Morphology of Dupuytren's Disease

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Dupuytren's disease has a prevalence of 1%–3% (Viljanto 1973) and usually occurs in middle aged or elderly men (>40 years). Females suffer much less frequently from this disorder (Fig. 1), as shown by Yost et al. (1955), who found a male:female ratio of 3:1. Although there is an often mentioned "causal" association with diabetes mellitus (Pal et al. 1987), this is not etiologically significant.

Histologically, the disease is characterized by cellular nodules inside the fibrous tissue of the palmar aponeurosis. These foci are irregularly demarcated with regard to the normal surrounding tendon tissue; no capsule is present between the hypercellular areas and the aponeurosis (Fig. 2). This situation is also reflected in the electron microscopic appearance of the disease. Ultrastructurally, there is no clear distinction between the accumulation of fibroblast-like cells and normal tissue, which is rich in collagenous fibrils (Fig. 3). The fibroblasts of the hypercellular foci seem to become intermingled with the

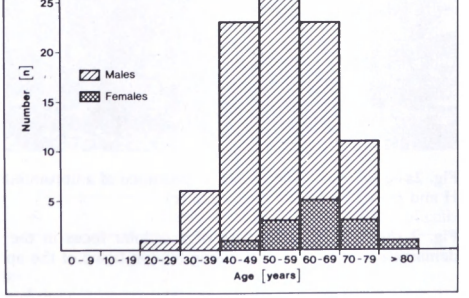
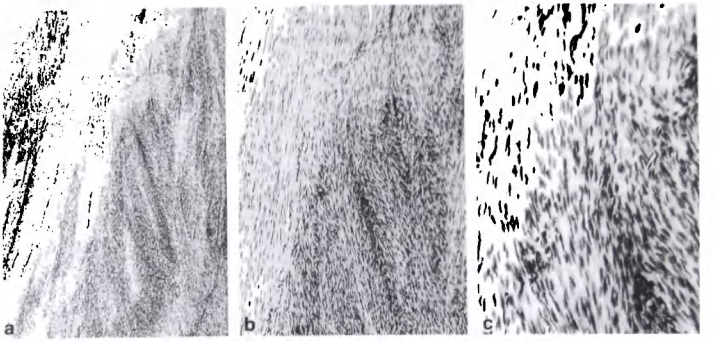


Fig. 1. Age and sex distribution of patients with histologically proven Dupuytren's disease (1980–6/1990; Orthop. Klinik Bad Abbach)



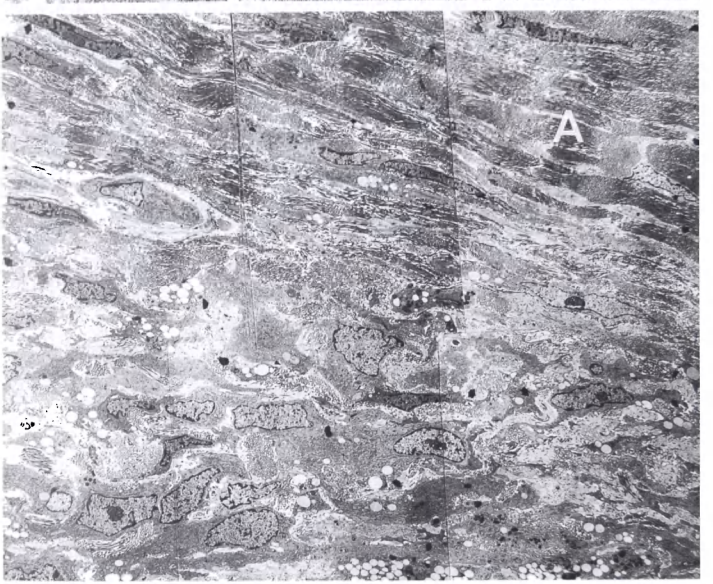


Fig. 2a–c *(above)*. Histological appearance of a fibromatous focus in the proliferative phase H and E, ×35 (**a**), ×85 (**b**), ×220 (**c**)

Fig. 3 *(below)*. Ultrastructure of a cellular focus in the proliferative phase with irregula demarcation from the surrounding tendon tissue of the aponeurosis (*A*). ×3000

collagenous tissue of the preserved aponeurosis. In contrast to desmoid tumors, no invasion of voluntary muscles occurs (Allen 1977).

