

The Myofibroblast in Dupuytren's Contracture

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Early studies of the myofibroblast in Dupuytren's contracture used the electron microscope to detect their presence.¹⁰ These studies demonstrated myofibroblasts in the nodular tissue of Dupuytren's contracture but not in the cord-like structures.^{6, 13, 17} Others suggested that the palmar fascia progressed from a proliferative stage through an involutional stage, while the proliferative tissue was undergoing contraction.¹³

Studies in our laboratory have confirmed the presence of myofibroblasts (Fig. 1) primarily in the nodules rather than in the cords. In our first study, fascial specimens were obtained from 24 patients with Dupuytren's contracture.¹² Both nodules and cords were examined by electron microscopy and biochemical analysis. Electron microscopy showed myofibroblasts in the nodules from seven of these individuals. Microtubules were prominent in the fibroblasts of ten patients. Biochemical studies showed that the fascia contained type III collagen, increased amounts of collagen per unit of dry weight, and increased amounts of reducible crosslinks of collagen.

Clinical postoperative contracture recurrence was correlated with the electron microscopic findings of myofibroblasts in the nodules as well as of fibroblasts containing prominent microtubules in the palmar fascia. In this study, the presence of myofibroblasts was not related to

the length of time that the contracture had been present.

Further electron microscopic studies evaluated the ultrastructural relationship of the overlying skin to the nodule and cord in Dupuytren's contracture. Clinically, because the skin may be intimately inherent to both nodule and cord, we were interested in knowing the morphology of this relationship. In this study,³⁶ the interface of skin and either nodule or cord was studied in 11 patients who had surgery for Dupuytren's contracture. Both light and electron microscopy were used. Four distinct anatomical zones were seen in the skin and nodule specimens with three zones in the skin and cord specimens. A striking horizontally layered dense band was found in skin and cord specimens. Another band was found just beneath the dermis in the skin and nodule specimens, a feature that was also found in skin and cord specimens. Electron microscopy demonstrated myofibroblasts in the lower two zones in the skin and nodule specimens, with both active and degenerating cells seen side by side. Myofibroblasts were not seen either at the skin and cord interface or in any skin specimen.

These findings³⁶ suggest that the nodule is the active source of contraction in Dupuytren's contracture. The skin itself does not cause the contracture, but is drawn passively by underlying contractile forces. These studies also

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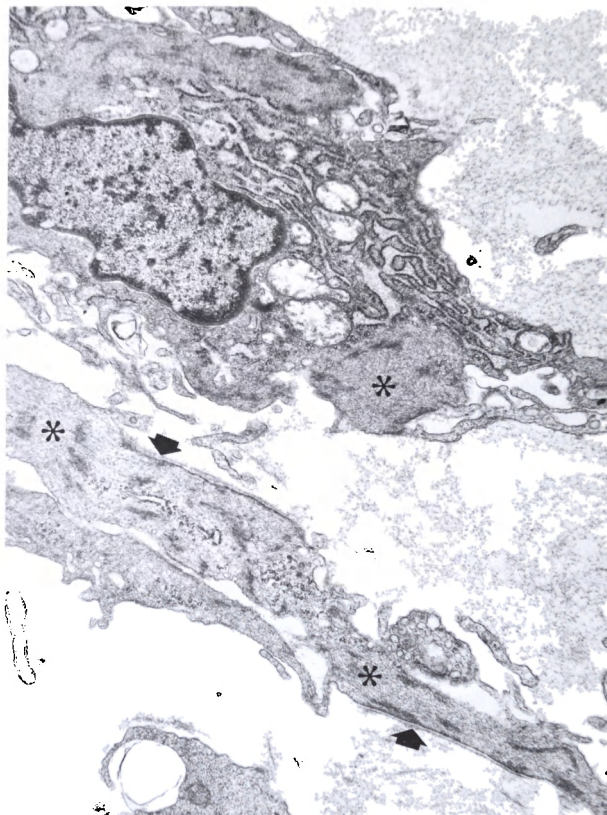


Figure 1. Typical myofibroblasts from a Dupuytren's contracture nodule. Microfilament bundles with electron-dense bodies (*) are present. Basal lamina (arrows) around cell membrane may help to connect cell to stroma (magnification $\times 15,300$). (From Rudolph R: Contraction and the control of contraction. *World J Surg* 4:279, 1980; with permission.)

showed that it is quite difficult to ensure that all actively contracting fascial tissue is removed from areas of dense skin adherence because of the apparent fusion of the dermis and the fascia. More aggressive resection of the fascia and dermis interface may well be indicated in skin and nodule areas.

