The lichenoid reaction pattern

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There is some confusion about the origin of the term lichen to describe skin diseases but it appears to have been a popular name for many conditions. An impressive list of dermatoses that begin with the term lichen or lichenoid could be colled from the index of a major textbook (Table 1)[1]. It is difficult to conceive of a way to unify all these conditions but there are some features that some of these diseases share. These features are also shared by diseases that do not have lichen in their names. Briefly, the common clinical denominator is the presence of small papules, purple or skin coloured, and histologically, damage to the basal keratinocytes.

Table 1.

Lichen amyloidosus
Lichen aurcus
Lichen fibromucinodosis
Lichen myxoedematosus
Lichen nitidus
Lichen nuchae
Lichen pigmentosus
Lichen planopilaris
Lichen planus
Lichen planus pemphigoides
Lichen planus pigmentosus
Lichen purpuricus
Lichen rubber moniliformis
Lichen sclerosus et atrophicans
Lichen scrofulosorum
Lichen simplex
Lichen simplex chronicus
Lichen spinulosus
Lichen striatus
Lichen verrucosus et reticularis
Lichenoid drug eruptions
Lichenoid melanodermatitis

It is easier to bring these diverse conditions together based on the histopathological appearance. Histologically, the defining characteristic of lichenoid tissue reactions is basal cell damage[2-3]. The damage occurs by apoptosis or liquefactive degeneration, processes that appear to be mediated by different pathogenetic mechanisms. Apoptosis, a special type of single cell death, consists of the condensation of single cells followed by active budding and fragmentation[4]. Unlike necrosis, cell membranes and organelles remain intact till late in the apoptosis. On light microscopy, apoptotic keratinocytes appear as pink, shrunken globules (known as Civatte bodies) which may show pyknotic nuclear remnants. The Civatte bodies may be phagocytosed by other keratinocytes and macrophages or may drop down into the papillary dermis as colloid bodies. Liquefactive degeneration leads to keratinocyte damage by the accumulation of fluid within basal cells. On microscopy, the keratinocytes appear swollen and vacuolated. It appears that apoptosis is mediated by cellular immunity and liquefactive degeneration by humoral immunity.

Other histological accompaniments of the lichenoid reaction are an infiltrate of lymphocytes and melanin incontinence. The lymphoeytes are present in the papillary dermis closely applied to the undersurface of the epidermis and infiltrating the lower layers in some disorders. Apototic keratinocytes are sometimes found in close contact with lymphocytes, an appearance referred to as satellite cell necrosis. In some diseases, the infiltrate obscures the junction between the epidermis and dermis, an appearance that has been referred to as interface dermatitis. Some accounts exclude this group of disorders from the lichenoid reaction pattern but we have chosen to use a broader definition. Other cells, chiefly histiocytes, may be part of the infiltrate. Melanin incontinence refers to the presence of melanin within melanophages of the upper dermis. This results from disruption of the epidermal-melanin unit by basal cell damage. Once it occurs, melanin incontinence persists for long periods and in some situations may serve as the only histological signpost of a lichenoid reaction in the past.

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The sequence in which they appear and the pathogenetic significance of these histological findings is unclear but they constitute a recognizable pattern.

The clinical features that correspond to these findings are dependent on whether the lichenoid reaction is acute or chronic. The prototype disease is lichen planus which represents the chronic type of lichenoid reaction and is characterized by small, purple papules. In addition, skin coloured or shiny, minute papules may also occur and have exactly the same histopathological appearance. Occasionally, a lesion may show a combination of shiny papules and violaceous papules. In such lesions, the shiny papules are aggregated closely together and show a purple coloration at the censer of the lesion while papules tend to remain skin coloured and discrete at the periphery. We have also seen shiny macules that have the colour and sheen of fine lichenoid papules. They may represent evolving or subsiding lesions. The, clinical appearance is also modified by the site of the lesion; the characteristic purple colour is hardly visible at sites such as the scalp and nail. In these locations, other clues such as scarring alopecia and pterygium provide clues to a lichenoid process.

