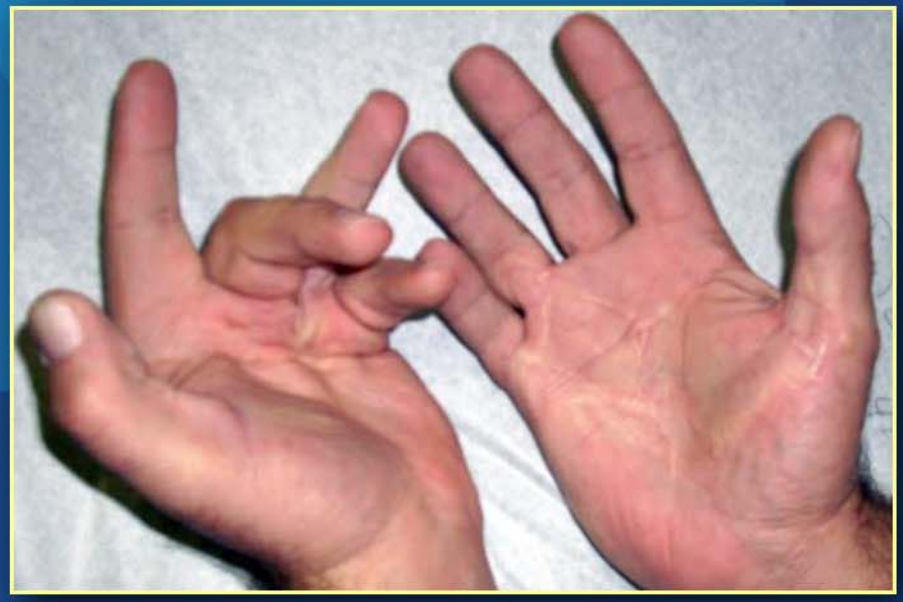
Dupuytren's Disease



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Acknowledgements

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Chief of Hand Surgery
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Professor
Department of Orthopaedics
SUNY at Stony Brook, NY

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Dupuytren's Disease

- Background
- Pathophysiology
- Clinical Presentation
- Diagnosis
- Treatment

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Dupuytren's Disease

Background

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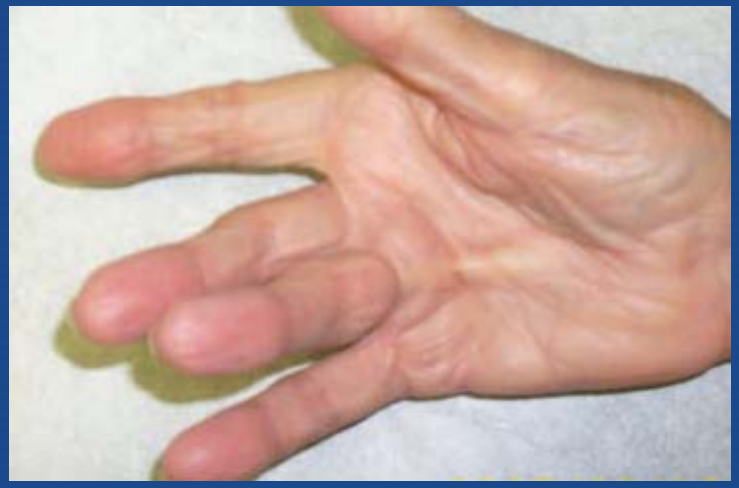
Dupuytren's Disease

Progressive and irreversible fibromatosis of the palmar and digital fascia

- Transformation of fibroblasts to myofibroblasts → produce excessive collagen
- Collagen becomes pathologic cords
- Cords thicken and shorten → flexion contractures result

Functional impairment often accompanies deformities



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Guillaume Dupuytren

Dissected cadaveric hand from a patient with “Dupuytren’s disease”

- Concluded exaggerated tension of the aponeurosis was starting point for the disease
- Contracture was released when cord was cut

Guillaume Dupuytren (1777-1835)

First to perform successful open transverse fasciotomy on a patient with Dupuytren’s disease

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Dupuytren's Disease:

Epidemiology

Global Prevalence

- Estimated at 3% to 6% among adult Caucasians
  - 13.5 to 27 million people in the United States and Europe
- Present in all races

Incidence

- Peaks in 40s and 50s
  - Men: 50 years of age; women: 60-70 years of age
- Rises with increasing age

Gender

- More common in men

Luck JV. *J Bone Joint Surg [Am].* 1959;41:635-664.
Tubiana R et al. *Dupuytren's Disease*. London: Martin Dunitz Ltd.; 2000:53, 55.
Auxilium estimates using US (2000) census and United Nation, World Population (2002).

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Dupuytren's Disease:

Hereditary Expression

One of the most common hereditary connective tissue diseases in Caucasians

- Familial clustering
- Autosomal dominant pattern with variable penetrance
- Associations described
  - Heteroplasmic mitochondrial mutation
  - Single nucleotide polymorphism in Zf9 gene
  - HLA-DRB1*15 phenotype
- Differential expression of genes in fibroblasts and biopsies derived from patients with Dupuytren's disease

Other contributory factors are not clearly understood

Bayat A et al. *Plast Reconstr Surg.* 2003;111:2133-2139.
Bayat A et al. *Plast Reconstr Surg.* 2005;115:134-141.
Brown JJ et al. *Tissue Antigens.* 2008;72:166-170.
Hindocha S et al. *J Hand Surg [Am].* 2006;31:204-210.
Hu FZ et al. *Clin Genet.* 2005;68:427-429.
Rehman S et al. *J Hand Surg.* 2008;33A:359-372.
Satish L et al. *BMC Med Genomics.* 2008;1:10.
Shih B et al. *J Hand Surg.* 2009;34:124-136.

Dupuytren's Disease:

Associated Conditions

	Estimated Incidence of Dupuytren's Disease in Patients with Condition	Estimated Incidence of Condition in Patients with Dupuytren's Disease
Diabetes	17.5%–24.4%	5%–19.6%
Epilepsy	11%–55%	2%–3%
Alcoholism	25%–66%	NR

NR, not reported.

Tubiana R et al. *Dupuytren's Disease*. London: Martin Dunitz Ltd.; 2000:53, 55.

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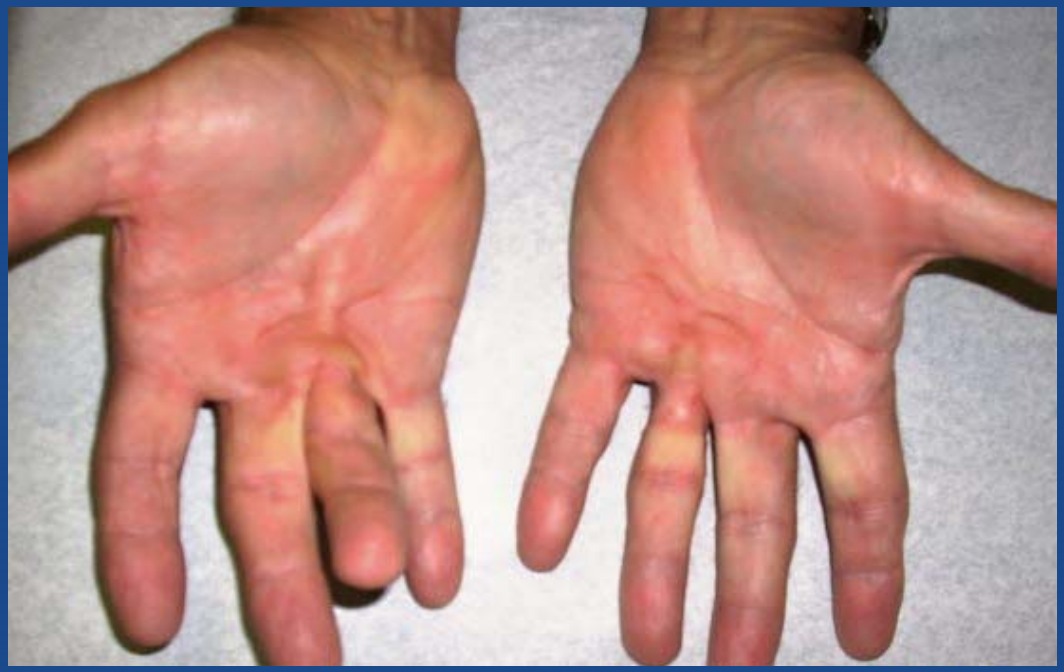
Dupuytren's Disease:

Hand Involvement

Commonly bilateral

- Higher incidence of family history, ectopic manifestations, and poorer prognosis than unilateral disease



Townley WA et al. *BMJ*. 2006;332:397-400.
Tubiana R et al. *Dupuytren's Disease*. London: Martin Dunitz Ltd.; 2000:86, 90.