Histologically, nodules often have a polar pattern, with cells (usually myofibroblasts) converging at the ends¹¹ (Figs. 2, 3, and 4). In contrast, cords have layered collagen similar to

tendons (Fig. 5). On electron microscopy, myofibroblasts and fibroblasts in Dupuytren's contracture nodules and cords appear similar to those seen elsewhere in the body.

Merlo and associates²¹ believe that during the proliferative phase, the nodule forms as a result of progressive adhesion and aggregation of fibroblasts with fibrin.²² Such small nodular masses are essentially dense aggregations of hyperplastic fibroblasts.¹⁰ From this nodular development stage of Dupuytren's contracture,

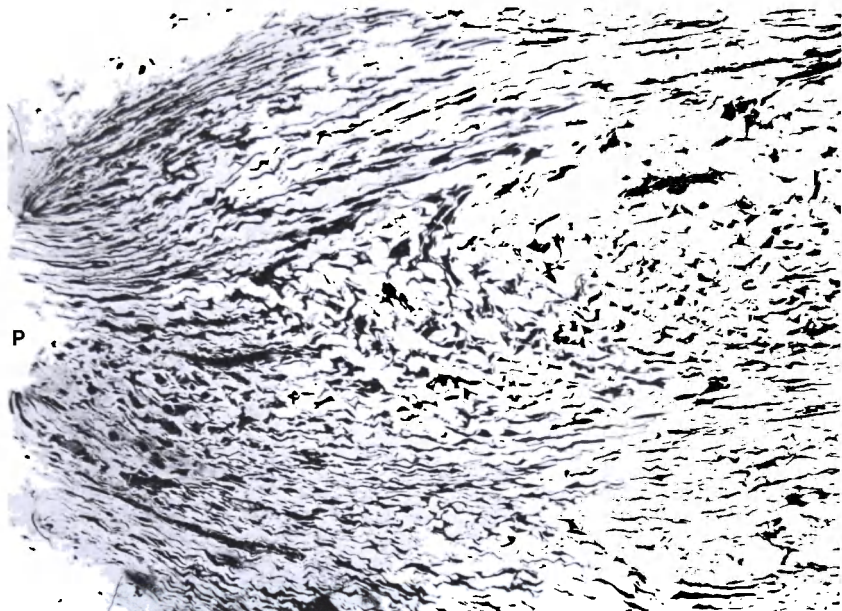


Figure 2. Light microscopy of Dupuytren's contracture nodule. Nodules usually have greater cell density than cords (see Fig. 5). In this nodule, cells and dense collagen appear to be drawn toward one of the poles (*P*) (magnification $\times 361$). (From Vande Berg J, Gelberman R, Rudolph R, et al: Dupuytren's contracture: Comparative growth dynamics and morphology between cultured myofibroblasts (nodule) and fibroblasts (cord). *J Orthop Res* 2:247, 1984; with permission.)

larger nodule development may result from further fibroblast aggregation rather than from collagen production.

During the involutional stage, it appears that some or most of the hyperplastic fibroblasts modulate into the myofibroblast phenotype, an intermediate cell form undergoing transitional differentiation. Merlo and associates²¹ believe that in this stage the myofibroblasts represent a temporary cell population whose numbers decrease as the disease progresses. They also suggest the possibility that nodular myofibroblasts decline in activity with time and are not detectable by standard procedures. Lending some credence to this theory is our observation that aggregations of densely packed nodular myofibroblasts exhibit a senescent appearance.³⁶ The cytoplasm of the myofibroblast appears vacuolated, and there is often a loss of endoplasmic reticulum and general organelle integrity. The nodule, at this time, presents the

appearance of a mass of myofibroblasts "strangled" in densely packed collagen, the product of their synthesis (Fig. 6).

