DUPUYTREN’S DISEASE

RAY B. RAVEN III, MD, MBA
DISCLOSURES

• Royalties and Consulting Fees
  • Osteomed
  • Advanced Orthopaedic Solutions

• Paid Speaker/Educator
  • Auxilium Pharmaceuticals
GUILLAUME DUPUYTREN (1777-1835)

• French anatomist and military surgeon
• Treated Napoleon’s hemorrhoids
• Dissected cadaver of patient with “DD”
  • Concluded exaggerated tension of aponeurosis
  • Noted contracture was released when cord was cut
• First to perform successful fasciectomy
DUPUYTREN’S DISEASE (DD)

- Progressive disease of genetic origin
- Fibromatosis of the palmar fascia
- Flexion contracture
  - Cords thicken/shorten
  - May result in functional impairment
EPIDEMIOLOGY

- Global Prevalence
  - 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
- Gender
  - More common in men
- Hereditary Expression
  - AD pattern with variable penetrance

Luck JV. JBJS. 1959
Tubiana R et al. Dupuytren’s Disease 2000
NON-DD PALMAR FIBROMATOSIS

- Often unilateral involvement
- No family history
- No ectopic manifestations
- Prior ipsilateral hand surgery or trauma
- Diabetes mellitus and cardiovascular disease
- Non-progressive or partially regressive
- Does not appear to be genetically inherited

Rayan, Moore. JHS Br 2005
PATHOGENESIS OF DD

Genetic predisposition

Influencing factors
(diabetes, alcohol use, etc)

Fibroblast proliferation

Differentiation of fibroblasts into myofibroblasts

Organization of myofibroblasts

Splicing of fibronectin

Collagen production and deposition

Contractile forces of myofibroblasts contract collagen fibrils

Activation of platelets

IL-1, free radicals

TGF-β, other growth factors
COLLAGEN

• 30 types - each encoded by a different gene
• 5 fibrillar collagens - triple helix conformation

<table>
<thead>
<tr>
<th></th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tendons, bone, and skin</td>
</tr>
<tr>
<td>II</td>
<td>Cartilage</td>
</tr>
<tr>
<td>III</td>
<td>Forms heterotypic fibrils with type I</td>
</tr>
<tr>
<td>V</td>
<td>Forms heterotypic fibrils with type I</td>
</tr>
<tr>
<td>XI</td>
<td>Forms heterotypic fibrils with type II</td>
</tr>
</tbody>
</table>

Canty EG and Kadler KE. J Cell Sci. 2005
BALANCED COLLAGEN TURNOVER

- Normal remodeling in trauma/inflammation growth
- Strength responses to mechanical forces
COLLAGEN BALANCE IN DD

- Unbalanced turnover
- Change in the proportion of collagen types
ALTERATION OF THE PALMAR FASCIA

- Fibroblasts ➔ Myofibroblasts
- Myofibroblast proliferation
- Excessive collagen production
- Altered collagen matrix (type I to type III)
- Formation of pathologic cords/nodules

- Normal Fascia
  - Type I = 95%
  - Type III = 5%
- Dupuytren’s Fascia
  - Type III = 40%
ECTOPIC MANIFESTATIONS

- Regional
  - Garrod’s nodes (knuckle pads)
- Distant
  - Lederhose disease (plantar fibromatosis)
  - Peyronie disease (penile fibromatosis)
• Diagnostic
• Results in predictable deformities

<table>
<thead>
<tr>
<th>Normal</th>
<th>Pathology</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretendinous band</td>
<td>Pretendinous cord</td>
<td>MP joint deformity</td>
</tr>
<tr>
<td>Natatory ligament</td>
<td>Natatory cord</td>
<td>Limits digital abduction</td>
</tr>
<tr>
<td>Central fibrofatty tissue</td>
<td>Central cord</td>
<td>PIP joint deformity</td>
</tr>
<tr>
<td>Spiral band</td>
<td>Spiral cord</td>
<td>Displaces neurovascular bundle superficially</td>
</tr>
<tr>
<td>Lateral digital sheet</td>
<td>Lateral cord</td>
<td>PIP/DIP joint contracture</td>
</tr>
</tbody>
</table>

Rayan GM. *Hand Clinics*. 1999
Tubiana R et al. *Dupuytren’s Disease* 2000
## JOINT CONTRACTURES

<table>
<thead>
<tr>
<th>MCP</th>
<th>PIP</th>
</tr>
</thead>
</table>
| - Collateral ligaments  
  - Slack in ext / tight in flx  
  - MP volar plate attachments  
    - Relatively mobile  
  - DD Contractures  
    - Pretendinous cord  
    - Natatory cord < abduction  
  - Longstanding contractures easily corrected  
| - Collateral ligaments  
  - Rapidly contract in flexion  
  - Prolonged flexion  
  - Extensor tendon elongated  
  - DD Contractures  
  - Occur in later stages  
  - Central Cord  
  - Longstanding contractures difficult to correct |

