

History of Dupuytren's Disease

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Early history of Dupuytren's Disease and surgical treatments

The earliest reference that we found in the medical literature to the condition that ultimately came to be known as Dupuytren's Disease was a report by Felix Plater in the 17th century. Plater described a stone mason with "contraction of the fingers of the left hand into the palm" [1]. However, he mistakenly attributed the condition to contracture of the tendons, rather than of the palmar fascia [1], an error that persisted for nearly 200 years.

In the 18th century, the British surgeon John Hunter accurately described this condition as a disorder of the palmar fascia [2]. In 1777, Henry Cline, a student of John Hunter, first dissected a hand with this condition and recognized the role of the palmar aponeurosis in the pathology [1], [3]. Cline later proposed treatment by palmar fasciotomy, although he did not, as far as we know, perform the procedure [1]. In the early 1800s, Cline's apprentice, Astley Cooper, observed that disease of the palm (i.e., when the aponeurosis is the cause of the contracture) was amenable to subcutaneous fasciotomy (in contrast to disease in which the flexor tendon/sheath was contracted) [1], [3], [4]. However, there remained confusion in the French surgical community as to the pathology of the condition. In 1826, Alexis Boyer, the personal surgeon to Napoleon Bonaparte, attributed this contracture of the fingers to a condition called 'crispatura tendinum', which was a drying and stiffening of the flexor tendons and overlying skin [1], [3].

Guillaume Dupuytren, one of the most well-known and respected surgeons of his time, materially helped to advance the understanding and treatment of the disease which now bears his name. In a widely known and acclaimed lecture in 1831, at the Hôtel Dieu, he summarized his observations on the disease and approach to treatment. Dupuytren described the subcutaneous fascial bands crossing the palm and their exaggeration upon extension of the fingers. He outlined the clinical course of the disease, including its most common occurrence in the ring finger, its spread to other fingers, particularly the little finger; and the progressive lifting of the palmar skin into folds ("pitting" or "dimpling") over the bands [5]. Dupuytren asserted that the contracture was not due to abnormalities of the tendons, skin, or joints, but to retraction of the palmar aponeurosis [5], [6]. Dupuytren also introduced the open transverse fasciotomy as a viable treatment option [5], [7]. Like others before him, Dupuytren attributed the cause of the disease entirely to occupational exposure or repetitive trauma; although a genetic influence and other factors were later to be shown as very important [5].

Shortly thereafter, Jean-Gaspard Goyrand suggested that the bands that held the fingers in flexion ("pre-digital bands") were formations of new fibrous tissue and that these bands extended into the fingers [3], [7], [8]. Goyrand also introduced limited fasciectomy, and advocated longitudinal incisions (rather than transverse) to allow better healing as well as some fascial excision [3], [8]. He also questioned the hypothesis that chronic palmar trauma was the primary etiology and suggested a hereditary component for the disease [3], [8].

Following the introduction of ether anesthesia in 1846, Fergusson performed the first complete fasciectomy [9]. However, the subcutaneous method/closed fasciotomy was the mainstay of surgical practice for most of late 19th century [7], [8]. Surgical interventions continue to be the most commonly utilized procedures for correction of Dupuytren's contracture into the 21st century [10], although multiple surgical methods and approaches have since been described, and trends have shifted over time.



During the first half of the 20th century, most surgery for Dupuytren's Disease was focused on managing palmar lesions [3]. Extensive, radical or total fasciectomy with excision of digital lesions, developed by McIndoe and reported by Skoog [11], was introduced and became popular in Western Europe and the U.S. following World War II [3], when the availability of anesthesia plus consistent antiseptic techniques made longer and more complex procedures reasonable [7]. This surgery was intended not only to release the contracture, but also to prevent recurrence by excising fascia that appeared normal but that might be the source of recurrence disease [7]. However, extensive fasciectomies produced a high incidence of complications, primarily due to hematomas or skin necrosis, but left many with considerably stiff and inflexible joints [3], [12], [13]; and – unfortunately – recurrence rates were not significantly reduced [7]. No less an authority than Sterling Bunnell advocated fasciotomy as a prerequisite to fasciectomy surgery to limit the extent of dissection that would ultimately be required [14].

