Dupuytren’s Contracture

Features and Consequences

BY

STEPHAN WILBRAND
ABSTRACT


Dupuytren’s contracture (DC) is a fibromatous disease of the palmar fascia of unknown etiology. The present study was undertaken in order to assess pathophysiological mechanisms and consequences.

In a cohort study of 2,375 patients operated for DC at the Department of Hand Surgery, Uppsala there was a male: female ratio of 5.9:1. Women had a higher mean age at first operation than men. One-third of the men and one-quarter of the women required repeated surgery. Early age at first operation was associated with recurrent disease.

The risk of cancer was determined in 15,212 patients operated on for DC in Sweden. The overall relative risk was increased by 24%. There was a significantly increased risk for buccal, oesophageal, gastric, lung and pancreatic cancers, which indicates that smoking and alcohol abuse are probable risk factors for DC.

Furthermore, there was an increased frequency of fibrosarcoma and malignant fibrous histiocytoma, the cause of which is unexplained.

The causes of death were evaluated in a national cohort of 16,517 patients operated for DC. There was an overall increased mortality (SMR=1.06), inversely related to age and significant for both sexes, in patients under 70 years. The risk estimate was highest for endocrine-, gastrointestinal-, and respiratory diseases, and accidents. There was also an increased SMR for cardiovascular diseases in younger patients more than 10 years after surgery. The most probable mechanism is related to smoking and other lifestyle factors.

Outcome after surgery was not related to the immunohistochemical expression of connective tissue activation markers, such as collagen type IV, integrin α5, laminin, smooth muscle α-actin, procollagen type I, and desmin, in surgical specimens in a prospectively investigated group of patients. Furthermore, there were no associations between gender, age at onset of DC, number of operations, heredity, diabetes mellitus, or medication for cardiovascular disease, and the expression of the different markers. The individual characteristics that place a person at high risk are, thus, not obviously related to ongoing connective tissue production at time of surgery or to connective tissue activity in its conventionally used sense.

Key words: Dupuytren’s contracture, epidemiology, outcome study, cohort, prognostic factors, immunohistochemistry

Stephan Wilbrand, Department of Hand Surgery, University Hospital, SE-751 85 Uppsala, Sweden

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Dupuytren’s contracture

A challenge - not a blessing
LIST OF PAPERS

This thesis is based on the following papers, which will be referred to by their Roman numerals:


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ABBREVIATIONS

CI  confidence interval
DC  Dupuytren’s contracture
ICD International Classification of Diseases
MCP metacarpophalangeal
NRN National Registration Number
OR  Odds ratio
PA  palmar aponeurosis
PB  pretendinous bands
PIP proximal interphalangeal
SIR standardised incidence ratio
SMA smooth muscle α-actin
SMR standardised mortality rate
INTRODUCTION

HISTORY
Records dating back to the twelfth and thirteenth centuries contain descriptions of a condition resembling Dupuytren’s contracture (DC). In 1614 the Swiss physician Felix Plater described what became known as the stonemason's hand (30). In his report, Obsevationum in Hominis Affectibus, Plater described a digital contracture and attributed the typical flexion deformity to a flexor tendon contracture. This misinterpretation persisted until 1777, coincidentally the same year, which the person, who is by name linked to the condition, Guillaume Dupuytren was born. The British surgeon Henry Cline dissected two diseased cadaver hands and found that the true nature of the condition was contracture of the palmar fascia. The London surgeon Astley Paston Cooper later described the condition as a contraction of the palmar aponeurosis and in 1822 suggested in his book, On Dislocations and Fractures of the Joints, subcutaneous fasciotomy as the appropriate treatment.

On 5 December 1831, the French surgeon Guillaume Dupuytren described permanent retraction of the fingers in an oral presentation at the Hôtel Dieu in Paris. He was a brilliant physician-scientist, a captivating lecturer, and a demanding, egocentric personality (15). Unlike Cline and Cooper, Dupuytren published his findings in the 1832 edition of the Lécons Orales, where he proclaimed that the deformity was caused by retraction of the palmar aponeurosis. The demonstration of this important fact gave the disease its eponym in the late 1800s.

EPIDEMIOLOGY
Incidence
Dupuytren’s contracture is very common in northern Europe, including Scandinavia. It is common in the United Kingdom, Ireland, Australia and northern America, uncommon in southern European countries around the Mediterranean and in South America, and rare in Africa and Asia. The disease is very common among descendants of the Celts and Caucasians of northern Europe, common among Caucasians of north
America, uncommon among native Australians and Asians, and rare among native Africans, African Americans, native Americans and Gypsies (83) (Table 1). Since 1979 only 23 cases have been observed in the purely black population (1). Hueston stated that DC is a “disease of the Vikings,” after noting that areas of increased prevalence coincide with the known historical migration patterns of this ethnic group (47). The prevalence of DC in Northern Europe is between 18 and 30% in men over 65 years of age (18). In a Norwegian study of 15,950 individuals (6,888 men and 9,062 women) over 16 years of age, DC was detected in 9.4% of the men and 2.8% of the women. The prevalence among men increased from 0.2% in the 20-24-year age group to a maximum of 36.8% at 70-74 years of age, and then declined in the oldest age groups (67). Egawa and colleagues suggested that the incidence of DC in Japan differs little from that in Northern Europe. In their series of 1,154 individuals over 60 years of age, 19.7% of the men and 9% of the women were found to have DC. Most of these (90%) had nodules alone without contracture (29).

In a Spanish population of 1,455 patients undergoing general medical examinations, Guitian (41) documented an increasing prevalence of DC with age, 9.9% between the ages of 45 and 54, and 25.5% in those 75 years or more. These figures have been taken as an indication that the difference between northern and southern European populations with respect to prevalence of DC is not as great as has been suggested. DC has even been diagnosed at birth (32).

<table>
<thead>
<tr>
<th>Country</th>
<th>Age</th>
<th>Prevalence (percent)</th>
<th>Percent females</th>
<th>Sample size</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norway</td>
<td>60+</td>
<td>28%</td>
<td>10</td>
<td>3704</td>
<td>(67)</td>
</tr>
<tr>
<td>England</td>
<td>65+</td>
<td>16%</td>
<td>8</td>
<td>658</td>
<td>(28)</td>
</tr>
<tr>
<td>Australia</td>
<td>60+</td>
<td>28%</td>
<td>20</td>
<td>1245</td>
<td>(43)</td>
</tr>
<tr>
<td>Japan</td>
<td>60+</td>
<td>16-25%</td>
<td>3-10</td>
<td>~6000</td>
<td>(29)</td>
</tr>
</tbody>
</table>

Adapted from (18).
Gender

Dupuytren’s contracture is less common in women than in men (59). It has been stated that although DC is probably an autosomal dominant disorder, penetrance in males is much higher (60). The male to female ratio has been reported to be as high as 9:1, although with advancing age there is an increase in the disease among women, decreasing the ratio to 1.2:1 (67). Furthermore, it is postulated that DC behaves differently in women (84). This includes both the natural history of the disease as well as the perioperative and postoperative courses. Thus it is known that DC has its onset roughly a decade later in women than in men. Furthermore, women seem to have a higher risk of developing a postoperative reflex sympathetic dystrophy than men (63, 112). Men tend to have a more severe form of DC and require repeated surgery due to recurrence, which is more common among men (65). Other authors state that neither the incidence of extension nor of recurrence of DC in women appears to be any higher than in men (66, 113).