The clinical course and corresponding histological appearance of the disease are usually divided into three more or less distinct phases. According to Luck (1959), the initial proliferative phase is followed by an increase in collagen synthesis by the infiltrating cells, leading to the involution phase. The final residual phase is characterized by scar tissue with few fibroblasts and a dominant, extracellular, fibrillar matrix. Histologically, it is apparent that the aponeurotic tissue may contain disease foci that are in the various phases of development (Mohr 1987).

Ultrastructural investigations have shown that different cell populations predominate in each of the three phases (Vossbeck 1986). During the proliferative phase, there is an abundance of fibroblasts with prominent rough endoplasmatic reticulum (Fig. 4a), some myofibroblasts, and few collagenous fibrils. During the involution phase myofibroblasts with indented nuclei and intracellular microfilaments surrounded by collagenous fibrils predominate (Fig. 4b). These cells (specialized contractile fibroblasts: Tomasek et al. 1987) are surrounded by bundles of filamentous material, presumably fibronectin (Tomasek et al. 1987). In the residual phase the tissue consists of collagenous fibrils with few fibroblasts (Fig. 4c).

From these observations and from the results of Meister et al. (1979) it may be assumed that the appearance of myofibroblasts is not the initial step in the evolution of Dupuytren's disease. Furthermore, doubt as to the specifity of myofibroblasts has recently arisen. Comparing the ultrastructure of the fibrous tissue in carpal tunnel syndrome and Dupuytren's disease, Murrell et al. (1989) observed identical myofibroblastic cells in both conditions. It should also be mentioned that the occurrence of myofibroblasts is by no means restricted to Dupuytren's disease (Mohr 1983).

From immunohistological investigations it may be concluded that in the proliferative phase only some cells express vimentin, which is more prominent in scar tissue. Skalli et al. (1989) observed that vimentin is usually present in cells inside the foci of Dupuytren's disease and is often coexpressed with α smooth muscle actin. In most instances, there is also coexpression of vimentin, α smooth muscle actin, and desmin (Table 1). Recently it has been found that cells of aggressive fibromatoses express the Ki-1 antigen (CD30), which had been considered to be restricted to activated lymphocytes and related tumors (Mechtersheimer and Möller 1990).

Table 1. Distribution of cytoskeletal proteins in Dupuytren's disease, total of 25 cases

Protein	Cases detected	Percent of cells
Vimentin	25	not mentioned
Vimentin and α smooth muscle actin	25	70–90
Vimentin, α smooth muscle actin, and desmin	22	10–30

From Skalli et al. 1989.

