

HISTIOCYTOSIS X WITH SKIN LESIONS AS THE SOLE CLINICAL EXPRESSION

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Abstract. The case is presented of a patient with histiocytosis X of the skin of some 25 years' duration. Extensive investigation failed to reveal any other signs of the disease in other organs. The light and electron microscope findings are described. The electron microscope study revealed an abundant cytoplasm with numerous mitochondria, vacuoles, dense bodies, a well-developed Golgi apparatus and numerous Langerhans' cell granules.

Key words: Histiocytosis X; Histiocytosis X, skin lesions; Histiocytosis X, electron microscopy; Langerhans' cell granules

Histiocytosis X is a disorder characterized by a disseminated, invasive proliferation of large pale histiocytes with homogeneous nuclei (4). All three diseases included under this term—Letterer-Siwe disease, Hand-Schüller-Christian disease and eosinophilic granuloma of the bone—are considered to be variations of the same pathologic process (1, 2, 3, 5, 10, 11, 14, 17, 18) which may affect a number of organ systems, including the bones, lungs, central nervous system and, often, the skin.

In spite of the different names, the three syndromes grouped under the common name of histiocytosis X cannot always be separated one from the other into three clearly distinct entities. Although their clinical description may be well enough characterized in very typical cases, intermediate forms are often encountered.

The skin lesions may occur in association with the systemic involvement of the disease or, more rarely, as its sole clinical expression (16). A review of the literature gives rise to the impression that they are less frequently found in adults than in children; e.g. Enriquez et al. (4) found skin lesions in only 4 of 36 affected adults, as compared with 23 of 81 children.

The following is a case report, including histological and electron microscope studies, of an adult in whom the skin lesions were the only manifestation of the disease.

CASE REPORT

In 1971 a 62-year-old male of Romanian origin was hospitalised in our department because of skin lesions which had first appeared some 20 years earlier in the axillary and inguinal skin folds and on the neck. Following X-ray treatment in Romania in 1957, 1962 and 1964, the lesions had disappeared for 5, 2 and 7 years respectively. In 1971, 3 months prior to hospitalisation, there was a recurrence of lesions identical with those of the previous episodes.

Examination revealed a man in good general condition, with the sole pathological finding being the skin lesions. The lesions were localized on the face (Fig. 1), the neck, in the retroauricular region, the back, especially in the interscapular region (Fig. 2), and in the axillary, sacral

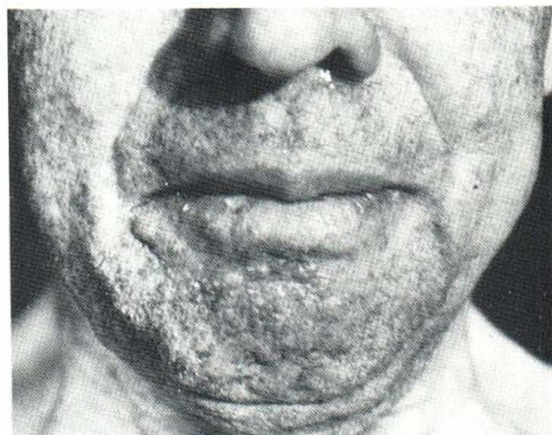


Fig. 1. Face: small, pink to reddish-brown nodules, with an occasional tendency to grouping.



Fig. 2. Dorsal skin: similar nodules disseminated all over the skin of the back, some of them with a central ulceration and/or crust.

and inguinal regions. They consisted of papules and small nodules ranging in size from that of a pin-head to 2–3 mm in diameter. They were of a pink to reddish-brown colour, some with a pustule on top or a small central ulceration covered with a thin crust. In the interscapular, intergluteal and inguinal regions, and occasionally also elsewhere, plaques of deeper infiltration could be seen which were 1–5 cm in diameter and had groups of papules and nodules on their surface similar to those described above. In the retroauricular, inguinal and intergluteal folds there were also longitudinal oozing fissures (Fig. 3) covered with a slight sero-purulent discharge. Of note among the laboratory examinations was the highly accelerated ESR, which was as high as 94/110. All of the other examinations carried out repeatedly during the years 1971–74, including extensive blood tests, urinalysis, X-rays and others, were without pathological findings.

A typical nodule was removed for examination by light and electron microscopy, with the following findings.

