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Pathogenesis of Dupuytren's contracture: A correlative clinical-pathological study

The tissue from 38 patients with Dupuytren's contracture was submitted for light and electron microscopy. The clinical and pathological data were correlated so that three stages of disease were recognized: early, active, and advanced. The cell of early disease was the perivascular fibroblast; whereas, the cell of active disease was the myofibroblast. Because the myofibroblasts have cell-to-cell and cell-to-stroma attachments, the collagen not only becomes oriented as it is formed, but it also is subjected to a contractile force.

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According to Ling,[1] Dupuytren's contracture is a genetic disease due to a single dominant gene. Burch[2] states that it is also a disturbed tolerance, autoimmune disease generated by a "forbidden clone" of lymphocytes. Assuming that the conclusions of these authors are correct, the pathogenesis of Dupuytren's contracture remains to be elucidated. Then it would be apparent how such etiological factors as systemic disease, alcohol, and trauma affect the disease process. Also, if the biological mechanisms that result in contracture were understood, the present empirical methods of treatment could be replaced by a more rational approach.

Peacock[3] states that the problems of Dupuytren's contracture seem to be primarily in the realm of cellular and subcellular biology. Even so, the observations of basic scientists will not be relevant to the problem of pathogenesis until it is shown that their observations have been correlated with the duration and clinical activity of the disease. Also, specific areas of normal and diseased fascia should be analyzed separately. In this study the pathological findings by light and electron microscopy on specific locations of the palmar fascia have been correlated with the clinical state of the disease before and at operation. From the data a clinical-patholgical staging of the disease has been established and a theory of pathogenesis postulated.

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Materials and methods

Palmar fascia from 38 patients with Dupuytren's contracture was removed at operation and submitted for pathological examination. Particular care was taken to identify the tissue as having been obtained from the nodule, the cord, or the adjacent and apparently normal fascia. For light microscopy the specimens were pro-

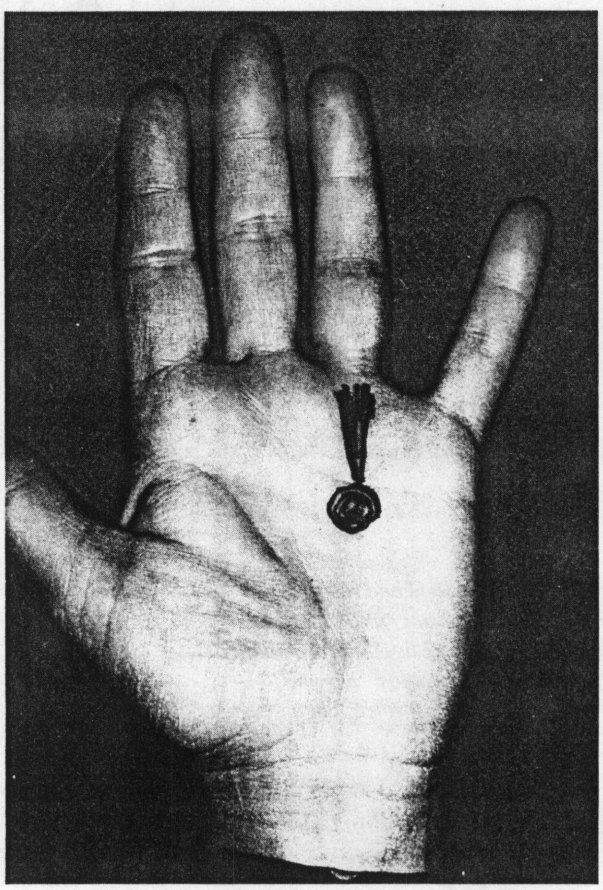

Fig. 1. A. F. a 38-year-old white woman, presented because of a left ring trigger finger. An example of early disease. The The palpable (diseased) fascia was marked and removed for examination.

cessed in the usual manner, and sections were stained by hematoxylin and eosin (H&E), periodic-acid-Schiff's (PAS), and Masson's trichrome stains. For electron microscopy, the tissue was minced in 3% glutaraldehyde in phosphate buffer, postfixed in osmium tetroxide, then dehydrated and embedded in an Epon-Araldite mixture. Initial 1 micron sections were used to select areas for ultrastructural examination. Ultrathin sections were stained with uranyl acetate and lead citrate, and in some cases, phosphotungstic acid (PTA).

The morphological studies were carried out by one of us (H.F.C.) without his prior knowledge of the clinical histories. The cases were grouped together according to similarities in their morphological features. Finally, the data were compared with the clinical histories, noting specifically the duration and activity of the disease in each case. There was a good correlation between the morphological features and the duration and activity of disease.

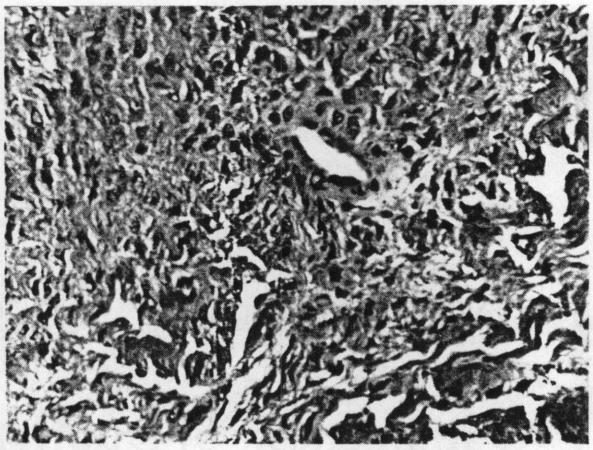

Fig. 2. Early disease. Note proliferation of perivascular fibroblasts within the fascia. (Original magnification × 110.)

