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Cellular Composition of the So-Called Dermatofibroma (Histiocytoma Cutis)

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Summary. 9 typical cases of dermatofibroma or histiocytoma cutis resp. were studied by the aid of histochemical, enzyme histochemical and electron microscopical methods to examine the cellular composition of these lesions. The results suggest an anabolic and katabolic function of cells. Electron microscopically a broad spectrum of patterns of mesenchymal cells was found. Besides defined fibroblast-like and histiocyte-like elements a cell type was detected which was characterized by particular traits, as irregular nuclear outline, abundant rough endoplasmic reticulum, free ribosomes, bundles of filaments with single dense zones, micropinocytotic vesicles and a basement membrane-like material on the outer cell surface. This cell type constitutes the majority of cells in dermatofibroma or histiocytoma cutis resp. In some cells an arrangement of filament bundles resembling that in smooth muscle could be seen. By reason of these findings a certain resemblance to the so-called myofibroblasts can be stated. The variegation of the morphological picture suggests a multipotent precursor cell; the possibility of an origin from pericytes is discussed.

Zusammenfassung. An Hand 9 typischer Fälle von Dermatofibrom bzw. Histiocytoma cutis wurde mittels histochemischer, enzymhistochemischer und elektronenmikroskopischer Methoden die celluläre Zusammensetzung untersucht. Dabei waren Hinweise auf anabolische und katabolische Eigenschaften der Zellen zu erheben. Elektronenmikroskopisch ergab sich ein breites Spektrum mesenchymaler Zellformen. Neben definierten fibroblasten- und histiocytenähnlichen Zellelementen fand sich eine Zellart, die das morphologische Bild zahlenmäßig beherrschte und die durch besondere Merkmale, wie unregelmäßige Kernformen, reichlich rauhes endoplasmatisches Reticulum, freie Ribosomen, Filamentbündel mit einzelnen Verdichtungsbezirken, Mikropinocytosevesikel und ein basalmembranähnliches Material an der Zellaußenseite charakterisiert war. Gelegentlich konnte eine Anordnung der Faserbündel wie in der glatten Muskulatur nachgewiesen werden. Auf Grund dieser Befunde ist eine gewisse Ähnlichkeit zu sogenannten Myofibroblasten festzustellen. Die Vielgestaltigkeit des morphologischen Bildes weist auf eine multipotente Vorläuferzelle hin; die Möglichkeit, daß es sich dabei um Pericyten handelt, wird diskutiert.

The historical point of view that dermatofibroma and histiocytoma cutis are separate entities cytologically not related to each other (literature summarized by Niemi, 1970) is now replaced by the opinion that these lesions are different functional states of the same basic condition (Helwig, 1963; Mihatsch-Konz *et al.*, 1973). The cells in these lesions are considered to be histiocytes whose action as facultative fibroblasts is known from cultural studies (Corazza *et al.*, 1959; Stout, 1960; Ozzello *et al.*, 1963; O'Brien and Stout, 1964). On the basis of this fact the concept of fibrous histiocytoma was developed. This designation comprehends several diseases (Stout and Lattes, 1967; Vargas-Cortes *et al.*, 1973), e.g. fibrous xanthoma, dermatofibroma (syn. histiocytoma cutis, subepidermal nodular fibrosis, sclerosing hemangioma), giant cell tumor of tendon sheath, localized

villonodular synovitis, xanthogranuloma, atypical fibroxanthoma of skin, juvenile xanthogranuloma and histiocytoma of soft tissues.

Electron microscopically Fisher and Vuzevski (1968) reported the occurrence of typical histiocytes and fibroblasts. Recently, however, Mihatsch-Konz and coworkers (1973) concluded from their electron microscopic studies that all variants of dermatofibroma are composed of true fibroblasts and not of histiocytes. On the other hand, Carstens and Schrodt (1974) emphasized the endothelial origin of so-called sclerosing hemangiomas. These findings question the opinion that dermatofibromas belong to the "fibrous histiocytomas".

Taking these concepts as a point of departure we examined the cellular composition of dermatofibromas or histiocytomas, comprising a histological spectrum from apparently pure fibroblastic growths to only histiocytic lesions. In 9 representative cases we made an extensive electron microscopical examination.

Material and Methods

100 dermatofibromas or histiocytomas cutis resp. were chosen from material coming to histological routine examination. H & E sections were reexamined by both the authors independently, in the most of the cases sections stained by Prussian blue, Sudan III and aldehyde fuchsin were additionally at our disposal.

