

# **Complex Regional Pain Syndrome: Pathophysiology**

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# Complex Regional Pain Syndrome: Diagnosis

## Complex Regional Pain Syndrome I (RSD)

- History of initiating injury or immobilization
- Continuing pain, allodynia, or hyperalgesia out of proportion to the initiating event
- Evidence at some time of edema, changes in skin blood flow or abnormal pseudomotor activity in the painful area
- No other cause of the pain exists

## Complex Regional Pain Syndrome II (causalgia)

- Differs from CRPS I by the presence of a known nerve injury

**LOW INTENSITY STIMULUS**



*thermal- ?mechanical*

**sensitized**

**(HIGH) THRESHOLD AFFERENT**



*A delta and C nociceptors*

**SPINAL CORD**



***PAIN***

*(primary hyperalgesia)*

**HIGH INTENSITY STIMULUS**



*mechanical-thermal-chemical*

**HIGH THRESHOLD AFFERENT**



*A delta and C nociceptors*

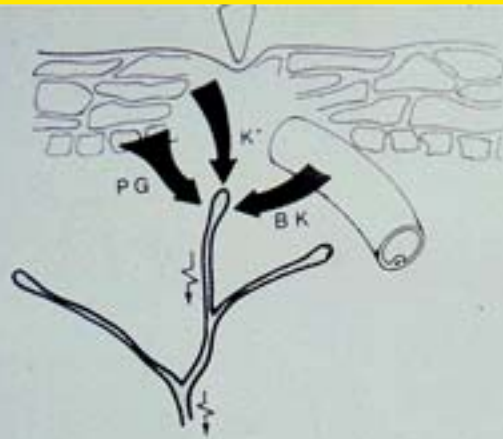
**SENSITIZED  
DORSAL HORN**



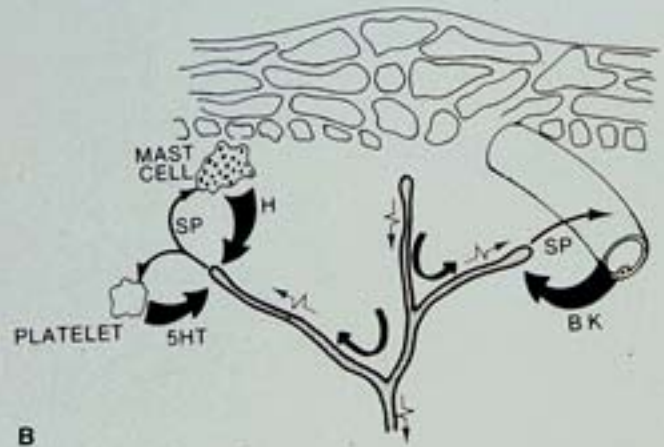
***PAIN***  
*(hyperalgesia)*

# HEAT HYPERALGESIA IN CRPS

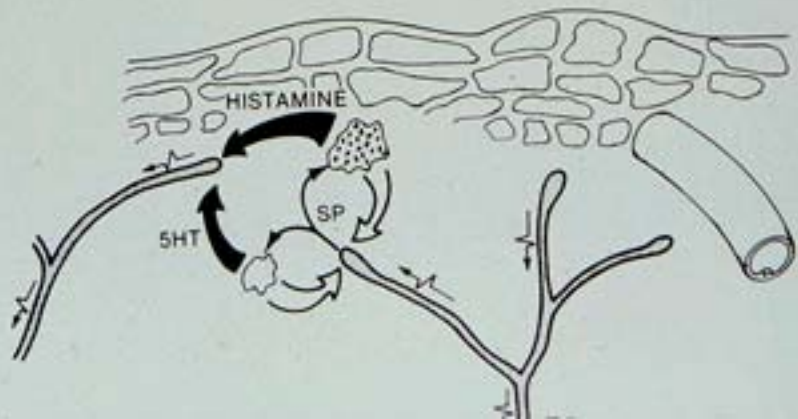
- Early in course of disease
- Hot pain thresholds approach warm sensation thresholds
- Warm, cool and cold pain sensation thresholds normal
- Skin temperature elevated
- “Angry backfiring C-fiber?”



