

A Histological and Anatomical Profile of Pacinian Corpuscles from Dupuytren's Contracture and the Expression of Nerve Growth Factor Receptor

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The etiology of Dupuytren's disease is unknown. The causes of the fibroplastic response of nodules, fibrosis of cords, and prominence of pacinian corpuscles are not evident. Histological and immunohistology differences in pacinian corpuscles from the hands of five patients with Dupuytren's disease compared with 17 Dupuytren's-free patients are presented. Histological sections of pacinian corpuscle specimens were stained with hematoxylin and eosin and immunostained for nerve growth factor receptor. The length and width of intact pacinian corpuscles were measured, and the number of layers within each corpuscle was counted and recorded. Grossly, the pacinian corpuscles from Dupuytren's patients were larger and more numerous compared with those from unaffected patients. When measured microscopically, the pacinian corpuscles from Dupuytren's diseased fascia were significantly larger (2.0×1.1 mm) compared with controls (1.5×0.78 mm). The pacinian corpuscles from Dupuytren's-affected patients had significantly more layers (64 ± 14) compared with those from control patients (40 ± 9). Nerve growth factor receptor staining of pacinian corpuscles from patients affected with Dupuytren's disease showed greater intensity and more area stained compared with unaffected controls. It is suggested that nerve growth factor may be involved in the increased size of pacinian corpuscles in Dupuytren's-affected fascia. It is proposed that the cellular outgrowth from pacinian corpuscles may generate the cells that develop into Dupuytren's nodules. (*Plast. Reconstr. Surg.* 114: 721, 2004.)

Dupuytren's contracture is a palmar fibromatosis characterized as a progressive flexion deformity of the fingers.^{1,2} In a northeast Scotland hospital, 200 random patients over the age of 60 years were selected and studied. The report states that 21 percent of the women and

39 percent of the men are afflicted with the disease.³ A greater proportion of people of Celtic origins have Dupuytren's disease. The estimate in Australia is that 40 percent of men over the age of 60 years have the disease. The exact cause of the disease is unknown, but there appear to be both traumatic and inherited components to acquiring the lesion.

Fibromatosis of the palmar fascia is a bothersome fibrotic lesion. The disease is characterized by irregular or nodular thickening in the palmar fascia either unilaterally or bilaterally. The attachment of the inflamed palmar fascia to the overlying skin gradually causes puckering and dimpling of the skin over the tendon. At the same time a slowly progressive flexion contraction develops, mainly involving the fourth and fifth fingers. The disease is progressive and usually involves the metacarpophalangeal and proximal interphalangeal joints.^{4,5} Progressive scarring and shortening of the palmar and digital fascia cause the deformity in the absence of a deformity to the tendon. There are two definable fibrotic anatomical features of the lesion, the nodule and the cord. It is proposed that the nodules represent an early stage of the disease process, whereas the cords represent a later stage. A number of theories have been proposed to explain the cause of the disease. McFarlane⁶ proposed that nodules and cords are derived from the palmar fascia. Murrell and Hueston⁷ proposed that a

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local allergic response results in the de novo appearance of nodules. Saar and Grothaus⁴ theorized that age, genetics, and environmental factors contribute to microvessel narrowing. The reduced blood flow results in localized ischemia and the release of superoxide free radicals, which stimulate fibroblast proliferation that lead to fibromatosis. A large comprehensive study shows blood vessel abnormalities are common in the disease process with leakage and the accumulation of hemosiderin.⁸ Despite the numerous theories for Dupuytren's pathogenesis, there is agreement with Luck's classification of the disease process into proliferative, involutionary, and residual stages.⁹ Fibroblast proliferation distinguishes the initial stage of the disease when a palpable palmar nodule characterizes this stage of the disease process. The histological features of the nodule are well-vascularized, cell-rich tissues replete with fibroblasts. The involutionary stage follows the proliferative stage, where the fibroblasts are sedentary and oriented along the lines of tension in a developing cord. In the residual stage of the disease, the cord matures with a collagen-rich matrix having a modest cell density.