HISTOLOGICAL EXAMINATION

The epidermis was intact except for one small area in which it was necrotic and in which there

was a crust infiltrated with polymorphonuclear leukocytes. The dermis was heavily infiltrated by pleomorphic cells, the majority of which were large histiocytes with abundant cytoplasm, and a few multinucleated giant cells, eosinophilic polymorphonuclears and lymphocytes (Fig. 4). The histiocytes contained large, oval-shaped nuclei and abundant amphophilic cytoplasm, but no nucleoli were visible. In a few histiocytes there were multiple minute vacuoles dispersed in the cytoplasm (Fig. 5). The vacuoles in the cytoplasm of the histiocytes stained positively with Sudan III stain. The giant cells were composed of 2–3 nuclei centrally located and surrounded by abundant amphophilic cytoplasm, and a few cells contained numerous small, empty-looking vacuoles. Mitotic figures were rare.

ELECTRON MICROSCOPE STUDY

The tissue specimen was fixed in 2% phosphate-buffered glutaraldehyde, post-fixed in 1% OsO_4

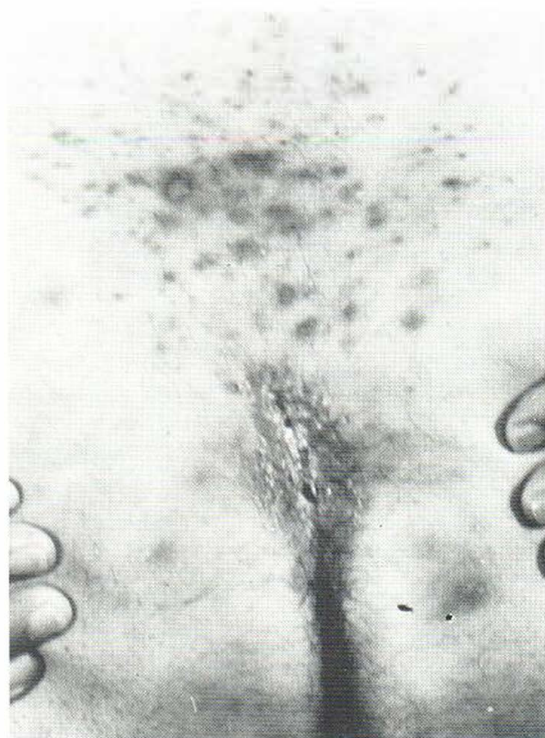


Fig. 3. Intergluteal region: deep infiltration with longitudinal, oozing fissure, partly covered with a crust.

DISCUSSION

The skin lesions may occasionally be the main symptom in histiocytosis X. Enriquez et al. (4) found cutaneous eruption to be the chief complaint in 8 of 117 cases of histiocytosis X. The skin lesions and their localization may mimic other skin conditions and therefore may be diagnosed erroneously if one does not bear in mind the possibility of histiocytosis X. For those who do, this sign may be of particular value in indicating the presence of this disorder at an early stage, when the internal involvement has not yet manifested itself. The diagnosis will be conclusively confirmed by the histological picture of the characteristic infiltration of histiocytes.

Morphologically, the skin lesions seen in all the three syndromes grouped under the term histiocytosis X are identical. These may sometimes be mistaken as a seborrhoeic eruption because of the erythema and scaling seen in the typical seborrhoeic areas, viz. the scalp, face, retroauricular, axillary



Fig. 4. Hyperkeratosis, normal epidermis, abundant subepidermal pleomorphic cellular infiltration (H. E., $\times 120$).

and embedded in Epon. Ultrathin sections were stained with uranyl acetate and lead citrate.

The cellular infiltrate in the dermis was composed of histiocytes. The nuclei were large and lobulated, with dispersed heterochromatin. A few showed extreme indentation-lobulation with only a thin rim of nuclear material connecting the nuclear segments (Fig. 6). The cytoplasm was abundant and contained numerous mitochondria, vacuoles, dense bodies, a well-developed Golgi apparatus and numerous Langerhans' cell granules (Fig. 7). Each granule was composed of two parallel, electron-dense membranes, in between which there was either a third, parallel membrane or multiple transverse membranes (Fig. 8). A few granules appeared to be adhering to a large, empty vacuole (Fig. 9). Examination of the Golgi apparatus at high magnification showed formations indistinguishable from the Langerhans' granules located between the cisterns (Fig. 10).

