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Interepithelial Cells of the Oral Mucosa in Mice

An Ultrastructural Classification With Reflections on the Origin of the Langerhans Cell

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Summary. Non-epithelial mesenchymal and neuroectodermal cells occur between the keratinocytes in the stratified squamous epithelium of the oral mucosa. These cells cannot be classified adequately by light microscopy. In the present study the oral mucosa of the lip, cheek and tongue of 50 mice were studied by light and electron microscopy. 3,025 mononuclear interepithelial cells were documented and analysed.

Monocytogenic macrophages, plasma cells and mast cells were not found interepithelially and cannot be regarded as a regular constituent of the epithelium. Only a few neuroectodermal cells – in mice these are exclusively Merkel cells, with no melanocytes – were localized in the epithelium. The majority of the interepithelial cell population is made up of lymphocytes (22.8%) and Langerhans cells (56.8%). They are an integral constituent of the epithelium. Lymphocytes with rounded and indented nuclei can be identified. The larger and dendritic Langerhans cells are a specific cell of squamous epithelium and also occur in the oral mucosa. Not all cells which feature the cytological characteristics of Langerhans cells contain Langerhans or Birbeck granules. Accordingly these granules cannot be considered an exclusive identification characteristic. Two types of Langerhans cells can be differentiated. 80.9% have the more or less typical appearance known from the epidermis and were termed macrophagocytoid Langerhans cells. The nuclei are irregularly indented and moderately heterochromatic. 19.1% possessed conspicuous large, spherical, euchromatic nuclei and an electron-lucent cytoplasm. These were termed reticuloid Langerhans cells. About 20% of the interepithelial cell population could not be identified, neither as typical lymphocytes nor as Langerhans cells. These were small to medium sized cells with deeply indented "cerebriform" strongly heterochromatic nuclei. They are similar to the "Sézary cells" or mycosis fungoides cells of epidermotropic human T-cell lymphomas. The lymphocytic nature of these cells has been

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confirmed. It seems likely that differentiation of lymphocytes to cerebriform cells occurs within the epithelium. It is further discussed whether cerebriform cells are precursors of Langerhans cells, a conclusion suggested morphologically by transitional forms. This would imply that Langerhans cells originate from lymphocytes, and that the cerebriform cell is an intermediate step of differentiation. The microenvironment of the squamous epithelium may play a role in the process of differentiation, which could explain the epitheliotropy of lymphocytes. The possibility is considered that Langerhans cells and interdigitating reticulum cells of the T-cell area of lymph nodes are identical. The close functional cooperation of Langerhans cells, lymphocytes, and interdigitating reticulum cells in immunological defenses against external antigens is discussed.

Key words: Oral mucosa – Interepithelial cells – Lymphocytes – Langerhans cells – Cerebriform cells.

Zusammenfassung. Im mehrschichtigen Plattenepithel der Mundschleimhaut finden sich neben den Keratinocyten auch nichtepitheliale mesenchymale und neuroektodermale, sog. interepitheliale Zellen, welche lichtmikroskopisch nur unzulänglich klassifizierbar sind. In der vorliegenden Studie wurde die Lippen-, Wangen- und Zungenschleimhaut von 50 Mäusen licht- und elektronenmikroskopisch untersucht. Dabei konnten 3025 mononucleäre interepitheliale Zellen dokumentiert und analysiert werden. Monocytogene Makrophagen, Plasmazellen und Mastzellen waren interepithelial nicht nachweisbar und sind nicht als fester Bestandteil des Epithels anzusehen. Nur sehr wenige neuroektodermale Zellen – bei der Maus fast ausschließlich Merkelzellen und keine Melanocyten – liegen im Epithel. Die überwiegende Mehrzahl der interepithelialen Zellen sind Lymphocyten und Langerhanszellen als integrale Bestandteile des Epithels. 22,8% der gesamten interepithelialen Zellen erwiesen sich ultrastrukturell als Lymphocyten. Etwa je die Hälfte hiervon wiesen runde und gekerbte Kerne auf. Als zweite Gruppe von interepithelialen Zellen kommen die größeren dendritischen Langerhanszellen in der oralen Mucosa ebenso wie in allen anderen mehrschichtigen Plattenepithelien vor. 56,8% der interepithelialen Zellen können als Langerhanszellen eingestuft werden. Nicht alle cytologisch den Langerhanszellen entsprechenden Zellen enthalten Langerhansgranula. Diese können somit nicht als alleiniges Identifizierungsmerkmal gelten. Zwei Typen von Langerhanszellen können unterschieden werden. 80,9% haben das mehr oder weniger typische Erscheinungsbild, wie es von der Epidermis bekannt ist und wurden als makrophagocytoide Langerhanszellen bezeichnet. Die Kerne dieser Zellform sind unregelmäßig gekerbt und mäßig heterochromatinhaltig. 19,1% der Langerhanszellen besaßen auffällig große, runde euchromatische Kerne und ein helleres Cytoplasma. Diese werden als retikuloide Langerhanszellen bezeichnet. Etwa 20% der interepithelialen Zellen konnten weder Lymphocyten noch Langerhanszellen zugeordnet werden. Es waren kleine bis mittelgroße Zellen mit stark gekerbten „cerebriformen" heterochromatinreichen Kernen. Diese sind den sog. Sézary-Zellen und Mycosis fungoides Zellen der epider-

motropen T-Zell-Lymphome ähnlich, deren lymphocytäre Natur gesichert ist. Auch uns erscheint eine Entwicklung dieser Zellen aus Lymphocyten im Epithel wahrscheinlich.

Weiterhin wird diskutiert, ob die cerebriformen Zellen Vorstufen der Langerhanszellen darstellen. Eine solche Auffassung wird durch morphologische Zwischenstufen nahegelegt. Dies würde bedeuten, daß Langerhanszellen aus Lymphocyten entstehen, wobei die cerebriforme Zelle eine Zwischenstufe der Differenzierung darstellt. Möglicherweise spielt das mehrschichtige Plattenepithel hierbei eine Rolle für diese Zelldifferenzierung und erklärt die Epitheliotropie der Lymphocyten. Eine mögliche Identität von Langerhanszellen und interdigitierenden Retikulumzellen der T-Zellareale der Lymphknoten sowie eine enge funktionelle Kooperation von Langerhanszellen, Lymphocyten und interdigitierenden Reticulumzellen bei der immunologischen Abwehr externer Antigene werden diskutiert.

Introduction

Interepithelial (i.e. intraepithelial, intercellular[1]) cells have been described in all epithelia of the internal and external surface of the mammalian body. Their proportion in stratified squamous epithelium has been estimated to be 10% (Sagebiel et al., 1971). An important function as a first immunological barrier has been ascribed to interepithelial lymphocytes, which make up the majority of interepithelial cells in monostratified epithelium (review: Otto, 1973). The highest degree of penetration ("lymphoepitheliale Durchdringung") of epithelium by lymphocytes is found in the "lympho-epithelial" tissues (Waldeyer's tonsillar ring, Peyer patches, thymus), and probably represents an effective symbiosis of both tissues (Doerr, 1956, 1973).

Besides lymphoid cells, a second larger mononuclear cell type has been observed in stratified squamous epithelium by light microscopy (Andrew, 1968: epidermis; Rupec and Uhlarik, 1969: vaginal epithelium; Vakilzadeh et al., 1970: oral epithelium; Silberberg, 1973: epidermis). This cell type has been designated a dendritic or histiocytic interepithelial cell. Most of these cells correspond to Langerhans cells (Langerhans, 1868), which can be identified only by special histochemical methods or by electron microscopy (Langerhans'granules). The Langerhans cell is also an immunologically important cell (Silberberg et al., 1975; Shelley and Juhlin, 1976, 1978; Bos and Burkhardt, 1977, 1979). Less frequently melanocytes, Merkel cells, mast cells and polymorphonuclear granulocytes occur in stratified squamous epithelium, which assume no specific immunological functions.

All interepithelial non-keratinocytes mentioned are also found in the oral

[1] For these non-keratinocytes within the epithelium the term intraepithelial and interepithelial cells has been used. The latter has been favoured by us, because it implies that these cells are situated intercellularly and clearly markes them as non-epithelial cell (epithelial cell i.e. spinous cells of course are also intraepithelial). For example an intraepithelial mitosis can refer to the mitosis of an epithelial cell or a non-epithelial cell, while the term interepithelial mitosis clearly refers to a mitotic non-epithelial cell within the epithelium.

mucosa (overview: Squier et al., 1975; Burkhardt, 1979). However, their function, distribution, frequency and ultrastructural differentiation or classification are as yet incompletely known.

The present investigation is an ultrastructural analysis of 3,025 interepithelial cells of the murine oral mucosa.

Material and Methods

Animals. 50 male and female NMRI mice and athymic (nude) mice weighing 12.5 to 33 g and aged 3 to 4 weeks (Zentralinstitut für Versuchstierzucht, Hannover) were used as experimental animals. The mice were kept under different antigen exposure (germfree, specified pathogen-free, conventional, oral candida albicans exposure). As there were no *qualitative* changes of the interepithelial cell population in the different groups of animals, we combined the findings of all groups for this qualitative study. The *quantitative* differences will be considered in separate publications (Bos and Burkhardt, 1979; Burkhardt et al., 1979).

Animals were killed by decapitation in anaesthesia (Valium®, Roche, 2,5 mg i.p.; Ketanest®, Parke Davies, 5 mg i.m.)

Light Microscopy. Tongue, cheek and lip were fixed in formalin, embedded in paraffin and 3 µ thin sections stained with H.E., Giemsa, PAS, methyl green-pyronin (Lillie, 1965). Activity of naphthol-AS-D-chloroacetatesterase was demonstrated according to Lillie (1965). Immunoglobulins (A, G, M) were identified by the indirect immuno-peroxidase technique (Taylor, 1974; Löning et al., 1977).

Electron Microscopy. Specimens of tongue, cheek and lip oral mucosa were taken under anaesthesia, immersed in fixation fluid and immediatly cut into small cubes with sides 1 mm in length. Further preparation was performed according to Dalton (1955) and Luft (1971 a, b). Ruthenium red impregnation was chosen for better visualisation of the cell membranes. After dehydration in ascending alcohol concentrations, embedding was done in Epon 812. Semithin sections were stained with toluidine blue. The ultrathin sections were contrasted with alcoholic uranyl acetate. Electron microscopy was performed with a Zeiss electron microscope EM 9 S-2. All interepithelial cells were documented photographically. Analysis and classification were done by two authors independently.

