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Cellular Features in Desmoid Fibromatosis and Well-Differentiated Fibrosarcomas

An Electron Microscopic Study

Dankwart Stiller and Detlef Katenkamp

Institute of Pathology, Faculty of Medicine,
Friedrich-Schiller-University of Jena (Head: Prof. Dr. F. Bolck)

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Summary. In the study presented here the ultrastructural cellular features of three desmoids and four well-differentiated fibrosarcomas were compared. Electron microscopically, the tumors were almost identical relative to qualitative traits. The majority of cells corresponded to fibroblast-like cells with certain morphological variations. Especially cells with characteristics of myofibroblasts must be emphasized, whereas cells with an organelle composition of classical fibroblasts were surprisingly seldom. Considering the relations of cells to each other and to vessels the prevailing origin of tumor cells from preexisting fibroblasts is suggested.

Abdominal and extraabdominal fibromatosis (desmoid) and well-differentiated fibrosarcoma are clinical entities closely related to each other. The desmoid is considered to be a locally invasive growth with high recurrence rates but without metastatic dissemination (Dahn *et al.*, 1963; Stiller and Katenkamp, 1972). By contrast with it well-differentiated fibrosarcoma which may have almost the same local growth characteristics is principally able to metastasize (Hitchens and Platt, 1972). Apart from this theoretical distinction between both the lesions the practical light microscopic differential diagnosis may be extremely difficult if not impossible because of sometimes identical morphological pictures (Prior and Sisson, 1954; Soule *et al.*, 1968) and because of the well known fact of a gradual transformation of a non-metastasizing desmoid to a potentially metastasizing fibrosarcoma in the sense of tumor progression (Soule and Scanlon, 1962; Sträuli, 1965).

The step from fibromatosis to malignant fibrosarcoma has no light microscopic correlate (Stout, 1962; McKenzie, 1964). Both the lesions offer a rather uniform cellular composition in the light microscope without a remarkable vascular component. The ultrastructural cytology is expected to give information whether the desmoids and fibrosarcomas are composed of a homogenous cellular population or not and whether they are comparable to each other as well as to other cellular variants in connective tissue proliferations.

Material and Methods

Out of a pool of 5 abdominal fibromatoses (desmoids), of 10 extraabdominal aggressive fibromatoses (extraabdominal desmoids) and of 10 well-differentiated fibrosarcomas 7 tumor specimens were available for electron microscopic examination. There were 1 abdominal fibromatosis (34-year old female patient, E. Nr. 23057/74), 2 extraabdominal aggressive fibromatoses (57-year female patient, E. Nr. 14132/74; 71-year old female patient, E. Nr. 20878/75),

and four Fibrosarcoma specimens (50-year old female patient, E. Nr. 21968/73 and 24636/74; 79-year old female patient, E. Nr. 10465/75; 31-year old female patient, E. Nr. 15031/75).

For the light microscopical characterization the following stains and histochemical procedures were used: H and E, elastica-Domagk stain, Goldner's trichrome stain, PAS-hematoxylin, alcian blue (pH 2.5) – PAS, Hale's colloidal iron binding reaction in the modification after Mowry.

The electron microscopical preparation followed in the usual manner: immediately after operative removal the material was fixed in 4.5% glutaraldehyde and postfixed in OsO_4, embedded in Epon and contrasted by uranyl acetate and lead citrate.

