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Langerhans Cells as Macrophages in Skin and Lymphoid Organs

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Properties of epidermal Langerhans cell were compared with those of a number of other dendritic cells in lymphoid organs and of mononuclear phagocytes. Among the dendritic "reticulum" cells included were indeterminate dendritic cells from the epidermis, interdigitating "reticulum" cells from T-dependent areas of lymphoid tissue and thymus, follicular dendritic cells of Nossal, and the dendritic cells described by Steinman and Cohn. Interdigitating cells with typical Birbeck granules, in the thymus and in the paracortices of lymph nodes, which are morphologically indistinguishable from Langerhans cells and indeterminate dendritic cells in the epidermis, appear to belong to the same system and possibly represent a subpopulation of "macrophages." On the basis of their similarity to these other dendritic cells, we believe Langerhans cells may function in antigen presentation, lymphokine production, provision of a microenvironment for T lymphocytes, and prostaglandin secretion.

The identification of Birbeck granules in the cytoplasm by electron microscopy, and the histochemical demonstration of surface ATP have allowed a number of morphological observations on LCs [1–3], e.g., their presence in histiocytosis X, evidence that Langerhans cells (LCs) migrate from the dermis into the epidermis [2], and the apposition of cells containing Birbeck granules and lymphocytes in epidermis, dermis, lymph nodes, and thymus [3]. These observations opened the way to investigations of a possible immunologic function of LCs.

Breathnach [2] summarized the problem of the origin of LCs by remarking that the presence of LCs within the epidermis had, perhaps, in the past led to an overly concentrated effort to relate their prime function to purely epidermal processes, while embryologic evidence suggesting a mesenchymal origin of LCs showed that their function was related to the whole skin. There is a growing body of information that shows LCs can migrate and have many properties in common with the mononuclear phagocyte series. This article compares LCs to monocytes and to a few types of dendritic cells found in lymphoid tissue.

STUDIES ON THE ORIGIN AND TURNOVER OF LANGERHANS CELLS

Major approaches to the study of the origin of LCs are summarized in Table I. Our own studies led us to propose that the LC may be a highly differentiated end stage of a bone-marrow-derived cell line similar to, but separate from, the known phagocytic macrophage cell line [3,17]. The finding that bone marrow is a characteristic location of histiocytosis X, e.g., eosinophilic granuloma of the bone [18], is of relevance to the possible derivation of LCs from bone marrow. Cells containing LC granules have also been found in patients with monocytic leukemia [15]; this is particularly noteworthy since macrophages are derived from monocytes, which originate in the bone marrow [19].

Recent studies by Tamaki and Katz [16] have made use of the fact that LCs exhibit Ia antigens on their surfaces. They found that in murine chimeras, observed up to 11 wk after injection of bone marrow from one strain into irradiated recipients of another (H-2-different) strain, a large percentage of LCs in the epidermis were of donor origin. (These studies are described elsewhere in this issue [16].) This type of result may indicate something about the turnover rate of at least some LCs.

Autoradiographic studies have shown that the LCs can incorporate thymidine into newly synthesized DNA and this has led to the belief that LC populations are stable and self-replicating [20,21]. At the ultrastructural level occasional mitotic figures of LCs have been reported [22,23].

There is much evidence that LCs are capable of movement. Ultrastructurally, they sometimes display networks of microfilaments [3], with the dimensions of actin [24], as well as a prominent system of microtubules [24]. These two features are usually found in cells that move. Tissue cultures of human and guinea pig epidermis have shown that LCs have active pseudopodial movements and dendrites that extend and retract. Strong contact inhibition has been observed, such that LCs never pass over continuous monolayers of cultured keratinocytes [25,26]. The possible movement from epidermis to dermis and the subsequent appearance in dermal lymphatics during immunologic reactions involving skin also suggest migration of LCs (discussed elsewhere in this issue [27]).

The tape-stripping method eliminates LCs from the epidermis [28]. Normal numbers of LCs are reestablished by the 15th day after injury, even though the rest of the epidermis is regenerated in 4 days. Tape stripping might be a good way to study LC kinetics, but the preliminary results on the mechanism of LC reappearance have been inconclusive. During wound healing LCs migrate with other epidermal cells into the injured area. Some of them incorporate tritiated thymidine, an indication that they respond to injury both by migration and by an increase in mitotic activity [29]. There is, after a time, a tendency to reestablish a fairly constant LC:keratinocyte ratio [28].

In summary, then, little is known about the turnover of LCs, and they most likely originate in bone marrow. Yet, bone marrow under normal conditions does not show any cells with LC granules. In the rest of this article we will make a survey of the properties of a variety of cells that could be relatives or precursors of the LC.

Comparison of Langerhans Cell Properties to Those of Macrophages

Epidermal LCs express Fc-IgG and C3 receptors [30] and those antigens (Ia antigens) of the major histocompatibility complex [31–35] known to be involved in geneticaly determined immune responsiveness (HLA-D, human, and Ir-region, guinea pig and mouse). The presence of such cell surface components, which are also present on a variety of lymphoid cells and macrophages, suggests that LCs are functionally related to cells

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Abbreviations:
DRCs: dendritic reticulum cells
LCs: Langerhans cells
L-dopa: naturally occurring form of 3,4-dihydroxyphenylalanine
2-ME: 2-mercaptoethanol
inner PALS: inner portion of the periarteriolar lymphatic sheath
RCs: "reticulum" cells
UVL: ultraviolet light

TABLE I. *Summary studies on the origin of Langerhans cells*

Tissue or cell system of origin considered	Experimental approach	Conclusion	Reference
Neural crest	Neural crest removed in the embryo	Neural crest excluded	[4,5]
Thymus	Study of athymic mice	Thymus excluded	[6][a]
Embryonic epidermis	Epidermal transplant of mouse to chicken	Ectodermal origin likely[b]	[7]
Keratinocytes	Detection of LC granules in fetal keratinocytes	Relationship possible[c]	[8]
Melanocytes	Use of depigmenting agents	Melanocytes unrelated	[9-12]
Indeterminate dendritic cells	Detection of surface markers	Probably related	[13]
	Quantitative relationships to LCs during delayed hypersensitivity reactions	Probably related	[14]
	Study of fetal skin	Probably related	[2]
Monocytes	Detection of LC granules in monocytic leukemia	Possibly related	[15]
Bone marrow	Skin transplants bone marrow chimeras	Bone marrow origin likely	[16]

[a] Silberberg-Sinakin I, Thorbecke GJ, unpublished data.

[b] Only true if cells of mesenchymal origin are totally lacking in epidermis of 10.5-day-old mouse embryo.

[c] Bell [8] points out that other interpretations are possible; this phenomenon is not frequently observed.

Abbreviation: LC, Langerhans cell.

found in lymphoid organs. At the ultrastructural level, the Ia antigens have been found on cell surfaces and on dendrites of LCs but not on Birbeck granules [36].