After fixation in neutral buffered formalin, embedding in paraffin and sectioning in the usual manner the material of 20 cases was additionally subjected to the following staining and histochemical methods: Goldner's trichrome stain, elastica stain, Gomori's silver impregnation, coupled tetrazonium reaction after Danielli, oxidative deamination followed by treatment with Schiff's solution, PAS, alcian blue (pH 2.5)-PAS, Hale's colloidal iron reaction in the modification of Müller and Mowry, Hale-PAS, alcian blue at pH 0.5, 1.0 and 2.5. Moreover, the alcian blue procedure was additionally preceded by hyaluronidase digestion. For the purpose of removing of iron from the tissue a pretreatment with oxalic acid was performed. Mucopolysaccharide stains were made following this technique and without such a pretreatment.

The presence of the following enzymes was tested employing frozen sections of 8 cases: acid and alkaline phosphatase, alpha-naphthyl acetate esterase, naphthol AS acetate esterase, NADH diaphorase and ATPase. The demonstration of naphthol AS D chloracetate esterase as a marker enzyme for monocytic, granulocytic and mast cells was undertaken on paraffin sections.

From 9 cases material was reserved for electron-microscopical preparation which was done in the usual manner. Moreover, semithin sections were made from embedded material and stained with toluidine blue.

Results

1. Light Microscopy

By reason of many detailed histological descriptions of dermatofibroma or histiocytoma cutis present in the literature we only want to give a summary of our observations. The lesions usually localized in the dermal connective tissue without sharp demarcation are composed of fibroblastic and/or histiocytic elements. The proportion of these cells to each other varies from lesion to lesion and sometimes within the same lesion. Some lesions obviously consist of fibroblast-like cells exclusively, the other extreme is the preponderantly histiocytic lesion. Not seldom a cell arrangement resembling superficially a storiform pattern can be seen. Fibroblast-like cells are often arranged in interlacing and anastomosing bands, in bundles or whorls. Here, fiber-rich centers surrounded by elongated

nuclei are visible. Giant cells are only present in areas where histiocyte-like cells predominate. Intracellular iron storage and lipid accumulation are more striking in lesions consisting of histiocyte-like cells, but several lesions composed only of fibroblast-like elements do not show these phenomena. The number of blood vessels varies and is independent of the preponderant cell type. As a rule a little to moderate number of vascular channels can be observed. However, the most blood vessels are noted in histiocytoma-like regions. The content of collagen and reticular fibers is correlated to the presence of fibroblast-like cells. Single histiocyte-like cells or groups of them are surrounded by reticular fibers whereas collagen fibers are to be hardly seen here. Furthermore, the fact is noteworthy that fibroblast-like cells with a reddish hue in the Goldner stain can be observed sometimes.

In semithin sections the configuration of nuclei can be easily assessed. The nuclei are round to oval and are often markedly indented possessing then bizarre contours. They frequently show a distinct large nucleolus occasionally also two. The amount of chromatin is very different ranging from hypochromatic to hyperchromatic. In times binucleate cells or multinucleated giant cells can be detected. Mitoses are rare. Atypical mitoses or atypical giant cells as they are to be expected in atypical histiocytomas (fibroxanthomas) are missing. In spite of the relative variegation of pictures of nuclei they seem to be related to each other. Where capillary vessels were present constituting the lesion border directly hemosiderin could be noted on the endothelial cell layer. In such areas tumor cells with more histiocyte-like appearance prevail.

2. Histochemistry and Enzyme Histochemistry

The methods for demonstration of *protein groups* (coupled tetrazonium reaction, alloxan-Schiff) yielded rather similar results. Histiocyte-like cells are stronger positive than fibroblast-like ones, giant cells give the strongest reaction. Referring to the intercellular substance the strongly positive result is almost completely associated with the presence of connective tissue fibers. The results after employment of the PAS method show that more PAS reactive groups are harboured by histiocytic cells because fibroblast-like cells reveal a fainter hue. Therefore, these groups may partly originate from phagocytosed material. The behavior of giant cells is not uniform; some contain only PAS-positive granules whereas other giant cells are deep violet. Obviously cells containing abundant lipid are not so clearly positive. The PAS reaction also gives positive results where connective tissue fibers are deposited.

