

The Pathogenesis of Dupuytren's Contracture

EXPERIMENTAL AND FURTHER CLINICAL OBSERVATIONS*

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In 1833 Dupuytren first described the contracture of the hand that has since borne his name. He believed the affliction to be caused by repeated trauma to the palm. From that time on a great deal was written concerning this disease and the idea that trauma is an etiological factor was either supported or condemned repeatedly.

In 1948 Skoog published an extensive monograph on Dupuytren's contracture. In this monumental work he incorporated a comprehensive description of the pathological changes in this disease, including the nodular hypercellular areas within the aponeurosis. He believed these cellular nodules to be the early stages of the disease. At the margins of these lesions he noted microscopic ruptures of the collagen fibers of the palmar fascia and hemosiderin deposits within the cellular areas. These, he believed, were evidence of previous small hemorrhages. Skoog concluded that Dupuytren's contracture began when microscopic ruptures of the collagen fibers of the fascia occurred.

In 1958 we (Larsen and Posch) reported our interpretation of the abnormal microscopic anatomy observed in sixty-one surgical specimens of Dupuytren's contracture (Series I). We too noted hemosiderin deposits present in the early stages of the contracture. We could not identify any areas that conclusively demonstrated rupture of the collagen fibers. Nevertheless, we felt that the presence of hemosiderin in the early lesions of Dupuytren's contracture was quite important and that this finding made the entire matter worthy of further study.

A method of attacking the problem experimentally was suggested to us by some unpublished work by Pedersen and Gardner of our institution. They scarified the plantar fascia of monkeys, examined it under the microscope, and noted a lesion histologically similar to Dupuytren's contracture.

To determine whether trauma could be an etiological factor in the production of Dupuytren's contracture, we studied additional surgical specimens handled in a special way and also investigated the effects of experimental trauma to the fascia of the hands and feet of monkeys.

CLINICAL INVESTIGATION

Method

Sixty-nine additional surgical specimens of Dupuytren's contracture were examined (Series II). After excision, each specimen was sutured to a piece of stiff white cardboard (Fig. 1) with several sutures placed in both the proximal and the distal ends of the specimen and tied with enough tension to restore and maintain the original length of the specimen during the process of fixation of the tissue. In this manner, curling, kinking, and overlapping of the tissues during the process of fixation were prevented. The areas where the contracture had

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seemed to be most pronounced on gross inspection were noted on an outline tracing of the entire specimen. After fixation, the specimens were removed from their cardboard backing. Long segments of the diseased portions of the fascia were cut from the whole specimen. These segments were then embedded in paraffin, sectioned in the sagittal plane (Fig. 2), and stained.

By preparing the tissues in this manner, we obtained long uninterrupted sections of fibrous tissue both proximal and distal to the nodules of hypercellular connective tissue. We thought such sections would enable us to determine whether the fibrous tissue in the regions of the cellular areas had been ruptured. In addition,



FIG. 1

Technique of mounting the entire surgical specimen on stiff cardboard before fixation in 10 per cent neutral formalin.

multiple sections through the cellular areas were studied in an effort to determine if a more complete histological study of these areas would show a higher incidence of hemosiderin deposit than we found in the specimens of Series I.

The tissue in this study was fixed with 10 per cent formalin buffered to pH7 with monosodium and disodium phosphate and stained with hematoxylin and eosin, Mallory's and Masson's connective-tissue stains, Verhoeff's elastic-tissue stain, and with toluidine blue to demonstrate metachromasia. Bennhold's Congo red method to demonstrate amyloid was also used⁷.

Findings

The contracted bands in the fascia were observed to be made up of relatively hypocellular collagenous tissue (Fig. 3). The cell nuclei in these areas were stained

very intensely; little or no nuclear detail was visible. The nuclei were fifteen to twenty times longer than they were broad and were widely separated by collagen fibers. These fibers stained intensely reddish orange with eosin. Some of the very dense areas had a reddish blue color in the hematoxylin and eosin preparations.

The cellular areas contained numerous immature nuclei of fibroblasts (Figs. 4 and 5). Some of these nuclei were round, but most were elliptical, their length being only about twice their breadth. A nucleolus and many fine granular strands

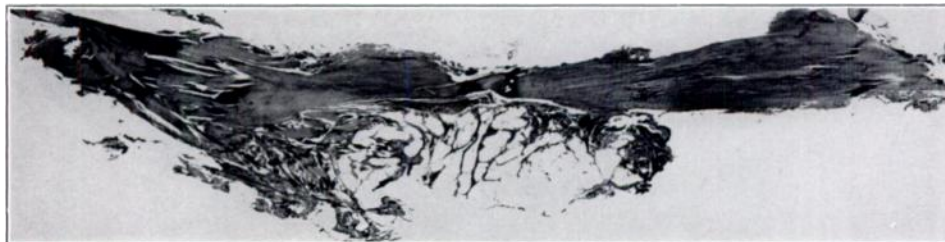


FIG. 2

A slide prepared by the method described in the text.

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FIG. 3

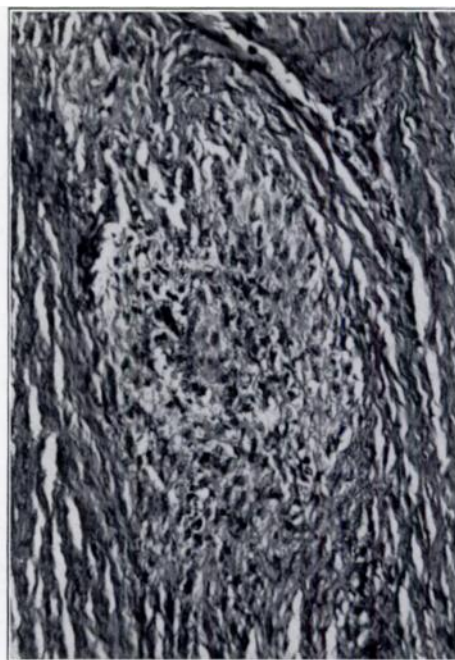


FIG. 4

Fig. 3: Photomicrograph of a dense contracted band of collagen tissue characteristic of the late or lamellar stage of Dupuytren's contracture (hematoxylin and eosin, $\times 135$).