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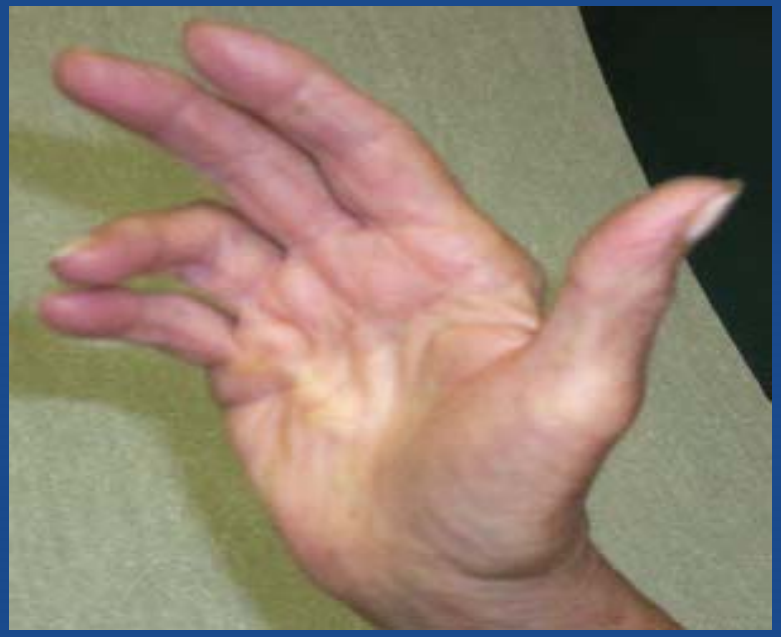
Dupuytren's Disease:

Finger Involvement

Most commonly affects ring and little fingers

- Little: 51%
- Ring: 60.7%
- Middle: 22.5%
- Index: 5.8%
- Thumb: 7%



First web involvement also seen

Initially limited to single finger

- Usually progresses to other fingers

Tubiana R et al. *Dupuytren's Disease*. London: Martin Dunitz Ltd.; 2000:87-88.

Ectopic Manifestations of Collagen Deposition Disorders

Regional

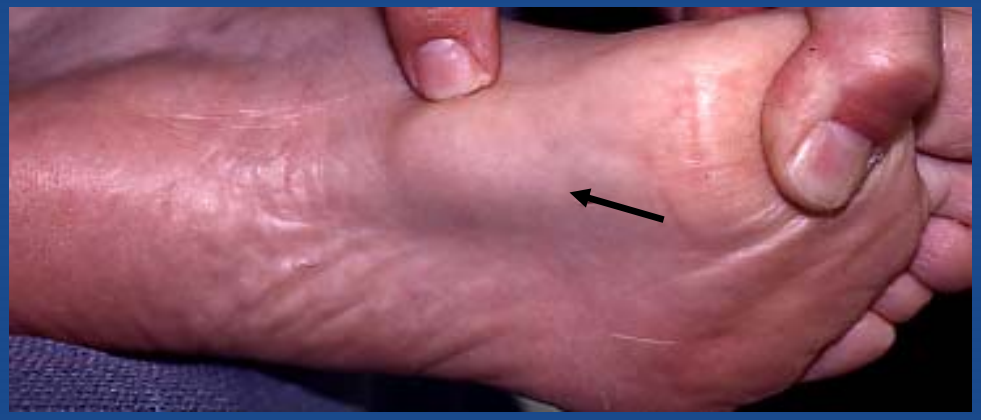
- Garrod's nodes (knuckle pads)

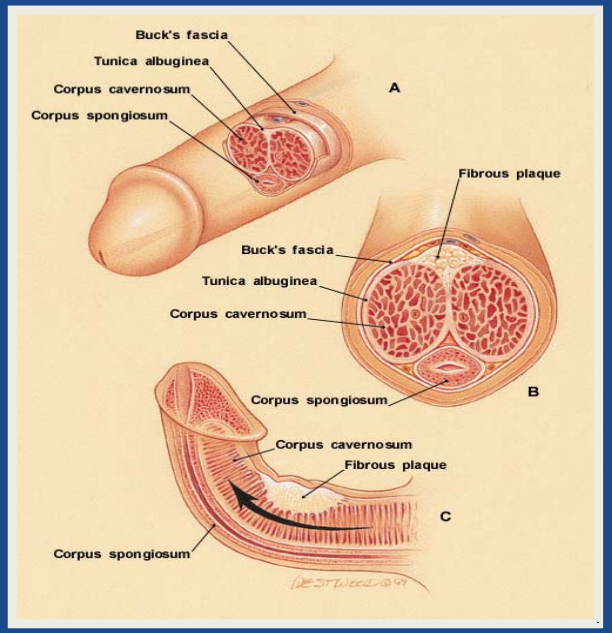
Upper extremity other than the hand

- Rare

Distant

- Lederhose disease (plantar fibromatosis)
- Peyronie disease (penile fibromatosis)





Rayan GM. *Hand Clinics.* 1999;15:87-96.

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Dupuytren's Disease:

Functional Impairment

Personal life

- Washing
- Brushing hair
- Dressing
- Driving
- Shaking hands
- Putting hands in pockets

Work and hobbies

- Manual labor
- Handling tools
- Wearing gloves
- Typing
- Playing sports
- Playing musical instruments
- Releasing objects

Bayat A, McGrouther DA. *Ann R Coll Surg Engl.* 2006;88:3-8.
Gudmundsson KG et al. *Scand J Rheumatol.* 2001;30:31-34.
Luck JV. *J Bone Joint Surg [Am].* 1959;41-A:635-664.
Townley WA et al. *BMJ*. 2006;332:397-400.
Tubiana R et al. *Dupuytren's Disease*. London: Martin Dunitz Ltd.; 2000:86.

