

REACTION OF THE DERMIS IN LEPROSY¹

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Leprosy, whether tuberculoid or lepromatous, early or late, infiltrates the skin with the formation of circumscribed granulomatous foci which spread when the infection is active and regress when it is treated successfully. Histologically these foci are also the principal sites of lepra reactions. The various forms of granuloma have been described repeatedly, but the reaction of the dermis itself to the infective or reactional processes has received little consideration, although Richter (4) and the earlier German authors have studied the dermis in erythema nodosum leprosum (ENL). The primary importance of the granulomatous masses of infective material is undisputed, but the dermis around them provides some useful indications of the state of the infection, and of activity or regression, reaction or quiescence, which we thought deserved a more nearly complete account than has yet been given. Consideration of the reaction of the dermis to the reactions of leprosy, furthermore, raises the question whether the latter are not to some extent reactions against the tissue of the dermis.

MATERIALS AND METHODS

Many skin biopsies of untreated leprosy of all types have been made. Follow-up biopsies at six month intervals during treatment have been performed in the majority of cases. We have received biopsy specimens of reactions in lepromatous, borderline and tuberculoid leprosy, and of exacerbations and relapses, both in the early and the late stages. This material has come from the Jordan Hospital, Redhill, in England and from the Sungei Buloh Settlement in Malaya. Specimens were fixed in a modified "FMA" mixture (40% formaldehyde, 10 cc.; mercuric chloride 2 gm.; glacial acetic acid, 3 cc.; and water to 100 cc.) After two hours the specimen is transferred to 70% alcohol and dispatched to the laboratory. This fixative was used in preference to Zenker or FMA of Lowy (1), because of its better preservation of collagen and enhanced nuclear staining properties. Sections were stained as a routine by hematoxylin and eosin, and for acid-fast bacilli (1). On occasion the following stains were employed: van Gieson's, Mallory's stain for connective tissue, Verhoeff's for elastic tissue and Gomori's for reticulin; also in some cases, when formalin-fixed tissue was available: oil red, a modified Bielschowsky stain (6) and a modified Weil-Davenport stain for metallophil cells (2). Formalin fixation was not satisfactory for the study of collagen and elastic tissue.

The leprosy biopsies were compared from the point of view of dermal reactions with sections of many other dermatologic abnormalities, especially those involving mycobacteria, epithelioid cell granulomata, and conditions in which hypersensitivity or foreign-body reactions were known to play a part.

Biopsies were made of lepromin and of normal skin extract reactions in tuberculoid leprosy patients. In addition lesions induced by the injection of human leprosy bacilli into monkeys (3) were reexamined from the point of view of the dermis.

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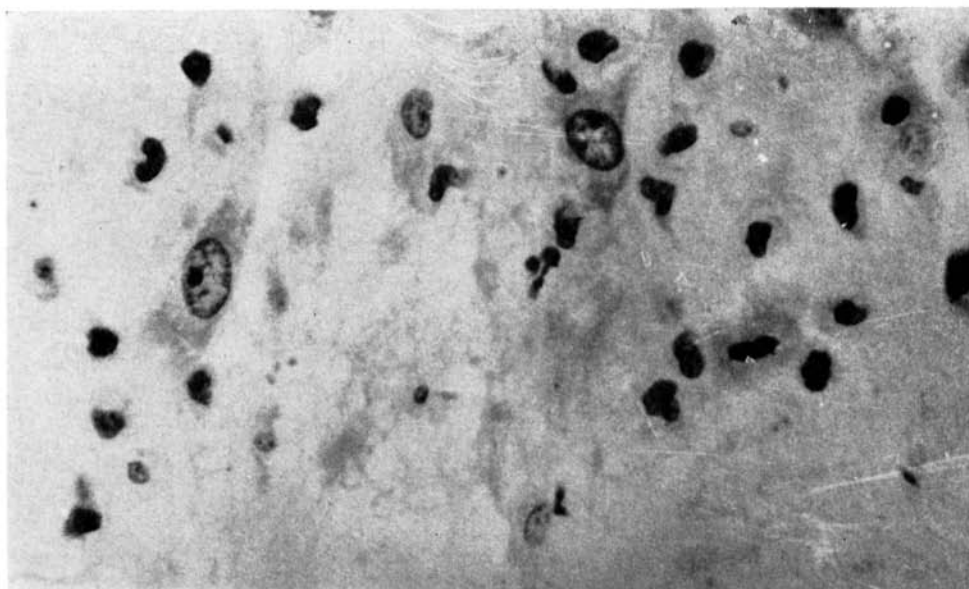


FIG. 1.—A number of small dark histiocytes, with two large pale histiocytes, and two exceptionally large primitive cells (720 \times). The sections corresponding to this figure and subsequent figures, unless otherwise stated, were stained with hematoxylin and eosin.