Fig. 4: Photomicrograph of a nodule of proliferating fibrous tissue characteristic of the proliferative phase of Dupuytren's contracture (hematoxylin and eosin, $\times 180$).

were visible within each nucleus. The cellular margins in these areas were indistinct, and interspersed between the nuclei was a haphazard network of many fine fibers. The finest of these fibers stained a light lavender in hematoxylin and eosin preparations, whereas the slightly larger ones had a pale orange color.

The cellular areas were more or less nodular in shape but were not encapsulated. The fine fibers within these nodules could be seen to blend insensibly into the bundles of more mature collagenous tissue at the margins of the nodules. The dense mature collagen bands and the quite immature fibrous tissue of the nodules appeared to represent the two extremes of the disease between which

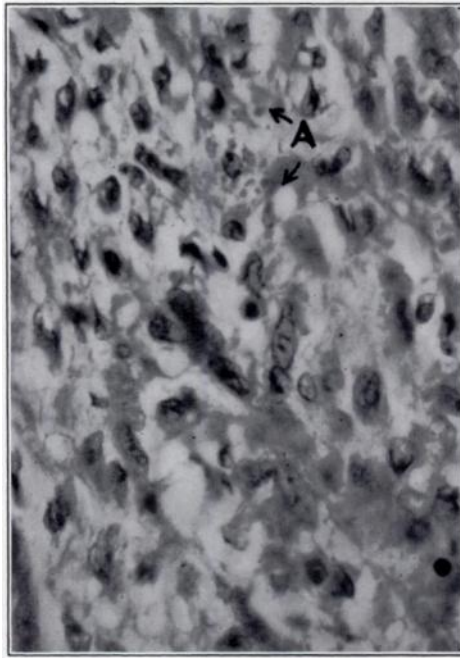


FIG. 5

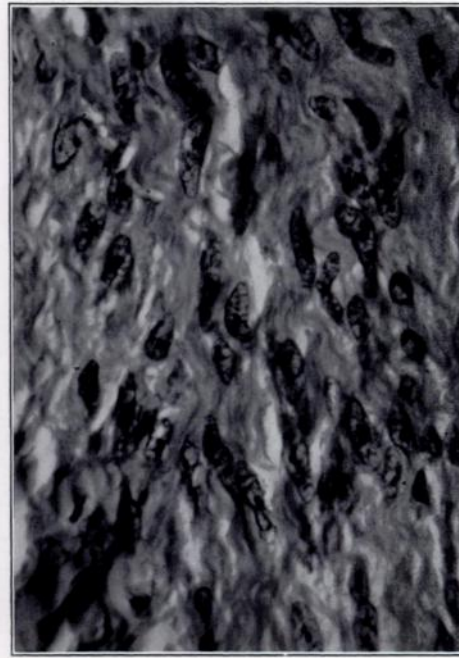


FIG. 6

Fig. 5: Photomicrograph shows the detail of the cellular and fibrous structure of the nodule shown in Fig. 4 (hematoxylin and eosin $\times 600$). The granules marked A are hemosiderin granules; note their small size at this magnification.

Fig. 6: Intermediate stage of Dupuytren's contracture. The fibers are thicker and the nuclei are more elongated than in Fig. 4 and are oriented in a single direction (hematoxylin and eosin, $\times 600$).

there were numerous intermediate stages (Fig. 6). The plump nuclei of the immature nodules tended to elongate as the collagenous fibers became thicker. At the same time the nuclei stained more intensely and became more widely separated by the collagen fibers, which stained orange or red-orange with eosin. As the tissues matured these fibers were more numerous and appeared to be thicker. Finally, the mature contracted scarlike stage was reached.

Masson's connective-tissue stain showed that the fine fiber network in the hypercellular nodules was made up of collagen fibers. The finest fibers did not take the green stain, but the fibers that were slightly larger than the very finest did. Verhoeff's elastic-tissue stain failed to demonstrate proliferation of new elastic tissue in these lesions.

Sections stained with toluidine blue showed metachromatic staining in the areas of proliferating tissue. Metachromatic staining was not present in the normal aponeurosis, nor did this reaction occur in the mature bands of the contracture. In the more advanced cellular stages of the contracture occasional areas of very pale pink metachromatic staining were noted. Bennhold's Congo red method failed to demonstrate amyloid in any areas of the normal palmar aponeurosis or in any stage of the contracture.

