THE FINE STRUCTURE OF THE LANGERHANS CELL GRANULE

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INTRODUCTION

During the last few years increasing attention has been focused on Langerhans cells and their peculiar granules (1–5). These organelles were considered specific products of the intraepidermal dendritic cells (1–3), but recently identical structures have been observed in osseous and pulmonary lesions of histiocytosis X (6). The Langerhans cell granule resembles a tennis racket. It is rodlike with a striated central line and a partly expanded limiting membrane at one end (1–3). Birbeck et al. (1) consider it disc-shaped and suggest that the tennis-racket image represents a formative stage of the granule. The present study provides more information on the fine structural features of this organelle.

MATERIALS AND METHODS

Specimens of normal human skin measuring 1 mm^3 were fixed in 1% buffered osmium tetroxide (pH 7,3), rapidly dehydrated, and embedded in Epon (7). Ultrathin sections were cut on a Reichert OMU 2 ultramicrotome, contrasted with uranyl acetate and lead citrate, and examined with a Zeiss EM 9 electron microscope.

RESULTS

Langerhans cells have a lobulated nucleus and lack desmosomes as well as tonofilaments. Their cytoplasm contains a well-developed Golgi apparatus, endoplasmic reticulum, mitochondria, centrioles, and lysosomes (Fig. 1). They produce characteristic granules which exhibit different morphologic features in different planes of section. Their most common electron microscopic image is that of a rodlike profile with rounded ends and a limiting membrane approximately 55–60 A thick (Figs. 2 *a–d*, 3 *a*). The internal face of the membrane is lined by a one-dimensional array of small particles spaced at 50–60 A intervals which form a leaflet attached to the membranous envelope (Figs. 2 *d*, 3 *a*). Midway between the limiting membranes is a central lamella composed of electron-opaque particles separated by 50–60 A wide spaces (Figs. 2 *a–d*, 3 *a*) and aligned in two closely set, parallel lines (Figs. 2 *d*, 3 *a*). Owing to the regular spacing of these particles, the rodlike structures acquire a definite pattern of cross-striation.

These profiles are very often continuous with round vesicles and thus resemble tennis rackets (Figs. 2 *a–d*, 3 *a*, *c*). Usually, the vesicle is located at one end of the granule but may also be seen in its center, with the rodlike structures projecting from its circumference (Figs. 2 *b*, 3 *c*). The vesicles have a clear center and the internal face of their limiting membrane is coated by a fuzzy or finely granular material (Figs. 2 *b*, *d*, 3 *a*). Vesicles lacking rodlike components but showing a "fuzzy zone" are frequently seen in the Golgi region (Fig. 2 *a*). These structures may represent tennis-racket granules cut through the racket portion or may really be devoid of the rod-shaped structures. The fuzzy zone of their limiting membrane permits their differentiation from smooth-walled Golgi vesicles. If the granules are cut face on, they appear as rounded or oval bodies containing a two-dimensional, square lattice of small particles (Fig. 3 *b*). In slightly different planes of section these particles seem to merge into linear bands giving the organelle a cross-striated appearance (Fig. 3 *c*). The vesicle portion of the granule appears "stuck on" to the periphery of such platelike profiles or is seen in their center (Fig. 3 *b*). The large majority of Langerhans cell granules is found within or in the vicinity of the Golgi region, but they can also be seen in other areas of the cytoplasm and in the dendritic processes. Not infrequently, the granules are attached to the plasma membrane and their interior is continuous with the extracellular space (Figs. 4, 5).

THREE-DIMENSIONAL STRUCTURE OF THE GRANULE: From its variable images in different planes of section the Langerhans cell granule emerges as a flat, platelike structure approximately 50 mμ thick and up to 1 μ in diameter (Fig. 6). However, the platelike body may be also slightly bent or curved to acquire a shape similar to a cup (Fig. 3 *c*). As demonstrated by the stereo model in Fig. 6, the individual particles form a three-dimensional lattice composed of four separate, two-dimensional sheets. The global or hemispherical bleb protruding from the granule's surface corresponds to its vesicle portion in cross-sections.

FIGURE 1 Langerhans cell in suprabasal layers of the epidermis. Note desmosome-free cytomembrane (arrows) and absence of tonofilaments from cytoplasm. *G*, Golgi complex; *N*, nucleus; *L*, rod-shaped Langerhans cell granules; *V*, vesicle portions of granules. × 16,500.