CHARACTERISTICS OF DERMAL REACTION

There are a number of characteristic patterns of reaction in the dermis, which are the same for all types of leprosy.

Cellular infiltration in the dermis is usually due to histiocytes, of which two types may be distinguished: those with large pale nuclei and others with smaller darker nuclei. The "pale histiocytes" are the more active and undifferentiated, being closely related to mesenchymal cells. The "dark histiocytes" are the wandering cells; whether they are resting or amoeboid cannot be determined in routine histologic preparations. (Fig. 1)

Fibroblastic and fibrocytic activity is often apparent in association with histiocyte infiltration. The pale histiocytes usually infiltrate widely through the substance of the collagen bundles of the dermis, and readily become transformed into fibroblasts. As a result of the two processes the influx of pale histiocytes is usually followed by disruption of the normal collagen pattern and its replacement by broad sweeping bundles of new collagen. This will be referred to as "fibroblastic activity" (See Fig. 11). Later the normal collagen pattern is reestablished. This is seen only in reactional states.

The dark histiocytes usually infiltrate the dermis around the periphery of a granulomatous mass in the interfascicular spaces of collagen. Sometimes, but not always, this infiltration is associated with a proliferation of the dermal fibrocytes in the interfascicular spaces, and slight swelling of the elastic fibers, which become more eosinophilic.



FIG. 2.—Active spread in a small superficial leproma causing local damage to elastic fibers (170 X).

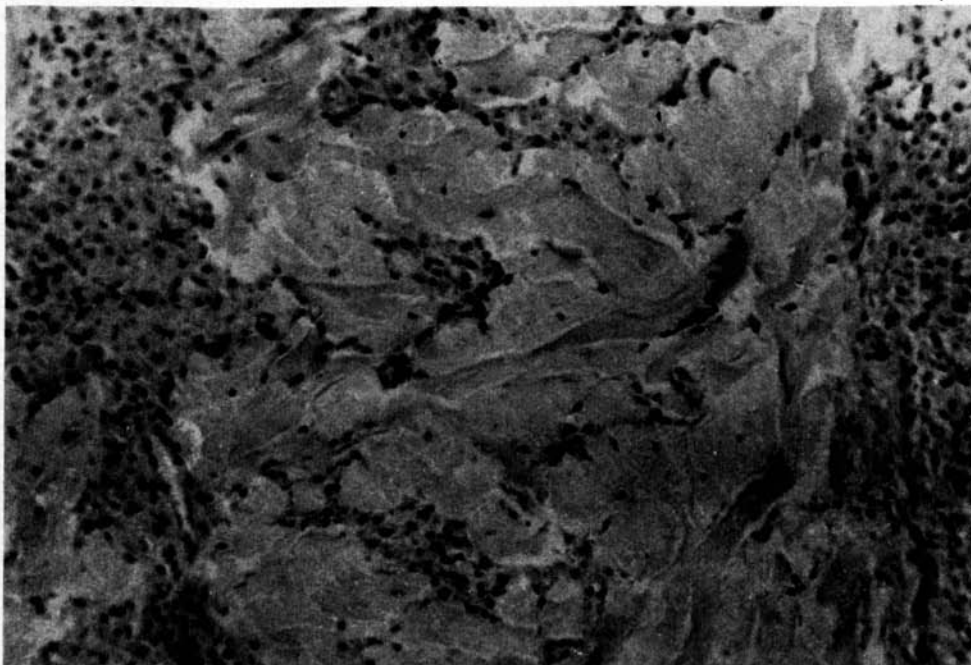


FIG. 3.—Active spread of an advanced leproma (170 X). There is infiltration between collagen bundles leading to the formation of new foci. Fibrocytic activity is minimal.

As a result, the planes between the collagen bundles are emphasized to give a "crazy-paving" effect, which will be referred to as "fibrocytic activity" (See Fig. 4).

The infiltration of dark histiocytes around a granuloma indicates its expansion. It does not indicate a reactional state.

Fibrosis may occur around the periphery of a granuloma and spread inward; this leads to destruction of the granuloma and repair of the dermis.

