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Histoid (High-resistance) Lepromatous Leprosy[1]

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Recent writers have drawn attention to a form of lepromatous leprosy designated "histoid" ([3]) or "resembling nodular subepidermal fibrosis ([2]). This type is not uncommon in Ethiopia; the present paper reports ten such cases collected over a period of six months. The clinical picture and effect of therapy, combined with a study of the histology, suggest that it is useful to maintain this type as a separate entity because the response to treatment is, in our experience, different from that of classic lepromatous leprosy. In Ethiopia time can certainly be saved by recognizing this at once.

Interest in the cases was aroused by the appearance of the gross nodulation (Fig. 1), and by the resistance to sulfone, thiambutosine (Ciba 1906), and sulfamethoxypyridazine (SMP, Lederkyn). The long-acting sulfonamide (n'-(5,6-dimethoxy-4-pyrimidinyl) sulfanilamide (sulforthomidine, Fanasil) produced a marked improvement, and later cases of this type were placed immediately on the drug. The range of response varied from rapid (Fig. 2), to slow; one of the ten did not improve.

MATERIAL

The present group of ten cases shows a continuous gradation between classic nodular leprosy, and the extreme histoid type where the pedunculated nodules on skin of normal appearance bear a resemblance to neurofibromatosis (Fig. 1). Three cases are presented on detail, with photographs and histology, and the rest are summarized.

All were Ethiopian, of either sex, aged between 10 and 40 years when first seen. The presenting symptom was always the gross appearance of the nodules on the face, with a history of long and unsuccessful treatment with sulfones. The patient asks for treatment because of the appearance, not for other reasons. The general condition was good and remained so during treatment.

The nodules were most numerous and pronounced on the face, where they tended to occur in clusters in the middle of the forehead, on the cheeks, at the tip of the nose, and on the chin (Fig. 2). Those on the lower part of the face were typically larger and more numerous than those on the upper part. The ears often showed little change, even when the face was grossly affected. The nodules appeared to arise deep in the corium, were of varying sizes, and grew at varying rates, so that actively growing nodules became tense and pedunculated, with shiny, stretched, overlying epidermis. Ulceration did not occur spontaneously, but could be provoked by hasty therapy.

A noticeable feature was the persistence of the eyebrows. Even when hairs were lost over a nodule, they usually grew again as the nodule receded (Fig. 1). The lips were affected, but the nasal mucosa showed much less involvement than would be expected, in comparison with the face, and no case showed destruction of the nasal

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cartilage, even after years of uncontrolled disease (Fig. 1). No case presented symptoms of laryngeal affection.

On the other parts of the body, the knees and elbows and outer aspects of the lower arms and legs were sometimes affected, but in these regions the eruption was compressed and flat, with epithelial thickening and scarring following damage to the surface. The buttocks characteristically showed a number of small, flat, hyperpigmented areas where the skin was thin and shiny, with intact epithelium, but pronounced skin markings. We learned later that this appearance follows healing of the nodules, a finding suggesting that the earliest lesions may, in fact, be on the buttocks.

HISTOPATHOLOGY

The histopathology of these cases is described in detail after the clinical notes. The following features are characteristic of the series:

1. A subepithelial clear zone, under thinned and flattened epithelium overlies the nodule; epithelium adjacent to the nodule is normal.

2. The typical nodule lies deep in the dermis and consists of densely-packed macrophages, all of which contain bacilli. Large nodules were divided into smaller ones by connective tissue septa.

3. The bacillary density is so marked in some peripheral areas as to give crimson spots on low power examination of stained sections. These areas also show the most marked foamy change.

4. The bacilli are large enough to be observed without the use of the oil immersion lens; some occur in globi.

5. The peripheral cells of a rapidly growing granulomatous nodule lie tangentially and give the impression of being stretched along its surface. Some of the central cells may be multinucleated and contain deformed and degenerate bacilli.

6. In cases in which the lesions are clinically pedunculated, the connective tissue adjacent to the nodule forms a capsule of collagen fibers from which the nodule may retract cleanly on shrinkage by the fixative. Nonpedunculated cases, as shown, for example, in Figure 3, do not show this demarcation.

7. The skin appendages are resistant to the granulomatous tissue, and may be seen perforating it without apparent damage.

8. The connective tissue between nodules contains small areas of looser granulomatous tissue similar to that seen in classic lepromatous leprosy.