The nodule and the cord are clearly identifiable in the lesion.^{5,9,10} The nodule, a highly vascularized tissue, contains a dense population of myofibroblasts.^{1,5,11,12} Myofibroblasts are specialized fibroblasts, identified by their expression of the α smooth muscle actin isoform of actin within cytoplasmic stress fibers.¹³ In contrast, the cord is relatively avascular, acellular, and devoid of myofibroblasts but enriched in collagen. There are numerous proposals of how cords develop. One idea is that over time nodules develop into the cords.¹⁴ This implies that the nodule myofibroblast phenotype changes into cord fibroblast phenotype. Another idea is that the two structures represent different stages of the disease and arise independently.¹⁵ It has been proposed that the nodule cell type and the cord cell type are derived from two separate precursor cells.

A less examined feature of the fibrotic lesion is the pacinian corpuscle.¹⁶ It is reported that the pacinian corpuscles from diseased fascia show edema.⁸ The mechanism for the enlargement and change in the structure of the pacinian corpuscle is unknown. The pacinian corpuscle is the largest nerve receptor found in the skin (0.5×1.0 mm) and is visible to the naked eye. It has a globular structure of multi-

ple layers, like an onion, and is found in various tissues that include the subcutaneous layer of both glabrous and hairy skin, the external genitalia, and mammary glands. The receptive field of pacinian corpuscles is large. This receptor is very quick to adapt to displacement of the skin; making it specialized for the reception of high-frequency touch or vibration. When the corpuscle is moved relative to the axon, the membrane depolarizes. Ion channels are opened by the mechanical displacement of long carbohydrate chains that are anchored to protein filaments that in turn attach to the membrane beneath the channels. The layered structure of the corpuscle renders it briefly responsive to both the bending and release of the organ. The pacinian corpuscle does not detect steady pressure.

Here the investigation of pacinian corpuscle focuses upon documenting morphological differences between pacinian corpuscle isolated from Dupuytren's lesions and from palmar fascia from Dupuytren's-free patients. Comparative differences will be documented in the size, number of layers, and presence of the high-affinity nerve growth factor receptor p75 on the surface of cells found in the outer capsule of pacinian corpuscle.¹⁷ Nerve growth factor promotes fibroblast proliferation and migrations.¹⁸ This study compares the proliferative and migration responses to nerve growth factor of cultured fibroblasts derived from Dupuytren's nodules and cords.

METHODS

The pacinian corpuscles were isolated from the palmar fascia of 22 patients undergoing various surgical procedures by a tissue protocol approved by the Milton S. Hershey Medical Center Human Study Review Committee. Tissue was collected from five patients (one woman) affected with Dupuytren's disease whose average age was 68 ± 3 years and from 17 other patients (seven women) whose average age was 61 ± 11 years who underwent surgery for conditions unrelated to Dupuytren's disease. Specimens were fixed in 10% phosphate buffered formaldehyde, embedded in paraffin, cut into $5\text{-}\mu\text{m}$ -thick sections, and stained. All tissues processed for histological evaluation were stained with hematoxylin and eosin. Using a microscope equipped with a ruler scale within an ocular, the length and width of pacinian corpuscles within sections through the center of the cor-

puscle were measured and recorded. The number of layers within each corpuscle was also counted and recorded.

The presence of nerve growth factor receptor p75 has been reported on cells within pacinian corpuscle.¹⁸ After the immunostaining protocol previously described,¹⁹ six paraffin sections were processed for the presence of nerve growth factor receptor p75 using a monoclonal antibody (clone NGFR5; NeoMarkers, Fremont, Calif.).