A

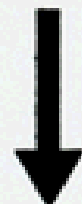


B



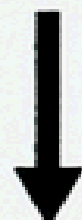
C

**LOW INTENSITY STIMULUS**



*touch-brush-pressure*

**LOW THRESHOLD AFFERENT**



*A beta mechanoreceptor*

**SENSITIZED  
DORSAL HORN**



***PAIN***  
*(mechanical allodynia)*

# Hyperalgesia vs Allodynia

## Allodynia

- Pain to stroking stimuli
- A-beta fiber mediated
- Decreases with ischemic block

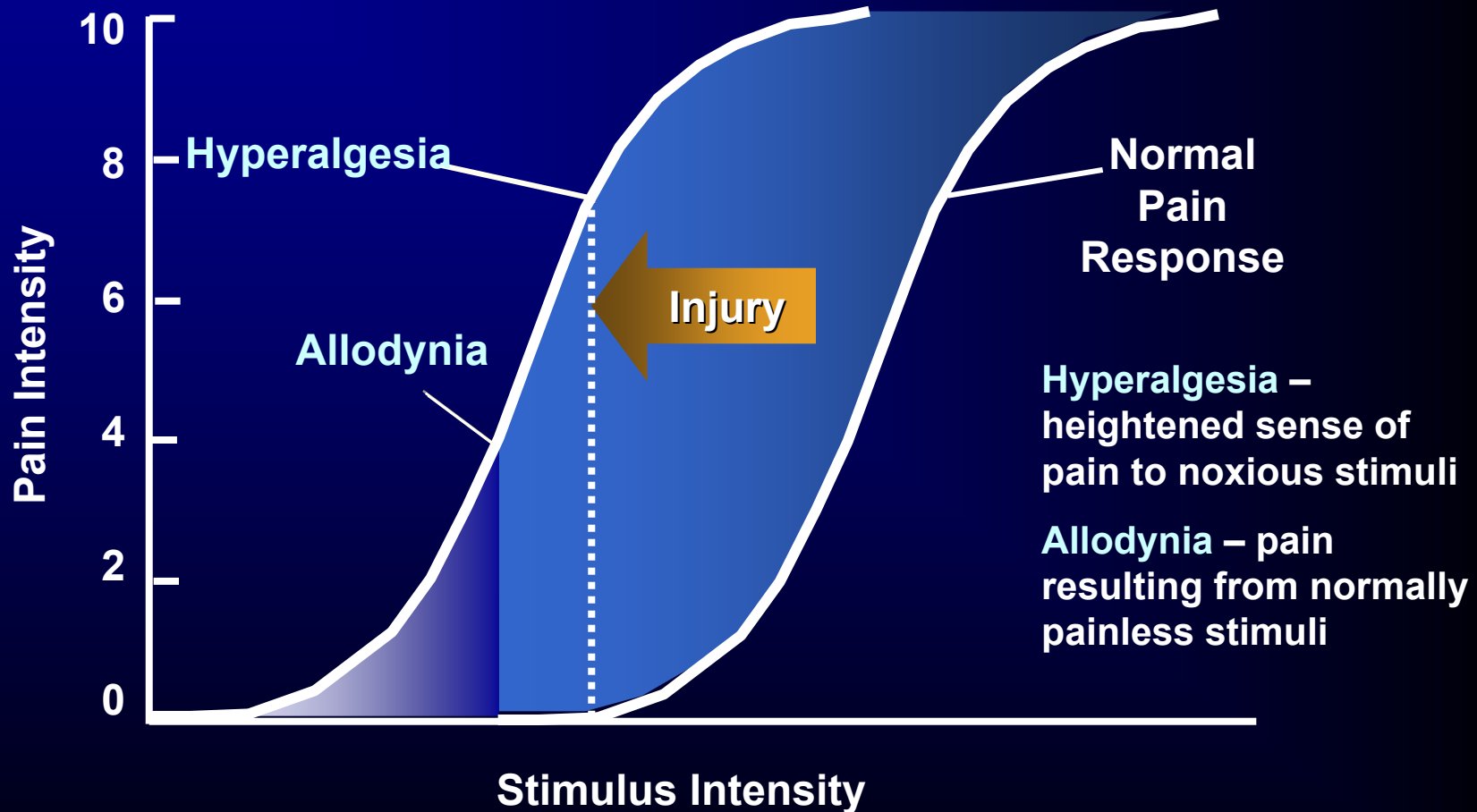
## Hyperalgesia

- Pain to punctate stimuli (von Frey)
- A-delta and C-fiber mediated
- Persists with ischemic block