9. Nerve tissue contains bacilli, but is not invaded by macrophages or other cells.

10. A few lymphocytes are present in the granulomatous mass, but other cells are usually absent. Plasma cells may appear in an active phase.

CLINICAL HISTORIES

The ten cases are summarized in Table 1. In eight cases the patients were male. Three are chosen for more detailed presentation.

Case 1. (Fig. 1). (Z.S.) male, aged 14 years. This patient had received sulfones, thiambutosine and sulfamethoxypyridazine successively during three years without clinical or bacteriologic improvement.

Histology.—A section of a nodule of the face was described by Dr. D. J. Harman of the Leprosy Study Centre, London, as follows:

"The epidermis shows some flattening of the rete pegs. The upper part of the dermis contains patches of infiltrate of varying size; some are fairly loose and spreading. Others, especially those deeper in the dermis, are quite dense, discrete masses. There is a zone of separation between infiltrate and basal layers of epidermis. The main part of the section, however, consists of large, almost encysted masses of infiltrate in the deep dermis. The infiltrating cells are histiocytes with some lymphocytes; many histiocytes show foamy change, and all contain innumerable bacilli. In the nodular areas there is active multiplication of organisms and some globi. In the center of the largest nodule there are some gross foamy giant cells, containing large masses of degenerating bacilli. Nerves are bacillated, but clear of any cellular involvement. Bacilli are also present in the endo-

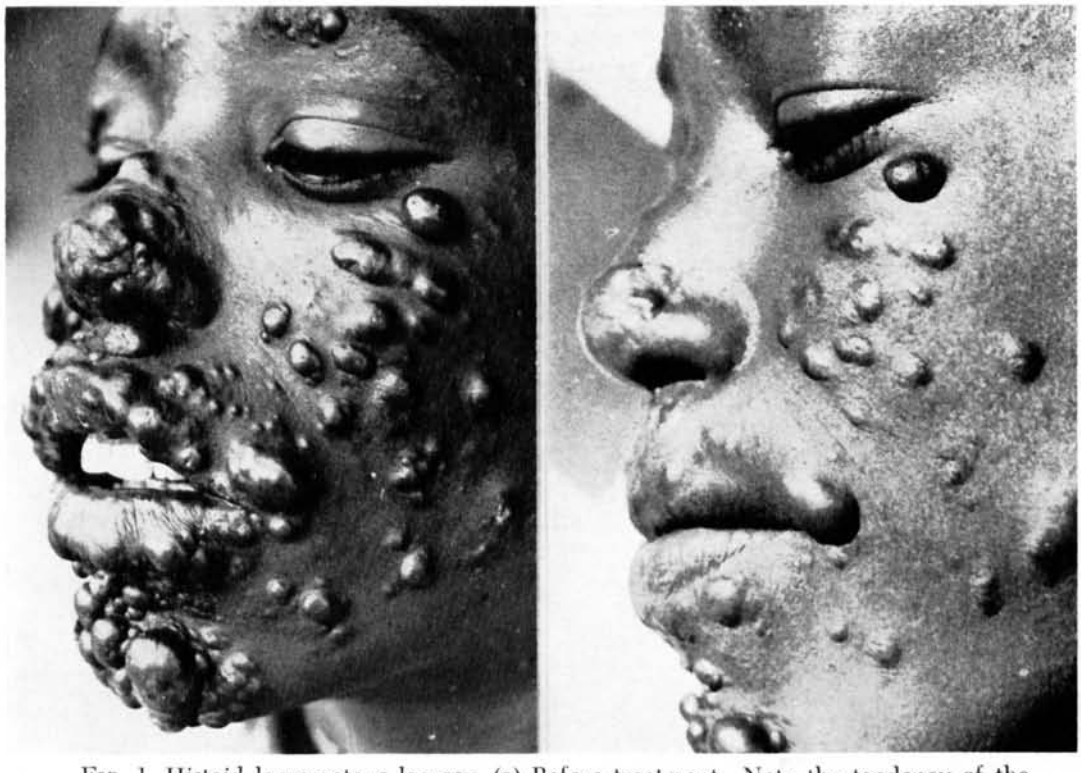

FIG. 1. Histoid lepromatous leprosy. (a) Before treatment. Note the tendency of the nodules to cluster in the middle of the forehead, tip of the nose, cheeks, and chin. The nodules push through the eyebrows. Bacteriology 5+. (b) After one year's treatment with sulforthomidine. Note the restoration of eyebrows over the nose, the absence of nasal destruction, and the integrity of the epithelium in spite of long-standing underlying nodulation. Bacteriology 2+.

thelial cells of many of the small blood vessels."