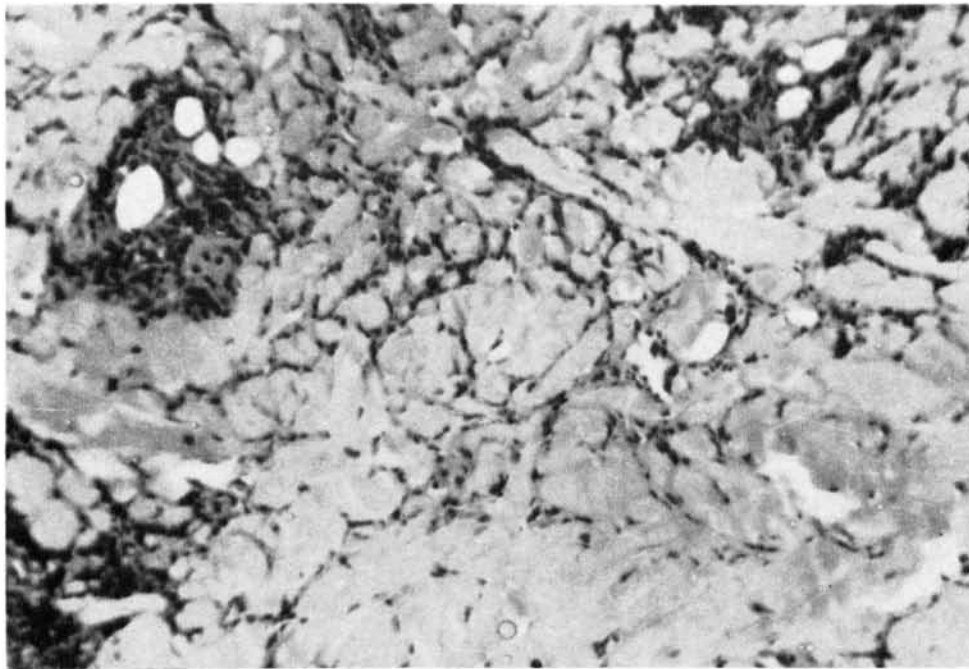


FIG. 4.—Active spread of borderline leprosy associated with much fibrocytic activity (170 \times).

Disruption of collagen is seen only in severe reactions. It takes the form of widespread fraying of fibers due to edema, and small localized patches of fibrinoid necrosis within the granuloma. In actively spreading lesions the collagen between the granulomatous masses shows signs of atrophy due to compression; it appears to be homogenized and eosinophilic. In general, collagen disease is not a feature of leprosy.

Disruption of elastic fibers is of frequent occurrence. Usually the affected fibers are fragmented and swollen; occasionally they are fine and granular. The disruption may be due to edema or to infiltration by histiocytes. It is severe and generalized in reactions and mild, localized and superficial around a spreading granuloma. It should not be confused in elderly patients with elastosis senilis.

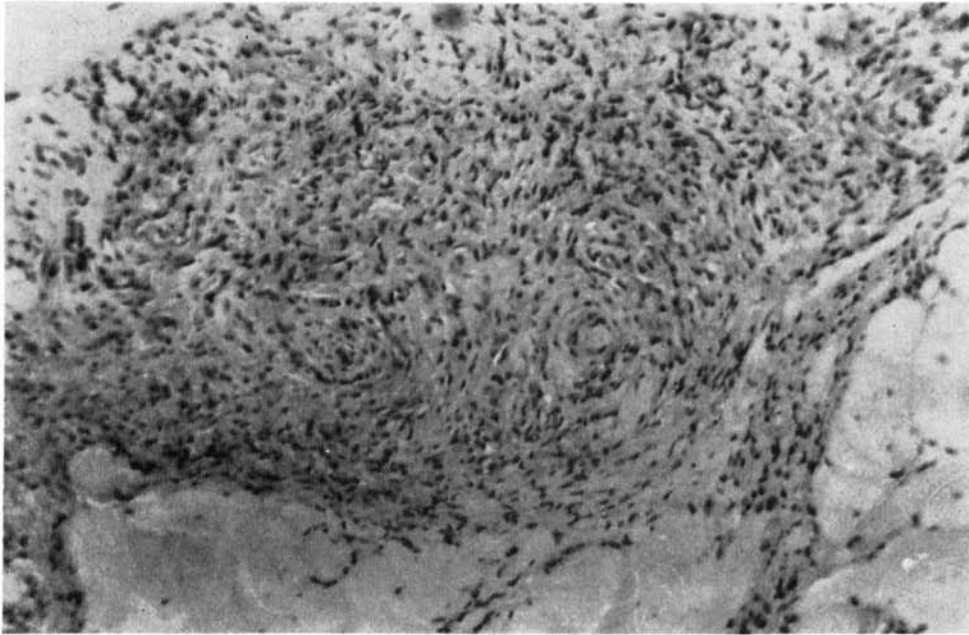


FIG. 5.—Relapse (due to drug resistance) in an early phase of a healing leproma (170 \times). The granuloma shows fibrocytic infiltration. Its edge is becoming irregular because of outward spread between collagen bundles.

Edema is a prominent feature of all severe reactional states. It is almost indicative of a reaction when it is located chiefly in the superficial layer of the dermis, or an incipient reaction when it is found in and immediately around the granuloma.

SPECIAL FEATURES IN DIFFERENT PHASES

The following descriptions of activity and regression in leprosy emphasize the state of the dermis in each phase of the infection. Reference is made to the condition of the granuloma only on occasion. No attempt is made to give a full account of reactional states or their classification, the object being rather to emphasize their points in common.