Tubiana R et al. *Dupuytren’s Disease*. 2000
DIATHESIS

Condition that predisposes an individual to a disease

- DD diathesis
  - Positive family history
  - Bilateral involvement
  - Ectopic manifestations
  - Ethnicity
- Predicts progression and severity
- More aggressive course
- Greater tendency for recurrence

Hindocha et al. JHS 2006
Hueston JT. Dupuytren’s Contracture 1963
DISEASE PROGRESSION

- Extension
  - Appearance of new lesions
- Recurrence
  - Reappearance of DD tissue previously treated zone
# Diathesis and Progression

3 year follow-up after surgery

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

**Recurrence vs. nonrecurrence**
- Family history: 2 times more frequent
- Knuckle pads: 3.5 times more frequent
- Plantar lesions: 8 times more frequent
- Young age at initial presentation

FACTORS AFFECTING RECURRENCE

- Positive family history
- Bilateral involvement
- Garrod’s pads
- Male gender
- Onset age <50 years

Predictive risk of recurrence
- 22% when no factors are present
- 71% when all 5 factors are present

Hindocha S et al. JHS 2006
Tubiana R et al. Dupuytren’s Disease. 2000
TREATMENT CONSIDERATIONS

• Evaluate each patient individually
• Patient should be advised in the context of their
  • Complaints and impact on ADLs
  • Examination
  • Goals and expectations
FASCIECTOMY

- Surgical treatment is the most reliable method Rx
- A means to control rather than to cure the disease
NEEDLE APONEUROTOMY (NA)

• Debevre, French rheumatologist
• Percutaneous Fasciotomy
• Early treatment method
• Special blade or needle
# NEEDLE APONEUROTOMY

## Efficacy
- 93-98% MCP
- 57-67% PIP

## Recurrence
- 35-65%

<table>
<thead>
<tr>
<th>Publication</th>
<th>N</th>
<th>Recurrence</th>
<th>Mean F/U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Badois et al</td>
<td>90 patients</td>
<td>50%</td>
<td>5 y</td>
</tr>
<tr>
<td>Badois et al</td>
<td>100 digits</td>
<td>35%</td>
<td>6 mo</td>
</tr>
<tr>
<td>Foucher et al</td>
<td>100 patients</td>
<td>58%</td>
<td>3 y</td>
</tr>
<tr>
<td>van Rijssen and Werker</td>
<td>55 digits</td>
<td>65%</td>
<td>33 mo</td>
</tr>
<tr>
<td>Pess et al</td>
<td>1,013 digits</td>
<td>48%</td>
<td>3 y</td>
</tr>
</tbody>
</table>
NA COMPLICATIONS

• Infection or tendon injury rare
• Risk of digital nerve injury increased with PIP joint
• Postoperative gain prominent at MCP joint level
• Reoperation rate 24%
• Recurrence rate 58%
• disease “activity” 69%

Foucher et al. JHS Br 2003
NA TWO YEARS OUT
CLOSTRIDIAL COLLAGENASE

- Consists of type I and type II collagenases
- Immunologically cross reactive
- Cleaves collagen molecule at different sites
- Type III > I
- Approved by US FDA in 2010
Two randomized, double-blind, placebo-controlled studies

CORD* I

N = 306
United States
(16 US sites)

CORD II

N = 66
Australia
(5 sites)

<table>
<thead>
<tr>
<th>Joint Contracture</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCP joint contracture</td>
<td>20° - 100°</td>
</tr>
<tr>
<td>PIP joint contracture</td>
<td>20° - 80°</td>
</tr>
</tbody>
</table>

CORD: Collagenase Option for Reduction of Dupuytren’s
EFFICACY: MP AND PIP JOINTS

Subjects achieving a reduction in contracture to 0° to 5° of normal in 30 days

- **MP Joints**:
  - **XIAFLEX (CORD I)**: 77%
  - **Placebo (CORD I)**: 7%
  - **XIAFLEX (CORD II)**: 65%
  - **Placebo (CORD II)**: 9%

- **PIP Joints**:
  - **XIAFLEX (CORD I)**: 40%
  - **Placebo (CORD I)**: 6%
  - **XIAFLEX (CORD II)**: 28%
  - **Placebo (CORD II)**: 0%
COLLAGENASE