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Dupuytren's Disease

Pathophysiology

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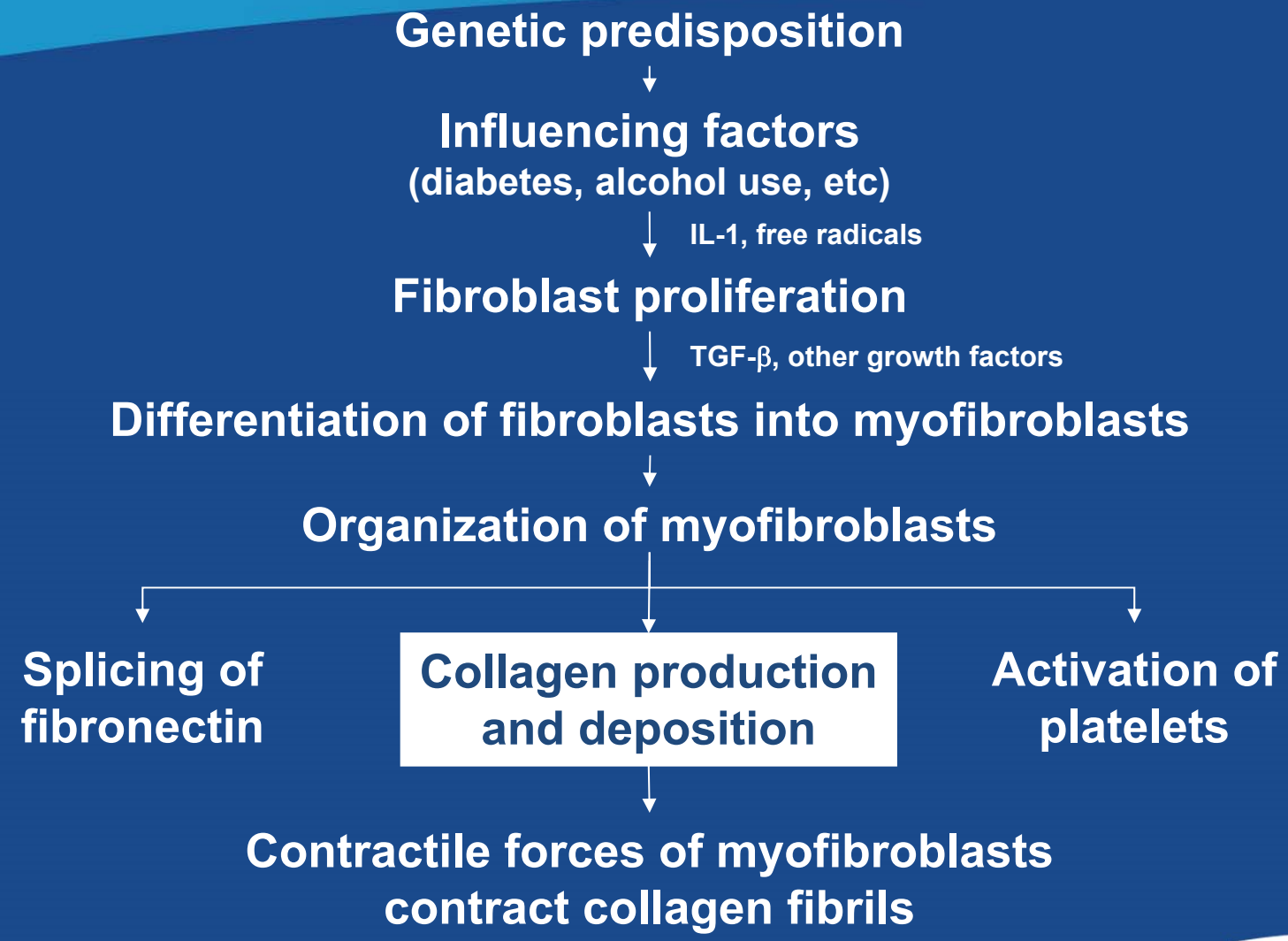
Dupuytren's Disease:

Pathogenesis



Al-Qattan MM. *J Hand Surg.* 2006;31A:1527-1534.

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Collagen

Almost 30 collagen types

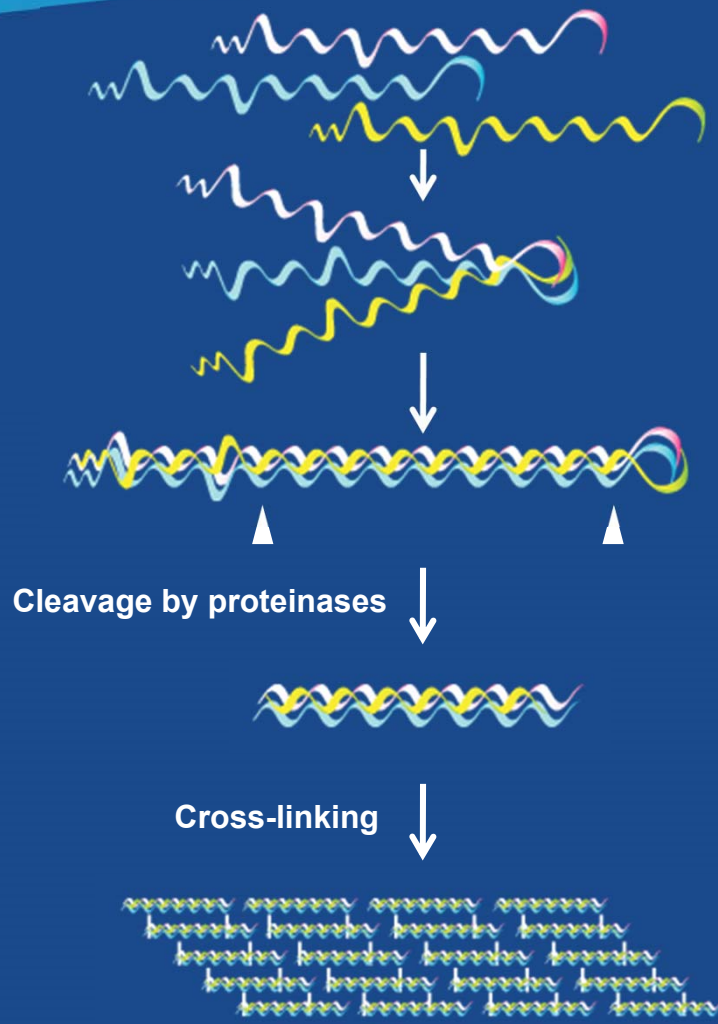
- Encoded by different genes

5 fibrillar collagens characterized by triple helix conformation

I	Tendons, bone, and skin ▪ Predominant type overall and in normal palmar fascia
II	Cartilage
III	Forms heterotypic fibrils with type I
V	Forms heterotypic fibrils with type I
XI	Forms heterotypic fibrils with type II

Canty EG and Kadler KE. *J Cell Sci.* 2005;118:1341-1353.

Collagen Synthesis



Procollagen chains

Procollagen trimer

Triple helical collagen

Collagen fibril

Canty EG and Kadler KE. *J Cell Sci.* 2005;118:1341-1353.

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Collagen Degradation

Specific proteases are required because triple helical collagen is highly resistant to general proteolysis

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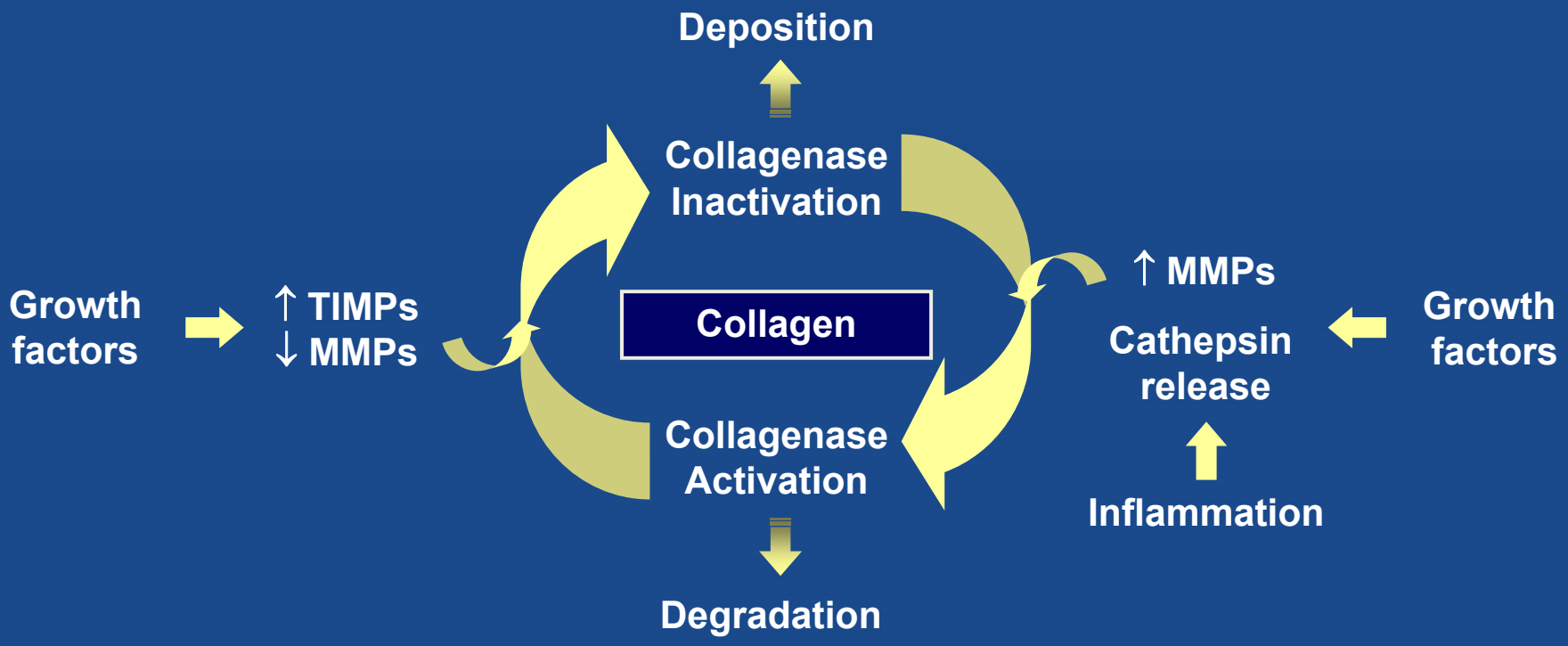
Mammalian Enzymes in Collagen Degradation