In acute lesions, the clinical appearance is dominated by erythema. The brown-black colour of epidermal necrosis is often seen in erythema multiforme and fixed drug eruption. It is overshadowed by dermal necrosis presenting as a necrotic crust in pityriasis lichenoides et varioliformis acuta (PLEVA). The subsidence of an acute lichenoid reaction is characteristically followed by a persistent pigmentation which represents the melanin incontinence that is prone to occur in these dermatoses.

An account of some of the major diseases that belong to this group and which are likely to be encountered in clinical practice follows.

Lichen planus

Lichen planus is the prototype of a lichenoid tissue reaction. The typical clinical lesion is an itchy, violaceous papule that shows whitish streaks known as Wickham striae. The papules occur on the legs, the wrists and the lower back but may develop at any site and can present as a generalized eruption. At all these sites, they retain their characteristic appearance. However, the presentation of the disease may be modified by the site.

On the palms and soles, lichen planus is skin coloured and hyperkeratotic and diagnosis is difficult when lesions are confined to this site. On the mucosa, there is a white or violaccous plague. White plaques may be lacy and reticular. Some white plaques show violaceous discoloration. Erosions are frequent.

On the scalp and at other hair-bearing sites, slightly purple, follicular papules are seen when lichen planus involves the hair follicles. These papules heal with follicular scarring and a blue-black pigmentation of the recently scarred area is a useful clue. Scarring is also a helpful diagnostic sign when the nails are affected and a pterygium is highly suggestive of lichen planus. Other less specific signs include roughening of the surface of the nail plate, longitudinal ridging and thinning.

H stologically, there is a dense upper dermal band of lymphocytes that is closely applied to the epidermis but does not invade it[5]. The basal keratinocytes show evidence of injury as necrotic pink cells with a pyknotic nucleus or as vacuolated cells. The necrotic cells drop down into the epidermis as colloid or Civatte bodies. The basal cell damage may lead to the appearance of a split between the epidermis and the dermis, the so-called Max-Joseph space. The damage to basal keratinocytes of the rete ridges leads to a saw-tooth appearance. Melanin is found within macrophages in the upper dermis. There is compact orthokeratosis and hypergranulosis which is wedge shaped over the acrotrichia and acrosyringia.

When lichen planus affects the hair follicles, oral mucosa or nail, the changes are essentially similar but the appearance must be interpreted in the light of the normal histology of the area.

In follicular lesions of lichen planus (ichen planopilaris), the lymphocytic infiltrate is seen around the hair follicle with damage to the basal cells of the follicular epithelium. This may occur in isolation or in conjunction with involvement of non-follicular epidermis. Lichen planopilaris heals with scarring of follicles and biopsies of late lesions show selerosed follicular units.

Lichen planus of the oral mucosa shows changes similar to cutaneous lesions. The finding of parakeratosis is not compatible with a diagnosis of lichen planus on the skin but it is a normal feature of oral mucosa and is seen in oral lichen planus. Basal cell damage is less prominent than in cutaneous lesions.

Lichen planus hypertrophicus demonstrates compact hyperkeratosis and acanthosis. The dermal infiltrate of lymphocytes is not band-like and is localized to the tips of the rete ridges with damage to the overlying basal keratinocytes. Papillary fibrosis is frequent.

Lichenoid drug eruptions

Itchy, violaceous papules that resemble idiopathic lichen planus may develop following exposure to certain drugs. Some drugs may cause oral lesions of

lichen planus, alone or in association with skin lesions. The list of drugs implicated is long and includes thiazide diuretics, antimalarials, gold, streptomycin, isoniazid, ethambutol and beta blockers among many others[7]. Oral lichenoid eruptions are induced by a smaller number of drugs[8] including lithium carbonate[9] and imatinib[10]. (Histologically, lichenoid drug reactions may be indistinguishable from lichen planus[11]. Clues include the presence of necrotic keratinocytes high in the epidermis along with parakeratosis and a superficial and deep perivascular infiltrate. Eosinophils and plasma cells in the infiltrate are often used as a diagnostic clue but this not a helpful finding because it is uncommon in lichenoid drug eruptions and occurs occasionally in lichen planus as well. The diagnosis is documented by noting improvement in the eruption following withdrawal of the drug and confirmed by re-challenge.

