 1% to 5% promin ointment as well as subconjunctival injections of 5% promin.

Episclera and Sclera

The episclera, according to Fuchs, is the earliest site of ocular involvement. Valle believed that the rich anastomosis between the anterior ciliary arteries and posterior conjunctival vessels is responsible for the preferred episcleral location. Yellowish, gelatinous, leprous nodules containing bacilli usually abound in the episclera near the limbus. These nodules are often symmetrical and are more commonly situated on the temperal halves of the bulb. They tend to spread around the limbus and infiltrate the cornea. They may even invade the angle of the anterior chamber. They temporarily respond to topical or in severe cases to systemic administration of cortisone, hydrocortisone, or some of the other steroids. However, they frequently recur.

The sclera itself usually does not harbour bacilli. A yellowish discolouration of the sclera has been reported by several authors. Anterior, intercalary, or scleral staphyloma follow repeated acute attacks or chronic forms of episcleritis or scleritis. Tissue therapy consisting of intramuscular or subconjunctival injections of placenta extracts has been recommended by Pennec for these unsightly lesions. In a few clinics in India, staphyloma are resected. We feel that if the lesions are sufficiently large to cause cosmetic deformity or pain, the eye should be removed.

Cornea

The cornea is the most vulnerable of all ocular structures affected by the Mycobacterium leprae. Bacilli may be found in corneal scrapings.

Infiltration of the corneal nerves may be demonstrated by slit lamp examination. This process is essentially similar to the infiltration that takes place in the peripheral nerves elsewhere in the body. Beading of the corneal nerves in the superior lateral quadrants of both eyes was observed by Pillat. Thickening of the nerves

in the stroma with minute granulomatous infiltrations has been described by Boshoff.

Partial or total loss of corneal sensitivity is an important sign, as either may be the forerunner of neuroparalytic keratitis with consequent visual impairment. Thomas stated that sensory nerves are believed to exert some controlling effect upon the metabolism of the corneal cells, chiefly the epethelial cells. When this proper, regulatory effect is lacking, there is an accumulation of cellular metabolites causing an edema and tissue destruction. The cellular edema and disturbed nutrition with its accumulated extracellular and intracellular deposits leads to a breakdown and exfoliation of the epithelium so that minor trauma, bacteria, and foreign bodies can readily damage this structure.

Exposure keratitis or keratitis lagophthalmos is a serious complication of tuberculoid leprosy. It is the aftermath of paralysis of the orbicularis muscle. The involvement is usually in the lower, exposed portions of the cornea. As the cornea derives some of its nutrition from the tears as well as from the limbal vessels and the aqueous, abrasions, ulcers, and scars that accompany this type of keratitis are partly due to evaporation of tears.

The prophylactic treatment of both neuroparalytic and exposure keratitis includes protection of the cornea with goggles. If goggles are equipped with side shields they create a moist chamber and afford added protection and comfort. Especially constructed plastic cups which can serve as moist chambers are commercially available. If such are not available, at least eyeglasses or sunglasses should be provided for added protection. Patients should also be instructed to apply 1% methyl cellulose to their eyes before retiring and to keep their eyes patched at night. Methyl cellulose is preferable to bland ointments and oils such as U.S.P. lanolin or U.S.P. petrolatum, as the latter tend to produce mechanical irritation, delay or inhibit wound healing despite lubrication. If patients do not fully appreciate the potential hazards of neuroparalytic or exposure keratitis, their eyes should be permanently protected by a lateral tarsorrhaphy or a lateral and a medial tarsorrhaphy. Two small adhesions between the upper and lower lids afford considerableble protection to the cornea, and still permit patients to see through a central unobstructed narrow slit.

The active treatment of corneal abrasions and ulcers consists of the application of local, subconjunctival or systemic antibiotics, the use of mydratics and patching the eye. Grossly infected corneal ulcers may require curettement and thermal or chemical cautery.

The systemic administration of vitamins A, C and D, riboflavin, or multivitamin preparations has been recommended to assist the healing or corneal ulcers.

Superficial punctate keratitis is considered pathognomonic of the disease. Shionuma found it in 21.7 per cent cases of lepromatous leprosy. It usually begins at the superior limbus as a light milky haze in the substantia propria, dotted by tiny, white, irregular spots resembling dust or grains of chalk. As it spreads downwards, its lower margin is delineated by a wavy line. Lepra cells and lepra bacilli may be seen in the scrapings from such lesions.

Leprotic pannus may be seen in all stages of vascularization and granulomatous infiltration. Clinically it resembles the pannus of phlyctenular kerato-conjunctivitis. It differs from that of trachoma by the absence of involvement of the tarsal plates. The lepromatous pannus encroaches and often destroys Bowman's membrane as it advances into the parenchyma. In doing so, it causes a partial or complete hyperplastic keratitis and ultimately brings on severe visual loss. Its progress may be checked by peridectomy and recession of the vascularized tissue four to five millimeters back of the limbus. Large limbal or corneal vessels may be destroyed with the electrocautery. These operations should be followed with local applications of cortisone drops or ointment for weeks and months. Beta radiation has also been recommended as an effective means to control extensive vascularization of the cornea.

Sclerosing keratitis originates as a white, milky band in the episclera or sclera. It gradually advances to the cornea, often giving rise to sclero-corneal leproma. These lepromas are generally bilateral and may attain very large proportions. Mitsuda reports that 94 per cent of his patients with lepromatous leprosy developed leproma of the cornea. This figure is out of proportion with our statistics (less than 10 per cent) and with my personal observations in Korea, Formosa, and India.

Another type of leproma occurs in the centre of the cornea surrounded by relatively transparent tissue (Ruato's corneal leproma). Large, isolated corneal leproma, according to De Souza, may be extirpated surgically or treated with galvanocautery or with carbon dioxide snow. However, when light perception is lost and the eye becomes red or painful, little can be gained by temporizing procedures, and enucleation is the treatment of choice.