Results

Light microscopy did not permit reliable differentiation or classification of interepithelial cells. Only mononuclear cells could be distinguished from polymorphonuclear granulocytes. By electron microscopy 3,025 mononuclear interepithelial cells were documented and analysed. These were mainly lymphocytes and Langerhans cells. As in all other epithelia, *interepithelial lymphocytes* (Fig. 1) occur in the oral mucosa. 22.8% of the total number of interepithelial cells can be classified as typical small lymphocytes. Like circulating lymphocytes they are characterized by a small compact rounded nucleus and scanty cytoplasm with few organelles. However, only about half of them show a smooth circular nucleus (Fig. 1 a), the nuclei of the rest are more or less crenated and indented (Fig. 1 b). In a larger number of cells these indentations were so deep and multiple that a classification as simple lymphocytes did not seem justified (see below).

As a second group of non-keratinocytes, the dendritic *Langerhans cells* (Figs. 2–4) can be differentiated. Two different types can be observed. Cells

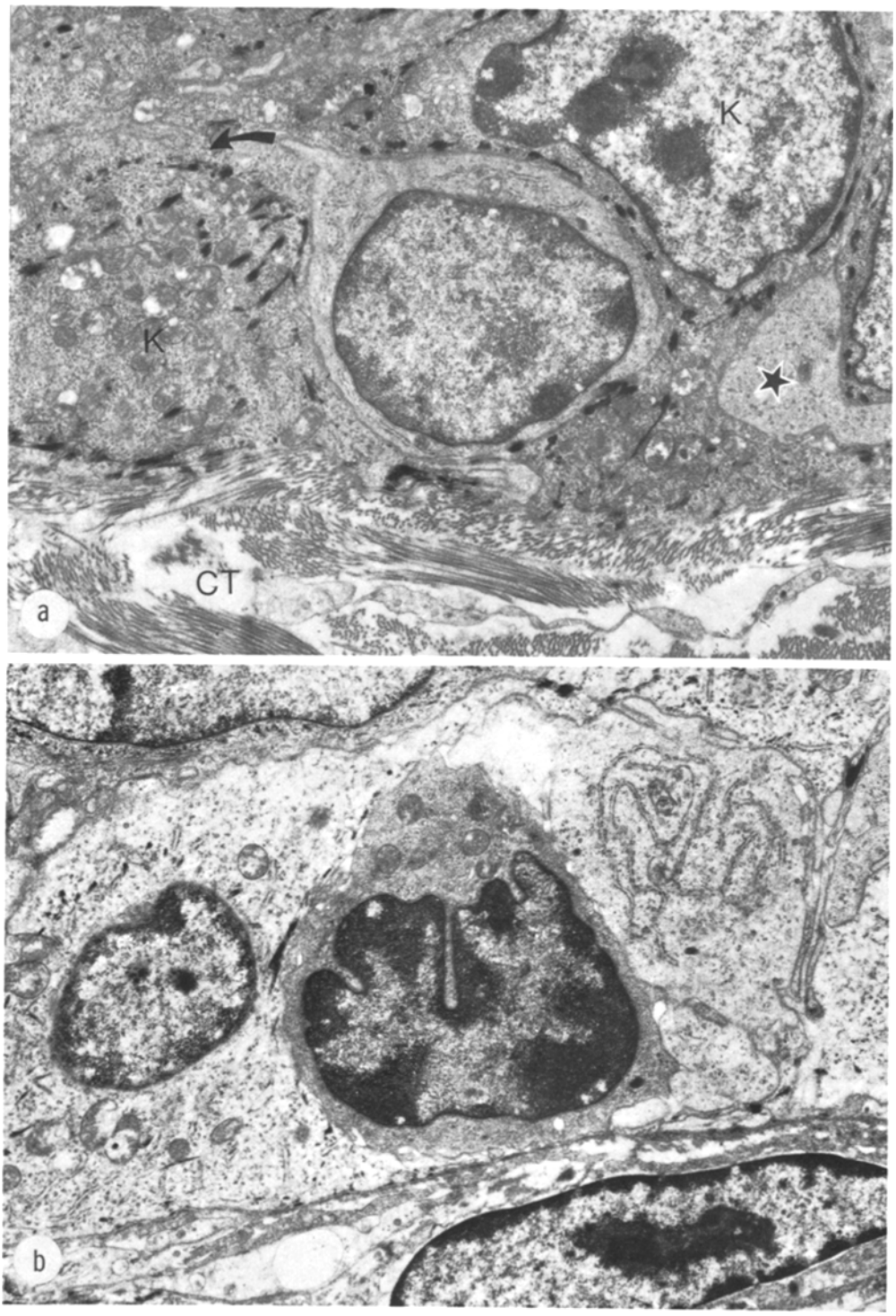

Fig. 1 a and b. Interepithelial lymphocytes of the murine oral mucosa. **a** Basally localized lymphocyte with rounded nucleus. The cell is separated from the connective tissue (*CT*) by cytoplasmatic processes of the adjacent keratinocytes (*K*). A small uropod (*arrow*) formed by the lymphocyte and a trailing "tail" (*asterix*) are both signs of active locomotion. Buccal mucosa. ×12,000. **b** Lymphocyte with deeply indented nucleus and prominent heterochromatin in basal position. Mucosa of the lip. ×12,000

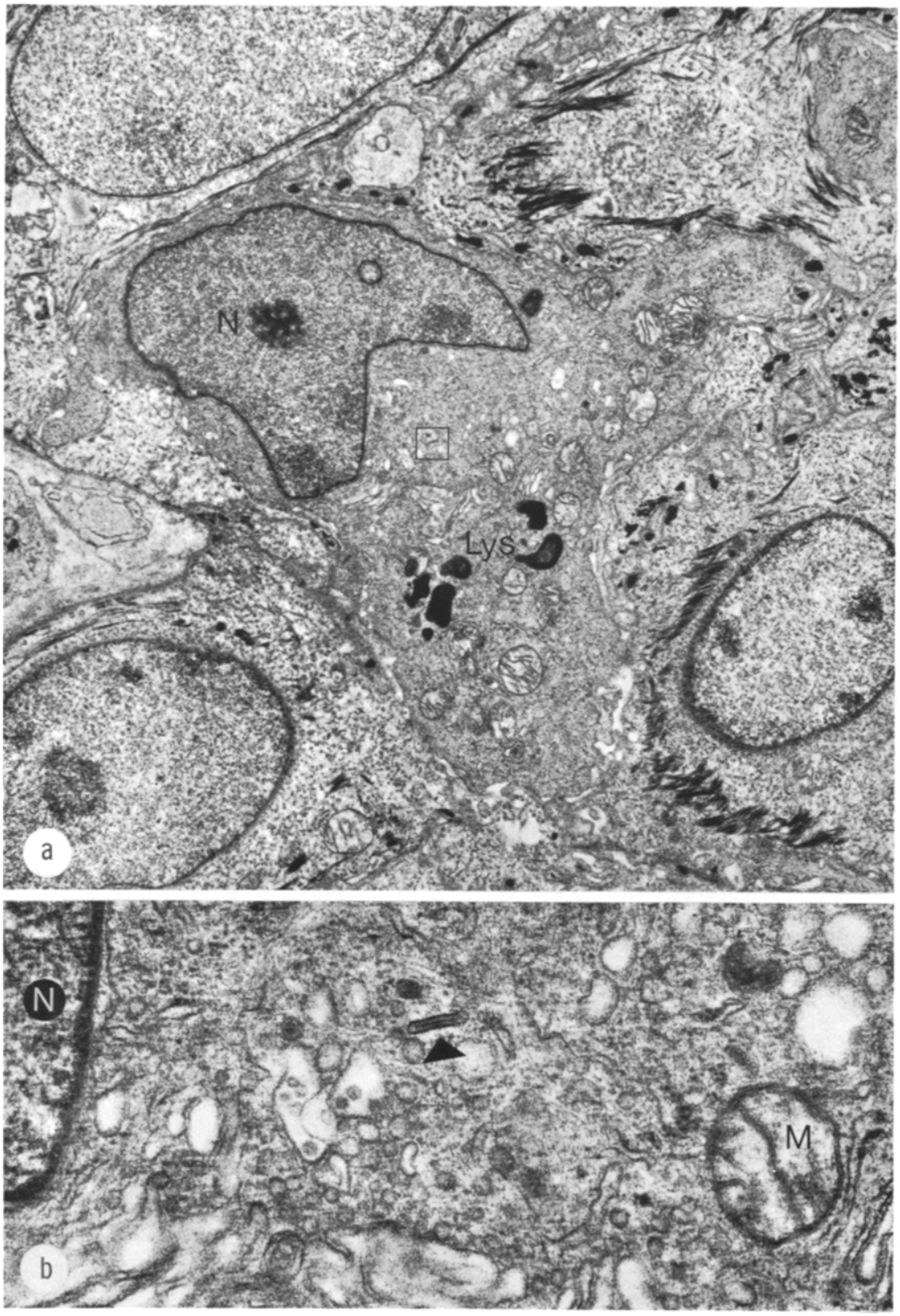

Fig. 2a and b. Langerhans cells of the macrophagocytoid type. **a** Large interepithelial cell with irregular, indented, and moderately heterochromatic nucleus (*N*). The abundant cytoplasm shows dendritic ramification and contains a few primary lysosomes (*Lys*). Near the nucleus a Langerhans' granule can be seen (*frame*). Buccal mucosa. ×10,900. **b** Detail with Langerhans' granulum (*arrow*). Note the internal lamellation. *N*, nucleus, *M* mitochondrium. ×61,000