Techniques used for evidence of *acid mucopolysaccharides* (colloidal iron method, staining with alcian blue at controlled pH) gave different features. The Hale method results in a somewhat stronger positive reaction of many histiocyte-like cells particularly in iron-storing areas. The digestion with hyaluronidase somewhat enhanced the Hale-positivity in some cases, again predominantly in histiocytic areas. After removal of iron these cells showed a strongly decreased staining intensity. Therefore, the iron content of these cells must be considered in the interpretation of the results and it is to be assumed that carboxyl groups are responsible for the intravital iron binding. Taking that into consideration all histiocyte-like cells exhibit only occasionally a weak mucopolysaccharide content.

Fibroblast-like cells are negative. The alcian blue method did not give any positive cellular reaction. Only the connective tissue fibers could be demonstrated in a positive faint blue hue, the reaction at pH 0.5 being relatively the strongest, at pH 2.5 the weakest.

The *enzyme histochemical examination* revealed the presence of acid phosphatase, alpha-naphthyl acetate esterase, naphthol AS acetate esterase and NADH diaphorase. However, the intensity of reaction products showed a slightly variation. Generally acid phosphatase was distinctly present especially in histiocyte-like cells whereas spindle cells were only weakly positive. Likewise the unspecific esterase had the same distribution. NADH diaphorase could be detected in almost all cells. ATPase and alkaline phosphatase were predominantly localized in cells of vessel walls although in one case histiocyte-like cells were weakly positive. Naphthol AS D chloracetate esterase could only be noted in mast cells occurring in a moderate number in all lesions, in other cells this enzyme was lacking. The complete absence of naphthol AS D chloracetate esterase in the tumor cells cannot be taken into account answering the question if tumor cells are blood born or not, because histiocytes arising undoubtedly from blood stream contain this enzyme (Pollack *et al.*, 1973), whereas dermal fibroblasts originating under certain conditions likewise from blood monocytes (Sumrall and Johnson, 1973) are always without this enzyme.

3. Electron Microscopy

Electron microscopically it can be observed in analogy to light microscopical findings that the histological appearance of the lesions reaches from cell rich forms to types with abundant intercellular substances (Fig. 1a and 1c). Moreover, in looking at the single pictures various cell types are encountered.

The majority of cells is not without greater difficulties to be attributed to classical cell types defined cytologically as fibroblasts, histiocytes etc. It is interesting to note that the nuclei show the same basic structure while the cytoplasm exhibits a varying organelle content resulting in different electron densities of these polyhedral and elongated cells. The characteristic sign of the moderate chromatin rich nuclei are frequent indentations reaching up to deep folds (Fig. 2). Thereby pseudoinclusions are occasionally formed whose content corresponds to cytoplasm. As a rule one or occasionally two nuclei are demonstrable. Sometimes the nuclei contain a spheroidal nuclear body with a diameter of 400–450 nm which is suggested to be associated with a state of nuclear hyperactivity (Henry and Petts, 1969). The heterochromatin was usually condensed at the nuclear periphery.

The cytoplasmic organelles are encountered in different patterns of occurrence and distribution (Figs. 1a, b, 2, 3a). The cytoplasm of the most cells is endowed with free ribosomes scattered loosely, moderate to abundant rough endoplasmic reticulum partially dilated forming cisternae or sacs, a changing amount of smooth endoplasmic reticulum and a moderate number of mitochondria exhibiting a round or oval, occasionally also rod-like or club-like shape. In places non-dilated ergastoplasm forms parallel stacked arrays of membranes. The Golgi apparatus being mostly in juxtanuclear position is well developed, partly also hypertrophic and multicentric. If present inclusion bodies complete the feature of cytoplasm; such inclusions may be: numerous incompletely membrane-bound