Clinical-pathological staging of Dupuytren's contracture

Stage I. Early disease. This stage is characterized clinically by the presence of a nodule (or nodules) in the palmar fascia without joint contracture. Seven patients were seen with trigger finger and an incidental palmar nodule of Dupuytren's contracture. The opportunity was taken not only to correct the trigger finger surgically but also to remove the nodule for pathological examination. A typical clinical history is as follows:

A. F., a 38-year-old white woman who had diabetes since she was 7 years of age, presented because of a left ring trigger finger of 2 years' duration. A nodule of Dupuytren's contracture was present in the palm just proximal to the distal palmar crease along the ring finger ray (Fig. 1). At operation on May 8, 1975, a longitudinal incision was made over the left fourth ray in the distal palm. The nodule, which was not attached to skin, was removed, leaving the underlying superficial transverse ligament of the palm undisturbed. The proximal portion of the fibrous tendon sheath* and the synovial tendon sheath* were sent for examination by light and electron microscopy. When last seen 18 months after operation, the trigger finger remained corrected, but two new nodules were noted in the same ray of the palm.

Comment. Histologically, the nodules were located just deep to the subcutaneum or within the fascia. They were composed of proliferated perivascular spindle-shaped cells with irregular, rather hyperchromatic nuclei (Fig. 2). The intercellular spaces contained materials which were basophilic on the H&E stain and positive on the PAS stain. There was no increased

*In seven patients with trigger finger, myofibroblasts were not seen in the fibrous or synovial tendon sheaths.

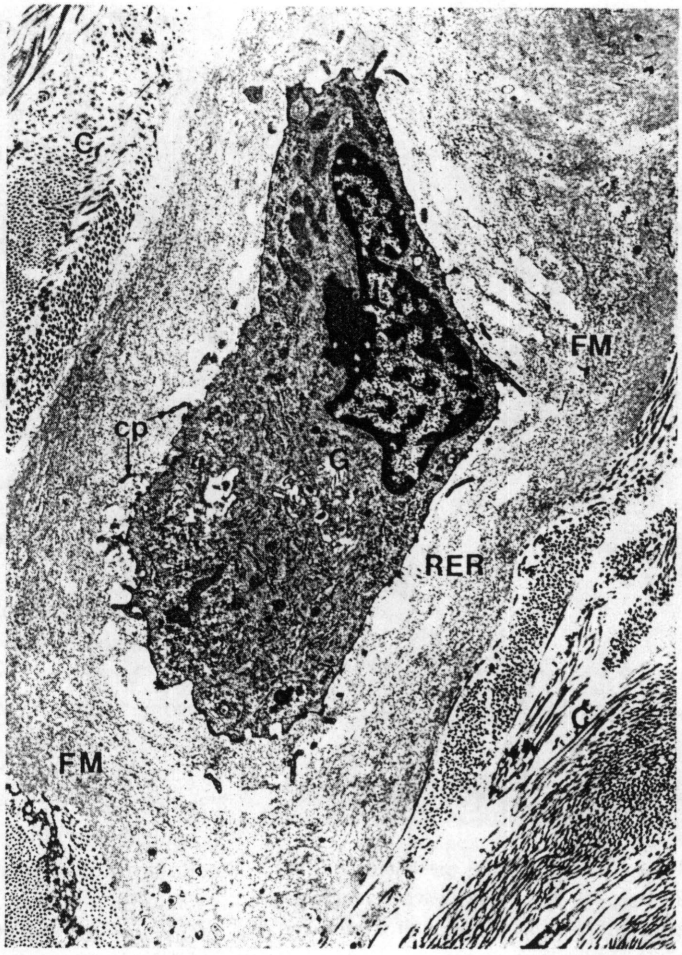

Fig. 3. Early disease. The fibroblast shows filiform processes *(cp)* on its surface and contains prominent rough endoplasmic reticulum *(RER)* and Golgi apparatus *(G)*. It is surrounded by a mantle of fine fibrillary material *(FM)* which separates it from the collagen fibres *(C)* of the palmar fascia. (Original magnification ×7,300.)

collagen deposition within the nodules, as demonstrated by the Masson's trichrome stain. In fact, the proliferated cells and their stroma appeared to have penetrated the dense fibrous bundles of the fascia, disrupting their continuity.

Ultrastructurally, the proliferated spindle-shaped cells proved to be hyperplastic fibroblasts. The nucleus was smooth and elongated, and some cells were binucleated. The cell border was irregular and showed numerous filiform processes. In the cytoplasm there was prominent hypertrophy of the rough endoplasmic reticulum, the Golgi apparatus, and the smooth vesicles. Microtubules and microfilaments generally were scanty, and no myofilaments with attachment zones could be found. A striking and consistent electron microscopic finding was the presence of abundant electron-dense granulofibrillary deposits around individual fibroblasts (Fig. 3). These deposits, which were of variable thickness, separated the cell from the bundles of mature collagen fibers and from the blood vessels. In micrographs of low magnification, the individual cells seemed to be lying in lacunae filled with these substances. Short fibrils with periodicity were seen at the outer edges of the deposits. The fibroblastic hyperplasia with pericellular deposition of ground substance was not seen in sections taken from normal fascia.