Genetics

A genetic influence in DC was first mentioned in the literature in 1833, when Goyrand (37) described a patient with DC whose father was also affected. Skoog (93) reviewed two studies published by Stackebrandt and Schröder, who investigated the relatives of patients suffering from DC. Stackebrandt suggested that there were two forms of DC - a hereditary (dominant) form and a sporadic form. It was suggested that the latter type was to a certain extent also genotypical, and that the disease occurred spontaneously when the hereditary tendency was particularly strong (96). Schröder considered that he could establish dominant hereditary in 10 of his 30 cases (89).

Many authors have reported families in which DC occurs much more often than would be expected for a common non-genetic disease. Systematic investigations of a genetic effect have, however, been sparse, although it has been postulated that DC is a malady with autosomal dominant inheritance with age-related and incomplete penetrance (109). However, the limited data that are available are consistent with other models of inheritance. A special difficulty is the late age of onset of DC, which in most cases
limits examination to two generation’s (18). In 1963 Ling examined all available relatives of a number of patients with DC, and from these individuals he obtained knowledge of the whereabouts of their first, second and third degree relatives, resulting in a total of 832 relatives. He made adjustments for age of onset and compared the observed number of affected relatives with the number expected in dominant inheritance. He concluded that his findings suggested the extreme importance of genetic factors in the pathogenesis of the common form of DC, and that a single gene, behaving as a Mendelian dominant, is probably involved in the pathogenesis (54).

ANATOMY
In order to be able to perform the required surgical procedure, thorough knowledge of the structures of the normal palmar aponeurosis is necessary so as to understand the sometimes chaotic pathoanatomic changes in DC. Normal aponeurotic structures are referred to as bands and ligaments. The two major forms of diseased tissue are referred to as nodules and cords. The palmar fascia includes the palmar aponeurosis (PA) and lateral extensions to the thenar and hypothenar regions, where they are reinforced in their course by two fasciculi that originate interdigitated from the transverse carpal ligament. The palmar aponeurosis is triangular in shape with one angle directed towards the wrist. Its longitudinal fibres consist partly of a continuation of the tendon to the palmaris longus muscle. On the ulnar side this reinforcement consists of a strong fibrous band, while the band on the radial side is considerably thinner. The PA has a three-dimensional orientation - longitudinal, transverse and vertical. The longitudinal fibres form the principal part of the aponeurosis and are condensed into five fascicles or pretendinous bands (PB), one for each digit. Each PB divides into two slips. Distally the PB trifurcates into three layers (Figure 1). The superficial layer (1) inserts into the dermis. The fibres of the middle layer (2) partly terminate in the proximal digit; the remaining fibres run deep to the neurovascular bundle and natatory ligament as the spiral band, and eventually insert into the lateral digital sheet. Fibres of the deep layer (3) run almost vertically and attach to the extensor mechanism (Figure 1).

The transverse fibres strengthen the PA transversely and form the natatory ligament and the superficial transverse ligament of Albinus, which runs deep to the pretendinous bands. The superficial transverse palmar ligament is a two-dimensional fascial structure running approximately perpendicular to the pretendinous bands across the distal third of the palm. The natatory ligament is also a transversely orientated structure running almost parallel to the superficial transverse palmar ligament and travelling between the web spaces. However, the natatory ligaments, like the spiral bands, have extensions travelling in three planes and blending into soft-tissue attachments around the metacarpophalangeal (MCP) joints (98). The natatory
ligaments have some deep fibres that attach to the flexor tendon sheath at the MCP joint, while the other fibres travel in the coronal plane and blend into the skin and fascia creating the web space. The web space is therefore a coalescence of fibres from the natatory ligaments, the spiral bands and the septa of Legueu and Juvara (Figures 2 and 3).

Figure 2. The web-space coalescence, consisting of the natatory ligament, the spiral bands, and the septa of Legueu and Juvara. © 1998 American Academy of Orthopaedic Surgeons. Reprinted from (13) with permission.
The vertical fibres are of two types. One comprises multiple very small bands that are superficial to and bind the PA to the dermis, where they give rise to the distal palmar crease and also form the typical dimpling of palmar skin. The other type comprises 8 vertical septa, called the septa of Legueu and Juvara, forming seven compartments, for the passage of four flexor tendons ulnarly and three groups of neurovascular bundles and lumbrical muscles radially (Figure 4).
Distal to the web space, fibres continue to form a fascial structure known as the lateral digital sheet, which runs in the sagittal plane on either side of each finger. As the lateral digital sheet passes distally in the finger, it sends off fibres attaching to the periosteum, the joint capsule and the tendon sheath. The fibres passing volarly to the neurovascular bundle are referred to as Grayson’s ligaments and those passing dorsally to the neurovascular bundle are termed Cleland’s ligaments (Figure 3).

As DC develops, the normal anatomy becomes distorted in a predictable fashion. Pathological nodules tend to form in fatty zones, particularly between the MCP and proximal interphalangeal (PIP) flexion creases. The affected palmar aponeurosis includes the pretendinous cord, originating from the PB, and causes a flexion contracture of the MCP joint. The natatory cord, originating from the natatory ligament, extends dorsally along the lateral side of the digit and causes web space contracture. Skin dimplings develop due to contracture of the superficial layer of the
PB. The diseased digital fascia, the central cord and the lateral cord cause flexion contracture of the PIP joint. Often the surgeon observes a blending of tissue, allowing the pretendinous cords, spiral cords, and web space tissue and lateral digital sheet to coalesce in a continuous cord. On the ulnar aspect of the hand, the abductor digiti minimi cord is less defined than other cords. It is often adherent to the skin and extends to the ulnar side of the proximal phalanx. The vertical cord develops from fibres of the PB deep vertical layer or from the vertical septa. The radial side of the hand is less commonly affected. Diseased thumb fascia compromises the pretendinous cord and the first web commissural cords, causing contracture of the first web space. Sometimes a less distinct thenar cord can be observed on the radial side of the thumb. The thenar cord course along, blends with thenar muscle fascia and inserts on the radial aspect of the thumb MCP joint.

Skoog (93) reported that roughly 50 % of the cases with DC show small subcutaneous nodules on the dorsal aspect of the PIP joints. These so-called "knuckle pads" are fairly well defined, round or somewhat irregular in shape, and vary in size from moderate thickenings to bean-size. The knuckle pads are movable over the finger joints but closely adherent to the covering skin. The histological appearance of the knuckle pads closely resembles the nodular fibrous thickening of the palmar aponeurosis in DC (20, 46). There is almost no impairment of the flexion or extension capacity of the affected fingers and the nodules appear gradually and without known cause.