Interstitial, nodular or discoid keratitis is also seen in the lepromatous form of the disease.

Iris and Ciliary Body

Lepromatous iritis and cyclitis may be caused by actual invasion of the uveal tissue by the bacillus itself—granulomatous uveitis—or it may be due to hypersensitivity to anaphylaxis resulting from protein sensitization—non-granulomatous uveitis.

Granulomatous uveitis of leprosy is a chronic, nonpurulent inflammation of the uveal tract which results from actual infection. It runs a prolonged course and causes tissue necrosis. In this type of inflammation, bacilli are present in enormous numbers. Fuchs demonstrated large nests of lepra bacilli in the iris and in the ciliary body on histologic examination. The essential pathologic change is characterised by exudation, mobilization, and proliferation of inflammatory cells. These changes may be observed under the slit lamp. They consist of an aqueous flare with mutton fat type of keratic precipitates and fibrinous exudate in the anterior chamber. The clinical course is characterized by slow, often insidious onset and gradually decreasing visual acuity. Pericorneal injection is usually slight. If the disease progresses, multiple—according to Mendonca de Barros, myriads of—miliary, glistening lepromatous nodules considered pathagnomonic of the disease, can be seen near the pupillary margin or in the iris stroma. There is marked tendency to form heavy posterior synechiae. The latter are usually permanent and are difficult to break. Whole sectors of iris may become atrophic, depigmented, and lead to heterochromic iridocyclitis. Seclusio and occlusio pupillae and secondary cataract frequently supervene.

Each exacerbation produces increased damage to the eyes. In severe cases, the eye may progress to phthisis.

Non-granulomatous iridocyclitis has been described by Woods as a sterile reaction. He states: " It is the result of acute and later chronic recurrent insult to the tissues. The latter could be due to bacterial hypersensitivity, or to an anaphylaxis caused by protein sensitization. The absorption of the soluble bacterial protein from a focus of infection may readily explain the inflammatory reaction in these eyes. The clinical course in this type of involvement is characterized by sudden onset of considerable pain which reaches its maximum intensity in two or three days. Intense pericorneal congestion, hyperemia, muddy iris, contracted pupil, photophobia, and lacrimation are present. On slit lamp examination, fibrinous exudation into the anterior chamber with many cells and intense aqueous ray are noted. There is only slight tendency to the formation of posterior synechiae. The attacks are short-lived, and run a self-limited course in one or several weeks.

" After repeated attacks, however, annular posterior synechiae may be found. The iris becomes thinned and atrophic. There may be clouding of the lens with secondary cataract. Organized fibrinous exudates on the iris may simulate the picture of severe granulomatous disease."

Ashton called attention to the frequent co-existence of uveitis with infective, usually streptococcal, foci in the tonsils, teeth, etc., and the improvement which sometimes follows the removal of such foci. He felt that these findings offered at least persuasive support for regarding focal sepsis as a factor of importance in the etiology of non-granulomatous uveitis. For this reason, in non-granulomatous types of uveitis of leprosy a thorough medical search should be carried out and infected foci should be eradicated.

There is no uniformly beneficial treatment for acute iridocyclitis. In both granulomatous and non-granulomatous forms of the disease, the local instillation of mydriatics (1-2% atrophine, 0.2% scopolamine, 10% neosynephrine) and 1 to 2% dionin are used. Cortisone and other steroids are of great value in the treatment of acute attacks of iridocyclitis, choroiditis, and occasionally optic neuritis. Treatment with these preparations was discussed in conjunction with acute lepra reactions.

External heat in the form of hot, moist compress, heating pads, or short-wave diathermy is gratefully received by most patients. The parenteral administration of certain enzymes, such as trypsin, occasionally provides relief in the management of recalcitrant cases of uveitis. The intravenous administration of calcium gluconate or lactate is also occasionally used in arresting refractory cases of iritis.

Lesions of the Posterior Segment

Lesions of posterior segment are rare. Valle advised that all conditions capable of producing changes in the retina and choroid, such as syphilis, tuberculosis, and others, should be ruled out before the diagnosis of chorioretinitis due to leprosy is made. Changes in the retina are believed to be secondary to those in the uveal tract. Neither Kirwan nor Prendergast was able to demonstrate the bacillus leprae in the retina or optic nerve. However, Mancione and Inatomi reported acid fast organisms in both the choroid and retina. Prendergast observed involvement of the fundus in 42 out of 241 patients. Trantas and Pupert reported uni- or bilateral isolated punctate lesions in the periphery of the choroid with some pigmentary proliferation. Stallard noted clumps of lepra bacilli in types of changes in the fundus, during acute leprous reactions, in 43 the suprachoroidal lymph spaces. Verne described four different

out of 120, or 35 per cent, of his patients. They consisted of: congestion of the disc with blending of the shades of the nasal and temporal halves of the disc; papilloedema, which varied from blurring to complete disappearance of the disc margins; infiltration of the posterior pole seen as an increase of the retinal glimmer; a brilliant perimacular circule with or without vascular changes; persistent venous dilatation accompanied by vascular undulations; and a decrease, sometimes amounting to collapse, of the central artery. In addition to the foregoing, at times, Verne also observed perivascular infiltration of the afferent and efferent central vessels and a grayish, edematous appearance of the macula.

Kennedy reported nine cases of leprous choroiditis. Elliott reported six cases of retinal pearls visible through the ophthalmoscope. They appeared as small, waxy and creamy white pedunculated nodules projecting into the vitreous. Somerset and Sen described round, yellow homogenous nodules situated superficially on the retina.

Van Poole described 49 cases of optic neuritis among 206 patients. He believed that these were transitory and were caused by bacterial allergy. Takahashi, in lepromatous cases, was able to demonstrate bacilli in the optic nerve. He ascribed the involvement to an extension of the lepromatous infiltration.

