His toid (High-resistance) Lepromatous Leprosy

E. W. Price and M. Fitzherbert

Recent writers have drawn attention to a form of lepromatous leprosy designated “histoid” (*) 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, thiamphenicol (Ciba 1906), and sulfamethoxypyridazine (SMP, Lederlyn). 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 in 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 symp-
toms 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 af-
tected, but in these regions the eruption
was compressed and flat, with epithelial
thickening and scarring following damage
to the surface. The buttocks characteris-
tically showed a number of small, flat, hy-
perpigmented 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 de-
scribed 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
odule 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
tissue 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 im-
mersion lens; some occur in globi.

5. The peripheral cells of a rapidly
growing granulomatous nodule lie tangen-
tially 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 clin-
ically pronounced, the connective tissue
adjacent to the nodule forms a capsule of
collagen fibers from which the nodule may
retract cleanly on shrinkage by the fia-
tive. Noncalculated 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
penetrating it without apparent damage.

8. The connective tissue between nod-
ules contains small areas of looser granu-
lonomatous 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 ap-
ppear 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 presen-
tation.

Case 1. (Fig. 1). (Z.S.) male, aged 14
years. This patient had received sulpha-
thionulose and sulfamethoxydiazine
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 Leprax Study Centre, London, as fol-
lovs:

"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 der-
mis, 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 cen-
ter 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 involve-
ment. Bacilli are also present in the endo-
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 sulforthionine. 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+.

Histioi.
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. sulforothomidine. 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 sulfathomidine as initial treatment. Bacteriology 4+. (b) After nine months' treatment with sulfathomidine.

The rapid resolution (bacteriology negative) shows pigmented scarring of nodules, which ulcerated as a result of treatment, compared to those that resolved without ulceration.

dle 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 (Schöpfelin 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 sulfathomidine, 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, thiambutone (Ciba 1960), sulfamethoxypyridazine (Ledercyn) and ditophal (Eitsul). The later cases were treated immediately with sulfathiazinone, given in single weekly doses by mouth. The preparation used was Fansil, 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 congestive 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 sulfathiazinone 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

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

\[\text{Table I. Summary of data on ten patients treated by sulfathiazinone.}\]
with sulforthomidine seven showed notable diminution of the nodules, which was the more remarkable because of the lack of response to sulfones, thiambutoxine and sulamethoxypridazine. One of the patients developed erythema nodosum lepromatous 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 manifestations 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, thiambutoxine or sulamethoxypridazine, 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 non-specific condition known as "nodular sub-epidermal 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 thiambutoxine.

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 histoida, con características especiales que establecen un tipo clínico.

Los rasgos característicos incluyen grosse nodulaciones principalmente de la cara, con compromiso profundo del dermis, destrucción escueza de las cejas y de los cartilagios nasales y resistencia al tratamiento a base de sulfonas y thiambutoxine.

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."

RESUME

Dix cas de leprie lepromateuse, de nature histoida, sont décrits, avec les caractéristiques spéciales qui définissent ce type clinique.

Les caractéristiques particulières comprennent l'existence de gros nодules, 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 thiambutoxine.

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 lepromatense "avec résistance élevée."

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**REFERENCES**

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