Contraction Versus Contracture: Considerations on the Pathogenesis of Dupuytren Disease

9

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Contents

9.1 Introduction

Dupuytren contracture (DC) is regarded as a strange disease occurring on the palmar side of the hand. Following cell proliferation, collagen tissue is produced, forming thick bands. These bands shrink and cause deformities and loss of certain hand functions. DC usually does not cause pain and is not life threatening.

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In spite of intensive research spanning more than 150 years, we still do not know:

1. How Dupuytren Disease starts.
2. To what extent similar diseases at the plantar aponeurosis (Ledderhose Disease) and at the tunica albuginea (Peyronie disease) are related to Dupuytren Disease and why.
3. Why other adjacent collagen structures such as the flexor tendons are never involved.
4. The mechanism of shrinkage. Is it a process of active contraction similar to the shortening of muscle, or is it a passive contracture similar to a post-immobilization joint contracture?

9.2 The Involved Tissue of the Hand

A fundamental understanding of Dupuytren Disease and its pathogenesis will require taking into account the specific tissue and function of the hand. All tissue at the palmar side of the hand which is necessary to perform a soft and a firm gripping function may be involved in DC. Millesi (1959) performed anatomical studies of this tissue describing it as *dense connective tissue body of the palmar side of the hand* (Figs. 9.1 and 9.2). Flint (1990) used the term *palmar connective tissue continuum*.

One common feature of the connective tissues composing the dense connective tissue body of the palmar side of the hand is that they contain a high

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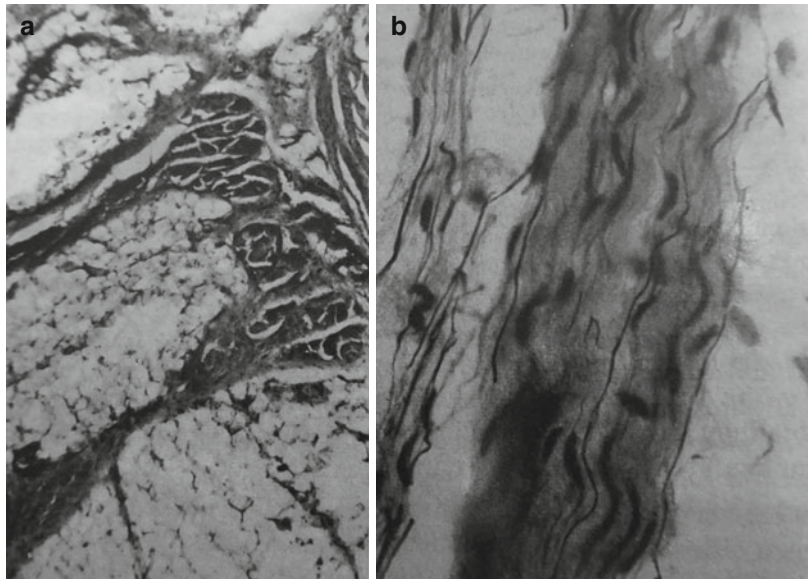


Fig. 9.1 Normal palmar aponeurosis. (**a**) Transverse section palmar aponeurosis. The skin is on the left side. Collagen fiber bundles ascend to the skin between fat lobules forming a three-dimensional network to permit soft gripping and distribute pressure. These fiber bundles emerge from the palmar aponeurosis, which fills the right upper quarter of the picture. The fiber bundles are cut transversely. In the right upper angle, one sees longitudinally cut collagen fibers, which belong to the deep transverse ligament of the palm. Hematoxylin–eosin, 1:28. (**b**) *Center*: Two collagen fiber bundles with collagen fibers showing the crimp structure of the collagen fibers and very few tiny elastic fibers between. This corresponds to a tension-bearing fiber bundle of a tendon. *Left side*: A fiber bundle with few collagen fibers and relatively more elastic fibers. This corresponds to gliding tissue. Prantner's elastic stain, 1:250