Pre-operative
TWO WEEKS AFTER COLLAGENASE
## ADVERSE REACTIONS

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>XIAFLEX N=249</th>
<th>Placebo N=125</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse events</td>
<td>98%</td>
<td>51%</td>
</tr>
<tr>
<td>Edema peripheral&lt;sup&gt;a&lt;/sup&gt;</td>
<td>73%</td>
<td>5%</td>
</tr>
<tr>
<td>Contusion&lt;sup&gt;b&lt;/sup&gt;</td>
<td>70%</td>
<td>3%</td>
</tr>
<tr>
<td>Injection site hemorrhage</td>
<td>38%</td>
<td>3%</td>
</tr>
<tr>
<td>Injection site reaction&lt;sup&gt;c&lt;/sup&gt;</td>
<td>35%</td>
<td>6%</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>35%</td>
<td>4%</td>
</tr>
<tr>
<td>Tenderness</td>
<td>24%</td>
<td>0%</td>
</tr>
<tr>
<td>Injection site swelling&lt;sup&gt;d&lt;/sup&gt;</td>
<td>24%</td>
<td>6%</td>
</tr>
<tr>
<td>Pruritus&lt;sup&gt;e&lt;/sup&gt;</td>
<td>15%</td>
<td>1%</td>
</tr>
<tr>
<td>Lymphadenopathy&lt;sup&gt;f&lt;/sup&gt;</td>
<td>13%</td>
<td>0%</td>
</tr>
<tr>
<td>Skin laceration</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>Lymph node pain</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>Erythema</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Axillary pain</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>NA Group</td>
<td>Collagenase Group</td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td>30 patients</td>
<td>29 patients</td>
<td></td>
</tr>
<tr>
<td>32 MCP joints 37°</td>
<td>22 MCP joints 40°</td>
<td></td>
</tr>
<tr>
<td>18 PIP joints 41°</td>
<td>12 PIP joints 50°</td>
<td></td>
</tr>
<tr>
<td>67% clinical success</td>
<td>56% clinical success</td>
<td></td>
</tr>
</tbody>
</table>

Nydick J, et al. JHS 2013
<table>
<thead>
<tr>
<th></th>
<th>NA</th>
<th>Collagenase</th>
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<tr>
<td><strong>Efficacy</strong></td>
<td>• 93-98% MCP</td>
<td>• 53-90%</td>
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<td></td>
<td>• 57-67% PIP</td>
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</tr>
<tr>
<td><strong>Recurrence</strong></td>
<td>• 35-65%</td>
<td>• 35-67%</td>
</tr>
</tbody>
</table>

Pess et al JHS 2012
Hurst et al NEJM 2009
Watt et al JHS 2010
Peimer et al JHS 2013
# NA VS. COLLAGENASE: COSTS

<table>
<thead>
<tr>
<th>NA Group</th>
<th>Collagenase Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT 26040 - $341.60</td>
<td>J70775 - $3,438.72</td>
</tr>
<tr>
<td></td>
<td>E&amp;M 99203 - $117.59</td>
</tr>
<tr>
<td></td>
<td>CPT 20527 $90.99</td>
</tr>
<tr>
<td></td>
<td>CPT 26341 - $108.5</td>
</tr>
</tbody>
</table>

**Total Cost:** $341.60  **Total Cost:** $3,755.8

*Medicare fee schedule, Los Angeles, CA 2013*
# NA VERSUS COLLAGENASE: PATIENT EXPERIENCE

<table>
<thead>
<tr>
<th>NA Group</th>
<th>Collagenase Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1 visit</td>
<td>• 2 visits</td>
</tr>
<tr>
<td>• + Local anesthesis</td>
<td>• +/- Local anesthesis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>NA</th>
<th>Collagenase</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>5</td>
<td>29</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>3</td>
<td>28</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Skin Tear</td>
<td>15</td>
<td>10</td>
<td>0.29</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>0</td>
<td>6</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>7</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Nydick J, et al. JHS 2013
NA VS. COLLAGENASE:
~ VALUE ~

\[ \text{VALUE} = \frac{\text{OUTCOME}}{\text{COST}} \times \text{PATIENT EXPERIENCE} \]

NA offers patients and insurers **Superior Value**

• Observation
  • Asymptomatic or contractures less than 20°
• Needle Aponeurotomy
  • MP joint contractures
  • Rapid progression PIP contractures
• Collagenase (patient request)
  • MP joint contractures
  • Rapid progression PIP contractures
• Surgery
  • Significant PIP involvement
  • Recurrence
  • Symptomatic nodules
THANK YOU

RAY B. RAVEN III, MD, MBA
WHICH OF THE FOLLOWING TYPES OF COLLAGEN IS LEAST AFFECTED BY THE COLLAGENASE COMPOUNDS UTILIZED IN COLLAGENASE CLOSTRIDIUM HISTOLYTICUM INJECTION FOR THE TREATMENT OF DUPUYTREN'S CONTRACTURE?

A. Type I
B. Types II
C. Type III
D. Type IV
E. Type V
Discussion: The compounds that comprise the collagenase clostridium histolyticum injection are derived from the bacterium Clostridium histolyticum. Type IV collagen is least affected by these collagenase compounds. This is felt to be significant as type IV collagen makes up the basement membranes of the digital arteries and nerves that are closely opposed to the contracted collagen cord.

