CHAPTER III

Pathology and Pathogenesis

I. PATHOLOGY

1. Survey of the Literature

PLATER (1614) interpreted the cords in the palm of the hand as flexor tendons. This opinion was still held as late as the beginning of the 19th century, when the condition was called *crispatura tendinum*.

In 1822 COOPER stated that the deformity was produced by contraction of the palmar fascia. DUPUYTREN (1832) however, appears to be the first surgeon to investigate the condition by dissection and to reveal its true localization. He gave the following description of one case: "Exposing the palmar fascia I was astonished to perceive that this fascia was tense, retracted and shortened. From its lower portion were given off kinds of cords, which passed to the diseased fingers . . . I cut through the prolongations extending from the fascia to the fingers; the state of contraction immediately ceased . . . I examined the tendons with care. Their surfaces were smooth and they enjoyed their usual degree of motion; the joints also were in a healthy state . . ." Several workers were later able to verify DUPUYTREN's classical observations and it is only correct that his name should be associated with the disease.

Despite its indisputable nature, this discovery was not accepted for some time. ALIBERT (1832), for example, described the condition as a skin disease, *Paratrimma palmare*. The fact that in advanced stages the palmar skin loses its normal characteristics and becomes intimately connected with the aponeurosis caused a number of writers to believe that the primary seat of the disease was in the skin (CRUVEILHIER 1849, BAUM 1878, and others). As late as 1886, AMAT regarded the changes in the aponeurosis as secondary to the dermatitis which he believed was present.

In Skoog, T: Dupuytren's Contraction With Special Reference To Aetiology And Improved Surgical Treatment Its Occurrence In Epileptics Note On Knuckle-Pads. Acta Chirurgica Scandinavica 1948;vol 96, Suppl 139.

GOYRAND (1833) was also unwilling to acknowledge the decisive importance of DUPUYTREN's discovery. On the basis of a dissection of a case of this kind, he stated that the palmar aponeurosis was entirely normal and that the flexion of the fingers was due to a new formation of abnormal subcutaneous fibrous fasciculi. A number of other workers shared his opinion (FERGUSSON 1846, MALGAIGNE 1862, EULENBURG 1863, and others). As late as in 1917 HUTCHINSON found it difficult to explain why the proximal interphalangeal joints should be the most affected by the contraction, since it is generally assumed that there are no fibrous bands going to the fingers, which by their shortening could possibly produce flexion of those joints. He therefore asserted that the disease "does not limit itself to the normal anatomical bands, but that fresh fibrous prolongations are developed."

All these often heated and polemic discussions can now be considered as beside the point. They paid no attention to the vastly more important question of why and how these bands were formed. The description of the anatomy of the palmar aponeurosis in Chapter I of the present study shows that it is not necessary to assume the formation of fresh fibrous bands outside the aponeurosis in order to explain the clinical picture. The deep extensions of the aponeurosis are attached to the sides of the proximal phalanges and extend to the bases of the second phalanges and in addition the pretendinous bands continue onto the fingers. The effect of these bands when they undergo hypertrophy and retract is demonstrated in a dissected specimen (Fig. 14).

It is natural that if the fingers, as a result of changes in the aponeurosis, are kept for a long time permanently flexed, *secondary changes* occur gradually in the joints involved as well as in the other tissues of the fingers. It was demonstrated, for example, on dissection preparations that in cases of long standing when all the structures were removed with the exception of the ligaments, the fingers could not even then be extended freely (REID 1836, FERGUSSON 1846, and others). It has also been shown that the surfaces of the joints are changed and the joint cartilages show degeneration (RICHER 1877, LANE 1885, and others). In addition, EULENBURG (1864) observed hyperostotic formations on the dorsal aspects of the flexed middle phalanges.

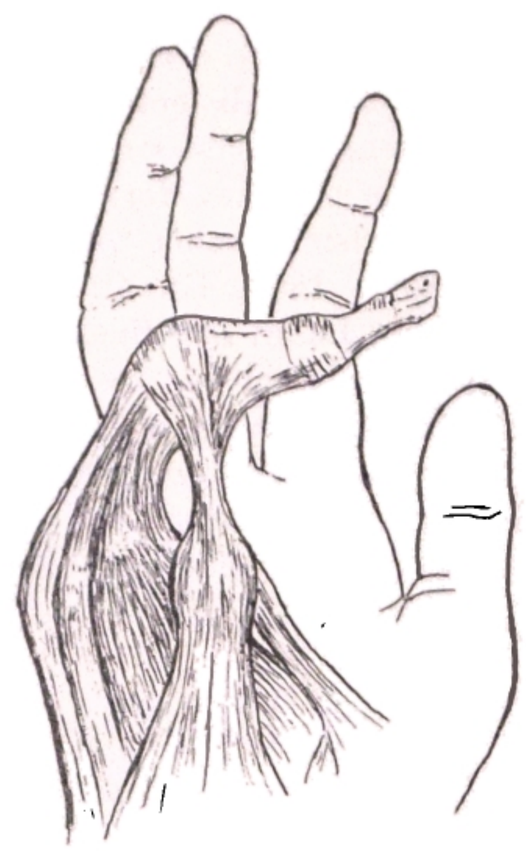

Fig. 14. Nodular aponeurotic band causing flexion deformity of the little finger. Dissected specimen in the Museum of King's College (after ADAMS, 1878).

Pathohistology

The first descriptions of the microscopic pictures of the disease were based on single observations. More experience of larger material does not, however, appear to have increased our knowledge of these tissue changes to any great extent.

RICHER (1877) observed that the fibrous tendon-like bundles were more compact and more numerous in the retracted bands and that the subcutaneous tissues were indurated in the parts adherent to the skin, but the skin itself was normal.

DUREL (1888) reported an observation made by DOYEN concerning the appearance of small nodules in the aponeurosis in this disease and called them "véritables fibromes." LANGHANS (1887) was, however, the first to give an accurate microscopical description of these diffuse cellular areas of connective tissue which are so characteristic of Dupuytren's contraction, and considered that a process of proliferation without true inflammatory phenomena was present. He found an increase of cells in the nighbouring areas of the aponeurosis, specially in the adventitia of the adjacent vessels.

JANSSEN (1902) mentioned the presence of blood pigment in the aponeurosis. This was regarded as remains of haemorrhages caused by injury in operation. He categorically denied a traumatic origin of the disease.

Anderson (1897) described the condition as inflammatory hyperplasia or neoplastic growth commencing in the skin, and McWilliams (1904) regarded it as chronic hyperplastic inflammation with subsequent formation of scar tissue.

Iklé (1928), as did Janssen (1902), described the cellular areas as sarcoma-like but pointed out at the same time that there was no question of infiltrative growth or metastasis, and the area was also too diffuse to be considered as a fibroma.

No essentially new observations or opinions are to be found in the works of Tarnowski (1887), Schmidt (1889), Merker (1897), Walter (1920), Kanavel et al. (1929), amongst others, and therefore only the most important investigations of recent date will be mentioned briefly.

Meyerding et al. (1941) studied the microscopical sections of the palmar aponeurosis in 57 cases of Dupuytren's contraction. They specially stressed the signs of inflammation in the surrounding tissues and regarded the condition as not merely a disease of the palmar aponeurosis but a disease probably beginning in the interstitial connective tissue and usually spreading to involve all structures from the skin down to the tendon sheaths. They classified the pathological picture as a chronic inflammatory process. They also assumed that the cellular nature of the fascia indicated the activity of the proliferative process and stated that no definite correlation was found between the degree of contraction and the grade of maturity.

With the wide variation in histological characteristics within the same specimen in this disease it is hardly possible, without serial sections, to make a satisfactory classification in the way described by Meyerding et al. It is therefore difficult to accept the theory they brought forward, i. e. that in cases in which histological examination reveals a low grade of maturity of the pathological tissue, recurrence is more likely to occur than in those in which higher grades of maturity are found.

Horwitz (1942) compared the microscopical anatomy of the normal palmar aponeurosis in 27 specimens from human cadavers to the histological features in Dupuytren's contraction in 35 cases. He found the essentials of the disease to be a "benign fibroplasia of the palmar connective tissues". He also pointed out the striking resemblance of the fibroplastic process to those of other localized fibroplasias such as keloids and fascial desmoids, as did

CLAY (1944). In a study of tissues removed from 22 hands with Dupuytren's contraction, CLAY came to the conclusion that the disease was due to a neoplasm a cellular fibroma of the palmar fascia.

Finally, it must be mentioned that KROGIUS (1921), DECKNER (1938), and others, believed the new formation of connective tissue to originate in embryonic remains of a superficial layer of primitive muscles of the palm. SCHAUMANN (1944) based an aetiological theory on the histological conformity of Lupus erythematosus and the aponeurotic process. These hypotheses will be referred to in Chapter VII.

2. The Writer's Observations

A. Macroscopical Changes

The material on which the present investigations were carried out consisted of a number of patients who were treated for the disease by aponeurosectomy, an operation which gives at the same time a material complete enough for a general survey of the pathological anatomy of the disease. From this material, the writer is convinced that the anatomical basis of Dupuytren's contraction lies within the palmar aponeurosis itself, that structure being defined as in Chapter I of the present work. Involvement of every part of this structure occurred from time to time.

The main characteristic of the condition was the formation of masses of firm, greyish-white fibrous tissue, which thickened the structure of the aponeurosis. The tissue masses could vary from small nodules to larger and more extensive indurated areas. These phenomena occurred especially in the distal part of the palm and at the bases of the fingers, originating in the longitudinal fasciculi, in the paratendinous septa, in the natatory ligaments and in the attachments of the aponeurosis to the skin. Though sometimes excessive, spreading beyond the limits of the aponeurosis in a manner reminiscent of a tumour, the process of tissue change never involved adjacent formed structures: tendon sheaths, lumbrical muscles, digital nerves or blood vessels. These structures always remained distinct though in intimate physical contact with areas of tissue change. The digital nerves in particular were at times considerably displaced as a result of the expanding process in the aponeurosis. Indeed, owing to the position and shape of the aponeurosis, these nerves were

often entirely surrounded by massive fibrous tissue. Even so, it was possible to dissect them clear. Superficially, they always appeared normal.