Lichen nitidus

Lichen nitidus presents with minute, 1mm shiny, skin coloured papules that are often grouped together but tend to remain discrete. Slight umblication of the papules is evident. When located on the palms and soles, the papules demonstrate central keratotic plugs. Some papules may be located in a short, straight line indicating Koebnerisation. Lesiom may develop anywhere but have a predilection for the tips of the fingers and the penis.

Histologically, lichen nitidus characteristically demonstrates a compact collection of epithelioid histiocytes and lymphocytes enclosed within a single papilla by inward bending rete ridges[12]. Ocassionally, the infiltrate spans more than one papilla. The epidermis overlying the granuloma is thin and basal keratinocytes show necrosis and vacuolization. The stratum comeum is compact and orthokeratotic in some cases and parakeratotic in the remainder.

Lichen scrofulosorum

Lichen scrofulosorum may cause diagnostic confusion with lichen nitidus. Small, discrete skin coloured papules are seen in small groups. A minute central crust is a feature of many papules. Subtle features to differentiate them from lichen nitidus are the lack of shininess, a predilection for the trunk and a waxing and waning course. Lichen scrofulosorum is associated with a strongly positive Mantoux test and an extracutaneous focus of tuberculosis can be detected in many patients. Treatment with antitubercular drugs is curative. Histologically, the classical appearance of lichen scrofulosorum with small epithelioid cell granulomas around sweat glands and hair follicles is diagnostic[13]. However, we have seen some biopsies that showed features indistinguishable from lichen nitidus and the diagnosis was established by the Mantoux test and response to therapy.

Lichen striatus

Lichen striatus is much easier to diagnose clinically than on biopsy because its distinguishing characteristic of linearly arranged papules cannot be appreciated under the microscope. The papules are skin coloured and shiny and often coalesce. The condition occurs mainly in children and spontaneous regression is the rule. This may occur in one part of the lesion while another shows papules. If a biopsy is performed, the latter area must be sampled. On brown skin, the papules subside to leave a streaky hypopigmentation that may persist for several months. If patients present at this stage, a biopsy is likely to show non-diagnosfic changes.

Lichen striatus demonstrates a lichenoid pattern with a superficial and deep perivascular and periadnexal infiltrate[14]. There is a patchy infiltrate of lymphocytes and histiocytes in the upper dermis with overlying basal cell necrosis and vacuolization. Mid spongiosis and exocytosis are usually associated. The infiltrate is also present around the vessels of the superficial and deep plexuses and around the sweat glands. Epithelioid histiocytes may be prominent in the infiltrate in some cases.

Photosensitive lichenoid eruption

Photosensitive lichenoid eruption is the term that we use for a commonly encountered condition that does not appear to have been described in detail. We are aware that others use different names for this condition including polymorphous light eruption, actinic lichen nitidus and summertime actinic lichenoid eruption[15]. The dermatosis occurs in young adults and many patients are aware of the relationship of their eruption to sun exposure while some are not. The condition presents with grouped, shiny, 1-2 mm discrete and coalescing papules on the extensor surfaces of the forearm, the dorsae of the hands and the nape and V of the neck. The face is usually not affected but may show papules on the forehead. A purple colour often develops at the thicker central part of larger plaques that form from the coalescence of papules. The individual discrete papules resemble lichen nitidus but the distribution on sun-exposed skin and the tendency to coalesce and develop a violaceous hue serve to distinguish the two. Photosensitive lichenoid eruption reveals a mild to moderately dense superficial perivascular infiltrate of lymphocytes with slight papillary edema. There are small foci of lichenoid change and spongiosis. The circumscribed papillary granulomas

of lichen nitidus are not a feature of photosensitive lichenoid eruption.

Ashy dermatosis (lichen planus pigmentosus. melanodermatitis toxica, erythema dyschromicum perstans)

This common but poorly understood dermatosis suffers from an excess of inadequate synonyms. The characteristic lesion is an asymptomatic violaceous or ashy macule that often begins on the sun-exposed skin of the face and upper limbs. With time, the macules increase in size and coalesce into confluent areas of hyperpigmentation that may affect large parts of the skin including non-exposed skin.