Dupuytren's fibroblast primary cell lines were developed from discarded surgical tissue as previously described.^{20,21} Human recombinant nerve growth factor was purchased from R&D Systems (Minneapolis, Minn.). To document the effects of nerve growth factor on nodule-derived fibroblasts or cord-derived fibroblast cell proliferation, either 100,000 nodule-derived fibroblasts or 100,000 cord-derived fibroblast cells were plated in 16-mm wells of a 24-well dish. Cells were allowed to attach for 6 hours, at which time the medium was replaced with complete Dulbecco's modification of Eagle medium supplemented with 10% fetal bovine serum and 10 μ g/ml gentamicin, containing either 0.01 ml of phosphate-buffered saline, 10 ng/ml of nerve growth factor or 10 pg/ml nerve growth factor. The cells were incubated for 24 hours, the cell layers were rinsed with phosphate-buffered saline, the cells were released by trypsinization, and the cell number was determined with a Coulter counter. To measure possible differences in cell migration in response to nerve growth factor, four cell-cloning towers, each with a 5-mm inner diameter (Bellco Glass, Vineland, N.J.), were placed evenly apart in 35-mm tissue culture dishes. Either 6000 nodule-derived fibroblasts or 6000 cord-derived fibroblasts contained in 0.2 ml of complete Dulbecco's modification of Eagle medium were placed into each cloning tower. For 6 hours the cells were incubated in cloning towers to allow their attachment to the surface of the dish. The towers were carefully removed and the culture medium replaced with 1 ml of fresh test medium. There were three treatment groups containing two dishes each, for a total of eight measurements of cell migration per treatment group. The treatment groups were 0.01 ml of phosphate-buffered saline, 10 ng/ml of nerve growth factor, or 10 pg/ml of nerve growth factor in complete Dulbecco's modification of Eagle medium. After 2 days, the medium was

TABLE I
Experimental Design: Histology

	Hematoxylin and Eosin Stained (<i>n</i>)	Nerve Growth Factor Receptor Stained (<i>n</i>)
Dupuytren's patients	5	3
Normal patients	17	3

removed, the cells were rinsed in phosphate-buffered saline, and the cells were fixed and stained with Hema 3 kits (Fisher Scientific, Pittsburgh, Pa.). Using a dissection microscope with a ruler scale contained in one of the oculars, the diameter of each circular outgrowth of cells was measured and the area was calculated and recorded.

The experimental design is shown in Tables I and II. Statistical significance between treatment groups was $p \leq 0.05$, which was determined by the *t* test.

RESULTS

Grossly the pacinian corpuscles from Dupuytren's patients were larger and were more numerous compared with pacinian corpuscles from unaffected patients (Fig. 1). When their length and width were microscopically measured and multiplied (mean \pm SD), the pacinian corpuscles from Dupuytren's diseased fascia were statistically larger (2.6 ± 0.4 mm²) compared with those from non-Dupuytren's disease fascia (1.0 ± 0.5 mm²) ($p \geq 0.001$). The pacinian corpuscles from Dupuytren's-affected fascia had significantly more layers (64 ± 14) compared with those from controls (40 ± 9) ($p \leq 0.01$).

The immunostaining of pacinian corpuscles from the fascia of patients affected with Dupuytren's disease showed the presence of nerve growth factor p75 receptors. Previous reports showed the pacinian corpuscles from the fascia of patients without Dupuytren's disease expressed nerve growth factor receptors p75.¹⁸ The cells within the outer capsule of the pacinian corpuscles from the fascia of Dupuytren's fascia were strongly positive for nerve growth factor receptor on their surface (Fig. 2). Most

TABLE II
Experimental Design: Cell Culture Study

	Cell Proliferation (<i>n</i>)	Cell Migration (<i>n</i>)
Nodules cell dishes	3	3
Cord cell dishes	3	3