Bacteriology.—Smears from nodules for *M. leprae* gave the following results.

March	1965	5+
November	1965	3+
March	1966	2+

Treatment.—This began with 125 mgm. sulforthomidine weekly, and reached a maximum of 1 gm. weekly after two months, on which dose it has been maintained for one year.

Course.—The course has been uneventful. There was no ulceration of lesions or symptom of any sort during treatment. The present condition is shown in Figure 1b, where the integrity of the eyebrows, and the relatively small amount of scarring, especially on the nose, will be noted.

Case 2. (Fig. 2). (A.S.) female, aged 15 years. This patient had also received sulfones, thiambutosine and sulfamethoxypyridazine over a period of three years without clinical or bacteriologic improvement.

The first photograph was taken about ten days after the beginning of therapy with sulforthomidine. Early superficial ulceration can be seen on one nodule above the left eye. This was an indication for slowing down the rate of treatment to avoid permanent scarring. The improvement can be noted by comparing the shadow cast by the pedunculated masses on the forehead with the second photograph; both were taken with the sun at a similar elevation.

Histology.—This was reported by Dr. R. G. Cochrane before treatment.

"The subepidermal zone is relatively clear and broad. In the deeper parts of the

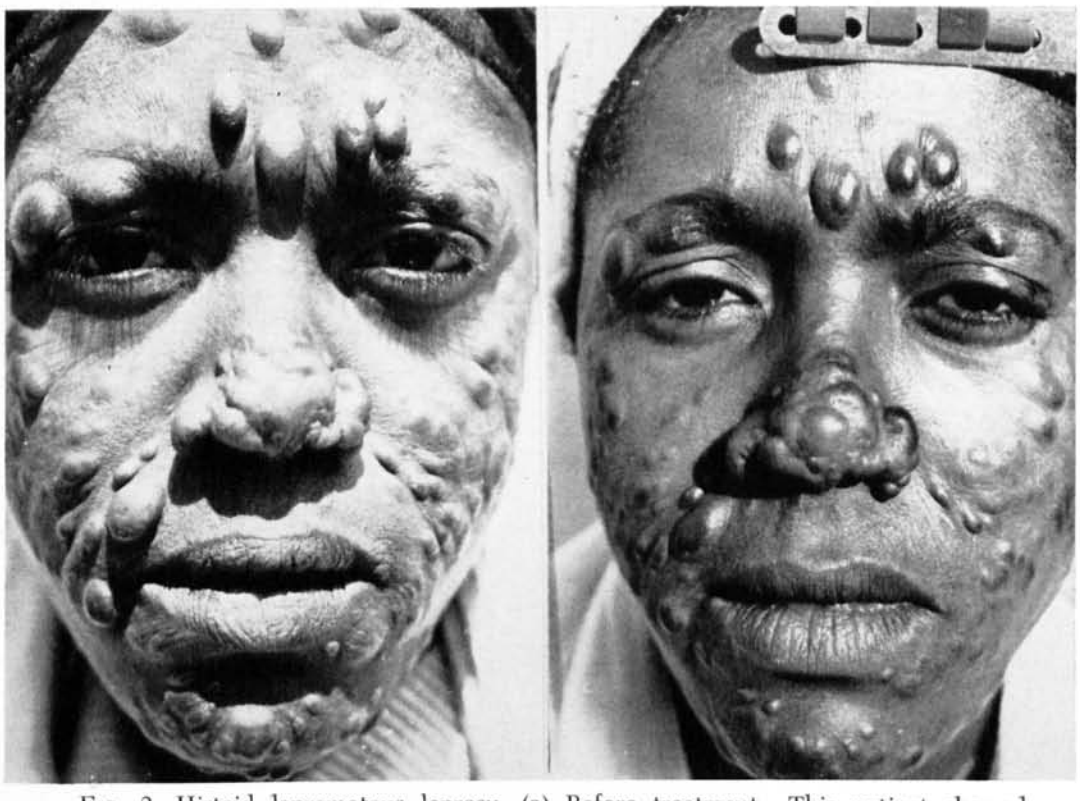

FIG. 2. Histoid lepromatous leprosy. (a) Before treatment. This patient showed gross nodulation, unchanged by prolonged treatment with sulfones, and unaffected by six months of thiambutosine and sulfamethoxypyridazine. Note the typical distribution, the pushing of the nodules through the eyebrows, and the superficial ulceration of one nodule over the left eye, due to treatment. Bacteriology 5+. (b) After nine months' treatment with sulforthomidine. There is no damage to the nasal cartilages. The eyebrows are returning where temporarily lost over nodules. Bacteriology 1+.