DISCUSSION

Our results support previous conclusions that the Langerhans cell granule represents a plate- or disc-shaped body. The model proposed by Birbeck et al. (1) pictures its interior as a single sheet of regularly spaced particles, but our observations indicate that its structure is more complex and that four such leaflets are present. Two leaflets form the central lamella while two are attached to the membranous envelope, one on each side. It is also apparent that the "racket" portion of the granule does not represent a single, membrane-

limited vesicle, but that an ill-defined, fuzzy zone of amorphous material is interposed between its clear center and limiting membrane.

Two different modes of granule formation have been advanced so far: the granules either are derived from Golgi vesicles which convert into platelike bodies (2, 3) or they are formed by an infolding and subsequent nipping off of a portion of the plasma membrane (2). The first possibility would infer that the granule acquires its final shape by an out-pouching and a collapse—taking place in stages—of a segment of the vesicle wall (2). In this instance the corresponding portions of the vesicle's fuzzy zone would fuse in a zipper-like fashion (Fig. 2 *b*, *d*) and could provide the matrix for the three-dimensional lattice of particles in the disc portion of this organelle. This mode of formation and the intracytoplasmic distribution of the granules would also suggest that the granules move from the Golgi region to the periphery of the cell, attach to the cytomembrane, and open to the extracellular compartment (2, 3). Such a sequence of events could be considered suggestive of a secretory activity of the Langerhans cell. The other alternative would imply a different direction of granule movement, i.e. from the cell periphery to the Golgi region, and this could signify a process by which substances, such as the particles of their crystal-like internal lattice, are taken up from the extracellular space. Although our findings do not provide definite evidence for either of these two postulated processes, the much greater number of granules in the Golgi region, their close topographic relationship to Golgi cisternae (Fig. 2 *a*, *c*), and above all their complex and highly organized internal structure seem to indicate that they originate from Golgi vesicles. However, until Langerhans cell granules can be labeled and unequivocally traced through all stages of their life cycle, their morphogenesis and fate remain open to discussion.

The nature of Langerhans cells is still an enigma, but there is now sufficient evidence that they are neither neural elements (2) nor derivatives of melanocytes (4, 5). Their relationship to the histiocytes in histiocytosis X which contain identical granules (6) also remains to be solved. A clarification of the biological significance of Langerhans cell granules should definitely improve our understanding of this problem.

SUMMARY

The fine structure of the Langerhans cell granule was studied in osmium tetroxide–fixed specimens of human skin. It was shown that the granule represents a flat or curved disc-shaped body containing four sheets of regularly spaced particles forming a three-dimensional lattice. A model of the granule is presented and its mode of formation discussed.