Tables II through V list some of the similarities and differences between LCs and typical macrophages (such as are found in the peritoneal cavity). The heterogeneity of such macrophages is beginning to be explored; for instance, only 8 to 15% of peritoneal cells have been found to bear Ia antigen [65]. It is this Ia-positive subpopulation of cells of the monocyte family that might be a precursor of LCs.

For a comparison with macrophages it is important to consider the reports describing the ability of LCs to take up substances *in vitro* [83,97–100] and *in vivo* [1,17,83,84,101, 102]. Shelley and Juhlin [99,100] have shown that LCs can selectively absorb or remove the following compounds, each of which can cause contact dermatitis: formaldehyde, glutaraldehyde, paraphenylenediamine, ethylenediamine, toluenediamine, nickel, cobalt, chromium, mercury, and gold. Some of the same substances taken up by LCs can be used to stain them [103]. Also, LCs take up L-dopa (the naturally occurring form of 3,4-dihydroxyphenylalanine), serotonin, and catecholamines [97,98], a phenomenon of which the significance is not known.

The pinocytic or phagocytic activities of LCs have also been studied. Pinocytosis of ferritin [83,101], thorotrast [104], and peroxidase molecules [105] is less evident in LCs than in keratinocytes. Phagocytic activity studied *in vivo* with antigen-antibody complexes is much less than that of typical macrophages [24].

The property of paramount importance for the recently shown ability of LCs to present antigen to T lymphocytes *in vitro* [88] may be their ability to bind antigens to their surfaces [17,100]. Comparison of LCs and macrophages that are important in presenting antigen to lymphoid cells is difficult with respect to this property since this Ia-positive [106] subpopulation [65] has not been studied in this regard as a separate entity. The highly phagocytic nature of the majority of classical macrophages makes it difficult to study the binding of antigen to the cell surface.

Comparison of Langerhans Cell Properties to Those of Indeterminate Dendritic Cells in Skin

There are dendritic cells in the epidermis without recognizable Birbeck granules. Although it cannot readily be excluded that there might be occasional granules in these cells that are missed in electron microscopy, these cells are called "indeterminate dendritic cells" [107]. They have also been called Type 3 cells [108] or α dendritic cells [109]. These cells appear to be more numerous in the basal than in the suprabasal layers, but there are usually fewer of them than of LCs. Indeterminate cells are also found in oral mucosal epithelium, in the lamina propria of oral mucosa, in the dermis of fetal and adult skin [1,2,109,110], in dermal lymphatics [27], and in marginal sinuses of lymph nodes [27]. (The relationship between epidermal indeterminate dendritic cells and LCs is reviewed elsewhere in this issue [111].)

The presence of Ia antigen on these cells as well as on LCs reemphasizes their similarity [13] (Table 1). When comparing LCs to other dendritic cells and macrophages, however (Tables II through V), we have chosen not to include indeterminate dendritic cells, but only the typical epidermal LC with LC granules to avoid confusion. Results obtained with electron microscopy of rosette-forming epidermal cells in mice suggest that Fc receptors are also present on indeterminate dendritic cells [73]. Since it is difficult to combine electron microscopy with some of the enzyme stains and with detection methods for surface receptors, indeterminate dendritic cells have not yet been examined for some of the other properties of LCs.

Comparison of Langerhans Cell Properties to Those of Interdigitating Reticulum Cells of Lymphoid Organs

Lymph nodes: Interdigitating "reticulum" cells (RCs) occur in the thymus-dependent, paracortical areas of lymph nodes [38–40,46,48,52,58,92,112]. These cells, like LCs, bear Ia antigens [64], are ATPase-positive, and resemble LCs, but the majority of them, like epidermal indeterminate dendritic cells, lack LC granules (Tables II through V). Langerhans-cell-granule-containing cells are present in normal lymph nodes [17,113,114], but are seen more frequently in lymph nodes draining injection sites of antigen [17,48] (Fig 1 through 4). Cells that look like indeterminate dendritic cells and LCs have also been found in dermal lymphatics [17,27], afferent lymph vessels [50], and in lymph node sinuses [17,27] (Fig 1) after intradermal challenge with antigen. Kamperdijk and Hoefsmit [115] have suggested that the paracortical interdigitating RCs may be derived from afferent lymph since they disappear 6 wk after ligation of all afferent lymph vessels. Therefore, it appears that interdigitating RCs with or without typical LC granules may arrive in the paracortices of lymph nodes from the skin. An alternative explanation for the transient increase in LC-granule-containing cells seen after local stimulation with antigen in paracortical areas could be that interdigitating RCs form LC granules in response to stimuli [48]. These were detected only during the induction phase of the immune response for approximately 1 day, after which either the cells containing the LC granules, or just the LC granules themselves, disappeared [48]. It is difficult to differentiate between skin-derived LCs migrating into the paracortices of lymph nodes and interdigitating RCs rapidly producing LC granules. The similarity between LCs and paracortical interdigitating RCs has also been stressed by Rausch, Kaiserling, and Goos [112], who have suggested that these cells may have similar functions. More conclusive evidence, such as the ability to fix antigen on the cell surface of paracortical interdigitating RCs, needs to be obtained before such a functional relationship between LCs and interdigitating RCs can be put on a firm base. A schematic representation of the areas in lymph nodes and spleen where interdigitating RCs have been observed is given in Fig 5 and Fig 6.

Spleen: Within the spleen, each thymus-dependent area and each inner portion of a periarteriolar lymphatic sheath (inner

TABLE II. *Comparison of Langerhans cells with other dendritic lymphoid cells and macrophages: Structure*

Cell type	Morphological criteria							
	Location	Cell shape[a]	Nuclear shape	Micro-filaments	Vesicles	Lysosomes	Rough endoplasmic reticulum	Birbeck granules
Langerhans cell [2,3,37]	Squamous epithelia	Dendritic	Irregular	+	+ − +++	+ − ++	+ − ++	+ − +++[b]
Interdigitating reticulum cell[c,d] [38-41]	Spleen-PALS thymus-medulla lymph node paracortex	Dendritic	Irregular	+	+++	+ − ++	+ − ++	(+)[e] [48]
Monocyte or macrophage [42,43]	Spleen red pulp lymph node sinuses and medulla peritoneal cavity	Irregular	Bean-shaped	+	++ − +++	+++	++	−
Nossal's follicular dendritic reticulum cell [44-46]	Mantle zone of lymph node follicles	Dendritic	Oval to quadrangular		+++	(+)[e]	+	−
Steinman-Cohn's dendritic cell [43-47]	Spleen white pulp lymph nodes Peyer's patches	Dendritic	Irregular		+	+	+	−

[a] As is true of the structure and appearance of other cells, the structure of the Langerhans cell and the appearance of the cell membrane (ruffled [49,50] invaginations and protrusions, number of dendrites, etc.) may be influenced by its location (epidermis, dermal lymphatics, or marginal sinus of a lymph node) (Fig 1).

[b] In Tables II through V we are comparing Langerhans cells (LCs) from squamous epithelia containing typical LC granules with other cell types. Although we regard the indeterminate dendritic cell from epidermis as a closely related, if not identical, cell that is poorly supplied with or lacking in LC granules, we have not included it since few of its properties have been specifically studied.