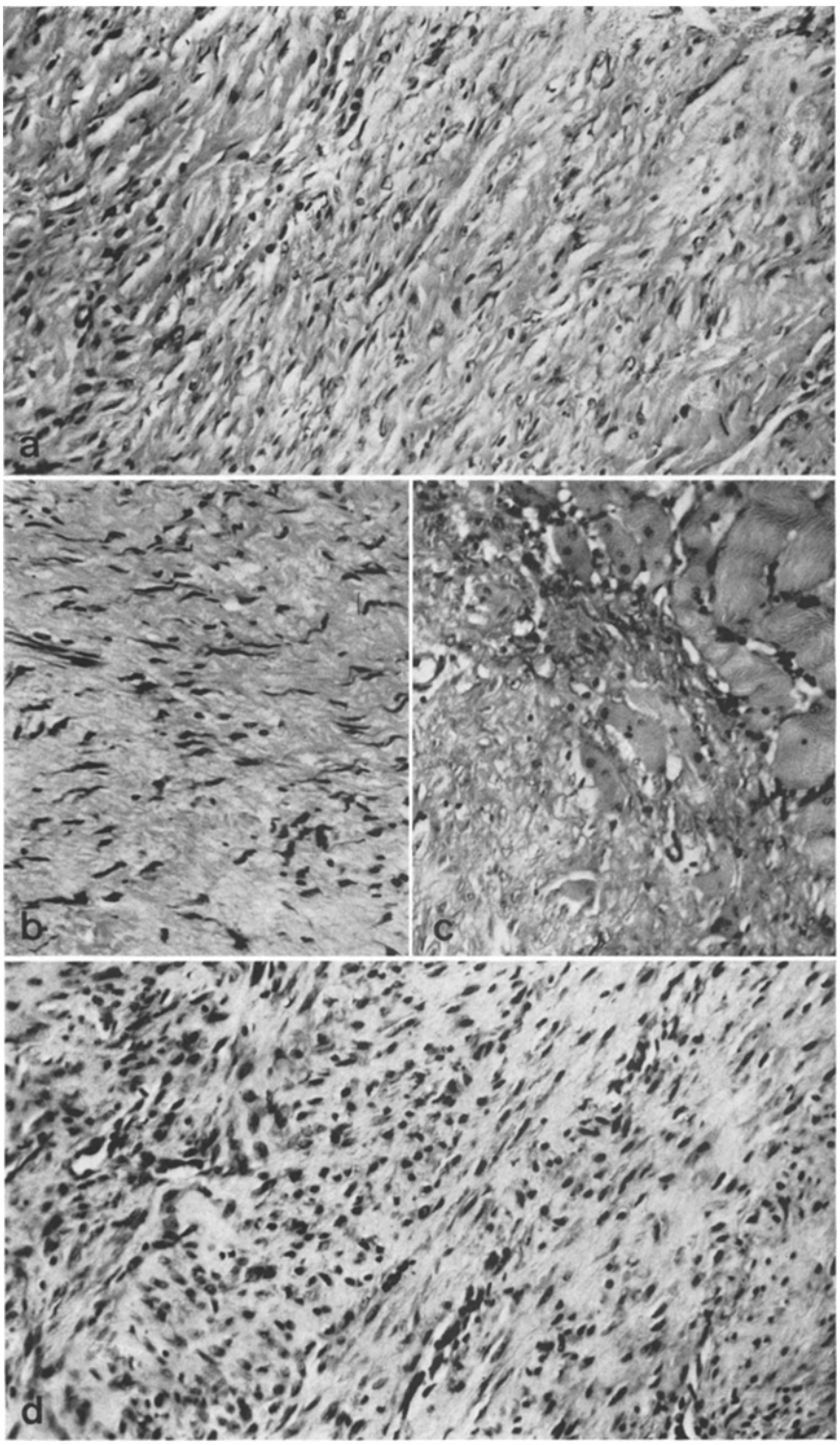
Results

Light microscopically, the *desmoids* (abdominal and extraabdominal) reveal relatively uniform pictures despite some variation from one lesion to another and in different parts of the same lesion. Generally, desmoids are moderately hypocellular and consist of mostly avascular bands of mature fibrous tissue with resemblance to tendinous structures. Only infrequently the desmoids are focally (often around vessels) more cell-rich, then the plump cells possess hyperchromatic nuclei, and some mitotic activity is perceivable, too. The lesions extend between adjacent striated muscle bundles, isolate and destroy muscle cells and thus induce the formation of typical muscular giant cells. The abundant collagen fibers are interwoven or fasciculated. The fibroblast-like tumor cells are orderly arranged and their uniform nuclei can be seen parallel to the long axis of collagen bundles (Fig. 1).

The well-differentiated *fibrosarcoma* has a quite similar appearance. Fibroblast-like tumor cells and fibers are arranged in bundles and bands in an interlacing fashion. The cellularity is somewhat greater than in typical desmoids, but the single cells are mostly indistinguishable from those of desmoids (Fig. 1). Mitoses are rare. Intercellular collagen may be abundant, the single cells are reticulin-wrapped. As expected, the degree of invasion of the adjacent tissue by the well-differentiated fibrosarcoma is only slight; some authors point to the tendency for pseudocapsule formation being of importance for the differential diagnosis (see Gentele, 1951; Arlen, 1974). The herring-bone pattern of less differentiated fibrosarcomas was not observed in our cases.