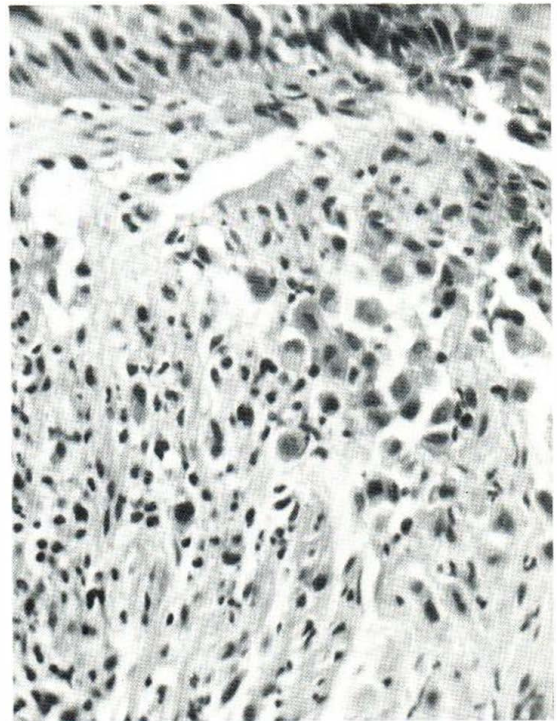


Fig. 5. Detail of subepidermal cellular infiltrate: large histiocytes with abundant cytoplasm, lymphocytes, polymorphonuclear leukocytes and eosinophils (H. E., $\times 285$).