Stage II. Active disease. In this stage, which included 18 patients, nodular thickening of the palmar fascia was associated with joint contracture. While it is appreciated that an accurate history of the duration of disease is difficult to obtain, usually the patients had noted progressive joint contracture for about 3 years. A representative clinical history is as follows:

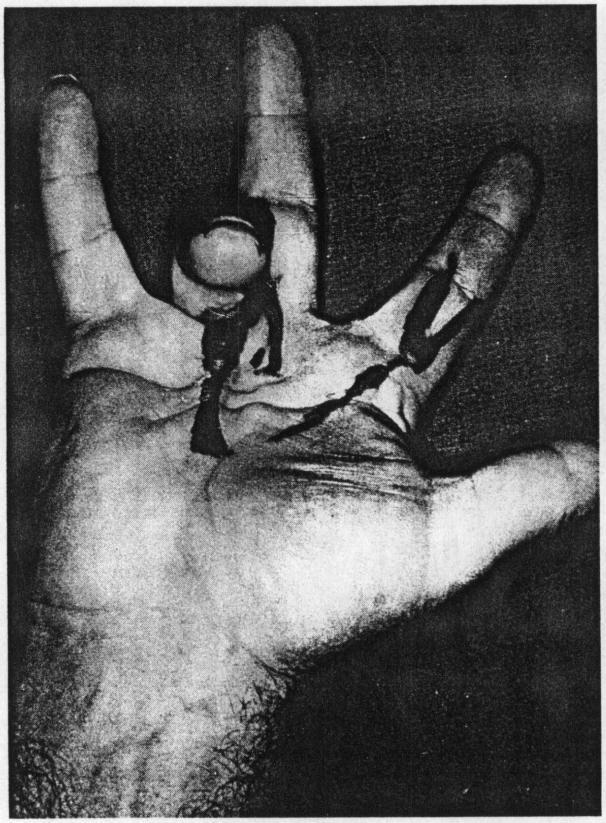

Fig. 4. K. M., a 58-year-old white man, presented with an example of active disease. The ring finger was contracted severely at the metacarpophalangeal and proximal interphalangeal joints.

K. M., a 58-year-old white man, had noticed palmar thickening in both hands for about 25 years. He was troubled by contracture in the right hand for about 2 years. All fingers were contracted at the metacarpophalangeal joints, but the ring finger was severely contracted—70° at the metacarpophalangeal and 65° at the proximal interphalangeal joints (Fig. 4). At operation on July 15, 1975, the diseased fascia in all four rays was removed. When seen 1 year later, the other hand had sufficient contracture to warrant operation.

Comment. On light microscopy, the nodules consisted of closely packed cells with very little intervening collagen (Fig. 5). Most cells had irregular hyperchomatic nuclei. There was scanty PAS-positive material in the stroma.

Ultrastructurally, the predominent cell type was the myofibroblast which showed aggregated bundles of microfilaments measuring 60 to 80 mU in width, with dense attachment zones interspersed (Figs. 6 and 7). The rough endoplasmic reticulum and the Golgi apparatus were prominent. Intercellular junctions, mostly of the nexus type and some of the zona adherents type,

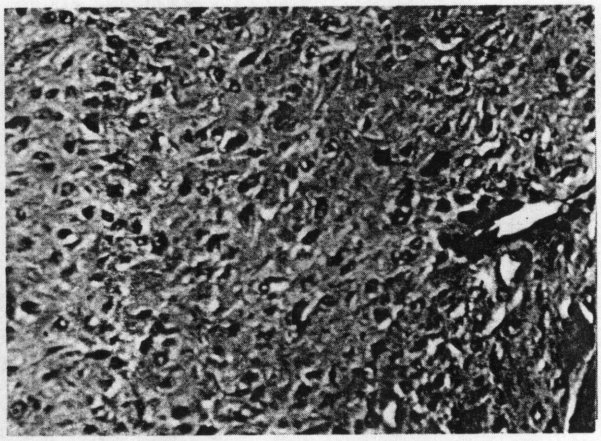

Fig. 5. Active disease. There is marked cellular proliferation with scanty collagen in the nodules. The nuclei are irregular and hyperchromatic. (Original magnification ×110.)

were observed frequently (Fig. 8). At the sites of attachment of the myofilaments to the cell membrane, partial basement membrane formation and hemidesmosomes could be seen and the collagen fibers were intimately associated with these attachment sites. The nucleus was elongated and showed deep indentations. The intercellular spaces were filled with a pale, granular substance which was no longer limited to the pericellular location as in the nodules of early disease. Associated with the ground substance were loose bundles of mature collagen fibers.

The ultrastructure of the cords taken from lesions of different ages was similar. They were composed almost entirely of well-aligned collagen fibers with a few scattered cells. Among these cells definite myofibroblasts were identified (Fig. 9). Myofilaments with dense zones as well as cell-to-stroma attachments were present in the cytoplasm. Intercellular junctions could not be found. The scattered fibroblasts were spindle-shaped or triangular. The cytoplasm was occupied by dilated cisternae of rough endoplasmic reticulum. The Golgi apparatus was inconspicuous. No fibrillary deposits could be seen around the cells or among the collagen fibers.

Stage III. Advanced disease. These patients had progressive joint contracture for more than 3 years, with diffuse fibrotic thickening of the palmar fascia. A typical example of the 13 patients in this group was as follows:

J. O., a 67-year-old man, had noticed some finger contracture, at least 15 years previously, with gradual progression (Fig. 10). At operation on Nov. 12, 1975, the offending fascia was removed. A skin graft was needed to close the palmar wound because of the long-standing contracture.