**AETIOLOGY**

The literature is filled with theories concerning possible contributing factors in the development of DC. The current concept is that the disease is caused by interplay between one or more endogenous or exogenous factors and an intrinsic susceptibility (72). The aetiology is, however, still unknown.

**Cellular factors**

During the 1970s and 1980s, researchers established the presence of myofibroblasts in
the diseased tissue as the hallmark of DC. This was done by carefully studying and describing the appearance of these cells and their relation to the surrounding matrix. Myofibroblasts were first described and named based on their morphologic characteristics, as they resemble both fibroblasts and smooth muscle cells (34). The myofibroblasts have features in common with both smooth muscle cells and fibroblasts, in that they have a contractile apparatus in the form of smooth muscle α-actin (SMA). Myofibroblasts connect with each other through gap-junctions, and to the surrounding extracellular matrix, above all collagen types I and III, via fibronectin fibres (90). The myofibroblast phenotype of cells from DC specimens persists in culture for several cell passages (25).

An established hypothesis is that myofibroblasts derive from various existing populations of fibroblasts (87), and in DC especially from perivascular fibroblasts around narrowed microvessels (51, 70), and that a differentiation into myofibroblasts subsequently occurs (103). Evidence has recently been reported that myofibroblasts actually originate from vascular pericytes (48, 100), which seem to include cells with the potency to migrate out from vessels and to differentiate in various directions. Murrel et al. have hypothesised that in DC, microvessel narrowing causes local ischemia and free radical generation, which leads to damage to surrounding stroma and stimulation of further perivascular cell proliferation, thereby encouraging microvessel ischemia in a self-propagating way (71).

DC has been divided into three distinct histopathological stages, largely based on myofibroblast morphology (56), reflecting clinical phases of the disease. First, the proliferative stage, reflecting early disease, with nodules with abundant proliferated perivascular fibroblasts; second the involutional stage, reflecting active disease, with nodular thickening with predominantly myofibroblasts, and third the residual stage, reflecting advanced disease, with fibrotic thickening with less numerous myofibroblasts and fibroblasts in mature collagen stroma (21).

The vessels in the palmar fascia of patients with DC are narrowed and have multiple
layers of basal laminae, an appearance similar to that of the microvessels of patients with diabetes (108). It has, therefore, been hypothesised that the palmar fascia in DC is at high risk for developing a relative ischemia and free radical-mediated ischaemic damage with secondary fibrosis (71) (Figure 5).

The myofibroblast proliferation in DC can be mediated by various growth factors. A number of established growth factors, as well as their ligands, are thus observed in increased levels in Dupuytren-diseased palmaris fascia. This includes basic fibroblast growth factor (b-FGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), as well as transforming growth factor-β (TGF-β) (2, 9, 12, 35, 53).

**Figure 5.** Modified Murrel’s unifying hypothesis of the pathogenesis of DC. © 1998 American Academy of Orthopaedic Surgeons. Reprinted from (13) with permission. Platelet-derived growth factor-B is actively expressed by diseased palmaris fascia, but
not in normal fascial structures (101). TGF-β2 has a significant effect on myofibroblast proliferation in both the proliferative and involutional stages (10). TGF-β2 is also present intracellularly in the proliferative and involutional stages, but not in the residual stage or in normal fibroblasts (10). Of all the growth factors studied so far for a possible role in the development of DC, it seems that TGF-β is the most likely candidate, whereas other growth factors such as PDGF and bFGF probably play a minor role.

Some of the most current myofibroblast research is focused on understanding why the myofibroblasts disappear in normal healing wounds but persist in fibroproliferative disease. The most likely explanation appears to be in the control of apoptosis or programmed cell death of the myofibroblasts, suggesting that these cells are terminally differentiated (24, 26, 27). The inducers of apoptosis are unclear, although certain genes such as ced-3 and c-Myc have been suggested. Other factors controlling apoptosis are growth factors such as transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF) and tumour necrosis factor-α (TNF-α) (27).

**Genetic and immunological aspects**

There have been numerous theories suggesting that DC may be caused by an inflammatory process, and it has been suggested that the condition is a T-cell mediated autoimmune disorder (12, 38). Release of growth factors from macrophages may also be important in the development of DC, as is the case in other fibroproliferative diseases (4). Moreover, chromosomal abnormalities have been demonstrated in cells from diseased fascia in patients with DC (92). It has also been postulated that dermal dendrocytes may be an important source of cytokines in initiating fibroblast proliferation in DC (99). Association with certain HLA-DR subclasses and a high prevalence of collagen autoantibodies has also been reported (74).
ASSOCIATION AND FACTORS

Alcoholism

Guillaume Dupuytren was probably the first to suggest an association between the disease and alcohol. Even now, however, the exact role of alcohol in the pathogenesis of DC is not clear. In a controlled study including alcoholics, non-alcoholics with liver disease, and a control group, it was found that both alcoholic patients and those with non-alcohol related liver disease had a higher rate of DC (28% and 22%, respectively) than the controls (8%) (76).

Smoking

In a case-control study of 222 patients it was noted that the relative risk of developing DC was nearly three times higher in smokers than in non-smokers. This was found despite controlling for alcohol intake (19). The results of this investigation were interpreted as indicating a strong effect of smoking, while alcohol had a moderate effect on the risk of developing DC. Furthermore, in an Icelandic study of 2,165 cases it was reported that a history of smoking was significantly associated with the occurrence of DC. Most of this seemed to be attributed to heavy smoking, i.e. smoking more than 25 cigarettes per day (OR=2.61; P<0.02) (39). The combined effects of smoking and alcohol could explain the high frequency noted in alcoholics, given that heavy smoking is common in alcoholics (3, 7, 19). A tentative pathophysiological mechanism, linked to the hypothesis that DC is related to microvascular impairment, could be that smoking has a profound effect on blood flow to the hand (69).

Diabetes

The incidence of DC among diabetics varies between 2% and 32% (110). In a prospective study of 297 patients with type I diabetes and 139 patients with type II diabetes, the prevalence of DC and its association with clinical characteristics of type I and type II diabetes were evaluated (6). The incidence of DC was 14% in both type I and type II diabetes, and was associated with patient age as well as the duration of diabetes in type I patients. There were no gender differences in the prevalence of DC in patients with diabetes. The only diabetic complication found to be related to DC was macroalbuminuria in the type II patients.
Lipids

Patients with DC have been shown to have higher mean serum triglyceride and cholesterol levels than a control group. However, no correlation was observed between severity of disease and serum lipid levels (88). Furthermore, there is a different lipid composition in hands affected with DC than in normal hands, which is consistent with mild local tissue hypoxia (82). The importance of these observations for an understanding of the pathophysiology of DC is not clear, although they have been taken as arguments for increased lipid peroxidation in the palmar fascia as a disease mechanism.