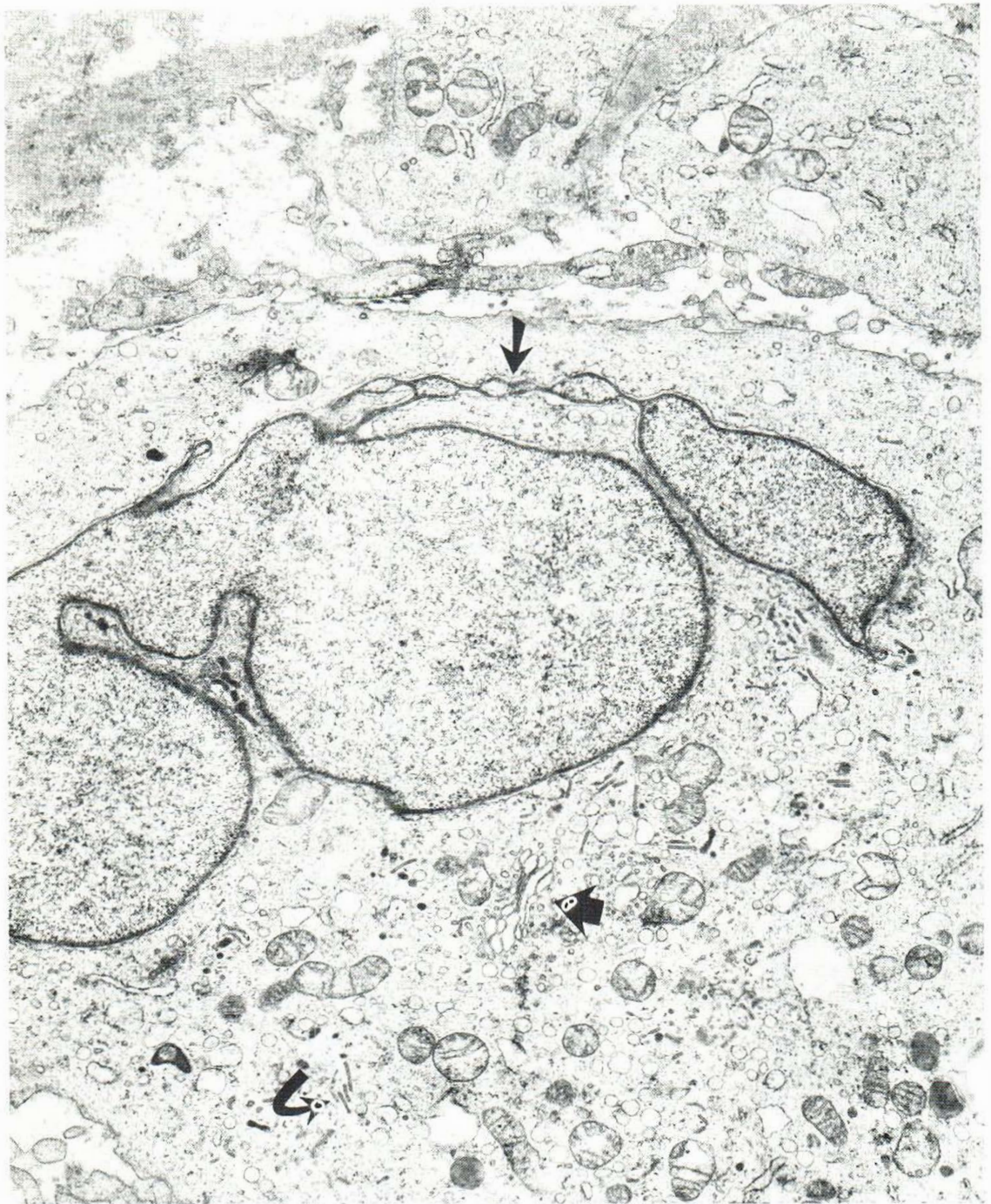


Fig. 6. Large histiocytes with lobulated nucleus (arrow); in cytoplasm, abundant mitochondria, vacuoles, Langerhans' granules (curved arrow) and well-developed Golgi apparatus (thick arrow) ($\times 38\,000$).



Fig. 7. Histiocytes with abundant vacuoles and Langerhans' granules (arrows) singular or in groups; a few dense bodies (upper right) ($\times 17\,700$).

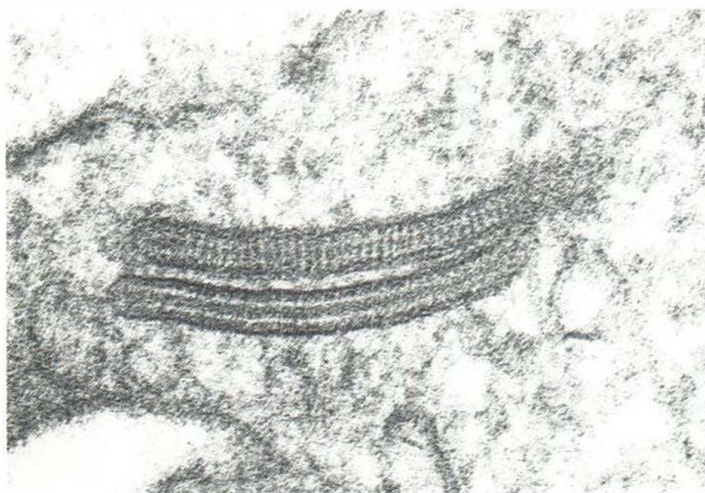


Fig. 8. Langerhans' granules, one showing a centrally located longitudinal band, the other containing many transverse band ($\times 46\ 000$).

and inguinal regions (1). Even though they may be widely disseminated, they are apt to be more conspicuous in these seborrhoeic areas. The careful observer, however, will find the clinical picture to be quite different from that in seborrhoea. The eruption consists of yellow to brown or red-brown papules which sometimes coalesce and sometimes remain discrete. Oozing may be seen, especially in the skin folds. Necrosis and ulceration of the infiltrations may develop. In the skin folds, particularly of the axillary, inguinal, retroauricular and intergluteal regions, longitudinal fissures may appear, suggestive of candidiasis.

In our patient the clinical picture was typical of the skin lesions in histiocytosis X. The localization of the eruption largely in the seborrhoeic regions (face, retroauricular and interscapular regions, axillary and inguinal folds), and the lesions which consisted of pink to reddish-brown papules, sometimes with a central ulceration and crust, and occasional deeper infiltrations and longitudinal fissures in the skin folds, were suggestive of the diagnosis of histiocytosis X. The search for evidence of the disorder in other organs was negative. During the 3 years the patient has been under our care and observation, repeated laboratory and other investigations have all been without pathological findings, with the exception of the accelerated ESR. The history of the disorder in this patient extended back some 25 years. It can only be concluded, therefore, that he represents a case of histiocytosis X limited to the skin alone.