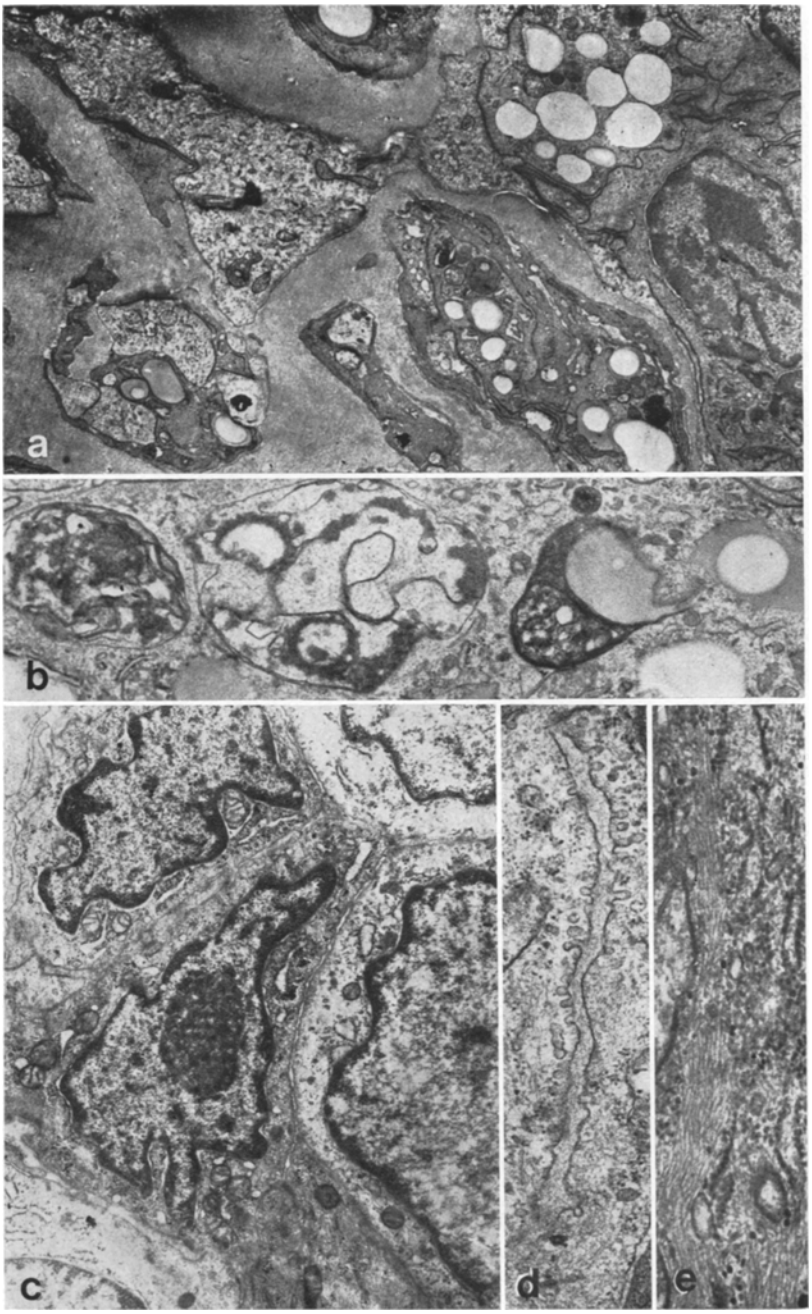

Fig. 1a—e. Examples for different structural patterns of dermatofibroma. (a) Besides an abundant intercellular substance cells with interdigitating processes and with differing density of the hyaloplasm and varying content of vacuoles, lipid droplets, lysosomes and siderosomes can be seen (5400:1). (b) Different types of phagosome bodies (19800:1). (c) Cell-rich form with "light" and "dark" cells. The nuclei are indented and cleftet. The light cells contain less organelles, the dark ones show different amounts of microfilaments. Along the plasma membrane numerous micropinocytotic vesicles are present (9600:1). Details of plasma membrane associated with microvesicles and of ordered microfilaments are given in (d) (21600:1) and (e) (33000:1)