A second characteristic of the condition was pronounced retraction of the parts affected, causing flexion of the fingers. The thickening of the aponeurosis frequently took the form of cords, extended in an axial direction to each flexed finger. As described in the symptomatology, these cords were sometimes reminiscent of "bowstrings". They were never isolated in their course, but were always integrated with other fibrous masses. In a number of cases the cords were particularly well defined and up to approximately five mm in diameter. In transverse section they were tendon-like in appearance. Not infrequently the normal subcutaneous fat layer had disappeared over these cords and they were fibrously attached to the skin at these sites.

B. Pathohistology

Specimens of the palmar aponeurosis removed from 29 patients were examined microscopically. As comparative material the palmar aponeuroses from 10 post-mortem cases (5 men and 5 women) were examined.

In the opinion of the present writer, earlier workers in this field have given too little consideration to the structure of the diseased aponeurosis as a whole. This was seldom possible earlier, since it is only modern methods of operation, permitting complete aponeurosectomy, that have afforded the requisite material. Even with these methods it is seldom suitable from a technical point of view, to remove by complete excision the aponeurosis *en bloc*. Even in those few previous cases where this was done, only "typical" parts were apparently taken for microscopical examination.

In order to obtain a better survey of the localization of the disease and its extent, the present writer has, when operating, endeavoured to obtain the complete preparation for microscopical study. It is then easiest to examine the dominant, longitudinal fibre bundles. A longitudinal section is shown in Fig. 15, stained with a stale solution of Weigert's iron haematoxylin. With strong differentiation, the nodules in the aponeurosis, corresponding to richly cellular connective tissue, appeared light

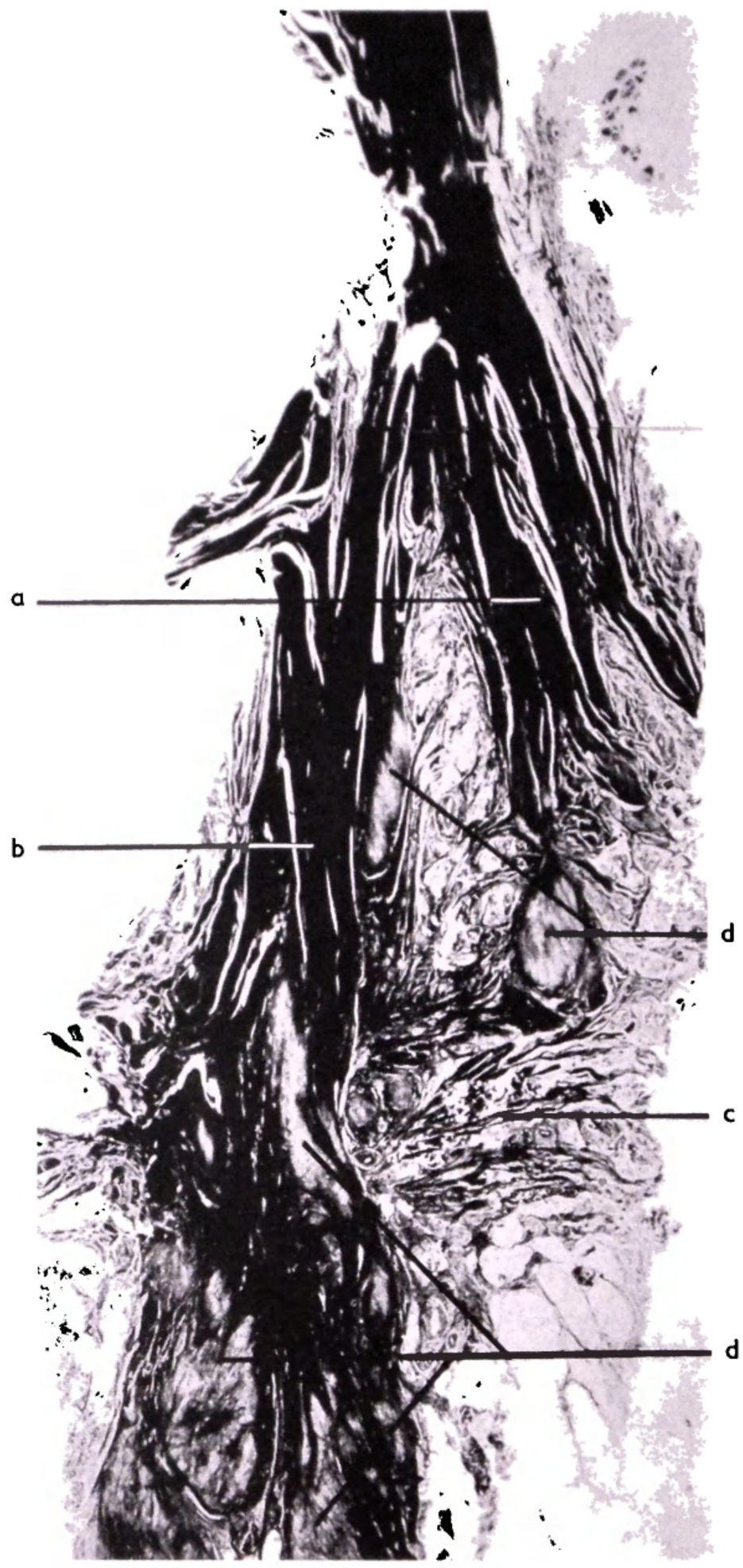

Fig. 15. Longitudinal section through ulnar part of palmar aponeurosis in the plane of its palmar surface in a 45-year-old man with Dupuytren's contraction of 6 years standing. Stained with Weigert's iron haematoxylin (see footnote p. 45). (× 5.5.)

a — band to little finger; b — band to ring finger; c — natatory ligament between little and ring finger; d — hypercellular areas (cf. **Fig. 17 A**).

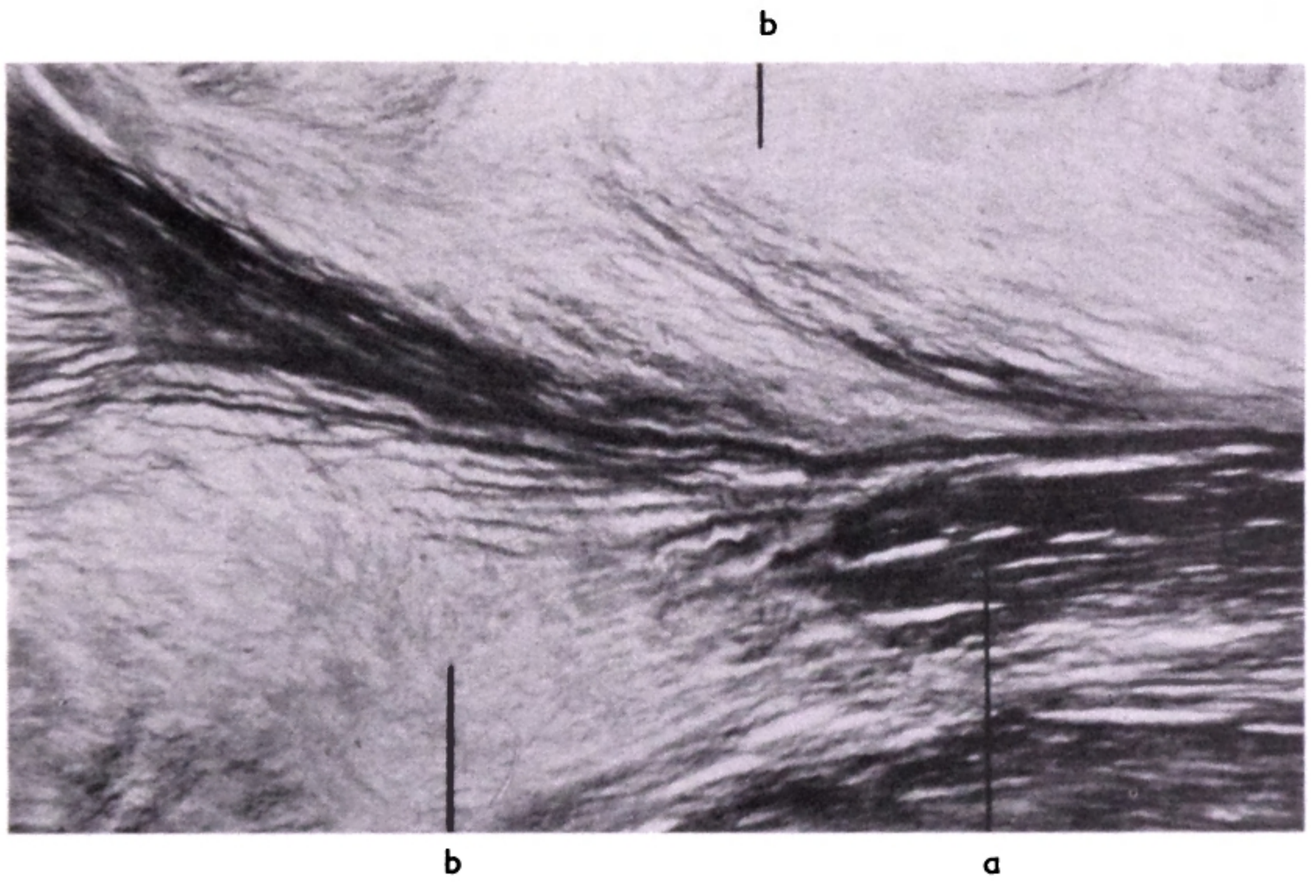

Fig. 16. Photomicrograph from the section shown in Fig. 15 at greater magnification (× 100).