Biopsies of ashy dermatosis demonstrate changes that appear to represent different stages of disease activity[16]. Early biopsies show a fairly dense band-like infiltrate of lymphocytes with damage to the overlying basal keratinocytes associated with melanin incontinence. Later biopsies show a moderately dense and patchy lichenoid infiltrate with melanin incontinence. Biopsies taken in the late stages of disease may reveal only melanophages in the upper dermis with no lichenoid infiltrate and a reconstituted basal layer. At this stage the histopathology is indistinguishable from post-inflammatory pigmentation. Clinically, however, it is not possible to recognize the different histopathological stages; the appearance of the macules is similar irrespective of the histological findings. A biopsy from a recent lesion may be expected to provide the most useful information.

Lichenoid secondary syphilis

One of the protean manifestations of secondary syphilis is violaccous papules. Lichenoid papules around the anogenital region should prompt a search for syphilis but patients will often not mention these lesions and only present papules on the limbs or trunk for examination. These papules can resemble lichen planus very closely. Oral mucosal lesions typical of lichen planus do not occur. Hyperpigmented macules on the palms or condyoma lata, when present, may suggest the diagnosis. On biopsy, lichenoid secondary syphilis shows a combination of psoriasiform and lichenoid changes[17]. There is parakeratosis and acanthesis accompanied by basal cell damage and an upper dermal infiltrate of lymphocytes. The infiltrate also involves the deep dermis and may be centred around the adnexal structures. An ill-formed epithelioid granuloma is observed in some biopsies. Plasma cells are not numerous. This lack of concordance between the clinical and histological appearances should arouse the suspicion of syphilis which is confirmed by serological testing.

Lupus erythematosus and dermatomyositis

Lupus erythematosus may present with a variety of cutaneous lesions ranging from a blanchable erythema to indurated paques. The erythema of LE is easily recognizable when it occurs on the cheeks (butterfly erythema) but may occur at other sites including the trunk. Erythema is associated with acute flares of disease and may be accompanied by evidence of disease in other organ systems. On brown skin, the erythema subsides with a persistent brown-black pigmentation which may obscure recurrences of active disease. Slight indurated and scaly annular plaques are a feature of subacute lupus erythematosus. Discoid lupus erythematosus presents as an indurated and atrophic scaly plague with adherent follicular scales. The plaque is usually depigmented and has a rim of hyperpigmentation. Some lesions or parts of plaques may show a purple colour usually around the periphery. The plaques develop on sun-exposed skin; the concha is a characteristic site. On the scalp, DLE causes cicatricial alopecia.

Lupus erythematosus reveals a patchy lichenoid infiltrate with a superficial and deep perivascular and periadnexal infiltrate of lymphocytes[18-19]. In established lesions of discoid lupus erythematosus, there is a patchy infiltrate of lymphocytes and vacuolization of the overlying basal cells; nocrosis is less prominent. The epidermis is thickened in parts and thin in others. There are follicular plugs and patchy parakeratosis. Basement membrane thickening is a useful diagnostic feature but is present in a minority of cases. The dermal infiltrate is present around vessels and adnexal structures. Connective tissue mucin is seen in increased quantities. Usually, it is easy to differentiate lichen planus from LE however, in some cases, the histopathological appearance may be indistinguishable and direct immunoflourescence to demonstrate a lupus band, scrological tests and clinicopathological correlation and follow up may be required to settle the diagnosis.

Dermatomyositis shows changes similar to those in early lupus erythematosus with a patchy lichonoid infiltrate of lymphocytes, necrotic and vacuolated keratinocytes, a thickened basement membrane and increased connective tissue mucin[20].