Collagenases	Neutrophil Elastase	Cathepsin K
• Members of matrix metalloprotease (MMP) family of enzymes • Secreted as zymogens, which require activation • Cleaves collagen at a specific single site on each chain producing 3/4 and 1/4 fragments	• Serine protease • Broad specificity • Cleaves collagen to produce 3/4 fragments	• Lysosomal cysteine proteinase • Functions at acidic pH • Broad specificity • With chondroitin sulfate, forms collagenolytic active complex • Cleaves collagen type 1 at multiple intra- and extrahelical sites
• MMP-1: interstitial collagenase or collagenase-1 ▪ Substrates: I, II, III, VI, VII, X • MMP-8: neutrophil collagenase or collagenase-2 ▪ Substrates: I, II, III, V, VII, VIII, X • MMP-13: collagenase-3 ▪ Substrates: I, II, III, IV, VII, IX, X, XIV	• Substrates: III > I > II • Implicated in inflammatory disorders	• Substrates: I, II • Mostly expressed in osteoclasts ▪ Important in bone resorption
• Inhibited by tissue inhibitors of metalloproteinases (TIMPs)		• Regulated by glycosaminoglycans

Garnero P et al. *J Biol Chem.* 1998;273:32347-32352.
Kafienah W et al. *Biochem J.* 1998;330:897-902.
Kafienah W et al. *Biochem J.* 1998;331:727-732.
Li Z et al. *J Biol Chem.* 2004;7:5470-5479.
Mainardi CL et al. *J Biol Chem.* 1980;255:12006-12010.
Nagase H and Woessner JF. *J Biol Chem.* 1999;274:21491-21494.
Starkey PM. *Acta Biol Med Ger.* 1977;36:1549-1554.
Woessner J. *FASEB J.* 1991;5:2145-2154.

Collagen Turnover

Normal part of growth, bone formation, wound healing, and strength responses to mechanical forces



MMP, matrix metalloprotease; TIMP, tissue inhibitors of metalloproteinases.

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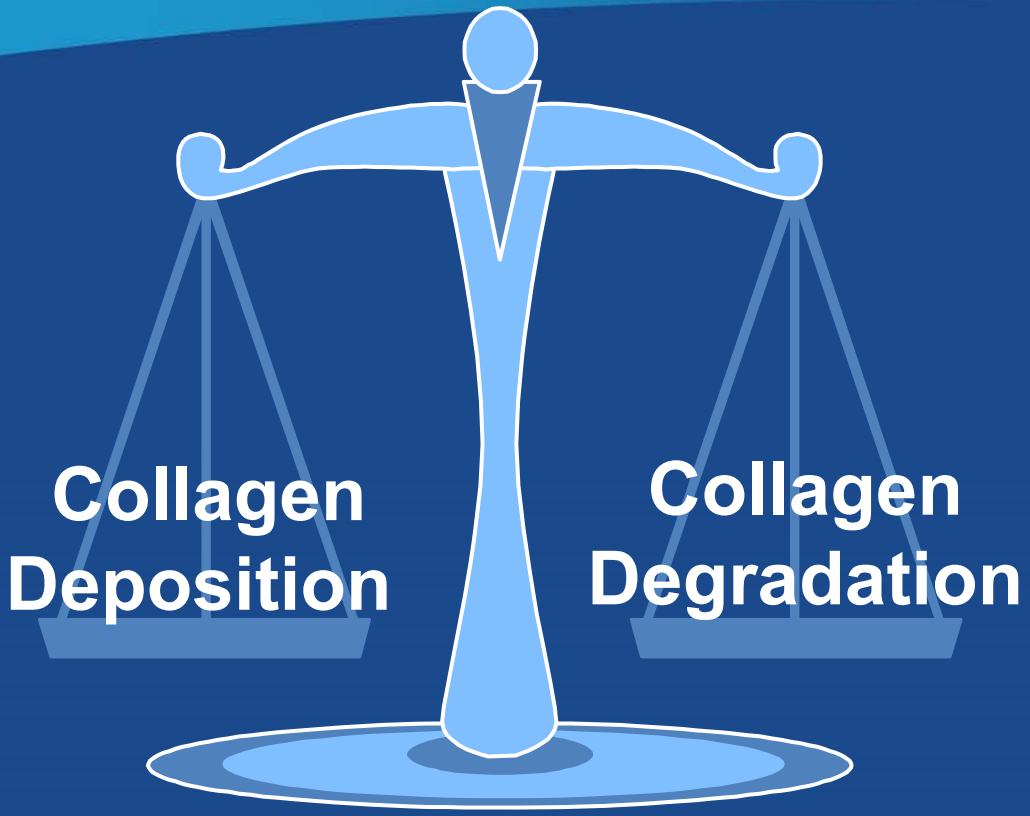
Balanced Collagen Turnover



Result is normal remodeling of collagen matrix following trauma/inflammation and during growth

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Unbalanced Collagen Turnover: Dupuytren's Disease

Also a change in the proportion of collagen types

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Dupuytren's Disease:

MMPs and TIMPs

Balance between MMPs and TIMPs is disturbed

- Differential expression of MMP and TIMP genes between Dupuytren's disease samples and controls
- Decrease in MMP-to-TIMP expression can cause increased synthesis and deposition of collagen

In vitro studies

- Inhibition of MMP activity in Dupuytren's disease-derived fibroblasts reduces extracellular matrix contraction

In vivo studies

- Correlation between MMP gene expression and recurrence

Johnston P et al. *J Hand Surg.* 2007;32A:343-351.
Johnston P et al. *J Hand Surg [Am]*. 2008;33:1160-1167.
Rehman S et al. *J Hand Surg.* 2008;33A:359-372.
Townley WA et al. *J Hand Surg [Am]*. 2008;33:1608-1616.
Ulrich D et al. *Arch Orthop Trauma Surg*. 2008; E-pub on-line early.

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Dupuytren's Disease:

Collagen Changes

Increase in ratio of type III to type I collagen

- 1% to 2% increase in type III in unaffected tissues
- 10% to 20% increase in type III in nodules
- 30% to 40% increase in type III in cords

Type III collagen

- Content correlates closely with clinical stages of contracture
- Proportion increases parallel to increasing tissue involvement
- Structural changes associated with disproportionate type III collagen
  - May influence biophysical properties of connective tissues in the involved palmar aponeurosis
  - May influence alterations of the cross-linking pattern

Melling M et al. *Arch Pathol Lab Med*. 2000;124:1275-1281.
Tubiana R et al. *Dupuytren's Disease*. London: Martin Dunitz Ltd.; 2000:71.