Note how some bundles of collagen fibres (a), stained black, pass through the gray areas (b) (cellular tissue) whereas others show signs of interruption in the border zone of the cellular area.

in contrast with the poorly cellular fibrous tissue of the aponeurosis, which stained dark.[1] The figure shows how the cellular areas are distributed in the homogeneous fasciculi of the aponeurosis. Sections corresponding to the cellular areas and those poor in cells, stained with haematoxylin and eosin are shown in greater magnification in Figs. 17 A and B. These areas of hypercellular connective tissue occurred irregularly and in variable numbers in the pathological aponeurosis. They were diffusely defined towards the surrounding aponeurotic tissue and showed varying degrees of maturity. The areas shown in Fig. 15 are small and represent a relatively early stage with young connective tissue. Others at times were of such a size that they protruded in the form of nodules on the surface of the aponeurosis.

As was pointed out earlier, these nodules can clinically be regarded as the initial stage of the disease and the writer wishes, on the basis of his own investigations and the statements available in the literature,

[1] These staining conditions were observed by chance in trial staining with stale solution. The fibrous tissue does not stand out as distinctly when newly mixed Weigert's iron haematoxylin is used.

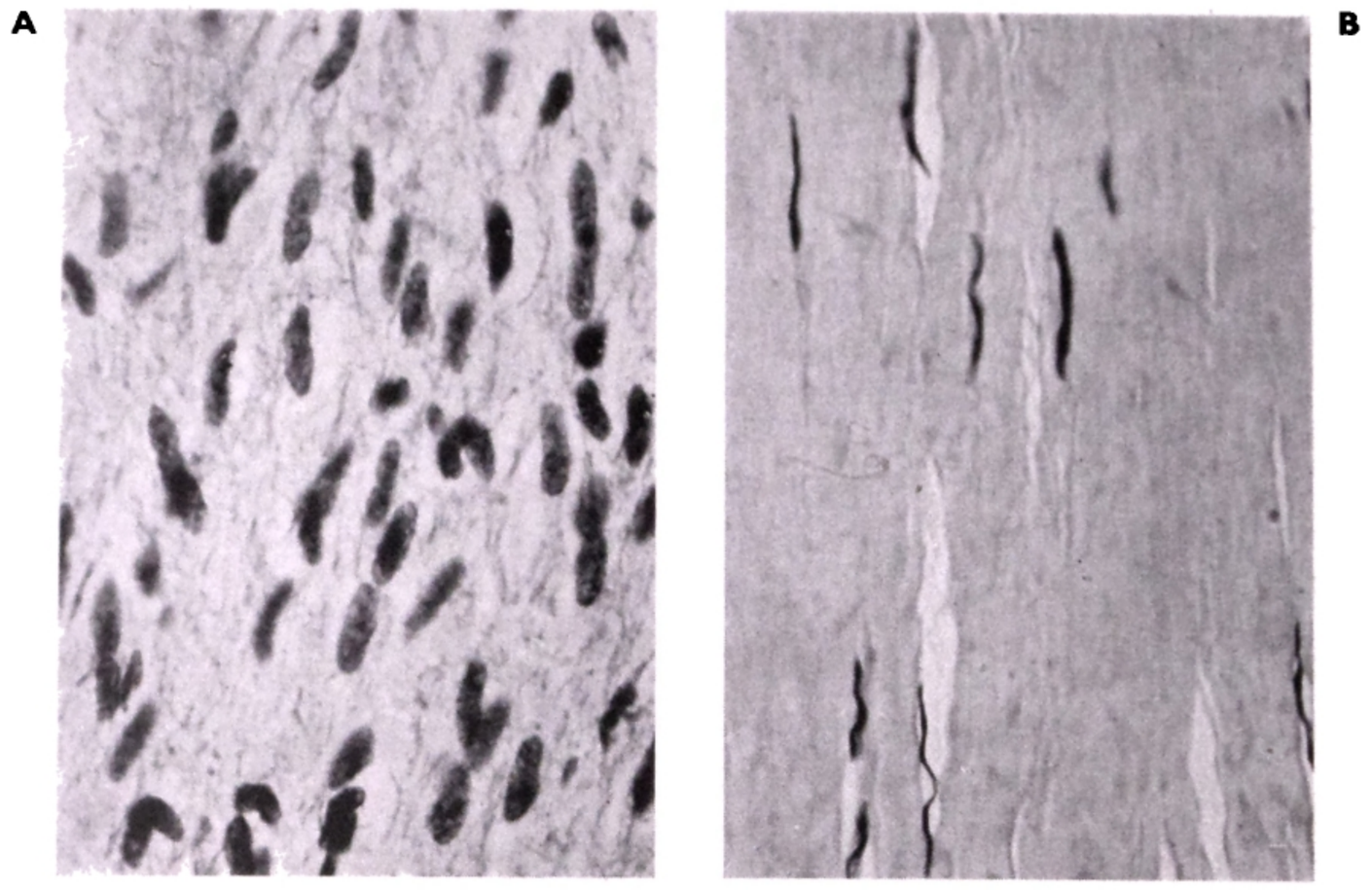

Fig. 17. **A** — Section corresponding to the gray areas in Fig. 15 (d) and Fig. 16 (b) showing undifferentiated connective tissue. Such localized hypercellular areas substantiate the nodular thickening of the palmar aponeurosis characterizing Dupuytren's contraction.

B — Section corresponding to the aponeurotic bands stained black in Fig. 15 (a, b) showing tendon-like poorly cellular connective tissue almost entirely composed of compact bundles of collagen fibres. The nuclei are thin and elongated. A and B stained with haematoxylin-eosin. (× 500.)

to consider these hypercellular areas as pathognomonic for the pathohistology of the disease. It is therefore surprising that their morphogenesis has been so little studied. The question has been the subject of particular attention by the writer and the observations made will be given here.

It appears to the writer that even the general picture in Fig. 15 gives the impression that there is an interruption in the fasciculi of the aponeurosis at these sites. If the borderline of such a light cellular area is examined at a higher magnification (Fig. 16) it is seen that the fibre bundles of the aponeurosis are partly split by the expansile proliferating connective tissue, but that a number of fibres also unmistakably show signs of interruption in this region. In the same figure it is seen, for example, how a number of fibres look frayed and have the wavy structure characteristic of ruptures of collagen fibres. It was only in areas whose structures indicated

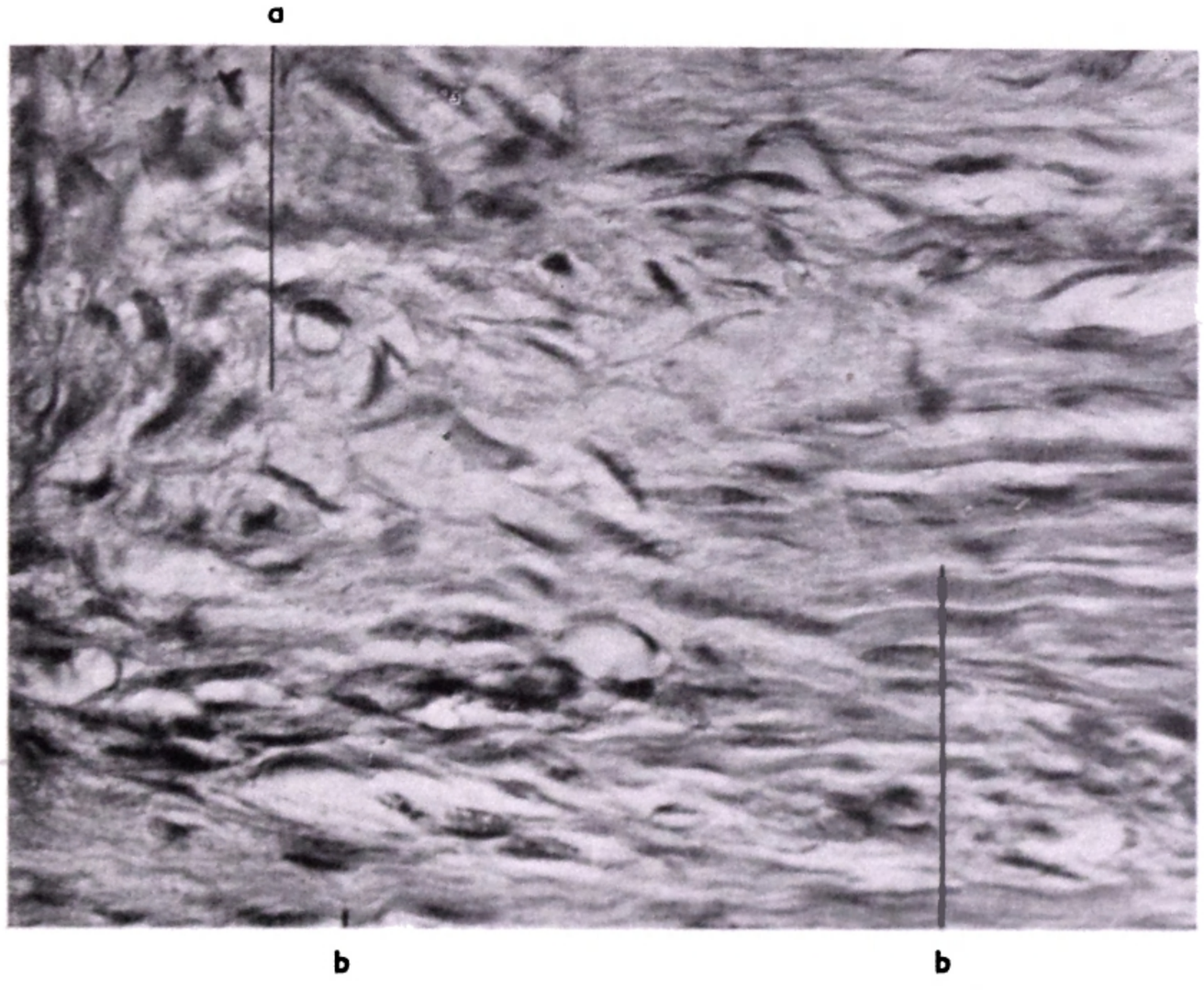

Fig. 18. Section from the palmar aponeurosis in Dupuytren's contraction, showing the periphery of a cellular area of young fibroblasts (a). Note how a number of the collagen fibre bundles (b) in the aponeurotic tissue show signs of interruption in the border zone of the cellular area. Stained with haematoxylin-eosin. (· 470.)

that they were relatively new in which such distinct interruptions in the aponeurotic tissue could be observed. In other areas the fibrillar elements of the aponeurosis merged more organically with the intercellular substance. In a number of places the border was relatively distinct, with a zone of connective tissue cells towards the aponeurotic tissue.