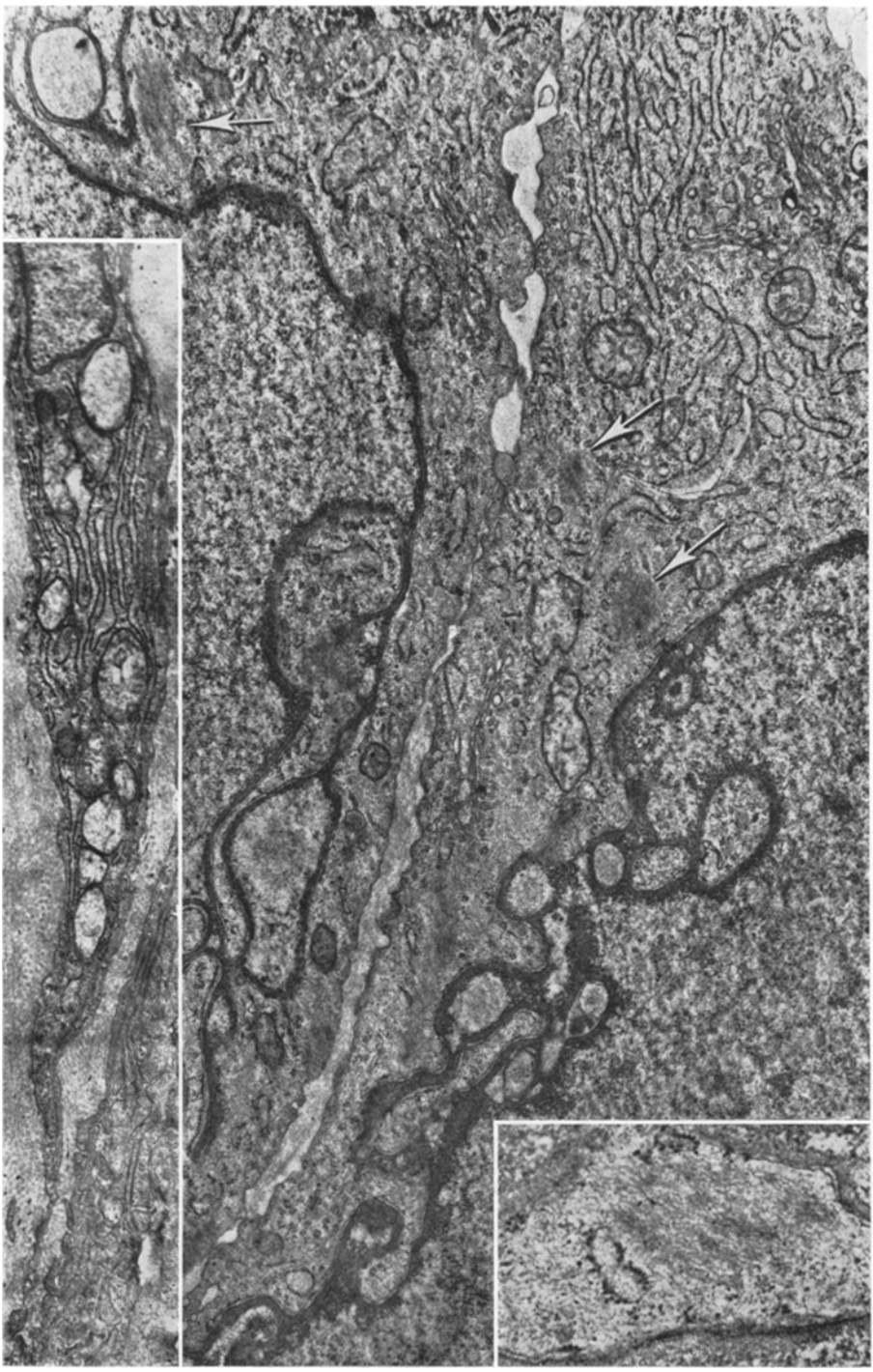

Fig. 2. Comparison between a fibroblast (inset, 13200:1) and cells constituting the majority of cell elements in the lesions. The latter are characterized by bizarre nuclear outline with infoldings and indentations resulting in small pseudoinclusions, a rich content of tubes of rough endoplasmic reticulum, free ribosomes and bundles of microfilaments (arrows) with dense patches (18000:1). A filament bundle in greater detail see inset (32400:1)

