

SECONDARY INFECTIONS AND NEOPLASMS
IN LEPROSY PATIENTS

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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 poikiloderma 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

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

We think these cases are not exceptional; in other Spanish and foreign leproseries 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 Lavalley 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 streptococci 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 leptotic 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 Bjarnhjedinnsson, 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 leprosia 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 (micro-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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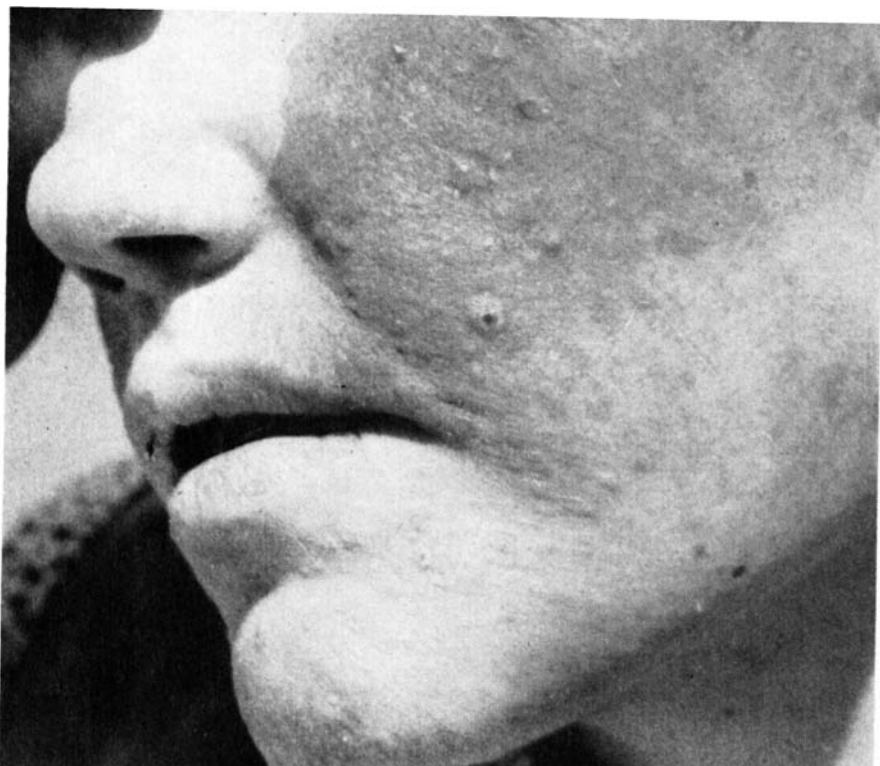
PHOTOGRAPH 1. Epithelioma and epidermodysplasia verruciforme, diagnosed mistakenly as leprosy.



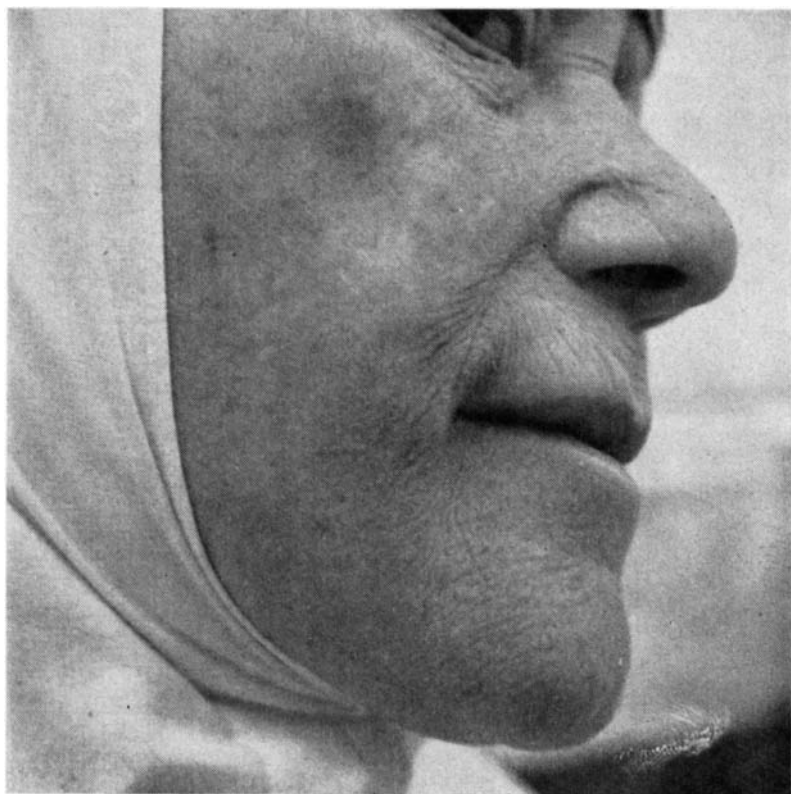
PHOTOGRAPH 2. Epithelioma and xeroderma pigmentosa, diagnosed mistakenly as leprosy.