Evolution of infection.—The earliest histologic manifestation of the infection in all types of leprosy is an increased fibrocytic activity in small areas of the dermis. Usually it is located in the superficial dermis, following the course of the blood, lymph and nerve channels. Frequently there is some mixed cellular exudate around the pilosebaceous apparatus. Small dark histiocytes are seen among the fibrocytes. With the progression of the disease, the area of fibrocytic activity is gradually replaced by a growing histiocytic granuloma that has all the characteristics of a leprosy focus, tuberculoid or lepromatous.

Spread of infection.—Fibrocytes and small dark histiocytes, seen now at the periphery of the spreading granuloma, infiltrate slightly in

advance of it between the collagen bundles. Elastic tissue shows signs of degeneration (Fig. 2). When a granuloma is small and superficial this may be the best indication of activity. But there is no edema in the dermis. In the most actively spreading granuloma, whatever its type, the granulomatous masses assume an irregular outline. Small newly formed foci appear a short distance from the granuloma, especially in the lepromatous form, and connected to it by radiating fibrocytic activity (Fig. 3). In borderline and tuberculoid leprosy the development of satellite foci is less marked, but often there is a considerable proliferation of histiocytes around the granuloma, and sometimes extensive fibrocytic activity (Fig. 4).

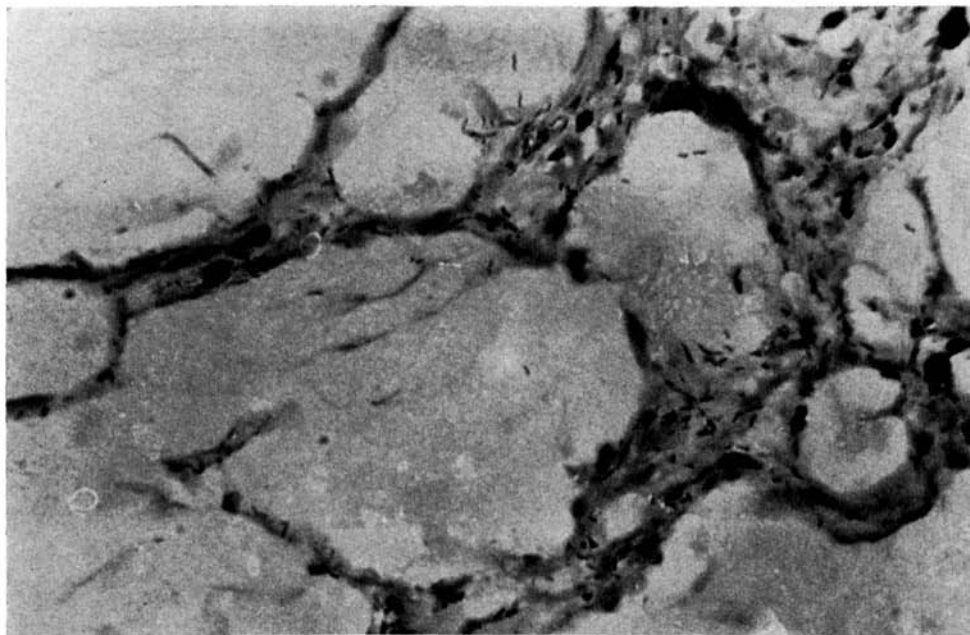


FIG. 6.—Highpower view of Fig. 5 after staining for bacilli. Spreading edge with penetration between collagen bundles.

The active granuloma is cytologically typical according to its classification. In lepromatous leprosy Virchow cells have healthy nuclei and there is an influx of pale histiocytes. Phagocytosis is predominant. There is no edema.

There is only an approximate correlation between the numbers of solid-staining bacilli and the degree of histologic activity of the granuloma. Cellular activity and solid bacillary forms are both present as a rule in untreated leprosy. Histologic evidence of activity usually begins to decline after about three months of treatment. Thereafter it recurs intermittently in individual lesions, in which nearly all bacilli may be granular. The significance of this cellular activity is not clear,

but it accounts for many of the fluctuations in the biopsy index (⁵) during treatment.

The description given above for an actively spreading granuloma applies to the common type of spread by infiltration. There is, however, another type of activity, seen occasionally when lepromatous nodules appear to expand by multiplication of their constituent macrophages, which are heavily loaded with bacilli. The nodule has a tumor-like appearance. Then there is no infiltration at the periphery, but rather a compression of fibrous tissue producing a false capsule.