TISSUE CULTURE IN DUPUYTREN'S CONTRACTURE

Additional support for this theme of provisional existence of the nodular myofibroblast is found by comparing the tissue culture replicative life span of nodular fibroblasts, cord fibroblasts, and normal skin fibroblasts.³³ The control fibroblasts from normal palmar skin showed an altered rate of growth at passages 12 and 15, at a time when the cord fibroblasts were displaying declining growth; cultured nodule myofibroblasts showed cell degeneration and essentially no growth by passage 15. The last stage, the residual phase, contained typical fibrocytes

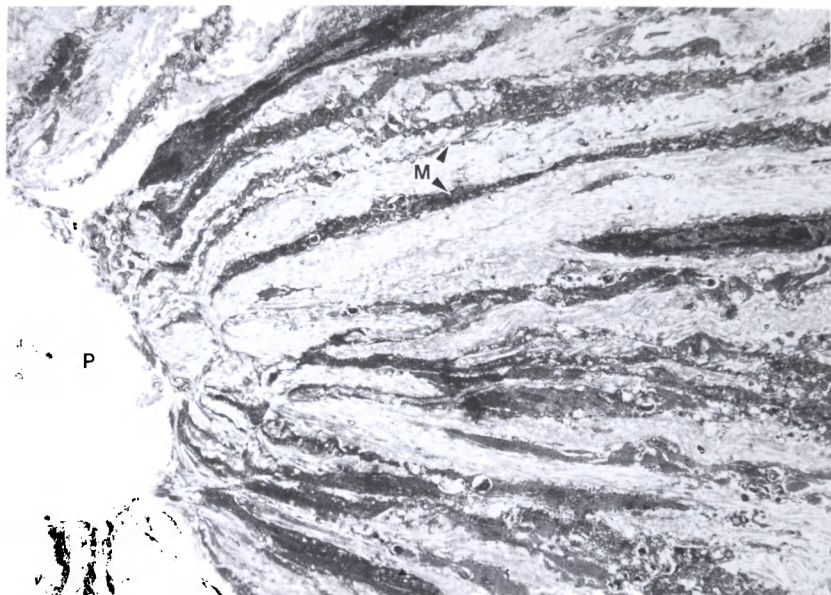


Figure 3. Electron micrograph of nodule in Figure 2 showing polar area (*P*). All cells appear to be myofibroblasts (*M*, *arroncheads*). Probable contraction is shown by the drawing of collagen to a localized area leaving space containing only cellular fragments (magnification $\times 9,265$). (From Vaude Berg J, Gelberman R, Rudolph R, et al: Dupuytren's contracture: Comparative growth dynamics and morphology between cultured myofibroblasts (nodule) and fibroblasts (cord). *J Orthop Res* 2:247, 1984, with permission.)

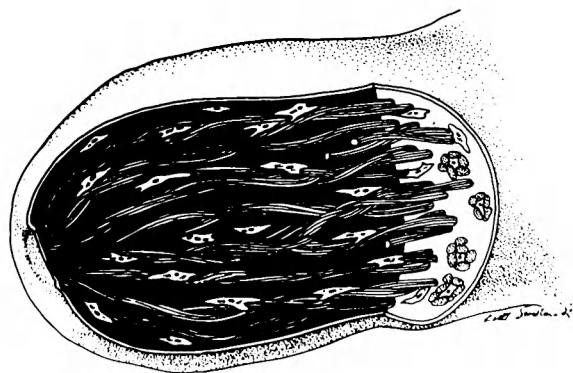


Figure 4. Dupuytren's contracture nodule shown in Figures 2 and 3 (From Vaude Berg J, Gelberman R, Rudolph R, et al: Dupuytren's contracture: Comparative growth dynamics and morphology between cultured myofibroblasts (nodule) and fibroblasts (cord). *J Orthop Res* 2:247, 1984, with permission.)