[c] Interdigitating "reticulum" cells (interdigitating RCs) were first given that name by Veldman [38] because they showed an interlocking of cell membranes and because of the presence of fingerlike protrusions, into their cytoplasm, extruding from lymphocytes trapped between their cytoplasm extensions.

[d] In this article we have used the word "reticulum" for both the interdigitating reticulum cell and the follicular dendritic reticulum cell (called indeterminate dendritic cell [IDC] and dendritic reticulum cell [DRC] by Hoefsmit et al [40,46], respectively) to help differentiate these cells in lymphoid tissue from the indeterminate dendritic cell in skin. The name does not imply that we assume a derivation from the reticulum for these cells since another possibility is that they are bone-marrow-derived.

[e] The (+) indicates sometimes present, sometimes absent. Langerhans cell (LC) granules are seen in these cells most frequently in the thymus [41]. When cells with this appearance show LC granules in the lymph nodes, the possibility that they have just migrated into the lymph nodes and are epidermally derived typical LCs cannot be excluded. The inner portion of the periarteriolar lymphatic sheaths: interdigitating reticulum cells have no LC granules.

Abbreviation: PALS, periarteriolar lymphatic sheath.

TABLE III. *Comparison of Langerhans cells with other dendritic cells and macrophages: Histochemical characteristics*

Cell type	Histochemistry					
	ATPase	Aminopeptidase	Nonspecific esterase	5'Nucleoside	Peroxidase	Acid phosphatase
Langerhans cell	+ [12,51]	−; +[a] [54]	+ [56,57]		−	(+)[c] [12]
Interdigitating reticulum cell[d]	+ [52]		(+)[c] [58]	− [52]	(+)[c] [46]	(+)[c] [58]
Monocyte or macrophage	+ [43,53]	+ [55]	++ [59]	+ [53]	+ [46]	+ − +++ [43,53]
Nossal's follicular dendritic reticulum cell	−; +[e] [52,53]		+ [58]	+; −[f] [52,53]	− [46]	− [58]
Steinman-Cohn's dendritic cell	− [43]				− [43]	(+)[c] [43]

[a] The + is for guinea pig and the − for human being.

[b] Usually negative in normal Langerhans cells (Silberberg-Sinakin I, unpublished data), but positive in Langerhans cell granulomas (Basset F, personal communication).

[c] The (+) indicates sometimes present, sometimes absent (within same species).

[d] See Table II, footnote d.

[e] The + is for rat and the − for human being [54].

[f] The − is for rat and the + for human being.

PALS) contain a network of interdigitating RCs similar to that of paracortices of lymph nodes [38–40], but cells containing typical LC granules have not yet been seen in this location.* Tight junctions [38,39] and gap junctions [39] between T cells and interdigitating RCs have been described as occurring regularly. In studies by van Ewijk et al [92] on lethally irradiated mice reconstituted with thymocytes, an intimate contact between the interdigitating RCs of the PALS and the T lymphocytes was observed in the form of fingerlike protrusions, extending from the lymphocytes and protruding into the cytoplasm of the interdigitating RCs. Electron-dense material, often seen as cross-bridges about 120 Å in length, were present in the extracellular spaces of these contact regions.

Thymus: A close relationship between lymphocytes and mes-

* Hoefsmit ECM, personal communication.

TABLE IV. *Comparison of Langerhans cells with other dendritic cells and macrophages: Membrane receptors and antigens*

104	Cell type	Membrane receptors and antigens				
		Fc (IgG)	C3b[a]	Ia[b]	T cell markers	Surface IgM
109	Langerhans cell	+ [30]	+ [30,62]	+ [31–35]	– [30]	– [30]
110	Interdigitating reticulum cell[b]	(–)[d]	(–)[d]	+ [64]		
111	Monocyte or macrophage	+ [60]	+ [63]	8-15%+ [65]	– [67]	– [67]
112	Nossal's follicular dendritic reticulum cell[c]	+[e] and/or	+[e]			
113	Steinman-Cohn's dendritic cell	– [61]	– [61]	+ [66]	– [61]	– [61]

[a] Some of the cells have receptors for other determinants of C3. Among receptors for C3b and among Fc receptors there is variability in resistance to trypsin digestion [62].

[b] Although the comparison between cells at this time can best be made for the mouse, the equivalents of Ia antigens have also been found on Langerhans cells in the guinea pig [35] and man [33,34]. In the mouse the products of at least 2 loci, both needed on the same macrophages for antigen presentation to T cells [71,72], and called I-A and I-E/C, respectively, have been identified on Langerhans cells [73,74].

[c] See Table II, footnote d.

[d] Binding of erythrocyte with antibody (EA) or erythrocyte with antibody plus complement (EAC) to thymus-dependent regions in lymph nodes and spleen has not been observed in frozen tissue sections [68]. This, however, does not exclude the presence of the Fc and C3 receptors on a minor population in these areas. These receptors have not yet been found on indeterminate dendritic cells in skin.

[e] Follicular dendritic "reticulum" cells (DRCs) are known to bind the Fc but not the Fab fragments of IgG and therefore appear to have an Fc receptor [69]. However, the absence of C3 in the serum inhibits localization of immune complexes in follicles [70], a fact that suggests a role of C3 and therefore of a C3 receptor on DRCs as well. Consequently, in this table we have indicated the presence of these receptors.

TABLE V. *Comparison of Langerhans cells to other dendritic cells and macrophages: General properties*

Cell type	Apposition to lymphocytes	Glass adherence	Phagocytosis	Pinocytosis	Antigen binding	Ability to present antigen to lymphoid cells	Induction of mixed lymphocyte reaction	X-irradiation resistance	Bone marrow origin
Langerhans cell	(+)[a,b] [49,75,76]	+ [79]	(+)[b] [24]	+ [1,83,84]	+ [17]	+ [88]	+ [88]	High [17]	+ [16]
Interdigitating reticulum cell[c]	+ [38,39,80]		(+)[b]	+ [46]				Medium[d] [64,92]	
Monocyte or macrophage	+ [77]	+ [42,81]	+++ [81,82]	+ [85]	+ [67]	+ [67,89]	+ [88,90]	High [67]	+[e] [96]
Nossal's follicular dendritic reticulum cell[c]	+ [44,45]		–	(+)[b] [44,45]	+[f] [44,86,87]			Low [93,94]	[g]
Steinman-Cohn's dendritic cell	+ [78]	+[h] [43,61]	– [61]	(+)[b] [61]	– [61]		+ [91]	Low [95]	+ [95]

[a] Applicable only when lymphocytes are present in their vicinity, such as in contact dermatitis [75].

[b] The (+) indicates sometimes present, sometimes absent.

[c] See Table II, footnote d.