With the *electron microscope* the spectrum of cellular differentiations is identical in the three desmoids and the four well-differentiated fibrosarcomas. There are only certain obvious differences regarding the quantitative relations of the single cell types to each other. In desmoids relatively more fibroblast-like cells are noticed than in the well-differentiated fibrosarcomas, whereas in the latter tumors, despite the predominating fibroblast-like cells, cells with histiocyte-like features and "undifferentiated" cells are present in increasing numbers. In the

Fig. 1 a–d. Light microscopic comparison of a typical desmoid and a well-differentiated fibrosarcoma. (a) Typical hypocellular picture with fibroblast-like cells and an intercellular substance containing abundant collagen fibers (H&E, 150:1). (b) Slender fibrocytes in orderly arrangement and abundant intercellular collagen fibers resemble tendinous tissue (Goldner stain, 150:1). (c) Infiltration and destruction of striated muscle cells by proliferating fibroblast-like cells (Goldner stain, 150:1). (d) Well-differentiated fibrosarcoma consisting of fibroblast-like tumor cells and a moderate amount of intercellular collagen (H&E, 150:1)


a
b
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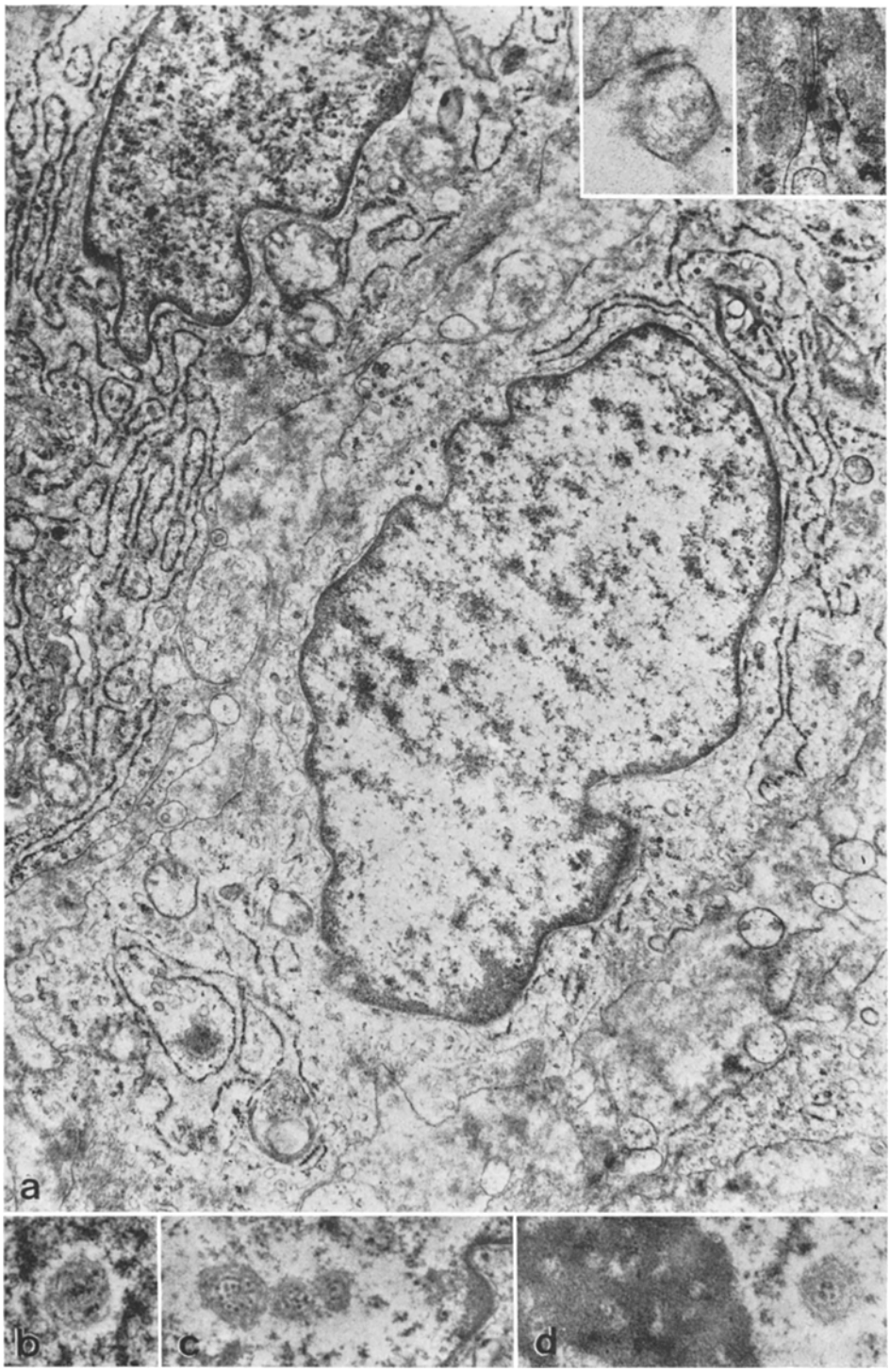
d