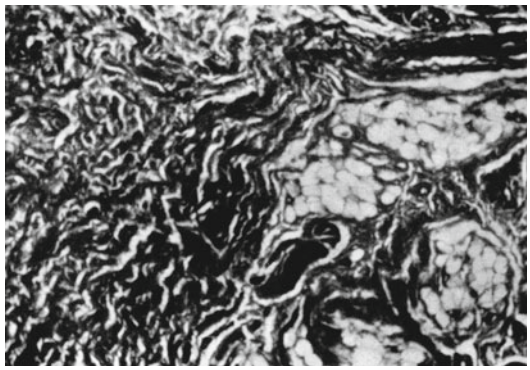


Fig. 9.2 Dermis–aponeurosis connections. An ascending collagen fiber bundle from the palmar aponeurosis merges into the dermis. This figure demonstrates the formation of a functional unit between the dermis, the ascending collagen fibers, the palmar aponeurosis, and the whole tension transmitting system of the palmar side of the hand. It is impossible to define a border between collagen fibers of the ascending segment of the palmar aponeurosis and the ones of the dermis. Hematoxylin–eosin 1:100

amount of elastic fibers and consequently have a high degree of elasticity. Another common feature is their involvement in Dupuytren Disease. In contrast, tendons are force-transmitting structures with a low elastic component and do not develop Dupuytren contracture. Figure 9.3 shows the difference in response to load bearing between normal flexor tendons and palmar aponeurosis (Millesi 2012).

Figure 9.3 shows that each tissue type lengthens (strain) moderately under low tensile load (stress). This is referred to as the *toe-in region* of the stress–strain curve. The toe-in region of connective tissues represents tissue lengthening under tension accommodated by the elastic capacity of the tissue. However, beyond this elastic capacity, tissue lengthens less for a given increase in load, and the slope of the stress–strain curve rises abruptly. This segment, between elastic tissue deformation and mechanical tissue failure, is referred to as the *linear region* of the stress–strain

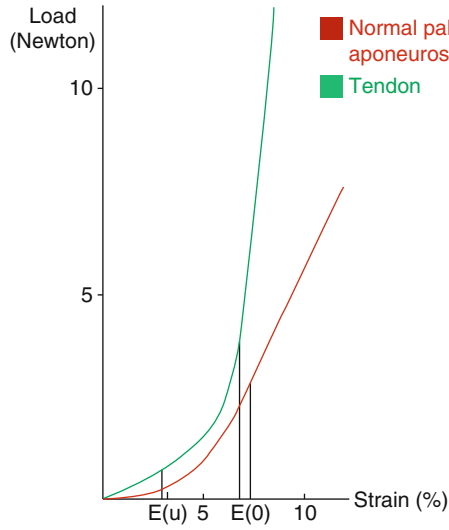


Fig. 9.3 Stress–strain test of flexor tendon and of palmar aponeurosis. Comparing the stress–strain test of fiber bundles of flexor tendon (*green*) and fiber bundles of palmar aponeurosis (*red*). The flexor tendon tissues are more stiff, and the palmar aponeurosis tissues are more elastic (Millesi 2012)

curve. The slope of the linear region reflects tissue stiffness. Figure 9.3 shows that palmar aponeurosis tissue is less stiff than flexor tendon tissue.

Elastic fibers are present in all dense connective tissue, including tendons and ligaments. These elastic fibers have two functions. The first is to recoil collagen fibers back into their resting crimp conformation when stress subsides. The second is mechanical energy storage and release through which tissue stretch and recoil supplement the force of intermittent muscle action. Compared to tendon tissue, the palmar aponeurosis tissue contains more elastic fibers in different arrangement, which may be a reason why the palmar aponeurosis may develop Dupuytren contracture, while tendons do not.