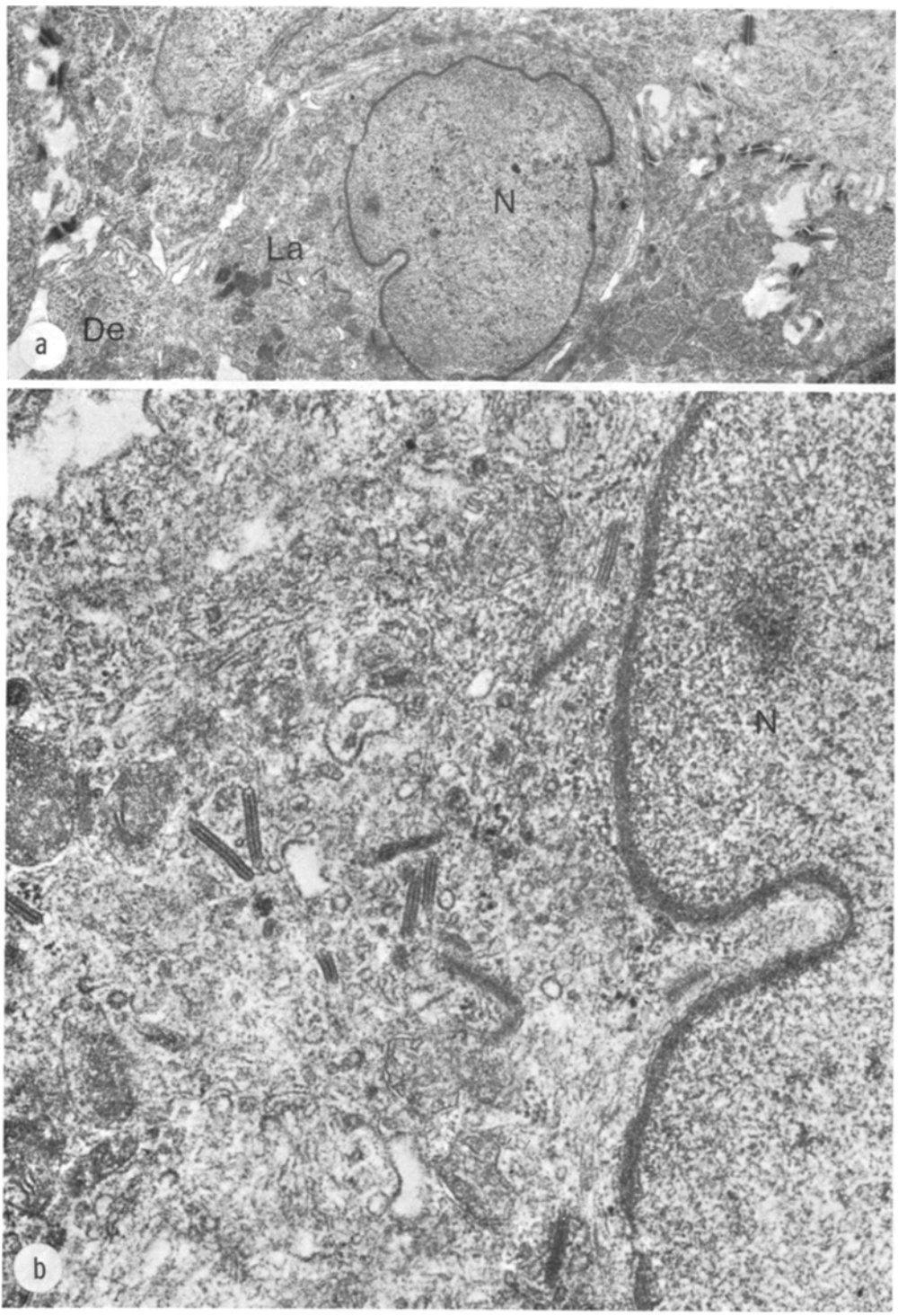

Fig. 3a and b. Langerhans cell of the reticuloid type. **a** Interepithelial cell with a large rounded euchromatic nucleus (*N*) and dendritic cytoplasmic process (*De*). Near the nucleus numerous Langerhans' granules (*La*) are found. The adjacent keratinocytes show typical desmosomal connections, which are lacking on the cell surfaces toward the Langerhans cell. Mucosa of the tongue. ×12,000. **b** Detail with several typical lamellated Langerhans granules. *N*, nucleus. ×63,000

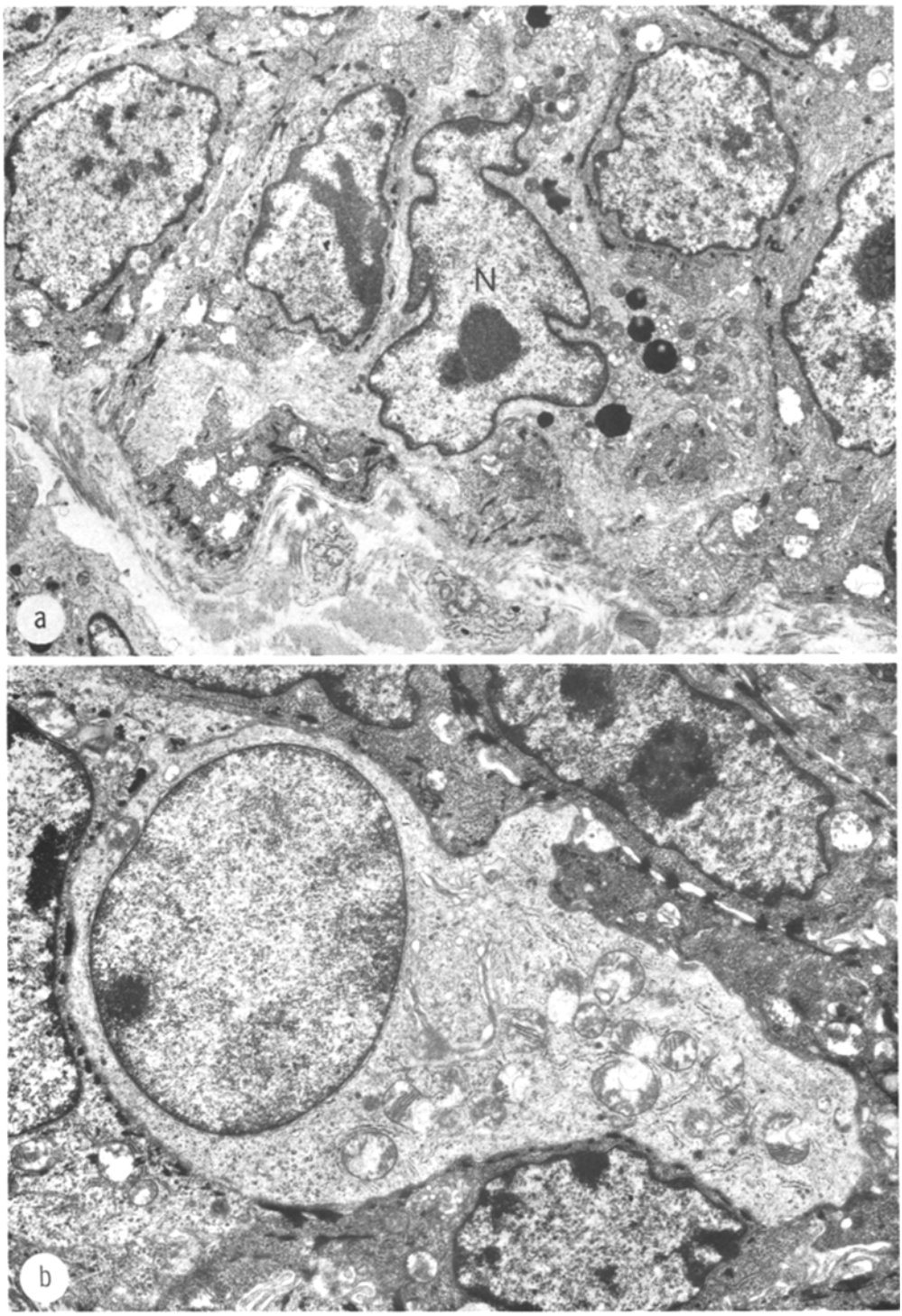

Fig. 4a and b. Interepithelial Langerhans cells without Langerhans' granules in the plane of section. **a** Large cell with dendritic cytoplasm corresponding to the macrophagocytoid type of Langerhans cell. The nucleus (*N*) is indented and moderately heterochromatic, the cytoplasm contains numerous lysosomes. Buccal mucosa. ×6,500. **b** Large cell with electrolucent, moderately dendritic cytoplasm corresponding to the reticuloid type of Langerhans cell. Spherical and euchromatic nucleus, organelle-rich cytoplasm. Buccal mucosa. ×12,000

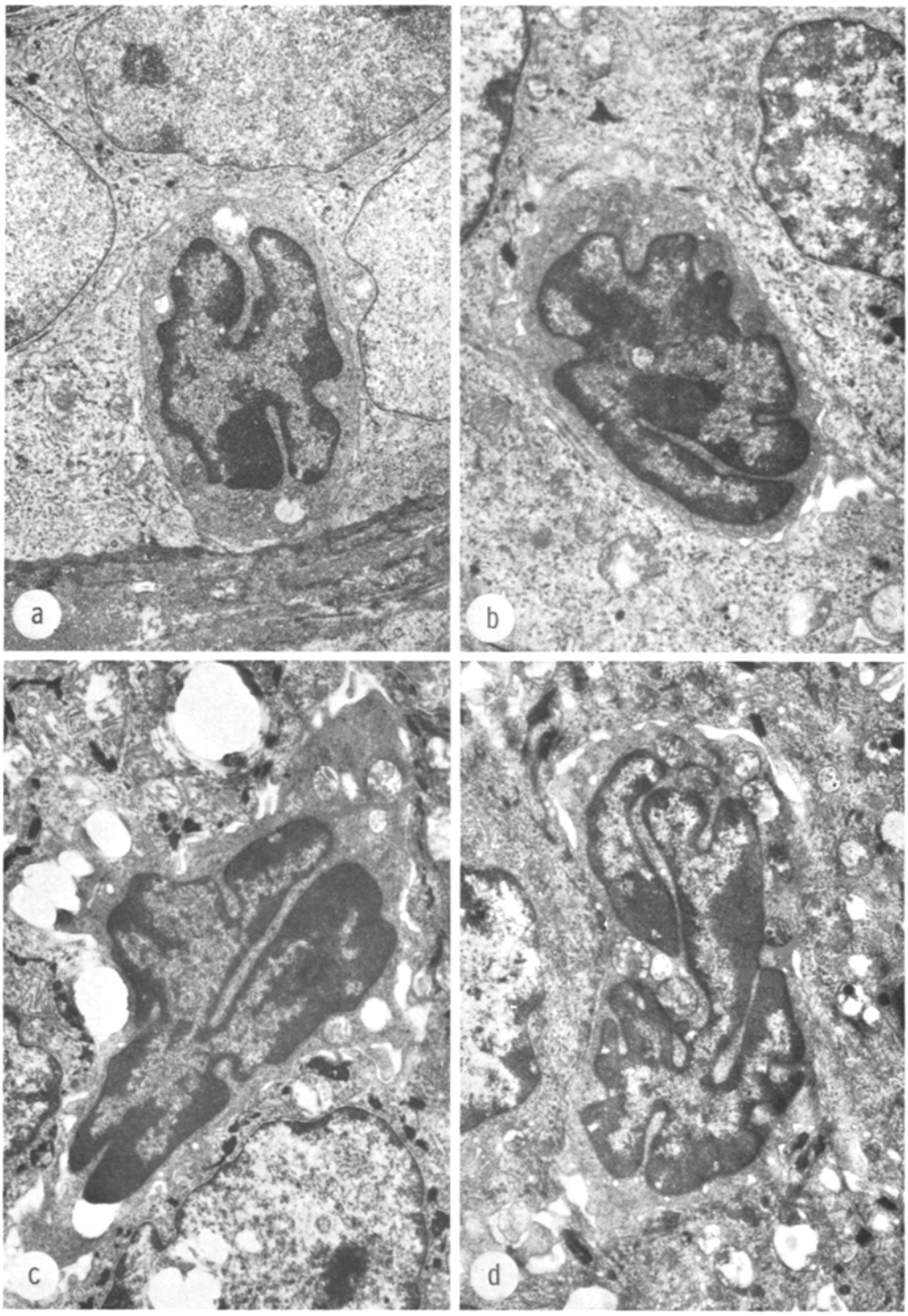

Fig. 5a–d. Small and medium sized cerebriform interepithelial cells of the murine oral mucosa. **a** and **b** Small interepithelial cells similar to lymphocytes with prominent heterochromatin and deeply indented nuclei. Buccal mucosa. ×12,000. **c** and **d** Medium sized interepithelial cells with deeply indented cerebriform heterochromatic nuclei and little electron-dense cytoplasm with few organelles. Buccal mucosa. ×12,000