following the ultrastructural details of cells encountered commonly in desmoids and well-differentiated fibrosarcomas are presented.

The most frequent cellular picture corresponds to a fibroblast-like cell with certain morphological variants (Figs. 2, 3). The cells are elongeted with long slender cytoplasmic processes or sometimes of more rounded shape. The nuclei oval or roundish show an undulated contour, or posses clefts and deep infoldings resulting occasionally in bizarre and convoluted nuclear forms with multiple lobulations and so-called pseudoinclusions with cytoplasmic ingredients. The heterochromatin is evely distributed in moderately coarse clumps and clearly condensed at the nuclear periphery. The single nucleolus is not conspicious. Rarely socalled nuclear bodies are met which as a rule have fibrillar and granular components (see Bouteille *et al.*, 1967) (Fig. 2). The most striking cytoplasmic organelle is the predominant rough ergastoplasmic reticulum. The ergastoplasmic tubes are not seldom dilated reaching to the formation of ergastoplasmic sacs with granular or fine-fibrillar content. The second significant component of the cytoplasm in the most fibroblast-like cells are microfibrils with a diameter of about 60 Å. They are generally arranged in bundles running almost parallel to the long axis of the cells. These bundles are frequently noticed beneath the plasma membrane and exhibit dark bodies similar to those of filament bundles in smooth muscle cells (Fig. 4). Moreover, the filaments partially inserted in the plasmalemm, form in part hemidesmosome-like structures. Typical caveolae as found in smooth muscle cells in abundance are only seldom observed. As further cytoplasmic constituents, which varied markedly in their quantity, a more or less well-developed Golgi apparatus, free ribosomes, some mitochondria and smooth vesicles as well as some microtubules measuring 250 Å in diameter, and single dense bodies with a limiting membrane probably lysosomal in nature must be mentioned. Several of these cells present on their outer cell surface a basement membrane-like material which for the most part surrounds the cell only incompletely. A spatial relation to the filament bundles is not obvious. Another finding are primitive desmosomes (Fig. 2).

A second cell type which is, however, encountered far less in the tumors presented here reveals histiocyte-like features. These cells are roundish or more seldom oblong. Likewise the nuclear shape varies. So, round or oval nuclei with smooth outlines or with shallow undalutions and occasionally deep indentations are seen. The chromatin distibution is similar to that of the fibroblast-like cells. That is also true for the sporadic occurrence of nuclear bodies. The organelle content of the cytoplasm shows marked quantitative differences, but in comparison with the fibroblast-like cells it can be stated that the rough ergastoplasmic reticulum profiles are scarce and non-dilated whereas mitchondria and lysosomal structures are more abundant. Futhermore, the cells possess a prominent Golgi