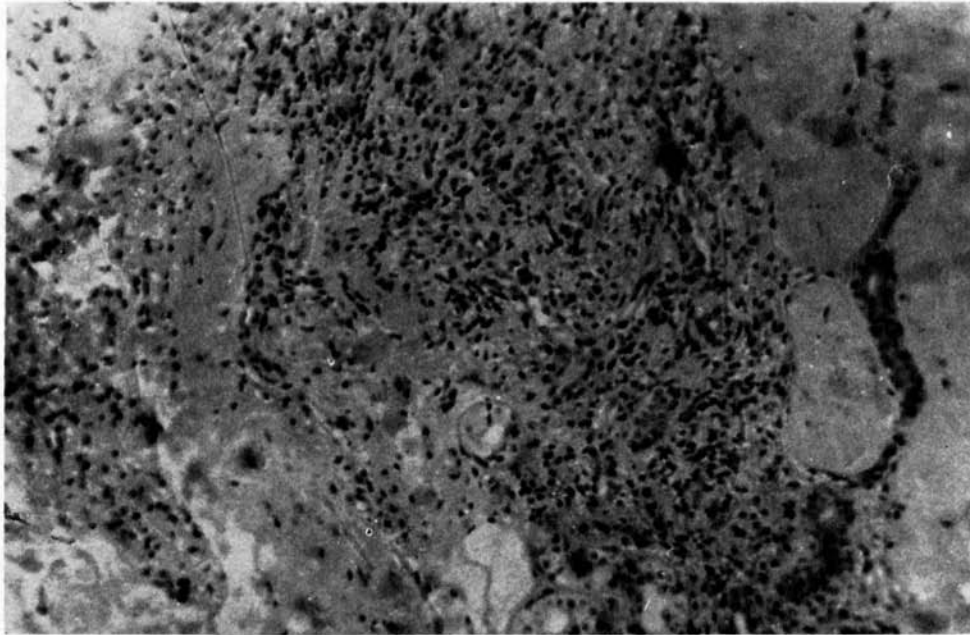


FIG. 7.—Healing in a leproma (170 \times). Note the smooth edge (due to absence of infiltration) and regressive cytologic structure.

Relapse in lepromatous leprosy.—Just as fibrocytic activity is the earliest manifestation of a new leprosy lesion, so an influx of fibrocytes is the first indication of renewed activity in a regressing granuloma (Figs. 5 and 6). At this stage a relapse is not easily distinguished from healing. Solid-staining bacilli may be few. The fibrocytes, however, are quickly followed by the appearance of new phagocytic cells, often elongated; it is not clear whether they are derived from fibroblasts or histiocytes. Their shape is that of a pseudoepithelioid cell and may falsely suggest that the patient has developed a borderline tendency. Sometimes there is whorled formation. At this stage there is no difficulty in demonstrating clumps of solid-staining bacilli. Gradually the granuloma assumes the conventional cytologic structure of activity, with peripheral infiltration.

Healing.—The period of treatment before signs of healing first

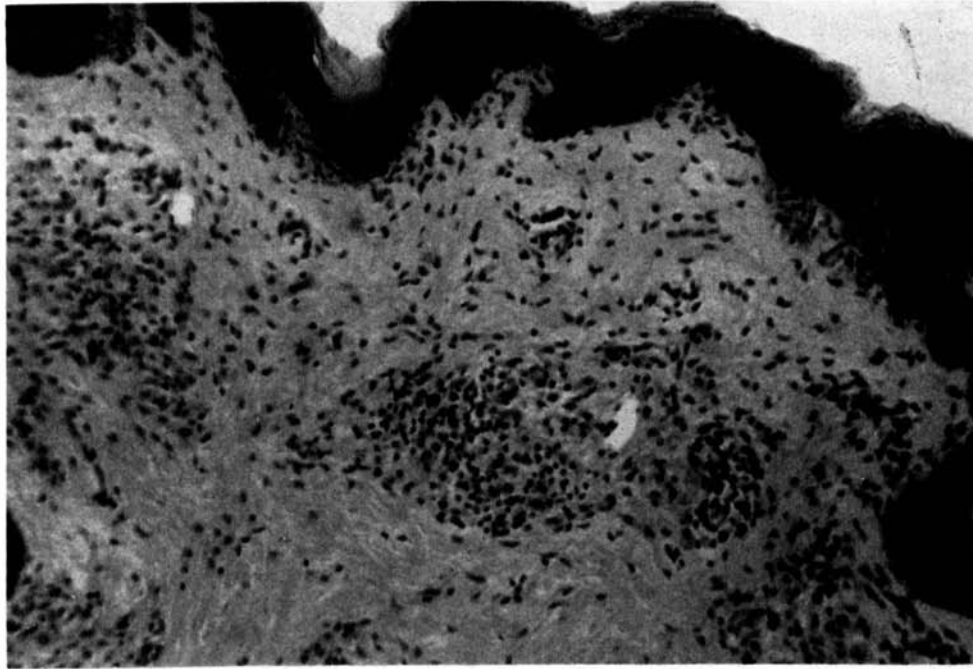


FIG. 8.—Influx of histiocytes in subepidermal zone (170 \times). This is probably an aspect of resolution, but it occurs usually during the later stages of ENL.

become apparent histologically varies according to the type and severity of the infection, from eight weeks in tuberculoid or borderline cases to six months in the most actively progressing leproma.