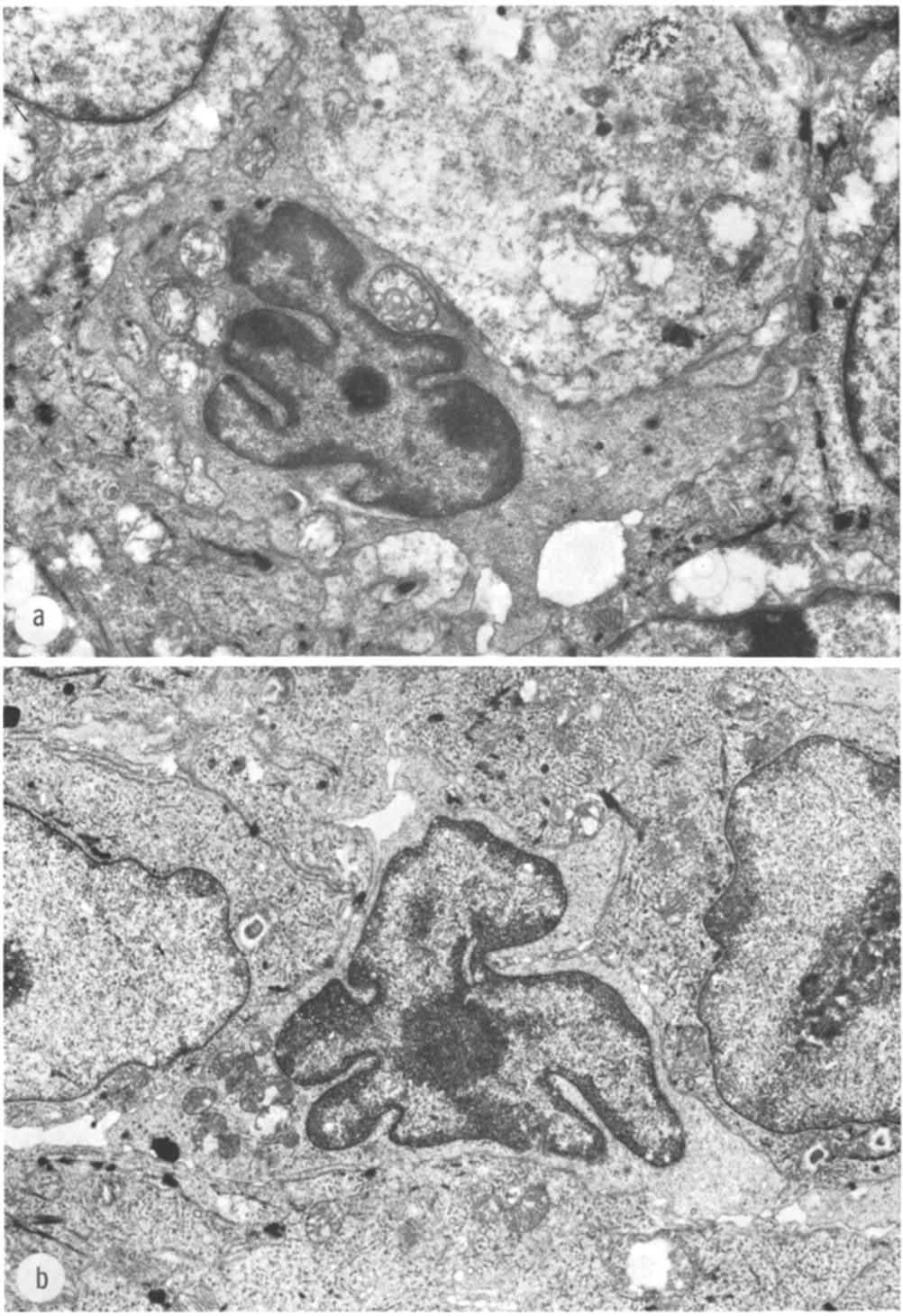

Fig. 6a and b. Large cerebriform interepithelial cells and possible transitional forms to Langerhans cells. **a** Larger cell with irregular deeply indented heterochromatic nucleus and increased, moderately dendritic cytoplasm. The cytoplasm contains numerous large mitochondria and few small lysosomes. Buccal mucosa. × 12,000. **b** Similar cell with a larger, less heterochromatic nucleus. This cell possibly represents a transitional form between cerebriform cells and Langerhans cells. Buccal mucosa. × 12,000

with a moderately heterochromatic, irregular, indented nucleus and abundant dendritic cytoplasm were termed "macrophagocytoid Langerhans cells" (Figs. 2, 4a). A second type is characterized by a rounded, smooth euchromatic nucleus and also abundant dendritic, very light cytoplasm. This type was termed "reticuloid Langerhans cells" (Figs. 3, 4b) with reference to Honma (1976), who found similar cells in lesions of aphthous stomatitis.

Reticuloid and macrophagocytoid Langerhans cells can contain lysosomes. Both types occur with and without the characteristic Langerhans or Birbeck granules (Birbeck et al., 1961). The Langerhans cells constitute 56.8% of the mononuclear interepithelial cells; 80.9% of these are macrophagocytoid and 19.1% reticuloid Langerhans cells.

Apart from these two known cell groups – lymphocytes and Langerhans cells – a residue of about 20% interepithelial cells did not seem to be classifiable at first. These are the cells with deeply indented nuclei and prominent marginated heterochromatin mentioned above (Figs. 5, 6). Some of these cells were small and similar to lymphocytes (Fig. 5) while others were larger with increased cytoplasm and less heterochromatic nuclei (Fig. 6).

In addition to lymphocytes, Langerhans cells, and these cells with "cerebriform" nuclei, only a very few Merkel cells were observed in the epithelium. Melanocytes, which are sometimes difficult to differentiate from the similarly dendritic Langerhans cells, are not regular constituents of the oral mucosa of mice (Dummet and Barens, 1978). Mast cells, which can occasionally be localized inside the epithelium (Carranza and Cabrini, 1955), were not observed in the mice we studied. Under normal conditions macrophages and plasma cells are only found subepithelially. Accordingly, cells with a positive marking for immunoglobulins, pyroninophil cells or mononuclear cells with naphthol-AS-D-chloroacetatesterase activity (a marker of macrophages, mast cells and granulocytes: Leder, 1967; Schäfer et al., 1970) are not situated inside the epithelium. Likewise plasma cells or cells with phagolysosomes are not found in an interepithelial location. Only occasionally did a cytoplasmic process of a macrophage extend through the basal membrane into the epithelium.

Discussion

With the exception of plasma cells and monocytogenic macrophages, some inflammatory cells are always found in the normal oral epithelium. In addition, a few neuroectodermal cells can be observed, in mice these are almost exclusively Merkel cells (Table 1). The mononuclear interepithelial cells – especially lymphocytes and Langerhans cells – proved to be an integral part of the oral mucosa independent of antigenic stimulation, in germfree and specific pathogen free mice a mean of 7.4 cells per 1,000 basal cells is found (Bos and Burkhardt, 1977, 1979).

Weinmann (1940) and Cattoni (1951) were the first who paid attention to the interepithelial lymphocytes of the oral mucosa. Cattoni (1951) studied the lymphocytes in the gingival epithelium and stressed the fact that they are situated intercellularly and are a regular part of the epithelium. In some electron

Table 1. Classification of interepithelial cells of the oral mucosa

Origin	Type of cell	Function	Morphological characteristics
Neuro-ectoderm	Melanocytes	Formation of pigment	Melanosomes, premelanosomes
	Merkel cells	Neurohumoral transmitter cell	Merkel cell granules, apposition to neurites
Mesenchyme	Lymphocytes	Immunological defense, recognition of antigen, precursors of Langerhans cells?	Little cytoplasm with few organelles, heterochromatic nuclei
	Cerebriform cells	Precursors of Langerhans cells?	Cerebriform, strongly heterochromatic nuclei
	Langerhans cells	Recognition and concentration of antigen, Cooperation with lymphocytes in immune response	Dendritic ramification, primary lysosomes, Langerhans (Birbeck) granules
	– Macrophagocytoid		Indented moderately heterochromatic nuclei, dense cytoplasm
	– Reticuloid		Spherical euchromatic nuclei, light cytoplasm
	Neutrophilic granulocytes	Microphagocytosis	Neutrophilic granula
	Eosinophilic granulocytes	Participation in immunological processes (phagocytosis of immunocomplexes)	Eosinophilic granula
	Mast cells	Secretion of mediators of inflammation (e.g. histamine, serotonin)	Mast cell granules

microscopic investigations of the normal oral mucosa, interepithelial lymphocytes or "clear cells" were described without further comment (Listgarten, 1964; Hashimoto et al., 1966; Thilander and Bloom, 1968).