Epilepsy

The relationship between DC and epilepsy was first described in epileptic inmates (57). In 1947 Skoog examined all patients, all of whom were males, at an epileptic centre in Sweden and noticed that the palmar aponeurosis was affected in 42% of these patients (93). The reported incidence varies from 8% to 57% in the literature (110). In another study the association between DC and epilepsy was evaluated in residents of two epileptic centres. The incidence of DC in the epileptic population was found to be 12% and 38%, respectively, in the two centres, and 16% in a matched control group. No differences were found in individuals less than 50 years of age, while the severity of DC was greater in epileptics over the age of 50 years (5). In a study of chronic epileptics in a residential centre, Critchley et al. recorded a 56% incidence of DC, which the same both in those with idiopathic and those with symptomatic epilepsy. The incidence increased with the duration of epilepsy, and was suggested to be a consequence of the long-term administration of phenobarbital. The mechanism was thought to be a peripheral stimulation of growth factor release, rather than a central release of growth hormone or through alterations in liver metabolism (23).

HIV

Recent reports have suggested an association between DC and infection with human immunodeficiency virus (HIV). Bower reported a prevalence of DC of 36% in a group of 50 men admitted to a large British urban hospital for complications of HIV infection
(14). In another British study the prevalence among 50 HIV-positive men was only 6%, which is similar to the prevalence in the population as a whole (33). It has recently been suggested that antiviral drugs used in HIV may lead to DC-like symptoms (31).

Manual work
The idea that DC results from manual work is based in part on the statement made by Dupuytren in 1831: “Most individuals who are affected with this condition have been obliged to use the palms of their hands constantly and to handle hard objects”. Microrupture of collagen fibres, with capillary haemorrhage caused by minor trauma, was suggested to be the explanation (94). A higher prevalence of DC was found in patients who where engaged in hard rather than light work, although these findings were not statistically significant until after the age of 60 years (68). A number of arguments have been advanced to dispute this relationship. First, the flexion crease is protected during normal grasp, yielding less evidence to support the concept that the disease is work related (110). Furthermore, an increased incidence has not been demonstrated in professional golfers, baseball players, tennis players or professional musicians who apply severe and repetitive stress to their hands (64).

Trauma
Dupuytren-like nodules or contractures can occur after a single injury. This has been described after distal fractures to the radius where an incidence of DC was observed in 11% of elderly patients’ (97). Dupuytren-like conditions have also been described after soft tissue injuries of the hand (36) and even from surgical trauma (52). A possible explanation might be that the trauma per se can trigger a pre-existing tendency to develop DC, and that the pathology was present prior to the injury but was unnoticed until the injury drew attention to it. It is possible that there is an individual propensity to develop an unspecific fibrosis during trauma. It has been reported that some individuals with a tendency to develop frozen shoulder have an overrepresentation of DC (95).
CURRENT TREATMENT OPTIONS
Operative management is suggested when metacarpophalangeal or proximal interphalangeal joint contracture exceeds 30 degrees. The main indication for surgery in such patients is disability. What is disabling for one person may, however, not be of importance to another, which is why the reasons patients desire surgery may vary. From the time the disease was defined, excision of the damaged tissue in the form of local fasciectomy has been the prevailing treatment (22, 49). In individuals at high risk for recurrence, or after a number of previous recurrences, more extensive surgery including excision of the skin of the palm and replacement with full thickness skin autografts has frequently been used (17, 42). Important complements to surgery are early active-flexion range-of-motion exercises to restore grip strength.

Alternative treatments are radiotherapy (91) and injection of collagenase (8), but appropriate indications for these modalities have not yet been determined.
AIMS OF THE STUDIES

The aims of the studies presented in this thesis were:

I. To evaluate changes over time, and age and gender distributions among patients treated surgically for DC at the Department of Hand Surgery, University Hospital, Uppsala, between 1965 and 1996, and to assess characteristics of those who underwent multiple and/or bilateral operations with regard to age and gender.

II. To investigate risk factors for DC by assessing cancer morbidity over time in a defined group of DC patients, and specifically to analyse whether there is an excess risk of malignancies associated with smoking and alcohol abuse, and whether there are endogenous characteristics in DC patients associated with other specific cancer forms.

III. To evaluate whether there were distinctive features in individuals suffering from DC and sarcoma.

IV. To assess the causes of death among patients treated surgically for DC and to determine differences compared to the general population.

V. To identify whether the risk for recurrence could be foreseen by analysing tissue markers for connective tissue activation in biopsies taken prospectively.
PATIENTS AND METHODS

For detailed information the reader is referred to the individual papers (I – V).

ADMINISTRATIVE DATA SOURCES
The National Registration Number The 10-digit national registration number (NRN) (58) is a unique identifier for all Swedish residents. It is used in all registers and medical charts, making it possible to identify each individual and to carry out computerised linkages between different registries.

The Swedish Population Registry The register includes continually updated information on all residents in Sweden, i.e. date and place of birth, address and date of death.

The Swedish Cancer Registry Since 1958 all newly diagnosed cases of malignant disease have been reported to the National Cancer Registry. Repeated analyses have shown that registration is almost complete, with a deficit of less than 2% (61). Dates and causes of deaths are transferred annually from the Causes of Death Registry by computerised linkage.

The Swedish Causes of Death Registry The register is based on the compulsory death certificate and contains information on all deaths (date, primary underlying cause of death) of Swedish residents since 1952, whether they died abroad or in Sweden.

The In-patient Registry Beginning in 1965, the National Board of Health and Welfare started collecting data on all individual hospital discharges in Sweden. The registration expanded steadily to cover 85% of the Swedish population in 1983 and the coverage was complete in 1987. The register, based on the NRN, includes information on the date of the admission, the duration of hospital stay, performed operations, and up to eight discharge diagnoses according to the International Classification of Diseases (ICD). The register is almost complete with a deficit of only 2% (73).
STUDIES

Paper I

The study group consists of patients treated surgically for DC at the Department of Hand Surgery, University Hospital, Uppsala, from 1965 to 1996. For the period 1965 to 1968, we identified all in-patients, based on their NRN, operated for DC using a Swedish adaptation of the ICD-7 code (744.20). For the period 1969 to 1986 the ICD-8 code (733.90) was used, and from 1987 to 1996 we used the ICD-9 code (728G). Until 1986, outpatient records were not registered with ICD-codes. In order to include this group we checked the manual registers of operations year by year and identified those who had been treated by local fasciectomy in the hand by means of the operation code 8631. From 1987 to 1996 we were able to identify all patients operated for DC through our hospital data patient administrative system by using the ICD-9 code combined with the operation code 8631.