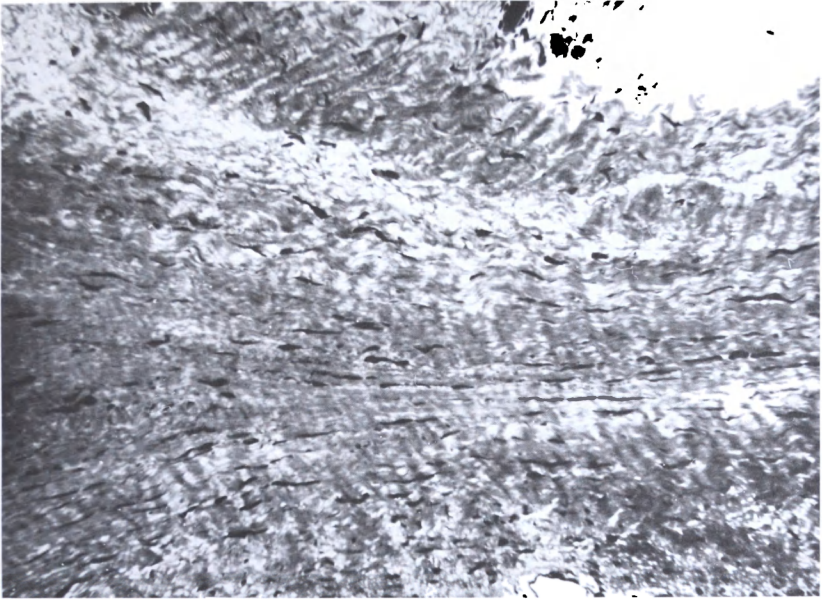


Figure 5. Light microscopy of a cord, showing few cells in a parallel pattern among dense layered collagen fibers (magnification $\times 361$). (From Vande Berg J, Gelberman R, Rudolph R, et al: Dupuytren's contracture: Comparative growth dynamics and morphology between cultured myofibroblasts (nodule) and fibroblasts (cord). *J Orthop Res* 2:247, 1984; with permission.)

characteristically found in immature connective tissue.

Tissue culture growth curves of cells derived from Dupuytren's cord, nodule, and normal palmar fascia showed specific differences.³³ At passage 5, cultured myofibroblasts from nodules grew significantly more slowly than did fibroblasts cultured from cord and palmar skin (Figs. 7 and 8). In culture, myofibroblast characteristics (40–80A microfilaments with electron-dense bodies) were maintained in early passages.

Bailey and associates⁴ observed that palmar connective tissue containing nodules and unaffected aponeurosis of Dupuytren's contracture contained type III collagen, whereas normal aponeurosis contained type I collagen. The association between the myofibroblast and type III collagen suggests that this modulated cell may be in part responsible for altering the environment of the aponeurosis. Recent tissue culture studies have shown that both fibroblasts

and myofibroblasts have the ability to synthesize both collagen types I and III.²³ At early passage, myofibroblasts produce twice as much protein for collagen production as undifferentiated fibroblasts. At late passage, equal amounts of both collagen types are produced by both cell types. The Dupuytren's contracture-derived cell may be transitional, unstable in culture, and after sequential passage, revert back to a fibroblast appearance.

Although historically cell culture systems have proved valuable in identifying metabolic and genetic defects of a variety of clinical conditions, it is always important that one use caution in relating cell interpretation from *in vitro* to the *in vivo* pathologic situations. Research related to Dupuytren's contracture has aptly demonstrated the value of tissue culture in studying the pathogenesis of this disease. Delbruck and Schroder⁷ showed that cultured fibroblasts from Dupuytren's contracture have higher incorporation rates of labelled precursors