# COLD ALLODYNIA IN CRPS

- Late phenomenon
- Cold pain threshold approaches cool sensation threshold
- Cool sensation threshold elevated
- Warm sensation and hot pain thresholds normal
- Skin temperature decreased

# Sensitization



# Pathophysiologic Mechanisms of CPRS

- Sensory abnormalities
- Autonomic dysfunction
- Neurogenic inflammation
- Motor abnormalities

# Sensory Abnormalities in CRPS

- Hypoesthesia/hypoalgesia throughout the affected half of the body (Rommel et al, 2001)
  - Increased thresholds to mechanical and thermal stimuli on the affected side
- Due to changes in the thalamus and cortex (Maleki et al, 2000)
  - PET studies have demonstrated adaptive changes in the thalamus (Fukumoto et al, 1999)
  - Shortened distance between little finger and thumb representations in the primary sensory cortex (Juottonen et al, 2002; Baron et al, 2000)

# Sensory Abnormalities in CRPS

## What we know

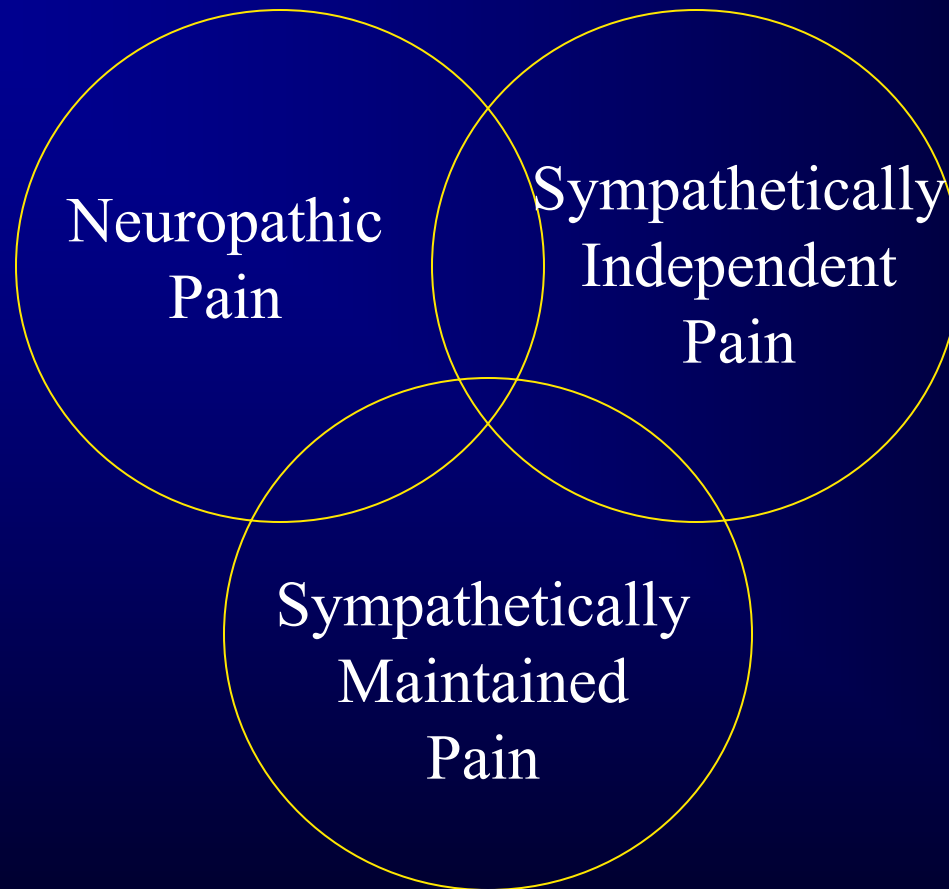
- Numerous sensory abnormalities exist
- Sensory abnormalities not limited to the painful area but may include entire half of body\_\_\_\_\_