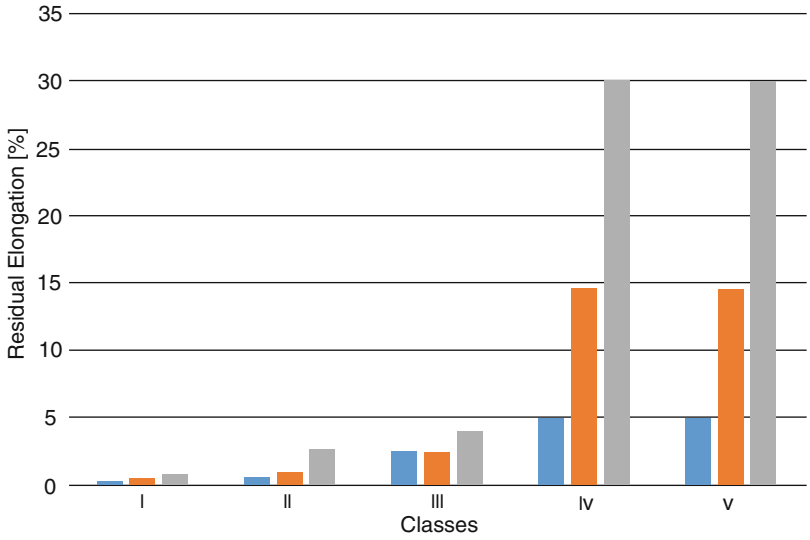
The majority of the body's elastic fibers are created early in life and normally have a low rate of degradation and turnover during one's life span (Sherratt 2009). Their life span may be shorter in the elastic connective tissue and due to genetic factors. Various other conditions may influence the properties of elastic fibers (alcohol, smoking, diabetes mellitus, etc.). Loss or weakness of elastic fibers causes loss of crimp structure, changing the mechanical characteristics of collagen fiber bundles. With loss of recoil and crimp, residual elongation increases (Table 9.1). This mechanical role of elastin is demonstrated by significant increase of the residual elongation of specimens of normal palmar aponeurosis treated with elastase to remove elastin (Reihsner et al. 1991).

9.3 How Does Dupuytren Contracture Start?

The cellular nodule, described by Langhans (1887), is the first stage of Dupuytren contracture (Luck 1959). On average, at least 2.5 years pass from the earliest diagnosis to the earliest surgery (DiBenedetti et al. 2011).

The author performed a unique series of cadaver dissections to define the earliest stages of the onset of Dupuytren contracture. All palmar aponeuroses of all cadavers dissected during one semester at the Department of Anatomy of the University of Vienna were studied by the author for signs of Dupuytren Disease. Specimens with very early, subclinical changes and their gradual transition into the full picture of DC could be studied. These results were compared with surgical specimens after complete fasciectomy containing apart from the contracture bands all stages of beginning DC and also apparently normal segments. The result was that the cellular proliferation is preceded by significant changes of collagen fibers and collagen fiber bundles (Millesi 1959). The most impressive change identified was the loss of the crimp structure (Fig. 9.4). The collagen fiber bundles thicken and fuse partially to form major units, but the original structure can still be recognized (Fig. 9.5). The elastic fibers disappear between the thickened fiber bundles exposed to traction. They survive in transverse fiber bundles of the deep transverse palmar ligament, which never is involved by DC (Fig. 9.6). Elastic fibers of the gliding tissue between the bundles lose their function and can be viewed as collections of deformed remnants of elastic fibers (Fig. 9.7; Millesi 1965).