Fig. 2 a—d. Ultrastructural features of proliferating fibroblast-like cells. (a) Typical arrangement of the prominent rough endoplasmic reticulum. Heterochromatin is marginated at the periphery of the moderately undulated nuclei (16,500:1). Inset: Examples for intercellular junctions. The structures correspond to primitive desmosomes (46,500:1, 19,500:1). (b—d) So-called nuclear bodies with fibrillar and granular components sometimes in vicinity of the activated nucleous (b 23,400:1, c 16,400:1 d 27,800:1)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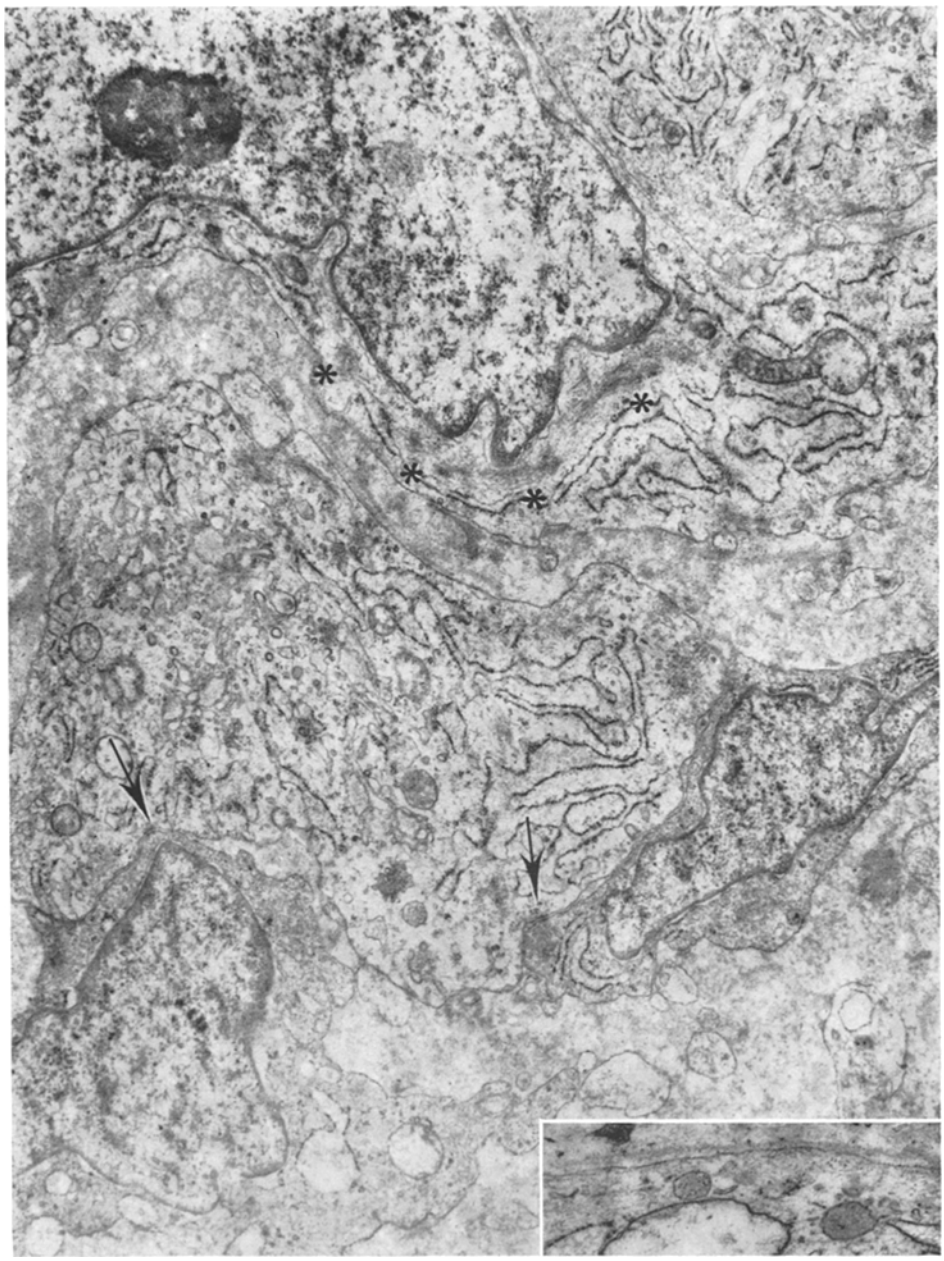

Fig. 3. Activated fibroblast-like cells showing variations of the organelle content. At the top a so-called myofibroblast-like cell with microfilament bundles exhibiting dark bodies and being arranged typically parallel to the long axis ot the cell (*). In the lower half of the picture a fibroblast-like cell with reduced rough endoplasmic reticulum and more abundant mitochondria and a prominent multicentric Golgi zone is seen. Furthermore, two "undifferentiated" cells are located in its neighbourhood. Intercellular junctions between these mentioned cells are present (→) (12,800:1). Inset: Basement membrane-like material on the outer cell surface (21,600:1)