In all cases the first sign of healing is shrinkage and disappearance from the dermis of the proliferating fibrocytes and small dark histiocytes. The satellite foci are next to resolve. At this time the granulomatous masses are sharply circumscribed, with fibrocytes at their periphery. Only occasionally is there fibrosis within a healing granuloma. Imperceptibly the granuloma shrinks from the periphery inward, as replacement fibrosis reestablishes the normal collagen pattern. Cytologically the granuloma is regressive. The bacteria are granular (Fig. 7).

A more readily noticeable form of resolution is commonly seen toward the end of an ENL reaction. An influx of wandering cells is seen in the subepidermal zone, dipping into the dermis between the lepromatous areas, which they surround and penetrate (Fig. 8). In routine stains these cells resemble the small dark histiocytes already described. By Weil-Davenport staining they are shown to be metallophilic. They are phagocytic and, on ingesting the foamy material of the leproma, are transformed into macrophages, which migrate away from the granuloma.

Reactions.—Edema is the most prominent feature of all reactional



FIG. 9.—Same section as Fig. 8, stained by the Weil-Davenport method (170 \times). The histiocytes in the subepidermal zone are distinguished from other small dark histiocytes in the metallophilia of their branched cytoplasm.

states. It is most severe in the most severe reactions. The granuloma is often swollen by edema both inter- and intra-cellularly; in the dermis edema fluid fills the spaces between the collagen bundles and destroys them and the elastic tissue by compression. Throughout the dermis is a widespread infiltration of large pale histiocytes, which gradually give place to fibroblastic activity. In tuberculoid and borderline reactions, as a result of these dermal responses, the swollen granulomatous masses often coalesce. As the reaction subsides there is gradual absorption of edema, and the granuloma, if any remains after the reaction is over, appears in its previous circumscribed form.

Infiltration of pale histiocytes and fibroblastic activity in the dermis are sometimes seen in routine biopsies of ordinary lepromatous lesions from patients undergoing ENL, although these lesions are not reacting clinically. This dermal reaction, which is almost diagnostic of ENL, may be severe (Figs. 10 and 11).

Lepromin reactions deserve mention because in them, as in all reactions to injected material, the dermis itself is not involved except at the actual site of injection. The core of the reaction is densely packed with inflammatory cells. Peripherally these cells push out a short way into the surrounding dermis, always between collagen bundles where there is some marginal fibrocytic activity. Edema, rarely present, is confined to the reaction area (Fig. 12).

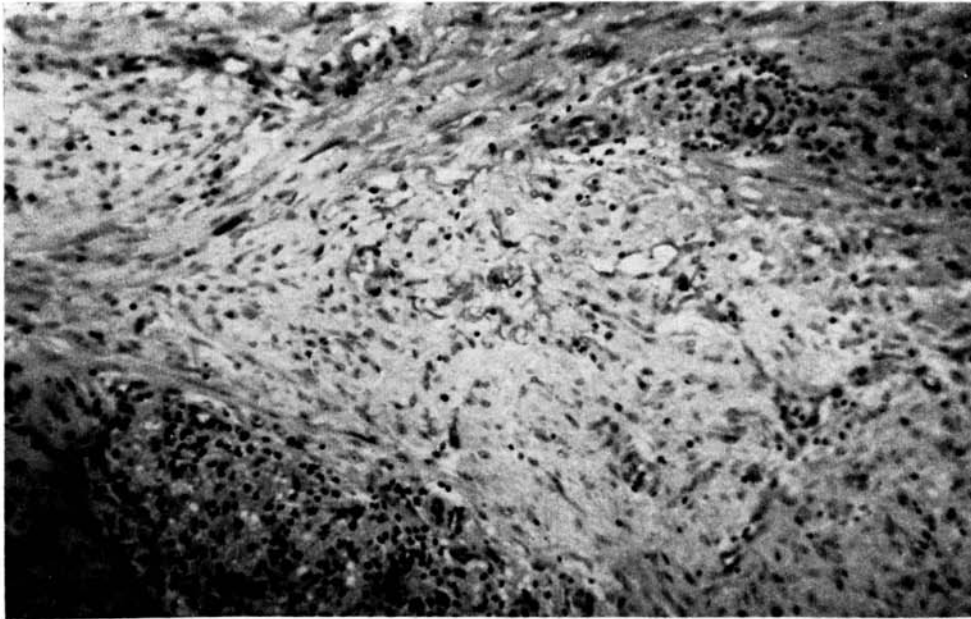


FIG. 10.—Reaction pattern in dermis (170 X). Destruction of collagen and elastic tissue by infiltration of large pale histiocytes. Also edema. This biopsy is of a nonreacting lepromatous lesion during an ENL attack.