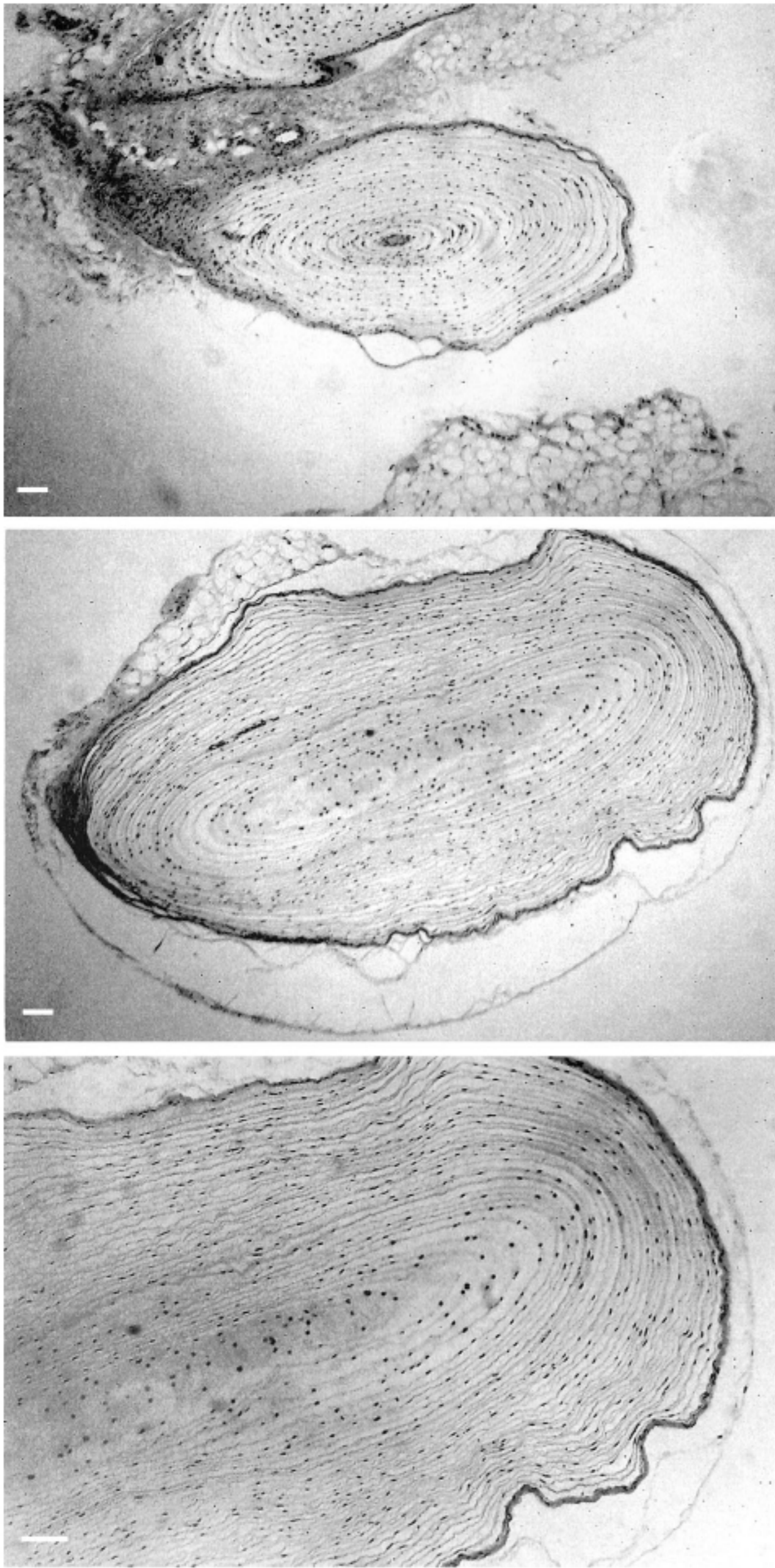


FIG. 1. Hematoxylin and eosin-stained sections through the center portion of pacinian corpuscles from patients with and without Dupuytren's disease. (*Above*) A pacinian corpuscle specimen taken from a patient free of Dupuytren's disease, showing the typical layer structure of the outer capsule of the pacinian corpuscle. (*Center*) A pacinian corpuscle from a Dupuytren's lesion, showing a greater size and more numerous layer structures within the outer capsule of the pacinian corpuscle. (*Below*) A higher-power view of the layers within the outer capsule of a pacinian corpuscle from a Dupuytren's lesion. The white bar in each panel represents 100 μm .

cells within the outer capsule from the pacinian corpuscles of fascia from patients free of Dupuytren's disease also expressed nerve growth factor receptor on their surface. The stain intensity of the outer cells of pacinian

corpuscles from the fascia of Dupuytren's patients was greater and a larger area was stained compared with unaffected controls.