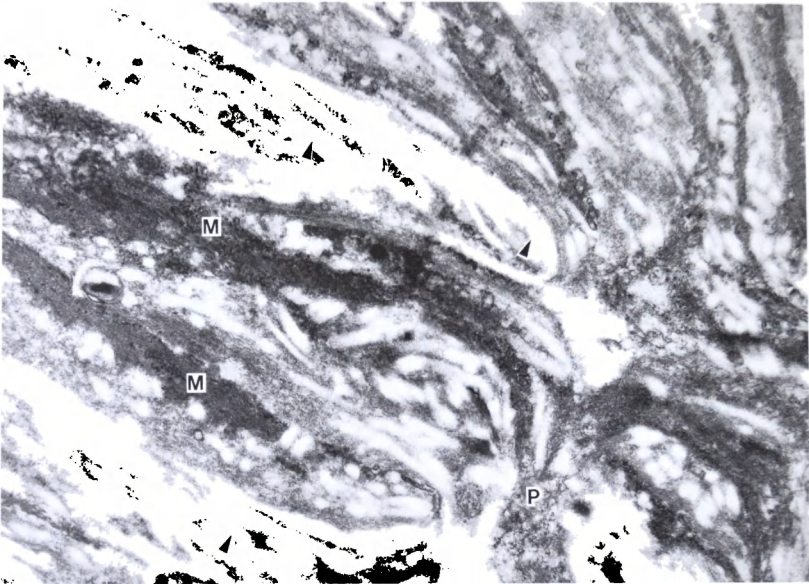


Figure 6. Approaching the polar region (P), the compact nature of the nodule is demonstrated among myofibroblasts (M) and collagen fibers (arrows). Note apparent dissolution of cellular integrity (magnification $\times 31,875$).

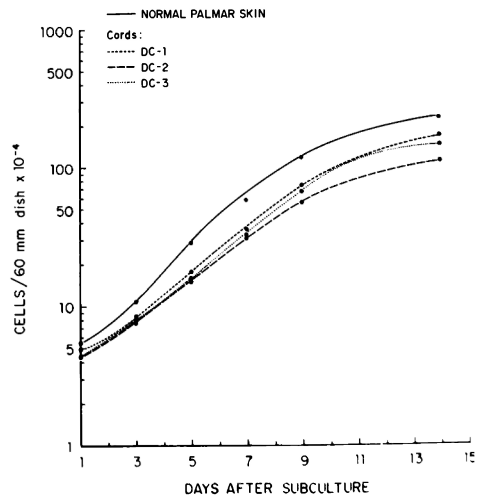


Figure 7. Growth curve data comparing rate of population growth at passage 5 between cultured fibroblasts from cord explants and normal palmar skin. The rate of growth of all cord fibroblasts was significantly slower than control cells. Each point represents the average count from three replicate dishes. (From Vande Berg J, Gelberman R, Rudolph R, et al: Dupuytren's contracture: Comparative growth dynamics and morphology between cultured myofibroblasts (nodule) and fibroblasts (cord). *J Orthop Res* 2:247, 1984; with permission.)

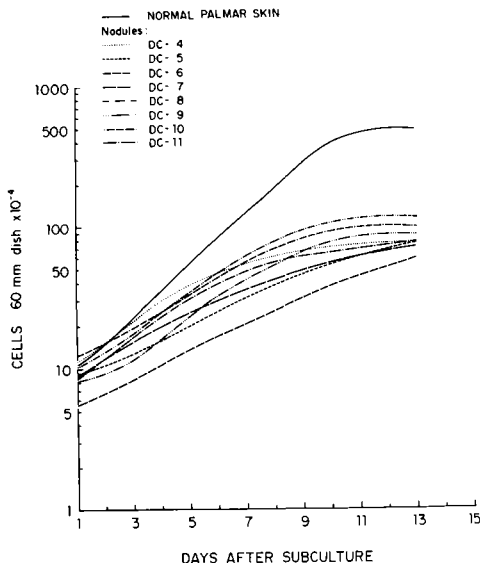


Figure 8. Growth curve data comparing rate of population at passage 5 between cultured myofibroblasts from eight nodule explants and fibroblasts from normal palmar skin. The rate of growth of all nodule myofibroblast populations was varied, but significantly slower than either cord fibroblasts and control fibroblasts. Each point represents the average count from three duplicate dishes. (From Vande Berg J, Gelberman R, Rudolph R, et al: Dupuytren's contracture: Comparative growth dynamics and morphology between cultured myofibroblasts (nodule) and fibroblasts (cord). *J Orthop Res* 2:247, 1984; with permission.)

into glycosaminoglycan and collagen than do cells from normal palmar fascia. Their observations suggested that some abnormal metabolic characteristics of cells from diseased proliferating tissue could be cultivated from one generation to another. Additional significant findings of a genetic nature from cell cultures have been derived from the appearance of type III collagen in Dupuytren's contracture.^{5, 12}