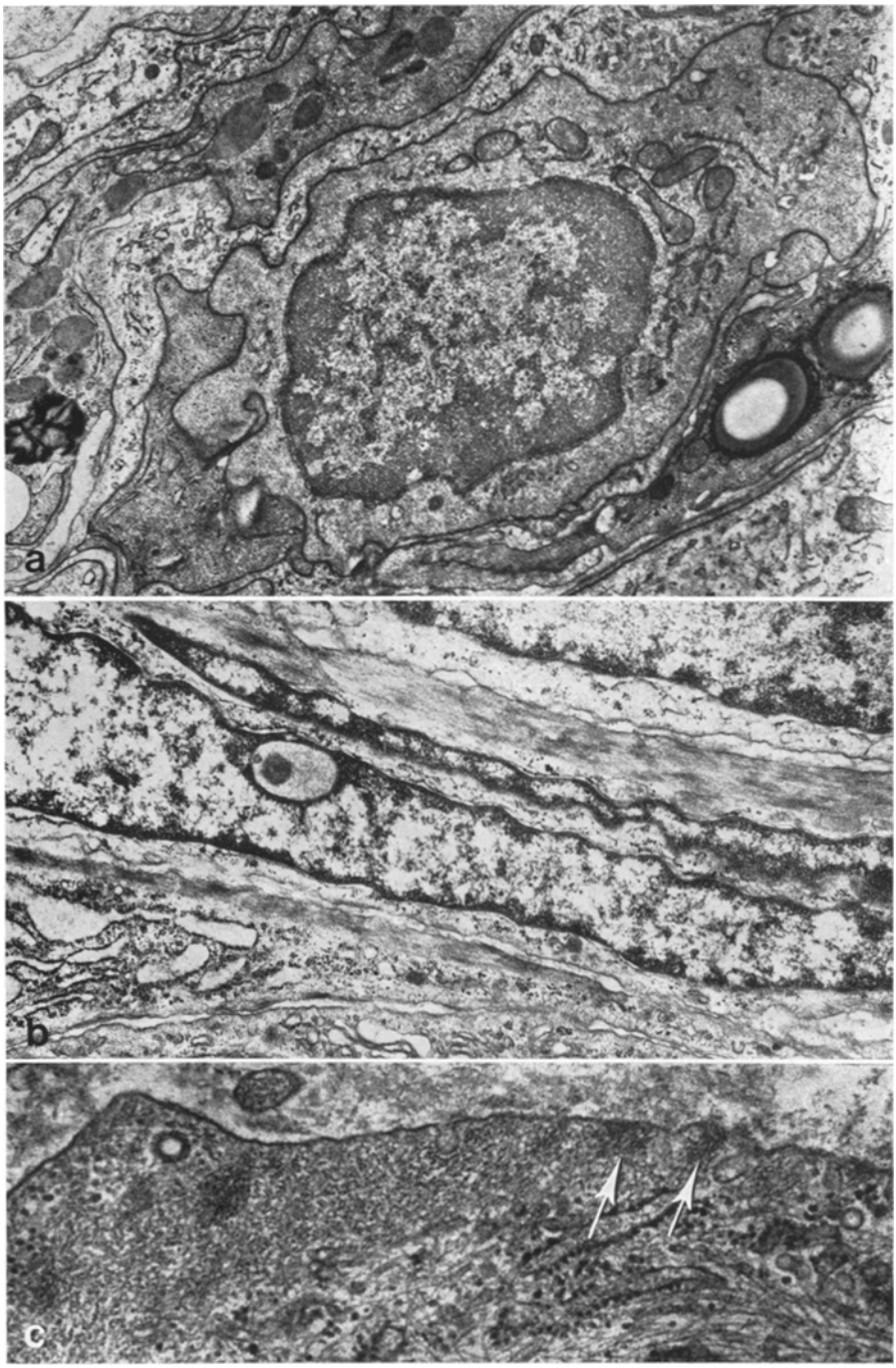

Fig. 3a—c. Cells with different content of microfilaments. (a) Rather undifferentiated cell with randomly distributed microfilaments (14400:1). (b) Dense microfilament bundles resembling filament bundles in smooth muscle. Note the pseudoinclusion of the nucleus (15000:1). (c) Scattered microfilaments in vicinity of plasma membrane intermingled with dense zones (arrows) (54000:1)

lipid droplets, iron deposits and/or membranous structures ("myelin figures"). Primary and secondary lysosomes (cp. Carr, 1968) are not seldom. Besides autophagic vacuoles with destroyed cell organelles and membranes can be observed. Frequently numerous vesicles, pinocytotic vesicles near the cell membrane and some clear vacuoles are visible (Fig. 1 d).

In the vicinity of the nucleus partly bundled delicate microfibrils are not infrequently localized. They are either straight or slightly wavy, without periodicity and measure about 50 Å in width, their length is undetermined. Sometimes these bundles also show some electron dense focal condensations resembling dense bodies of smooth muscles (Figs. 2 and 3 b). Such microfibrils may also be randomly distributed throughout the cytoplasm (Fig. 3 c), in single cells they additionally form bundles running parallel to the cell border (Fig. 1 d). In such cells no or few pinocytotic vesicles can be found. Less frequently, microtubules with an average diameter of 240 Å are to be noticed.