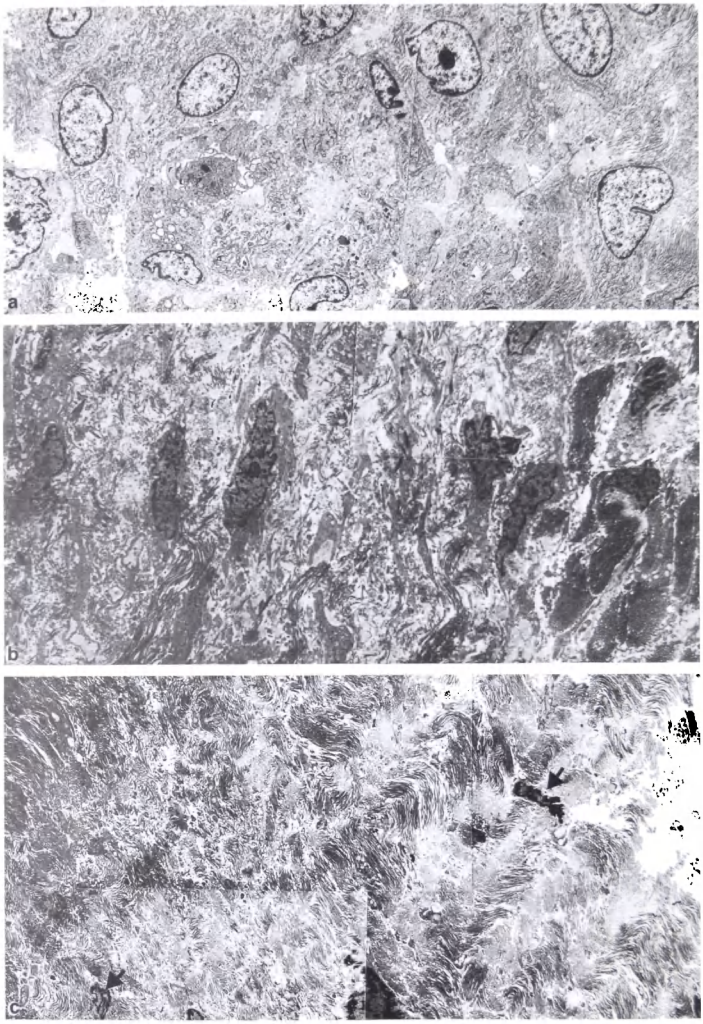


Fig. 4a–c. Electron micrographs of the different phases of Dupuytren's disease. **a** Prolifer ative phase with predominance of fibroblasts. **b** Involution phase with myofibroblasts sur rounded by collagenous fibrils. **c** Residual phase with a predominance of collagenous fibril and only some fibroblasts (*arrows*). ×2500

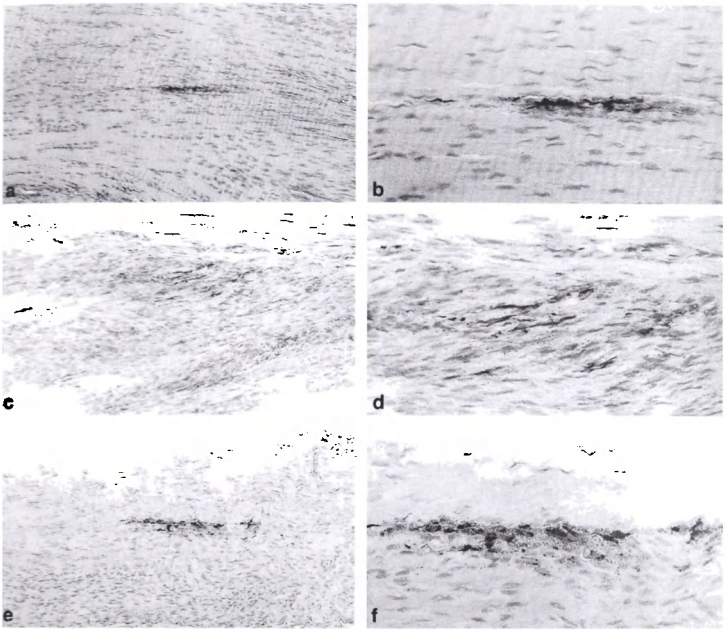


Fig. 5a–f. Iron deposits in Dupuytren's foci. **a** Small focus of iron deposits; ×85. **b** Spindle-shaped cells with siderin; ×220. **c** Irregular focus of siderin deposits; ×85. **d** Spindle-shaped cells with iron deposits; ×220. **e** Small focus with iron deposits; ×85. **f** Granular deposits of iron inside round and spindle-shaped cells; ×220. All sections stained with Prussian blue and nuclear fast red

Nodules of Dupuytren's disease may also contain other constituents. Not infrequently iron deposits are present in the cellular foci (Fig. 5). According to Viljanto (1973) siderin is present in about 20% of the cases; in our own sample, we found that in about 40% of 24 unselected cases some iron deposits could be observed. Ushijima et al. (1984) noted that iron is present especially in early stages of the disease.

Elastic fibers are rarely encountered; they may be observed either as small fibers running parallel to the woven collagenous fibrils or as irregular depositions of elastin (Fig. 6).

Alcian blue staining showed a slightly increased stainability for glycosaminoglycans inside the fibromatous foci in the proliferative phase compared to the normal fibrous aponeurotic tissue.

In recent years the relationship between mast cells and fibrotic diseases has been extensively studied, and it has been suggested that either mast cells or