[d] Although some decrease in interdigitating reticulum cell numbers may occur in the spleen of irradiated mice, thymocyte-reconstituted animals have a fairly normal appearance [92]. Thus, quantification of the X-irradiation resistance of these cells is still needed, and the possibility that thymocytes "replenish" them also must be evaluated. However, the Ia plus reticulum cell in the inner part of the periarteriolar sheath of the mouse spleen appears to survive 900-R whole-body irradiation.

[e] A bone marrow origin has also been shown for the Ia-positive subpopulation of macrophages, which is needed for antigen presentation to T cells [72].

[f] See footnote d, Table IV. Some so-called sticky antigens and nonantigenic substances may become localized on dendritic reticulum cells without antibody [87]. This phenomenon may be due to activation of C3 via the alternate pathway rather than to antigen binding as such.

[g] Reconstitution of antigen binding function in irradiated animals on days 1 and 8 post irradiation is shown after spleen or peritoneal exudate cell transfer, but not after bone marrow transfer [93].

[h] In a recent publication [66], it has been shown that Steinman-Cohn's dendritic cells initially adhere to surfaces, but then come off after overnight incubation.

enchymal interdigitating RCs in the thymus (particularly in the medulla) has also been described, and has been interpreted as an integral part of thymocyte maturation and proliferation since more mitotic figures have been seen in thymocytes around these glycoprotein-containing interdigitating RCs than elsewhere in the thymus [116].

These mesenchymal RCs in the thymus, which also interdigitate with surrounding lymphocytes, have been described by Veldman [38] as being similar to interdigitating RCs in the thymus-dependent areas of peripheral lymphoid organs, i.e., the spleen and lymph nodes. Hoefsmit and Gerver [117] have suggested the presence of glycoprotein in the lysosome-like structures of these cells. These cells have been described as containing typical LC granules, particularly in the rat thymus [41,118]. They are more resistant to cortisone than the majority of thymus cells and are, therefore, more prominent in cortisone-injected than in control rats [118]. It is of interest that the thymus contains keratinizing epithelial elements. Could it be this vicinity of keratinizing cells that determines whether the interdigitating cells contain LC granules?

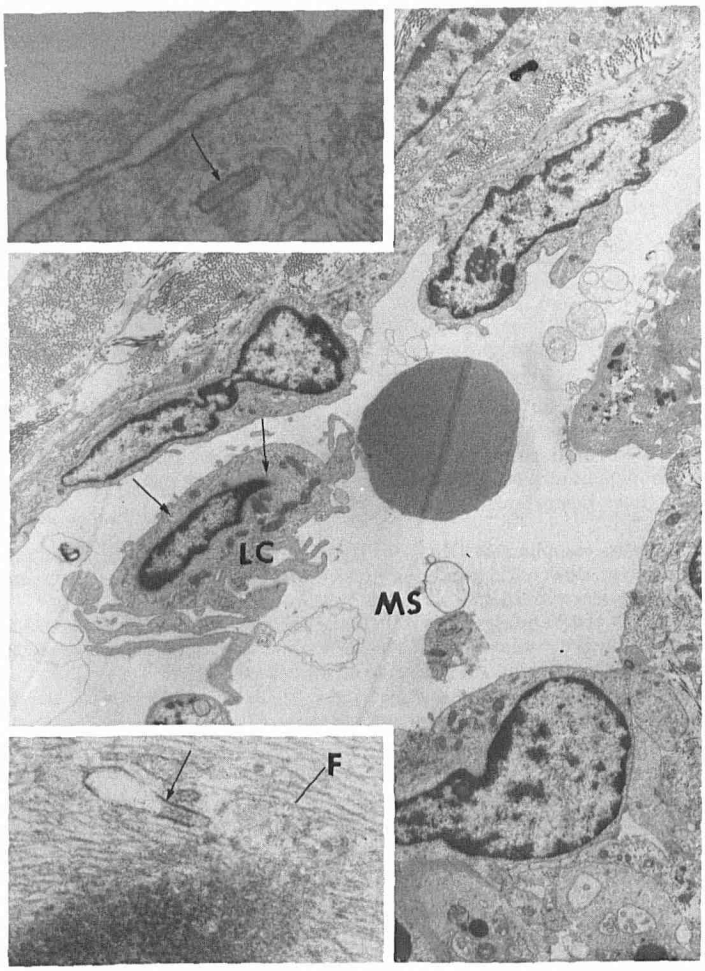

FIG 1. A Langerhans cell (*LC*) in the marginal sinus (*MS*) of a draining lymph node of a guinea pig killed 6 hr after intradermal challenge with 30 μg of ferritin. Note the ruffled appearance of the cell membrane. This guinea pig had been exposed to 800 R of whole-body X-irradiation 3 days before injection. The photograph therefore also illustrates the X-irradiation resistance of LCs. Areas denoted by *arrows* are enlarged in the *insets*. Section stained with uranyl acetate and lead citrate (× 6,000). *Insets*, LC granules (*arrows*). Note the presence of numerous fine filaments (*F*) in the cytoplasm (× 120,000).

Staining for the presence of Ia antigen on these thymic mesenchymal interdigitating RCs and examination by fluorescence microscopy have given inconclusive results because the epithelial reticulum cells that are also present throughout the thymus are strongly Ia-positive [119].

Nossal's follicular dendritic "reticulum" cells: Tables II through V include some of the known properties of the dendritic reticulum cells (DRCs) of lymphoid follicles described by Nossal et al [44,45,120]. These cells bear antigen or antigen-antibody complexes on their surfaces. They are located in the coronas of lymphoid follicles, where antigen can be detected long after injection [121] (Fig 5 and Fig 6). Although these cells can bind some antigenic and nonantigenic "sticky" substances in the absence of antibody [87,120], the presence of antibody of the IgG class greatly enhances antigen uptake in follicles [122–124]. Conversely, the presence of antigen causes the localization of passively administered antibody on DRCs [125]. Even though intact IgG localizes itself much better on DRCs than $F(ab^1)_2$ fragments [126], and Fc fragments much better than Fab [69], the presence of an Fc receptor on DRCs has not been directly shown. The presence of a C3 receptor on DRCs has been suggested because C3 depletion greatly reduces intact IgG localization on DRCs in the spleen [70]. The follicular DRCs are considered specialized forms of the RCs in the outer rather than the inner portion of the splenic PALS and as such would be separate from the interdigitating RCs. They show extensive membrane invaginations and protrusions, which often enfold electron-dense material and viruses [127]. The degree of membrane folding may depend on the amount of stimulation by antigen or antigen-antibody complexes recently experienced [39]. Their morphological appearance is not very similar to that of interdigitating RCs or LCs (Table II), and when the membrane invaginations of the DRCs are at a minimum their structure approaches that of ordinary RCs. Their contact with neighboring lymphocytes is relatively intimate and involves B lymphocytes in the follicles rather than T lymphocytes, which are the neighbors of interdigitating RCs. In contrast to antigen-presenting spleen cells [128], interdigitating RCs in T-dependent areas (see footnotes for Table V), and LCs (Fig 1, Fig 3, and Fig 4), DRCs in follicles have been shown to be X-irradiation-sensitive [93,94,129,130]. This quality, in combination with their morphological properties, tends to identify DRCs as a separate cell type. However, the X-irradiation sensitivity of all these cell types needs to be quantified before any definite statements can be made about this aspect. Neither the studies by Hoefsmit and co-workers [40,48] nor our own [17] have indicated the presence of LCs in follicular areas of lymph nodes draining sites of antigen injection, although in both studies LCs have been seen in the paracortical areas.