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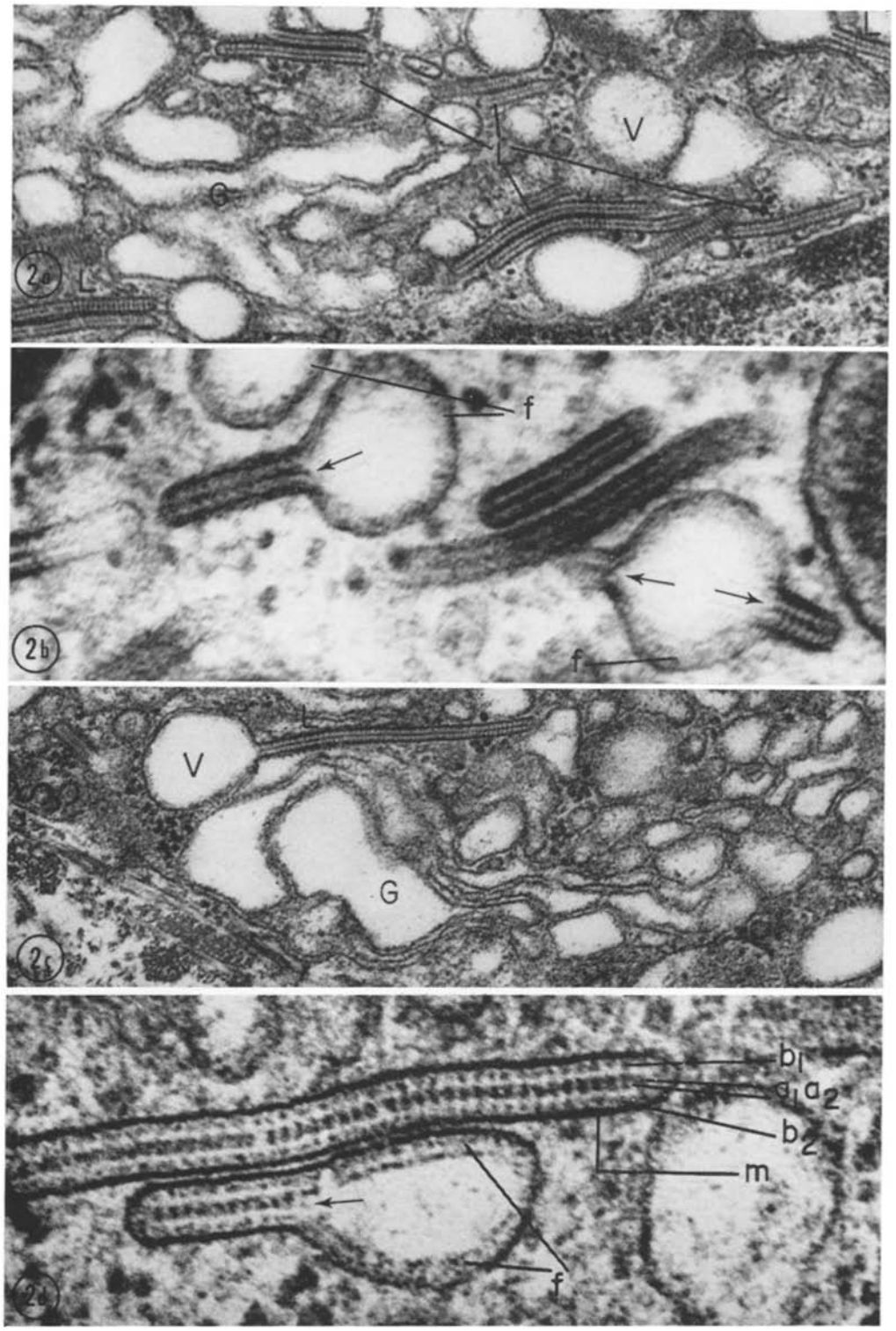
FIGURE 2 (*a*) Langerhans cell granules (*L*) in Golgi region (*G*). Simple rod-shaped and tennis-racket profiles and vesicles (*V*) representing the vesicular portion of such granules are present. × 50,000. (*b*) Rod-shaped and tennis-racket profiles of Langerhans cell granules. Note cross-striation of central lamella of the rod-portion and fuzzy zone (*f*) of the vesicle. Arrows indicate probable point of fusion of two opposite fuzzy zones and formation of central cross-striated lamella. × 111,000. (*c*) Langerhans cell granule (*L*) in Golgi region. Note proximity of the vesicle portion of granule (*V*) to Golgi cisternae (*G*). × 52,000. (*d*) Fine structure of the granule. The membrane (*m*) envelops two sheets of particles (b_1 and b_2) attached to it and a central lamella composed of two linear arrays of particles (a_1 and a_2). Similar particles, though less well oriented, are seen in the fuzzy zone (*f*). Arrow indicates probable site of fusion of the two fuzzy zones. × 174,000.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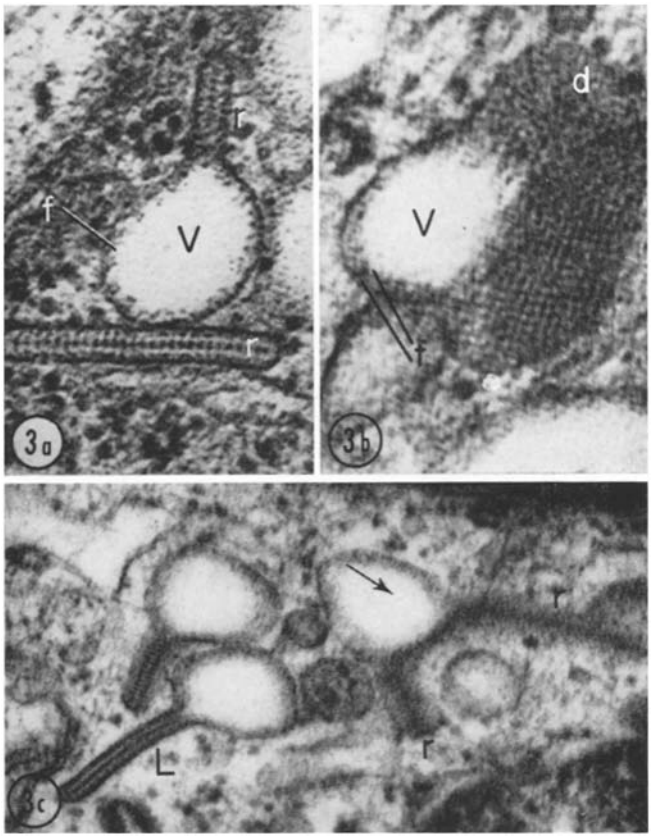