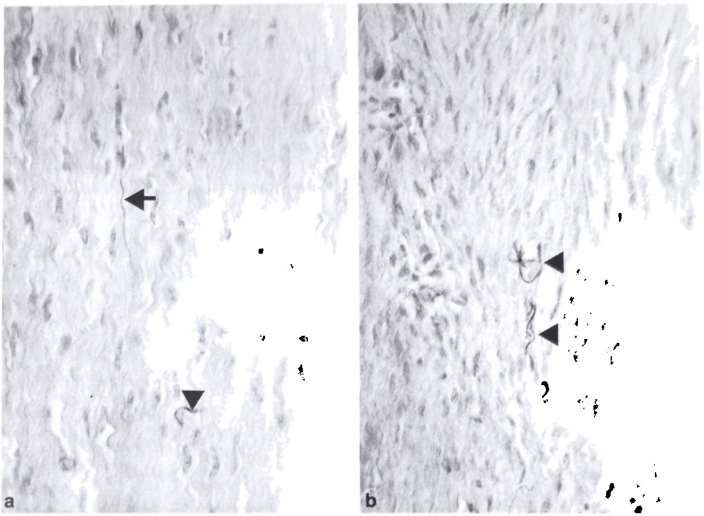


Fig. 6a,b. Elastic fibers in Dupuytren's focus either arranged in parallel with the woven collagenous fibers (*arrow*) or occurring as irregular deposits of elastin (*arrowheads*). Weigert's resorcin-fuchsin, nuclear fast red. **a** ×220, **b** ×350

Table 2. Role of mast cells in fibrotic diseases

Disease or condition	Findings	Reference
Systemic sclerosis	Elevated plasma histamine level; activated mast cells	Falanga et al. (1990) Claman (1989)
Tsk mouse with cutaneous fibrosis	Increased number and increased proportion of degranulated mast cells	Walker et al. (1985)
Tsk mouse with cutaneous fibrosis and blocking mast cell degranulation	Inhibition of fibrosis	Walker et al. (1987)
Collagen synthesis in polyvinyl sponges with compound 48/80	Increased collagen synthesis	Sandberg (1962)
Rat mesentery in vitro treated with compound 48/80	Increased proliferation of fibroblasts	Druvefors and Norrby (1988)
Cultured fibroblasts and histamine	Increased collagen synthesis	Hatamochi et al. (1985)
Cultured microvascular endothelial cells and histamine	Increased proliferation	Marks et al. (1986)
Cultured capillary endothelial cells and mast cells or lysate	Increased migration (no increased proliferation)	Azizkhan et al. (1980)

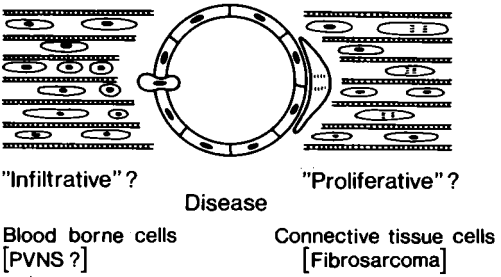


Fig. 7. Hypothetical mechanisms that may lead to Dupuytren's disease. *PVNS*, pigmented villonodular synovitis

histamine is responsible for the increased fibroblast proliferation and collagen synthesis (Table 2). Histological examination of Dupuytren's disease only rarely reveals mast cells, located either perivascularly or between connective tissue cells of the foci. This may indicate that neither mast cells nor their products are involved in the pathogenesis of the disease.

Except for the study by Andrew et al. (1990), there have been no reports on the presence of macrophages in Dupuytren's nodules.

With regard to the pathogenesis of the disease, two mechanisms may be discussed (Fig. 7). On the one hand, Dupuytren's disease may be regarded as an infiltrative disease caused by the differentiation of blood-borne cells. Such a mechanism has recently been assumed as the basic process in the development of nodules in pigmented villonodular synovitis (Ghadially 1983). No reports, however, are found in the literature that would support such an idea for Dupuytren's disease. On the other hand, Dupuytren's disease may be interpreted as a proliferative disease, resembling tumorous connective tissue proliferation such as occurs in fibrosarcoma.

To acquire more information about the proliferative aspect of the disease, we have performed autoradiographic investigations on specimens of Dupuytren's disease after [^{3}H]thymidine labeling in vitro (Mohr and Vossbeck 1985). For this purpose the tissues were divided into normal tendon, cords, nodules, and scars (Fig. 8). Labeled cells were rarely encountered in the normal tendon, while an increased number of labeled cells was present in the cords and nodules and especially in the perivascular region (Fig. 9). With regard to the distribution of the proliferating cell population, we did not observe areas in which labeling was more intense, either in the border or center zones of the fibromatous foci (Fig. 10). From the quantitative evaluation presented in Fig. 11 it may be concluded that proliferating cells are preferentially present in vascular or perivascular areas. This is in accordance with the findings of Murrell et al. (1989) who "suggest that the crucial phenomenon of fibroblast proliferation begins around narrowed microvessels."