A very early stage in the development of these nodules is shown in Fig. 18 with young undifferentiated connective tissue. In a number of sections it was possible to observe how these new formations of connective tissue issued from the perivascular tissue of the adjacent vessels. The vessels in the vicinity were dilated and increased in number and were surrounded by perivascular sheaths consisting of fibroblasts as well as a few leucocytes and round cells (Fig. 19) and at times even a few mast cells. The round cell elements predominated beside more mature areas. It was certainly not a question of an inflammatory tissue reaction.

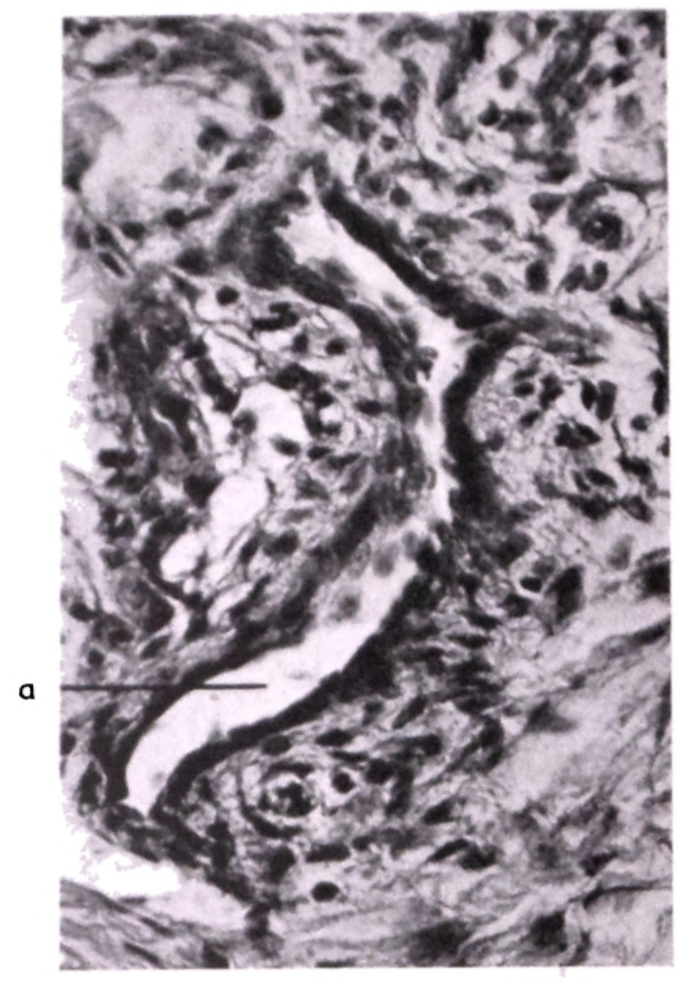

Fig. 19. Photomicrograph showing blood vessel (a) with perivascular cellular tissue mainly consisting of fibroblasts. Section taken from the periphery of a cellular area in Dupuytren's contraction similar to that seen in Fig. 17 A. Stained with haematoxylin-eosin. (× 370.)

Figs. 20 A–D show the development of the cellular areas from a relatively early stage of undifferentiated connective tissue to a fibrous tissue. In the earlier stages there were mitotic figures but the growth was uniform and regular. The intercellular fibres were very thin and stained brownish-black on silver impregnation (Bielschowsky's method) indicating that they were precollagen in character. In later stages these fibres stained in a manner typical of collagen substances. There appeared to be no new formation of elastic fibres. In the smaller nodules the intercellular substance and the cell nuclei showed a relatively regular arrangement parallel to the surrounding fibre bundles. In cases in which the nodules had extended beyond the true aponeurosis, their transverse section gave a confused impression, with the general direction of the cells in various parts traversing each other in several planes. Moreover, the degree of maturity in the various parts of these large nodules varied at times. It was not possible to establish any relation between the histological picture and the clinical features of the disease. It is particularly interesting that the cellular areas in the central parts contained iron pigment

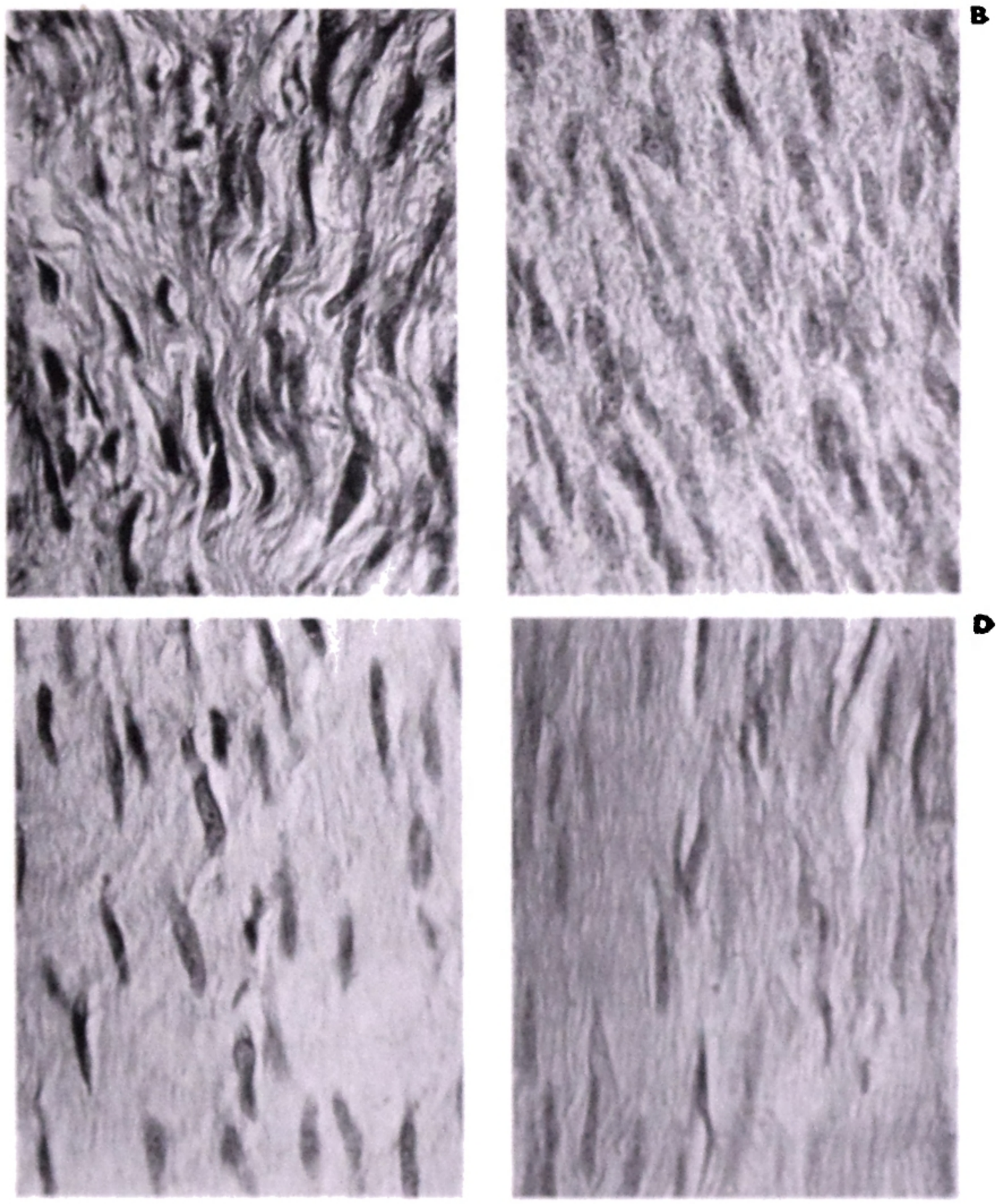

Fig. 28. Sections showing various stages of maturity in the cellular areas of the palmar aponeurosis in Dupuytren's contraction. Stained with haematoxylin-eosin. (× 500.)

A early stage in which mitotic figures occur. Plentiful young connective tissue cells, appearing to form a syncytium. The tissue is basophil. **B** The cells are now regularly directed than in the earlier stage. The nuclei are oval, relatively large, and stain rather purely. The intercellular substance is basophil. **C** Shows a later degree of maturity than B. The cells are more markedly spindle-shaped and the nuclei stain more strongly. There is an increase of intercellular substance. **D** Is more scar-like fibrous tissue. The intercellular substance is markedly acidophil and now are numerous collagen fibres. Even at this stage the tissue is fairly cellular.

A certain irregularity in the general structure is seen on examination of larger areas than in these sections.