In the sixty-one specimens in Series I we were able to demonstrate iron pigment within the cellular nodules nine times. In the hematoxylin and eosin preparations, the iron pigment appeared as golden yellow or yellow-brown granules that stained blue with the Prussian-blue reaction. We looked carefully for hemosiderin in all sixty-nine specimens of palmar fascia in Series II; over 500 different areas were removed from the sixty-nine specimens for study, and serial sections made of several of the areas. In twenty-four of the sixty-nine specimens, only mature

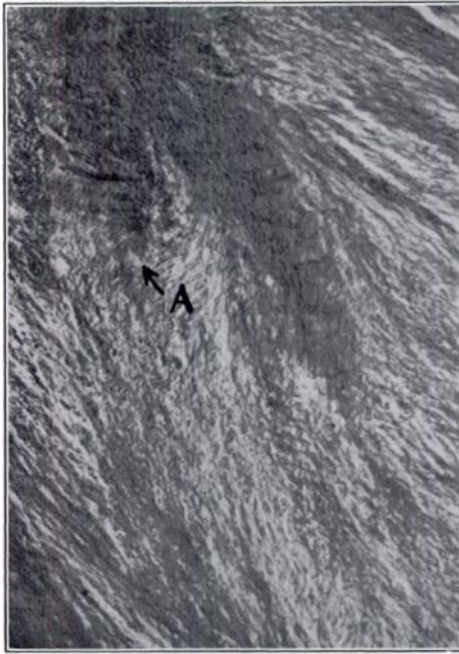


FIG. 7



FIG. 8

Fig. 7: Edge of a proliferating nodule of fibrous tissue showing abrupt termination of collagen fibers. The area opposite the arrow is shown in greater detail in Fig. 8 (Mallory's connective-tissue stain, $\times 180$).

Fig. 8: The area opposite the arrow in Fig. 7, $\times 1100$ (Mallory's connective-tissue stain).

contracted bands were found; however, the remaining forty-five specimens contained actively proliferating fibrous tissue in one or more areas. Nineteen of the forty-five contractures (42 per cent) that contained actively proliferating tissue had hemosiderin within the proliferating areas. Hemosiderin was found only in the most cellular stages of Dupuytren's contracture (Fig. 5); it was not found in the more advanced stages, nor was it found in the normal aponeurosis.

Skoog published photomicrographs illustrating the areas which he believed showed rupture of the aponeurosis. Tissues handled in the same manner as those in Series II provided long sections that were cut parallel to the long axis of the contracted bands. In our Series II we found many areas which closely resembled Skoog's illustrations (Figs. 7 and 8). In these areas the fibers of the aponeurosis were observed to end abruptly at the edge of an area of cellular proliferation. Other fibers lying adjacent to the interrupted fibers continued through the areas of proliferation uninterrupted. The fibers that appeared to have been interrupted had a more sinuous appearance than the fibers that did not appear to have been interrupted.

Serial sections were made of the areas in which we observed abrupt termination of collagen fibers. These demonstrated that the fibers did not continue uninterrupted in the next section. For example, the abruptly-terminating fibers shown in Figures 7 and 8 did not continue on into the sections superficial or deep to this section. The appearance of these abruptly ending fibers seemed to be produced by the actual termination of the fibers.

When it was found that interruption of collagen fibers could be demonstrated in the tissues of Series II, we reviewed the sections of Series I but found no evidence of interruption of the fibers. It appears, therefore, that the sections must be cut parallel to the longitudinal fibers of the aponeurosis in order to demonstrate interruption of the fibers.



FIG. 9

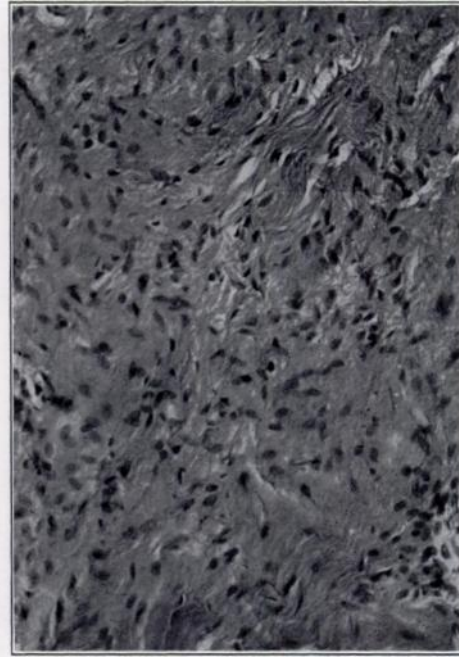


FIG. 10

Fig. 9: Section of a nodule of proliferating fibrous tissue removed from the patient described in Case 1 (hematoxylin and eosin, $\times 180$).

Fig. 10: Section through the nodule of proliferating fibrous tissue removed from a monkey's palmar fascia three months after partial rupture of the fascia. Note the abrupt termination of the mature fibers (hematoxylin and eosin, $\times 180$).

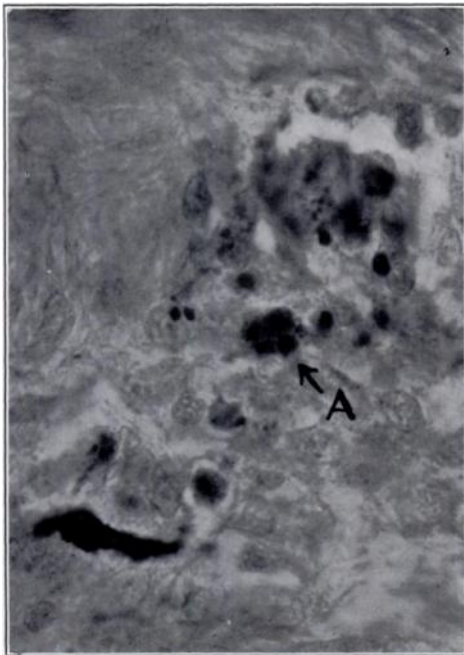


FIG. 11

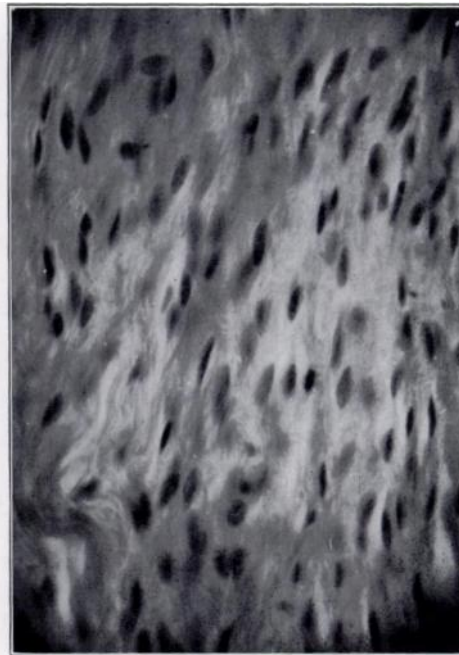


FIG. 12

Fig. 11: Section through the nodular lesion in the monkey palmar fascia (Prussian-blue stain, eosin counterstain, $\times 800$). The dark areas at A are hemosiderin and are blue in this section. This lesion was one month old when excised.