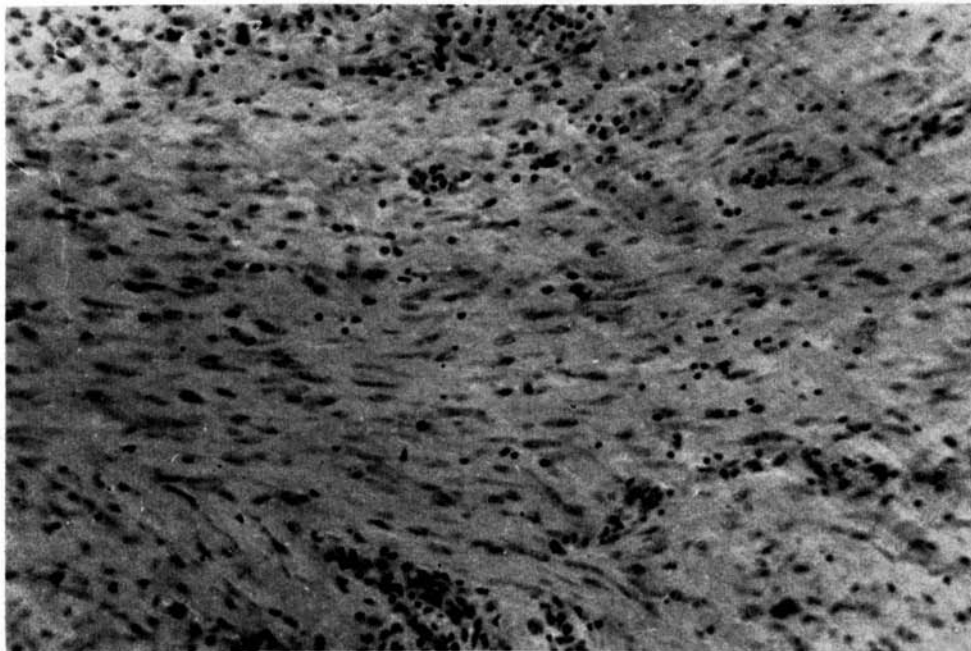


FIG. 11.—Subsiding reaction with fibroblastic activity (170 X). Note the loss of normal collagen pattern. From another part of the section of Fig. 10 (170 X).

In lesions produced in monkeys (³) by the injection of leprosy bacilli, whether fresh or killed, circumscribed lesions follow a course similar to that of a lepromin reaction in the human skin.

There is no diffuse dermal reaction. In lesions due to injected extracts of normal skin in lepromin-positive patients the reaction is again localized. In the central area there is phagocytosis of particles by cells indistinguishable from fibroblasts. Peripherally fibroblasts give place to fibrocytic activity.

REACTION IN DISEASES OTHER THAN LEPROSY

Before conclusions can be drawn about the possible significance of the dermal reactions of leprosy, the dermis in other conditions must be examined. Sections representing some 36 dermatologic conditions were available for study.

More often than not a histologic lesion in skin showed an irregular or diffuse edge corresponding to that of an active rather than a quiescent leproma. Small dark histiocytes of the type found in leprosy were of common occurrence and, not surprisingly, could often be seen infiltrating some distance into the interfascicular space of otherwise healthy dermis.