Table 9.1 Residual elongation



Elongation of 2.5 % (blue), 5 % (orange), and 10 % (gray)
I. Palmar aponeurosis
II. Apparently normal palmar aponeuroses of a patient with DC
III. Thickening of collagen fiber bundles
IV. Contracture bands
V. Advanced contracture bands

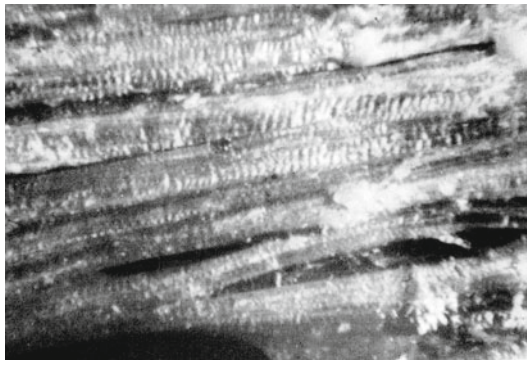


Fig. 9.4 Normal crimp structure. Palmar aponeurosis showing the crimp structure of the normal collagen fiber bundles in relaxed state. Note the rather transparent parallel running fiber bundles. The "cross striation" is caused by the undulated fiber bundles in relaxed state. The light illuminates the height of the waves and causes shadow in between. View by loupe with oblique light, 1: 20

Fig. 9.5 Loss of normal crimp structure in DC. Palmar aponeurosis with initial changes of Dupuytren contracture. The collagen fiber bundles are thicker than in Fig. 9.4. They have lost their transparent appearance and the crimp structure. There is a tendency to fuse with neighboring bundles. View by loupe with oblique light, 1: 20

Very early changes of mechanical properties occur. The stress–strain test of normal tendon shows initially a rise in elongation with little increasing force (the toe-in region) and a steep rise thereafter. When the extending force is removed, de-loading occurs along a different curve as an expression of lost energy (hysteresis). *Residual elongation* is the difference between the starting point of the stress–strain curve and the end point after de-loading (Table 9.2).

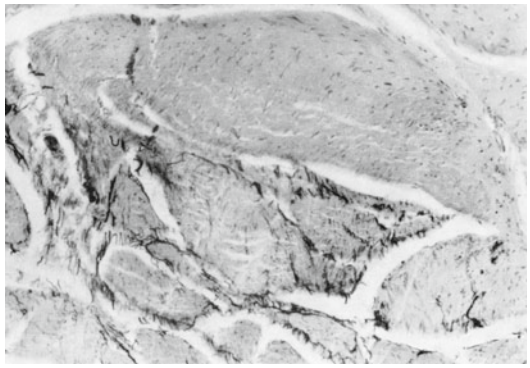


Fig. 9.6 Palmar aponeurosis with early DC. Longitudinal section at the level of the deep transverse ligament. Prantner's elastic stain. At the *upper right part* of Fig. 9.6, a thickened fiber bundle of the palmar aponeurosis is sectioned longitudinally. The thickening, corresponding to an early stage of DC, can clearly be seen. There is no cellular proliferation. There are no elastic fibers. In the *lower left part* of Fig. 9.6, the transversely running collagen fiber bundles of the deep transverse palmar ligament are cut transversely. This ligament is never involved in DC. Here the elastic fibers appear normal and are normally distributed. This supports the concept that the function of the elastic fibers plays a role in the early phase of DC

Residual elongation is the remaining elongation of a specimen that was exposed to a stress–strain test. Initial elongation of up to 3 or 4% occurs with minimal force (the toe-in region). Thereafter, the necessary force rises steeply. After the stress subsides, the specimen retracts again following a different curve. The area between the