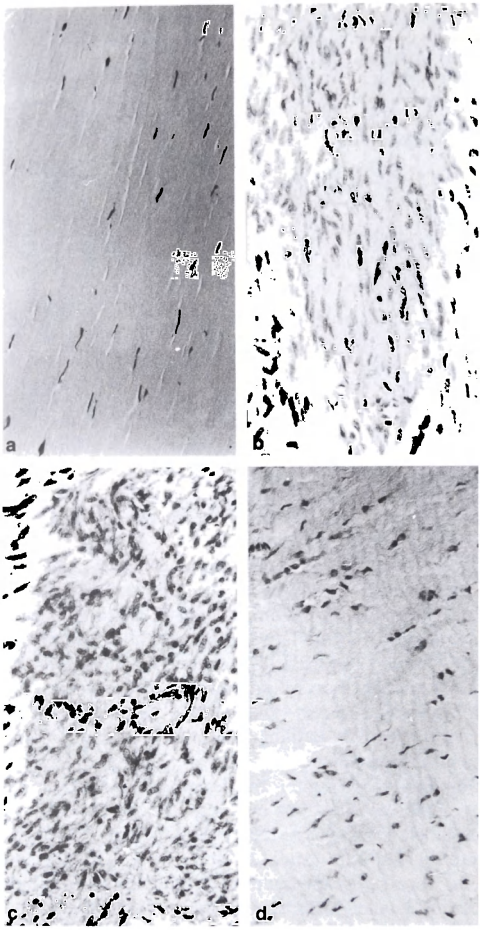


Fig. 8a–d. Structures evaluated for evidence of cell proliferati
d scar. H and E, ×220

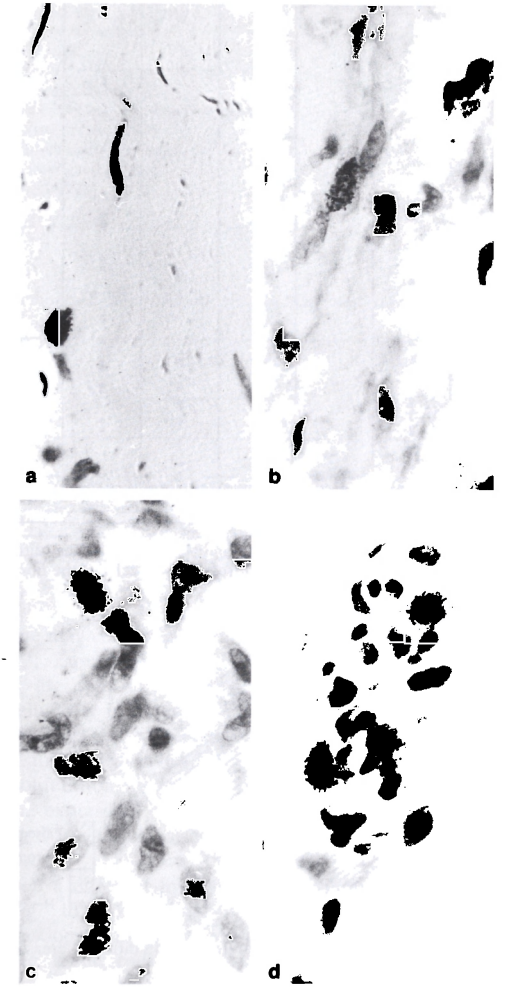


Fig. 9a–d. Autoradiography of [^{3}H]thymidine incorporation in: a normal tendon tissue of the aponeurosis; **b** Dupuytren's cord; **c** Dupuytren's nodule; **d** perivascular cells inside a fibromatous focus. Hematoxylin, ×875

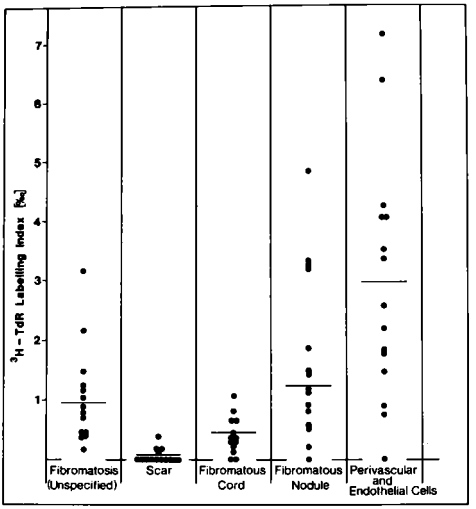


Fig. 10. [^{3}H]thymidine labeling index of cells in the different anatomical structures of Dupuytren's disease (*unspecified* refers to all cells of the fibromatosis)