The 1960s saw a return to the popularity of limited fasciectomy [3], [7], [15], which is still the most common surgical approach [7], [10], [16]. Tubiana recommended this methodology to avoid the complications of radical/total fasciectomy for this non-malignant disease [3], [7], [17]. Hueston also recommended limited fasciectomy, noting that it allowed correction of contracture with more rapid recovery and no increase in the risk of recurrence [18]. He reported that the late results of surgery (i.e., recurrence) seemed to depend less on the extent of fasciectomy than on the particular patient [18], and defined the concept of *Dupuytren's diathesis* — a genetic predisposition; and the influence of factors that favor disease development [3], including family history, younger age of onset, distribution of lesions, and ectopic (non-palmar) lesions [19].

McCash introduced a modification to limited fasciectomy technique: the open palm method of transverse palmar and digital crease incisions with subcutaneous dissection to excise diseased fascia. This approach was developed as an alternative to skin grafts to deal with skin deficit after palmar fasciectomy [20], [21]. While this approach has advantages over skin grafts, such as avoiding postoperative hematomas and later stage edema [20], [21], it is also associated with gradual healing of the transverse wounds [3]. The Jacobsen flap, a modification of McCash's technique that allows the surgeon to expose Dupuytren's tissue in both the palm and fingers using only two longitudinal incisions, was introduced in the late 1970s as another alternative for treating advanced contracture [22], [23].

Enzymatic fasciotomy (discussed in more detail later) was first attempted in the 1960s and 1970s. Bassot reported correction of severe deformities by injecting Dupuytren's cords with a combination of enzymes that included trypsin, alpha-chymotrypsin, hyaluronidase, and thiomucase [24]. Hueston reported similar findings (i.e., successful cord rupture) using a modified formulation of trypsin and hyaluronidase injection [24].

In the early 1980s, Hueston reported his use of dermo-fasciectomy [25], based on the observation that the disease did not recur beneath skin grafts [3], [25]. Although the use of skin grafts decreases the likelihood of recurrence, there is still risk of recurrent deformity [7] as disease progression is possible in surrounding tissue [3]. This approach is presently used most often in young patients with recurrent and aggressive Dupuytren's with skin involvement or skin deficiency [7], [26].

Segmental aponeurectomy (i.e., segmental limited-open fasciectomy) was introduced in the 1990s by Moermans [27]. His method is an intermediate surgical approach that offers the advantages of limited areas of surgical dissection to minimize secondary scarring, but retains the value of fasciectomy [7]. Short- and long-term outcomes have been reported as comparable to other surgical interventions in effectiveness [27], [28].

Percutaneous needle fasciotomy was recommended by Badois early in the 1990s [2], [29]. This technique has become popular due to its relatively noninvasive nature [30]. Badois reported good initial outcomes [2] with only minor complications [29], [30]; however, it has been noted that the incidence of complex regional pain syndrome seems to be as frequent as with other surgery methods [30]. Additional studies have described short- and long-term outcomes after needle fasciotomy [31], [32], [33], [34], [35] and a comparative study by van Rijssen showed that although the extent of correction of contracture may be less than what is achieved with limited fasciectomy. Needle aponeurotomy is generally associated with fewer major complications, discomfort and improved hand function after treatment [31]. However, a very high rate of recurrence is an issue [29], [32], [33], [35].

Recent understanding of Fibroblasts, Myofibroblasts, and Wnt Signaling

As the approach to surgical correction of Dupuytren's contracture has evolved, so has the understanding of its pathology. Although many aspects of Dupuytren's Disease still need to be illuminated, advances in the understanding of the cells involved and mechanisms by which contractures occur can help advance treatment of all types.

Recent studies by Dolmans et al. showed that Dupuytren's Disease is associated with variations in genes that encode proteins in the Wnt signaling pathway, suggesting that imbalances in this pathway may confer susceptibility to development of the disease [36]. In addition, Verjee and colleagues reported that TNF (but not other proinflammatory cytokines) promoted differentiation of fibroblasts into myofibroblasts and drove contraction and profibrotic signaling in myofibroblasts via the Wnt signaling pathway; this suggests that TNF may be a potential therapeutic target to help down-regulate myofibroblast proliferation and activity [37].

Non-surgical treatments

Although surgical correction of Dupuytren's contracture has proven successful it has also been fraught with significant problems; and as new techniques have reduced complications of surgery, there has been a desire to find a viable non-surgical treatment. Many approaches have been used, including splinting, ultrasound, radiation, various drugs (steroids and others), and various attempts at enzymatic fasciotomy; but, until collagenase, most with – at best – limited success.