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Dupuytren's Disease

Clinical Presentation

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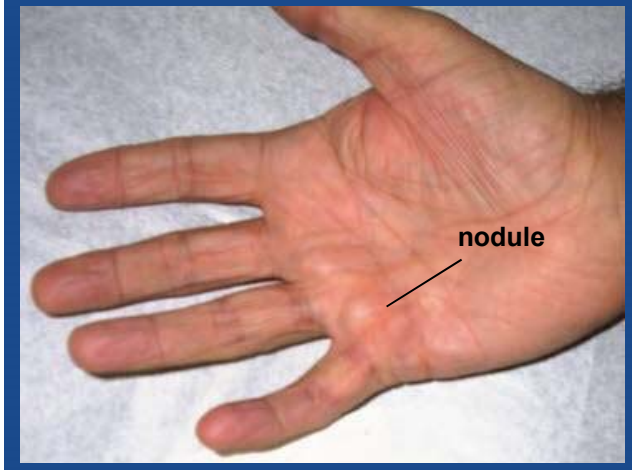
Dupuytren's Disease Is Progressive

Early Disease → **Advanced Disease**

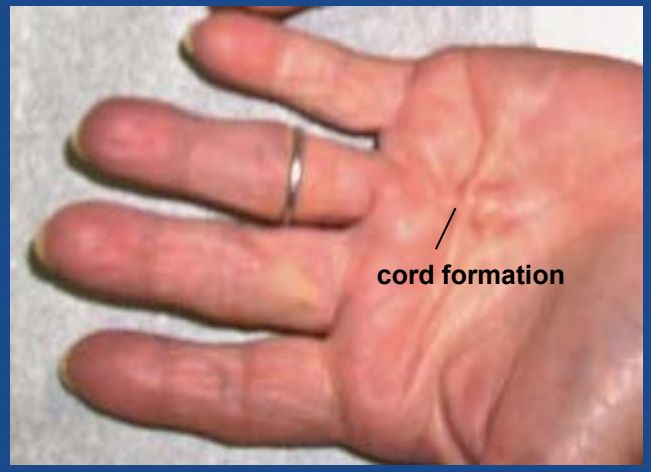
Proliferative Phase
- Random accumulation of myofibroblasts to form nodules, which are cellular and vascular

- Palmar lesions
- Nodule formation



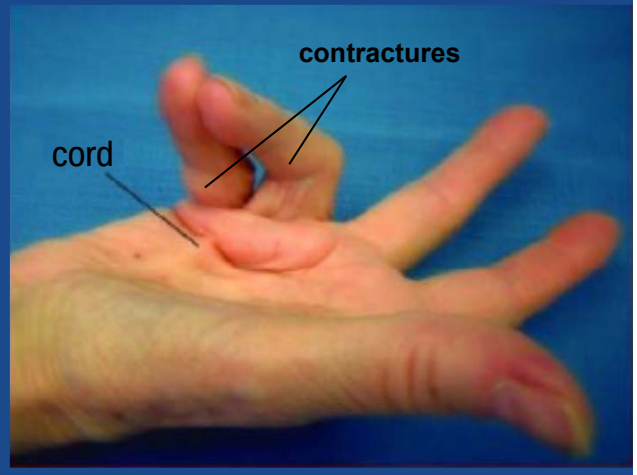
Involutional Phase
- Myofibroblasts align along tension lines passing through nodules
- Cord-like structures form
- Decreased cellularity
- Increased collagen production

- Cord formation
- Digital contracture begins



Residual Phase
- Nodule disappears leaving a focus of dense adhesions
- Collagen cords are relatively acellular, avascular, and tendon-like

- Contracted cords
- Flexion deformities



Luck JV. *J Bone Joint Surg [Am].* 1959;41:635-664.

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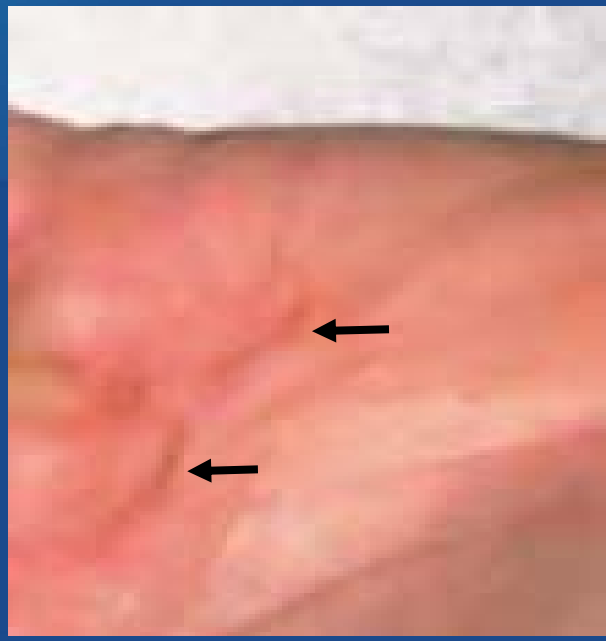
Dupuytren's Disease:

Skin Pitting or Dimpling



Early manifestation

Involvement of pretendinous bands that connect the dermis to the palmar fascia

Deep, full-thickness skin retraction into the SQ tissue

- Diseased longitudinal fibers of the pretendinous band insert into the dermis
- Contracted fibers pull the dermal layer of the skin inward

Rayan GM. *Hand Clinics.* 1999;15:87-96.
Townley WA et al. *BMJ* . 2006;332:397-400.
Tubiana R et al. *Dupuytren's Disease*. London: Martin Dunitz Ltd.; 2000;79-82.

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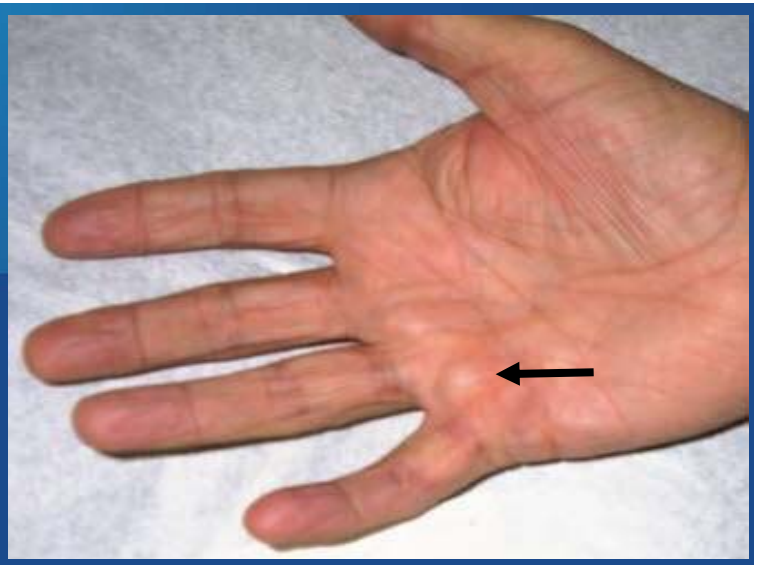
Dupuytren's Disease:

Nodules



Diagnostic

Originate from pretendinous bands

Firm, soft-tissue mass fixed to skin and deeper fascia

- Usually well defined
- Localized
- Raised
- Generally painless
- Located around proximal or distal palmar creases or off the finger axis

Cellular and vascular

- Contain abundant myofibroblasts that produce collagen

Rayan GM. *Hand Clinics*. 1999;15:87-96.
Townley WA et al. *BMJ.* 2006;332:397-400.
Tubiana R et al. *Dupuytren's Disease*. London: Martin Dunitz Ltd.; 2000;79-80.