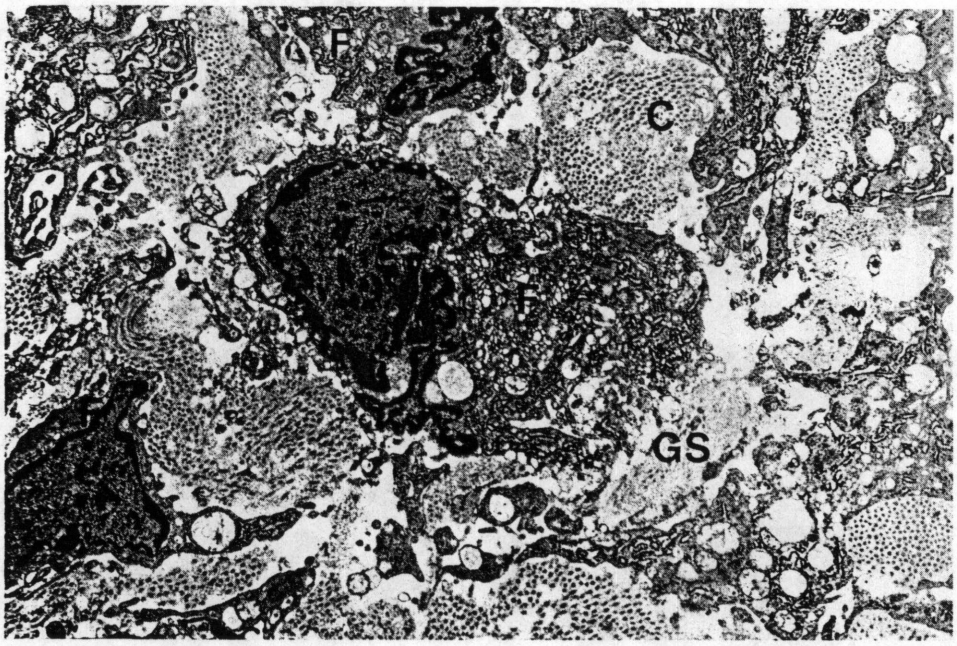

Fig. 6. Active disease. Three hypertrophied fibroblasts *(F)* are shown. There is orderly disposition of collagen fibres *(C)* and even distribution of ground substance *(GS)* in the intercellular spaces. (Original magnification ×6,600.)

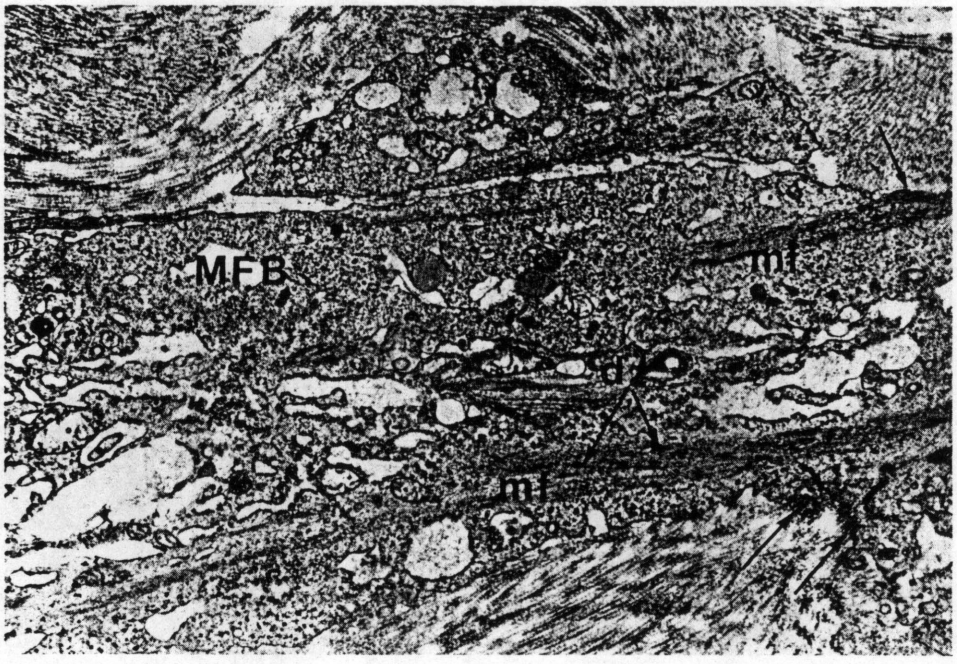

Fig. 7. Active disease. A typical myofibroblast *(MFB)* showing bundles of myofilaments *(mf)* with interspersed dense zones *(dz)*. Note cell-to-stroma attachments *(arrows)*. (Original magnification ×9,000.)