PHOTOGRAPH 3. Epithelioma diagnosed mistakenly as leprosy.



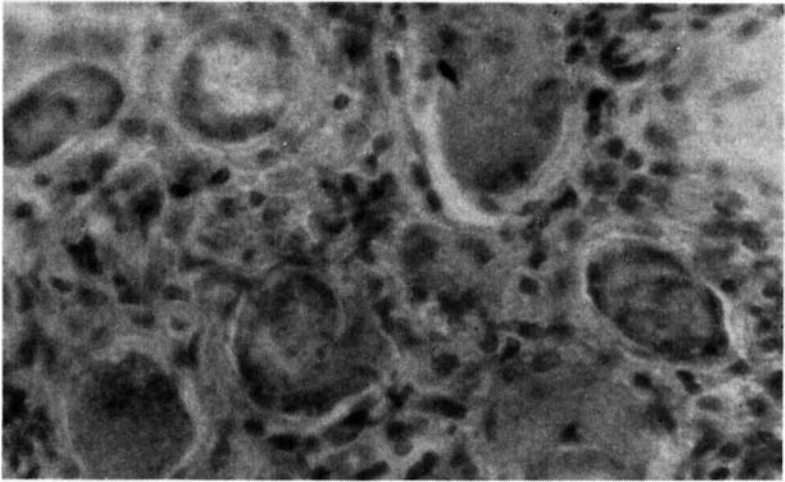
PHOTOGRAPH 4. Lepromas similar to lupomas even to positive vitropressure test.



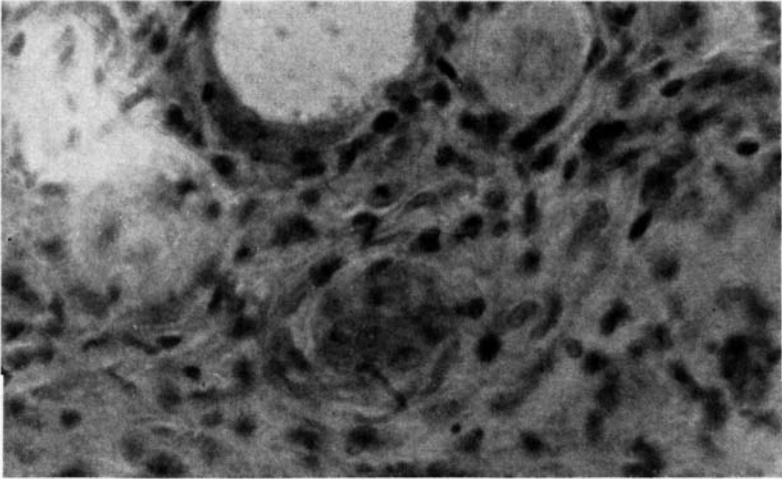
PHOTOGRAPH 5. Oriental Sore in a lepromatous female patient.



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.