Fig. 12: Lesion of a monkey's palmar fascia excised five months after partial rupture of the fascia (hematoxylin and eosin, $\times 400$).

The specimens from Series II provided no additional information with regard to the relationship of the cellular stages of the disease to the increase in capillary vascularity in the cellular regions. The same observations were made repeatedly by numerous authors in the past⁵. There is an increase in capillary vascularity in the region of the proliferating tissue and at times the wall of a capillary vessel seems to blend insensibly with the proliferating fibrous tissue. In these areas the fibrous tissue appears to arise directly from the wall of these small vessels. As the mature contracted stage of the disease is reached, the vascularity of the tissue is markedly reduced.

CASE 1. We encountered one human lesion, apparently the result of trauma, that had great similarity to Dupuytren's contracture. A white boy, seventeen years old, had sustained a small laceration of the palm on a piece of glass eight months before coming to us. The flexor tendons of the ring finger were lacerated at the level of the distal palmar crease. The digital sensory nerves were not involved and the wound had healed primarily. A nodular mass, one centimeter in diameter, developed beneath the skin scar. The nodule, which had not been present prior to injury, was slightly painful at times but was not tender. At the time of tendon repair, no foreign body could be found in the palm and the nodular area was found to lie within the palmar fascia. The nodule was excised and on microscopic examination was found to consist of proliferating fibrous tissue with plump, oval nuclei enmeshed in a network of fine connective-tissue fibers (Fig. 9). Small areas of the lesion contained golden brown pigment granules that stained positively for iron with the Prussian-blue reaction. Histologically, this lesion could not be distinguished from one of the proliferating nodules of a Dupuytren's contracture. Interestingly enough, at the time of his first visit and before he was operated on, this patient was observed to have the knuckle-pads often found in Dupuytren's contracture.

EXPERIMENTAL RUPTURE OF THE PALMAR AND PLANTAR FASCIA IN MONKEYS

Method

All four extremities of three Cebus and nine rhesus monkeys were operated on. None of the monkeys had any evidence of any disease or deformity of the hands or feet. Intravenous sodium pentobarbital anesthesia was used and in each extremity a bloodless field was obtained by an Esmarch bandage. Sterile surgical technique was used throughout. An incision was made in the proximal end of the palm or sole and the skin and subcutaneous tissue were elevated as gently as possible from the superficial surface of the palmar or plantar fascia. A strip of fascia about three to four millimeters wide and two and a half centimeters long was then elevated from the interstitial tissues, which adhere to its deep surface, leaving the ends of the fascial strip attached. (In the foot, a muscle arises from the deep surface of the plantar fascia and the strip of plantar fascia was dissected away from this muscle.) Two sterile dural silver clips were then clamped on the strip of fascia, leaving a segment of fascia about one and a half centimeters long between the clips. The strip of fascia outside the clips (proximal and distal to them) was then grasped with hemostats. The hemostats were gently pulled apart until partial tearing of the fibers of the fascia lying between the clips could be detected (the band of fascia was not completely ruptured, except in one instance in which the entire band suddenly gave way). The fascia was then laid back in its bed in the hand or foot and the tourniquet was removed. Bleeding was controlled by compression until clotting occurred, and the skin was closed with interrupted nylon or cotton sutures. A piece of gauze moistened in collodion was made to adhere to each wound. Each animal was given 300,000 units of penicillin intramuscularly and returned to its individual cage where it remained throughout the postoperative period. All the monkeys removed their own skin sutures with their teeth; usually, all sutures were out by the end of the first week. One of the forty-eight wounds became infected; the remainder healed by primary intention.

Each animal served as its own control as follows. In one extremity the fascia was partially ruptured between the dural clips just described. In a second extremity of the same animal partial rupture of the fascia was accomplished, but the clips were not used. In the third extremity the strip of fascia was elevated as described but was not ruptured; it was simply placed back in position and the wound was closed. In the fourth extremity the fascial strip was elevated and clips were applied, but the strip was not ruptured; it was returned to its bed and the wound was closed.

In this manner there were two extremities in each animal with a strip of fascia that had been partially ruptured, one with and one without clips. We also had two unruptured fascial strips, one with and one without clips.

The hands and feet of each monkey were operated on a second time from one to nine months after the original operation. The portion of fascia lying between the clips was excised from each of the four extremities. Two monkeys were reoperated on at one month, two at two months, two at three months, and one each at four, five, six, seven, eight, and nine months. The excised fascia was fixed in formalin, embedded in paraffin, and sectioned and stained in a manner similar to the method employed in Series II.

Gross Findings

When the skin of the hand or foot was opened a nodular lesion was lying within the palmar or plantar fascia. In the partially ruptured areas, which were identified by dural clips, the lesion was noted to lie between the clips. In the partially ruptured fascia in which clips were not used, the nodular lesion was still easily identified. The presence or absence of the clips made no grossly recognizable difference.