In conclusion, I should like to quote my former colleague, Dr. Paul W. Brand, distinguished orthopedic surgeon of the Christian Medical College, Vellore, South India. Dr. Brand, in his Hunterian lecture before the Royal College of Surgeons in 1952, called on " orthopedic and plastic surgeons to come forward and open the door that leads the leprosy patient from isolation back to his family and job." Dr. Brand's timely challenge is equally applicable to the ophthalmic profession. With adequate sulfone therapy, timely and appropriate prophylaxis, we can prevent much suffering and eliminate needless blindness. With proper medical and surgical management, we can conserve eyesight and restore useful vision to patients who were previously considered beyond help.

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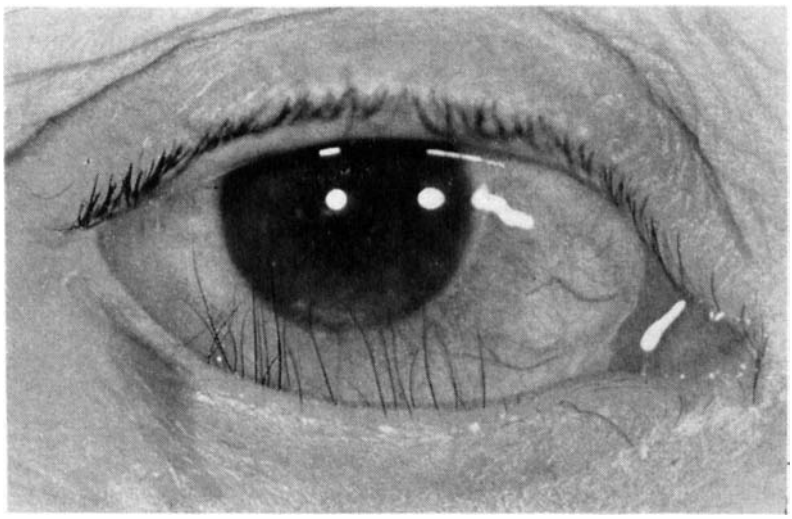
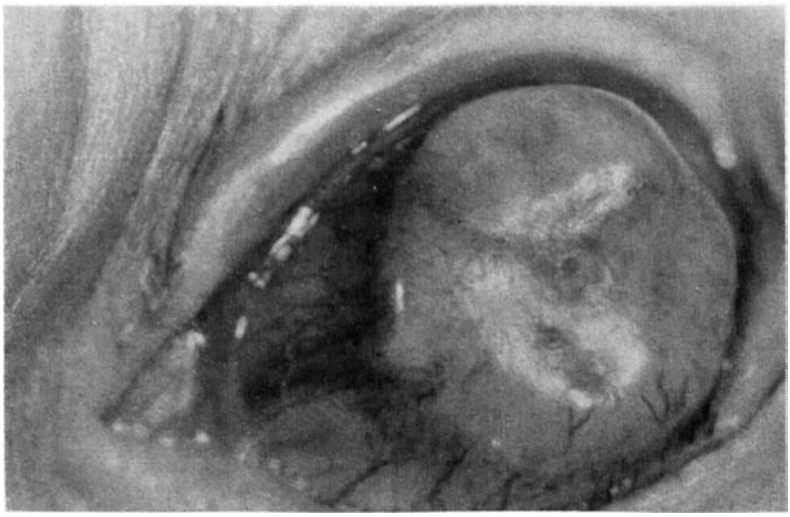
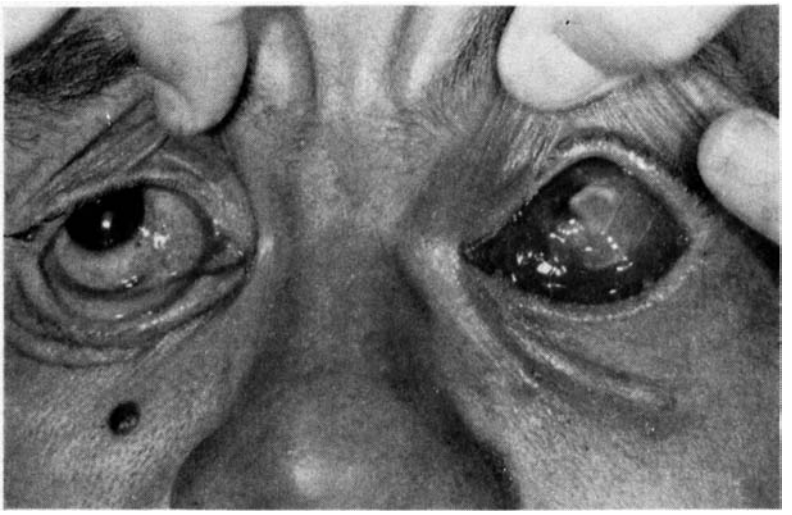


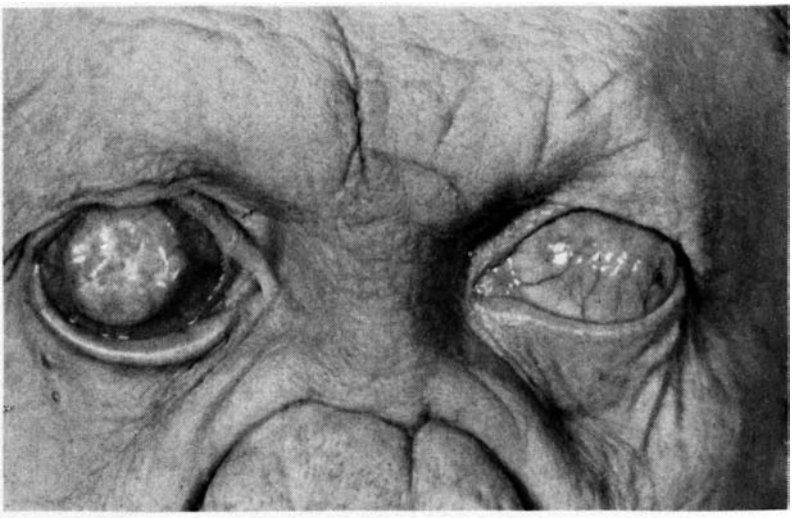
Trichiasis, lower lid.