Interepithelial lymphocytes have also been found in a number of pathological conditions (gingivitis: Freedman et al., 1968; Schroeder, 1973; Holthuis et al., 1975, 1977; aphthous stomatitis: Lehner, 1969; Saito et al., 1971; Honma, 1976; lichen planus: Tyldesley and Appleton, 1973; Barnett, 1976; psoriasis: Fischman et al., 1977; erythema multiforme exudativum: von Bülow et al., 1966). In contrast Schroeder and Theilade (1966), Gavin (1970), Hutchens et al. (1971), Lange and Schroeder (1971) and Sagebiel et al. (1971) do not mention interepithelial lymphocytes in normal oral mucosa or in gingivitis. Holthuis et al. (1975, 1977) described two forms of interepithelial lymphocytes – an inactive, resting form (oval shape, indented and heterochromatic nuclei, abundant free ribosomes)

and an intermediate form (larger, less heterochromatic nuclei, increased endoplasmatic reticulum) as a consequence of antigenic stimulation. They postulate a transformation into actively antibody synthesizing cells. Similar forms of lymphocytes have been described by Barnett (1976) in lichen planus, and by Saito et al. (1971) and Honma (1976) in the Behçet syndrome and recurrent aphthous stomatitis. However, typical mature plasma cells do not occur inside the epithelium. In mice interepithelial lymphocytes are an integral part of the oral mucosa and make up 22.8% of the interepithelial mononuclear cell population. Lymphocytes with rounded and with indented ("cleaved") nuclei can be differentiated.

In lymph node cytology rounded lymphocytes are considered to be T-cells and cleaved lymphocytes are thought to belong to the B-cell series. It seems questionable whether this distinction can be applied to interepithelial lymphocytes. Similarly it cannot be decided whether the rounded and cleaved lymphocytes are different cell populations, or whether they represent steps of differentiation.

Langerhans cells are found in all homo- and heterotopic multistratified squamous epithelium (Thiery and Wildhagen, 1969). Their origin is not clear. They have been thought to derive from or to be related to neural cells, melanocytes, keratinocytes, histiocytes or macrophages (Langerhans, 1868; Breathnach and Goodwin, 1965; Breathnach, 1963; Reams and Tompkins, 1973; Basset and Turiaf, 1965; Riley, 1974). The Langerhans or Birbeck granule is considered to be the identification mark of these cells. However its origin, significance and function are completely unknown (cp. Breathnach, 1964; Zelickson, 1966; Hashimoto, 1971; Reams and Tompkins, 1973). On the basis of experimental observations on lymph node reticulum cells containing such granules, Kamperdijk et al. (1978) suggest that these granules are immunologically specific organelles associated with the induction of a primary humoral response. The specifictiy of the Langerhans granule as an identification mark of Langerhans cells has been questioned (Wolff, 1972; Böck, 1973; Reams and Tompkins, 1973; Kamperdijk et al., 1978), especially since these granules are also found in other cell species like the atypical histiocytes in histiocytosis X (Basset and Turiaf, 1965; Shamoto et al., 1976) and even keratinocytes (Böck and Hanak, 1971; Bell, 1969). Most of the "unspecific dendritic cells" (Snell, 1965; Zelickson and Mottaz, 1968; Hutchens et al., 1971; Sagebiel et al., 1971; Squier et al., 1975) must thus be considered to be Langerhans cells (Böck, 1974; Reams and Tompkins, 1973).

The occurrence of Langerhans cells in the oral mucosa has been well documented (Schroeder and Theilade, 1966; Waterhouse and Squier, 1967; Hashimoto et al., 1968; Hutchens et al., 1971; Mäusle et al., 1971; Schenk, 1975). However, no systematic investigation on their frequency, distribution and differentiation has been undertaken. Saito et al. (1971) distinguished 3 types of "macrophages" in the epithelium of oral lesions in the Behçet syndrome: macrophages I with abundant cytoplasm, frequently in contact with degenerating keratinocytes, macrophages II with fewer organelles, frequently in contact with lymphocytes and macrophages III, the typical Langerhans cells. Probably all three cell types are different froms of Langerhans cells. Honma (1976) described

two types of "reticuloid" cells in lesions of recurrent aphthous stomatitis, which he delineates from the reticulum cells of lymph nodes. Type 1 has few organelles and rounded nuclei without heterochromatin, type 2 has more endoplasmatic reticulum and slightly indented nuclei with little heterochromatin.

Langerhans cells are found regularly in the murine oral mucosa and make up 56.8% of the total mononuclear interepithelial cell population. 80.9% of these have the more or less typical appearence of the Langerhans cells known from the epidermis. This "macrophagocytoid" Langerhans cell has a characteristically irregular indented, moderately heterochromatic nucleus. 19.1% of the Langerhans cells exhibit a spherical euchromatic nucleus and an electron lucent cytoplasm. They are similar to the "reticuloid" cells described by Honma (1976).

Apart from lymphocytes and Langerhans cells we were able to differentiate a third mononuclear interepithelial cell type. These were cells of the size of lymphocytes, or a little larger, with deeply indented and folded nuclei and marginated dense heterochromatin. These cells have previously been illustrated in various lesions of the oral mucosa (leukoplakia, psoriasis, erythema multiforme exudativum) by a few authors (von Bülow et al., 1966; Hashimoto et al., 1968; Fischman et al., 1977). They have been termed "intraepithelial mononuclear cells, probably small lymphocytes" (Fischman et al., 1977) or "rather dense cells which appear to be histiocytes" (Hashimoto et al., 1968).

Some authors described similar cells in the epidermis and called them "dark Langerhans cells" (Ebner and Niebauer, 1967), type 2 Langerhans cells with few Langerhans granules (Breathnach, 1977), α-dendritic cells with a possible delineation from melanocytes (Mishima and Matsunaka, 1976) or simply "nonkeratinocytes" (Breathnach and Goodwin, 1965). Apparently they are less frequent in epidermis than in oral epithelium.

Looked at more closely, these cells correspond to the so-called cerebriform mononuclear cells (CMC) or Sézary cells found in the infiltrate of cutaneous T-cell lymphomas (Sézary syndrome, mycosis fungoides), first described by Sézary and Bouvrain (1938) as "monsterous cells". In particular the configuration of the nucleus with deep infoldings and indentations is identical (cp. Brownlee and Murad, 1971). These cells were thought to be histio-monocytic (Sézary and Bouvrain, 1938), atypical histiocytes or reticulum cells (Sézary, 1949; Fisher et al., 1972).

Crossen et al. (1971) demonstrated that these cells could be stimulated by phytohaemagglutinins and today there is no doubt that the cerebriform cell is lymphocytic in origin (Labaze et al., 1972; Lutzner et al., 1973; Flandrin and Brouet, 1974; Lutzner et al., 1975; van Leeuwen et al., 1975; Yeckley et al., 1975; Broder et al., 1976; Hamburg et al., 1976; Robinowitz et al., 1976; Rowden and Lewis, 1976; van Leeuwen et al., 1976; Meijer et al., 1977; Burg et al., 1978; Worman et al., 1978).

Investigations on the cell membrane determinants of cerebriform cells (Table 2) indicate a T-cell nature, as the majority of the cells have typical receptors for uncoated sheep red blood cells (Broome et al., 1973; Brouet et al., 1973; Edelson et al., 1974a, b; Zucker-Franklin et al., 1974; van Leeuwen et al., 1976; Gupta et al., 1978; Worman et al., 1978; Chu and MacDonald, 1979). They also occur in healthy subjects in lymph nodes, spleen, blood, tissue culture

Table 2. Synopsis of membrane receptors of lymphocytes, cerebriform cells, Langerhans cells and macrophages (the data are based on authors cited in the text)

	T-lympho-cyte	B-lympho-cyte	Cerebriform cell	Langerhans cell	Macro-phage
E-rosette formation	+	−	+	−	−
theta-antigen (mouse)	+	−	?	?	−
B-cell-alloantigen	−	+	?	+	+
Ia-antigen (mouse)	+	+	?	+	+
Fc-receptors	−	+	−	+	(+)
C3-receptors	−	+	−	+	(+)
Easily accessible surface immunoglobulins	−	+	−	−	−

of epidermis and in various dermatoses (Flaxman et al., 1971, 1974; Lutzner et al., 1971; Ebner, 1973; Yeckley et al., 1975; Rosas-Uribe et al., 1974; Hamburg et al., 1976; Orbanea et al., 1976; van Leeuwen et al., 1976; Meyer et al., 1977). Their function or further fate is so far not known. They do not seem to be degenerated end products but rather transitional forms.

We have demonstrated that this cell is regularly found in the epithelium of the oral mucosa of mice and makes up about 20% of the total non-keratinocyte population. They occur in euthymic and in athymic mice (Burkhardt et al., 1979). This would mean that they are mostly not mature T-lymphocytes. From our observations a lymphocytic origin also seems to be probable as there are numerous transitional forms and the decision to call a particular cell a deeply indented lymphocyte or small cerebriform cell was often arbitrary. Apart from small cerebriform cells, larger cells of this type were observed. These had less heterochromatic nuclei and increased cytoplasm. Here again a differentiation from macrophagocytoid Langerhans cells was often impossible. Both cells – cerebriform cells and Langerhans cells – increase in number subsequent to exposure of the oral mucosa to antigens (Bos and Burkhardt, 1979). This may indicate a development of the Langerhans cells from cerebriform cells. Breathnach (1977) also considered the Langerhans cell type 2 – which appears to be similar to the cerebriform cell – to be a precursor of the typical Langerhans cell (type 1). On the other hand Ryan et al. (1973) suggested the formation of cerebriform cells in mycosis fungoides from Langerhans cells, before their lymphocytic origin was proved. In the skin both cells are often found in close contact (Meijer, 1979). Our thesis would further mean that Langerhans cells are possibly differentiation products of lymphocytes, the cerebriform cells being an intermediary step (Fig. 7).