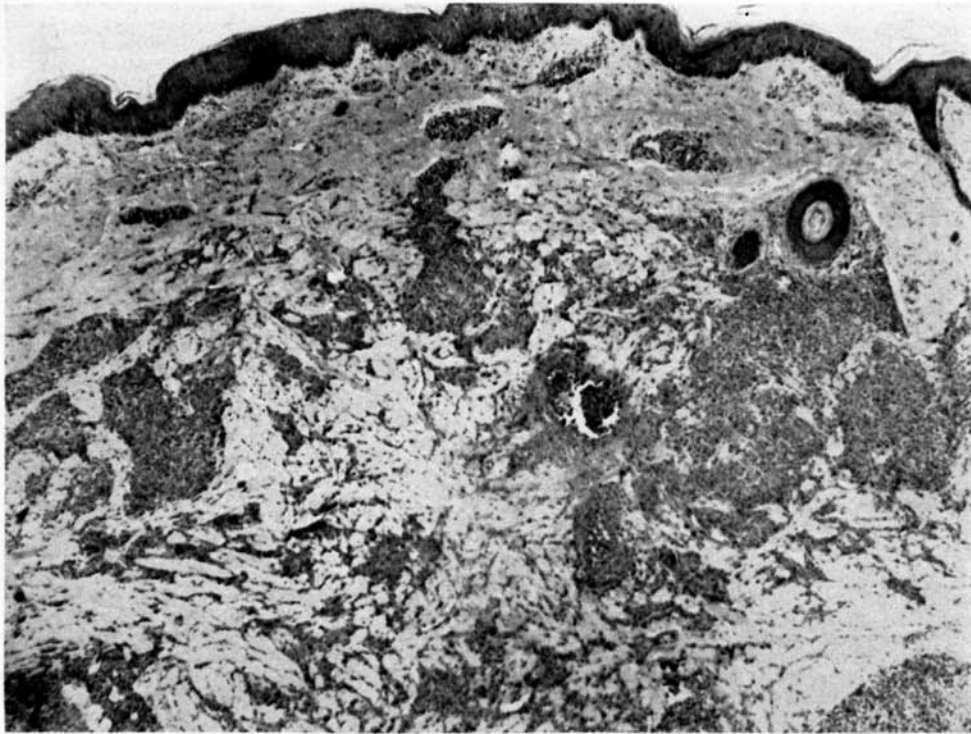


FIG. 12.—Lepromin reaction at 28 days (50X). Note that infiltration occurs between collagen bundles and does not extend beyond the area of reaction. The dermis does not participate.

In foreign-body reactions and mild inflammation without any hypersensitivity element, histiocytic infiltration was not associated with any fibrocytic activity. But intense histiocytic infiltration, as in leishmaniasis or histiocytoma, was in some cases associated with mild fibrocytic activity at the periphery of the lesion. This activity was more pronounced in relation to the degree of infiltration in onchodermatitis. It was maximal in some cases of sarcoidosis and, especially of tuberculides in which histiocytic infiltration was minimal.

The interpretation put on these observations was (1) that limited infiltration of the dermis by small dark histiocytes might occur in any condition in which these cells were congregated, and probably indicated a spread of the disease process; (2) that mild fibrocytic activity in association with histiocytic infiltration was most likely a localizing defense mechanism, or an attempt at such; and (3) that fibrocytic activity was maximal in relation to the degree of infiltration in conditions in which there was a hypersensitivity element.

The second dermal reaction pattern of leprosy, the widespread infiltration of large pale histiocytes with fibroblastic activity, elastic tissue destruction, and edema of the dermis, found no exact parallel outside leprosy. These features were observed in the walls of some abscesses and ulcers, but they were not widespread unless the inflammation was severe to a degree beyond anything seen in leprosy. They were not seen in collagen diseases. Their severity in some lepra reactions is peculiar, and suggests that the dermis, especially perhaps its elastic tissue, may play a role in these reactional states.

SUMMARY

A study of the dermis in leprosy reveals two main patterns of response, one characteristic of activity of the infection and the other of reactional states. The dermis also provides indications of healing and relapse.

The first manifestation of a new lesion or a relapse is proliferation of the dermal fibrocytes. Activity of a leprosy lesion is associated with histiocytic infiltration of the dermis, which shows a localized fibrocytic response. Reactional states are associated with widespread fibroblastic response, which results in temporary destruction of the collagen pattern.

Disruption of elastic fibers occurs locally around a spreading granuloma and diffusely in reactional states.

The widespread damage to collagen and elastic tissue in some reactions suggests that the dermis itself may be involved in certain hypersensitivity states in leprosy.

RESUMEN

El estudio de la dermis en la lepra revela 2 principales modelos de respuestas; una característica de la actividad de la infección y la otra, de los estados reaccionales.

La dermis también provee indicaciones de cicatrización y recidivas.

La primera manifestación de una nueva lesión o la recidiva, es la proliferación de los fibrocitos dérmicos. La actividad de una lesión leprosa está asociada con la infiltración histiocítica del dermis, la cual muestra una respuesta localizada fibrocítica. Los estados reaccionales están asociados con una respuesta fibroblástica difusa, la cual resulta en una temporaria destrucción del modelo colágeno.

La desorganización de las fibras elásticas ocurre localmente alrededor de un granuloma extendido y difusamente en los estados reaccionales.

En algunas reacciones el extenso daño a los tejidos colágeno y elástico sugiere que la dermis misma puede estar envuelta en ciertos estados hipersensitivos de la lepra.

RESUMÉ

Une étude du derme dans la lèpre révèle deux types principaux de réponses, l'une caractéristique de l'infection active, l'autre de phénomènes réactionnels. Le derme fournit aussi des indications sur le caractère de guérison ou de récurrence.

La première manifestation d'une nouvelle lésion ou d'une récurrence est la prolifération des fibrocytes du derme. L'activité d'une lésion lépreuse est associée avec l'infiltration histiocytaire du derme, qui montre une réponse fibrocytaire localisée. Les épisodes réactionnels sont associés avec une réponse fibroblastique largement disséminée, qui résulte en une destruction temporaire de la structure collagène.

Une rupture des fibres élastiques se produit localement autour d'un granulome qui s'accroît, et diffusément dans les états réactionnels.

Le dommage largement disséminé noté dans le collagène et le tissu élastique au cours de certaines réactions suggère que dans la lèpre le derme lui-même peut être entraîné dans certaines manifestations d'hypersensibilité.

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