FIGURE 3 (*a*) Langerhans cell granules appearing as rods (*r*) with vesicles (*V*) in cross-sections. *f*, fuzzy zone. × 110,000. (*b*) The granule cut in a plane perpendicular to that in Fig. 3 *a*. It now appears as a disc (*d*) composed of a square lattice of particles. *f*, fuzzy zone of the vesicle. × 81,500. (*c*) Tennis racket-like images of Langerhans cell granules (*L*). The arrow denotes a granule the rod portions (*r*) of which have been cut somewhat obliquely and form an angle of approximately 60°. Three-dimensionally, this organelle probably represents a cup rather than a plate.

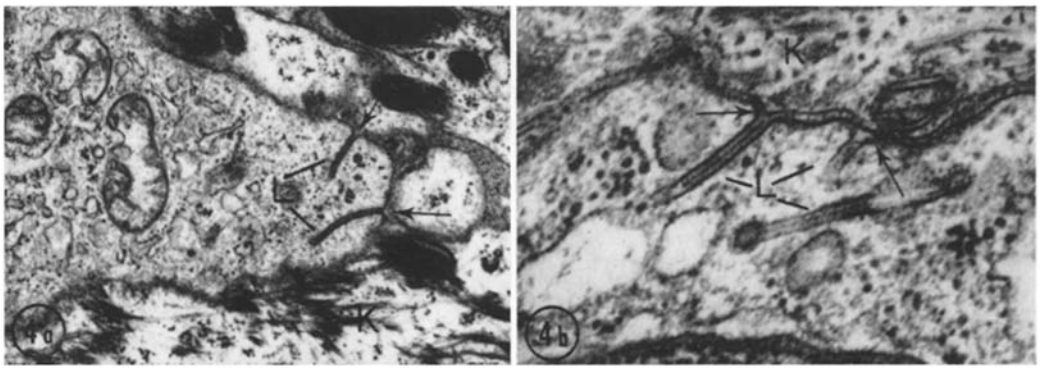

FIGURE 4 (*a* and *b*) Langerhans cell granules (*L*) attached to the cytomembrane. Their interior is continuous with the extracellular space (arrows). *K*, keratinocyte. Fig. 4 *a*, × 18,000; Fig. 4 *b*, × 57,500.

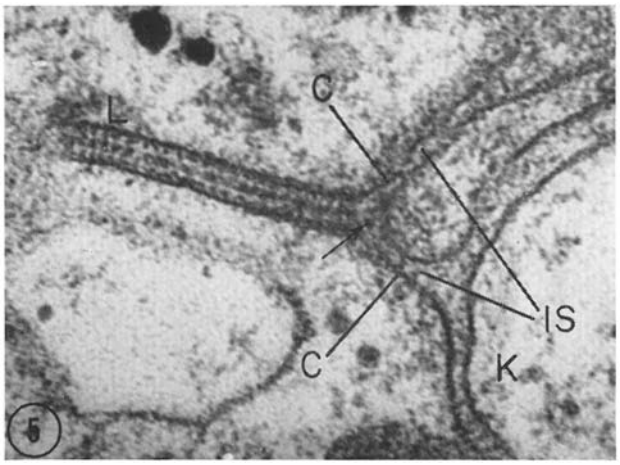

FIGURE 5 The limiting membrane of this Langerhans cell granule (*L*) is continuous with the cytomembrane (*C*) so that the interior of the granule is open to the intercellular space (*IS*). *K*, keratinocyte. × 110,000.

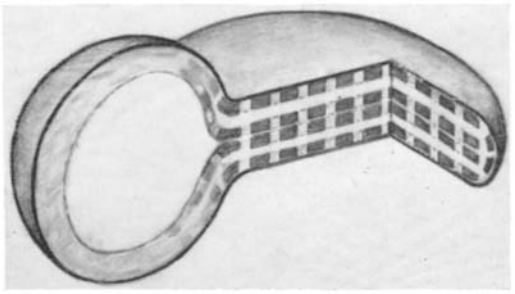

FIGURE 6 Schematic three-dimensional model of Langerhans cell granule.

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