A lymphocytic nature of Langerhans cells was first suspected by Ranvier (1875). Al Yassin and Toner (1976) stressed the similarity of stimulated lymphocytes and Langerhans cells. Recently Gerneke (1977) suggested, on the grounds of similar functions of lymphocytes and Langerhans cells, that the latter be called "epithelial lymphocytes". However, he did not give evidence for an actual cytogenetic relation of both cells. If Langerhans cells originate from

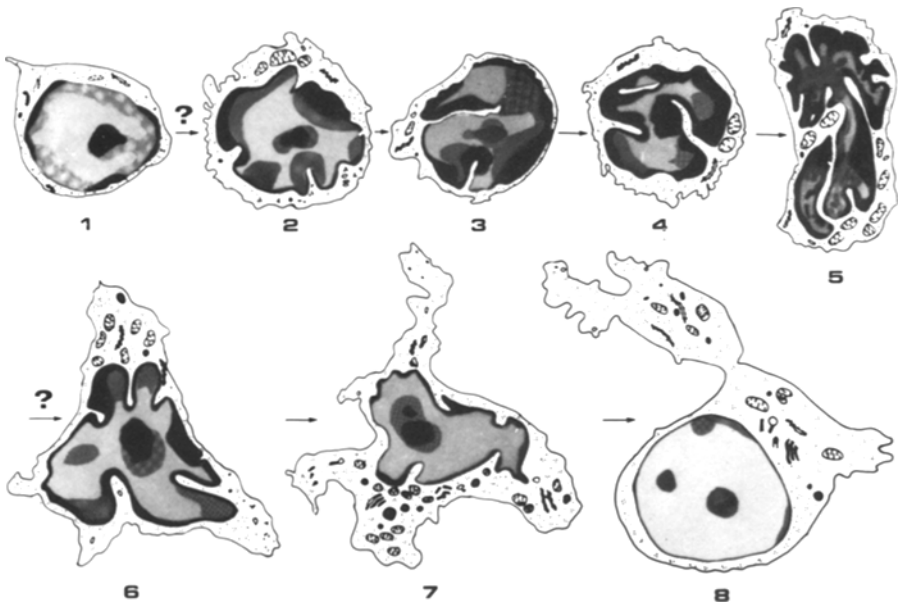

Fig. 7. Schematic synopsis of the different interepithelial cell populations and possible cytogenetic evolution: lymphocyte with rounded nucleus (**1**), lymphocytes with indented nuclei (**2, 3**), cerebriform cells (**4, 5**), possible transitional form (**6**), macrophagocytoid Langerhans cell (**7**) and reticuloid Langerhans cell (**8**)

circulating lymphocytes, the ubiquitous occurrence of lymphocytes could easily explain the appearance of Langerhans cells in metaplastic squamous epithelium without contact with pre-existing squamous epithelium. The only evidence against a lymphocytic nature of Langerhans cells was presented by Reams and Greco (1969) who observed no labelling of Langerhans cells by antilymphocyte serum. However, their paper leaves many methodological questions unanswered.

Of course the proposal of a cellular line of evolution on purely morphological grounds is very problematical. However, the high number of cells which were classified seems to justify such a discussion. If we consider the surface markers of lymphocytes, cerebriform cells and Langerhans cells that are known to date (Table 2), one can see that Langerhans cells have characteristics in common with T- and B-lymphocytes, but also with macrophages. They feature a specific combination of these receptors typical of immunologically important cells (Stingl et al., 1977a, b, 1978a, b,c). A lymphocytic as well as a macrophagocytic origin is therefore compatible with the evidence presented. On the basis of these observations and functional similarities to macrophages Stingl and his colleagues (1978c, d) and Hunziker and Winkelmann (1978) favour a macrophagocytic nature for Langerhans cells. Stingl et al. (1978c, d) stress the fact that Langerhans cells express neither E-receptors nor surface immunoglobulins. According to their investigations in guinea pigs I a antigens are "selectively expressed on lymphoid cells" and by 15–25% of peritoneal exudate macrophages but "in

the epidermis Langerhans cells are the only cell subpopulation to express I a antigens" (cp. Klareskog et al., 1977).

Furthermore it is not clear why interepithelial lymphocytes of the epidermis are not demonstrated by the studies on cell surface markers in epidermal cells.

The minimal phagocytic activity of Langerhans cells (Winkelmann, 1969; Wolff and Schreiner, 1970; Sagebiel, 1972), the lack of secondary lysosomes and the enzymatic activities do not favour the concept that they are a part of the mononuclear phagocyte system (MPS; van Furth et al., 1972; van Furth, 1976), which is derived from circulating blood monocytes. On the other hand there are strong morphological and functional similarities between interdigitating reticulum cells (IDC; Kaiserling and Lennert, 1974) of the T-cell area of lymph nodes and Langerhans cells (Rausch et al., 1977; Kamperdijk et al., 1978; cp. Goos et al., 1976). Both cells show activity of ATPase and lack phagosomes (Lennert and Müller-Hermelink, 1975; Kaiserling, 1977). Cells with Langerhans' granules occur in lymph nodes (Kondo, 1969) and are found in close association with IDC (Rausch et al., 1977) or are identical with interdigitating reticulum cells (Kamperdijk et al., 1978). Interestingly cerebriform cells also home specifically in thymus-dependent areas of lymph nodes and are often found next to interdigitating reticulum cells (van Leeuwen et al., 1976; Meijer, 1979). However, the origin and classification of IDC's is just as uncertain as that of Langerhans cells. Some authors classify them as non-phagocytic reticular cells (Kaiserling and Lennert, 1974; Kaiserling, 1977; Rausch et al., 1977) while others regard them as a special type of macrophage (Kamperdijk et al., 1978). But this latter theory again rests mainly on their similarity to Langerhans cells.

From the data presented one could speculate that Langerhans cells are an additional line of differentiation of lymphocytes which matures in the microenvironment of squamous epithelium (ecotaxis), the cerebriform cell being an intermediary form. This could account in part for the epitheliotropy of lymphocytes which has been known for a long time (cp. Doerr, 1956, 1973; Otto, 1973; Rappaport and Thomas, 1974). In close cooperation with T-lymphocytes they are responsible for the recognition of antigens and their defense on the external and on parts of the internal body surface. In this process they can populate the T-cell region of lymph nodes.

In this metaphorical sense, the theory of Fichtelius and his colleagues (1969, 1970), who postulated that the whole gastrointestinal tract and the epidermis function as a primary lymphoid organ, may be justified (cf. Bos and Burkhardt, 1977, 1979).

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References

Al-Yassin, T.M., Toner, P.G.: Langerhans cells in the human oesophagus. J. Anat. **122**, 435–445 (1976)

Andrew, W.: Differentiation of migrant cells in the human epidermis and the non-specificity of the germ-layers. Arch. Histol. Jap. **29**, 211–235 (1968)

Barnett, M.L.: The non keratinocyte intraepithelial cell population in lichen planus. An ultrastructural characterization of cells in gingival lesions. Oral Surg. **41**, 338–353 (1976)
Basset, F., Turiaf, J.: Identification par le microscopie electronique de particles de nature probablement viviale dans les lesions granulomateuses d'une histiocytosis-X pulmonaire. C.R.Acad.Sci. (Paris) **261**, 3701–3703 (1965)
Bell, M.: Langerhans granules in fetal keratinocytes. J. Cell. Biol. **41**, 914–918 (1969)
Birbeck, M.S., Breathnach, A.S., Everall, J.D.: An electron microscopic study of basal melanocytes and high-level clear cells (Langerhans cells) in vitiligo. J. Invest. Derm. **37**, 51–74 (1961)
Böck, P., Hanak, H.: Some remarks on the morphology of the guinea pig conjunctival epithelium. J. Submicr. Cytol. **3**, 1–8 (1971)
Böck, P.: Fine structure of Langerhans cells in the stratified epithelia of the esophagus and stomach of mice. Z. Zellforsch. **147**, 237–247 (1974)
Bos, I., Burkhardt, A.: Experimentelle Untersuchungen zur Bedeutung der interepithelialen Zellen in der oralen Mucosa. Verh. Dtsch. Ges. Path. **61**, 431 (1977)
Bos, I., Burkhardt, A.: Interepithelial cells of the oral mucosa – light and electron microscopic observations in germfree, specific pathogen-free and conventionalized mice. J. Oral Pathol. **8** (1979, in print)
Breathnach, A.S.: A new concept of the relation between the Langerhans cell and the melanocyte. J. Invest. Derm. **40**, 279–281 (1963)
Breathnach, A.S.: Observations on cytoplasmic organelles in Langerhans cells of human epidermis. J. Anat. **98**, 265–270 (1964)
Breathnach, A.S., Goodwin, D.P.: Electron microscopy of non-keratinocytes in the basal layer of white epidermis of the recessively spotted guinea-pig. J. Anat. **99**, 377–387 (1965)
Breathnach, A.S.: Variations in ultrastructural appearance of Langerhans cells of normal human epidermis. Br. J. Dermatol. **97**, Suppl. 15, 14 (1977)
Broder, S., Edelson, R.L., Lutzner, M.A., Nelson, D.L., MacDermott, R.P., Durm, M.E., Goldman, C.K., Meade, B.D., Waldmann, Th.A.: The Sézary syndrome. A malignant proliferation of helper T cells. J. Clin. Invest. **58**, 1297–1306 (1976)
Broome, J.D., Zucker-Franklin, D., Weiner, M.S.: Leukemic cells with membrane properties of thymus derived (T) lymphocytes in a case of Sézary syndrome: morphologic and immunologic studies. Clin, Immunol. Immunopathol. **1**, 319–329 (1973)
Brouet, J.C., Flandrin, G., Seligmann, M.: Indications of the thymus derived nature of the proliferating cells in six patients with Sézary syndrome. N. Engl. J. Med. **289**, 341–344 (1973)
Brownlee, T.R., Murad, T.M.: Ultrastructure of mycosis fungoides. Cancer **26**, 686–698 (1971)
von Bülow, F.A., Hjorting-Hansen, E., Ulmansky, M.: An electronmicroscopic study of oral mucosal lesions in erythema multiforme exudativum. Acta Path. Microbiol. Scand. **66**, 145–153 (1966)
Burg, G., Rodt, H., Grosse-Wilde, H., Braun-Falco, O.: Surface markers and mitogen response of cells harvested from cutaneous infiltrates in mycosis fungoides and Sézary's syndrome. J. Invest. Derm. **70**, 257–259 (1978)
Burkhardt, A.: Der Mundhöhlenkrebs und seine Vorstadien – ultrastrukturelle und immunpathologische Aspekte. Habil.-Schrift, Universität Hamburg 1979
Burkhardt, A., Bos, I., Gebbers, J.-O., Otto, H.F.: Interepithelial cells of the oral mucosa of athymic (nude) mice under different antigen exposure. Light and electron microscopic study. (1979, in preparation)
Carranza, F.A.:, Cabrini, R.L.: Mast cells in human gingivae. Oral Surg. **8**, 1093–1099 (1955)
Cattoni, M.: Lymphocytes in the epithelium of the healthy gingiva. J. Dent. Res. **30**, 627–637 (1951)
Chu, A.C., MacDonald, D.M.: Identification in situ of lymphocytes-T in the dermal and epidermal infiltrates of mycosis fungoides. Br. J. Dermatol. **100**, 177–182 (1979)
Crossen, P.E., Mellor, J.E.L., Finley, A.G., Rarich, R.B.M., Vincent, P.C., Gunz, F.W.: The Sézary syndrome. Cytogenetic studies and identification of the Sézary cell. Am. J. Med. **50**, 24–34 (1971)
Dalton, A.J.: A chrome-osmium fixation for electron microscopy. Anat. Rec. **121**, 281 (1955)
Doerr, W.: Über lymphoepitheliale Geschwülste Schmincke-Regaud. Ärztl. Wschr. **11**, 169–182 (1956)
Doerr, W.: Über die Bedeutung der pathologischen Anatomie für die Gastroenterologie. Aktuelle Fragen zur Pathologie der Verdauungsorgane. Sitzungsberichte der Heidelberger Akademie der