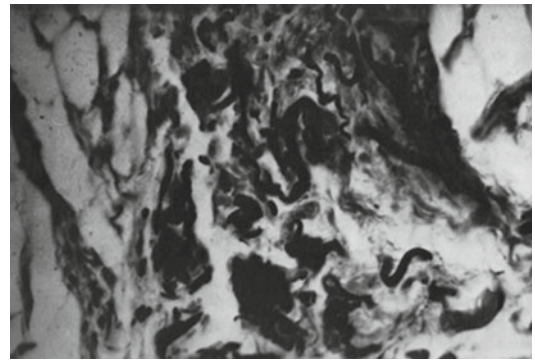
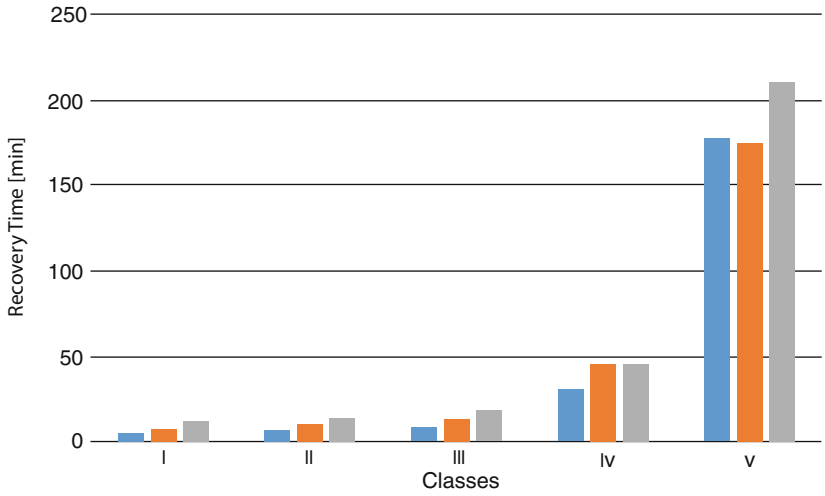


Fig. 9.7 Loose connective tissue between cords of DC. The peri-fascicular and inter-fascicular gliding tissue between the original fiber bundles has been lost. The elastin of the originally high content of elastic fibers cannot be resorbed and remain as fragmented and deformed elastin bodies. Pranter's elastic stain, 1:250

Table 9.2 Recovery time



Elongation of 2.5% (blue), 5% (orange), and 10% (gray)
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two curves (hysteresis) corresponds to the consumed energy. The original point of the stress curve is never fully reached at the 0-line. The distance between the two points at the baseline is the residual elongation. We have measured the residual elongation after elongation of 2.5, 5, and 10 % (Table 9.1; Millesi et al. 1997).

Repetition of a stress–strain test immediately after the first test produces a different result. The time of rest necessary to get again the original curve is called recovery time. The reason is that the first test initiates an optimizing of the arrangement of fibrils, fibers, and fascicles (warming up in sports). We have measured the recovery time after elongation of 2.5, 5, and 10 % (Table 9.2).

Tissues of palmar aponeurosis affected with DC, harvested and treated in exactly the same way, are characterized by a significantly increased residual elongation. In a macroscopically normal specimen of palmar aponeurosis of a patient with DC at another location, residual elongation was significantly increased if the test was performed with a 10 % elongation. This abnormal residual elongation was not found after elongation by 10 % in similar specimens obtained from patients without DC (Table 9.1). This biomechanical behavior of apparently normal palmar aponeurosis precedes cellular proliferation in Dupuytren Disease.

The basis of the disease may be a genetically defined abnormality of biomechanical behavior. The increased residual elongation of specimens of palmar aponeurosis of patients with DC is also seen after elastase treatment of palmar aponeurosis tissue (Reihsner et al. 1991). This result supports the view that elastic fibers normally play a decisive role in restoring normal tissue length after mechanical strain. In the phase of fiber thickening, before cell proliferation (Table 9.1), the efficiency of the elastic fibers is reduced and residual elongation is increased. The loss of elastin of the specimens results in further increase of residual elongation.

9.4 Pathogenesis and Aetiology

Considering our present knowledge, the conclusion is tempting that DC is related to, or caused by, a deficiency of elasticity in tissues that have special elastic functions. Changes of elastic fibers can explain the changes documented in early stage disease (Millesi 1965). The fact that the prevalence of DC increases with age coincides with known age-related loss of elastic fibers. There is growing interest in the possible role of elastic fibers in Dupuytren pathogenesis (Alfonso-Rodriguez et al. 2014).