Erythema multiforme

Erythema multiforme presents with erythematous macules and plaques with a predilection for the hands and feet though other areas including the oral mucosa may be affected. Characteristically, the center of the plaque develops a circular brown-black discoloration, which with its ring of erythema constitutes

the target lesion typical of this disease. Small vesicles may also develop within the plaque. The eruption is self-limited and subsides in about 2 weeks. When involvement is widespread and associated with extensive mucosal erosions and fever, it is known as Stevens-Johnson syndrome. Histologically, erythema multiforme demonstrates necrotic keratinocytes in the basal and upper layers of the epidermis, an upper dermal infiltrate of lymphocytes that obscures the dermal-epidermal junction and a normal stratum corneum[21]. A number of pink, necrotic keratinocytes are seen throughout the length and thickness of the epidermis. The acute nature of the process is borne out by the normal appearance of the stratum corneum. The infiltrate is composed predominantly of lymphocytes and is present within the lower layers of the epidermis and the papillary dermis. There is papillary edema that may be severe enough to form a vesitle. Occasional eosinophils have been described in the infiltrate but are uncommon.

Fixed drug eruption

Fixed drug eruption is an intriguing and distinctive drug reaction that manifests as circular areas of erythema and edema which subside with a persistent brown-black pigmentation. Re-exposure to the drug leads to the development of erythema at exactly the same locations; new lesions may also develop. In severe reactions, a blister may develop within the erythematous plaque and generalized bullous eruptions have been reported rarely. Fixed drug eruptions on the genital and oral mucosa are usually eroded and heal slowly. Histologically, fixed drug eruption shows several features in common with erythema multiforme such as eosinophilic necrosis of keratinocytes beneath a normal stratum corneum and an infiltrate that obscures the junction between the epidermis and the dermis. Some additional features help to identify fixed drug eruption. The infiltrate is present in both superficial and deep locations and tends to be denser and contain more eosinophils than in erythema multiforme. Melanin incontinence is a prominent feature[22-23].

Pityriasis lichenoides

Pityriasis lichenoides is a recurring, self-limited eruption that varies in severity from necrotic lesions that heal with scarring (pityriasis lichenoides et varioliformis acuta (PLEVA) to scaly papules that subside with hypopigmentation (pityriasis lichenoides chronica). In PLEVA, crops of erythematous, oedematous papules are associated with a mild prodrome of fever and malaise. The papules develop a necrotic crust at the center which sloughs off and heals with a depressed scars. PLC is characterized by asymptomatic, dully erythematous papules with a central scale that can be peeled off in its entirety. Papules subside with a persistent, ill-defined hypopigmentation that often worries the patient more than the papules. In both varieties of disease, new papules continue to develop for a variable and unpredictable period though PLEVA usually lasts a few months while PLC may continue for several years. Histologically, PLEVA demonstrates necrosis of keratinocytes accompanied by a superficial and deep infiltrate of lymphocytes. The infiltrate is wedge shaped with the broad base of the wedge aligned along the epidermis. There is extravasation of erythrocytes in the dermis. The epidermal changes include parakeratosis and the presence of erythrocytes and lymphocytes within the epidermis and may be accompanied by epidermal ulceration[24]. In pityriasis lichenoides chronica, the changes are similar but considerably less prominent[25].

Graft-versus-host disease

First described after bone marrow transplantation, graft versus host disease is now recognized to occur in other situations where a donor's lymphocytes are transferred to a host unable to inactivate them such as transfusion of non-irradiated blood and organ transplants. The acute disease presents usually in the second week following bone marrow transplantation as an exanthem that begins on the hands, feet and face and becomes generalized. The exanthem subsides with scaling. Toxic epidermal necrosis, bullae and ulcers have been described in severe cases. Bloody diarrhoea and hepatitis usually accompany the eruption. Chronic graft versus host disease usually follows acute disease and develops as violaceous papules initially on the face, hands and feet. Oral lesions of lichen planus may also develop. Later, there is binding down of the skin resembling systemic sclerosis associated with antinuclear autoantibodies.

Histologically, acute graft versus host disease reveals a spectrum of epidermal changes range from a few necrotic and vacuolated keratinocytes to complete epidermal necrosis. There is an accompanying sparse to morerate, superficial infiltrate of lymphocytes in the papillary dermis. Lichenoid graft versus host disease may be histologically indistinguishable from ordinary lichen planus. Early lichenoid GVHD demonstrates satellite cell necrosis. Sclerodermoid GVHD shows dermal sclerosis with an overlying atrophic epidermis. At this stage, lichenoid changes are absent[26].