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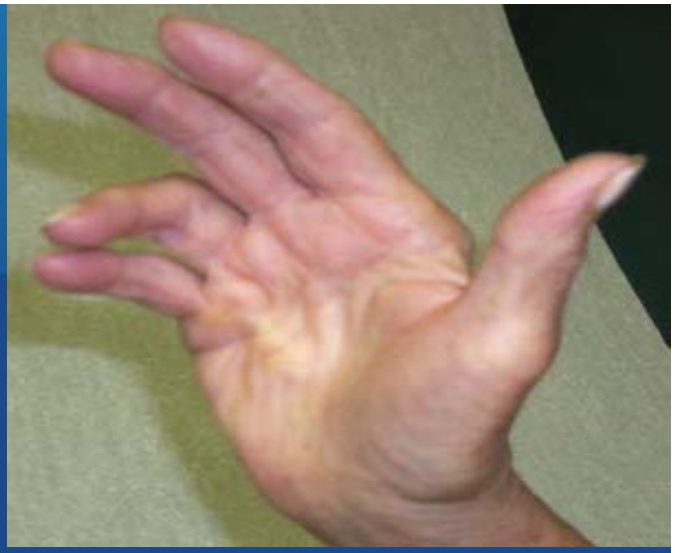
Dupuytren's Disease:

Cords and Contractures



Diagnostic

Contracture of cords results in predictable deformities as they cross joints

Normal	Pathology	Result
Pretendinous band	Pretendinous cord	MP joint deformity
Natatory ligament	Natatory cord	Limits digital abduction
Central fibrofatty tissue	Central cord	PIP joint deformity
Spiral band	Spiral cord	Displaces neurovascular bundle superficially
Lateral digital sheet	Lateral cord	PIP/DIP joint contracture

Rayan GM. *Hand Clinics.* 1999;15:87-96.
Townley WA et al. *BMJ.* 2006;332:397-400.
Tubiana R et al. *Dupuytren's Disease*. London: Martin Dunitz Ltd.; 2000;84.

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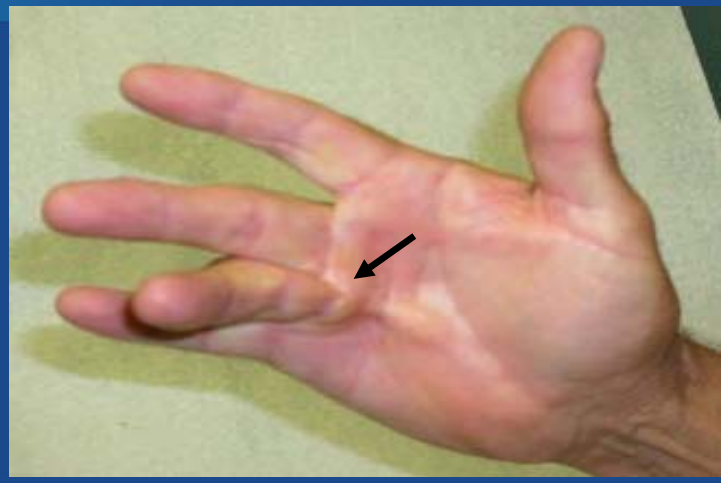
Dupuytren's Disease:

MP and PIP Joint Contractures

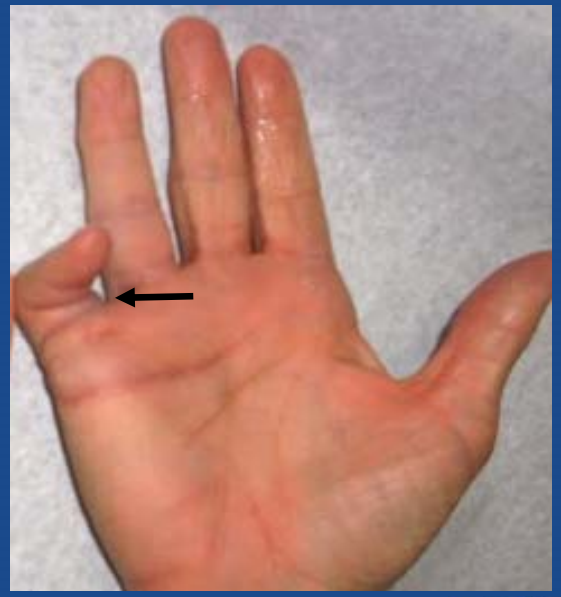
MP joint contractures

- Contracture of the palmar cord
- Natatory ligament involvement produces concomitant limitation of abduction of 2 adjacent fingers



PIP joints contractures

- Usually occur in later stages of disease
- Produce disability more readily than MP joint contractures



Both can occur in the same digit

Tubiana R et al. *Dupuytren's Disease*. London: Martin Dunitz Ltd.; 2000;48, 85-86.

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Dupuytren's Disease:

Secondary Lesions

Associated pathology in structures surrounding joints

- Contracture of flexor sheath
- Shortening of flexor muscles
- Lesions of the extensor mechanism
- Contracture of volar plate
- Contracture and adhesion of accessory collateral ligaments
- Contracture of collateral ligaments

Occur with longstanding contractures

Tubiana R et al. *Dupuytren's Disease*. London: Martin Dunitz Ltd.; 2000;48.

Dupuytren's Disease:

Secondary Lesions (continued)

Effects on MP and PIP joints are different

MP joints

Collateral ligaments

- Slack in extension and tight in flexion

MP volar plate attachments

- More mobile than PIP attachments

Longstanding contractures easily corrected

PIP joints

Tension of collateral ligaments

- Equivalent throughout range of motion
- Rapidly contract in flexion

With flexion

- Central extensor tendon elongated
- Lateral extensor tendons volarly displaced

Difficult to correct deformities

Tubiana R et al. *Dupuytren's Disease*. London: Martin Dunitz Ltd.; 2000;48.

Dupuytren's Disease:

Diathesis

Diathesis: A condition, constitution, or morbid habit that predisposes an individual to a particular disease

Dupuytren's disease diathesis

- Relates to certain characteristics of Dupuytren's disease
  - Positive family history
  - Bilateral involvement
  - Ectopic manifestations
  - Ethnicity
- Predicts progression and severity of disease
- Dictates an aggressive course and greater tendency for recurrence after surgery

Hindocha et al. *J Hand Surg*. 2006;31A:1626-1634.
Hueston JT. *Dupuytren's Contracture* . Edinburgh: E & S Livingstone; 1963.

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Dupuytren's Disease:

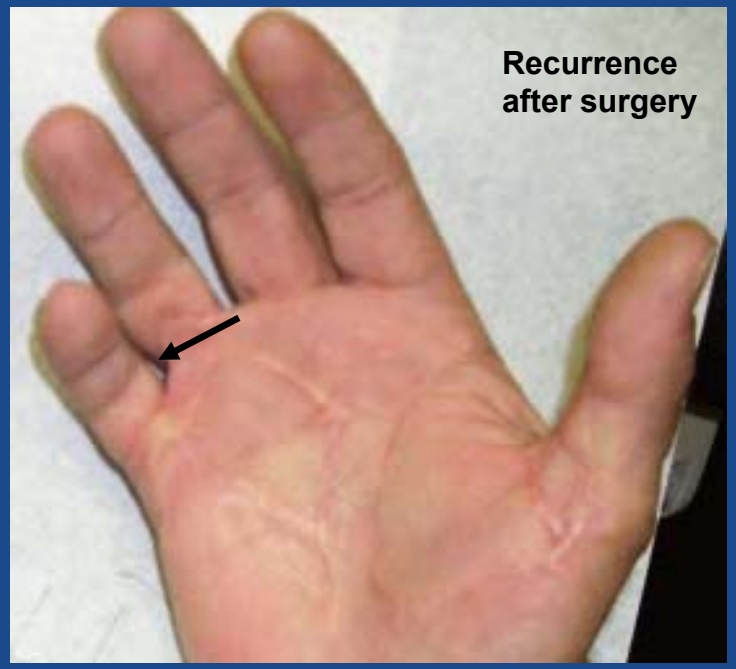
Progression

Extension of disease

Appearance of new lesions

Recurrent disease

Reappearance of Dupuytren's tissue in a zone previously operated on



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Dupuytren's Disease:

Influence of Diathesis on Disease Progression

Follow-up of patients for 3 years after surgery

	No Recurrence	Extension	Recurrence
No. of patients (n = 159)	70	41	48
Average age, y	58	55	45
Evidence of diathesis, n (%)			
Plantar lesions	3 (4)	4 (10)	12 (25)
Knuckle pads	14 (20)	17 (41.5)	36 (75)
Family history	10 (12)	4 (10)	13 (27)
Bilateral disease	56 (80)	39 (95)	47 (98)

Recurrence vs nonrecurrence

- Family history: 2 times more frequent
- Knuckle pads: 3.5 times more frequent
- Plantar lesions: 8 times more frequent
- Younger

Hueston JT. *Dupuytren's Contracture*. Edinburgh: E & S Livingstone; 1963.
Tubiana R et al. *Dupuytren's Disease*. London: Martin Dunitz Ltd.; 2000;118.