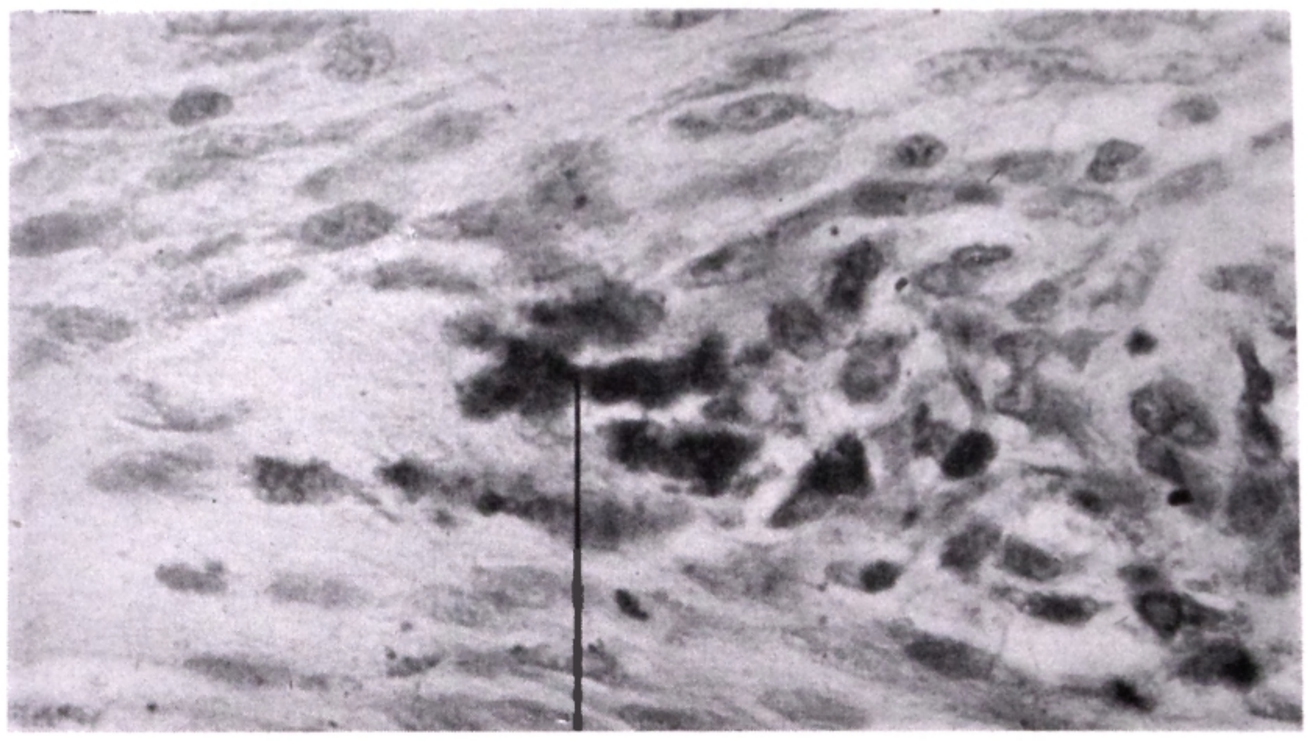

Fig. 21. Section from the centre of a fairly fresh nodule of the palmar aponeurosis in Dupuytren's contraction. The dark staining of the tissue at (a) is due to plentiful iron pigment in the cells and in parts of the intercellular substance. Stained Berlin blue. (× 500.)

(Fig. 21). This was most abundant in the younger areas. Iron pigment did not occur in the normal parts of the aponeurosis nor in the normal material.

The pathological tissue was also characterized by the tendon-like cords described earlier. These consisted of compact, fibrous connective tissue on the whole reminiscent of normal aponeurotic tissue. The relative cellularity was, however, smaller owing to a considerable increase of the intercellular substance. In particular the collagen fibres were coarser and more numerous whereas the elastic fibres only appeared in small numbers even on staining differentially for elastin. Histochemically, this connective tissue differed from the aponeurotic tissue of normal appearance in that it was less acidophil and stained yellowish-brown with van Gieson's method instead of a reddish colour as did the normal aponeurosis. Staining with azan gave a red colour in large areas of the otherwise blue tissue, when it could have been expected that the entire cord would have been homogeneously blue. Such deviations from the normal stainability were only exceptionally found in small areas in the normal aponeurotic tissue.

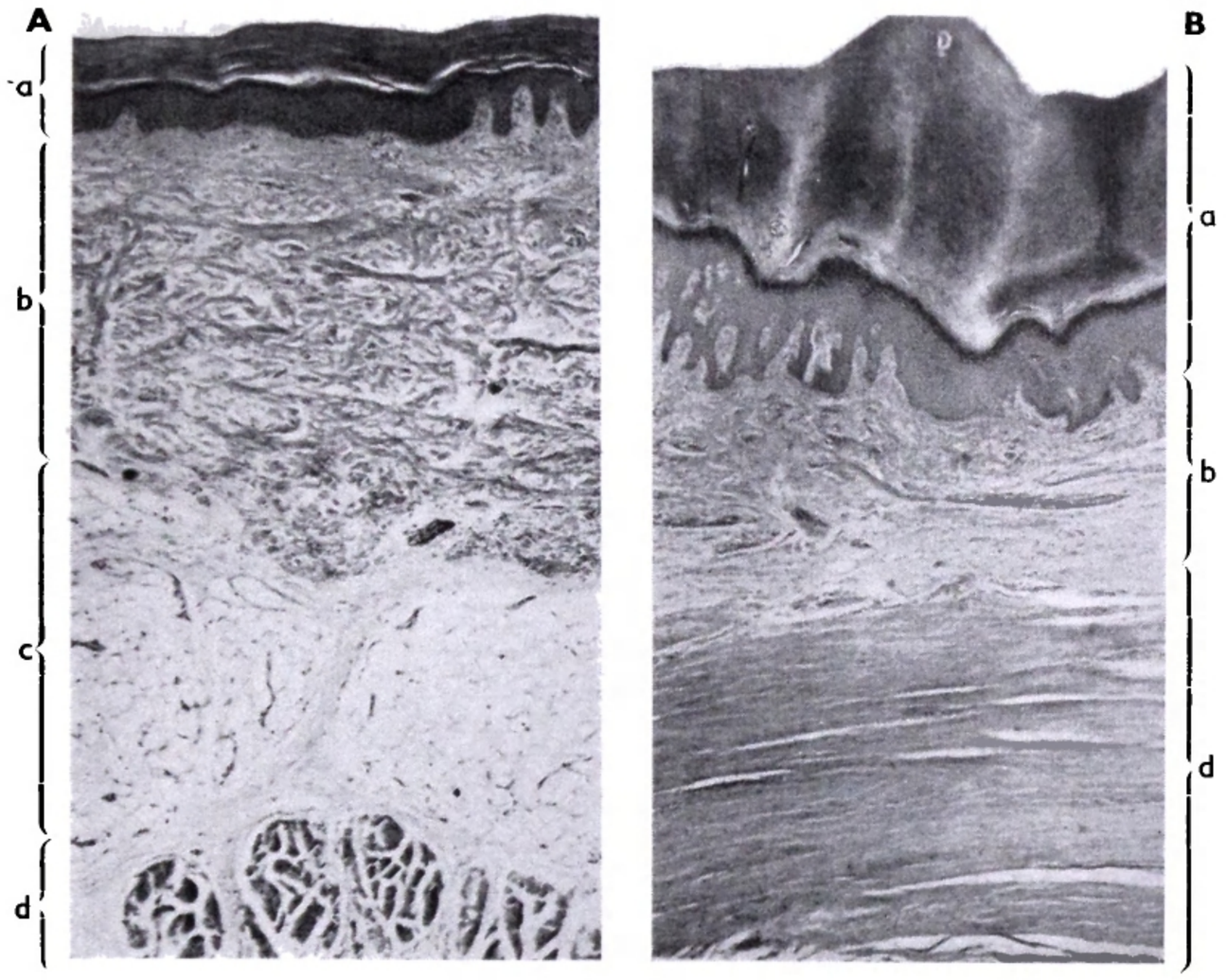

Fig. 22. Sections through the palmar skin and aponeurosis. **A** — in normal conditions; **B** — in Dupuytren's contraction Photomicrographs. (× 20.)
a — epidermis; b — corium; c adipose tissue; d — palmar aponeurosis.

Note in B thickening of the aponeurosis and epidermis as well as disappearance of the subcutaneous adipose layer.

Staining with toluidine blue[1] gave, within the cords, a very pronounced diffuse metachromasia. This was not the case in the rest of the aponeurotic tissue. This was a true metachromasia, i. e. it remained unchanged after heating and was not affected by absolute alcohol.

None of these unusual staining reactions can be regarded as the expression of any known pathological condition of the connective tissue.

Skin. In the operating technique used in the writer's material, the palmar skin was not excised. Only in seven cases were small portions removed for microscopical examination from areas in which the skin

[1] The preparations were stained with toluidine blue (Grübler & Co., Leipzig; made for staining of mucus) in 0.5 per cent solution, followed by differentiation in 96 per cent alcohol. The preparations were mounted in Canada balsam via absolute alcohol and toluol.