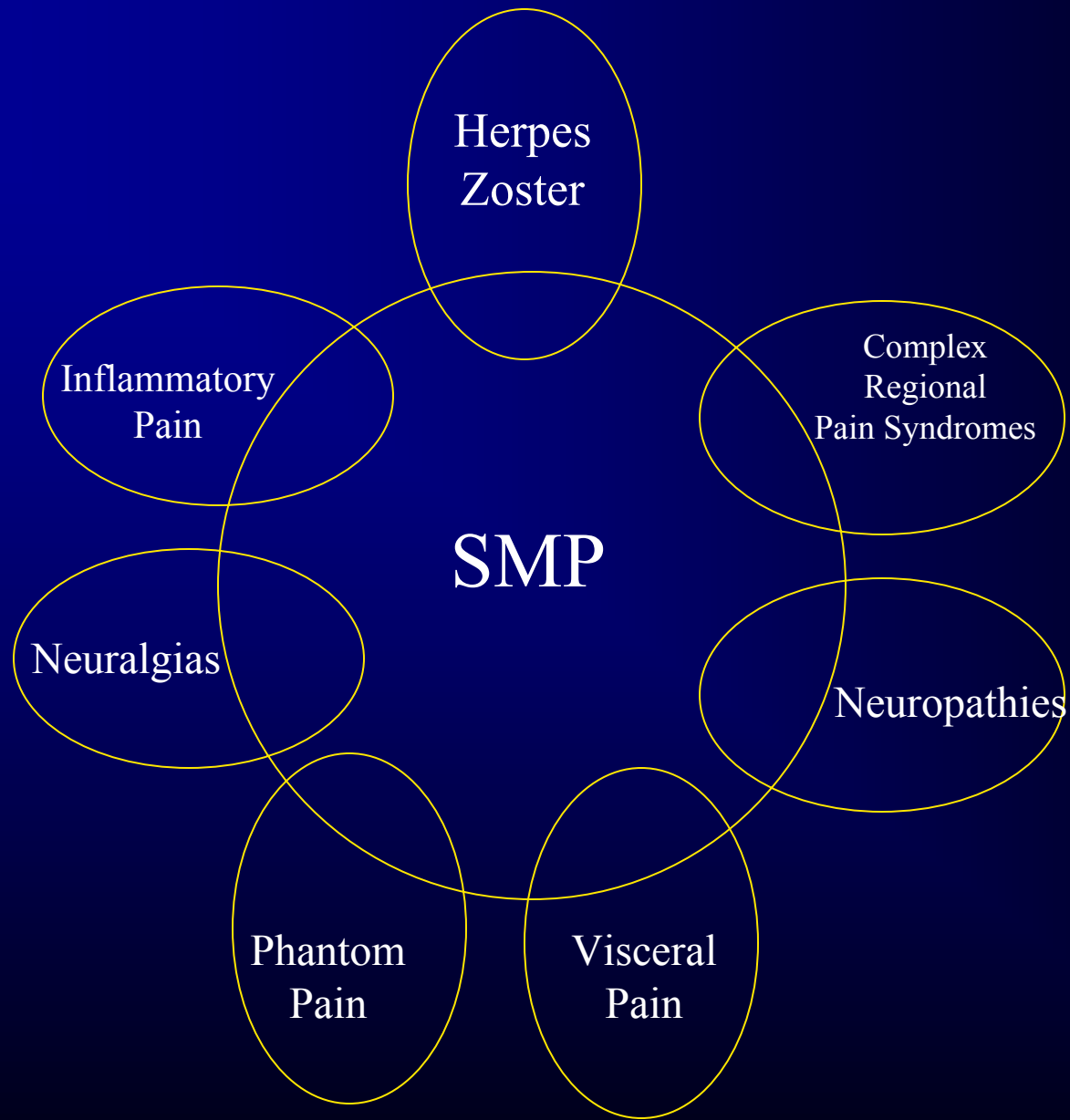
## What we don't know

- Are these sensory abnormalities the result of the ongoing nociceptive input or are they specific to the disease?