Furthermore the behavior of plasma membranes must be mentioned. They often demonstrate enfoldings and short cytoplasmic processes interdigitating with processes of neighbouring cells. Other cells were without such surface projections and had a smooth cell boundary. In some places an irregularly deposited osmiophilic material was perceived in vicinity of the outer cell membrane having superficial resemblance to basement membrane-like material which usually covered a part of the cell surface only (Fig. 4). Specialized intercellular junctions, however, could never be observed, although attachment sites between connective tissue cells are not uncommon (Ross and Greenlee, 1966).

Only some cells offered the pure features of fibroblasts or histiocytes: fibroblasts with an elongated shape, an oval nucleus with smoothly contoured outlines, abundant rough endoplasmic reticulum and few mitochondria; histiocytes with a roundish nucleus, lysosomal structures, sparse rough endoplasmic reticulum and a moderate number of mitochondria. Microfibrils occurred in both the cell types, but more randomly distributed and in a smaller amount than in the mesenchymal cells mentioned before.

Some smaller vessels showed hypertrophic endothelial cells with microvilli, distinct pinocytosis, well-developed Golgi-apparatus and bundles of microfibrils. In their vicinity typical pericytes or few smooth muscle cells could be seen to which the surrounding tumor cells were partially similar regarding their cytoplasmic organelles (Fig. 4).

Furthermore, the fact must be commented on that without relation to vessels more undifferentiated cells were to be found which revealed a cytoplasm poor of organelles. Here only ribosomes and few mitochondria were present. The nuclei possessed a roundish shape.

The search for Langerhans' granules or viruses was without any success. Mast cells and the intercellular material were without pecularities. Collagen when present exhibited a 640 Å periodicity, the remaining intercellular substance consisted of a fine fibrillar or granular material.

Discussion

The light microscopical and enzyme histochemical features of dermatofibroma or histiocytoma cutis resp. are somewhat different owing to their different archi-