Paper II

All patients recorded in the In-Patient Registry from 1965 to 1994 with a discharge diagnosis of DC (ICD-7, 744.20; ICD-8, 733.90; ICD-9, 728G and Swedish Classification of Operations and Major Procedures code 8631) (aponeurosectomy in the hand) were initially selected for inclusion in the study. After exclusion of records with inconsistencies and cases with cancer diagnosed earlier or diagnosed at the index hospitalisation, 15,212 patients were left for follow-up. By record linkage to the Swedish Cancer Registry we identified all cases of cancer during the period of study. The time of observation was calculated from the date of discharge after operation for DC to the date of diagnosis of a neoplasm, death, emigration or the end of the observation period on 31 December 1994. The expected numbers of cancers during the study period were calculated by multiplying the observed number of person-years by age-, gender, and calendar year-specific cancer incidence rates derived from the entire Swedish population. The standardised incidence ratio (SIR), defined as the ratio of observed to expected numbers of cancers, was used as a measure of relative risk. The 95% confidence interval (CI) for the SIR was then calculated on the assumption that the observed numbers followed a Poisson distribution (11).
Paper III
In the study of cancer incidence in patients treated surgically for DC (Paper II) we observed an increased risk for sarcomas of bone and connective tissue at 5 years or more after surgery for DC. The patient records of these 18 cases were obtained from their discharging hospitals and were studied for details regarding gender, age at time of initial surgery for DC, frequency of surgery for DC, presence of other diseases, age at time of sarcoma diagnosis, type and localisation of sarcoma, the presence of other malignancies and the possible cause of and age at death.

Paper IV
All patients registered in the In-Patient Registry during 1965 to 1995 with a discharge diagnosis of DC (744.20 in ICD-7, 733.90 in ICD-8 and 728G in ICD-9) and a Swedish Classification of Operations and major Procedures code 8631 were initially selected for inclusion in the study. After exclusion of records where the NRNs could not be found in the Swedish Population Registry, the Migration Registry or the Death Registry, 16,517 patients were left for follow-up. By record linkage to the Death Registry we identified all causes of death during the study period. The time of observation was calculated from the date of discharge after surgical treatment for DC until date of death or until the end of the observation period on 31 December 1995. The expected numbers of deaths were calculated with respect to 5-year age group, gender, and calendar year-specific death incidence rates derived from the entire Swedish population. The computation of person-years at risk started at the time of discharge after surgery for DC. Each cohort member was followed up either to the date of death or the closing date of follow-up. Official statistics from the Swedish Death Registry included annual gender- and age-specific incident rates for different ICD-codes for the entire country. Multiplying the number of person-years at risk by 5-year age group, gender, and year-specific mortality rates yielded the number of expected cases. The standardised mortality ratio (SMR), the ratio of observed to expected number of deaths, was used as a measure of risk. The 95% confidence interval (CI) for the SMR was then calculated on the assumption that the observed number of deaths in each group followed a Poisson distribution (11).
Paper V

One hundred ten consecutive patients were investigated in connection with local fasciectomy for DC at the Department of Hand Surgery, Uppsala University Hospital, from 1994 to 1998. The entire surgical specimens were retrieved for analysis and microdissected so that Dupuytren tissues from nodular areas were retrieved, as myofibroblast proliferation occurs almost solely in these areas (106), and finally snap frozen. All biopsies were first cryosectioned, stained with haematoxylin-eosin and reviewed with respect to DC activity. From each patient the biopsy that contained the most active nodule was chosen for further evaluation after serial sectioning. The haematoxylin-eosin-stained sections were staged according to the classification of Luck (56), depending on the degree of cellularity and fibrosis. Immunohistochemical staining for collagen type IV, integrin α5, laminin, smooth muscle α-actin, procollagen type I, and desmin was evaluated blindly in a conventional light microscope, and the intensity of staining within nodular tissue was judged on a scale from 0 to 3. The prevailing intensity was taken to represent the entire section.

A self-assessment questionnaire was subsequently sent to patients a mean of 4.4 years after operation. The patients were asked to report age at onset of the disease, age at first operation for DC, number of operations, heredity, ectopic lesions, other illnesses, medication, smoking habits, and whether recurrent bending of the finger(s) had occurred. They were also asked to compare their operated hand with schematic drawings of hands with five different levels of Dupuytren changes.

Associations between data derived from the questionnaire and the results of the immunohistochemical examinations of the surgical specimens were evaluated with the $\chi^2$-test and Fisher's exact test. The predictive value of clinical and immunohistochemical variables for recurrence was determined with logistic regression.
RESULTS

Paper I

Between 1965 and 1996 a total of 2,375 operations for DC were performed on 1,600 patients at the Department of Hand Surgery, University Hospital, Uppsala. Surgery was performed on 1,368 men and 232 women, giving a male: female ratio of 5.9:1. In those operated on only once, male predominance was less (Table 2).

<p>| Table 2. Gender distribution of patients undergoing operation for DC |
|-----------------------------------------------|-------------------|--------------------|-------------------|--------------------|</p>
<table>
<thead>
<tr>
<th>Patients operated once</th>
<th>Patients operated twice</th>
<th>Patients operated &gt;twice</th>
<th>Mean age at first operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Males</td>
<td>1368 (86)</td>
<td>888 (83)</td>
<td>324 (89)</td>
</tr>
<tr>
<td>Females</td>
<td>232 (14)</td>
<td>183 (17)</td>
<td>42 (11)</td>
</tr>
<tr>
<td>Total</td>
<td>1600 (100)</td>
<td>1071 (100)</td>
<td>366 (100)</td>
</tr>
<tr>
<td>Males : Females</td>
<td>5.9:1</td>
<td>4.9:1</td>
<td>7.7:1</td>
</tr>
</tbody>
</table>

Mean age at first operation was about three years older for women than for men. Fifty-seven percent of the study group had their first operation before the age of 65 years. This was more common in men (61.7%) than in women (51.2%). Repeated surgery was performed more frequently in men than in women. Sixty-five percent of the men had only one operation compared with 79% of the women. Out of the 1,343 subjects that had a primary operation before 1992, 481 (36%) had more than one operation. Out of those 481, 186 (39%) had another operation within 12 months and 243 (51%) within 24 months, involving a bilateral affliction in most instances rather than recurrence of the disease. Twelve percent or 155 cases had more than two operations, indicating a definite recurrence or extension of the disease. We observed that patients operated on for the first time early in life were more prone to recurrent disease.
Paper II
Of the 15,212 in-patients operated for DC and included in the study, 2,151 (14 %) were diagnosed with cancer (1,920 men and 231 women) during follow-up. There was a 24% overall increased risk for all types of cancer, which did not change with increasing follow-up time. There was a significantly increased risk for malignancies related to smoking, such as buccal, oesophageal, gastric, lung and pancreatic cancer. The increased risks for buccal, oesophageal and pancreatic cancer were, however, confined to men. Although renal, bladder and larynx cancers are known to be related to smoking, no increase in risk was noted for these cancers with the exception of an isolated increase in risk for renal cancer after 5 to 9 years of follow-up. Furthermore, a significantly increased risk for primary liver-, prostate- and rectal cancer was noted among men, regardless of duration of follow-up. Among women, there was a consistently increased risk for breast cancer one year or more after surgery for DC. An increased risk for sarcomas of bone and connective tissue was also noted five years or more after surgery for DC.

Paper III
Between 1965 and 1994 we identified 18 patients, 15 men and 3 women, who developed sarcomas 5 years or more after surgery for DC. Fourteen cases (78%) were diagnosed with soft tissue sarcoma and four cases (22%) with bone neoplasms. The distribution of the different types of sarcomas is presented in Table 3.