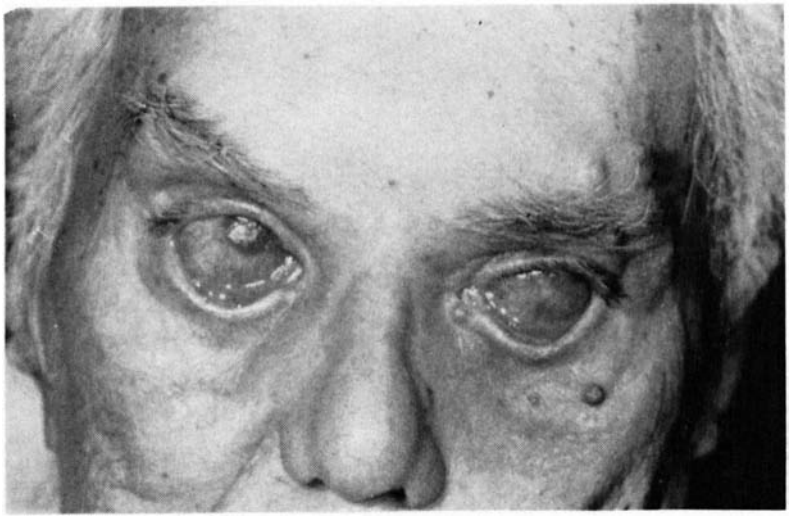
Corneal leproma.



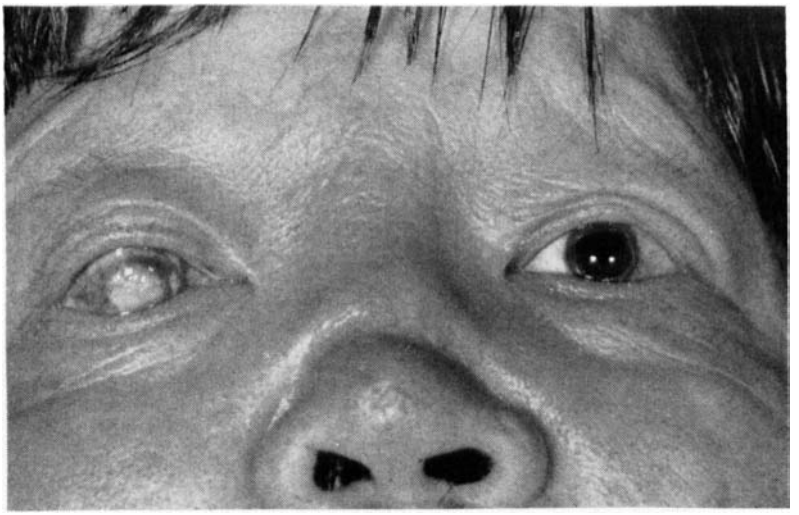
Left Corneal abscess.
Purulent endophthalmitis.



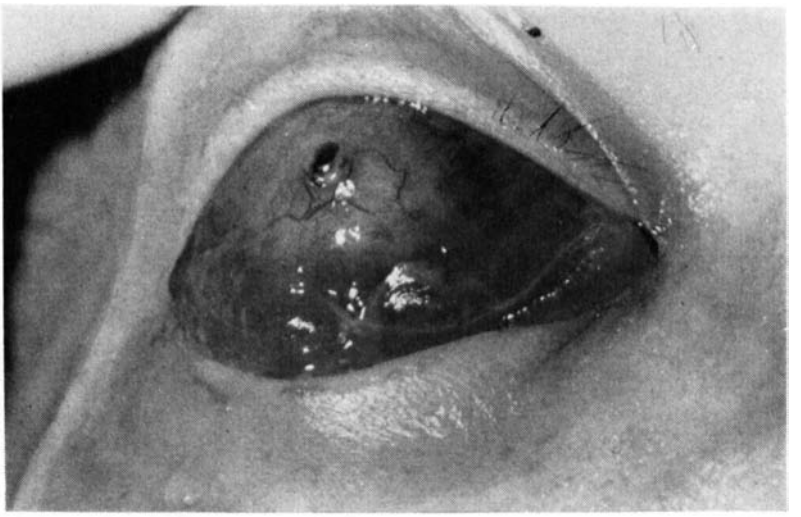
Corneal Leproma, right.
Anterior staphyloma, left.



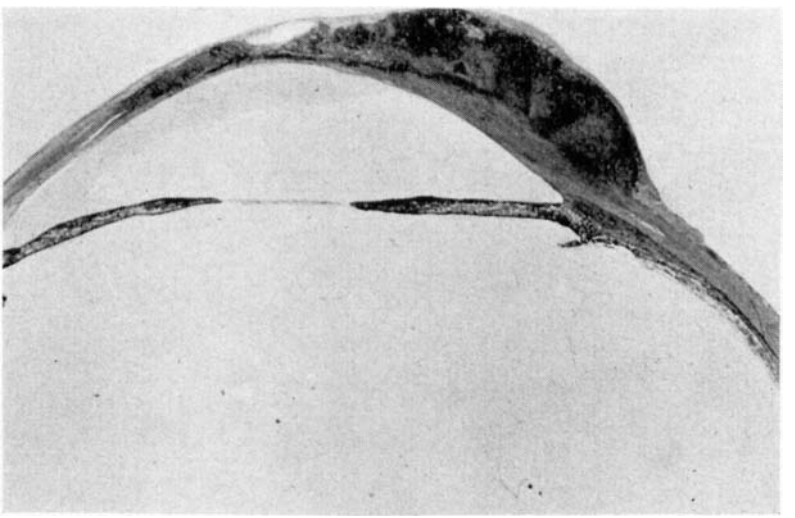
Right exposure keratitis.
Left lepromatous pannus.