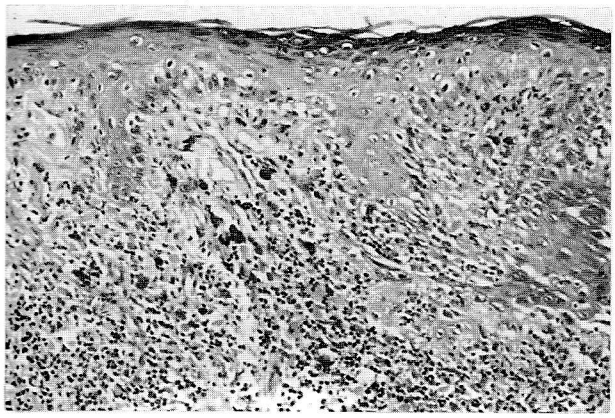

Figure 1. *Lichenoid reaction. Basal cell damage, dense upper dermal infiltrate of lymphocytes and melanin incontinence. (H & E × 100).*

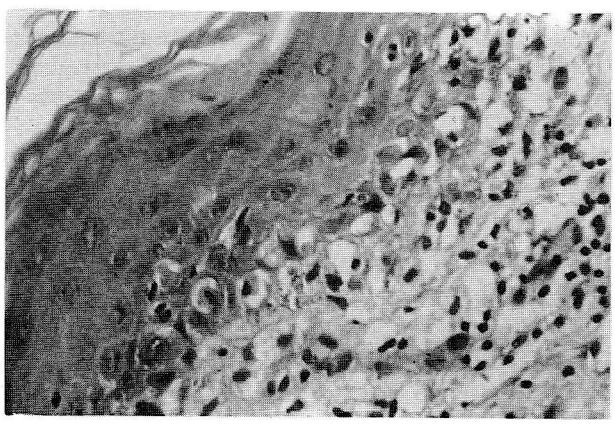

Figure 2. *Interface dermatitis. Lymphocytes extend into the epidermis and obscure the junction of the dermis and epidermis. (H & E × 400).*

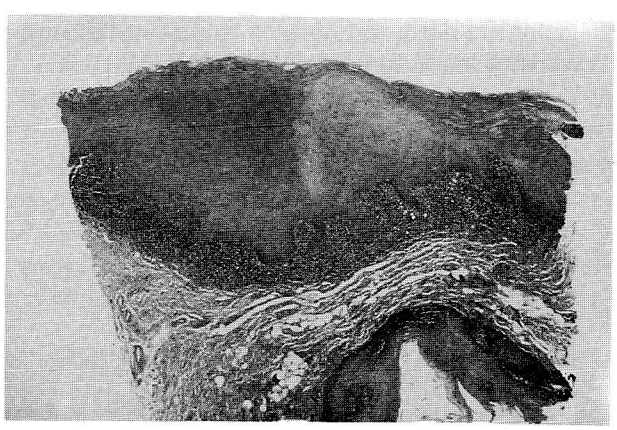

Figure 3. *Lichen planus. Band-like infiltrate of lymphocytes in close apposition to the epidermis with saw-toothing of rete ridges (H & E × 40).*

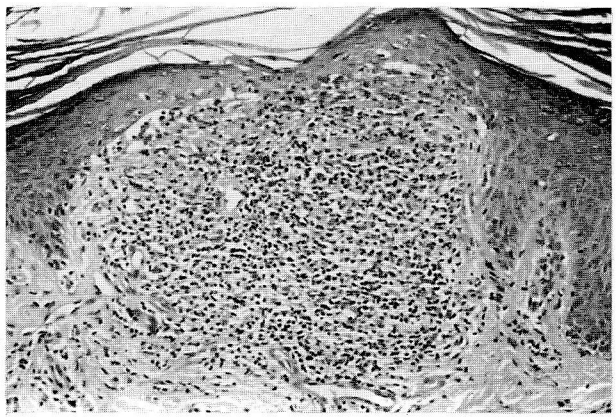

Figure 4. *Lichen nitidus. Collection of histiocytes and lymphocytes expanding one papilla with damage to the overlying basal keratinocytes. (H & E × 400).*