In the control extremities in which the fascial strips were elevated but not ruptured, only diffuse thickening of the fascia was found without nodularity. There was no grossly recognizable difference between the unruptured strips of fascia that had and did not have the clips.

During the first two or three months the nodular lesions were soft and reddish gray. After six to nine months the nodular shape was less marked, although still present. In these older lesions, the nodules were firmer in consistency and of a yellow-gray color which more closely resembled the color of the surrounding normal aponeurosis.

Microscopic Findings

In the lesions excised at one, two, and three months (Fig. 10) there was proliferation of fibrous tissue in the area of rupture. The ruptured mature fibers could be traced to the margin of the proliferating area where they ended rather abruptly. There was rather marked capillary vascularity associated with the proliferating fibrous tissue. The nuclei of the fibroblasts in the proliferating areas were round or oval and contained an easily visible nucleolus and finely granular material. The cellular margins were indistinct in these areas and the intercellular fibers stained poorly with eosin. The finest fibers did not stain at all with eosin but had a pale lavender color.

Scattered among the nuclei in the proliferating areas, there were golden yellow or yellow-brown granular deposits of hemosiderin (Fig. 11) that stained blue with the Prussian-blue stain. Masson's trichrome stain indicated that the fibrous network in the proliferating area was collagen. The finest fibers in the network did not take the green color of the Masson stain. Verhoeff's elastic-tissue stain indicated that there was no formation of new elastic tissue here.

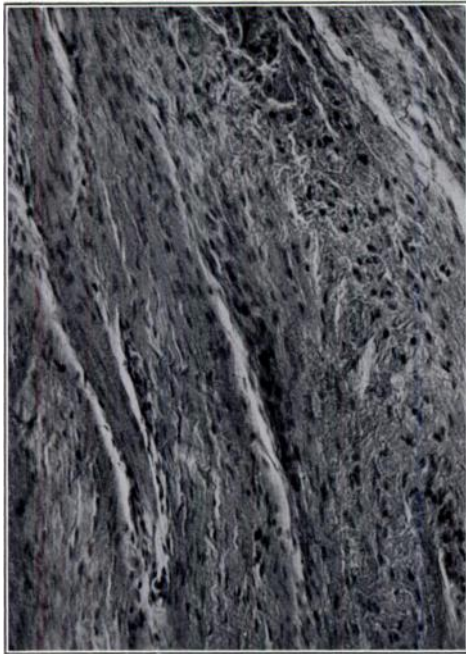


FIG. 13

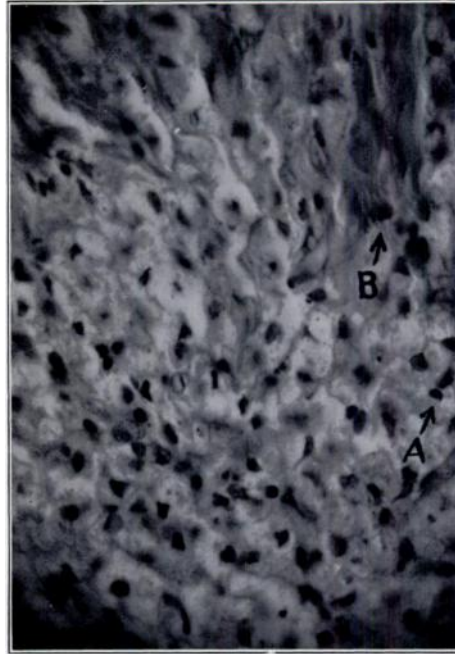


FIG. 14

Fig. 13: Lesion of a monkey's palmar fascia excised nine months after partial rupture of the fascia (hematoxylin and eosin, $\times 180$).

Fig. 14: Section through a nodule in the rectus sheath of a dog taken one month after partial rupture of the sheath. The granule at *A* is hemosiderin; note at *B* the abrupt termination of the mature collagen fibers (hematoxylin and eosin, $\times 400$).

Metachromatic staining of the proliferating areas was noted in toluidine-blue preparations.

In the older lesions, which were excised from the fourth to the ninth month after rupture, there was progressive maturation of the proliferating fibrous tissue (Fig. 12). The nuclei were oval and increasingly oriented with their long axes in the same direction. The collagen fibers became progressively thicker, losing their haphazard arrangement and becoming organized into a more regular lamellar pattern. By the ninth month the lesion resembled a mature scar (Fig. 13). The vascularity decreased progressively in the older lesions. The amount of iron pigment also decreased progressively. At the end of nine months only a very few granules of hemosiderin could be found.

In the control specimens the lesions that had been produced by partial rupture of the aponeurosis without the use of the identifying dural clips were histologically identical to the lesions in which the clips were used. The dural clips remained inert in this experiment, as far as we could determine.

Pedersen and Gardner found that scarification of the plantar fascia caused a fibrous-tissue proliferation that resembled Dupuytren's contracture. We found that the elevation of the fascial strip produced a diffuse thickening of the fascia. On microscopic examination the surfaces of the fascia showed proliferating immature fibrous tissue similar to that in the ruptured fascial strips. The reaction, however, was less intense and subsided more rapidly than did the lesion produced by rupture of the fascia. At nine months the unruptured strip of fascia was a thin regular structure which closely resembled the normal fascia. No nodular lesions were observed in the strips of fascia that were not ruptured. It would seem, therefore, that the fibrous-tissue proliferation is a response of the palmar or plantar fascia to trauma, whether the trauma be rupture of the fibers or simple

elevation of a strip of the fascia. The reaction is more intense and lasts longer when the fibers are actually ruptured.

In none of the monkeys did a contracture develop and all digits retained full extension. No functional loss could be detected by observing the animals in their cages.