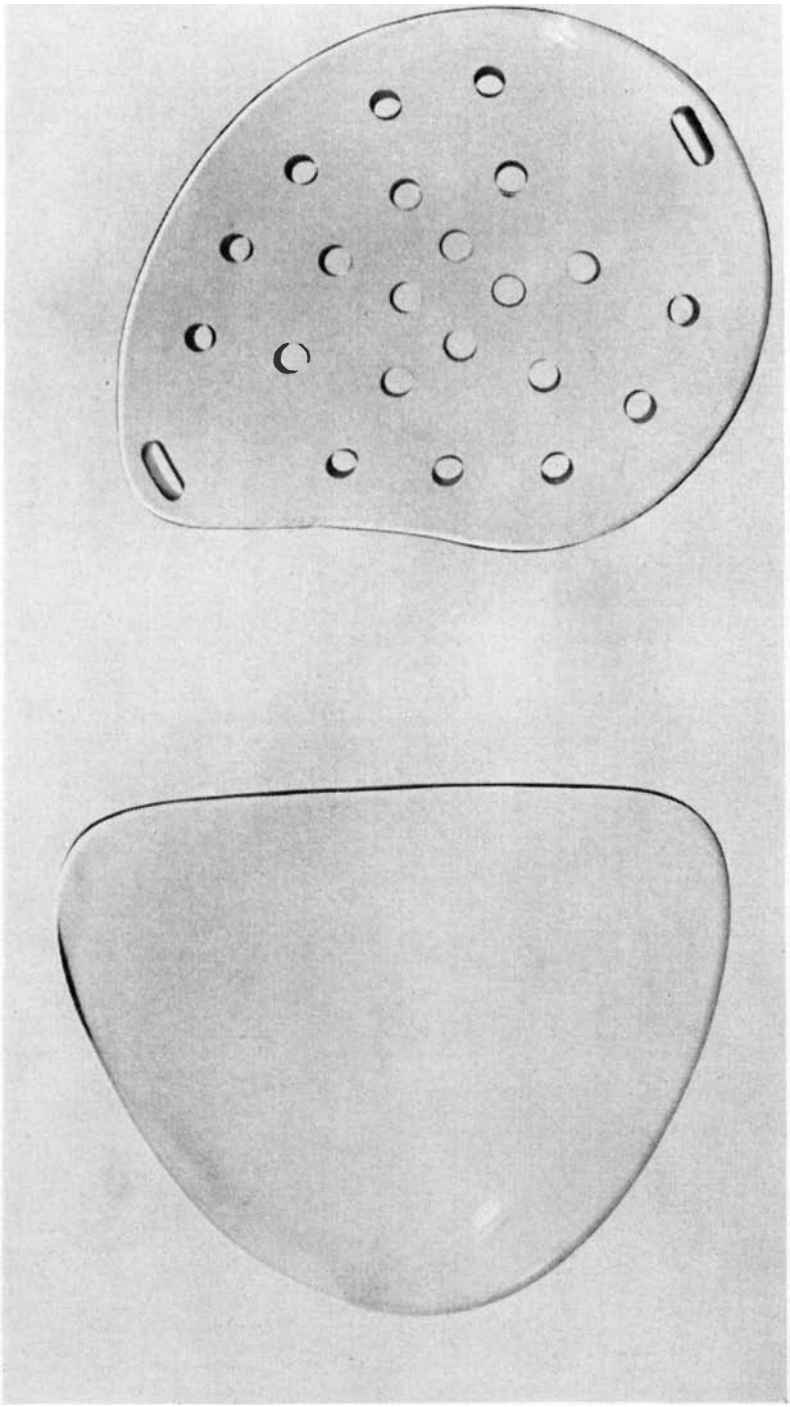
Partial madarosis both brows.
Corneal staphyloma right eye.



Perforation of eyeball.
Lepromatous pannus.



Corneal leproma.



Plastic cup to protect the eye during sleep.

STHIOSEMICARBAZONE IN THE TREATMENT OF THE REACTIONAL AND BORDERLINE FORMS OF LEPROSY

H. W. WHEATE, M.B., B.S., D.T.M. & H.

Makete Leprosarium, Tanganyika.

The first report of the use of thiosemicarbazone (TBI 698) in leprosy was a note of 6 months' treatment of one lepromatous case. (Hohenner, 1949.) This was followed by a preliminary communication by Vegas et al. (1950), working in Venezuela, on the treatment of 42 lepromatous cases for periods of 3 to 6 months. The therapeutic effect was marked and a notable feature was the tolerance exhibited to doses as high as 900 mgms, daily. Two papers by Lowe (1953, 1954), one covering 2½ years' and the other 38 months' experience in Nigeria, give a painstaking analysis of the relative advantages and disadvantages of this drug as compared with sulphone (DDS). He found a greater toxicity (agranulocytosis, severe anaemia, allergic dermatitis, drug fever and hepatitis occurred variously in 16 out of 273 patients), and that the need for closer medical supervision and the apparent development of drug resistance during the second year of treatment make it unsuitable for large scale use, especially in out-patient centres. Further disadvantages are the daily dosage regimen and the greater cost. Its value, as shewn by Lowe and now generally agreed by the majority of workers, is that it is a most useful alternative to sulphone in lepromatous cases in which, because of repeated reactions, sulphone therapy has to be interrupted or stopped altogether, and in cases which develop sulphone toxicity (follicular and exfoliative dermatitis being commonest manifestations of this).

Thiosemicarbazone in the Neuritis of Leprosy

In tuberculoid leprosy, Lowe (1953, 1954) found that, while on the whole the subsidence tended to be slower than with sulphone, his impression was that it had more often been accompanied by a return of pigment and of sensation to the affected area of skin. The subsidence of nerve thickening was also, perhaps, more marked. He reported one case of severe tuberculoid reaction and one of severe neuritis (tuberculoid), both occurring in the course of sulphone therapy, in which there was no clear indication that the response was any better than would have been given in continued sulphone therapy—it is in this respect that my own experience differs.