WHICH OF THE FOLLOWING GENES IS UP REGULATED WITHIN DUPUYTREN'S DISEASE TISSUE AS COMPARED WITH THE NORMAL FASCIA?

A. Frizzled-related protein  
B. Glutathione peroxidase  
C. TIMP metalloproteinase  
D. Tenascin C (TNC)  
E. Phosphatidic acid phosphatase type 2B
ANSWER: TENASCIN C (TNC)

Discussion: Glutathione peroxidase 3, aldehyde dehydrogenase 1, A1, lysyl oxidase-like 2, Phosphatidic acid phosphatase type 2B, tenascin XB, angiotensin II receptor, type1 frizzled-related protein and TIMP metallopeptidase inhibitor 3 are down regulated in Dupuytren disease. In tissue biopsies, significant fold changes were observed for ADAM12, POSTN, and TNC in the cord and/or nodule when compared with that of normal fascia. ADAM12 and POSTN are associated with accelerated or abnormal cell growth, whereas TNC has been associated with fibrotic diseases and cell migration.

THE CELL TYPE ASSOCIATED WITH THE DEVELOPMENT OF A DUPUYTREN’S CONTRACTURE IS:

A. Myofibroblast
B. Fibroblast
C. Osteoblast
D. Dermoblast
E. Pluripotential stem cell
WHICH OF THE FOLLOWING GENES IS UP REGULATED IN DUPUYTREN’S DISEASE TISSUE COMPARED W/ NORMAL FASCIA?

A. Frizzled-related protein
B. Glutathione peroxidase 3
C. TIMP metalloproteinase
D. Tenascin C (TNC)
E. Phosphatidic acid phosphatase type 2B
WHICH OF THE FOLLOWING ANATOMIC STRUCTURES IS NOT INVOLVED IN THE SPIRAL CORD IN DUPUYTREN’S DISEASE?

A. Pretendinous band
B. Spiral band
C. Cleland’s ligaments
D. Grayson’s ligament
E. Lateral digital sheath
A SPIRAL CORD IN DUPUYTREN’S CONTRACTURE WILL DISPLACE THE NEUROVASCULAR BUNDLE:

A. Distally, dorsally, and away from the midline
B. Proximally, volarly, and towards the midline
C. Distally, volarly, and towards the midline
D. Proximally, dorsally, and away from the midline
E. Distally, volarly, and away from the midline
INVOLVEMENT OF THE DIP JOINT IN DUPUYTREN’S DISEASE IS CAUSED BY WHICH CORD?

A. Spiral
B. Natatory
C. Pretendinous
D. Retrovascular
E. Central
A PATIENT WITH A KNOWN HISTORY OF DUPUYTREN’S DISEASE PRESENTS FOR EVALUATION OF THE LEFT HAND.

- Examination reveals 10 degrees of contracture at the MCP joint of the small finger.
- No involvement outside the palm.
- The patient has no functional deficit and can lay his palm flat on the examination table.
THE BEST INITIAL CHOICE IN MANAGEMENT IS:

A. Education and monitoring
B. Injection with collagenase
C. Needle aponeurotomy
D. Open fasciectomy in the palm
E. Full thickness skin grafting
WHICH OF THE FOLLOWING IS MOST PREDICTIVE OF RECURRENCE AFTER SURGERY?

A. Female gender
B. Dupuytren’s diathesis
C. The “flare” reaction
D. Presence of spiral cord
E. Simultaneous carpal tunnel release and fasciectomy
WHAT IS THE MOST COMMON LONG-TERM COMPLICATION FOLLOWING COLLAGENASE RX FOR DUPUYTREN’S CONTRACTURE?

A. Chronic regional pain syndrome
B. Tendon rupture
C. Recurrence
D. Neurovascular injury
E. Infection
# Billing and Coding

<table>
<thead>
<tr>
<th>HCPCS/ CPT Code</th>
<th>Clinical Description of Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>J0775</td>
<td>Injection, collagenase, clostridium histolyticum, 0.01 mg</td>
</tr>
<tr>
<td>99203</td>
<td>Office or other outpatient visit, for the evaluation and management of a new patient</td>
</tr>
<tr>
<td>20527</td>
<td>Injection, enzyme (eg, collagenase), palmar fascial cord (ie, Dupuytren’s contracture)</td>
</tr>
<tr>
<td>26341</td>
<td>Finger Extension- manipulation, palmar fascial cord (ie, Dupuytren’s cord), post enzyme injection (eg, collagenase), single cord (10 day global)</td>
</tr>
<tr>
<td>29130</td>
<td>Application of finger splint; static</td>
</tr>
</tbody>
</table>