EXPERIMENTAL RUPTURE OF THE ANTERIOR RECTUS SHEATH OF A DOG

Six similar operations were performed on the anterior rectus sheath of a dog. The resulting lesions were excised at intervals of one to five months.

The amount of cellular hyperplasia in these lesions seemed to be much less than in the monkeys' palmar and plantar fascia and the lesions healed rapidly. After one month the ruptured area was filled with numerous immature fibroblasts enmeshed in a network of fine connective-tissue fibers (Fig. 14). Iron pigment granules scattered between the nuclei of the immature fibroblasts stained positively with the iron stain (Prussian blue). The specimen removed two months after rupture of the sheath showed very few of these cellular areas. The specimen taken at the end of three months showed complete healing.

DISCUSSION

Much has been written regarding the etiology of Dupuytren's contracture. Almost all the authors concerned themselves with the statistical relationship between the contracture and various occupations or associated disease. The articles that concern the role of trauma in the causation of Dupuytren's contracture are also, for the most part, statistical studies that compare the incidence of this disease in manual laborers with that in persons with more sedentary occupations. The conclusions drawn are about equally balanced for and against trauma as a cause of Dupuytren's contracture. We doubt that a conclusive answer can be obtained from this type of study.

Skoog was the first to describe the abrupt termination of collagen fibers at the margins of the cellular areas of Dupuytren's contracture. He interpreted this finding as a partial or microrupture of the fibers. He also observed that the ruptured fibers had a wavy appearance, as if tension on these fibers had been released. Our observations confirm those of Skoog.

Lagier and Rutishauser, however, believed that the fibers are not ruptured; they stated that it is the wavy course of the fibers that causes them to pass out of the plane of the section. Thus, the fibers appear to terminate but actually pass on uninterruptedly into the next section. Our serial sections do not support this conclusion since we could not demonstrate that the fibers pass on uninterruptedly into the next section. They actually terminated at the margin of the cellular nodules in the material we studied.

Apparently, it is necessary to fix and section the tissues of Dupuytren's contracture in the manner employed in this study in order to demonstrate the abrupt ending of the aponeurotic fibers at the edge of a proliferating nodule. We do know from Skoog's illustrations that he prepared some of his tissues in this way. No other authors, except Nézelhof and Tubiana, stated whether they handled their tissues so that the plane of the section was parallel to the long axis of the fibers. Certainly, we were not able to observe the abrupt ending of the fibers in our first series, in which no special attention was paid to the plane of the section. Perhaps this explains why this observation has not been made more frequently. It should be stated, however, that Nézelhof and Tubiana did not observe the abrupt interruption of fibers in tissues that were prepared and sectioned in the same manner as ours.

The palmar and plantar aponeurosis of the monkey after experimental rupture showed similar abruptly terminating fibers at the margins of the cellular nodules. The experimental lesion of the anterior rectus sheath of the dog also had this appearance. Quite clearly, the termination of the collagen fibers in the palmar or plantar aponeurosis of the monkey and in the dog's rectus sheath was due to rupture of these fibers at the time of the experimental operation.

The fibroplasia present in the four types of tissue we described here (Dupuytren's contracture, Case 1, and the experimental lesions of the monkey and the dog) appears to be essentially the same. The maturation of the proliferating areas of Dupuytren's contracture and of the experimental lesions in the monkey and the dog was also histologically identical.

In each lesion hemosiderin deposits were demonstrated. In Case 1, in the monkeys, and in the dog the hemosiderin was quite clearly the result of hemorrhage into the areas at the time the fibrous tissue was injured. The presence of hemosiderin in the immature lesions of Dupuytren's contracture cannot be logically explained in any other way. In the monkey, the hemosiderin deposits are rare in specimens removed nine months after rupture of the fascia. In Dupuytren's contracture, they are found only in the most immature areas of cellular proliferation. Often, the hemosiderin granules appear to be within phagocytes; presumably, they are removed slowly from the proliferating area by the phagocytes.

Some authors did not find hemosiderin deposits in their specimens, whereas others stated that hemosiderin is only rarely or infrequently present⁷. Often, the granules are very fine and few in number; close search and high magnification ($\times 400$) are necessary in many sections before their presence can be demonstrated. In addition, they can be found only in the most immature cellular areas. Not all specimens of Dupuytren's contracture will contain these immature cellular areas. Furthermore, hemosiderin is removed from the tissues by acid fixatives that do not contain formalin and is also removed to some extent by acid formalin. One or more of these factors may explain the variations in the findings of different authors with respect to hemosiderin deposits in the proliferative phases of Dupuytren's contracture.

Metachromatic staining was observed in the proliferating areas of the experimental lesions of the monkey and in the areas containing immature fibrous tissue in Dupuytren's contracture. The metachromatic property of the less mature tissues indicates the presence of polymerized mucopolysaccharides, probably chondromucins or chondroitin sulphuric mucins. These compounds are believed to be essential components of the ground substance. Because amyloid is also a type of chondroitin-sulphuric-acid-protein complex, the tissues were stained for amyloid, but no amyloid was found in any of the monkey or human tissues. The metachromatic staining of the cellular areas of Dupuytren's contracture was observed by several authors^{6,9,11}. At the present time, metachromasia in the cellular stages of Dupuytren's contracture is only an interesting observation which really contributes little to our understanding of the pathogenesis of the disease.

Lagier and Rutishauser and Skoog observed that the "hyalinized" collagen fibers of Dupuytren's contracture stain red with Mallory's connective-tissue stain. Similar red staining of hyalinized tissue in other fibrotic lesions, such as perisplenitis, was not observed by Lagier and Rutishauser. We, too, observed that the fibers in the very dense mature areas of the contracture stain red instead of blue with Mallory's stain. The significance, if any, of this staining reaction remains obscure.