Steinman and Cohn's dendritic cells: The cells described by Steinman and co-workers [43,47,61,66,95] as dendritic cells pri-

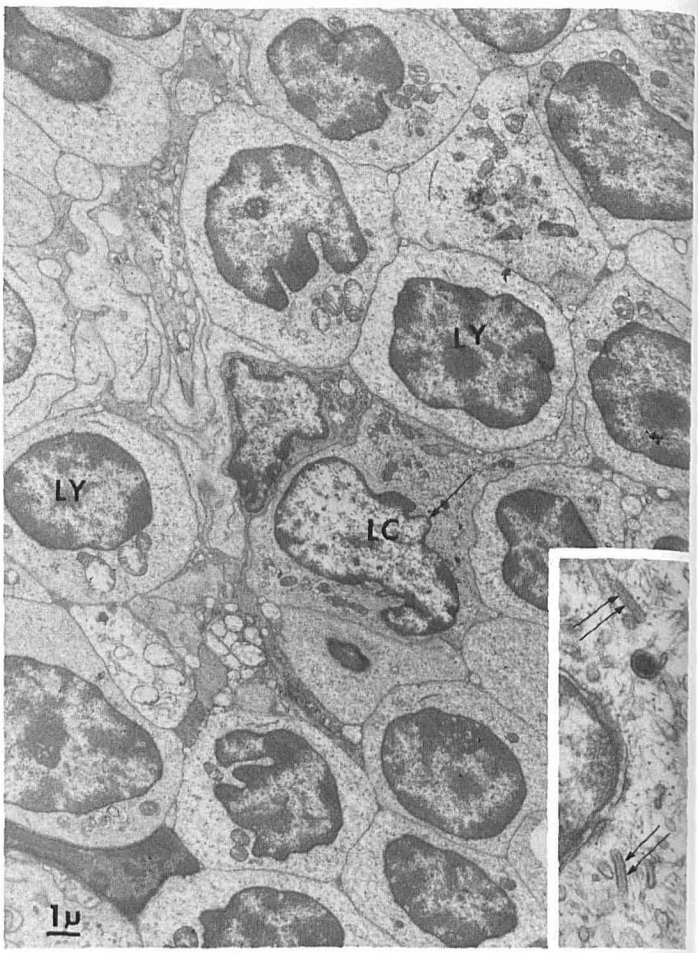

FIG 2. Draining lymph node from a guinea pig killed 4 hr after intradermal challenge with 5 μg of ferritin. One cell with Langerhans cell (*LC*) granules surrounded by numerous lymphocytes (*LY*) is present in the paracortical area shown here. The area denoted by the *arrow* is shown at a higher magnification in the *inset*. Section stained with uranyl acetate and lead citrate (× 6,000). *Inset*, LC granules (*double arrows*) (× 60,000).

marily present in spleen (also found in lymph nodes and Peyer's patches, but absent everywhere else) have been characterized with respect to some of the properties listed in the tables. The major problem in relating these cells to either LCs or follicular DRCs is that they lack both C3 and Fc receptors. It is, however, not clear whether interdigitating RCs, or, in fact, indeterminate dendritic cells in the epidermis, possess these receptors (Table IV).

In summary, the combined properties of the cells listed in Tables II-V suggest a strong similarity between the indeterminate dendritic cell plus LC family in the epidermis and the interdigitating RCs with or without LC granules in lymph nodes, spleen, thymus. The resemblance of LCs to typical monocytes or macrophages is less striking, but many of the properties listed for macrophages reflect Ia-negative and probably highly phagocytic populations of macrophages rather than Ia-positive mononuclear adherent cells capable of presenting antigen to T lymphocytes. Further studies are needed to evaluate the identity of interdigitating RCs with this Ia-positive subpopulation of macrophages. While the evidence now available does not suggest that Nossal's follicular DRCs and Steinman and Cohn's DCs have properties identical to those of interdigitating RCs, the possibility that they are a single family of cells with variations in characteristics due to location, stage of maturation, or both cannot be excluded. Thus, LCs might be the epidermal representative of a cell system with a much more widespread distribution in lymphoid organs.

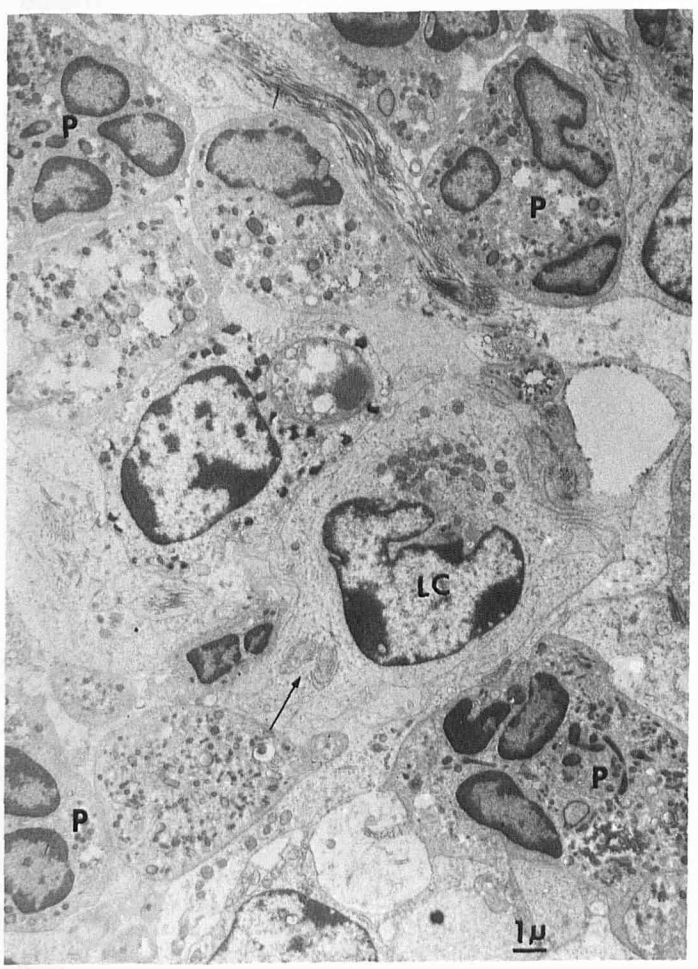

FIG 3. Draining lymph node from a guinea pig killed 4 hr after intradermal challenge with 5 μg of ferritin. One cell with Langerhans cell granules (LC) is shown. Since this guinea pig had been exposed to 800-R whole-body X-irradiation 3 days before challenge, there is a lack of lymphocytes (compare to Fig 2). Several polymorphonuclear leukocytes (*P*) are present. Section stained with uranyl acetate and lead citrate (× 6,000). Figure 8 is a higher-magnification micrograph of the area dented by the *arrow*.