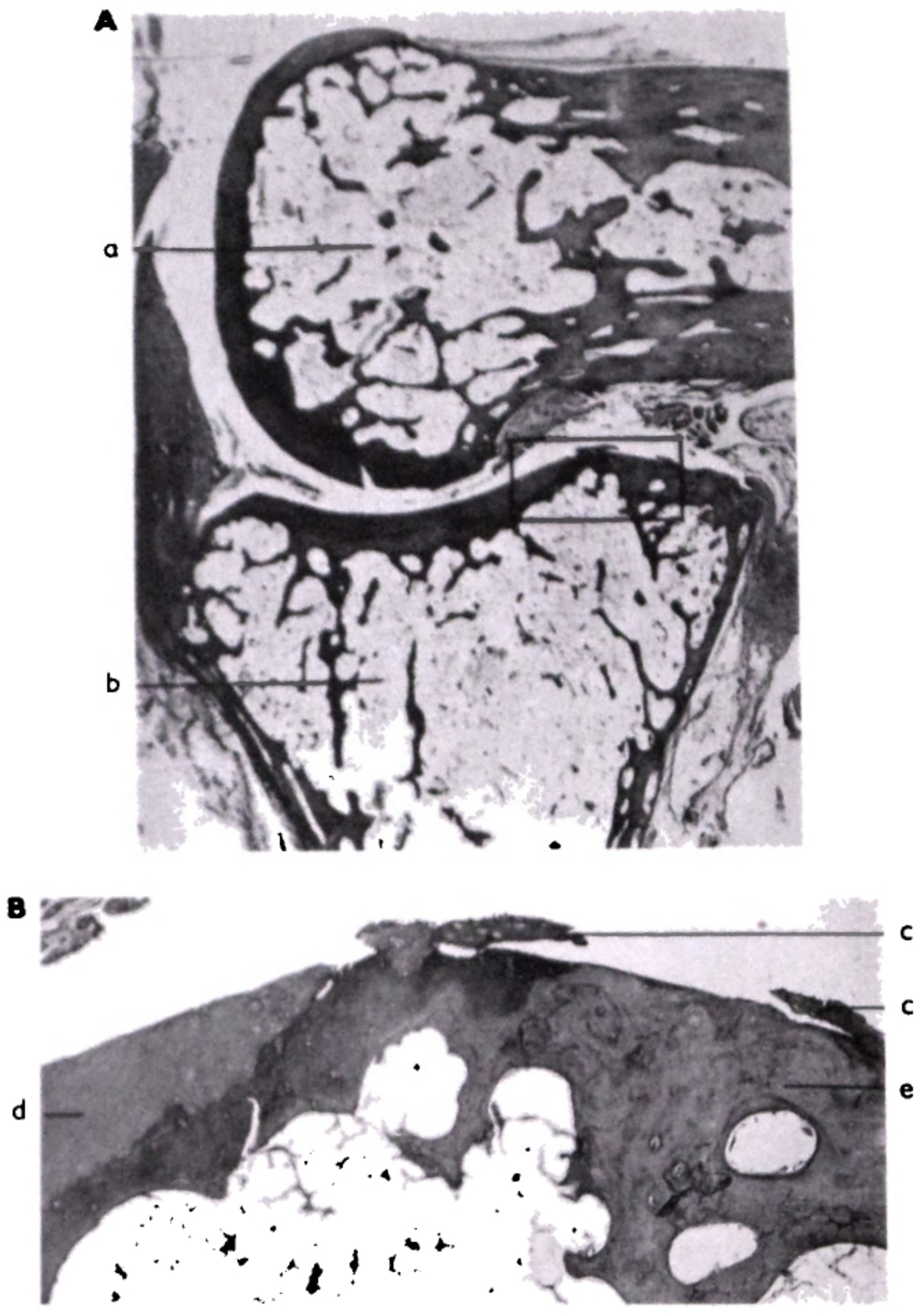

Fig. 23. Sections of the 5th proximal interphalangeal joint in a 74-year-old woman with Dupuytren's contraction of about ten years standing. B corresponding to square in A. Stained with haematoxylin-eosin. Photomicrographs. (× 5 and × 25.)

a — proximal phalanx; b — middle phalanx; c — fragment of cartilage; d — normal articular cartilage; e — bone.

Note deformity of the articular surface of the middle phalanx. Its volar third, which is not in contact with the articular head, lacks cartilage except for a few small fragments (c).

appeared to be affected by the changes in the underlying aponeurosis. In three cases there was slight hypertrophy of the epidermis in these areas, caused by thickening of the horny layer. In the papillary zone there was some irregularity. The corium was fibrosed, and in the

subcutaneous layer the normal, adipose tissue was replac dense fibrous tissue which attached the skin tightly to the apc sis. Fig. 22 shows some of these findings.

Finger-joints. The flexion deformity is usually most pron in the proximal interphalangeal joints. In one case the writ able to examine microscopically one of these joints in which perr flexion had caused subluxation of the second phalanx and owing great age of the patient amputation was decided on. The sect Fig. 23 show the deformity of the joints. This was most ap in the shape of the concavity of the second phalanx. It is inte to note that the cartilage of this articular surface had only disap in that region which was not in contact with the opposite ar surface. On the articular head the entire cartilage was although it showed signs of degeneration in small areas. however, pressure and friction from the articular concavity as from the joint capsule on the dorsal aspect is exerted on the surface of the head. These functional factors are naturally of d importance for the retention of the cartilage. This preparati showed that the joint capsule on the volar aspect had shrun tense thickened connexion in the angle between the two pha

No microscopical examinations of this kind are to be fo earlier works on Dupuytren's contraction.

These joint changes cannot be considered as specific to the c They can be satisfactorily explained as an effect of a faulty p of long duration and of abnormal pressure on the articular su From a practical point of view these secondary changes are great significance. If the cords which originally gave rise to the are removed, it is surprising to find that the changes are rev to a great extent with rational after-treatment (Fig. 48).

C. Electron Microscope Observations

The electron microscope technique provides a promising r for studying the fibrillar structures of collagen tissue. Micro made with the electron microscope have revealed that the collagen fibres which can be resolved by the light microsc formed by submicroscopic fibrils. SCHMITT et al. (1942) for in found that in the preparations of collagen tissue from various s

certain widths, of the order of 500—1,000 Å, greatly predominate. These authorities also thought that this implied that such units might exist in the intact tissues. Many collagen fibrils are characteristically cross-striated due to a regular alternation of relatively dense and transparent bands. SCHMITT et al. found the periodicity of this "spacing" as revealed by the electron microscope to vary considerably from one fibril to the next but the average value, 644 Å, coincided with the X-ray fibre-axis long spacing of 640 Å reported by BEAR (1942). These findings are interesting but further investigations are required before the relation of electron microscope observations to physical chemical data previously obtained can be estimated.

In the application of the electron microscope to biological investigations, there are as yet many unresolved sources of error. Provided, however, that its application is restricted to comparative investigations under strictly uniform conditions, the electron microscope can provide valuable information as to the submicroscopical structure of tissues. In this particular investigation, it has been applied to material collected from the diseased and normal parts of the palmar aponeurosis in patients suffering from Dupuytren's contraction. As far as the writer is aware, investigations such as are reported here, using this instrument, have not previously been carried out.

Material and Methods. In nine operated cases of Dupuytren's contraction, pieces a few millimetres in length were excised from the characteristic, tendon-like cords which extend within the aponeurosis towards the contracted fingers. The sections were taken at sites where the cords were well defined and with a completely homogeneous tendon-like appearance on the surface of the section. They were excised as proximally as possible in the palm, i. e. within a part of the aponeurosis where cellular areas were rarely observed. As described earlier, these cords are chiefly composed of collagen fibres.

The control material consisted of six preparations from the aponeurosis of the same persons, but taken from parts in which it was of normal appearance and without signs of shrinkage.

Immediately after the excision the preparations were transferred to 1 per cent osmic acid (OsO_4) and fixed for at least a week. They were then washed in running water and sectioned by the freezing method.

The sections were immersed in a few cc distilled water in a 50 cc retort with a plane bottom and placed in an ultrasonic field for 150 seconds. In addition, fractions of seven specimens were exposed to ultra-sound for 60 seconds only. A magnetostriction oscillator with a frequency of 22.7 kilocycles and an effect of 0.3 watt/cm^2 was used. The vibrations produced by the ultrasonic field exhibit strong dispersive powers. This has proved eminently suitable for converting collagen fibres into sub-microscopic fibrils.

A drop of this water suspension of the specimen was placed on a conventional electron microscope specimen screen with supporting film. Electron micrographs from five different parts of the visual field of each preparation were taken at a magnification of 20,000 times with a Siemen's electron microscope. Extremely hard paper was used for the photographic prints. The width of all the fibrils below 500 Å was measured on the prints with an ocular micrometer at a magnification of 16 times. At the narrowest part of each fibril three measurements were taken and the average was used. Thick fibrils were excluded since in many cases they were in all probability composed of a number of finer fibrils. Fibrils showing definite cross-striation were measured under a magnifying lens for as long a distance as possible and the average figure of the "spacing" was calculated. In order to obtain the maximum of objectivity the fibrils were measured without advance knowledge of the group of material to which the micrograph belonged.

The method was used earlier by INGELMARK (1948) on tendinous tissue. He discussed the sources of error of the method and made a partial study of them. In this connexion one of his observations is of interest, i. e. that neither the duration of the ultra-sound treatment (30, 90 and 100 secs.) nor the ultra-sound frequency (22.7 and 300 kilocycles) affected the width of the fibrils. The reader is referred to his paper for further details.

Results. Fig. 24 shows an electron micrograph of palmar aponeurotic tissue. The width of the fine fibrils ranged from 140 to 460 Å. Larger fibrils often branched and thus appeared to be bundles of thinner fibrils. The cleavage was always longitudinal. Moreover, when there was a break in a large fibril some of its finer fibrils were seen to continue their course without interruption.

In order to obtain sufficient material for statistical treatment, and to ensure that the extremely small preparations examined were representative, all the fibrils measured in each group were collected and their average width (M) calculated. The result (Table 6) shows

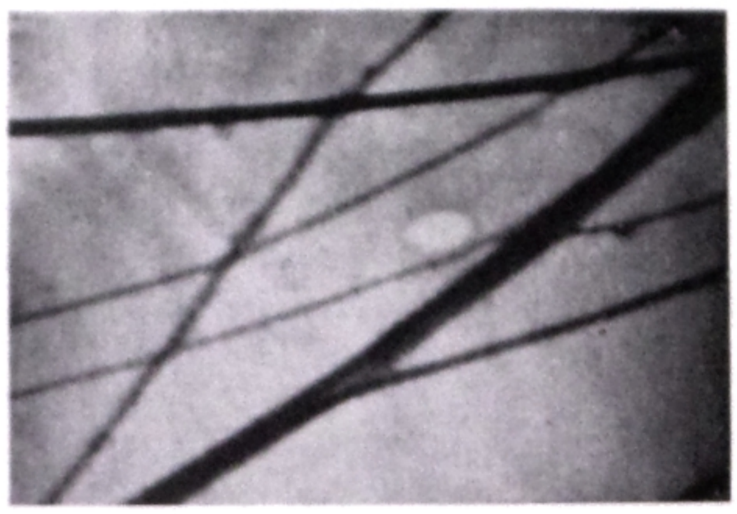

Fig. 24. Electron micrograph showing collagen fibrils from normal palmar aponeurosis. The finest fibrils cross-striated about 300 Å in width. Note branching of thicker fibril. (· 20,000.) (Cross-striation clearer in original micrograph.)

that the width of the fibrils is greater in the dense fibrous cords in the pathological parts of the aponeurosis than in the normal aponeurotic tissue. The difference, 27 ± 3.8 Å (approximately 10 per cent) is statistically significant. The fractions of the preparations which were only treated with ultra-sound for 60 seconds are also included in these figures since this deviation in the method does not affect the width of the fibrils. The widths of the fibrils in both groups are shown graphically in Fig. 25.