The very finest fibers in the proliferating areas do not take the orange stain

of hematoxylin and eosin but rather had a pale lavender color. These fibers do not take the green stain of the Masson connective-tissue stain. Probably, these are reticulin fibers. We did not do specific stains for reticulin. Nézelhof and Tubiana found marked staining of the intercellular areas with the Hotchkiss method (one of the periodic acid-Schiff techniques). This would seem to indicate the presence of reticulin in the intercellular areas.

The vascular proliferation observed in the tissue from both human Dupuytren's contracture and monkey lesions seems to be similar. The intimate relationship between the vessels and the proliferating fibroblasts in Dupuytren's contracture has often been observed^{5,7}. If human Dupuytren's contracture begins as an injury to the palmar fascia similar to the injury produced in the monkeys in these experiments, then the increased capillary vascularity noted in the proliferating nodules of tissue in human Dupuytren's contracture must be the same type of response noted in the monkey. At first, as the fibroblastic proliferation in the area of rupture of the aponeurosis proceeds there is an accompanying proliferation of angioblastic tissue with the formation of new capillaries, but in both the monkey and the human lesions the increase in capillary vascularity is no longer present when the mature scarlike state is reached.

It is generally known that in wound healing, differentiated or mature connective tissues cannot dedifferentiate and give rise to more immature forms of tissue. The fibroblasts that appear at the site of injury are derived from nests of cells around the blood vessels. As these fibroblasts migrate into the site of injury they are accompanied by new capillaries⁴.

This process seems to us to explain quite readily the sequence of events observed in the healing of the monkey lesions. It would also account for the frequent observation that the immature fibroblasts of Dupuytren's contracture appear to arise from the wall of nearby vessels.

Caution should be used in trying to correlate the experimentally induced lesion in a monkey with that of human Dupuytren's contracture. We have no assurance that the monkey lesion would progress to the formation of a contracture even if the lesion were reproduced repeatedly over a long period of time. Furthermore, we do not know if trauma is the only agent capable of producing the type of response that we produced in the monkey's palmar and plantar fascia. Other agents may be able to produce a similar lesion.

Finally, it is in no way established that the monkey lesion is comparable to human Dupuytren's contracture with respect to the magnitude of the trauma involved. Considering the total size of the palmar fascia of a monkey, it is evident that a great deal of trauma to the fascia was produced by our experimental operation. Certainly, nothing so severe as this occurs at the time of the supposed microrupture of human palmar fascia.

Much of the nature and behavior of connective tissue remains unknown. The composition of the connective tissues of the aged is known to be different in certain respects from that of younger persons¹ and the healing of connective tissue is altered by various nutritional and endocrine disorders. In addition, connective tissues do not always respond in the same way to the same stimulus; the state of the organism may alter the response of the tissues to a given stimulus³.

In the light of the preceding statements, it seems possible that certain individuals have some alteration of their connective tissues that causes these tissues to respond in an abnormal manner. It may be that their collagen fibers are more susceptible to microruptures. Possibly, in regular daily life, we all sustain microruptures of the collagen fibers, but only certain individuals hyperreact with profuse fibrous-tissue proliferation. The conditions or diseases that may alter the

connective tissue in this way are not known, except for age, hereditary factors, and, perhaps, sex.

If it is true that in certain persons there is a predisposition for the contracture to develop, we must then find the stimulus that starts its development. Since the lesion produced experimentally in the monkey appears to us to be the same as that seen in the proliferating nodules of Dupuytren's contracture, it would appear that partial rupture of the fibers of the palmar aponeurosis is one stimulus that may initiate the development of the proliferating nodules characteristic of the early stages of Dupuytren's contracture. The fibrous-tissue nodule encountered in the patient in Case 1 was apparently produced by laceration of the palmar fascia with glass. It is, as far as we can determine, histologically identical to the early lesions of Dupuytren's contracture. This observation lends additional weight to the assumption that this kind of cellular response can be provoked by division of the fibers of the palmar aponeurosis. Whether partial rupture of the aponeurotic fibers is the only stimulus that can start this lesion, either in the human being or in the monkey, is not known.

CONCLUSION

We can therefore summarize the pathogenesis or mode of development of the experimental lesion produced in the monkey as follows: A partial tearing of the collagen fibers in the palmar or plantar aponeurosis occurs, followed by hemorrhage into the area. Perivascular fibroblasts proliferate and invade the ruptured area. Fine new collagen fibers are formed, which ultimately become arranged into thick fascicles of dense collagen fibers. As the fibroblasts invade the area, new capillaries accompany them. When the mature stage of the lesion is reached, the number of vessels is markedly reduced. Metachromatic staining of the cellular areas with toluidine blue is present at first but this finding is not present in the more advanced stages of the lesion. Hemosiderin is gradually removed from the cellular areas by phagocytes. The newly formed fibers are collagen and not elastic-tissue fibers. Finger contracture does not develop in the monkey.

The lesion produced in the monkey is, as far as we could determine, histologically the same as one of the proliferative lesions encountered in Dupuytren's contracture. The staining reactions of the two lesions with hematoxylin and eosin, iron stains, toluidine blue, Bennhold's Congo red, Mallory's and Masson's connective-tissue stains, and Verhoeff's elastic-tissue stain are the same. The early cellular stages, the intermediate stages of maturation of the fibrous tissue, and the final stage of dense collagen fiber formation were all recognizable in both lesions.

SUMMARY

1. Sixty-nine additional specimens of Dupuytren's contracture have been studied. These specimens were fixed with the fascia under normal tension and sectioned longitudinally.