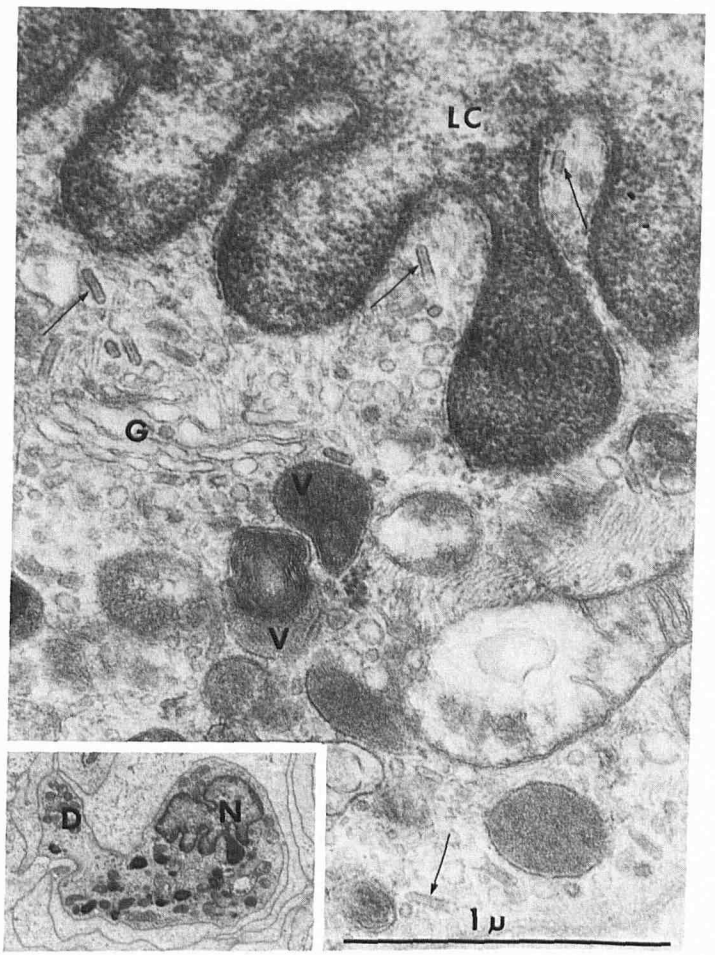

FIG 4. Portion of a Langerhans cell (*LC*) in the paracortex of a lymph node taken from an irradiated (800 R) guinea pig 6 hr after intradermal challenge with 30 μg of ferritin. Many lysosome-like bodies (*V*) are present; some of these contain lamellar structures. The Golgi region (*G*) is prominent, and several LC granules (*arrows*) are present. Section stained with uranyl acetate and lead citrate (× 60,000). *Inset*, the whole cell. Note the lobulated nucleus (*N*) and part of a dendrite (*D*), both typical of interdigitating reticulum cells as well as LCs, as well as the radioresistance of this cell.

Lymphomatous dendritic cells: It would be of interest if tumors or lymphomas that consist of 1 of the dendritic cell types represented in Tables II through V could be identified. Histiocytosis X (LC granuloma) is a candidate [18,131].† There are published reports of monocytic leukemias with cells containing LC granules [15]. These include the so-called hairy cell lymphomas [134,135], of which the cell type is dendritic in appearance, is phagocytic, contains peroxidase, and, in addition, has the B cell characteristic of surface Ig [136]. In recent years, we have studied transplantable RC sarcomas in SJL/J mice; the majority of the cells in these lymphomas have some B cell properties [137], but approximately 5% are dendritic cells with the ultrastructural characteristic of interdigitating RCs (Fig 7). It is of interest that these Ia-positive cells [138], like Steinman and Cohn's DCs [91], stimulate a strong mixed lymphocyte reaction in allogeneic T cells. Even more striking is the fact that they stimulate syngeneic T cells to proliferate [139]. The relationship of these cells to the normal dendritic inhabitants of

† Pinkus and Mehregan have changed the name histiocytosis X to LC granuloma [132]. Lieberman (see his article in this issue [133]) also considers histiocytosis X a LC granuloma rather than a tumor.

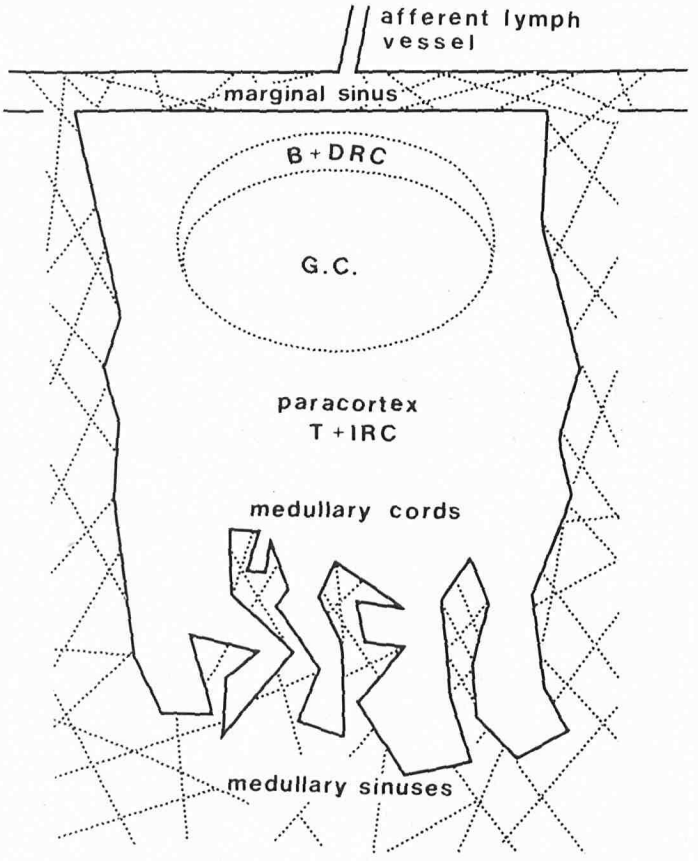

FIG 5. Drawing of lymph node section demonstrating the normal localization of interdigitating reticulum cells (*IRC*) and T lymphocytes in the paracortex, and of Nossal's dendritic reticulum cells (*DRC*) and *B* lymphocytes in the coronas of follicles. The letters *G.C.* indicate the normal localization of a germinal center when present in a follicle.

lymphoid tissue needs to be unraveled. The recently studied normally present Ia- and Fc-positive subpopulation of peritoneal exudate cells combines such macrophage-like properties as nonspecific esterase activity and adherence, with such B cell properties as surface IgM [140]. The occurrence of forms apparently intermediate between cells of the monocytic and B cell series may indicate a close relationship between these cell types and the general difficulty of making rigid distinctions between cell types.