# Autonomic Dysfunction

- About 85% of CRPS report pain relief after sympathetic interruption; however, the pain relief is temporary in the majority of patients
- Catecholamines can activate peripheral nociceptors after thermal or chemical sensitization in the absence of nerve injury
- After nerve injury, surviving cutaneous afferents develop noradrenergic sensitivity





# Complex Regional Pain Syndrome and the Sympathetic Nervous System

- Peripheral sympathetic-sensory interactions
- Interactions between sympathetic fibers and sensory fibers in the dorsal root ganglion
- Sensitization of dorsal horn cells secondary to activation of afferent fibers by sympathetic efferent actions
- Autonomic denervation

# **Sympathetically Maintained Pain (SMP) vs Sympathetically Independent Pain (SIP)**

- SMP - Describes the aspect of pain that is relieved by blockade of the efferent sympathetic nervous system
- SIP - Describes the aspect of pain that is unresponsive to sympathetic blockade
- Patients can present with pure SMP, pure SIP or a combination
- Pain tends to be SMP early in the disease process and progresses to SIP as disease progresses

# Sympathetic Nervous System and Pain

- Some neuropathic pain syndromes are characterized by abnormalities in autonomic function
  - Dystrophy
  - Alteration in skin temperature and sweating
  - Disturbances in sympathetic vasomotor and sudomotor function
- Prompt pain relief can be achieved by sympatholytic therapy in some patients (SMP)
- Activation of the sympathetic nervous system can exacerbate the pain
  - Mitchell, 1972; Walker and Nulsen, 1948; White, 1954

Nerve Injury



Spontaneous Afferent Activity  
Mechanical sensitivity

Origin:

Neuroma

Dorsal Root Ganglia

Mechanism:

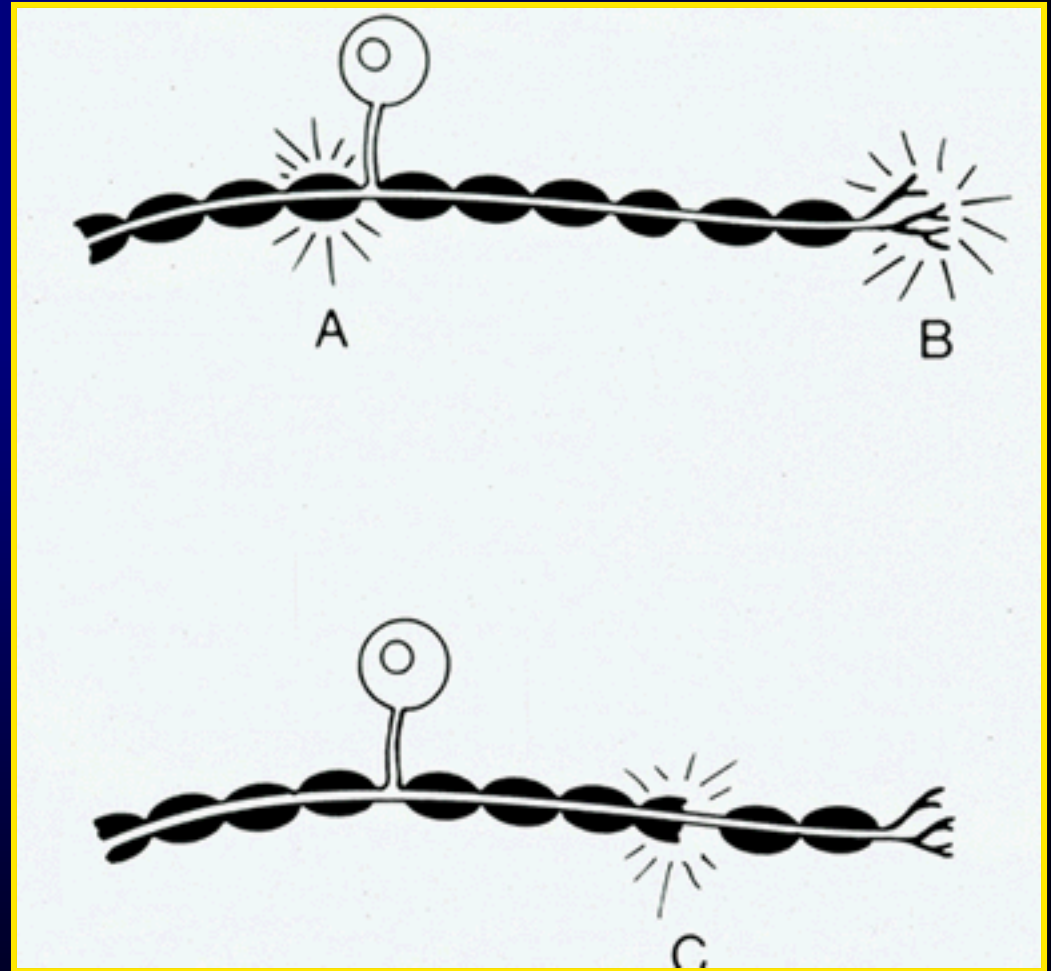
↑Na<sup>+</sup> Channel

↑Receptors

Transmitters (amines)<sup>1</sup>

Cytokines (TNFa)

Enzymes (trypsin)