Wissenschaften/Mathematisch-Naturwissenschaftliche Klasse Jahrgang 1973, 4. Abhandlung, S. 139–172

Dummet, C.O., Barens, G.: Animal oral pigmentations. J. Periodont. **49**, 206–213 (1978)

Ebner, H., Niebauer, G.: Die sogenannte „dunkle" Langerhanszelle. Arch. Klin. Exp. Dermat. **229**, 217–222 (1967)

Ebner, H.: Untersuchungen über die zelluläre Zusammensetzung des Lichen ruber planus-Infiltrates. Arch. Derm. Forsch. **247**, 309–318 (1973)

Edelson, R.L., Kirkpatrick, Ch.H., Shevach, E.M., Schein, Ph.S., Smith, R.W., Green, I., Lutzner, M.: Preferential cutaneous infiltration by neoplastic thymus derived lymphocytes: Morphologic and functional studies. Ann. Intern. Med. **80**, 685–692 (1974a)

Edelson, R.L., Lutzner, M.A., Kirkpatrick, Ch.H., Shevach, E.M., Green, I.: Morphologic and functional properties of the atypical T-lymphocytes of the Sézary syndrome. Mayo Clin. Proc. **49**, 558–566 (1974b)

Fichtelius, K.E., Finstad, J., Good, R.A.: The phylogenetic occurrence of lymphocytes within the gut epithelium. Int. Arch. Allergy **35**, 119–133 (1969a)

Fichtelius, K.E., Sundström, C., Kullgren, B., Linna, J.: The lympho-epithelial organs of homo sapiens revisited. Acta Path. Microbiol. Scand. **77**, 103–116 (1969b)

Fichtelius, K.E., Groth, O., Liden, S.: The skin, a first level lymphoid organ? Int. Arch. Allergy, **37**, 607–620 (1970)

Fischman, S.L., Barnett, M.L., Nisengaard, R.J.: Histopathologic, ultrastructural, and immunologic findings in an oral psoriatic lesion. Oral Surg. **44**, 253–260 (1977)

Fisher, E.R., Horvat, B., Wechsler, H.L.: Ultrastructural features of mycosis fungoides. Am. J. Clin. Pathol. **58**, 99–110 (1972)

Flandrin, G., Brouet, J.-C.: The Sézary cell: cytologic, cytochemical, and immunologic studies. Mayo Clin. Proc. **49**, 575–583 (1974)

Flaxman, B.A., Zelazny, G., van Scott, E.J.: Nonspecificity of characteristic cells in mycosis fungoides. Arch. Derm. **104**, 141–147 (1971)

Flaxman, B.A., van Scott, E.J., Goldman, L.I.: Sézary-like cells in cultures of normal skin. Arch. Derm. **109**, 577–578 (1974)

Freedman, H.L., Listgarten, M.A., Taichman, N.S.: Electron microscopic features of chronically inflamed human gingiva. J. Periodont. Res. **3**, 313–327 (1968)

van Furth, R., Cohn, Z.A., Hirsch, J.G., Humphrey, J.H., Spector, W.G., Langevoort, H.L.: The mononuclear phagocyte system. A new classification of macrophages, monocytes and their precursor cells. Bull. W.H.O. **46**, 845–852 (1972)

van Furth, R.: Origin and kinetics of mononuclear phagocytes. Ann. New York Acad. Sci. **278**, 161–175 (1976)

Gavin, J.B.: Ultrastructural features of chronic marginal gingivitis. J. Periodont. Res. **5**, 19–29 (1970)

Gerneke, W.H.: Langerhans cells in the epithelium of the bovine forestomach: their role in the primary immune response. J. South Afr. Vet. Ass. **48**, 187–192 (1977)

Goos, M., Kaiserling, E., Lennert, K.: Mycosis fungoides: model for T-lymphocyte homing to the skin? Br. J. Dermatol. **94**, 221 (1976)

Gupta, S., Safai, B., Good, R.A.: Subpopulations of human T lymphocytes. IV. quantitation and distribution in patients with mycosis fungoides and Sézary syndrome. Cell. Immunol. **39**, 18–26 (1978)

Hamburg, A., Brynes, R.K., Reese, C., Colomb, H.M.: Human cord blood lymphocytes. Ultrastructural and immunologic surface marker characteristics: A comparison with B- and T-cell lymphomas. Lab. Invest. **34**, 207–214 (1976)

Hashimoto, K., DiBella, R.J., Shklar, G.: Electron microscopic studies of the normal human buccal mucosa. J. Invest. Dermatol. **47**, 512–525 (1966)

Hashimoto, K., DiBella, R.J., Tarnowski, W.M., Shklar, G.: Electron microscopic studies of oral benign leukoplakia. Oral Surg. **25**, 901–1017 (1968)

Hashimoto, K.: Langerhans cell granules. An endocytotic organelle. Arch. Dermatol. **104**, 148–165 (1971)

Holthuis, A.F., Holm-Pedersen, P., Folke, L.E.A.: Interepithelial lymphocytes in experimental gingivitis in young and elderly individuals. AADR Abstracts, p. 121 (1975)

Holthuis, A.F., Holm-Pedersen, P., Folke, L.E.A.: Interepithelial lymphocytes in experimental gingivitis in young and elderly individuals. J. Periodont. Res. **12**, 166–178 (1977)

Honma, I.: Electron microscopic study on the pathogenesis of recurrent aphthous ulceration as compared to Behçet's syndrome. Oral Surg. **41**, 366–377 (1976)
Hunziker, N., Winkelmann, R.K.: Langerhans cells in contact dermatitis of guinea pigs. Arch. Dermatol. **114**, 1309–1313 (1978)
Hutchens, L.H., Sagebiel, R.W., Clarke, M.A.: Oral epithelial dendritic cells of the rhesus monkey: histologic demonstration, fine structure and quantitative distribution. J. Invest. Dermatol. **56**, 325–336 (1971)
Kaiserling, E., Lennert, K.: Die interdigitierenden Reticulumzellen in menschlichen Lymphknoten. Virchows Arch. B Cell. Path. **16**, 51–61 (1974)
Kaiserling, E.: Non-Hodgin-Lymphome. Ultrastruktur und Cytogenese. Stuttgart-New York: 1977 G. Fischer
Kamperdijk, E.W.A., Raaymaker, E.M., de Leeuw, J.H.S., Hoefsmit, E.Ch.M.: Lymph node macrophages and reticulum cells in the immune response. I. The primary response to paratyphoid vaccine. Cell Tiss. Res. **192**, 1–23 (1978)
Klareskog, L., Tjernlund, V.M., Forsum, U., Peterson, P.A.: Epidermal Langerhans cells express Ia antigens. Nature **268**, 248–250 (1977)
Kondo, Y.: Macrophages containing Langerhans cell granules in human lymph nodes. Z. Zellforsch. **98**, 506–511 (1969)
Labaze, J.J., Moscovic, E.A., Pham, T.D., Azar, H.A.: Histological and ultrastructural findings in a case of the Sézary syndrome. J. Clin. Pathol. **25**, 312–319 (1972)
Lange, D., Schroeder, H.E.: Cytochemistry and ultrastructure of gingival sulcus cells. Helv. Odont. Acta **15**, Suppl. VI, p. 65–86 (1971)
Langerhans, P.: Über die Nerven der menschlichen Haut. Virchows Arch. Path. Anat. **44**, 325–337 (1868)
Leder, L.D.: Der Blutmonozyt. Experimentelle Medizin, Pathologie und Klinik (Band 23). Berlin-Heidelberg-New York: Springer 1967
van Leeuwen, A.W.F.M., Meijer, C.J.L.M., de Man, J.C.H.: T-cell membrane characteristics of "mycosis cells" in the skin and lymph node. J. Invest. Derm. **65**, 367–369 (1975)
van Leeuwen, A.W.F.M., Meijer, C.J.L.M., van Vloten, W.A., Scheffer, E., de Man, J.C.H.: Further evidence for the T-cell nature of the atypical mononuclear cells in mycosis fungoides. Virchows Arch. B Cell. Path. **21**, 179–187 (1976)
Lehner, T.: Pathology of recurrent oral ulceration and oral ulceration in Behçet's syndrome. Light, electron and fluorescence microscopy. J. Path. **97**, 481–494 (1969)
Lennert, K., Müller-Hermelink, H.K.: Lymphozyten und ihre Funktionsformen – Morphologie, Organisation und immunologische Bedeutung. Verh. Anat. Ges. **69**, 19–62 (1975)
Lillie, R.D.: Histopathologic technic and practical histochemistry. 3 rd. edition. New York, Toronto, London: Mc Graw-Hill Book Company 1965
Listgarten, M.A.: The ultrastructure of human gingival epithelium. Am. J. Anat. **114**, 49–69 (1964)
Löning, Th., Burkhardt, A., Seifert, G., Gebbers, J.-O.: Zur Typisierung der Immunglobuline in oralen Leukoplakien und Karzinomen. Dtsch. Z. Mund-Kiefer-Gesichts-Chir. **1**, 168–177 (1977)
Luft, J.H.: Ruthenium red and violett. I. Chemistry, purification methods of use for electron microscopy and mechanism of action. Anat. Rec. **171**, 347–368 (1971a)
Luft, J.H.: Ruthenium red and violett. II. Fine structural localization in animal tissues. Anat. Rec. **171**, 369–416 (1971b)
Lutzner, M.A., Hobbs, J., Horvath, P.: Ultrastructure of abnormal cells in Sézary syndrome, mycosis fungoides and parapsoriasis en plaque. Arch. Derm. **103**, 375–386 (1971)
Lutzner, M.A., Edelson, R.L., Smith, R.W.: Two varieties of Sézary syndrome, both bearing T-cell markers. Lancet **2/1973**, 207
Lutzner, M.A., Edelson, R.L., Schein, Ph.S., Green, I., Kirkpatrick, Ch.H., Ahmed, A.: Cutaneous T-cell lymphomas: The Sézary syndrome, mycosis fungoides and related disorders NIH Conference, Ann. Intern. Med. **83**, 534–552 (1975)
Mäusle, E., Mootz, W., Schöndorf, J.: Elektronenmikroskopischer Nachweis von Langerhans-Zellen im Epithel der menschlichen Gaumenmandeln. Cytobiologie **3**, 359–366 (1971)
Meijer, C.J.L.M., van Leeuwen, A.W.F.M., van der Loo, E.M., van de Putte, L.B.A., van Vloten, W.A.: Cerebriform (Sézary-like) mononuclear cells in healthy individuals. A morphologically distinct population of T-cells. Virchows Arch. B. Cell. Path. **25**, 95–104 (1977)
Meijer, C.J.L.M.: Cutaneous T cell lymphomas: morphological aspects. Boerhaave Course on

