deciphering
/ˈdɛsɪfər.ɪŋ/
chronic
genital
pain

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disclosures
/'disˈklōzərs/

None.
/ˈnʌn/
A Clinical Vignette…
A Clinical Vignette…

Chris is a 34 yo trader who presents with diffuse pelvic pain and radiating abdominal pain that, when severe, can trigger bilateral testicle pain. Pain began following a vasectomy and has not responded to standard of care treatments. He also reports an intense cramping pain that begins 1-2 hr after ejaculation and develops into severe pelvic pain lasting several days. Pain also increases with stress, wearing belts, heat, and weight-bearing activity. Pain briefly decreases with pelvic floor physical therapy, relaxation, and local anesthetic blocks.
Chris is a 34 yo trader who presents with diffuse pelvic pain and **radiating abdominal pain** that, when severe, can trigger **bilateral testicle pain**. Pain began following a **vasectomy** and has not responded to standard of care treatments. He also reports an intense cramping pain that begins **1-2 hr after ejaculation** and develops into severe pelvic pain lasting several days. Pain also increases with **stress**, **wearing belts**, **heat**, and weight-bearing activity. Pain briefly decreases with **pelvic floor physical therapy**, **relaxation**, and **local anesthetic blocks**.

- **Pain affecting non-pelvic dermatomes**

- **Spinally-mediated referred pain and/or cross-talk sensitization**

- **Surgical origin: nerve injury?**

- **Muscular clenching with climax compresses organs**

- **Pain triggered by normally non-painful heat & pain with light rubbing of skin are consistent with central sensitization**
55 year old man

with abdomino-pelvic pain

**PRIMARY PAIN**

DAILY, PROVOKED
Hot metal rod, spasms

▲ beginning and during void
▼ after voiding or defecation
**1. PRIMARY PAIN**

- **DAILY, PROVOKED**
  - Hot metal rod, spasms
  - ▲ beginning and during void
  - ▼ after voiding or defecation

**2. AT NIGHT**

- (follows urethral/bladder pain)
  - ▲ with urethral/bladder pain, urination, extended sitting
  - ▼ after voiding or defecation

**3. HOT GOLF BALL AT PROSTATE**

- **PROVOKED, DAILY**
  - Sharp, growing, burning
  - ▲ urgency, voiding

**4. PROVOKED puborectalis muscles pulling on bladder**

- ▲ during urination, after defecation

**5. SPONTANEOUS, 4d/mo**

- Aching diffuse pelvic pressure and suprapubic pain
  - ▲?
  - ▼ after defecation

**6. RARELY, REFERRED PAIN IN TESTICLES**

- Transient with frequent urination,
What is *pain*? *nociception*?
What is *pain*? *nociception*?

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

*(International Association for the Study of Pain)*
What is pain? *nociception*?

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

(International Association for the Study of Pain)

Detection of intense thermal, mechanical, or chemical stimuli by primary afferent sensory neurons.

(Sherrington, 1906)
What is pain? nociception?

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

Detection of intense thermal, mechanical, or chemical stimuli by primary afferent sensory neurons.

(International Association for the Study of Pain) (Sherrington, 1906)

• Pain occurs when nociception has failed.
<table>
<thead>
<tr>
<th><strong>Temporal Scale:</strong></th>
<th><strong>Seconds → Minutes</strong></th>
<th><strong>Months → Years</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Function:</strong></td>
<td>Protects body from harm</td>
<td>Pathological</td>
</tr>
<tr>
<td><strong>Evocation:</strong></td>
<td>Physical stimulus</td>
<td>No clear relation to injury</td>
</tr>
<tr>
<td><strong>Input:</strong></td>
<td>Nociceptive</td>
<td>Emotional</td>
</tr>
<tr>
<td><strong>Brain Circuitry:</strong></td>
<td>Spinothalamic</td>
<td>Limbic</td>
</tr>
<tr>
<td><strong>Adaptations:</strong></td>
<td></td>
<td>Nervous system reorganization</td>
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</tbody>
</table>
Background

Unique physiological rules of chronic pain

Complex Regional Pain Syndrome
(formerly Regional Sympathetic Dystrophy, Causalgia)
Mechanisms
Primary Afferent Nociceptors

Somatic Afferents → skin muscle bone
• Intensity encoding

Visceral Afferents → organs viscera
• Intensity encoding
• High threshold encoding
Molecular Substrates of visceral pain sensitization

$\text{Na}_v \ 1.8$

 Voltage-gated sodium channels on C fiber nociceptor dorsal root ganglia

- Regulates membrane excitability
- TTX-resistant (prolongs depolarization)
- Potentiated by:
  - serotonin (5-HT)
  - prostaglandin E3 (PGE3)
  - adenosine
  - nerve growth factor (NGF)
  - tumor necrosis factor-α (TNF-α)

- Hyperalgesia and Allodynia
Molecular Substrates of visceral pain sensitization

TRPV1 (Capsaicin receptor)
\textit{transient receptor potential cation channel subfamily V, member 1}

- Detects noxious heat (43-53 °C)
  - protons (pH 5-6),
  - lipid derivatives (e.g., endocannabinoids)