Dupuytren's Disease:

Recurrence

Published recurrence rates vary dramatically

- Variations in assessment of "recurrence" based on definitions used

Estimated rates: almost 65% after 10 years

- 30% during the 1st and 2nd postoperative years
- Additional 15% during the 3rd to 5th years
- Additional 10% between the 5th and 10th years
- Additional <10% after 10 years

May not solely depend on extent of excised tissue, but may be related to rate of disease activity particular to each patient

Hindocha S et al. *J Hand Surg*. 2006;31A:1626-1634.
Tubiana R et al. *Dupuytren's Disease*. London: Martin Dunitz Ltd.; 2000;239, 243.

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Dupuytren's Disease:

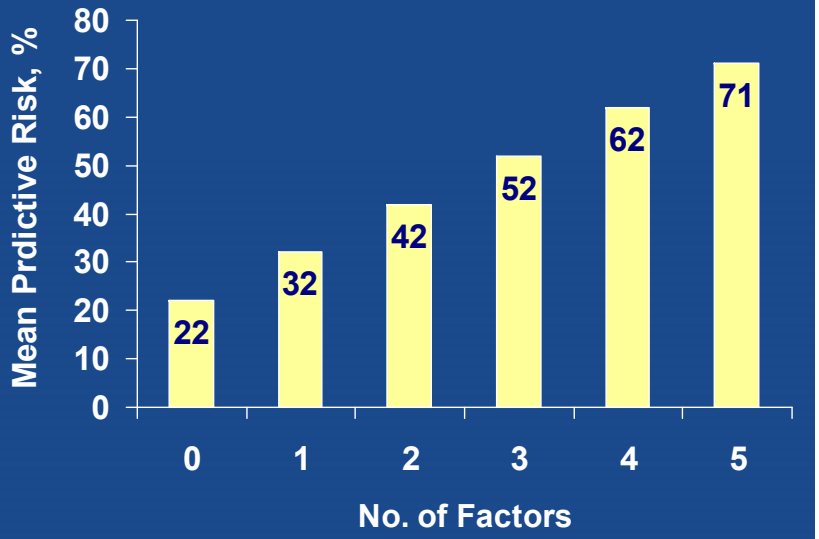
Factors Affecting Recurrence

Update of original diathesis factors

- Positive family history
- Bilateral involvement
- Garrod's pads
- Male gender
- Early age (<50 years) of onset

Predictive risk of recurrence

- **22% when no factors are present**
- **71% when all 5 factors are present**



Additional theoretical factors affecting recurrence include local trauma and inflammation

Hindocha S et al. *J Hand Surg.* 2006;31A:1626-1634.
Tubiana R et al. *Dupuytren's Disease*. London: Martin Dunitz Ltd.; 2000;243.

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Dupuytren's Disease

Diagnosis

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Dupuytren's Disease:

Relevant Patient History for Assessment

- Age, sex, ethnicity, profession, hobbies, right- or left-handedness
- Age at onset of symptoms
- Rate of progression of symptoms
- Pertinent medical history
  - Diabetes, epilepsy, other fibroproliferative disorders
- Impact on activities and quality of daily living
- Previous treatments and outcomes
- Family history

Bayat A and McGrouther DA. *Ann R Coll Surg Engl.* 2006;88:3-8.

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Dupuytren's Disease:

Investigating the Family History

Family incidence

- Reported rates are dependent on the extent of specific inquiries
  - Asking patient versus asking relatives versus examining relatives

In one report

- When asked whether any family member had Dupuytren's disease
  - 16% of 50 patients indicated positive family history
- After examination of 832 relatives
  - 68% had relatives affected with Dupuytren's disease

Ling RSM. *J Bone Joint Surg.* 1962;45B:709-718.

Dupuytren's Disease:

Physical Examination

Visual inspection and palpation of hands

- Skin pitting and dimpling
- Nodules (tender/nontender)
- Cords and contractures
- Degree of skin involvement
- Secondary boutonniere, swan neck, or other deformity

Measurements

- MP and PIP joint angles (active and passive range of motion)

Assessment of ectopic manifestations

- Hand (Garrod's nodes)
- Feet (Lederhose disease)
- Penis (Peyronie disease)

Recurrent disease

- Previous surgical scars, sensation in palm and tips/sides of digits, vascular exam with digital Allen's test

Bayat A and McGrouther DA. *Ann R Coll Surg Engl.* 2006;88:3-8.

Differential Diagnoses

- Epithelial sarcoma
- Occupational thickening of skin
- Hyperkeratosis
- Callous formation
- Localized pigmented villonodular synovitis
- Palmar ganglions
- Inclusion cysts
- Stenosing tenosynovitis
- Palmar bands
- Prolapsed flexor tendons
- Trigger finger
- Rheumatoid arthritis
- Giant cell tumor of the tendon sheath
- Ulnar nerve palsy
- Camptodactyly
- Fibromas and fibromatoses
- Palmar tendonitis

Lewis FS et al. *Dupuytren Contracture*. Available at: www.emedicine.medscape.com. Accessed February 2, Rayan GM. *Hand Clinics.* 1999;15:87-96.

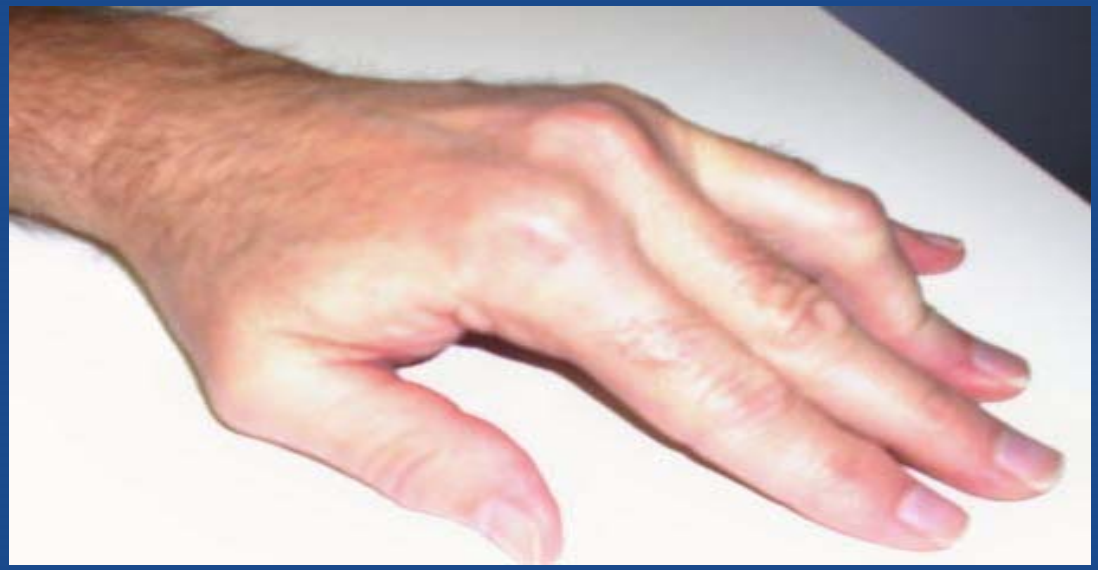
Dupuytren's Disease:

Assessing Contractures 羊 Table Top Test

Hand is placed palm down on a table

Gentle pressure is applied on the back of the hand

Positive: hand cannot be placed flat



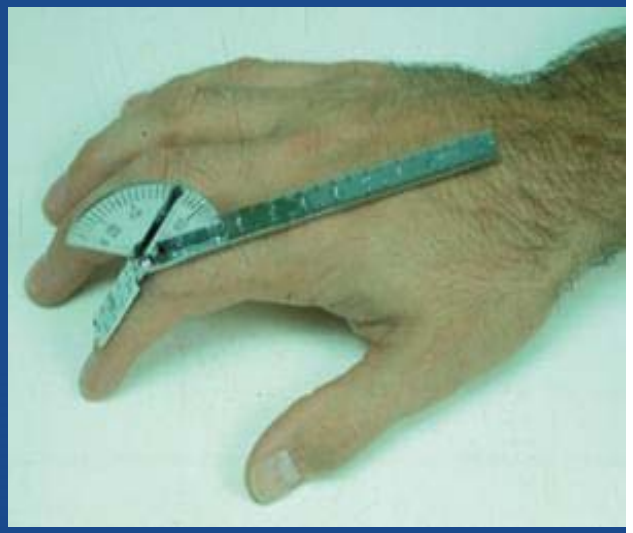
Hueston JT. *Hand.* 1982;14:100-103.