A significant increase in cell proliferation was noted with nodule-derived fibroblast cells treated with 10 ng/ml of nerve growth factor compared with saline-treated nodule-derived fibroblast cells. These findings, summarized in Table III, showed nerve growth factor stimulated the proliferation of nodule-derived fibroblast cells about 18 percent. However, added nerve growth factor at 10 ng/ml did not stimulate the proliferation of cord-derived fibroblast cells. Table IV summarizes the cell migration studies. Untreated nodule-derived fibroblast cells demonstrated greater cell migration capability compared with cord-derived fibroblast cells. Nodule-derived fibroblast cells migrated

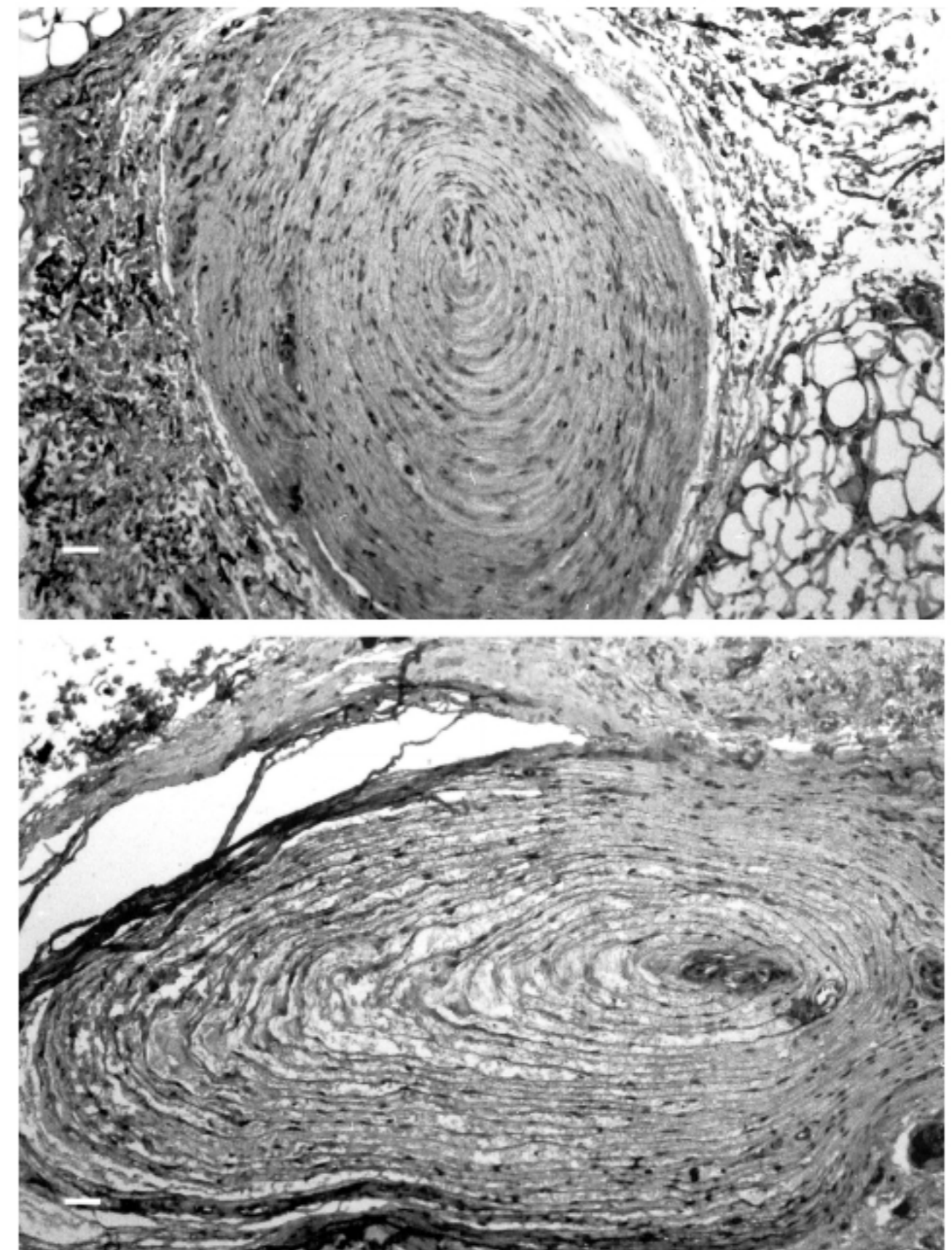


FIG. 2. Immunohistology of the expression of nerve growth factor receptor within pacinian corpuscle from patients with and without Dupuytren's disease. (*Above*) A pacinian corpuscle from a patient free of Dupuytren's lesions, showing the expression of nerve growth factor receptor restricted to the outer layer of the pacinian corpuscle capsule. (*Below*) A pacinian corpuscle from a patient with a Dupuytren's lesion, showing the more intense staining of nerve growth factor receptor in the more numerous outer layers of the pacinian corpuscle capsule. The white bar in each panel is 160 μm .

TABLE III
Nerve Growth Factor's Effect on Fibroblast Proliferation Cell Number

Fibroblast Type	Saline Treated	10 ng/ml Nerve Growth Factor	<i>p</i>
Nodule-derived			
Exp 1	15,147 ± 2,917 (<i>n</i> = 14)	19,514 ± 3,880 (<i>n</i> = 14)	≤0.002
Exp 2	16,920 ± 3,431 (<i>n</i> = 14)	19,314 ± 1,800 (<i>n</i> = 14)	≤0.03
Cord-derived			
Exp 1	7,679 ± 2,678 (<i>n</i> = 15)	6,867 ± 1,319 (<i>n</i> = 15)	Not significant
Exp 2	5,222 ± 457 (<i>n</i> = 15)	5,006 ± 924 (<i>n</i> = 15)	Not significant