The diagnosis was confirmed by the histological

examination, which revealed a dense infiltration composed mainly of large histiocytes with large, oval-shaped, homogeneous nuclei. The electron microscope findings showed an abundant cytoplasm in the histiocytes, with numerous mitochondria, vacuoles and Langerhans' cells granules. Vernon et al. (15) also reported this association of Langerhans' cell granules with cytoplasmic vacuoles in histiocytes of human lymph nodes, noting that there appeared to be a budding from the vacuolar membrane. In our study too, the association between the Langerhans' cell granules and the vacuoles was remarkable (Fig. 9). Although cells containing Langerhans' cell granules have been most frequently found in histiocytosis X (6), they have also been found in many other non-related diseases (8, 15). Prunieras (12) and later Vernon et al. (15) suggested that histiocytes with Langerhans' cell granules represent a special type of macrophage which may be related to the cellular response to antigens. The origin of Langerhans' cells is still a controversial topic. Hashimoto & Tarnowski (7) suggested that there is a migration of histiocytes into the epidermis from the dermis, whereas Zelickson (19, 20) postulated that the Langerhans' cells migrate from the epidermis to the dermis. The association of the Langerhans' cell granules with the Golgi apparatus or their similarity thereto, as observed in the present case, was also reported by Wolff (17), Wolff & Schreiner (18) and Zelickson (19, 20). Apparently there may be more than one mode of formation or origin of these granules, as has been suggested by several