- *Splinting* alone is not effective if applied intermittently, and continuous splinting is not a practical treatment option [12], [30], [38]. Preoperative splinting may be helpful and post-treatment static splinting may be recommended after some procedures [2], [30], [38].
- *Ultrasound* therapy has been found to lead to some softening of nodules and changes in interfibrillar cement substance of fibrous tissue, but has not been shown to be clinically effective for correcting Dupuytren's contractures (and that is, after all, the essential point) [2], [30], [39].
- *Radiotherapy* treatment of Dupuytren's has been most studied in Germany. Ortho-voltage radiotherapy has shown some slowing of disease progression during follow up from 5 to 13 years, primarily among patients in the earliest stages of disease [2], [30], [40], [41], [42]. However, at least one other study in disease progression found no differences after 7 years between patients treated with radiotherapy compared to untreated patients [2], [30], [43]. However, given the potential short- and long-term risks of radiotherapy, it has not been widely accepted as a useful treatment or "pre-deformity" prophylactic option for Dupuytren's [2], [30], [38].

- *Extracorporeal shock wave* therapy has been proposed recently to reduce contracture and improve function in patients with Dupuytren's disease, with potential use for primary and secondary prevention of progression as well as treatment. At this time, we believe that a randomized controlled clinical trial is recruiting patients (NCT01184586) [44].
- *A variety of drug treatments* have been studied. Topical application of high potency corticosteroids with 0.05% clobetasol propionate for up to 9 months was reported to have some beneficial effects in reducing contracture and was said to be associated with regression of digital cords and palmar nodules in one small series [45]. Steroid injections were initially proposed in the 1950s as an adjunct to surgery [46], [47]; and more recently have been studied as an alternative to operations. Injection of triamcinolone into Dupuytren's nodules was reported to result in their softening and flattening [48]. Complications of triamcinolone include transient depigmentation and temporary subcutaneous atrophy; flexor tendon ruptures were reported following multiple injections over short intervals [48]. Other drugs and chemicals that have been tried and reported include vitamin E [2], [49], methylhydrazine [50], [51], dimethylsulfoxide (DMSO) [2], [30], [52], allopurinol [30], [53], and gamma interferon [2], [30], [54].
- *The potential for use of enzymes* to treat Dupuytren's Disease was first considered as far in the early 1900s; the use of fibrinolysin injections was reported to soften and improve elasticity of Dupuytren's tissues [30]. As mentioned earlier, Bassot reported using a combination of enzymes in the late 1960s, including trypsin, alpha-chymotrypsin, hyaluronidase, and thiomucase; and in the early 1970s, Hueston used a modified formulation of trypsin and hyaluronidase injections [24]. Skin rupture was reported by Hueston, although it was observed that most healed rapidly without the need for skin grafts [24]. However, Hueston's paper did not address long-term outcome of contractures. In 1992, McCarthy reported recurrence in 7 of 14 patients within 3 years of treatment using Hueston's modification of Bassot's formula, and concluded that this procedure had a similar rate of recurrence as surgical fasciotomy, but had greater morbidity [55].

In the 1990s, clostridial collagenase began to be studied as a potential treatment [50]. The collagenolytic effects of culture filtrates from *Clostridium* bacteria were first identified around 1940 [50], [56]. In the 1980s, in vitro and in vivo pilot studies examined the effects of collagenase clostridium histolyticum (CCH) on tissue from patients with Peyronie's disease [50], [57]. Then, an in vitro (ex vivo) study by Starkweather demonstrated the collagenolytic effects of CCH in Dupuytren's cords harvested from patients who had undergone fasciectomy [58]. An open-label phase 2 study by Badalamente published in 2000 demonstrated the clinical efficacy of CCH in patients with Dupuytren's Disease [59]. Additional phase 2 and phase 3 trials further demonstrated the clinical efficacy of CCH [60], [61], [62], [63], and the drug was approved in the US in 2010 (XIAFLEX®) and in the EU in 2011 (Xiapex®). Details of CCH mechanism of action, data from clinical trials and from clinical use are reviewed at length in the Collagenase Chapter.

This is an ongoing story regarding etiology; treatment options and timing; and – perhaps ultimately – prevention through genetic intervention. The chapters that follow explore all of these matters.

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