Functional Comparison of Langerhans Cells, Monocytes and Dendritic Cells in Lymphoid Organs

Role in antigen presentation to T cells: Langerhans cells have macrophage-like functions in immune responses, particularly in antigen presentation to T cells and in induction of mixed lymphocyte reactions [88]. It is not clear what the role of the Ia antigens is in the interaction of macrophages with T cells, but they appear to be very important since antibody to Ia antigens can prevent the induction of proliferation in sensitized T cells [128,141]; antibody to the specific antigen to which the sensitization of the T cells was directed, however, frequently does not [142]. Direct conjugation of hapten to Ia-positive adherent macrophages leads to an effective stimulator cell for activation of hapten-specific T cells from contact-sensitive animals [89]. This suggests that hapten conjugation of the LC itself is a very effective method of sensitization. The tendency of monocytes to make rosettes with lymphocytes *in vitro*, particularly that of antigen-bearing monocytes with specifically sensitized lymphocytes [77], is reminiscent of the tendency of LCs to become apposed to lymphocytes in skin and lymph nodes during delayed hypersensitivity reactions [49]. Perhaps the intimate relationship between interdigitating RCs and lymphocytes in the inner PALS and paracortex are representative of this same phenomenon. This could also be of importance for antigen presentation. Although antigen does not usually become localized in large amounts in regions rich in interdigitating RCs, certain hydrophobic conjugation products of protein antigens, which are more effective than unmodified proteins in inducing delayed hypersensitivity, have an increased tendency to become localized in T-dependent areas [143,144]. The ultrastructural localization of such compounds has not yet been reported. Veldman, Molenaar, and Keuning [38,80] reported electron microscopic observations of interdigitating RCs in ferritin-injected rabbits, but they did not comment on the presence or absence of ferritin in the interdigitating RC-T cell junctions. The LC-granule-containing cells we saw in paracortical areas of draining nodes 4 to 24 hr after ferritin challenge [17] did have ferritin on the surfaces and in their cytoplasm.

Immunologically nonspecific influence on lymphoid cells: The intimate relationship between monocytes or interdigitating RCs and lymphocytes may have significance beyond a possible role in presenting antigens. There is ample evidence that mitogen-induced proliferation of both T and B cells cannot be adequately accomplished *in vitro* without adherent monocytes [145]. Although 2-mercaptoethanol (2-ME) can partially replace monocytes in some of these functions, its effect is usually synergistic with that of macrophages [146] or of macrophage supernatants [147]. It has, therefore, been postulated that monocytes play an important role in maintaining proper *in vitro* conditions for lymphocytes in an immunologically nonspecific manner, at least partly mediated through soluble products (lymphokines). Results of recent studies suggest that various lymphoma cells of both T and B cell origin also require mono-

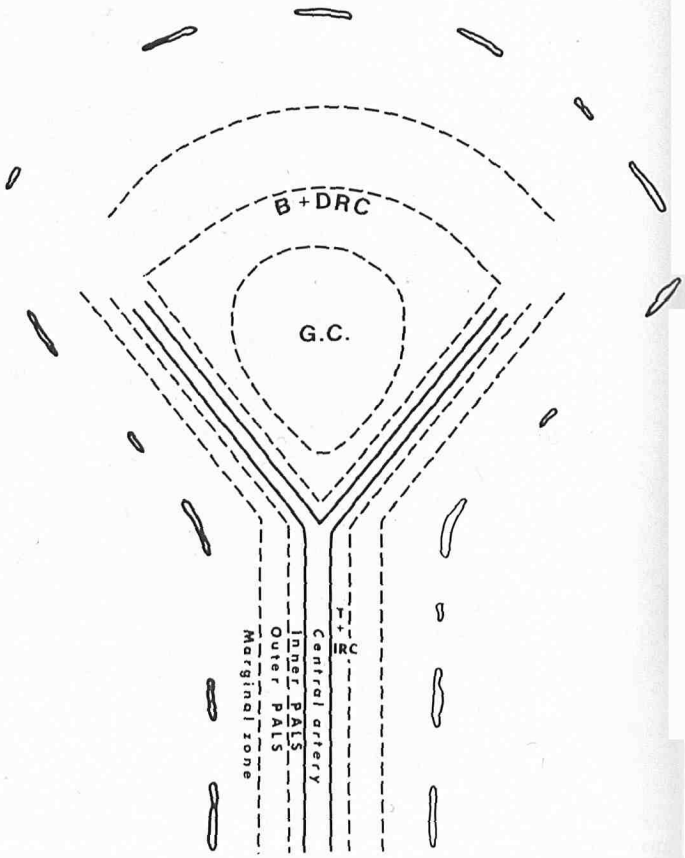

FIG 6. Drawing of the periarteriolar sheath (PALS) area of a spleen demonstrating the normal localization of interdigitating reticulum cells (*IRC*) in the T-lymphocyte-dependent area of the inner PALS, and of Nossal's dendritic reticulum cells (*DRC*) in the coronas of follicles.The letters *G.C.* indicate the normal localization of germinal centers in follicles (when present).

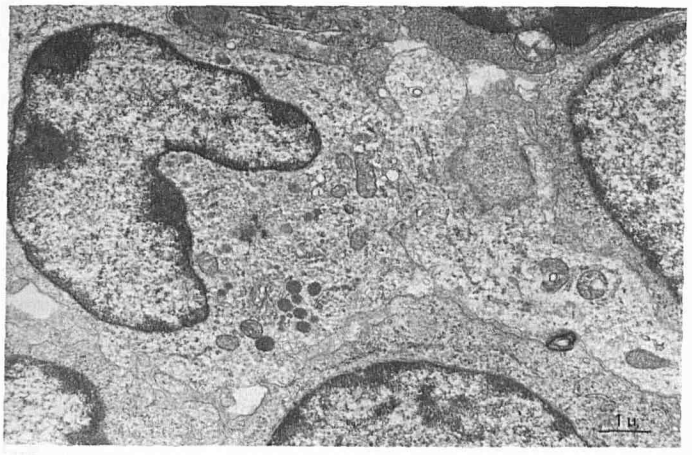

FIG 7. Lymph node from an SJL/J mouse given a transplantable reticulum cell sarcoma by injection. The dendritic cell from an area of tumor involvement shows features similar to those of interdigitating reticulum cells (× 14,000; *bar* indicates a distance of 1 μm).