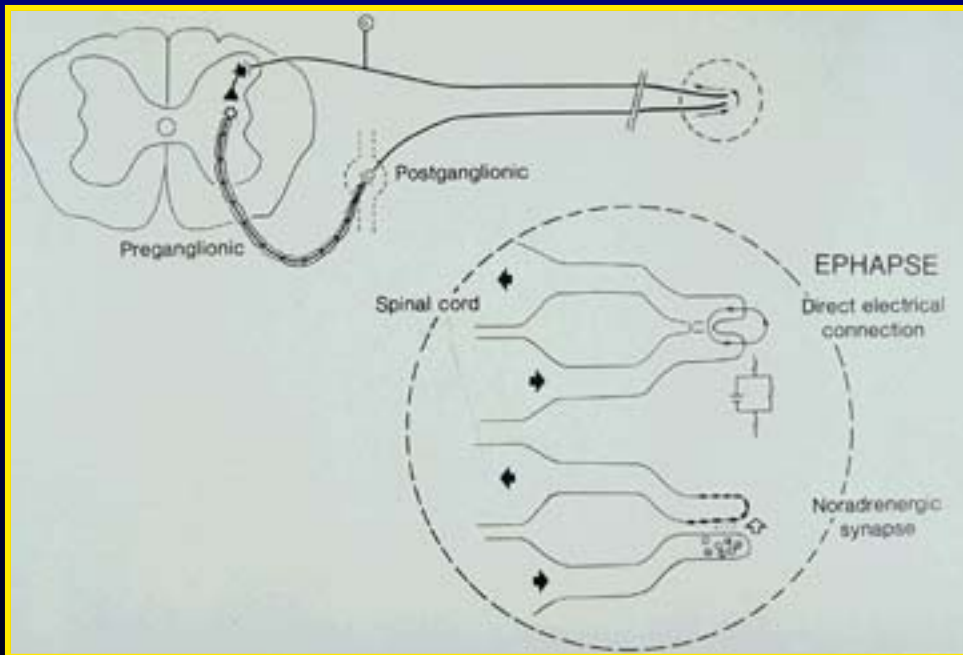


<sup>1</sup>Drummond et al, 1996

# Nerve Injury



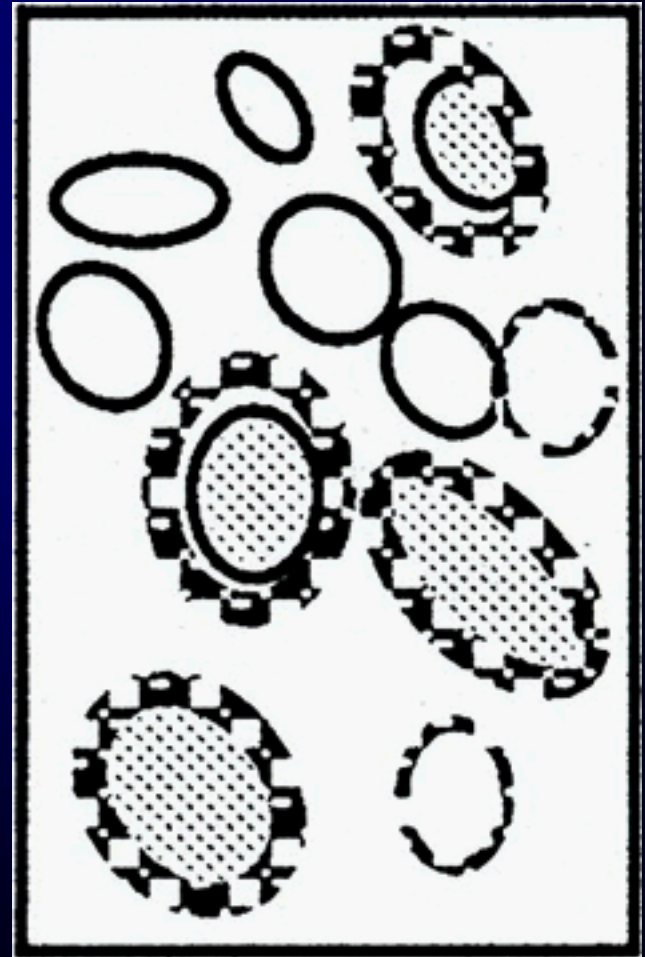
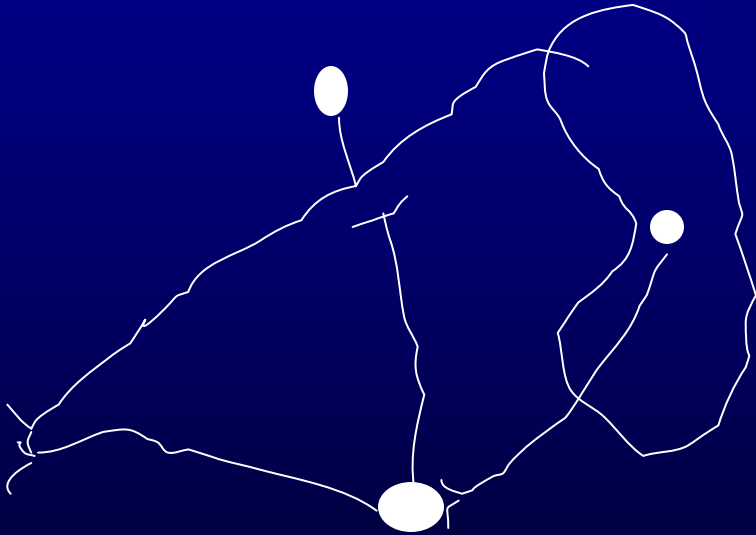
- Cross talk between large-small afferents
- **Cross talk between sympathetic and afferent fibers**
- Activation of large myelinated fiber evokes activity in small afferent fiber (allodynia)
- **Activation of sympathetic efferent evokes activity in small afferents**



Nerve Injury



Sympathetic Sprouting in peripheral terminals and DRG



# Autonomic Dysfunction

- Hyperhydrosis
- Early phase (<6 months)
  - Skin temperature and perfusion high
  - Norepinephrine levels low
- Intermediate phase
  - Temperature and perfusion either warmer or colder, depending on the level of sympathetic activity
- Late phase
  - Skin temperature and perfusion low
  - Norepinephrine levels low
  - Skin lactate increased

Wasner et al, 1999 and 2000; Birklein et al, 2000

# Autonomic Dysfunction

## What we know

- There is a peripheral and central autonomic reorganization in CRPS\_\_\_\_\_

## What we don't know

- What is the mechanism of the pain that results from the autonomic dysfunction (response to inflammation versus nerve injury)

# Neurogenic Inflammation

- Extensive plasma extravasation in patients with acute CRPS
- Increased joint effusions, protein and synovial hypervascularity
- Axon reflex vasodilatation increased after C fiber stimulation
- Increased systemic CGRP in the acute phase
- Increased tissue levels of TNF $\alpha$  and IL-6
- Increased production of nitric oxide from peripheral monocytes

Oyen et al, 1993; Graif et al, 1998; Renier et al, 1983; Birklein et al, 2001; Huygen et al, 2002; Hartrick et al, 2002

# Neurogenic Inflammation

## What we know

- Neurogenic processes are involved in the pathogenesis of early CRPS\_\_\_\_\_

## What we don't know

- The mechanisms that initiate and maintain the inflammatory reaction
- The role of the sympathetic nervous system in the early inflammatory state