2. The lesion of Dupuytren's contracture begins as an area of fibrous-tissue proliferation and ends as a band of thick collagen fibers. Hemosiderin deposits in the cellular areas are believed to be evidence of previous hemorrhage into the areas. Abrupt termination of collagen fibers at the edge of the cellular nodules has been observed.

3. Partial rupture of the palmar and plantar fascia was produced in twelve monkeys, together with appropriate control operations. By this method a lesion which resembles the cellular stages of Dupuytren's contracture has been produced. The monkey lesion matures into dense collagenous tissue in the same way that the

cellular stages of Dupuytren's contracture mature. Contracture of the finger did not develop in the monkeys in these experiments.

4. One patient has been encountered in whom a nodule developed within the palmar fascia after laceration of the fascia. The nodule had the microscopic characteristics of the cellular stage of Dupuytren's contracture.

5. A similar fibrous-tissue proliferation has been provoked by partial rupture of the anterior rectus sheath of a dog. The response in the dog was less intense than in the monkey and the lesion healed more rapidly.

6. These observations lead us to believe that partial rupture of the palmar aponeurosis is one way in which the type of fibrous-tissue proliferation observed in Dupuytren's contracture can be provoked.

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DISCUSSION

DR. J. M. BRUNER, DES MOINES, IOWA: At this meeting two years ago, Dr. Larsen presented his first paper on the pathogenesis of Dupuytren's contracture. Again, we are indebted to him for a well planned clinical and experimental study of this condition, for a beautiful microscopic depiction of the histopathology, and for an interesting cine-demonstration of his animal experiments.

The observation in the microscopic sections of two types of tissue, the immature and the mature; the absence of elastic fibers; the presence of hemosiderin pigment, suggesting hemorrhage; and the abrupt termination of fibers, suggesting rupture, are all exceedingly provocative.

It seems fairly well accepted that Dupuytren's contracture arises in predisposed persons, many of whom give a family history of the same condition. If there is also a traumatic factor, the question arises as to what kind of trauma this may be. Evidently, Dr. Larsen and Dr. Posch believe that this trauma is in the nature of tension stretching or rupture of the fascia rather than the direct trauma to the palm sustained by the manual laborer or the baseball or handball player.

Two cases in point may be cited:

CASE 1. A woman, fifty years old, fell on her outstretched palm and sustained a Colles' fracture. When she fell, she bent her fingers backward violently, thus causing severe pain in the palm. Soon after this, a thickening appeared in the distal part of the palm that gradually produced contracture of the long and ring fingers. Fasciectomy was done and examination of the resected specimen showed tissue characteristic of Dupuytren's contracture.

CASE 2. A hospital employee, forty-five years old, had advanced Dupuytren's contracture involving the ring and little fingers. He stated that the progress of the contracture was quite gradual, but when he started to forcibly and violently straighten the fingers many times a day, there was very rapid progress of the contracture. Fasciectomy was done, with the usual findings. Unfortunately, hemosiderin deposits were not looked for in the resected tissue.

In Case 1, a single episode of stretching appeared to be the inciting factor; in Case 2, repeated stretching seemed to be an aggravating factor. However, these were the only two cases seen during the past ten years in which the patient remembered any specific trauma. It is likely, therefore, that if rupture of fibers is the causative factor in predisposed persons, it must be minor in nature but repeated over a period of years.

In support of this theory are certain facts as to the distribution of Dupuytren's contracture in the human palm, the ring finger being first and the little finger second in frequency of involvement. Consideration of the dynamic factors causing stress and strain in the palmar fascia is most significant.

The hand consists of three elements or pillars, a radial element (the first metacarpal), which is freely movable; a central element (the second and third metacarpals), which is relatively fixed in relationship to the carpus; and an ulnar element (the fourth and fifth metacarpals), which has moderate but restricted mobility. The second and third carpometacarpal joints are relatively solid; the fourth and fifth have some mobility.

Longitudinal stress in the palmar fascia is produced by hyperextension of the fingers and is greatest in the ulnar element of the hand. When the fist is clenched, a torsion of the metacarpophalangeal axis occurs; this is reversed when the hand is widely opened. Range of hyperextension, as well as flexion, is greatest in the metacarpophalangeal joint of the little finger, slightly less in the ring finger, and progressively less in the long and index fingers.

Transverse stress in the palmar fascia is produced by intermetacarpal movement and this is greatest between the fixed and the movable pillars of the hand, that is, near the base of the ring finger. This coincides with the point at which the greatest hyperplasia of the palmar fascia is seen clinically.

Advancing age and a sedentary occupation are also probably important in rendering the fascial tissue more vulnerable to tension. This may explain why white-collar workers may be more susceptible to the trauma of stretching of the palmar fascia, than manual laborers, whose aponeurosis undoubtedly has greater tensile strength.

DR. S. BENJAMIN FOWLER, NASHVILLE, TENNESSEE: In considering the etiology of any disorder, and Dupuytren's contracture is no different no matter how beautiful the microscopic sections and how beautiful the work is, I have to think of the patient as a whole and his environment. I live in a section of the country that has a large Negro population and I have never seen Dupuytren's contracture in a Negro. I suppose it does occur. There are many Negroes who have "white blood", but I have never seen it in the light-colored Negro. Dupuytren's contracture usually does not exist as an isolated lesion: there is usually a pathological condition elsewhere in the body.

DR. LARSEN (closing): We did not intend to imply that microrupture of the fascia was the only etiological factor operative in Dupuytren's contracture. In the body of this paper it has been pointed out that microrupture of the palmar fascia may be one of the triggering mechanisms that starts the formation of the contracture in a person who has some type of predisposition that makes the palmar fascia susceptible to the contracture. We do see Negro patients with Dupuytren's contracture and Dr. Takagishi tells us that he has seen Dupuytren's contracture in the Japanese.