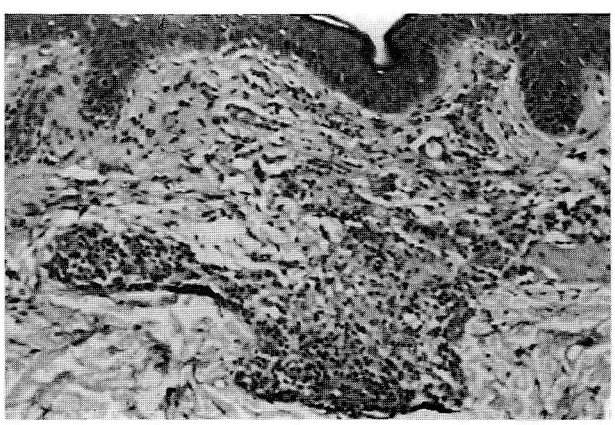

Figure 5. *Lichen scrofulosorum. Collection of lymphocytes and histiocytes in a superficial perivascular location extending into the papillary dermis. (H & E × 100).*

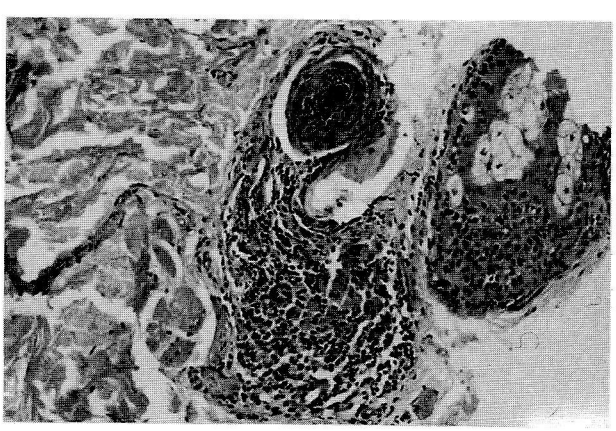

Figure 6. *Lichen scrofulosorum-granulomas around the hair follicle. (H & E × 400).*

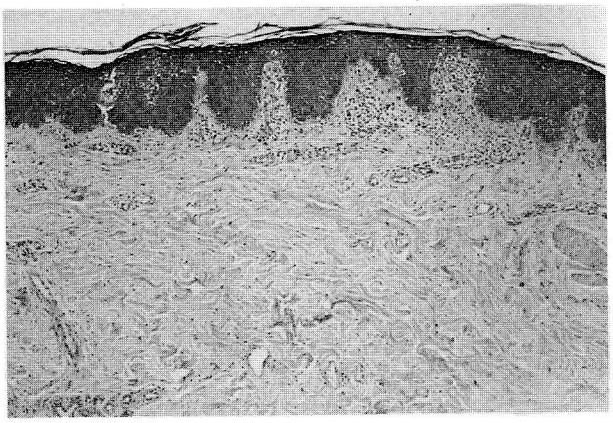

Figure 7. *Photosensitive lichenoid eruption. Infiltrate of lymphocytes and histiocytes in the papillary dermis with slight edema. (H & E × 40).*

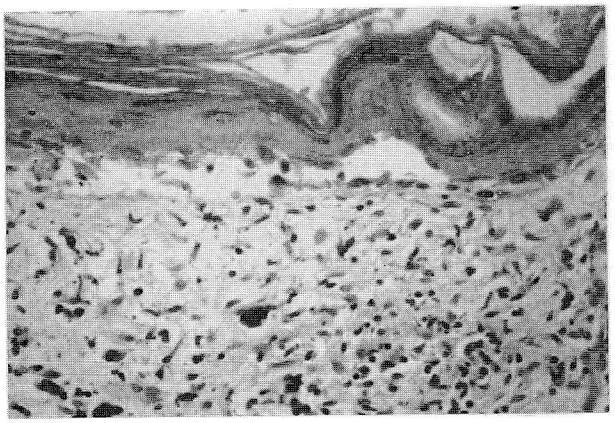

Figure 8. *Lichen planus pigmentosus. Patchy infiltrate of lymphocytes, basal cell damage and melanin incontinence. (H & E × 400).*

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