dermis there is a gross infiltration occupying 60%-70% of the corium. The masses are separated by collagen fibres. The infiltrate consists almost entirely of well-marked foamy cells, interspersed between with a considerable number of plasma cells. The lymphocytic response is not marked. Nerves are difficult to see, but where recognizable they are uninvolved. There are enormous numbers of acid-fast bacilli showing gross morphological change."

Bacteriology.—Smears from nodules for *M. leprae* gave the following results:

March	1965	5+
November	1965	2+
January	1966	1+

Treatment.—This was initiated with a weekly dose of 125 mgm. sulforthomidine. A maximum dose of 1,250 mgm. weekly was reached after 10 weeks, and was maintained during the period of observation (9 months).

Course.—This was uneventful. Slight ulceration occurred in one nodule. The clustering of nodules on the forehead, tip of the nose, cheeks and chin is more readily evident in the later than in the earlier photograph. The eyebrows still survive quite severe involvement in the nodules, and there is no destruction of nasal cartilage in spite of prolonged, gross involvement of the skin of the nose.

Case 3. (Fig. 3). (A.H.) male, aged 28 years. This case differs from the two previous ones in the absence of involvement of the tip of the nose. The nodules were not pedunculated, and the adjacent skin was normal in appearance. The large nod-

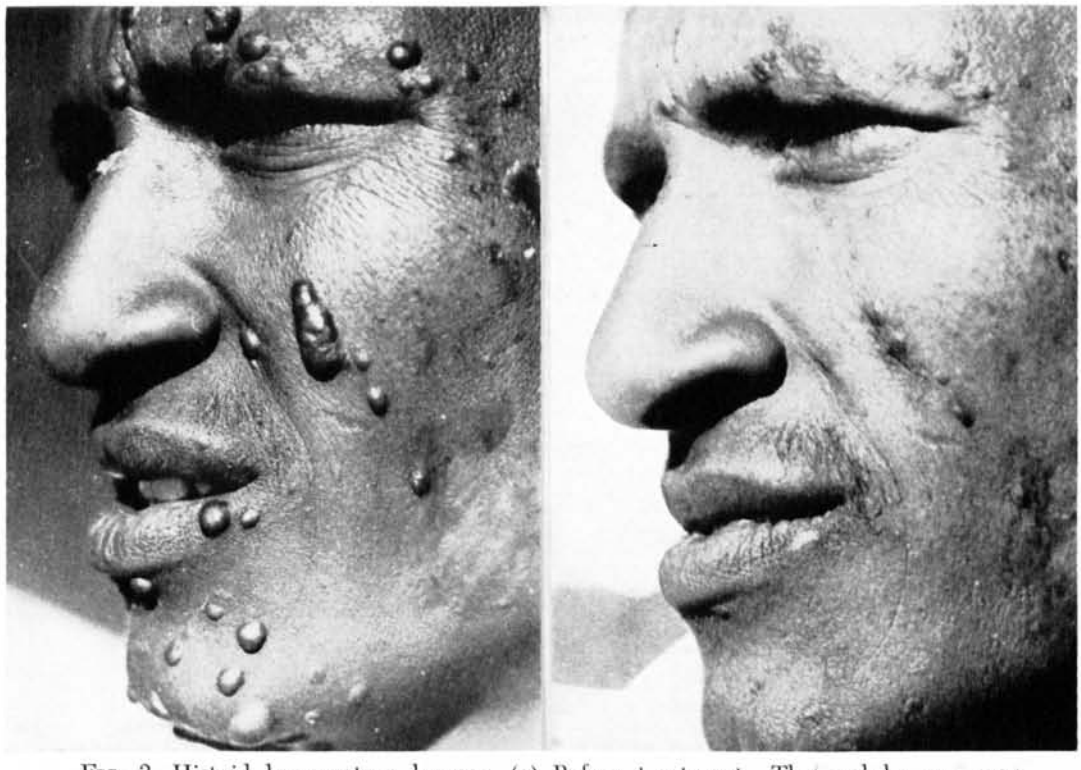

FIG. 3. Histoid lepromatous leprosy. (a) Before treatment. The nodules are more diffuse, and avoid the tip of the nose; one on the cheek, and two above one eye, are ulcerated in response to treatment. This patient received sulforthomidine as initial treatment. Bacteriology 4+. (b) After nine months' treatment with sulforthomidine. The rapid resolution (bacteriology negative) shows pigmented scarring of nodules, which ulcerated as a result of treatment, compared to those that resolved without ulceration.

ule on the cheek ulcerated rather deeply at the beginning of treatment; the resultant hyperpigmented scar can be seen in Figure 3b. The eyebrows are at present lost, but may grow again in the near future.

Histology.—The histology is that summarized earlier. The nodules are not pedunculated, and the granulomatous masses are not clearly separated from the surrounding tissue by collagenous fibers. However, the more superficial histiocytes are spindle-shaped and lie lengthways along the edge of the masses. Skin appendages pierce the granulomatous masses without apparent involvement.

The section was examined by Dr. C. K. Job (Schieffelin Research Sanatorium, Karigiri, India), who reported that it corresponded to "Wade's histoid type of lepromatous leprosy."

Bacteriology.—Smears from nodules for *M. leprae* gave the following results.

March 1965 4+
January 1966 neg. (1st time)

Treatment.—This began with sulforthomidine, 125 mgm. weekly, and rose to a maximum dose of 1,250 mgm. weekly after ten weeks, and continued at this dose for nine months.