malignant lymphomas, Noordwijkerhout, The Netherlands, April 3–6, 1979
Merkel, F.: Tastzellen und Tastkörperchen bei den Haustieren und beim Menschen. Arch. Mikrosk. Anat. **11**, 636–652 (1875)
Mishima, Y., Matsunaka, M.: Quantitative and three-dimensional analyses of dendritic cells and keratin cells in the human epidermis revealed by transmission and scanning electron microscopy. In: Recent progress in electron microscopy of cells and tissues, E. Yamada et al. (Eds.). Stuttgart: G. Thieme, 1976
Orbanea, J.G., Pietz, L.J., Lozano, J.L.S., Salazar, L.C.: Lymphomatoid contact dermatitis. A syndrome produced by epicutaneous hypersensitivity with clinical features and a histopathologic picture similar to that of mycosis fungoides. Contact Dermatitis **2**, 139–143 (1976)
Otto, H.F.: The interepithelial lymphocytes of the intestinum. Morphological observations and immunological aspects of intestinal enteropathy. Curr. Topics Pathol. **57**, 81–121 (1973)
Ranvier, L.: Traite technique d'histologie. Paris: Savy édition 1875
Rappaport, H., Thomas, L.B.: Mycosis fungoides: The pathology of extracutaneous involvement. Cancer **34**, 1198–1229 (1974)
Rausch, E., Kaiserling, E., Goos, M.: Langerhans cells and interdigitating reticulum cells in the thymus-dependent region in human dermatopathic lymphadenitis. Virchows Arch. B Cell. Path. **25**, 327–343 (1977)
Reams, W.M., Greco. P.P.: An immunochemical study of epidermal Langerhans cells of the mouse. Virginia J. Sci. **20**, 113 (1969)
Reams, W.M., Tompkins, S.P.: A developmental study of murine epidermal Langerhans cells. Dev. Biol. **31**, 114–123 (1973)
Riley, P.A.: The Langerhans cell. In: The physiology and pathophysiology of the skin, A. Jarrett (Ed.), 3, p. 1199–1235. New York: Academic Press 1974
Robinowitz, B.N., Noguchi, S., Roenigk, H.H.: Tumor cell characterization in mycosis fungoides. Cancer **37**, 1747–1753 (1976)
Rosas-Uribe, A., Variakojis, D., Molnar, Z., Rappaport, H.: Mycosis fungoides: An ultrastructural study. Cancer **34**, 634–645 (1974)
Rowden, G., Lewis, M.G.: Langerhans cells: Involvement in the pathogenesis of mycosis fungoides. Br. J. Dermatol. **95**, 665–672 (1976)
Rupec, M., Uhlarik, S.: Lymphoide Zellen im Epithel der normalen menschlichen Vaginalschleimhaut. Klin. Wschr. **47**, 551–552 (1969)
Ryan, E.A., Sanderson, K.V., Bartak, P., Samman, P.D.: Can mycosis fungoides begin in the epidermis? A hypothesis. Br. J. Dermatol. **88**, 419–429 (1973)
Sagebiel, R.W., Clarke, M.A., Hutchens, L.H.: Dendritic cells in oral epithelium. In: Current concepts of the histology of oral mucosa, C.A. Squier and J. Meyer (Eds.), pp. 143–166. Springfield, Ill.: Ch. C. Thomas 1971
Sagebiel, R.W.: In vivo and in vitro uptake of ferritin by Langerhans cells of the epidermis. J. Invest. Dermatol. **58**, 47–54 (1972)
Saito, T., Honma, T., Sato, T., Fujioka, J.: Auto-immune mechanisms as a probable aetiology of Behçet's syndrome, an electron microscopic study of the oral mucosa. Virchows Arch. A Path. Anal. **353**, 261–272 (1971)
Schaefer, H.E., Käufer, C., Fischer, R.: Vergleichende fermentcytochemische Untersuchungen an Blut- und Knochenmarkzellen bei Laboratoriumstieren. Virchows Arch. Abt. B Zellpath. **4**, 310–334 (1970)
Schenk, P.: Melanocyten, Langerhanssche und Merkelsche Zellen in oralen Epithelien. Acta Otolaryngol. **80**, 301–311 (1975)
Schroeder, H.E., Theilade, J.: Electron microscopy of normal human gingival epithelium. J. Periodont. Res. **1**, 95–119 (1966)
Schroeder, H.E.: Transmigration and infiltration of leukocytes in human junctional epithelium. Helv. Odont. Acta. **17**, 6–18 (1973)
Sézary, A., Bouvrain, Y.: Erythrodermie avec présence de cellules monstrueuses dans le derme et le sang circulant. Bull. Soc. Franc. Derm. Syph. **45**, 254–260 (1938)
Sézary, A.: Une nouvelle reticulose cutanée. La réticulose maligne leucémique à histiomonocytes monstreux et à forme d'érythrodermie oedémateuse et pigmentée. Ann. Dermatol. Syphigr. (Paris) **9**, 6–22 (1949)
Shamoto, M., Hoshino, M. Suchi, T.: Cells containing Langerhans cell granules in human lymph nodes of "atypical hyperplasia" with fatal outcome and leukemic reticuloendotheliosis. Acta

Pathol. Jpn. **26**, 311–323 (1976)
Shelley, W.B., Juhlin, L.: Langerhans cells form a reticuloepithelial trap for external contact allergens. Nature **261**, 46–47 (1976)
Shelley, W.B., Juhlin, L.: Langerhans cell – its origin, nature, and function. Acta Derm. Venereol. **58**, Suppl. 79, 7–22 (1978)
Silberberg, I.: Apposition of mononuclear cells to Langerhans cells in contact allergic reactions. Acta Dermatovener. (Stockh.) **53**, 1–12 (1973)
Silberberg, I., Baer, R.L., Rosenthal, St.A., Thorbecke, G.J., Berenzowsky, V.: Dermal and intravascular Langerhans cells at sites of passively induced allergic contact sensitivity. Cell. Immunol. **18**, 435–453 (1975)
Snell, R.S.: An electron microscopic study of the dendritic cells in the basal layer of guinea-pig epidermis. Z. Zellforsch. **66**, 457–470 (1965)
Squier, C.A., Johnson, N.W., Hackemann, M.: Structure and function of normal human oral mucosa. In: Oral mucosa in health and disease, A.E. Dolby (Ed.), p. 1–112. Oxford, London, Edingburgh, Melbourne: Blackwell Scientific Publication 1975
Stingl, G., Wolff-Schreiner, E.C., Pichler, W.J., Gschnait, F., Knapp, W., Wolff, K.: Epidermal Langerhans cells bear Fc and C_3 receptors. Nature **268**, 245–246 (1977a)
Stingl, G., Wolff, K., Dien, E., Baumgartner, G., Knapp, W.: In situ identification of lymphoreticular cells in benign and malignant infiltrates by membrane receptor sites. J. Invest. Dermatol. **69**, 231–235 (1977b)
Stingl, G., Katz, S.I., Shevach, E.M., Wolff-Schreiner, E., Green, I.: Detection of Ia antigens on Langerhans cells in guinea pig skin. J. Immunol. **120**, 570–578 (1978a)
Stingl, G., Katz, S., Abelson, L., Mann, D.L.: Immunofluorescent detection of human B cell alloantigens on S-Ig-positive lymphocytes and epidermal Langerhans cells. J. Immunol. **120**, 661–663 (1978b)
Stingl, G., Katz, S.I., Shevach, E.M., Rosenthal, A.S., Green, I.: Analogous functions of macrophages and Langerhans cells in initiation of immune response. J. Invest. Dermatol. **71**, 59–64 (1978c)
Stingl, G., Katz, S.J., Clement, L., Green, I. Shevach, E.M.: Immunologic functions of Ia-bearing epidermal Langerhans cells. J. Immunol. **121**, 2005–2013 (1978d)
Taylor, C.R.: The nature of Reed-Sternberg cells and other malignant "reticulum" cells. Lancet **II/1974**, 802
Thiery, M., Wildhagen, R.G.J.: The occurrence of the Langerhans cell. Acta Zool. Pathol. Antverp. **48**, 137–141 (1969)
Thilander, H., Bloom, G.D.: Cell contacts in oral epithelium. J. Periodont. Res. **3**, 96–110 (1968)
Tyldesley, W.R., Appleton, J.: Observations on the ultrastructure of the epithelium in oral lichen planus. J. Oral Pathol. **2**, 46–57 (1973)
Vakilzadeh, F., Pfütz, E., Rupec, M.: Über lymphoide Zellen im Epithel der normalen menschlichen Mundschleimhaut. Stoma **3**, 152–153 (1970)
Waterhouse, J.P., Squier, C.A.: The Langerhans cell in human gingival epithelium. Archs. Oral Biol. **12**, 341–348 (1967)
Weinmann, J.P.: The keratinization of the human oral mucosa. J. Dent. Res. **19**, 57–71 (1940)
Winkelmann, R.K.: The skin in histiocytosis X. Mayo Clin. Proc. **44**, 535–548 (1969)
Wolff, K., Schreiner, E.: Uptake, intracellular transport and degradation of exogenous protein by Langerhans cells. J. Invest. Dermatol. **54**, 37–47 (1970)
Wolff, K.: The Langerhans cell. In: Current problems in dermatology, J.W.H. Mali (Ed.), Vol 4, p. 79. New York: S. Karger 1972
Worman, C.P., Burns, G.F., Barker, C.R.: Evidence for the presence of a receptor for IgM on the pathological cells of Sézary's snydrome. Clin. Exp. Immunol. **31**, 391–396 (1978)
Yeckley, J.A., Weston, W.L., Thorne, E.G., Krueger, G.G.: Production of Sézary-like cells from normal human lymphocytes. Arch. Dermatol. **111**, 29–32 (1975)
Zelickson, A.S.: Granule formation in the Langerhans cell. J. Invest. Dermatol. **47**, 498–502 (1966)
Zelickson, A.S., Mottaz, J.H.: Epidermal dendritic cells; a quantitative study. Arch. Dermatol. **98**, 652–659 (1968)
Zucker-Franklin, D.: Properties of the Sézary lymphoid cell. An ultrastructural analysis. Mayo Clin. Proc. **49**, 567–573 (1974)

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