The characteristic striated structure only appeared clearly in the fine fibrils. The distance in the direction of the long axis between adjoining bands of similar photographic density — the spacing — was fairly uniform in any given fibril but varied between 350 and 750 Å approximately in different fibrils. The average figure was found to be lower in the preparations from pathological tissue (Table 6). Owing to the infrequency of clearly striated fibrils (as shown in

TABLE 6

Electron Microscope Observations on Collagen Fibrils from the Palmar Aponeurosis in Dupuytren's Contraction (The Writer's Material)

	Normal tissue (N)		Pathological tissue (P)*		Difference
	Number	$M' \pm \varepsilon(M')$	Number	$M \pm \varepsilon(M)$	$N-P$
Width in Å	291	256 ± 3.0	492	283 ± 2.4	27 ± 3.8
Spacing in Å	73	488 ± 9.5	65	465 ± 7.8	23 ± 12.3
Percentage frequency of striated fibrils	—	25 ± 2.5	—	13 ± 1.5	12 ± 2.9

* Selected parts of well-defined cords in the diseased aponeurosis.

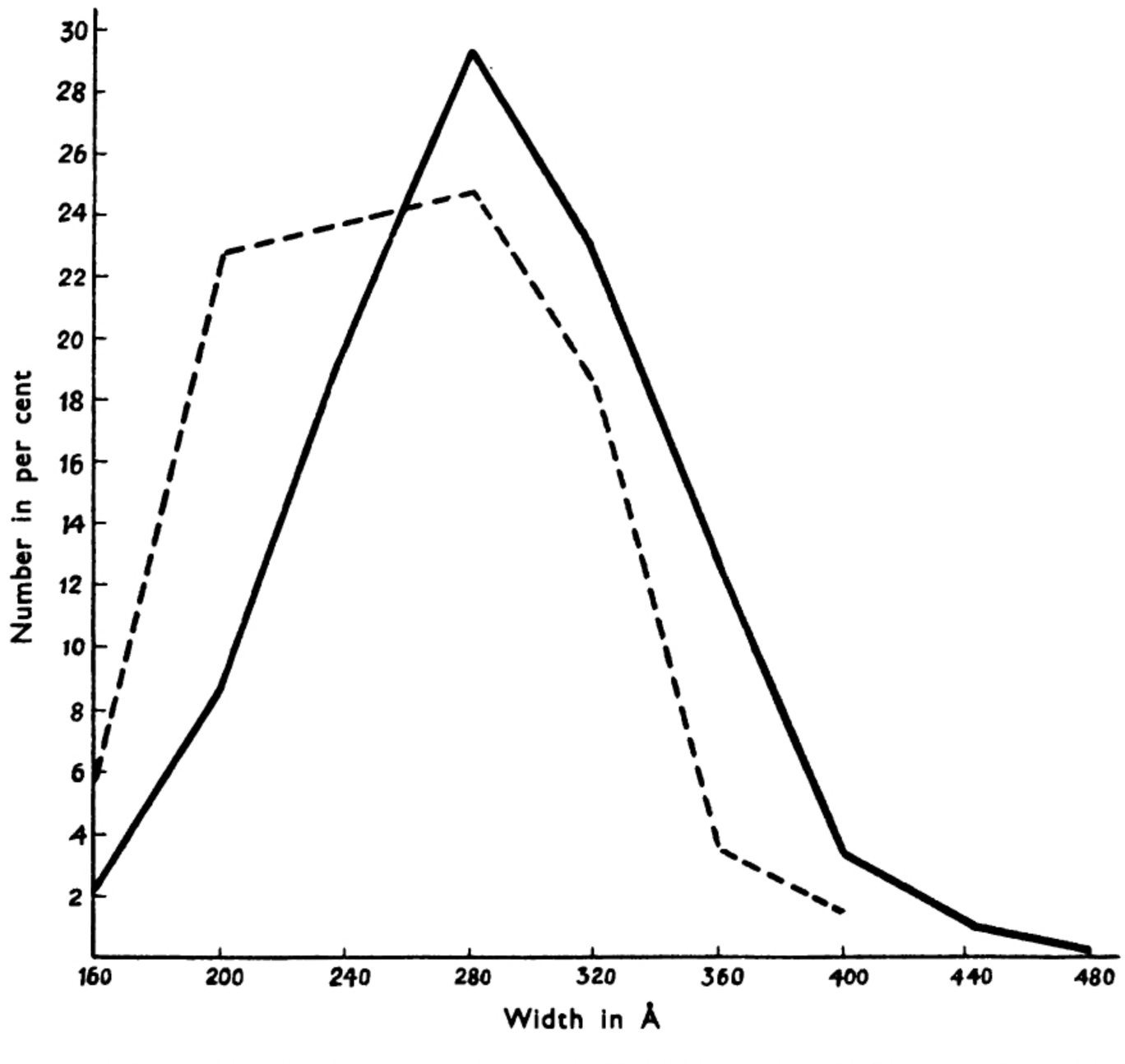

Fig. 25. Distribution of widths in the collagen fibrils given in Table 6. Note how, in comparison with the curve representing normal aponeurotic tissue (dotted line) that for the pathological tissue (unbroken line) is displaced in the direction of greater widths.

the same Table) the difference in spacing between the normal and pathological tissue is subjected to such large average errors that it is not possible to determine whether this is merely accidental.

Cross-striated fibrils, partly split into finer fibrils with identical striation, are at times seen on the electron micrographs. Since it is not possible to determine the frequency of such bundles in the striated fibrils measured in the respective groups, a comparison of the relation between the width of the fibrils and the spacing would give very indefinite information.

Discussion. It is of interest to note that in principle the collagen fibrils showed, with small deviations, the same structure in the normal and pathological parts of the aponeurosis, and also that these

observations agree on the whole with those made previously as regards collagen fibrils in general. The width of the fibrils was, however, throughout less than that generally stated. Shrinkage of the preparation through lengthy fixation may possibly have been a contributory cause. In this connexion it is to be noted that INGELMARK obtained somewhat higher figures for the width of collagen fibrils from tendon tissue, using the same method but with fixation for 24 hours only. The absolute figure for the width of the fibril is, however, of less importance in the present investigation. Even if collagen tissue is well able to withstand the considerable physical effects of various kinds in the electron microscope method, it is impossible to determine accurately to what extent the structures observed correspond to conditions in vivo.

It is also possible that, using an improved technique, the collagen fibrils studied here could be split into still finer morphological units. Using ultrasonic waves for dispersion, however, the fibrils are distinguished as a relatively uniform group with an average width comparable to that obtained for the collagen fibrils with another technique in preparing the specimens. The figures in Table 6 can only be afforded a relative value. Nevertheless, the statistically significant difference in the average width between the pathological and the normal tissue is still of interest, despite this limitation, since both materials were similarly treated. The significance of this fact will be considered in the section on pathogenesis.

If the regular cross-striation of the fibrils corresponds in any way to the arrangement of the long polypeptide chains which form these fibrils, it is of interest that a difference in the spacing of the two groups examined exists, even though this is not statistically significant. The pathological tissue with an average value of spacing below that of normal aponeurotic tissue represents in fact a retracted collagen tissue. On the basis of other investigations there is reason to believe that the shortening of collagen fibrils is caused by a change in the configuration of their polypeptide chain system (ASTBURY 1941, and others). Variations of the periodicity from one fibril to another within the same specimen would then imply a varying condition of retraction in the fibres. As has been mentioned previously, the method of examination can, however, have affected their structure in some unknown manner.

The importance of the statistically significant difference in the frequency of striated fibrils in the respective groups is uncertain. WOLPERS (1944) mentioned that cross-striation in collagen fibrils was lacking in a number of pathological conditions (myxoma, etc.). He did not give any explanation of this remarkable statement. As regards the present writer's material, it would appear probable that the histochemical peculiarities in the aponeurotic tissues manifested in staining with various media could in some way be connected with the various submicroscopical characteristics of the fibrils.

II. PATHOGENESIS

In the account given above of the pathological anatomy of the disease, it was described how the characteristic changed areas in the aponeurosis develop from a stage of young, richly cellular connective tissue into more or less scar-like tissue. This development appears to the writer to indicate that these local tissue changes arise on the basis of partial ruptures in the aponeurotic tissue. The extent of the pathological areas would in this case imply multiple ruptures and it is questionable whether a plausible trauma could in fact have such an effect.

In order to ascertain whether this was the case, the writer overstretched the longitudinal fibres of the aponeurosis by hyperextending the fingers. This was done in a few cases immediately before operation. Microscopical examination of these preparations verified the assumptions made. Partial ruptures, of varying size and irregular distribution, were present in the longitudinal fasciculi of the aponeurosis. Figs. 26 A and B show two such experimentally produced ruptures. If Fig. 26 B is compared with Fig. 18, which shows the border zone of a cellular area within the aponeurosis, the similarity in the fibrillar structure of the aponeurosis (b) in both pictures is striking.

The presence of iron pigment only in the newly formed connective tissue can be considered as strong support for this theory. Such pigment was found particularly in the centre of young hypercellular areas and can with all probability be interpreted as remains of small haemorrhages following local lesions in the aponeurosis.