Table 3. Distribution of different types of sarcomas

<table>
<thead>
<tr>
<th>Soft tissue sarcoma (14 patients)</th>
<th>Bone sarcoma (4 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>malignant fibrous histiocyteoma (7)</td>
<td>chondrosarcoma (3)</td>
</tr>
<tr>
<td>fibrosarcoma (3)</td>
<td>osteosarcoma (1)</td>
</tr>
<tr>
<td>xanthomatous fibrous histiocyteoma (1)</td>
<td></td>
</tr>
<tr>
<td>liposarcoma (1)</td>
<td></td>
</tr>
<tr>
<td>leiomyosarcoma (1)</td>
<td></td>
</tr>
<tr>
<td>malignant mesenchymoma (1)</td>
<td></td>
</tr>
</tbody>
</table>
The mean age at the initial operation for DC was 64 years (62 for men and 75 for women). At the time of sarcoma diagnosis the mean age was 73 years (71 for men and 82 for women). The mean age at death among the 14 patients who died was 79 years (78 for men and 85 for women). Four patients are still alive 7, 8, 9 and 23 years after the diagnosis of sarcoma. Eight patients were operated once for unilateral, four patients for bilateral and six patients for recurrent DC. In two cases there was a history of alcohol abuse and eight patients smoked. Patient data are presented in Table 4.

Paper IV
During the observation period a total of 16,517 in-patients (14,165 men and 2,352 women) were discharged from the hospital after surgery for DC. There were 7,579 deaths (6,660 men and 919 women) in the cohort during the 30 years of observation. The expected number of deaths in the cohort was 7,132, resulting in an SMR for both sexes of 1.06 (95% CI 1.04-1.09). The study population was divided into age groups based on the date of surgery for DC in order to determine if age at surgery had any impact on overall mortality. We observed a significant increase in overall mortality for both genders in all age groups except in patients under 20 years of age, in women between 30 and 39 years of age, and among patients over the age of 70 at the time of surgery. The increase in risk was as high as 67% among men in the age group 30-49 years, and in women the risk was more than doubled if they underwent surgery for DC before the age of 50. Analysing the overall increase in mortality according to the time since surgery for DC revealed no increase in risk up to five years after surgery. However, a clear increase in mortality was noted 5-9 years after surgery (8%), 10-14 years after surgery (13%), and >15 years after surgery (26%). When the different ICD-9 disease groups were analysed separately, we noted that cardiovascular diseases were the most common cause of death, with 3934 deaths (52%). Although there was no overall increased mortality for cardiovascular diseases in either male or female patients operated on for DC, a subgroup analysis revealed an overall risk that was apparent ≥10 years after surgery and being substantial in those operated on between the ages of 40 and 49 (65%). The risk was less prominent in those operated on between the ages of 50 and 59 (17%). In men, there was an increased risk of 53% and
Table 4. Patient data from paper III.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age at 1st op.</th>
<th>Number of op. for DC (left - right)</th>
<th>Other illness or cancer</th>
<th>Age at sarcoma diagnosis</th>
<th>Type of sarcoma</th>
<th>Localisation of sarcoma</th>
<th>Age at death</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>47</td>
<td>1</td>
<td>prostate cancer, AA</td>
<td>65</td>
<td>CS</td>
<td>left hand</td>
<td>69</td>
<td>prostate cancer</td>
</tr>
<tr>
<td>F</td>
<td>72</td>
<td>2</td>
<td>DM</td>
<td>79</td>
<td>MFH</td>
<td>left arm</td>
<td>alive</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>76</td>
<td>0</td>
<td>pyelonephritis, MI</td>
<td>79</td>
<td>CS</td>
<td>left thumb</td>
<td>81</td>
<td>MI</td>
</tr>
<tr>
<td>M</td>
<td>69</td>
<td>1</td>
<td>DM</td>
<td>74</td>
<td>MFH</td>
<td>left leg</td>
<td>alive</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>71</td>
<td>0</td>
<td>colloid goitre, HT</td>
<td>82</td>
<td>fibrosarcoma</td>
<td>left bottom</td>
<td>88</td>
<td>tumour</td>
</tr>
<tr>
<td>M</td>
<td>59</td>
<td>1</td>
<td>renal cancer, thyreotoxicosis</td>
<td>68</td>
<td>leiomyosarcoma</td>
<td>intra-abdominal</td>
<td>69</td>
<td>tumour</td>
</tr>
<tr>
<td>M</td>
<td>62</td>
<td>1</td>
<td>DM, HT, lung cancer</td>
<td>72</td>
<td>XFH</td>
<td>left axilla</td>
<td>82</td>
<td>tumour</td>
</tr>
<tr>
<td>M</td>
<td>60</td>
<td>0</td>
<td></td>
<td>74</td>
<td>MFH</td>
<td>left thigh</td>
<td>74</td>
<td>tumour</td>
</tr>
<tr>
<td>M</td>
<td>59</td>
<td>0</td>
<td>HT, carotid stenosis</td>
<td>61</td>
<td>CS</td>
<td>left arcus costae</td>
<td>70</td>
<td>unknown</td>
</tr>
<tr>
<td>F</td>
<td>76</td>
<td>1</td>
<td>colon cancer, HT</td>
<td>77</td>
<td>MFH</td>
<td>right scapula</td>
<td>82</td>
<td>colon cancer</td>
</tr>
<tr>
<td>M</td>
<td>65</td>
<td>1</td>
<td>MI</td>
<td>81</td>
<td>liposarcoma</td>
<td>left groin</td>
<td>88</td>
<td>pneumonia</td>
</tr>
<tr>
<td>M</td>
<td>53</td>
<td>2</td>
<td></td>
<td>65</td>
<td>MFH</td>
<td>left popliteal fossa</td>
<td>67</td>
<td>tumour</td>
</tr>
<tr>
<td>F</td>
<td>75</td>
<td>3</td>
<td>thyreotoxicosis</td>
<td>89</td>
<td>osteosarcoma</td>
<td>left femur</td>
<td>89</td>
<td>tumour</td>
</tr>
<tr>
<td>M</td>
<td>52</td>
<td>0</td>
<td></td>
<td>61</td>
<td>fibrosarcoma</td>
<td>right scapula</td>
<td>alive</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>66</td>
<td>1</td>
<td>lung tuberculosis</td>
<td>73</td>
<td>fibrosarcoma</td>
<td>retro- peritoneal</td>
<td>80</td>
<td>unknown</td>
</tr>
<tr>
<td>M</td>
<td>62</td>
<td>1</td>
<td>HT, MI</td>
<td>79</td>
<td>MFH</td>
<td>left arm</td>
<td>84</td>
<td>unknown</td>
</tr>
<tr>
<td>M</td>
<td>72</td>
<td>2</td>
<td>asthma, AA</td>
<td>82</td>
<td>mesenchymoma</td>
<td>retro-peritoneal</td>
<td>82</td>
<td>tumour</td>
</tr>
<tr>
<td>M</td>
<td>48</td>
<td>2</td>
<td></td>
<td>52</td>
<td>MFH</td>
<td>right bottom</td>
<td>alive</td>
<td></td>
</tr>
</tbody>
</table>