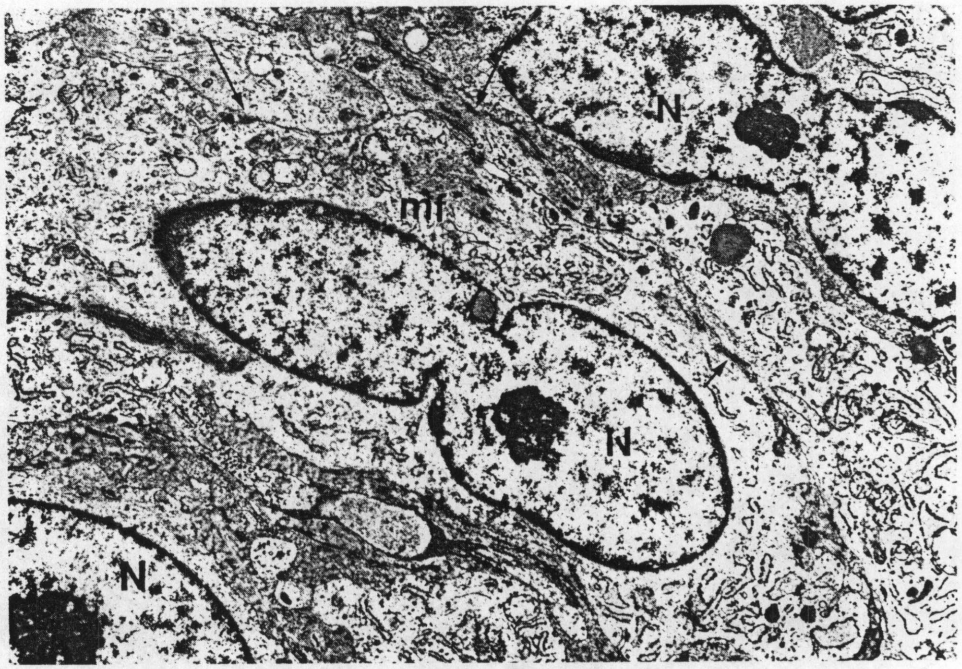

Fig. 8. Active disease. Note the intercellular junctions between adjacent myofibroblasts *(arrows)*. Myofilaments *(mf)* are present in the cytoplasm. The nuclei *(N)* are indented. (Original magnification ×6,600.)

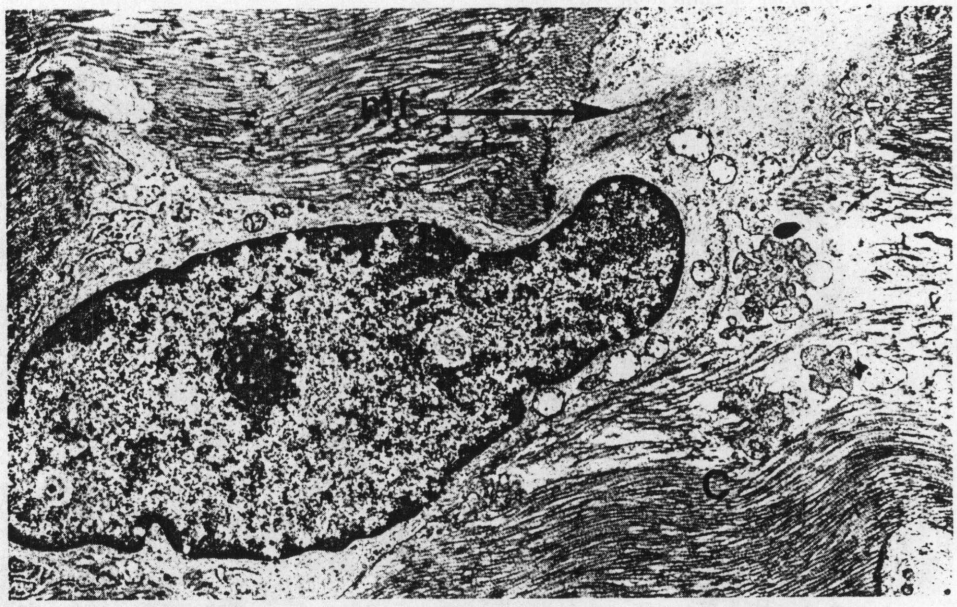

Fig. 9. Cord. A cell with myofilaments *(mf)* is shown. Note parallel wavy bands of mature collagen *(C)*. (Original magnification ×8,500.)

Comment. On light microscopy the tissue was more fibrotic than cellular. Elongated and apparently compressed cells were separated by broad parallel bands of collagen (Fig. 11). PAS-positive substances in the stroma were absent.

Under the electron microscope, both myofibroblasts and fibroblasts were identified (Fig. 12). They were less numerous than in the preceding group. Intercellular junctions were rare. Some cells were seen with mature collagen fibers lying intracytoplasmically

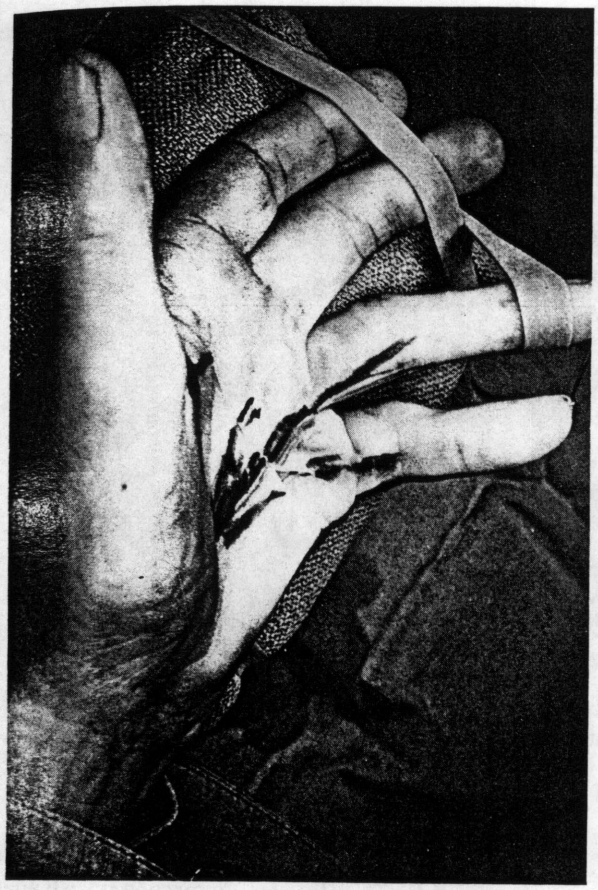

Fig. 10. J. O. a 67-year-old white man, had long-standing contracture of the little (metacarpophalangeal—55°, proximal interphalangeal—35°) and ring (metacarpophalangeal—40°; proximal interphalangeal—35°) fingers. The pretendinous cord was sectioned to open the little finger before the photograph was taken. Note the absence of palpable nodules in the mature cords.