9.4.1 Cellular Proliferation

Cellular proliferation is an essential component of the pathogenesis of Dupuytren Disease. But is it really the beginning of the disease? The evidence that it is preceded by earlier pathologic changing of the properties of the collagen fiber bundle suggests that cellular proliferation might be a consequence rather than the root cause of this disease.

Are these early pathological changes of elastic properties induced by heritable genomics, the environment, or both? We know that heritage, age, and environment may contribute to the disease. If the cells are abnormal from birth, we would expect to see Dupuytren Disease in children – but this rarely (if ever) occurs. Yet cumulative environmental influences associated with aging may slowly change the elastic properties of the palmar fascia over time. Those changes, occasionally also combined with traumatic influences, can eventually trigger abnormal cell proliferation in the palmar fascia in adults. Perhaps cells carrying predisposing genetic traits are easier to trigger into hyperproliferation than normal palmar fascia cells. Overall this is still a not fully understood complex process requiring more research into its root causes.

An alternative to this model would be that the cellular proliferation is a separate disease. It could be a tumor-like condition triggered by a preceding disease. If so, we would have to treat two different diseases which are linked together like twins, and we would have to explain the marked differences to other well-known fibromatosis. The early morphologic and the biomechanical changes would remain unexplained.

9.4.2 What Is the Natural Course?

Despite evidence to the contrary (Millesi 1965), a commonly published misconception is that the natural course of Dupuytren Disease is continuous progression (like a malignant tumor) and that successful treatment stops progression. This is certainly not true. Cases of spontaneous regression have been described. In many cases contracture bands can be observed for years without any sign of activity. Such low progression rates may explain differences of gender rates, racial distribution, incidence and prevalence, disease, and contracture. Consider that for patients in Central Europe under treatment for DC, the ratio of male to female patients is 5 to 1. The difference is much less pronounced if in a home for the elderly, all cases with DC including subclinical cases are counted. Japanese surgeons may report that DC is extremely rare, yet in elderly Japanese the frequency of subclinical cases is quite high (Egawa et al. 1985).The same conclusion can be drawn comparing incidence and prevalence (DiBenedetti et al. 2011).

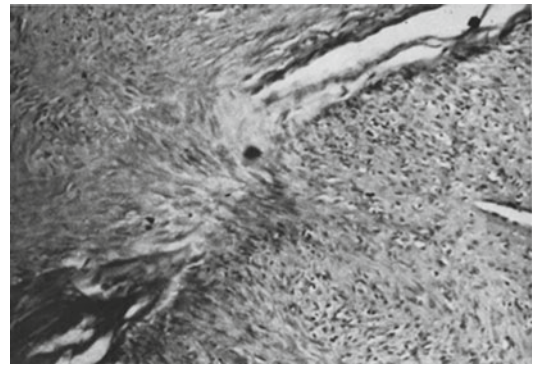

Fig. 9.8 Starting of a cord. Two thickened fiber bundles of a fairly advanced phase of DC with cellular proliferation are still separated by peri-fascicular tissue according to the original bundle structure. In both fiber bundles, cellular proliferation has already replaced the original deposition of collagen. In the center of the figure, the cellular proliferation has already perforated the separating peri-fascicular tissue. At the end of this process, the separating tissue will disappear completely. A large cord without internal structure will be the result. This change of structure also causes changes of the biomechanical behavior (see Tables 9.1 and 9.2). With time the content of cells will be reduced and the content of collagen increased. The end is a scar-like cord, full of collagen and few cells. Hematoxylin and eosin, 1:250

9.4.3 What Are the Activating Factors After Periods of No Proliferation?

In the very early stage, longitudinal traction on the collagen fiber bundles – not softened during the initial phase by the crimp structure – may cause loss of elasticity and thickening by collagen production. The thickened bands are palpable and impede further elongation but do not cause significant contracture. In this phase the stress–strain recovery time (RT) remains low. Fiber bundles thicken, but only to a limited extent. The movement of the fibrils during creep is still limited by the remnants of the fascicular pattern. At this stage, exposure to further mechanical stress causes further thickening.