The evident correlation of the disease to increasing age would

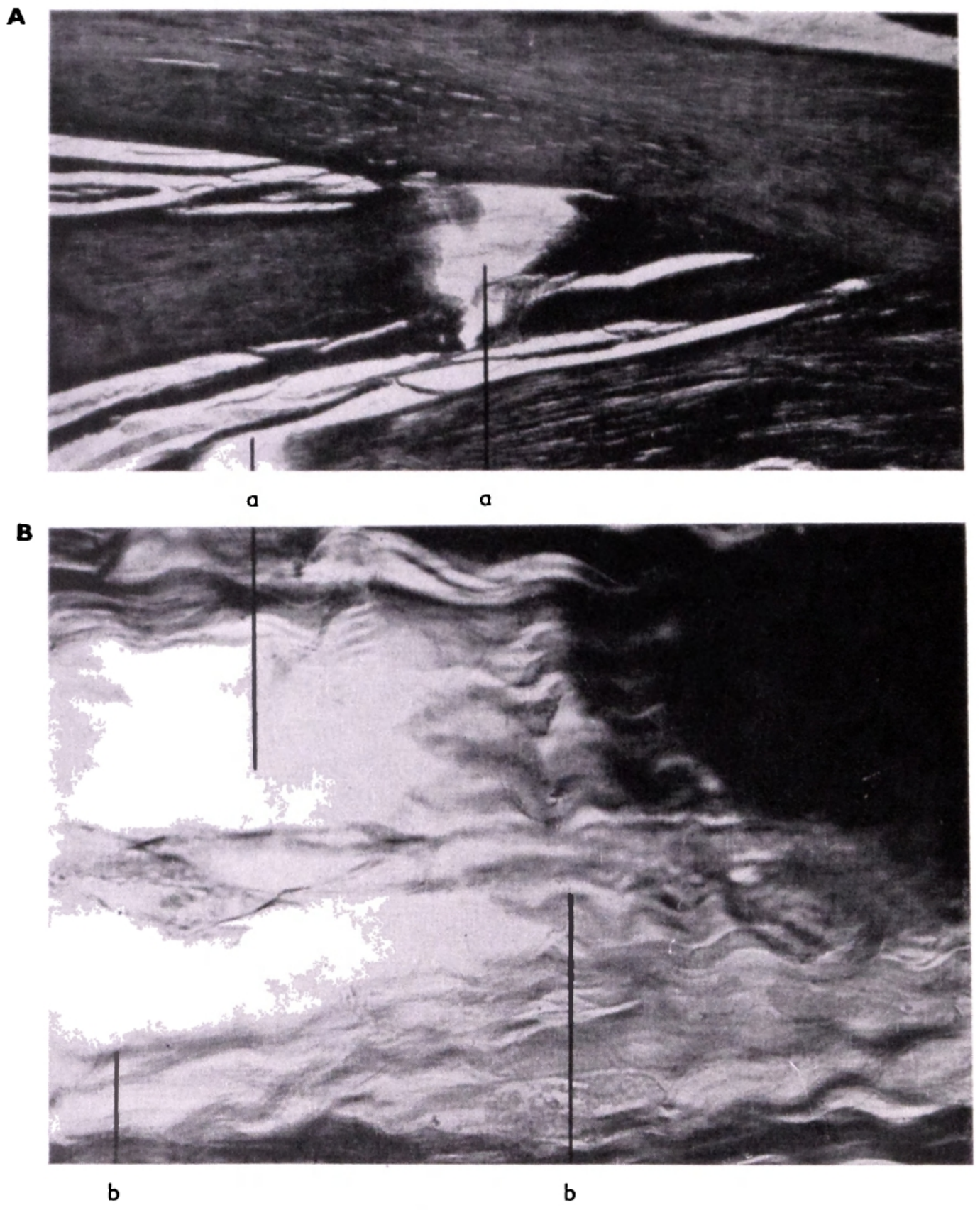

Fig. 26. Sections showing experimentally caused partial ruptures (a) of the palmar aponeurosis. For details see text. Stained with Weigert's iron haematoxylin.

A — (× 40) Note how some unbroken fibres pass through the main rupture;
B — (× 450) Note the wavy, frayed structure of the ruptured collagen fibre bundles (b).

be naturally explained in the light of the suggested pathogenesis since it is known that connective tissue undergoes changes in the course of years and, amongst other things, decreases in elasticity

and in stretching and breaking capacity (PAYR 1921, and others). Increased age, accompanied by these changes, thus increases the possibility of ruptures of the connective tissue.

The question then arises: *Is such a pathogenetic theory sufficient to explain the entire pathological process in the peculiar form found at the fully-developed stage?* The course of development, as envisaged by the writer, is described below.

A partial rupture in the aponeurosis arises for some reason and this heals with connective tissue with plentiful cells which gradually, by means of an increasingly fibrillar substance, arrives at a scar-like stage. Here, as in all similar processes, shrinkage takes place. This gives rise to a tenseness in the fascicular system within which the process lies. A condition is then present from which there are several developmental possibilities.

If there is very little shrinkage and the connective tissue in the fasciculi is sufficiently elastic, the condition should remain stationary. If, however, there is considerable shrinkage or the fasciculi in the aponeurosis are brittle, the possibility of fresh ruptures is increased. A vicious circle then arises, which should lead to increased finger contraction if, for example, the strong pretendinous bands are involved. If shrinkage of an individual fascicular system occurs, this causes in addition a disturbance in the balance between the various fibrous systems of the aponeurosis, which can be accompanied by increased tension even in parts which are not directly involved. There is then the possibility of the process spreading to the adjacent parts in a similar manner. There is also a third possible developmental process, i. e. despite considerable shortening, the fasciculi have still such tensile strength that they do not rupture. When the hand is used to its full capacity, these retracted parts are exposed to greater functional strain than the other parts of the aponeurosis. It would then be only natural if, as a result, they underwent activity hypertrophy and became thickened.

The present writer's theory would thus also explain the development of the second characteristic of the pathological process, i. e. the massive cords of collagen connective tissue. These have a considerable tendency to shrinkage and their denseness causes unfavourable nutritional conditions in their central parts. In this way conditions for fresh ruptures would also gradually arise within these cords.

In actual fact, clinical analogies exist to the different developmental processes described above which thus can be thought to arise as a result of partial lesions in the palmar aponeurosis. Satisfactory comparative material is found in the description of the symptomatology of the disease in the writer's material.

Several reasons appear to support the above hypothesis regarding the development of the cords in the aponeurosis. The writer was able to observe that those patients in whom the cords of this type were thickest had been employed in heavy work or, by lengthy and energetic extension practice, had endeavoured to conquer the finger contraction. Patients who had paid no attention to the deformity showed considerably thinner cords. Such a finding is naturally subject to several sources of error but the phenomenon was so evident in a number of cases that it is worthy of mention. As pointed out previously, these tendinous cords only developed axially towards the fingers, thus entirely corresponding to the dominating direction of the forces, concerned in finger movement. Moreover, it is known that the cord-like thickening of the aponeurosis can disappear after simple subcutaneous division (Fisher 1885, Hohmann 1936, and others).

It is also interesting that these cords showed very marked metachromatic stainability, in contrast to the normal aponeurotic tissue. The significance of the metachromatic staining reaction is not yet elucidated but it is assumed to be usually caused by high molecular ester sulphuric acids. According to Krauss (1944), and others, it is characteristic of tissue in which new formation of the fibrillar substance of connective tissue takes place and also of tissues exposed to mechanical strain. An investigation made by Wrete (1947) also gives certain comparative factors for the writer's material. He found that diffuse chromotrope substances occurred regularly in the connective tissue of the valves and tendinous cords of the heart in man. It thus appeared at that site in dense, poorly cellular connective tissue, which is under considerable functional strain.

The electron microscope investigations previously described are also in good argreement with the theory postulated regarding the development of the cords. These results are very interesting when compared with those of Ingelmark (1946, 1948).

He was able to demonstrate experimentally on white rats that systematic training was accompanied by a statistically significant increase (11.2 per cent) in width of the osmium impregnated collagen fibrils in the tendons of Achilles. Moreover, these tendons were thickened throughout. This agreement with the electron microscope findings in the palmar aponeurosis in the writer's material is not surprising, on the basis of the theory regarding the pathogenesis of Dupuytren's contraction brought forward here. It should be noted that the electron microscope investigation reported by INGELMARK was carried out by exactly similar methods and with the same equipment and technical assistance as the writer's investigation. The comparative value is thus increased since the possible sources of error must have influenced the results of both investigations in a similar manner.

This pathogenetic theory also explains why surgical intervention consisting only of section of the retracted cords, without further measures, causes new masses of subcutaneous connective tissue to develop at the site of operation with resultant progression of the deformity.

It can also be mentioned that the writer in several cases found the plantar aponeurosis affected by the same pathological process as the palmar aponeurosis and in the foot the clinical symptoms definitely favoured a similar pathogenesis. (See Chapter IV.)

It is known from other fields that a physiological shrinkage of connective tissue can be as excessive as that found in advanced cases of Dupuytren's contraction. An example is the shrinkage of scars following deep burns of the flexor aspect of the extremities. With regard to these cords, it is also known that the more it is attempted to counteract them by means of extension therapy, the stronger they become. It has never been attempted to seek the explanation of this condition in a specific disease.

Finally, it should be emphasized that the newly formed fibrous tissue was regarded as scar tissue, more or less hypertrophic. In order to give a complete clinical picture of the writer's opinion regarding the pathogenesis, it must be mentioned that the mechanical irritation which can be assumed to exist during the healing process would contribute to the formation of excessive scar tissue. Individual factors are also of considerable importance. This question, as well

as predisposing conditions for the occurrence of lesions in the aponeurosis, will be discussed in the chapter on aetiology.

There was nothing in the writer's preparations to contradict the opinion that the *skin changes* described were secondary to the process in the aponeurosis. It would otherwise be impossible to explain why, after aponeurosectomy, the palmar skin regained its normal appearance and elasticity. Nor was there anything to contradict the fact that the moderate, diffuse increase of cells which occurred in the vicinity of the localized changes in the aponeurosis was a sequel of the latter process. Regarded as an unspecific tissue reaction around these areas, it was no more pronounced than that acompanying any other process of regeneration. Moreover, as a result of the clinical characteristics of the disease, the area affected is in many cases exposed to considerable mechanical irritation.