within membrane-bound vesicles (Fig. 13). The stroma consisted of a large amount of mature collagen fibers. The granular ground substance seen in the previous groups was much less abundant and was limited to a few pericellular foci.

Discussion

In 1832, Dupuytren[4] stated that the pathologic change occurred in the palmar fascia, and it is for this reason that his name has remained associated with the disease. The following year, Goyrand[5] said that the disease began in the fibrofatty tissue and only affected the palmar fascia secondarily. It is the enigma of Dupuytren's contracture that the controversy exists until this day. Hueston[6] is the modern proponent of the view that the disease begins in the subdermal tissue as a cellular nodule. He supports the theory of Luck[7] that

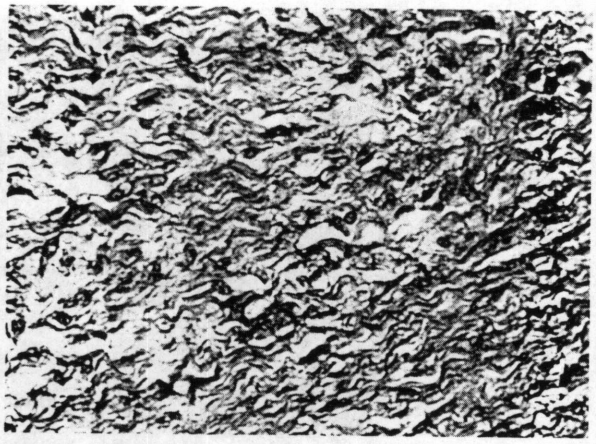

Fig. 11. Advanced disease. Note thick, wavy bundles of collagen fibres separating the cells. (Original magnification ×110.)

the nodule is the contracting structure which produces joint contracture upon becoming attached to the underlying fascia. Luck's theory gained additional support when Gabbiani and Majno[8] reported that contractile fibroblasts (myofibroblasts) were present in the nodule of Dupuytren's contracture.

Millesi[9] has interpreted his observations differently. Based upon gross and histologic studies of living and cadaver hands, he concluded that the nodule always developed in a fiber bundle. Further, he agreed with Skoog[10] that the initial lesion was a disruption of the fiber bundle and the cellular reaction (that produced a nodule) was secondary. He explained the location of nodules in the subdermal tissue on the anatomical fact that fascial fibers pass from the palmar fascia to the overlying skin and that these fibers can be the site of the disease process in the same way as other components of the palmar fascia. One of us (R.M.M.), in a study of the gross pathological anatomy of the diseased fascia,[11] made a similar observation that the diseased tissue may or may not be related to the overlying skin, depending upon the normal anatomical attachment of the fascia to the skin (Fig. 14). Beyond the distal palmar crease, the pretendinous band of the palmar aponeurosis attaches to the skin normally. If the disease begins there, the nodule that forms will be attached to the skin. If the disease begins in the same pretendinous band more proximally in the palm, the nodule will not be attached to the skin. If a nodule appears in the digit, it is likely to be attached to the skin because the superficial fascia of the digit that contributes to the central, lateral, or spinal cord on the digit is intimately attached to the skin (Fig. 15). A nodule arising in a spiral cord at the level of the metacarpophalangeal joint would bear no rela-