- Sensitization via phosphorylation by protein kinase C (PKC)
- Preferentially expressed in visceral afferents after inflammation/injury
- Potentiated by:
  - ATP
  - Bradykinin
  - nerve growth factor (NGF)

- Hyperalgesia and Allodynia (and paradoxical desensitization)
Molecular Substrates of visceral pain sensitization

P2X3

ATP-gated ion channel

- Mechanical allodynia
- Colocalizes with TRPV1
- Inhibited by estrogen receptor alpha binding
- Bladder distension, macrophage activation, apoptosis and neuronal–glial interactions

TRPV1 and CGRP, but not P2X3, expressed in uterine cervical DRGs (Tong et al 2006)
Mechanisms
Spinally-mediated crosstalk and referred pain

90% somatic
10% visceral

a) viscero-visceral pain
b) viscero-somatic pain
c) somato-visceral pain
Five mechanisms: ➔ Clinical Symptoms

a) Reduced excitation threshold............... Pain with normal stimulation (allodynia)

b) Increased magnitude of discharges....... Increased pain signaling (hyperalgesia)

c) Ectopic discharges (UNPROVOKED) ........ Spontaneous pain

k) Increase in discharge magnitude.............. Increased pain signaling with repeated input (wind-up) (hyperalgesia)

e) silent nociceptors are activate.............. Increased pain signaling
**Mechanisms**

**Spinal Central Sensitization**

Two mutually exclusive definitions:

a) A **hypothetical** umbrella term for all types of changes within the CNS leading to enhanced pain perception

b) An enhanced responsiveness of nociceptive neurons in the CNS to normal afferent input (= long-term potentiation)

*Woolf, 1983*
### Significance of sensory abnormalities

<table>
<thead>
<tr>
<th>Peripheral Sensitization</th>
<th>Spinal</th>
<th>Central Brain</th>
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</thead>
<tbody>
<tr>
<td>• Altered detection thresholds</td>
<td>• Temporal wind-up (heat)</td>
<td>• Pain before skin is touched</td>
</tr>
<tr>
<td>• Allodynia</td>
<td>• Dynamic mechanical allodynia</td>
<td>• Significant anxiety (at onset or current)</td>
</tr>
<tr>
<td>• Hyperalgesia</td>
<td>• Heat hyperalgesia</td>
<td>• Stress enhances pain</td>
</tr>
<tr>
<td>• Spontaneous sensation</td>
<td>• After sensation</td>
<td>• Excessive distress related to pain *</td>
</tr>
<tr>
<td>• Abnormal DNIC in affected dermatome</td>
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</table>

**Tools:** natural bristle brush, heat compress, von Frey filaments, capsaicin, Timer, metronome
Memory Strength

Long-term Memory (hours to months)

Short-term Memory (seconds to hours)

Long-lasting Memory (years to lifetime)

Basolateral amygdala

HPA axis

Cellular Consolidation

Systems Consolidation

Mechanisms

Fear Learning (synaptic plasticity)
Mechanisms
Brain Learning *(synaptic plasticity)*

- Greater **pain severity** correlates with higher grey matter density in anterior insula.
- Longer **pain duration** correlates with greater grey matter density in anterior cingulate cortex.
- Correlation between grey matter volume and white matter integrity is **disrupted** in CP/CPPS.

Mechanisms

Brain Learning (synaptic plasticity)

d-Cycloserine

Partial glycinerigic agonist at NMDA receptors in basolateral amygdala

![Graph showing pain intensity over time with d-Cycloserine administration and washout periods.](image-url)
♂ Open Arena:
Males show *no change* in sexual behavior with pain

![Graph showing total mounts for different conditions and body parts.](image)
More brain regions link to the *left amygdala*. 
More brain regions link to the thalamus.
Chronic pain is maintained by a different nervous system.
Chronic pain *reorganizes* the brain

Time Scale of Pain

- Sec
- Minutes
- Hours
- Days
- Weeks
- Months
- Years
- Decades

Function $\rightarrow$ Structure

- Brain Activity
- Axon Tracts
- Gray Matter
- Brain Networks
Take home messages

- End-organ measures are inadequate to explain pain
- Mechanisms of pain initiation ≠ maintenance
- Learning (neuroplasticity) underlies reorganization of brain
- Patient report & sensory testing can guide individualized interventions
- “Multi-dimensional” pain may require specific tx to target each dimension
Successful treatment of the **chronic phenotype** of genital pain…

- Does not focus on presumed etiological factors that are long gone
- Addresses the respective roles of peripheral nerve, spinal, and brain factors (unique to each individual)
- Can be guided by multifactorial algorithms that provide an evolving snapshot of maintaining factors
- Requires **new learning**—of pain perception, motor activity, coping strategies, etc.
Thank you!

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Essential take home messages

To Improve Your Practice…

• Detailed pain assessments must become routine
• New rules of chronic pain nervous system: time-course and sx
• Nerve, spinal cord, and brain contributions require compound tx
• Successful treatment will require **new learning**—
  of pain perception, motor activity, coping strategies, etc.