After cell proliferation the remnants of the original fiber pattern disappears (Fig 9.8). Thick homogenous cords filled with collagen microfibrils are the result. The micro fibrils are now more mobile within the large cord.

Based on these observations, a theory of passive contracture could be as follows: Strong traction may lengthen a cord by movement of the microfibrils. Because the volume of cord tissue is not changed, elongation is compensated by reduction of the transverse diameter. In physics this is called transverse “contraction” in spite of the fact that a true contracting force does not exist. This deformation produces compound force vectors in adjacent tissues which would reestablish the original state. However, the lag of prolonged recovery time (we have measured up to 3 h) can produce an oscillating mechanical feedback loop. This effect can vary enough to give the appearance of a random process. In addition to this, longitudinal traction remains the stimulus for further contracture. It is more active if the cord is longer and spans a wider arch. It loses force beyond certain angles. Usually contracture stops if finger flexion contracture progresses to the point that longitudinal traction on the cord stops, either from intrinsic joint contracture or severe deformity. Activity stops if a cord

is transected and the two stumps spread apart as it could be achieved by fasciotomy. However, after the subcutaneous fasciotomy wound has healed, scar tissue reestablishes continuity, and the stimulating effect of longitudinal traction returns (Millesi 1965), often resulting in recurrent contracture. The effect of fasciotomy could be prolonged by covering the fasciotomy wound by a full thickness skin graft (Armstrong et al. 2000). Recurrences can be slowed but not prevented.

9.4.4 Plantar Aponeurosis

The following argument supports the role of longitudinal traction to initiate and maintain contracture. It is a fact that thick bands at the medial margin of the plantar aponeurosis usually do not produce contractures of the toes. In contrast to the fingers, the metatarsophalangeal joints of the toes are normally in hyperextension. A connection from the plantar aponeurosis to the toes across the connective tissue of the foot does not develop as it does at the hand with the major tendency to flex the MPJ. No longitudinal traction by extending the toes is transferred to the plantar aponeurosis. Consequently, no contracture occurs.

The human plantar aponeurosis is the result of a different development as the ones of the nonhuman primates. The latter have developed the foot to a kind of gripping organ similar to the hand with an opposing thumb and digits in middle position of the tarsophalangeal joints. The plantar aponeurosis is consequently similar to the palmar aponeurosis of nonhuman primates.

The human foot has a completely different development. The foot is not used for gripping but for running. The calcaneus has developed to the dorsal bony support of the foot in an angle to the tibia and fibula. The ventral bony support is provided by the heads of the metatarsal bones, again in an angle to the tibia and fibula. A triangle is formed with the plantar aponeurosis as the hypotenuse. If weight presses the foot to the floor, the triangle widens a bit. The elastic plantar aponeurosis is placed under tension and conserves energy which helps to lift off the foot.

In addition, the plantar aponeurosis stabilizes the skin and prevents tangential motion, similar to the effect of the palmar aponeurosis. A patient that we treated suffered from a congenital absence of the plantar aponeurosis. This patient had extreme difficulties walking barefoot due to the mobility of the plantar skin.