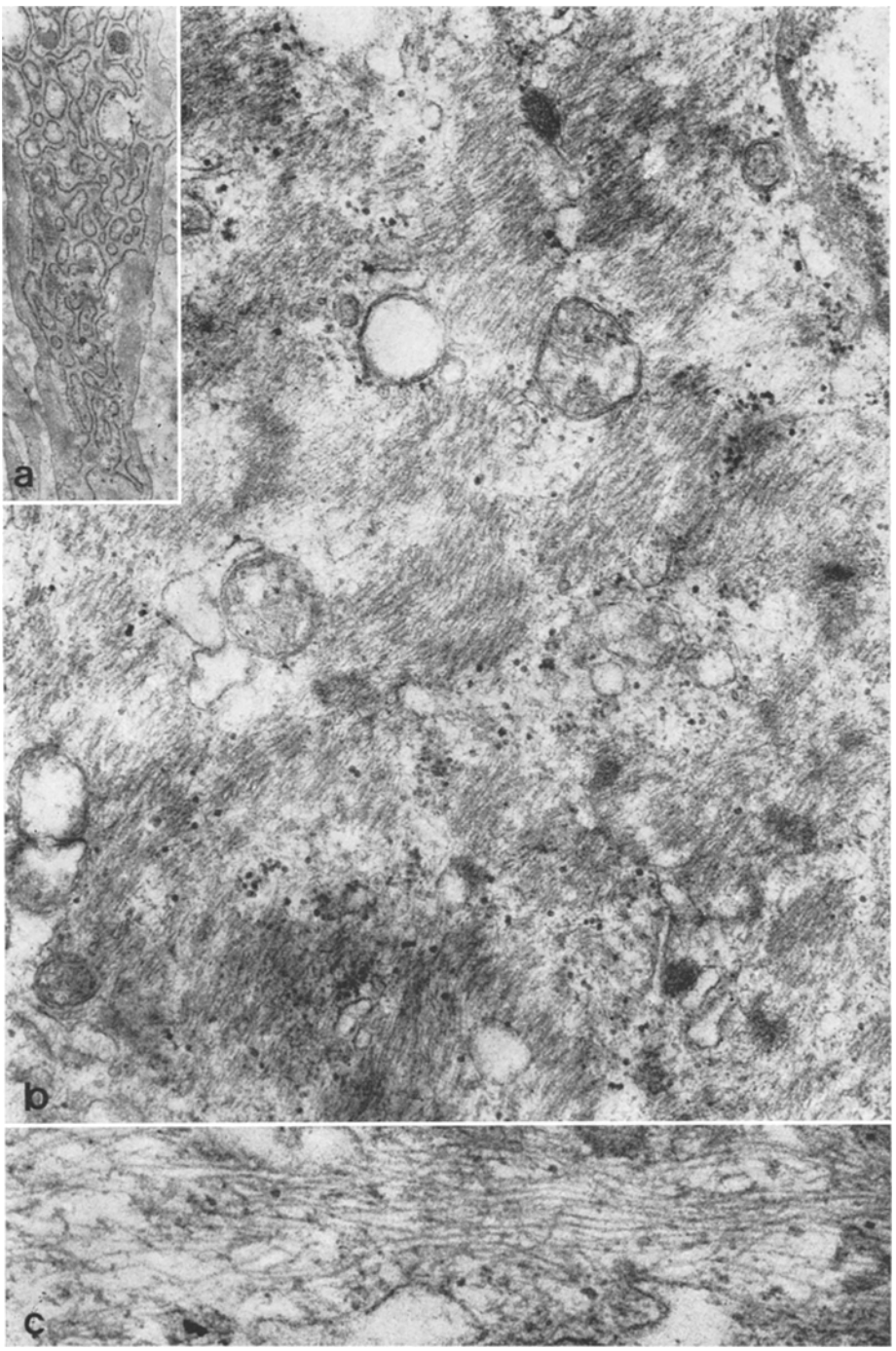

Fig. 4. (a) Cell with features of a typical myofibroblast (11,700:1). (b) Numerous myofilament bundles with dark bodies and some round mitochondria (40,800:1). (c) Fibrils with a diameter of about 110 A which are probably parts of the cytosceleton (41,000:1)

zone, microfilaments in the cytoplasm which are distributed randomly and appear only seldom arranged in bundles, some myelin-like figures, and coated vesicles, and sometimes dense bodies which could represent hemosiderin deposits. Moreover, the histocyte-like cells exhibit plump cytoplasmic finger-like projections. A basement membrane-like material is always lacking just as desmosome-like junctions. In the cytoplasm of a single cell of the fibrosarcomas collagen fibers enveloped by a smooth membrane were detected.