AA = alcohol abuse; DM= diabetes mellitus; HT= hypertension; CS= chondrosarcoma; MFH= malignant fibrous histiocytoma; MI = myocardial infarction; XMH=xanthomatous fibrous histiocytoma
15% in the age groups 40-49 and 50-59 years, respectively. In woman a similarly increased risk of 49% was noted in the age group 50-59 years. Cancer was the second most common cause of death (25%) with a significantly increased overall mortality of 20%. The risk for death caused by respiratory diseases, the third most common cause of death (8%), was significantly elevated (9%) only among men. A 61% increase and a 22% increase in death among patients operated on between the ages of 50-59 and 60-69 years, respectively, were thus noted. We also observed an overall increased mortality for endocrine diseases (45%), with a considerable increase in those operated on for DC between the ages of 40 and 49 (182%), and between the ages of 50 and 59 (144%), and a less prominent increase in those operated on between the ages of 60 and 69 (59%). There was also an increased risk of mortality caused by gastrointestinal disease (26%), but this was only significant among men. An increased risk was noted in particular among patients in the age group 40 to 59 years at the time of surgery. We also noted an increased risk for accidental death (35%), although significance was only attained in men operated on between the ages of 30 and 69 years. In order to test whether diabetes mellitus could be a possible confounder causing increased mortality, we constructed a new cohort in which patients with diabetes mellitus as one of their discharge diagnoses were excluded. This exclusion reduced the cohort from 16,517 to 14,603 patients, and the number of deaths from 7,579 to 6,387. Excluding patients with diabetes mellitus did not affect the overall pattern with respect to an increased mortality in patients with DC. As expected, there was no considerably decreased mortality from endocrine diseases. The risk estimates were highest for gastrointestinal diseases, accidents, and respiratory diseases.

Paper V
Follow-up data was obtained from 93 patients. At the time of surgery their mean age was 60.8 years (range 24.7 to 85.5). Surgery was performed on 45 right hands and 48 left hands. During the study period two thirds of the patients were operated on for primary disease and one third for recurrent disease. A positive family history of DC was noted in 44% of the patients and 26% had foot sole manifestations of the disease. Almost half of the study group (42 out of 93) noticed recurrent bending of the operated
finger/fingers during the study period, and of these, 18 patients stated that this occurred within six months, and 24 patients reported recurrence later than six months after surgery. The mean age at surgery for the patients with early recurrence and recurrence later than six months was somewhat lower than for the study group as a whole. Of the 93 patients, 51 were classified as being in the residual phase, 28 in the involutional phase and 14 in the proliferative phase. No differences concerning distribution of histological phases were noted in patients with early or later recurrence compared with patients without a history of recurrence postoperatively. Repeated surgery (three or more previous operations) and Dupuytren’s diathesis (early onset of disease, ectopic lesions and positive family history) predicted recurrent bending during the study period. However, nor recurrence or age at surgery was significantly related to the histological phase of disease. There were no differences in the expression of any of the investigated markers reflecting ongoing activation of the connective tissue in patients with recurrent bending of the operated finger/fingers either before or later than six months postoperatively. Furthermore, there were no relationships between gender, age at onset of disease, number of operations, positive family history, diabetes mellitus, or medication for cardiovascular disease on the one hand, and the intensity (grade) of the different immunohistochemical stainings on the other.
DISCUSSION

Epidemiology

The epidemiology of DC has attracted the attention of surgeons almost from the time the disease was first described. In his textbook of surgery, Keen (55) noted in 1908 that women were affected in “40 of 227 cases”, giving a male: female ratio of 5.7:1. Our study covering the period from 1965 to 1996 with a male: female ratio of 5.9:1 can only confirm Keen’s observations. In Skoog’s thesis on DC from 1948, four different series of cases operated on for DC were compiled and the result was a male: female ratio of 5.6:1 (93). Several authors have pointed out that the difference in distribution in terms of gender in DC is age-dependent, and that by the eighth and ninth decades of life the male: female ratio approaches 1. This was observed by Mikkelsen (67), who reported a male: female ratio that was 5.8:1 for cases aged 50 to 54 years and 1.2:1 for those aged 85 to 89 years. A similar pattern was observed by Early (28), with a male: female ratio that was 8.2:1 for those aged 45 to 54 years and 2:1 for those aged 75 years or more. In our series there was a male: female ratio of 9.4:1 for patients aged 50 to 59 years and 4.2:1 for those aged 70 years or more.

There is also nearly universal agreement that DC has its onset later in women than in men (16, 84). This observation could also be confirmed in our study. Statements concerning the gender ratio must, therefore, be accepted with some reservation, since the earlier affliction of males with DC results in more frequent surgery in males, a fact that will lead to an overestimation of the male: female ratio.

A possible explanation for men being afflicted earlier with DC could be that female sex hormones could have a protective function in the development of DC. Another possible reason could be the established differences in lifestyles between men and women concerning drinking habits, smoking habits and risk taking. An argument in favour of this hypothesis is that we observed lower mortality rates among the elderly age groups, indicating that lifestyle factors are of less importance for those developing DC at an older age. Furthermore, it has been postulated that women are less likely to complain about the disease and therefore are under-represented, particularly in surgical.
series (84). There is, however, little evidence to support this supposition. In agreement with McFarlane’s study (65), we observed that the frequency of repeated operations for DC was much lower among women than men. On the other hand, women tend to have a slightly worse outcome postoperatively compared with men (113). Perioperatively, the most important difference is an increased risk of developing a complex regional pain syndrome (reflex sympathetic dystrophy) after DC surgery in women (63, 112).

Risk factors
In their search for aetiological or triggering factors, many authors have found associations between DC and other diseases such as diabetes (6, 77), epilepsy (5), high blood levels of cholesterol and triglycerides (88), HIV (14), previous hand trauma (59), manual work (39, 68) and alcoholism (7). The true cause of DC continues, however, to be elusive. Several of the listed contributing or triggering factors can be linked to lifestyle.