In borderline leprosy, Lowe found a good clinical and bacteriological response ,but relapse occurred in one case—contrary to what is usual in sulphone therapy and possibly due to the development of drug resistance.

The only report specifically concerned with the beneficial effect of thiosemicarbazone in the painful neuritis of leprosy is by Farinas (1951). His series of cases comprised 4 lepromatous, 2 tuberculoid and 1 indeterminate. He concluded ,however, that this finding may have been due to a non-specific effect and that the drug might be equally efficacious in other forms of neuritis, a view which has not, as far as I know, been confirmed.

The Dangers of Sulphone in Atypical Forms of Leprosy

Garrett (1956), writing of his experiences of 5 years' mass treatment with DDS in Nigeria says:—

" In the borderline and atypical tuberculoid leprosy, particularly if the lesions are much raised and situated on the hands, feet or face, severe reactions with paralysis often occur early in treatment . This is particularly true if the dosage is rapidly raised."

It has long been known that East Africans appear to tolerate sulphone less readily than Nigerians and it is not therefore surprising that in my experience such reactions occur, not merely when the dosage is rapidly raised but *even after only one or two twice weekly doses of 100 mgms. DDS.*

DDS is being used on an increasingly wide scale in out-patient treatment centres, but there exists a minority group of leprosy cases for whom even the most cautious routine dosage regimen is likely to be disastrous. Prompt diagnosis, which is not beyond the ability of African subordinate medical staff given training in it, will avert the tragedy of permanent crippling. Having laid particular emphasis on this matter at this leprosarium, we have collected a considerable number of such cases, sent in by Mission and Native Authority out-patient treatment centres.

The Diagnosis of the Atypical Forms of Leprosy in which Sulphone is Dangerous.

1. *Those recognisable before sulphone therapy has commenced.*

(a) Cases presenting with lesions of the "major" tuberculoid type but with these differences—that there is a flat, hypopigmented zone, extending beyond the most raised portion of the patch and frequently involving:—
   (i) The palms of the hands and soles of the feet
   (ii) The mucosae of lip, nostril or conjunctiva.

The ulnar and peroneal nerves may be enlarged and tender and early palsy of the small muscles of the hand may be evident. In some cases these neural signs may be absent.

(b) " Reactional " and borderline cases ,in which there are grossly raised, succulent, plaque-like lesions, painful when pinched between finger and thumb. Some of the smaller lesions may resemble shotty, lepromatous nodules, extending deep into the cutis. The appearance of the ears is especially deceptive in its similarity to leproma, as is the tendency of the lesions to be symmetrical—whereas in typical tuberculoid leprosy the patches are asymmetrical. As in (a) above, some have enlarged tender nerves ,others do not.

Both these groups have positive skin smears, the latter (b) frequently up to 4 plus. The majority have a positive lepromin, though some of the borderline cases give a negative or doubtful reaction. Some—indeed the majority of the borderline cases—tolerate sulphone well and respond dramatically if treated with care, but the policy advocated is that all such cases should be admitted to a leprosarium, not only because of the dangers of crippling deformities but also because of their infectivity, as evidenced by their positive skin smears.

2. *Those recognisable after the commencement of sulphone therapy.*

(a) Cases, similar to Group 1(a) with minimal atypical signs missed at the initial examination, but " blowing up " after only a few weeks' treatment with a tuberculoid reaction and acute neuritis.

(b) Cases of the indeterminate type, with pale, flat macules and variable alterations of sensation in the patches, which undergo a metamorphosis to the major tuberculoid type during sulphone therapy. Some, particularly children, develop paralyses remarkably rapidly and it is a good practice to admit all children with flat, cafe-au-lait coloured macules to a leprosarium, where the facilities for close observation reduce the dangers of sulphone.

(c) A small minority of clinically lepromatous cases develop an unusual type of lepra reaction in the early stages of sulphone therapy, with oedema and subsequent desquamation of the infiltrated skin and acute neuritis, with incipient paralyses rapidly ensuing.

Case Histories

(1) Female, aet. 25 years: referred by Native Authority Clinic, which she first attended in January, 1956, at which time

she was given 100 mgm. of DDS. She failed to attend the clinic again because unable to walk the distance in the rainy season. She was admitted to Makete Leprosarium on 13th February, 1956 in a state of tuberculoid reaction involving the palms of the hands and mucosae; there was oedema of eyelids, and also enlargement of the left facial, both ulnar, and both peroneal nerves. She was given thiosemicarbazone and made good progress, apart from occasional ulcers of feet. About a year later, on 25th February, 1957, all lesions had resolved, and there was a slight degree of bilateral mobile claw hand, and shortening of the right thumb due to sepsis, and the nerve trunks were all normal clinically. She was considered fit to commence DDS in place of thiosemicarbazone.

(2) Male, aet. 32 years, was admitted on 12th September, 1955, with succulent borderline lesions, some peeling, particularly on the face and ears, shotty lesions on the arms, and the peroneal nerves slightly enlarged and tender. He was put on thiosemicarbazone and by 23rd December, 1955 the lesions were resolving and partially repigmented, and the peroneal nerves were clinically normal. On 9th March, 1956 he was changed to DDS and on 12th February, 1957 there were only a few residual hypopigmented lesions and the lepromin reaction was doubtful positive.

(3) Male, aet. 25 years, was admitted on 20th July, 1956 with extensive grossly infiltrated lesions, especially on face and ears, at that time thought to be lepromatous. The left ulnar nerve was enlarged and tender. He was given the routine twice weekly dosage of DDS, reaching 400 mgm. twice weekly in November. On 3rd December he developed severe reaction, with oedema of face, hands and feet, and there was no improvement on stopping the DDS. On 24th January, 1957 the skin smears were positive, averaging 2 plus. On 7th February of the same year he was considered to be of borderline type clinically, and had developed bilateral simian hand, with right drop foot. Both ulnar nerves and both peroneal nerves were enlarged and tender, the right peroneal more than the left. He was then on 25 mgm. of thiosemicarbazone daily. By 18th February there was slight improvement, and he was on 50 mgm. daily. By 27th February the lepromin reaction was 1 plus, the lesions showed some subsidence, and he was able to walk without discomfort.