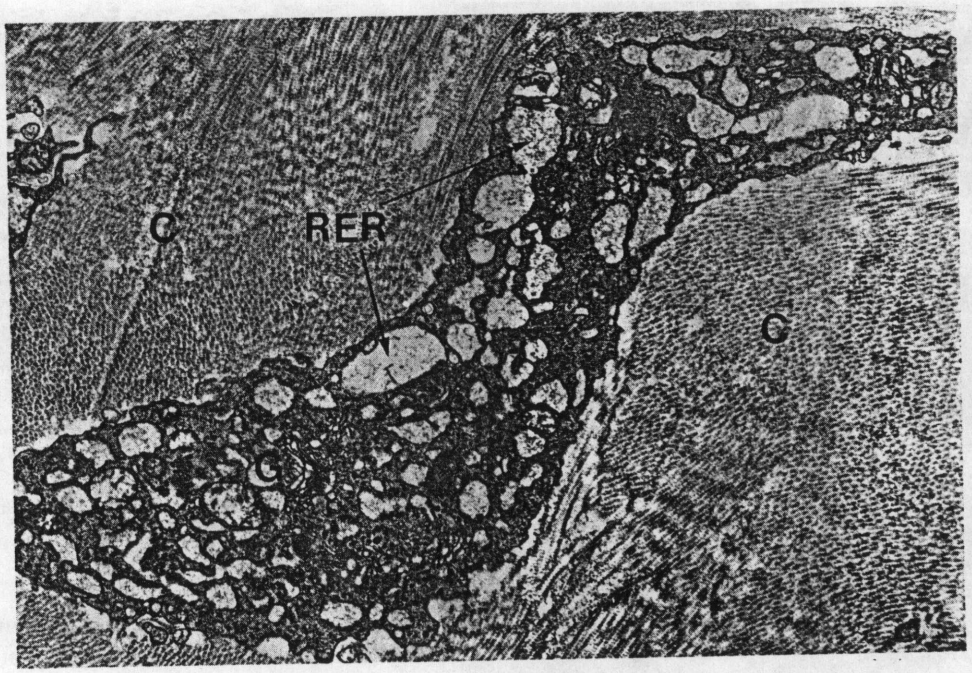

Fig. 12. Advanced disease. A fibroblast is shown among well-aligned collagen fibres *(C)*. Note the dilated cisternae of rough endoplasmic reticulum *(RER)* and small Golgi apparatus *(G)*. (Original magnification ×11,900.)

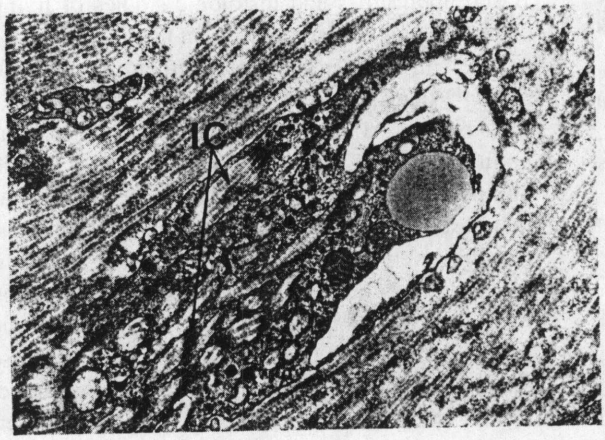

Fig. 13. Advanced disease. A cell with abundant intracytoplasmic collagen. *(IC)*. (Original magnification ×12,500.)

tionship to the skin, but a nodule of the same cord at the level of the mid portion of the proximal phalanx would be attached to the skin.

The clinically palpable nodule has received undue significance in the process of contracture. The concept of a single nodule, upon becoming attached to the palmar fascia, acting as a winch or a motor to produce a tight cord is too simplistic. Many areas of cellular activity are seen in the diseased tissue, some large enough to be palpated clinically, but most of microscopic size. The small as well as the large areas contribute to joint contracture. The electron microscope reveals that myofibroblasts may be present in areas of cellular activity in the active and advanced stages of disease, but not in the early disease. Even in the tendonlike cords of advanced disease, groups of cells are seen. Contrary to a recent report,[12] we have observed myofibroblasts in the cords. The contracting stage of the disease may be all but over, but there is still some slight potential for continuing contracture.

Based on the study of the earliest palmar lesion before the onset of joint contracture, we are able to show that the disease begins with activity in the perivascular fibroblast, within the fibrous bundles of the fascia. There is a pericellular mantle of fibrillary material separating the cells from the collagen. The nature of the material is not clear: it may be the precursor of collagen, but in the studies of fibroblastic collagen deposition by Goldberg and Green[13] and Ross,[14] such material was not described. It is weakly positive for the PTA stain, indicating that it contains mucopolysaccharides and may correspond to the PAS-positive substance seen in the intercellular spaces on light microscopy. This interpretation is supported by Hunter, Ogdon, and Norris[15] who found an increased glycoprotein and glycosaminoglycan content of Dupuytren's tissue compared to normal palmar fascia. Therefore we pos-

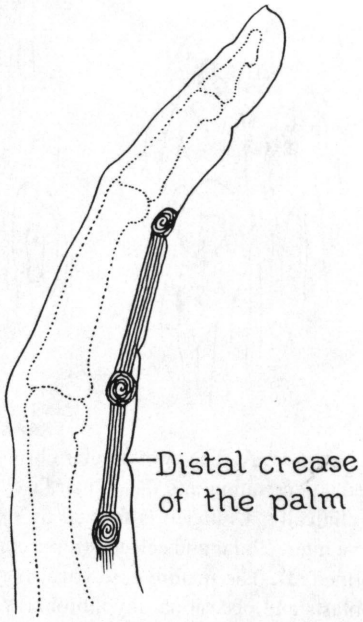

Fig. 14. A diagramatic cross-section of the palm and finger to illustrate the relationship of the pretendinous and central cords and nodules to the skin. Proximal to the distal crease of the palm the nodule and cord will be deep to skin whereas distal to the crease the diseased tissue will be adherent to skin.

tulate that this substance may facilitate the penetration of the activated fibroblast into the fascia and/or may be the medium into which new collagen subsequently is extruded.

During the active stage when progressive joint contracture occurs, myofibroblasts appear and are the predominant cell type in the nodules. They exhibit frequent cell-to-cell and cell-to-stroma attachments, confirming Gabbiani and Majno's original observation. Loosely spaced new collagen fibers are laid down among an evenly distributed granulofibrillary ground substance. Because of the contractibility of the myofibroblasts and the intercellular and cell-to-stroma attachments, a directional line of stress acts on the newly deposited collagen so that it becomes aggregated in a well aligned way. In other words, *the collagen fibers of Dupuytren's contracture become aligned as they are formed*. The altered chemical composition of the collagen[16] might favor the alignment of these fibers into cords.