MYOFIBROBLAST PHYSIOLOGY IN DUPUYTREN'S CONTRACTURE

Additional studies in other laboratories further elucidate the mechanism and the importance of the myofibroblast in Dupuytren's contracture. Badalamente, Stern, and Hurst³ studied the contractile mechanisms of the myofibroblasts. They noted that Dupuytren's contracture myofibroblasts contain an intracellular contractile mechanism that involves the dephosphorylation of adenosine triphosphate. Calcium adenosine triphosphatase (ATPase) studies verified that the site of this energy system was on the microfilaments of the myofibroblasts. The degree of ATPase activity correlated with the residual contracture noted clinically. Alcian

blue staining and electron microscopy showed that the myofibroblasts were connected to each other and to surrounding collagen by a glycosaminoglycan matrix 300 to 1000 angstroms thick. Badalamente and associates theorized that this connection of myofibroblasts to each other and to the surrounding collagen may be partly responsible for the residual clinical deformities seen in Dupuytren's contracture.

Further immunofluorescent studies on the nodular matrix by Merlo and associates²¹ demonstrated fibrin, fibrinogen, and decreased levels of fibrolytic activity (compared with uninvolved and cord aponeurosis) in the small nodules during the proliferative stage of the disease. They suggested that nodular growth seemed to occur by progressive adhesion of fibroblasts to polymerizing fibrin. According to Hynes¹⁸ the adhesive capability of fibroblasts is probably via fibronectin to fibrin and collagen type III. As nodular growth increased, there was an increase in fibrinolytic activity that Merlo et al²¹ considered a biochemical signal for fibroblast modulation to myofibroblasts during the involutinal stage.

Tomasek and associates³¹ studied the cytoskeleton and extracellular matrix of myofibroblasts from Dupuytren's contracture nodules

using indirect immunofluorescence. The antibodies were directed at various intracellular components, including smooth muscle myosin, nonmuscle myosin, laminin, and fibronectin. Laminin is an intracellular glycoprotein that is involved in cell-matrix attachment in smooth muscle, whereas fibronectin plays a similar role in nonmuscle fibroblastic cells. In this study, the Dupuytren's contracture nodule cells stained for nonmuscle myosin and fibronectin but not for smooth muscle myosin or laminin. These data confirmed the theory that myofibroblasts in Dupuytren's contracture are not derived from muscle but rather are fibroblasts. Fibronectin between nodular cells was greatly increased over that between fibroblasts of normal palmar fascia. Tomasek and associates concluded that the contractile cell type of Dupuytren's contracture nodule is not a muscle-type cell.

Tomasek, Schultz, and Haaksma³² studied, using electron microscopy, the extracellular filamentous material at the surface of the contractile fibroblasts. These extracellular fibrils were closely associated with intracellular bundles of active microfilaments. Thus, the contractile cytoskeleton would be brought in contact with surrounding tissue matrix. Badalamente, Hurst, and Sampson² studied the effect of prostaglandins on myofibroblast contractility in Dupuytren's disease. They noted an increased content using radioimmunoassay of prostaglandins PGE₂ and PGF₂, on Dupuytren's contracture palmar fascia.

Skalli et al²⁹ found that myofibroblasts in Dupuytren's contracture stain positive for the α -smooth muscle actin isoform and for desmin, confirming histologic features of contraction. These continuing studies are contributing to our knowledge of the contractile fibroblasts that must be the active force in Dupuytren's contracture.

PASSIVE VERSUS ACTIVE CONTRACTURE

Having discussed the function of contractile fibroblasts in producing Dupuytren's contracture, it is important to note that not all contracture is due to the contractile function of fibroblasts. "Contracture" is a clinical term

indicating a deformity resulting from tissue contraction, or a fixed, rigid deformity in an abnormal position. Contracture can result from prolonged position rather than from active contraction of tissue, a process we have called "passive contracture."²⁸ This phenomenon was studied using a rabbit model. In the same subjects, granulating, contracting wounds were established on the back and at the same time prolonged flexion was produced at the knee. Tissues were subsequently studied and myofibroblasts sought. As is typical of the skin in actively contracting wounds, myofibroblasts were present in the granulating wounds; however, in the knee contractures produced by position, myofibroblasts were absent. These data suggested that fixed-joint deformities can produce contracture via remodeling of collagen without the need for active cellular contractile processes.