(4) Female, aet. 27 years; referred by U.M.C.A. Hospital at Manda, where she began treatment in July, 1955 with twice weekly DDS, at that time having scattered tuberculoid macules. By October she was getting 200 mgm. of DDS twice weekly, the

macules were not anaesthetic, but there was anaethesia of fingers and enlargement of the right ulnar nerve. A tuberculoid reaction developed in February, 1956 and she was admitted to Makete. At that time she had gross oedema of the right hand, with several enlarged cutaneous nerves in the right forearm and hand. The skin smears were positive, averaging 2.4. She was put on thiosemicarbazone. In August the operation of stripping the right ulnar nerve was carried out by Mr. W. A. A. Hodges, at which time the condition of the nerve was not acute. By February, 1957 the reaction had subsided completely, and DDS was begun. There was mobile right claw hand ,and the patient reports an improvement in the palsy since before the operation. Massage and exercises were instituted since the oedema subsided.

(5) Male, aet. 27 years. Referred by Native Authority Leprosy Clinic as a major tuberculoid treated by 100 mgm. of DDS for 1 month only, when reaction developed. Admitted to Makete 14th March, 1956, he had right ulnar and both peroneals enlarged and tender and skin smears positive, averaging 1.2. On 21st August the left peroneal was still enlarged and tender, and was stripped. On 25th August the right ulnar was stripped and transplanted. There was slight wasting of the right interossei. Both operations were by Mr. W. A. A. Hodges. By 20th February, 1957 the skin lesions had resolved, equal power existed in both feet, and there was no increase in palsy of right hand. DDS was begun.

(6) Female ,aet. 19 years. Referred by U.M.C.A. Hospital, Manda. In January, 1956 had been lepromatous, macular on trunk, infiltrative on nose and left ear, and was given 100 mgm. of DDS twice weekly. She lapsed from attendance in March, while having 300 mgm. of DDS twice weekly, and reported again in April, having had a reaction at home. She was admitted to Makete on 22nd May, with atypical leproma, and desquamation from the macules on the trunk and diffuse infiltration of extensor surfaces of the limbs. She had small nodules on the ears, thinned eyebrows, infiltration of forehead and nose, and ulceration of the nose. The right ulnar nerve was much enlarged, left also enlarged, both tender. There was early mobile right claw hand. The peroneal nerves were enlarged and tender. Skin smears were 4 plus. Thiosemicarbazone was begun and massage to right hand. By 22nd February, 1957 there was excellent resolution, the claw hand completely recovered, nerve trunks all normal, without tenderness. The skin smears were now positive, averaging 0.6. DDS was begun.

Summary of Treatment

1. The dosage of thiosemicarbazone given is:—50 mgm. daily on 6 days per week for 2 weeks, then 100 mgm. for 2 weeks, and then 150 mgm. daily. On this regime no toxic manifestations have occurred.

2. When the reaction has subsided, as evidenced by the flattening of the raised, succulent lesions and the disappearance of nerve tenderness, TB1 is stopped and DDS given. This stage is usually reached after 6 months to one year.

3. The treatment of incipient palsies is of great importance. The surgical removal of the nerve sheath, with transplantation in the case of the ulnar nerve, is of value in the acute phase, but mainly as a means of relieving pain. Evidence that it actually prevents the development of paralysis is equivocal, though it is certain that no case with early palsy becomes worse after operation.

4. Simple massage and exercises to keep the fingers mobile are essential. A useful adjunct to these measures is a Bunnell knuckle-duster splint.

5. Concomitant infections, intestinal parasites, etc. are treated as a matter of course. The patient is kept under careful observation both as regards his general health and his response to specific therapy.

Summary

A brief resume of previous work on the use of thiosemicarbazone in leprosy is given and the evidence that it has an effect superior to that of sulphone in the neuritis of leprosy particularly noted. Attention is drawn to the dangers of sulphone therapy in cases of atypical tuberculoid and borderline leprosy, the diagnostic features of which are described. The value of thiosemicarbazone, given under close medical supervision in a leprosarium, in such cases is emphasised and illustrated by some case histories. A summary of the regimen of treatment, including a brief note on the place of surgery and simple physiotherapy is given.

My thanks are due to Mr. W. A. A. Hodges, District Medical Officer, Mbeya, who has operated on a number of these cases, to Dr. Hay of the U.M.C.A., who has referred cases of this type for admission to this leprosarium and to the Hon. the Director of Medical Services, Tanganyika, for permission to publish.

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SOME DATA ON THE INFLUENCE OF BCG VACCINATION IN LEPROSY PATIENTS

J. VAN DE HEYNING, M.D.,
St. Joseph Ziekenhuis, Heerlen, Holland.

Cases of leprosy were studied at Wafania, Congo Belge Firstly, 300 cases were submitted to the lepromin test by Wade's technique, and the late or Mitsuda Reaction read at 21 days. An area of reaction of 6 mm. or more was read as positive, of 2 mm. or less as negative, and 3, 4 and 5mm. as doubtful. The results were:—

Lepromatous			*Indeterminate*			*Tuberculoid*		
+	−	±	+	−	±	+	−	±
2	112	6	23	41	22	59	22	21

Next, the Mantoux Test was carried out in cases which had shown a negative Mitsuda. The Mantoux was done with 1/10 of 1% Tuberculin. The results were:—

Lepromatous		*Indeterminate*		*Tuberculoid*	
Strongly Positive	Negative or Slightly Positive	Strongly Positive	Negative or Slightly Positive	Strongly Positive	Negative or Slightly Positive
32	44	6	21	1	14

Thirdly, BCG vaccination was given in the Mantoux-negative and slightly positive cases, and two months later a second Mitsuda reading was made. The results were:—

Lepromatous			*Indeterminate*			*Tuberculoid*		
+	−	±	+	−	±	+	−	±
4	31	9	5	3	13	8	0	6

The results show that BCG has little influence on the Mitsuda status of the lepromatous type of leprosy, but there is a favourable modification in the tuberculoid type, for 8 cases out of 14 became positive. There is a difficulty in that the lepromatous patients who have the graver prognosis, are frequently Mantoux-positive. (32 out of 76 cases in this series), which prevents the BCG vaccination being done.