out to cover an area of $53.2 \pm 7.3 \text{ mm}^2$, whereas cord-derived fibroblast cell covered an area of $46.2 \pm 7.4 \text{ mm}^2$, an increase of approximately 12 percent. With added nerve growth factor at 10 pg/ml, the migration of nodule-derived fibroblast cells was significantly enhanced (67.1 mm^2 compared with saline-treated nodule-derived fibroblast cells, 53.2 mm^2) (Table IV). When nerve growth factor was added at 10 ng/ml, there were no differences between treated and untreated nodule-derived fibroblast or cord-derived fibroblast cell migration (Table IV). At concentrations of nerve growth factor 10 pg/ml and 10 ng/ml, cord-derived fibroblast cells migration was the same. Cord-derived fibroblast cells were unresponsive to added nerve growth factor at all concentrations tested.

DISCUSSION

Are pacinian corpuscles involved in the development of Dupuytren's disease fibrosis? Palmar fascia affected with Dupuytren's disease fibrosis has larger pacinian corpuscles. Because of their greater size, the outer capsule of pacinian corpuscles from Dupuytren's diseased fascia has a greater number of cell layers compared with pacinian corpuscles from the fascia of unaffected patients. It has been reported that cells making up the outer capsule of the pacinian corpuscle from normal fascia express the high-affinity nerve growth factor receptor, p75.¹⁷ The outer capsule of pacinian corpuscles from the fascia of patients afflicted with Dupuytren's disease also expresses nerve

growth factor receptor p75. As the pacinian corpuscles associated with the Dupuytren's lesion are greater in size, there is an increase in the number of cells expressing nerve growth factor p75 receptor. It is noted that the staining of nerve growth factor receptors appearing in the cells making up the outer capsule of the pacinian corpuscles within Dupuytren's lesions is more intense. It appears that more cells from Dupuytren's diseased pacinian corpuscles express nerve growth factor receptor on their surfaces and therefore a greater number of cells are responsive to nerve growth factor compared with cells in normal pacinian corpuscles.