Dupuytren's Disease:

Assessing Contractures 羊 Goniometry

Variability

- Repeated intrarater measures
  - May vary 4º to 5º of each other 95% of the time
- Repeated interrater measures
  - May vary 7º to 9º



Compared with composite finger flexion

- Equal interrater reliability
- Better intrarater reliability
- Most reliable when 1 measure is involved
  - Loses reliability when multiple joint measures are required

Better inter- and intrarater reliability than wire tracing

Ellis B and Brunton A. *Clin Rehabil.* 2002;16:562-570.
Ellis B et al. *Clin Rehabil.* 1997;11:314-320.

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Dupuytren's Disease:

Assessment

Difficult to diagnose in early stages

- Interobserver agreement
  - 70%: nodules
  - 80%: skin-tethering
  - 100%: flexion contractures

Frequently symptomless in early stages

- Consultation often delayed until the later stages of disease

Early assessment is beneficial

- Monitor disease progression and impact on functionality

Easier to diagnose in late stages

- More difficult to correct severely contracted digits

Bayat A and McGrouther DA. *Ann R Coll Surg Engl.* 2006;88:3-8.
Lennox IA et al. *J Hand Surg [Br].* 1993;18:258-261.

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Dupuytren's Disease

Treatment

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Dupuytren's Disease:

Treatment Considerations

Patient should be evaluated individually

Patient should be advised in the context of their

- Complaints and impact on quality of daily activities
- Examination
- Goals

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Dupuytren's Disease:

Nonoperative Treatment Options

No FDA-approved nonsurgical treatment options

Many nonsurgical alternatives have been investigated

- Physical therapy, splinting, radiotherapy, vitamin E
- Local injection therapy
  - Early-stage disease
    - Calcium channel blockers, azothioprine, procarbazine, prostaglandin E, γ-interferon, corticosteroids
  - Advanced-stage disease
    - Fibrinolysin, pepsin, trypsin, hyaluronidase, thiomucase, α-chymotrypsin, Clostridial collagenase

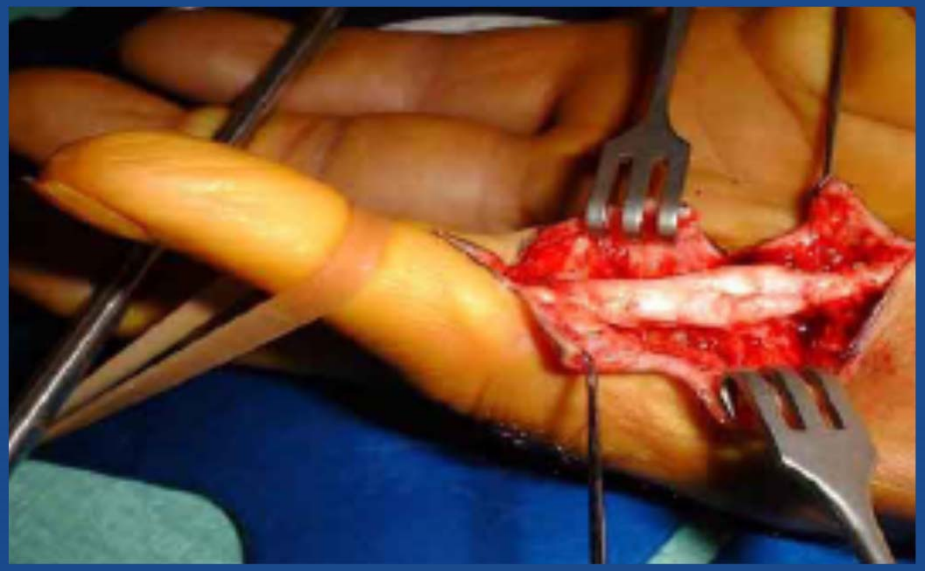
Rayan GM. *J Hand Surg*. 2008;33A:1208-1210.

Dupuytren's Disease:

Surgical Treatment Options

Fasciotomy

- Cord is divided
- Types
  - Open procedure
  - Closed procedure
    - Blade
    - Needle

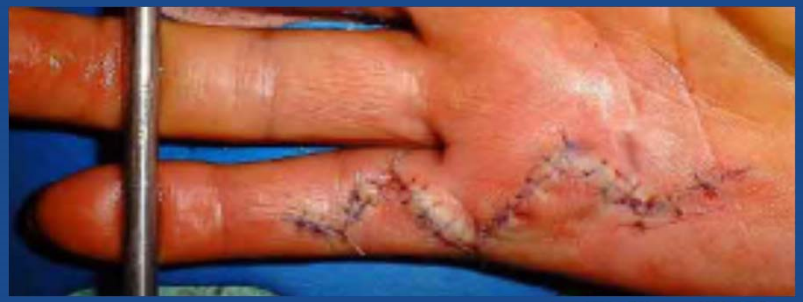


Fasciectomy

- Diseased fascia is excised
- Types
  - Limited—all macroscopically diseased tissue is excised
  - Radical—all palmar fascia is excised

Dermofasciectomy

- Skin and fascia are removed en bloc
- Skin graft is applied
- Limited to extensive cases or recurrences



Tubiana R et al. *Dupuytren's Disease*. London: Martin Dunitz Ltd.; 2000;199-201, 132-143.

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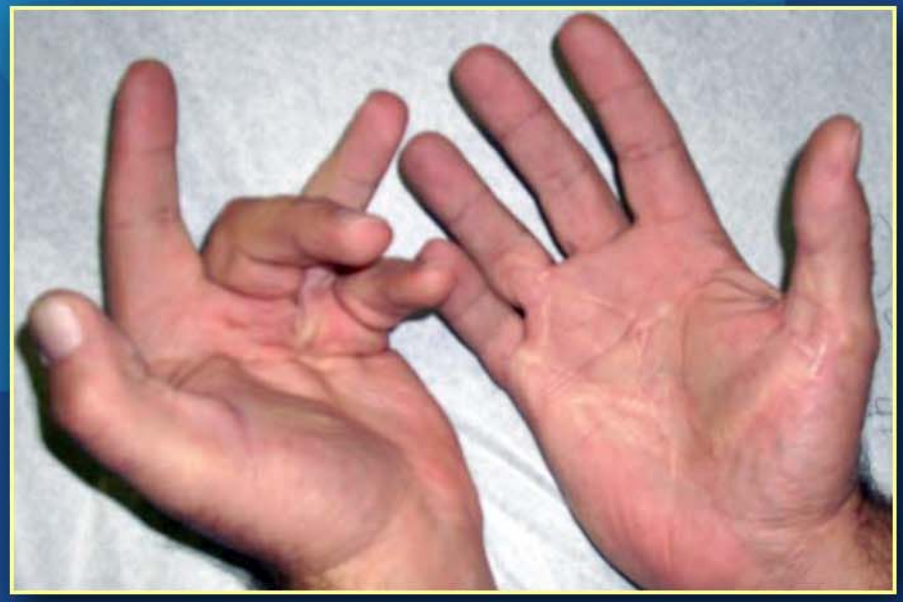
Dupuytren's Disease



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