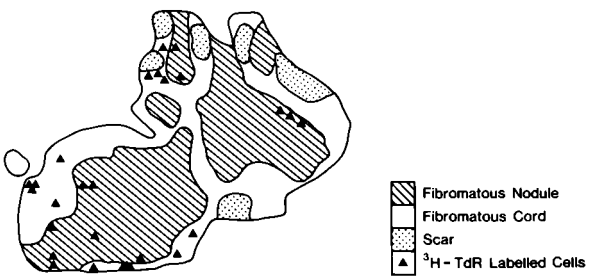


Fig. 11. Localization of proliferating cells in different areas of Dupuytren's disease

It is difficult, however, to histologically differentiate cells after ^{3}H-thymidine labeling. Therefore, it is not clear which cell population the proliferating cells belong to. Nevertheless, these investigations may lead to the hypothesis that precursor cells of the perivascular region are responsible for development of the hypercellular foci.

Table 3. Pericytes as a source of increased cellularity

Disease	Reference
Hemangiopericytoma	Stout and Murray (1942)
Intimal thickening (blood vessels)	Diaz-Flores and Dominguez (1985) Sarkisov et al. (1989) Beranek and Cavarocchi (1990)
Dupuytren's disease	Andrew et al. (1990)
Pigmented villonodular synovitis	Brax (1992)

Table 4. Immunohistological demonstration of smooth muscle actin and muscle actin in different tissue cells

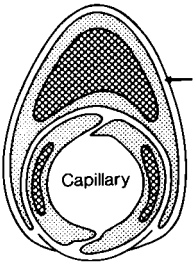
Cell type	Smooth muscle actin		Muscle actin
	α	γ	
Smooth muscle cells	+	+	+
Myofibroblasts (Dupuytren's disease)	+	+	+
Pericytes	+/-	+	+
Fibroblasts	−	−	−

From Roholl et al. (1990).

Perivascular connective tissue may contain a peculiar type of cell that has been termed "pericyte" (Fig. 12; Zimmermann 1923). Different conditions are known in which pericytes are said to be responsible for a tumorous or nontumorous increase of cellularity in tissues (Table 3). The assumption that pericytes may also be involved in the pathogenesis of Dupuytren's disease is supported by the immunohistochemical investigations of Andrew et al. (1990), who found that pericyte proliferation was present around occluded capillaries in the fibromatous foci. The expression of smooth muscle actin α and γ and muscle actin in pericytes and myofibroblasts (Table 4) further supports this finding.

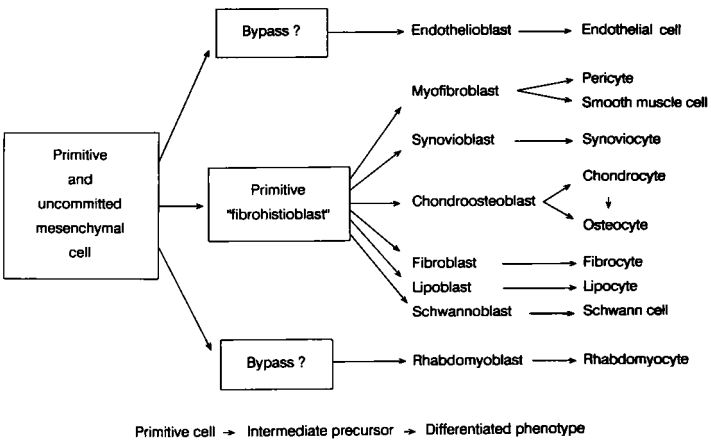
Brooks (1986) has developed a different hypothesis concerning the origin of connective tissue cells (Fig. 13). According to this author, there is an intermediate cell, the fibrohistiocyte, that is responsible for differentiation into various types of connective tissue cells. Thus, it may be that either an undifferentiated stem cell or an intermediate precursor cell is stimulated to proliferate and terminally differentiate into a fibroblast.

Since neither the etiology nor the pathogenesis of Dupuytren's disease has been clarified, the opinion of Viljanto (1973) remains valid: "The reader may feel frustrated by noticing that the puzzle of DC (Dupuytren's contracture) is still unsolved, even to so a great an extent, that the number of speculations can be compared with those concerning cancer or collagenoses."



◁ **Fig. 12.** Pericyte with branching processes. (Krstić 1984)

▽ **Fig. 13.** Hypothetical model of mesenchymal differentiation. (From Brooks 1986)



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