Course.—This was uneventful. The nodules shrank rapidly under treatment, and some came off in dry flakes. Slower treatment would have resulted in less scarring of the face. Note that nodules that diminish without ulceration leave unpigmented and only slight scarring.

SPECIFIC THERAPY

The early cases of the series had been treated without success for periods varying

from one to five years, by one or more of the following drugs: sulfones, thiambutosine (Ciba 1906), sulfamethoxypyridazine (Lederkyn) and ditophal (Etisul). The later cases were treated immediately with sulforthomidine, given in single weekly doses by mouth. The preparation used was Fanasil, produced by Roche of Switzerland.

The first indication that the latter drug is active, is swelling, followed by superficial ulceration of a number of lesions. This may occur as early as two weeks after the beginning of therapy. It was soon found that energetic ulceration of this sort is undesirable; the patient becomes pyrexic and feels unwell, and the swelling of the lesion is uncomfortable. The following modified regimen was therefore adopted, and used for all later cases:

> 1st two weeks—125 mgm. weekly
> 2nd two weeks—250 mgm. weekly, increasing by 125 mgm, each two weeks, until a maximum dose (for an adult) of 1,250 mgm. weekly was reached. This was then maintained as the standard dose, and given once weekly.

Experience shows that the best cosmetic results are obtained by increasing the dose of sulforthomidine slowly until one, or a few, nodules show slight superficial desquamation, and then maintaining this dose until the ulceration resolves. After that the dose is slowly increased. The patient illustrated in Figure 2 shows this effect on one nodule over the left eyebrow. The patient illustrated in Figure 3 was treated too vigorously at first, and several nodules ulcerated sufficiently to cause residual hyperpigmented scarring (Fig. 3b). This patient also shows that healing without ulceration gives minimal scarring without pigmentation.

Each patient was, therefore, treated individually, with notation of the effects of treatment, especially during the first few weeks of treatment. No patient showed albuminuria or jaundice.

Results. Of the ten cases under treatment

TABLE 1. *Summary of data on ten patients treated by sulforthomidine.*

Name	Sex	Age	Began treatment	Bacteriology		Effect on nodules	Complications	Maximum weekly dose (in mgm.)
				At start	At end (9-12 mos.)			
M.A.	M	16	Dec. '64	5+	3+	Flattening and scarring	None	1,000
G.T.	M	18	Dec. '64	3+	2+	No improvement	Joint pains	1,250
G.H.	M	15	Dec. '64	5+	1+	Considerable diminution	ENL twice	1,000, then 250
A.S.	F	16	Dec. '64	5+	1+	Considerable diminution (Fig. 2)	None	1,250
Z.S.	M	14	Mar. '65	5+	2+	Considerable diminution (Fig. 1)	None	1,000
Z.M.	M	30	Mar. '65	4+	3+	Considerable diminution	None	1,500
J.A.	F	24	Mar. '65	4+	1+	Considerable diminution	None	1,500
A.H.	M	25	Mar. '65	4+	Neg.	Considerable diminution (Fig. 3)	None	1,250
G.B.	M	15	Apr. '65	5+	4+	Slight improvement	None	1,250
S. J.	M	21	Jul. '65	4+	3+	Early ulceration	Repeated ulceration of nodules	1,000, then 250