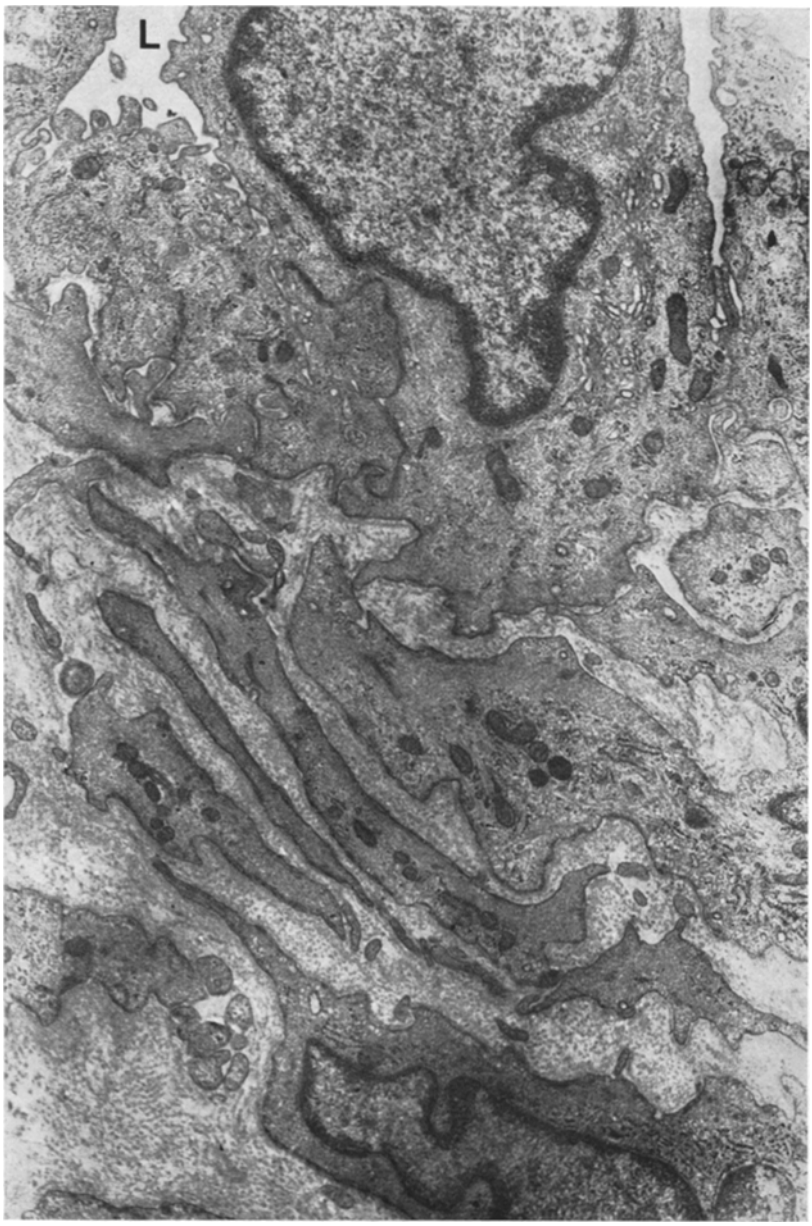

Fig. 4. Capillary vessel with hypertrophic endothelial cells (*L* lumen), pericytes with distinct basement membrane and pericyte-like cells in the surrounding tissue with rests of a basement membrane-like material. The dense structures in the cytoplasm do not correspond to Weibel-Palade bodies (14400:1)

tecture (Pallotti *et al.*, 1960). But the cellular composition appears to be similar relative to the quality, only clear quantitative differences exist expressed by the names "dermatofibroma" and "histiocytoma". This assumption is supported by

the enzyme histochemical patterns which point to a histiocyte-like katabolic function of numerous cells, besides an anabolic function can be stated. So the cells show a strong activity of hydrolases, as normal, inflammatory, proliferative and neoplastic histiocytes also do (Muller *et al.*, 1967; Braunsteiner and Schmalzl, 1970; Burg and Braun-Falco, 1974), as well as the presence of NADH diaphorase and a varying content of ATPase (cp. Klaus and Winkelmann, 1966).

With the aid of the electron microscope some fibroblast-like and histiocyte-like cells can be found. But the majority of cells shows nuclear characteristics and cytoplasmic features encountered in histiocytes as well as fibroblasts. The indented nucleus with equally dispersed chromatin, numerous cytoplasmic microfilaments, lysosomal structures and occasionally digitiform cytoplasmic processes are characteristics of histiocytes, while the abundant rough ergastoplasmic reticulum is a characteristic of fibroblasts. Furthermore, several cells of this group morphologically resemble the so-called myofibroblasts with regard to their nuclear form, the abundant rough endoplasmic reticulum, pinocytotic vesicles, basement membrane-like material and the bundles of filaments with scattered electron-dense patches (Gabbiani *et al.*, 1971, 1972; Gabbiani and Majno, 1972; Montandon *et al.*, 1973; Ryan *et al.*, 1973; Gorgas and Böck, 1974).

The presence of filaments in general is not unique for myofibroblasts because many non-muscular normal cells and tumor cells may have filaments (De Petris *et al.*, 1962; Sutton, 1967; Cireli, 1970; Ryan *et al.*, 1973; Weathers and Campbell, 1974), in some of these cells the filaments may consists of actin under certain conditions (Gabbiani *et al.*, 1973; Nagle *et al.*, 1973). After Gabbiani and coworkers (1973) numerous cells in adult animals can acquire these actin filaments (and lose them again) in response to particular stimuli or to changes in the microenvironment. In contrast to the original description and in agreement with Böck and coworkers (1972) we could not discern desmosomes or hemidesmosomes at the cell boundary of our myofibroblast-like cell type. Moreover, the filament bundles were mostly not located in vicinity of the plasma membrane. Langerhans' granules characteristically for typical histiocytic disorders (for review of these see Cline and Golde, 1973) are never to be found in dermatofibroma or histiocytoma cutis resp. or other tumors of "fibrous histiocytoma" group (cp. Carrington and Winkelmann, 1972).

In our electron micrographs we saw tumor cells in vicinity of blood vessels which resembled transition stages to pericytes. This is an observation, which was not made by Gonzales-Crussi and Campbell (1970) who studied a juvenile xanthogranuloma.

On the other hand we found a few primitive mesenchymal cells without relation to vessels. Crocker and coworkers (1970) reported on almost identical cells in wound healing.

The variegation of the histological picture suggests a multipotent precursor cell. In connection with the sporadical presence of basement membrane-like material and by virtue of the absence of Weibel-Palade bodies an origin from pericytes should be taken into consideration. Analogous conclusions are also possible from own electron microscopical examinations of subcutaneous rat tumors.

Our findings indicate the origin of the tumor from an undifferentiated mesenchymal cell with multipotential possibilities of development so that the concept of "fibrous histiocytomas" should be thought over again.

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