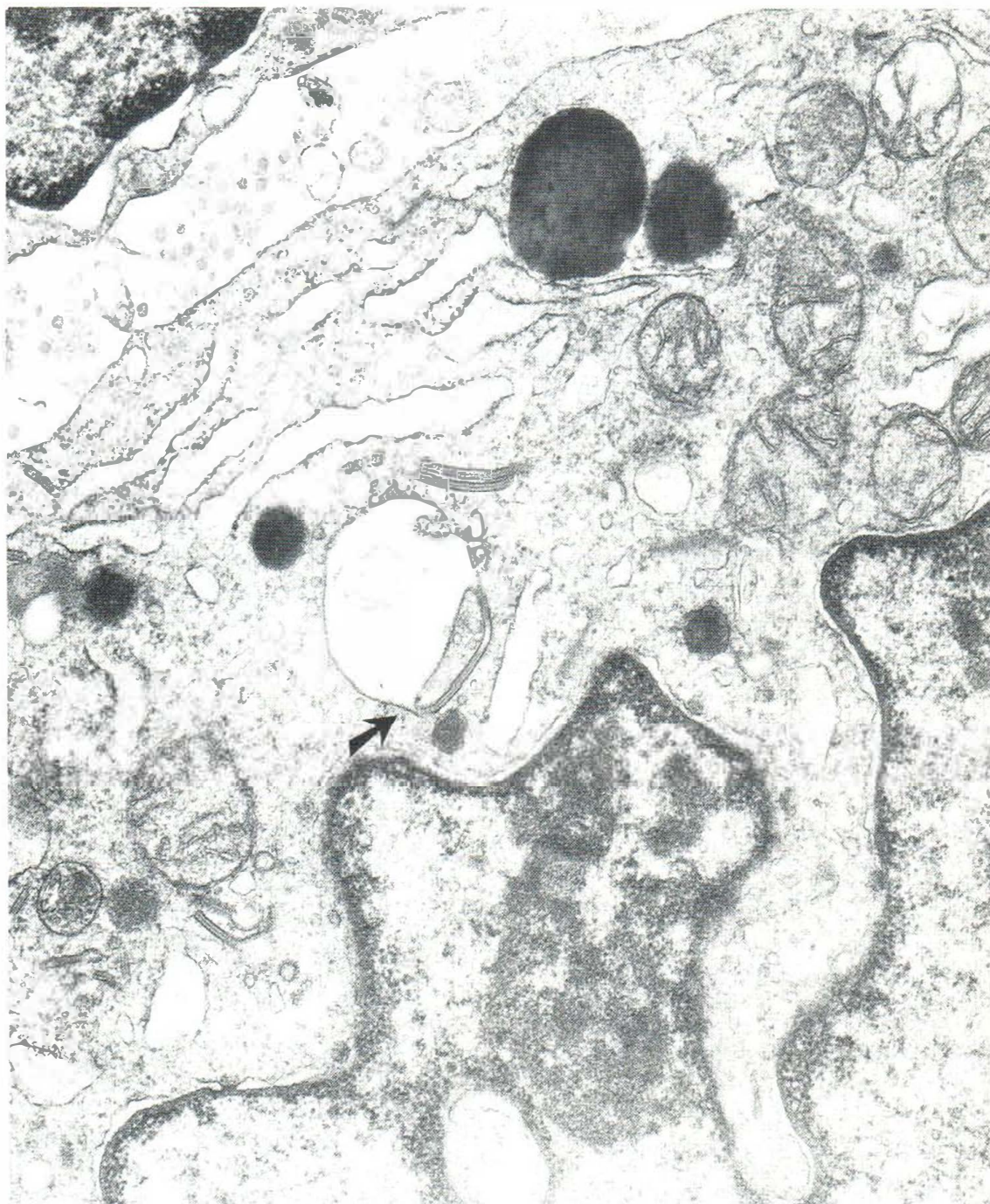


Fig. 9. Lobulated nucleus, mitochondria, rough endoplasmic reticulum, a few dense bodies and Langerhans' cell granules; one granule is contiguous with a membrane-bound empty vacuole (arrow) ($\times 12600$).

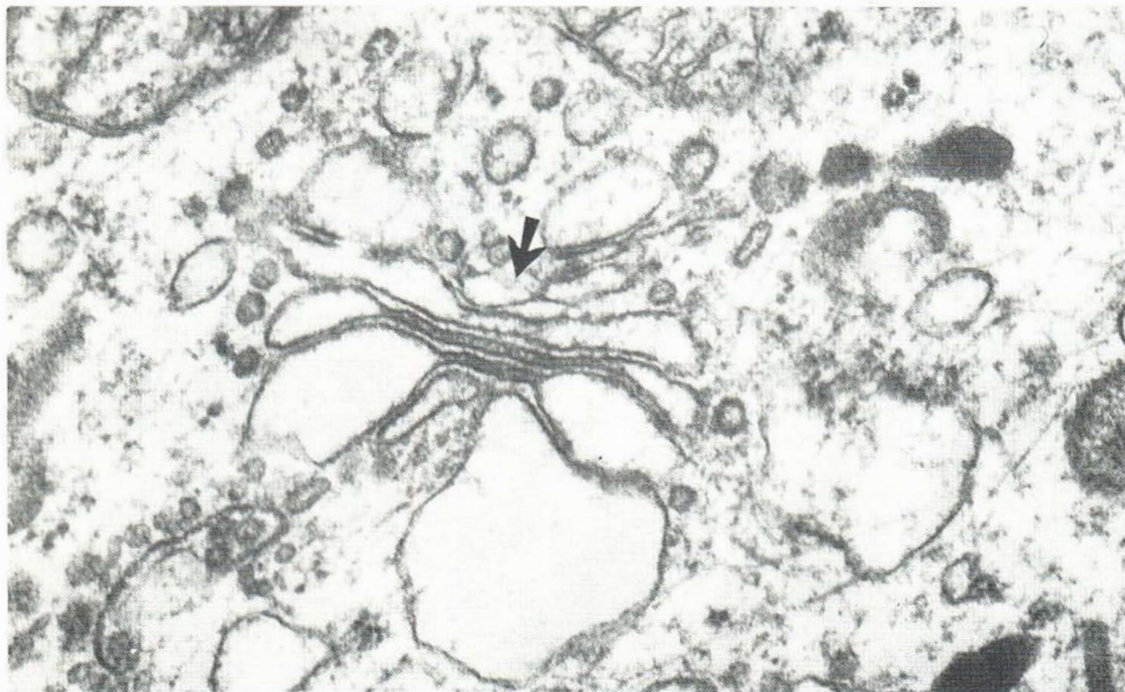


Fig. 10. Golgi apparatus: longitudinal formations connecting cisterns which resemble Langerhans' cell granules (arrow) ($\times 27\,000$).

authors (2, 3, 9). It is of interest that Rupec & Uhlarik (13), who demonstrated lymphoid cells in the basal layer of the epithelium of normal human vaginal mucosa, postulated a transition of these cells into Langerhans' cells.

Considering the relative rarity of (a) cases of histiocytosis X in adults, and (b) cases of histiocytosis X restricted to the skin alone, the present case, which combines these two features, is of particular interest and may be an aid to the diagnosis of similar cases encountered by the dermatologist.

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