with sulforthomidine seven showed notable diminution of the nodules, which was the more remarkable because of the lack of response to sulfones, thiambutosine and sulfamethoxypyridazine. One of the patients developed erythema nodosum leprosum during treatment, but this resolved without the need to stop treatment. There were no other complaints by the patients.

One patient showed only slight improvement. One showed severe ulceration of the lesions and treatment was abandoned, though, on reflection, much smaller doses might have been effective. One patient showed no improvement at all over a period of one year, though the bacteriology score decreased from 3+ to 2+, but the patient complained of frequent joint pains, and treatment was stopped.

DISCUSSION

There is a commendable reluctance on the part of workers to describe different clinical manifesations of lepromatous leprosy by different names. In the present series it was found useful to recognize early that cases that came into the present category were unlikely to respond to sulfones, thiambutosine or sulfamethoxypyridazine, and that it was wise to begin treatment with sulforthomidine. Wade, in his original description, remarked on the resistance of these patients to treatment. The pronounced collagenous reaction suggests that the group reflects a similar cellular response of the body. While this may not define a different disease entity, it may yet delineate a biochemical entity, such as a specific enzyme series of the macrophage lysosomes. This also occurs in the nonspecific condition known as "nodular subepidermal fibrosis" (1).

Pathologically, it can be described as a type of lepromatous reaction in which the granulomatous masses are dense and deep in the dermis, and separated from adjacent tissue by collagenous fibers, so that, clinically, the nodules may be pedunculated. The adjacent skin is remarkable for its relative freedom from involvement in the presence of gross pathology close by.

SUMMARY

Ten cases of lepromatous leprosy of histoid nature are described, with special features that delineate a clinical type.

Characteristic features include gross nodulation, mainly of the face, deep involvement of the dermis, sparing eyebrows and the nasal cartilages, and resistance to treatment by sulfones and thiambutosine.

A satisfactory response to treatment was obtained in seven cases, using sulforthomidine. It is suggested that this type marks a specific response that might be indicated as "high-resistance" lepromatous.

RESUMEN

Se describen diez casos de lepra de naturaleza histioide, con características especiales que establecen un tipo clínico.

Los rasgos característicos incluyen gruesas nodulaciones principalmente de la cara, con compromiso profundo del dermis, destrucción escaza de las cejas y de los cartílagos nasales y resistencia al tratamiento a base de sulfonas y thiambutosine.

Se obtuvo una respuesta satisfactoria al tratamiento en siete casos, cuando se usó sulforthomidine. Se sugiere que este tipo de lepra es una respuesta específica que podría ser catalogada como "alta resistencia lepromatosa."

RÉSUMÉ

Dix cas de lèpre lépromateuse, de nature histoïde, sont décrits, avec les caractéristiques spéciales qui définissent ce type clinique.

Les caractéristiques particulières comprennent l'existence de gros nodules, surtout sur le visage, l'atteinte profonde du derme, le fait que les sourcils et les cartilages du nez sont épargnés, et la résistance au traitement par les sulfones et par la thiambutosine.

Chez sept de ces cas, une réponse thérapeutique satisfaisante a été obtenue avec la sulforthomidine. On émet la suggestion que ce type dénote une réponse spécifique, qui pourrait être considérée comme lépromateuse "avec résistance élevée."

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REFERENCES

1. KLAUS, S. N. and WINKELMANN, R. K. The enzyme histochemistry of nodular subepidermal fibrosis. British J. Dermat. **78** (1966) 398-402.
2. SANCHEZ, J. Lepromatous leprosy with lesions resembling nodular subepidermal fibrosis. Internat. J. Leprosy **33** (1965) 179-185.
3. WADE, H. W. The histoid variety of lepromatous leprosy. Internat. J. Leprosy **31** (1963) 129-142.