ABSTRACTS

Electron Microscopy of the Leprosy Bacillus: A Study of Submicroscopical Structure, by **E. M. Brieger** and **Audrey M. Glauert.** Tubercle, The Journal of the British Tuberculosis Association, 1956, **37**, 195-206.

Dr. C. Becker and Dr. R. G. Cochrane helped Dr. Brieger to obtain tissue juices, rich in bacilli, from 6 lepromatous patients. Material was also obtained by punch biopsy from 2 macular cases and 1 tuberculoid, but this did not prove suitable for electron miscroscopy. The tissue juices were obtained uncontaminated, using a special method developed by Dr. Becker, and further processed and transported, and finally viewed by a Siemen's electron microscope in the Cavendish Laboratory, Cambridge.

The leprosy bacillus frequently appeared as a filament in the electron microscope, containing irregular condensations, and some of the condensations appeared to be beaded. The filaments were usually curved and sometimes pairs of them lay at an angle to each other, or the filaments lay parallel. Also among the smaller inclusion bodies were short dense rods or small dense granules; the former were also seen free. Apart from the filaments a great variety of other forms were seen.

When longitudinal sections of the bacilli were viewed, in some the general pattern of density was similar to that in unsectioned bacilli, with a central transparent and vacuolated area and dense material at both ends, and in others there seemed to be random variations in density along their lengths. The leprosy bacillus was seen to possess a continuous cell wall. In sections through groups of bacilli, there was no limiting membrane to some groups, but others had a definite boundary composed of dense granular material, or even an unmistakable membrane. Sometimes the bacilli were embedded in a highly-vacuolated foamy material of granular texture often containing small dense bodies of various sizes.

Search was made for intracellular bacilli in the intact cells which were present in the juices. The nuclei of such cells were well preserved, but the cytoplasm seemed to have broken down into a mass of granular elements. The bacilli were found lying in vacuoles in this highly granular cytoplasm, and were usually very transparent, and the vacuoles were associated with dense granules of various sizes. If there were many vacuoles containing bacilli, a foamy structure was formed.

In their discussion, the authors mention that previous workers (Bishop, Suhrland and Carpenter in 1948 and Malfatti in 1952) also described leprosy bacilli as electron transparent filaments containing dense inclusions. These dense inclusions were often rod-shaped, which suggests the possibility that in the course of reproduction, rods are formed within the filaments and are later released when the filaments disintegrate. The authors also confirm the difference in morphology between *Mycobacteria leprae* and *M. tuberculosis*. The latter have a smoothness and regularity that is in noticeable contrast to the ragged and irregular leprosy bacilli, and the system of electron transparent areas which is believed to represent the nuclear apparatus is not so clearly defined in *M. leprae*. The pleomorphism of leprosy bacilli may or may not be due to degenerative processes; if not, it may mean that there is a complex life history. Granules or beads they think are more likely to be accumulations of dense material than to be regarded as spores. New information about globi has been provided by electron microscopy. There are colonies of densely packed bacilli which have no limiting membrane, and the individual bacilli appear to held together by an amorphous matrix; there are also groups of bacilli contained within a limiting membrane. It is impossible to deduce the nature of this membrane, but one cannot disregard the possibility that it is the cell membrane of a disintegrating leucocyte. It is impossible to judge whether the bacilli in the clumps are viable. As regards lepra or foamy cells, electron microscopy give some support to the view of Chaussinand (1950) that they are cells which have ingested bacilli and then become transformed into lepra cells. Foamy material was seen forming within the cytoplasm of a cell: many of the contained bacilli appeared empty and swollen, others remained dense.

The paper contains 15 illustrations of electron micrographs. The findings reported in the paper are only preliminary, but deserve careful study.

The Use of Biopsies in Therapeutic Trials in Leprosy. by **D. S. Ridley.** Trans. Roy. Soc. Trop. Med. & Hyg., 1957, March, Vol. 51, No. 2, 152-153.

Improvement under sulphones is faster clinically than in the bacterial index. The author suggests that the nature of the healing process is at the back of this. The healing process has two aspects, a resolution of portions of the granuloma together with included bacilli, and a reduction of the density of bacilli in the unresolved foci of the granuloma, leaving at last empty foamy cells. The

bacterial index measures the density of the bacilli in the granulomata, and takes little account of their size; clinical progress takes account of the diminution of lesions. The two methods of assessing progress are complementary to each other, but it cannot be expected that they will always agree. Serial biopsies of skin lesions, however, give information on both aspects of healing. It has been found in the past four years that they give a general picture of slow and steady progress under the sulphones. Punch biopsies were taken on 17 lepromatous patients under treatment, at intervals of 2 to 3 months. Progress was assessed every 6 months by taking the mean of 2 or 3 biopsy indices, and the results are given in 3 tables. It appears that in a group under sulphone treatment the disappearance of bacilli is an exponential function, the mean biopsy index being multiplied at regular intervals by a fraction which is constant throughout the period of treatment, irrespective of the severity of the infection. For Europeans, the mean rate of fall of the index was 25 per cent for each 6 months. Despite individual variations, quite small groups produced means close to the mean of the whole series. The system of serial biopsies should be useful in the planning of further therapeutic trials in leprosy, as it would be possible to use previously-treated subjects, and to obtain an answer from small numbers.