Does nerve growth factor play a role in the Dupuytren's disease process? From in vitro studies, nerve growth factor at picogram concentrations promotes nodule-derived fibroblast migration but nodule-derived fibroblasts are not responsive at ng concentrations. Nerve growth factor at all concentrations tested had no effect upon cord-derived fibroblasts. At nanogram concentrations, nerve growth factor promotes nodule-derived fibroblast proliferation, but cord-derived fibroblasts were unresponsive to added nerve growth factor. It suggests that at low concentrations nerve growth factor promotes nodule-derived fibroblast migration, but at higher concentrations nerve growth factor promotes nodule-derived fibroblast division. Hence, differences in nodule-derived fibroblast behavior can be influenced by the concentration of a growth factor related to nerve tissue. With regard to cord-derived fibroblasts, nerve growth factor had no activity

TABLE IV
Nerve Growth Factor's Effect on Fibroblast Migration Area of Cells

Cell Origin	Nerve Growth Factor		
	10 ng/ml	10 pg/ml	Saline
Nodule-derived	$56.1 \pm 9.3 \text{ mm}^2$ (<i>n</i> = 12)	$67.1 \pm 20.1 \text{ mm}^2$ (<i>n</i> = 12)	$53.2 \pm 7.3 \text{ mm}^2$ (<i>n</i> = 12)
Cord-derived	$52.0 \pm 10.6 \text{ mm}^2$ (<i>n</i> = 12)	$49.5 \pm 12.8 \text{ mm}^2$ (<i>n</i> = 12)	$46.2 \pm 7.4 \text{ mm}^2$ (<i>n</i> = 12)

* Significantly different from saline treated cells $p \leq 0.01$.

in changing the rate of either cell migration or cell proliferation.

The outer and inner capsules of pacinian corpuscles have distinct characteristics. As an example, type II collagen is expressed by outer capsule cells but not by inner capsule cells. Cells residing within the inner capsule, however, deposit type V collagen although cells from the outer capsule do not.²² A role for type II collagen in the outer capsule may be related to the robust character of the pacinian corpuscle and the pacinian corpuscle's resistance to collapsing by crushing pressure. There are also differences in the makeup of proteoglycans between the inner and outer capsules.²³ Based on their appearance and protein synthesis products, the outer capsule cells of pacinian corpuscles have fibroblast-like characteristics. Dupuytren's nodules and cords show differences in cytoskeletal proteins, cell-surface receptors, and connective tissue components. The cell makeup of Dupuytren's nodule exhibits a chronic inflammation character, in which the macrophage is the major inflammatory cell type.²⁴ Macrophages are also identified within the outer capsule of pacinian corpuscles.²⁵ Injury to the pacinian corpuscle may cause the accumulation of macrophages within the pacinian corpuscle. The macrophage has many functions in fibrosis including synthesizing and releasing a number of growth factors involved in fibrosis. Dupuytren's nodule-derived fibroblast cells respond to numerous growth factors.^{24,26} Macrophages may play a role in advancing pacinian corpuscle fibroblast progression from pacinian corpuscle outer capsule cells into forming Dupuytren's nodules. Both the growth factor concentrations and the number of some growth factor receptors are elevated in the nodules of Dupuytren's disease.²⁷ There are reports of alterations in the connective tissue protein makeup within Dupuytren's nodules and cords. The concentrations of type III, IV, and VI collagens are elevated in Dupuytren's nodules and cords.^{28,29,30}

We speculate that nerve growth factor released from macrophages may play a role in increasing the size of pacinian corpuscles in Dupuytren's-affected fascia. In addition, nerve growth factor has the capacity to stimulate fibroplasia and migration of fibroblasts derived from nodules, but not cells derived from cords. One possibility is that cells from the outer capsule of the pacinian corpuscles migrate away,

then proliferate, which leads to the formation of Dupuytren's nodules. Does Dupuytren's disease result from the migration and proliferation of pacinian corpuscles' outer capsule cells? One widely held idea is that Dupuytren's disease results from repeated trauma to the palm. That repetitive trauma may damage the pacinian corpuscles. In an attempt to repair that damage, nerve growth factor is released and accumulates. The local appearance of nerve growth factor may activate the fibroblast-like cells residing in the outer capsule of pacinian corpuscle. Nerve growth factor may promote the migration and proliferation of these fibroblast-like cells from the outer capsule of the pacinian corpuscle.

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