The relation to DC is the fact that the plantar aponeurosis is also a dense elastic tissue. The same is true for Peyronie disease. This answers the initial question 2: *To what extent similar diseases at the plantar aponeurosis (Ledderhose Disease) and at the tunica albuginea (Peyronie disease) are related to Dupuytren Disease and why?*

9.5 Summary

The pathogenesis of DC is more complicated than usually reported. A tumor-like fibroblast proliferation leading to cords with contraction by myofibroblasts does not explain the very early changes, including loss of the elastic fibers and the biomechanical consequences of this. The special elastic properties of the dense elastic tissue complex of the palm, the plantar fascia of the foot, and the tunica albuginea of the penis are the link between Dupuytren, Ledderhose, and Peyronie diseases. In Dupuytren Disease, the loss of elastic properties initiates fibrosis and formation of thick bands, which prevent elongation, but causes little or no contracture. Biomechanically, this stage is characterized by the increase of the residual elongation following tensile stress (Table 9.2). This stage may continue for years, leading to big differences between incidence and prevalence of DC. For so far unknown reasons, a proliferation of fibroblasts originates from perivascular spaces and removes the collagen of the bundle, changing the infrastructure of the bundles (see Fig. 9.8). At the height of the cell proliferation, the whole bundle is full of cells. Such proliferations may occur in the same hand at different times and different locations. New collagen is produced, and eventually the number of cells decreases and a scar-like appearance results. Thick cords develop and undergo contracture if

under tension. At this stage, the mechanical tissue recovery time after is enormously increased (Table 9.2). Contracture progresses until traction on the cord no longer occurs.

Acknowledgments and Conflict of Interest Declaration Figures 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, and 9.8 and Tables 9.1 and 9.2 are being reproduced by permissions of Springer and Thieme Verlag. The author has no conflict of interest to declare.

References

Alfonso-Rodriguez CA, Garzòn I et al (2014) Identification of histological patterns in clinically affected and unaffected palm regions in Dupuytren's disease. PLoS One 9(11):e112457

Armstrong JR, Hurren JS, Logan AM (2000) Dermofascieclomy in the management of Dupuytren's disease. J Bone Joint Surg Br 82(1):90–94

DiBenedetti DB, Nguyen D, Zografos L, Ziemiecki R, Zhou X (2011) Prevalence, incidence, and treatments of Dupuytren's disease in the United States: results from a population-based study. Hand 6(2):149–158

Egawa T, Horiki A, Senrui H (1985) Dupuytren's Contracture in Japan. In: Hueston ED, Tubiana R (eds) Dupuytren's disease, 2nd edn. Churchill Livingstone, Edinburgh, pp 100–103

Flint MH (1990) Connective tissue biology. In: McFarlane RM, McGrouther DA, Flint MH (eds) Dupuytren's disease: biology and treatment, vol 5. Churchill Livingstone, Edinburgh, pp 13–25

Langhans T (1887) Histologische Teil im Rahmen der Arbeit Kocher TH, Die Behandlung der Retraktion der Palmaraponeurose. Zbl Chir 14:481–497

Luck JV (1959) Dupuytren's contracture: a new concept of the pathogenesis correlated with surgical management. J Bone Joint Surg Am 41:635–664

Millesi H (1959) Neue Gesichtspunkte in der Pathogenese der Dupuytren's chen Kontraktur. Brun's Beitr Klin Chir 198:1–25

Millesi H (1965) Zur Pathogenese und Therapie der Dupuytren'schen Kontraktur, Ergebnisse der Chirurgie und Orthopädie. Springer, Berlin/Heidelberg, pp 51–101

Millesi H, Reihsner R, Eberhard D et al (1997) The mechanical properties of the palmar aponeurosis and their significance for the pathogenesis of Dupuytren's contracture. J Hand Surg Br & Eur 22B(4):510–517

Millesi H (2012) Basic thoughts on Dupuytren's contracture. In: Eaton Ch et al. (eds) Dupuytren's disease and related hyperproliferative disorders. Springer, Berlin/Heidelberg, pp 21–26

Reihsner R, Menzel EJ, Mallinger R, Millesi H (1991) Biomechanical properties of elastase treated palmar aponeuroses. Connect Tissue Res 26:77–86

Sherratt MJ (2009) Tissue elasticity and the ageing elastic fiber. Age (Dordr) 31(4):305–325