Why epilepsy is associated with DC is still uncertain. The relationship was first described in epileptic inmates’ (57) and by Skoog in 1948 (93). A good deal of information exists that can be used in formulating a hypothesis. For instance, there is a negative correlation between seizure frequency and the percentage of patients with DC (23), a fact that has raised the idea that anti-epileptic drugs, rather than epilepsy as such, play a role in the disease process. All inmates in Skoog’s investigation (93) had been treated with phenobarbital for several years. No differences in the severity of DC were noted in patients receiving different dosages of anti-convulsive drugs (5). However, if phenobarbital is excluded as an anti-epileptic medication, the risk of acquiring DC falls dramatically (23). A possible mechanism in the development of DC in patients treated with phenobarbital could be an affected release of tissue growth factors that give rise to side effects like pathological liver-enzyme levels and simultaneously stimulate myofibroblasts. On the other hand, Zachariae and co-workers (111) observed that EEG abnormalities are more common in DC patients than in the normal population, suggesting a link to epilepsy as such.
Cancer and free oxygen radicals

The excess risk for cancer among patients with DC has been linked to lifestyle factors such as smoking and alcohol abuse. In a recently published paper from Island (40), the authors noted that 42% of the excess mortality could be attributed to cancer deaths. After adjustment for age, smoking habits, body mass index, fasting blood glucose, and manual or learned labour, individuals with clinical signs of DC showed an increased cancer mortality ratio of 1.9. One tentative explanation for the pattern of different cancers in patients with DC could be dietary factors, especially antioxidants. Oxidative stress occurs when there is an imbalance between free radical production and antioxidant capacity. Oxidative stress has been associated with DC (71, 110), as well as with the development of cardiovascular disease and diabetes (80). Free radicals are also known to be a pathogenetic factor in carcinogenesis and certain gastrointestinal cancers (81). Moreover, some antioxidants appear to have a protective effect against hormone-related malignancies, e.g. cancers of the breast and prostate (102). In our study of cancer incidence in patients operated for DC, we observed that gastric and colorectal cancers occurred more frequently than expected, as did cancers of the breast and prostate.

Risk for recurrence

Recurrence and extension of DC are still unsolved problems. The literature reports widely variable recurrence rates in DC, from 0% to 87%, depending on length of follow-up and patient and procedure selection (44).

A crucial issue in analysing the results of surgery for DC is to distinguish between recurrence and extension of the disease. Recurrence means new disease in a previously operated area, whereas extension means development of disease in areas not previously treated. Recurrence has been suggested to be more frequent in individuals with Dupuytren’s diathesis (47). On the other hand, Vigroux and Valentin have suggested that Dupuytren’s diathesis has no influence on the rate of recurrence, which is only influenced by the severity of the preoperative condition (107). Our data,
however, and data from Roush and Stern (85), support the tendency for recurrence in patients with Dupuytren’s diathesis.

Classification of the lesions into three histological phases was inspired by concepts expressed by Luck (56). In agreement with earlier studies (105), we observed that both proliferative and fibrotic phases could be identified in the same subjects. There were, however, no significant relationships between the histological classification and the rate of recurrence. Furthermore, there was no clear difference between the histological phases in the different age groups. The earlier is in agreement with the suggestions of Luck (56), Chiu and McFarlane (21), and Nézelof (75) that the three histologic phases represent three evolitional stages of the disease, rather than reflecting something about the severity of the disease.

We hypothesised that it would be possible to discern the risk for recurrence after analysing the extent of connective tissue activation in surgical specimens utilising immunohistochemical methods. Earlier studies have demonstrated that myofibroblasts, the key cells in DC, appear during the proliferative phase and come to comprise almost all of the cells present in the highly cellular nodule. In the involutional phase the myofibroblasts are smaller and tend to be aligned in the same direction (104). We selected immunohistochemical markers in order to identify differences in expression of a number of myofibroblast phenotype characteristics, i.e. expression of desmin and SMA, an ongoing production of collagen type I, and a high fibronectin binding ability. The immunohistochemical staining pattern for all investigated connective tissue activation markers was, however, very similar, with a positive reaction particularly in proliferative nodules. The presence of myofibroblast-like SMA-positive cells has also been observed in the subcutis and dermis in patients with DC (62). These cells were separate from the hypercellular Dupuytren’s lesion and frequently were even situated at some distance from the borders of the lesion. This could imply that there is no sharp border between pathological Dupuytren’s tissue and presumed unaffected surrounding tissue. This theory is strengthened by the work of Pasquali-Ronchetti and co-workers (79) who observed that apparently normal aponeurotic tissue already seems to be
affected by the pathological process, as the cells exhibit a phenotype that is different from unaffected controls and similar to that found in nodules and in fibrotic cords.

Since replacement of the volar skin with a full thickness graft is known to prevent recurrence of DC (45, 50, 86), it is postulated that the skin itself with remaining myofibroblasts may provide a pool from which new foci can develop. However, in contrast to those results, Norotte et al. (78) found that the recurrence rate is not affected by surgical procedure, including dermofasiectionomy with full-thickness skin grafting.

In our investigation of connective tissue activation markers we were not able to identify those individuals with a high risk for recurrence after surgery for DC. It therefore seems that the individual characteristics that cause a person to be at high risk are not clearly related to the ongoing connective tissue production at time of surgery, or to connective tissue activity in the conventional sense.

In recent years major technical advancements have resulted in reducing recurrences through skin grafting, and improving the immediate results of surgery and maintaining them post-operatively through rehabilitation. Furthermore, it seems that since recurrence is not influenced by connective tissue activity, when the operation takes place could be of less importance. Perhaps better results could be obtained in potentially aggressive cases through earlier surgery, and prospective clinical studies are therefore required for early identification of the disease in which the most severe stages are likely to develop.

In this context, one could refer to the conclusion of the clinical lecture on this subject given by Guillaume Dupuytren on 5 December 1831 at the Hôtel Dieu: “Permanent retraction of the fingers produced by an affection of the palmar fascia”. He expressed the hope that “these hints may become useful to science and humanity, in multiplying observations on the cause, symptoms, and treatment of this disease”. Now, almost 170 years later, although there is much better understanding of DC, surgical excision of the
diseased fascia still remains the best treatment available. Further advances in the basic science of the disease, however, will hopefully provide us with better options.
CONCLUSIONS

I. The annual number of operations for DC did not differ substantially during the observation period. There was an overall male: female ratio of 5.9:1, decreasing with increasing age. Women were on average 2.6 years older than men at their first operation. Men required more frequently repeated surgery for DC than women. Early age at first operation was associated with recurrent disease.

II. The overall relative risk for cancer in patients treated surgically for DC was increased by 24%. There were significantly increased risks for malignancies related to smoking, e.g. buccal, oesophageal, gastric, lung and pancreatic cancers. Significantly increased risks were also observed for prostate and rectal cancer in men and for breast cancer in women one year or more after surgery for DC. The study emphasises smoking and alcohol abuse as probable risk factors for DC.

III. There was an increased frequency of fibrosarcoma and malignant fibrous histiocytoma, but the affected patients did not differ from other patients in the study group. Our analysis suggests that neither smoking, diabetes nor cancer syndromes can explain why patients operated for DC have a higher incidence of sarcoma.

IV. There was an increased mortality in patients treated surgically for DC. This was inversely related to age and significant for both sexes in patients under 70 years. The risk was highest for endocrine diseases, gastrointestinal diseases, accidents, cardiovascular diseases, and respiratory diseases. The pattern suggests that smoking and other lifestyle factors mediate the increased mortality.

V. There were no associations between gender, age at onset of DC, number of operations, heredity, diabetes mellitus, medication for cardiovascular disease, and the expression of immunohistochemical markers for collagen type IV,
integrin $\alpha_5$, laminin, smooth muscle $\alpha$-actin, procollagen type I or desmin in affected DC tissue. Thus there were no indications that the individual characteristics that place a person at high risk for recurrence of DC are related to ongoing connective tissue production at the time of surgery or to connective tissue activation in its conventional sense.
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