Both "passive contracture" and "active contracture" can be seen in Dupuytren's contracture. The palmar fascia obviously undergoes an active contractile process that can be observed clinically. The fixed-joint deformities produced by prolonged Dupuytren's contracture at the metacarpophalangeal joint, and particularly the proximal interphalangeal joint, may be the result of collagen reorganization in an abnormal, flexed position rather than of actively contracting cells in these joint areas.

PEYRONIE'S DISEASE RESEARCH

Historically, a number of clinical studies have shown that approximately 10% of patients with Dupuytren's contracture also have Peyronie's disease.³⁰ The latter condition appears to start as a vasculitis in a connective tissue layer between the tunica albuginea and the corpora cavernosa in the penis. Fibrosis results in this area's adjacent connective tissues, developing into fibrotic plaques with calcification^{19, 34, 35} in some instances. The two diseases differ histopathologically in that Dupuytren's contracture is believed to originate as a noninflammatory process whereas Peyronie's disease has an inflammatory component with a lymphocytic and plasmaeytic infiltrate into the affected connective tissue.^{19, 34} Smith³⁰ noted that this inflam-

matory infiltrate was predominant in lesions of short duration (less than 3 months). Lesions that existed longer showed a greater fibrous component and less inflammatory infiltrate.

In Peyronie's disease, the presence of myofibroblasts has been questioned. Electron microscopic studies by Ariyan and associates¹ indicated the presence of myofibroblasts in fibrotic plaques, whereas a later study by Vande Berg and associates³⁴ did not observe myofibroblasts in 20 patients. In a continuing study by the same research group, myofibroblasts were observed. This discrepancy probably can be explained by the small sample size and the thin tissue sectioning requirements for examination by electron microscopy. If myofibroblasts are to be found in penile fibrotic plaques, their numbers are probably fewer than in nodules in aponeurosis of Dupuytren's contracture. In view of the new attention to fetal wound repair, where fetal wounds high in hyaluronic acid heal without contracture or scar formation, it is interesting to note that the plaque formation site is also high in hyaluronic acid.³⁰

CLINICAL SIGNIFICANCE

Because research in myofibroblasts in Dupuytren's contracture has concentrated on human studies, it is possible to draw a number of clinical correlations with that research.

Recurrence Rate

At least 20 years ago, it was noted by Hueston^{15, 16} that even with complete removal of the palmar fascia and abnormal tissue, recurrence of Dupuytren's contracture is common in patients if the original surgery occurred during the proliferative phase of disease. Although it is not possible to predict the extent of disease, our studies and those of others have nevertheless indicated a higher rate of recurrence if myofibroblasts are present in the nodules of Dupuytren's contracture. Thus, in a difficult setting, predictive value might be found in studying such tissues with electron microscopy.

The presence of myofibroblasts at the interface of nodules and overlying adherent skin suggests that such skin should be excised to

remove all the contractile tissue. This would leave an open wound due to skin loss that could be treated either by the open technique or by full thickness skin grafting.

Open Technique

The myofibroblast hypothesis helps to explain the success of the "open technique" in treating Dupuytren's contracture. This involves opening of wounds and allowing them to heal secondarily, which has been reported to lead to good success in some settings. Normally the creating of an open wound, if anything, would be expected to lead to more contraction and tissue shrinkage; however, in the open wound technique, it would appear that the contracted skin is unfurled by the contraction process, thus using the surface wound contraction process for benefit. In Dupuytren's contracture, when the skin is crinkled up by the contraction process, it is not in short supply but simply in the wrong place, and the open technique allows this skin to be redistributed.

Full Thickness Skin Graft Effect

Experimental findings about the effect of full thickness grafts on contracting cutaneous wounds help to explain the inhibitory effects of full thickness grafting on Dupuytren's contracture recurrence. Full thickness grafts cause the myofibroblast population to decrease rapidly.²⁷ Application of a full thickness skin graft to a palmar wound bed that would be prone to develop recurrent contraction may inhibit that contraction process.

SUMMARY

Dupuytren's contracture nodules, but not cords, contain myofibroblasts. These cells, which combine many electron microscopic, physiologic, and immunohistochemical characteristics of fibroblasts and smooth muscle cells, are probably the active force of contraction. Prominent myofibroblasts and intracellular microtubules correlate with increased likelihood of clinical recurrence after surgery. Tissue culture of cells derived from Dupuytren's contracture myofibroblasts show consistently slower cell replication than from fibroblasts and show persistence of electron microscopic characteristics in early passages.