As more collagen is produced, the cellular activity diminishes and the tissue becomes cordlike. This progression of events has been well studied by Hunter and Ogdon[17] who utilized scanning electron microscopy. They noted that in actively growing areas fibers are poorly formed and only tend to be oriented in one direction. In the mature nodule (advanced disease) and

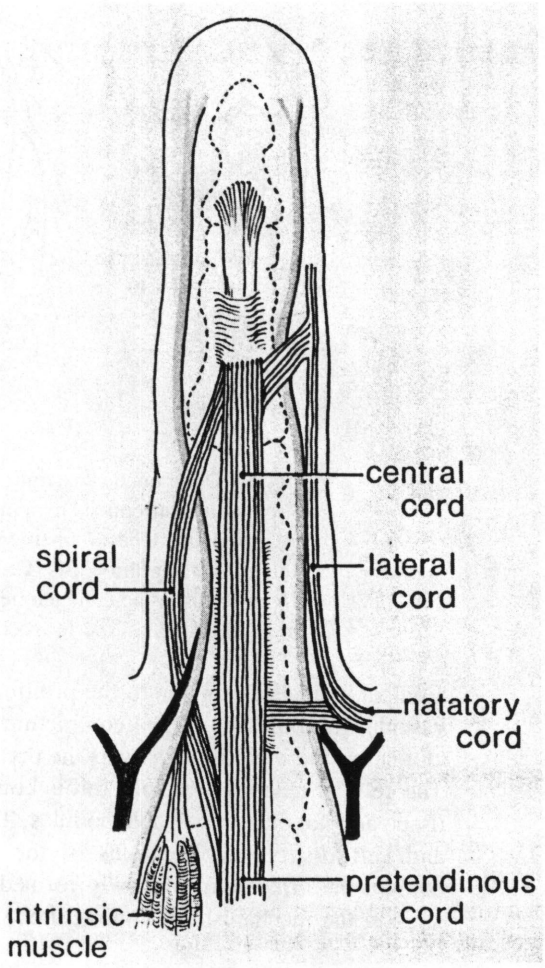

Fig. 15. A diagramatic summary of all of the diseased cords in the palm and digit. A nodule may appear anywhere along these cords and will be attached to the skin only if the fascia involved is normally attached to the skin.

fibrous cords, the fibers consist of closely packed parallel fibrils with a wavy appearance indistinguishable from tendon. The occasional cell observed in this stage that contains intracellular collagen is probably involved in collagenolysis, i.e., the process of remodelling, rather than in collagen synthesis. Even in advanced disease, occasional foci of perivascular cellular activity, including myofibroblasts, are present with the potential for continuing contracture. This theory of pathogenesis is illustrated in Fig. 16.

Conclusions

A theory of pathogenesis of Dupuytren's contracture is offered that is based upon the correlation of the clinical state of disease with the pathological findings seen under the light and electron microscope. It was observed that the initial cellular reaction that resulted in

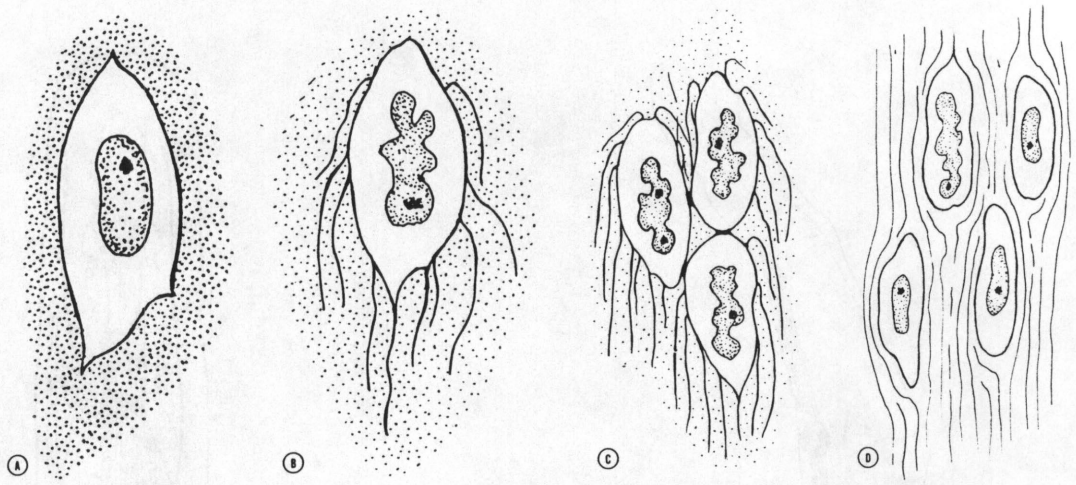

Fig. 16. Diagramatic description of our theory of pathogenesis. **A,** The perivascular fibroblast of an early nodule surrounded by a mantle of fibrillary material penetrating into the palmar fascia. **B,** The myofibroblast appears when contracture is apparent clinically. Collagen is formed by this cell as well as by other fibroblasts. **C,** The myofibroblasts have intercellular and cell-to-stroma connections which result in the collagen being aligned as it is formed. **D,** The mature cord consists mainly of oriented collagen. The few cells remaining are fibroblasts and occasional myofibroblasts.

a palpable nodule was due to the proliferation of perivascular fibroblasts. When contracture was evident clinically, the myofibroblast was the predominant cell. The cellular reaction was seen throughout the diseased tissue and not only in palpable nodules. The cell-to-cell and cell-to-stroma connections of the myofibroblast explain the orientation of newly formed collagen and suggest the mechanism of contracture.

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