The vessels which were observed must be considered normal vascular channels as encountered in the connective tissue (Rhodin, 1968). The endothelial cells line a vascular lumen and are joined by special cellular junctions. Their ultrastructure is in agreement with findings described in literature.

Finally, there are scattered "undifferentiated" mesenchymal tumor cells. The nuclei are surrounded by a narrow rim of cytoplasm which contains besides free ribosomes and occasional microfilaments only rare rough ergastoplasmic reticulum, tubes and mitochondria.

Discussion

The electron microscopic examination of three desmoids and four well-differentiated fibrosarcomas gives evidence to that as suggested by light microscopical results (McKenzie 1964); no fundamental differences between both the lesions are perceptible. They preponderantly contain fibroblast-like cells in different ultrastructural variants proved by varying organelle content. Besides, less histocyte-like and "undifferentiated" cells can clearly be demonstrated, so that the cytological picture is not completely homogeneous in general. The presence of relatively more "undifferentiated" cells in the fibrosarcomas could announce a more rapid growth than in desmoids. These "undifferentiated" cells need not indicate true immature tumor cells because differentiated cells in their growing phase exhibit such pictures.

The finding that tumor cells with features of classical fibroblasts are seldom in our lesions, especially in the desmoids and here moreover without the typical intracytoplasmic collagen deposition (Welsh, 1966; Allegra and Broderick, 1973), is somewhat surprising. Not a few cells in desmoids but far less in fibrosarcomas possess microfilament bundles with resemblance to those in smooth muscle cells and a partially dicsontinuous basement membrane-like material at the outer cell surface. These cells resemble modified fibroblasts (myoide fibroblasts, myofibroblasts) described in literature in many places and spesies (for literature see Katenkamp *et al.*, 1975). Recently several authors succeeded in demonstrating the contractility of such microfilament bundles (Ishikawa *et al.*, 1969; Gabbiani *et al.*, 1972; Perdue, 1973). They were also recorded in tumor-like conditions, as Dupuytren's contracture (Gabbiani and Majno, 1972), as well as in dermatofibroma (Katenkamp and Stiller, 1975) and in dermatofibrosarcoma protuberans (Hashimoto *et al.*, 1974) or in experimental rat sarcomas (Katenkamp and Stiller, 1975).

A special variant of fibroblast-like cells which shows an organelle composition like histiocytes does not necessarily correspond to a cell with the capability of phagocytosis. It is also conceivable that these cells are associated with a particular synthesis. Williams (1970) suggested a participation of similar structured cells in elastogenesis.

Although purely fibroblastic growths were described histocyte-like tumor cells were intermingled in the majority of cases (Fisher and Vuzevski, 1968) as also in our desmoids and fibrosarcoma specimens. Fibroblasts can assume features of histiocytes, similar to pericytes, but on the other hand most of tissue histiocytes are thought to be blood born and may take part in immunological reactions (Cohn, 1968).

Considering the idea on the derivation of fibroblasts in regenerating tendinous tissue (Katenkamp *et al.*, 1975) the proliferation of fibroblast-like tumor cells in desmoids and fibrosarcomas could take its origin from cells of the microvasculature and from preexisting fibroblasts. By reason of the normal vessels separated by a rim of collagen from the tumorous tissue in most cases, and the lacking vasoformative potencies of the tumor cells a prevailing origin from a local fibroblastic stem cell seems more probable. Also the indeted or lobulated nuclei speak for a cytogenesis related to dermatofibrosarcoma protuberans which is thought to be derived from modified fibroblasts (Hashimoto *et al.*, 1974). This would only mean that the tumors develop and enlarge by division of cells with characteristics of fibroblast, although fibroblasts may be no cell type per se but only the morphological expression of a functional state of certain mesenchymal cells.

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Doz. Dr. sc. Dankwart Stiller
Institute of Pathology
of the Friedrich-Schiller-University
Ziegelmühlenweg 1
DDR-69 Jena
German Democratic Republic