Research in Dupuytren's contracture myofibroblasts has been done on human tissue and so has clinical correlation. Myofibroblast presence may help to predict recurrence of disease and suggests that palmar skin should be excised when adherent to disease nodules. The theory of myofibroblasts helps explain why the open technique often succeeds, and why full thickness skin grafts inhibit recurrent contracture.

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Comment on "The Myofibroblast in Dupuytren's Contracture"

This valuable article presents a clear exposition of the excellent work produced in the past decade by the San Diego group, where fortunately we have the combination of an intelligent, inquisitive surgeon able to work closely with an imaginative and inventive investigator.

After the simplification of approach to the fibroblast in the previous article, the surgeon will sense the emergence of the desire for clinical application of the results and will not be disappointed.

The grouping of all Dupuytren's contracture manifestations as "a similar contraction problem" introduces the need to consider first whether contraction actually occurs in plantar lesions, or even in Peyronie's disease where fixation by the inextensible plaque leads to deformity on erection but not in flaccidity. Finally, one must reconcile the difference between the obvious longitudinal shortening that occurs with a dorsal digital plaque *between* the IP joints, but not with knuckle pads directly *overlying* IP or MP joints. One is led to ask whether a spectrum of contractility exists in hyperplastic nodules in different situations or whether the external application of physical forces can inhibit contraction; e.g., a far greater mechanical advantage acting in flexion of the IP joints to prevent knuckle pads from contracting, whereas between the IP joints this external force is very small indeed. With the flexed palm there is less physical opposition to contraction, but this hypothesis can scarcely be supported in Peyronie's disease! The difference in myofibroblast populations may account for this spectrum of contraction in ectopic deposits.

The authors' excellent introduction ends with the question whether myofibroblasts initiate contraction or not, and if not, then is it by

simple "active" fibroblasts? It is not irrelevant here that Murrell's colleague at Oxford, MJO Francis, claims that most cultured fibroblasts show some myofibroblast features.

Aggregation of fibroblasts under as yet incompletely determined stimuli leads to a concentration of these energy sources and hence to greater force for contraction. The waxing and waning of myofibroblast populations in areas of contraction and cord formation confirm again that they are not a specific "Dupuytren's cell" nor even the most active, but merely the most spectacular morphologic elements in wounds and in Dupuytren's nodules.

To an account of their own contributions, the authors have added a comprehensive survey of other recent relevant investigations, along with comments far more enlightened than I can offer. But it is the surgical implications of this whole review of myofibroblast research that are of the most practical interest.

It is relevant here that Murrell and Francis at Oxford, and even Gabbiani, claim that most cultured fibroblasts show some myofibroblastic features.

Recurrence rate after fasciectomy is related to fibroblast activity at the time of surgery. The presence of similar activity in palmar skin adherent to nodules is regarded here as a reason for its excision along with the nodule. This conclusion is rather too radical to accept freely because involution can occur clinically in infiltrated palmar skin when transplanted elsewhere in the body or in cases of mild to low diathesis if the longitudinal stress is lessened by a Z plasty or graft interpolation. It is a clinical rather than a histologic decision whether to proceed to dermofasciectomy, the diathesis dictates this.

Likewise, the leaving open of defects after

actual skin excision must be discommended, yet this forthright proposing of the practical significance of dermal involvement is the essence of future Dupuytren's research. What potential for contraction does dermal involvement carry in fact? If it can be seen to resolve in some changed physical situations clinically, what factors have been changed that have altered the pattern of cellular fibroblastic behavior?

One has observed clinical regression, involution with softening, of active Dupuytren's tissue when (1) an area of skin has been changed over a palmar plaque left in situ and (2) beneath

skin grafts in digits where extirpation of all visible Dupuytren's disease (always recurrent) would have endangered nerve continuity or extensively exposed flexor tendons. What valor there is in such discretion has not only preserved these digits but raised again the question for investigators of controlling Dupuytren's disease by changing its cellular and physical milieu.

These questions, and that of how recurrence is prevented by changing the skin over the fasciectomy wound, may soon be answered by further studies such as this article so elegantly proffers.

JOHN T. HUESTON, MD

Guest Editor