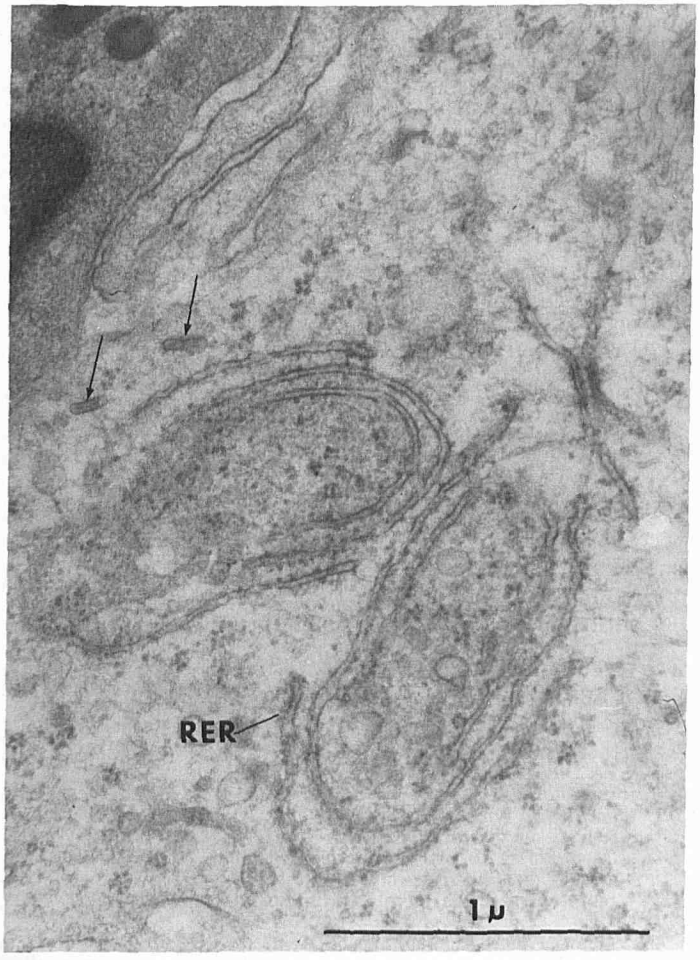

FIG 8. Cytoplasm of the cell shown in Fig 3. There are Langerhans cell granules (*single arrows*) and prominent channels of rough endoplasmic reticulum (*RER*) (× 60,000).

cytes for optimal *in vitro* growth [148]. In the case of a B cell lymphoma of BALB/c mouse origin we found that Ia-antigen-bearing adherent cells were required for optimal growth, although they did not have to be of the same mouse strain origin as the lymphoma cell [146]. The results strongly suggested that cell-to-cell contact was important for lymphoma growth and that 2-ME could not replace this monocyte function. Steinman and Cohn have described a cluster-forming property of their dendritic cell with lymphoid cells, particularly with B lymphoblasts, that appears to help the proliferation or differentiation of these blasts *in vitro* [78]. The lymphokine (lymphocyte-activating factor) that stimulates T cell proliferation, is one of the better characterized products of macrophages [149]. Macrophages have also been found to promote thymocyte maturation *in vitro*, presumably through cell-to-cell contact [150]. Interdigitating RCs with and without LC granules in the thymus may well have an important role in the proliferation of thymocytes on the basis of comparable secretion products or cell-to-cell contact. In addition, if LCs represent an epidermal equivalent of 1 or more of these monocytes or "DRC" types, it might be expected that they too would at times promote lymphoid cell proliferation of T cell origin in skin. The tendency of T cell lymphomas to infiltrate skin may be the result of such an influence by LCs. It has been proposed that mycosis fungoides represents a derailment of a chronic contact dermatitis resulting in lymphomatous proliferation of T cells [151].

Possible secretory products: It is known whether an Ia-positive or Ia-negative macrophage subpopulation is involved in various other macrophage and monocyte functions, e.g., production of enzymes [152,153], C factors [154,155], and lymphokines [149,152]. It is, therefore, difficult to predict which of these are relevant for a comparison with LCs. We wish to stress, however, that the ultrastructural features of LCs certainly indicate a variable activity in protein synthesis and secretion (Fig 3 and Fig 8). Identification of these products should be the subject of further experimentation. Hydrolytic enzymes produced by LCs have already been postulated as playing a role in the degradation of keratinocytes during the normal process of keratinization [156]. Another property of the monocyte-macrophage family is their role as the principal hematopoietic cell source of prostaglandins [157,158]. Langerhans cells can assume a morphological appearance consistent with that described for macrophages during prostaglandin synthesis [27,158] (Fig 5). Thus, if LCs represent the mononuclear phagocyte system in the epidermis, they might be an important source of prostaglandins in skin. The role of prostaglandins in producing erythema in skin has been reviewed [159]. After exposure to ultraviolet light (UVL), for instance, the amount of prostaglandins in skin increases [160]. The major portion of prostaglandin activity appears to be in the epidermis rather than in the dermis [161,162]. Since there is some evidence that UVL may affect LC structure or function [163,164], the erythematous response to UVL could partly be the result of an alteration in this prostaglandin production by LCs. Prostaglandins do not appear to affect LC structure after injection, although they do affect the epidermal cells [165]. Catecholamines, which are known to represent an initial trigger of the cycle of events leading to prostaglandin synthesis [166], have a hitherto unexplained affinity for LCs [97,98]. Prostaglandins synthesized by LCs might also be important for the control of keratinization. It has recently been shown that prostaglandin B1 selectively affects the structure of epidermal mitochondria in developing chick skin in organ cultures and also accelerates keratinization and differentiation [167]. In summary, there may be several other hitherto undetected functions of LCs that should be looked for on the basis of the similarity between LCs and the monocyte-macrophage cell system with its many varied properties.

Possible Consequences of Interference with Langerhans Cell Function

Inactivation of Ia antigens on LCs or removal of LCs from skin may be important in promoting skin allograft acceptance since tissues presenting both Ia antigens and other major histocompatibility antigens are more effective in inducing graft rejection than those lacking Ia antigens [168–170]. Similarly, inactivation of Ia antigens or of LCs themselves may interfere with local induction of contact reactions since Ia antigens are needed on antigen-presenting cells for induction of T cell re-

sponses. (This possibility is discussed elsewhere in this issue [27].) If LCs have a nurturing influence on T lymphoid cells in skin, their destruction might result at times in clearing of lymphomatous skin infiltrates. Ultraviolet light has been used to treat people with a variety of skin diseases, including some cutaneous lymphomas such as early-stage mycosis fungoides, with beneficial effects.

For a long time it was thought that the only disease in which LCs were involved was histiocytosis X (LC granuloma). It is now apparent that there may be many more diseases in which these cells have pathogenetic influences as a result of their interaction with other cells (lymphocytes and keratinocytes). The effects of a variety of commonly used therapeutic modalities on LC structure and cell membrane receptors need, therefore, to be studied for a greater insight into methods of monitoring LC function.

In summary, on the basis of a careful review of the known properties of LCs, it has been concluded that they are best thought of as a specialized class of cells in the mononuclear phagocyte system [171]. This categorization implies many shared characteristics, including structure, cytochemical properties, cell surface receptors, function, and bone marrow derivation.

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Announcement

The Western Section of the Society for Investigative Dermatology will meet jointly with the Western Section of the American Federation for Clinical Research and the Western Society for Clinical Research in Carmel, California, February 4, 5, and 6, 1981. Abstracts for the Carmel meeting are due by September 26, 1980, and should be mailed to Charles B. Slack, Inc., 6900 Grove Rd., Thorofare, New Jersey 08086.