# Motor Abnormalities

- About 50% of CRPS patients develop
  - Decreased range of motion
  - Physiological tremor
  - Reduction in active motor force
- About 10% of CRPS patients develop dystonia in the affected extremity

# Motor abnormalities

## What we know

- Motor abnormalities exist in a significant number of CRPS patients\_\_

## What we don't know

- The mechanisms of the motor abnormalities (neuromuscular junction versus central sensorimotor reorganization versus neglect)

# Other Possible Mechanisms

- Persistent afferent activity
- Changes in terminal sensitivity
- Cross-talk
- Changes in dorsal horn morphology
- Dorsal horn sprouting
- Spinal glutamate release
- Activation of non neuronal cells

Nerve Injury



Spontaneous Afferent Activity  
Mechanical sensitivity

Origin:

Neuroma

Dorsal Root Ganglia

Mechanism:

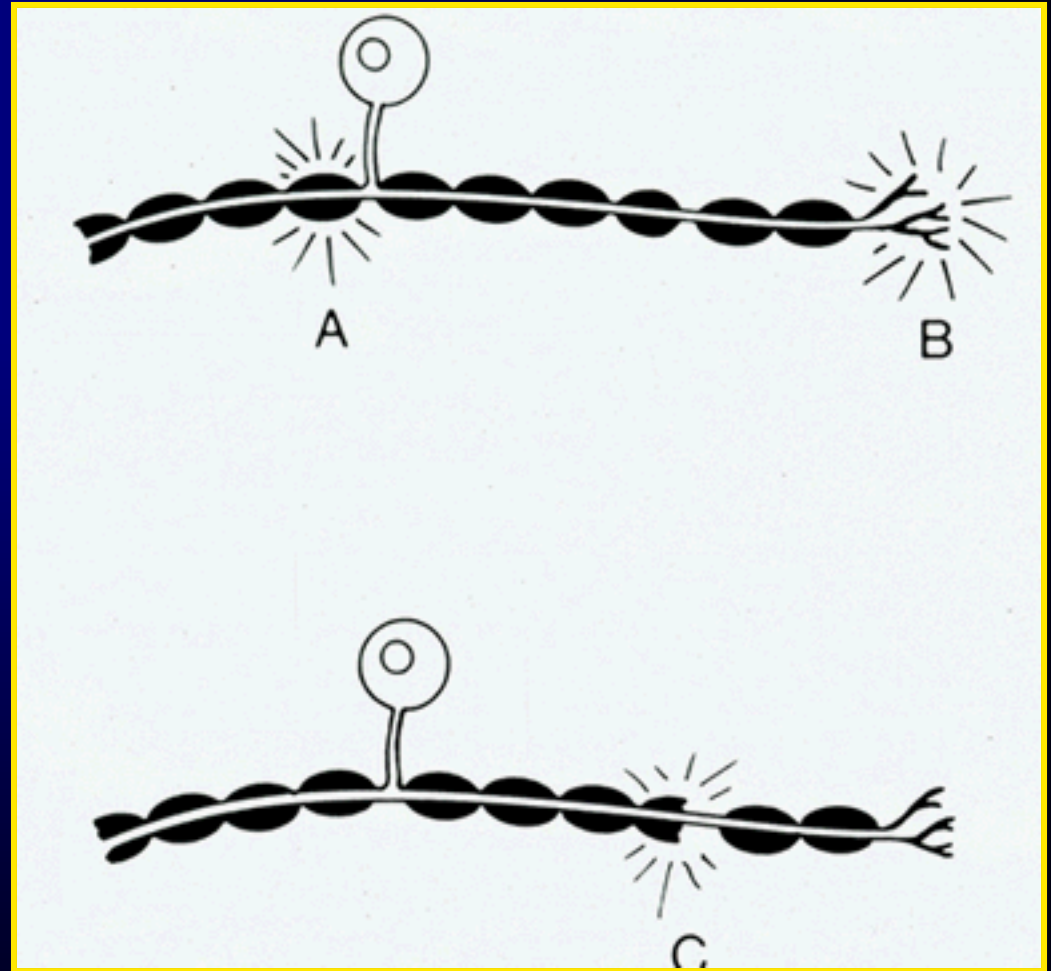
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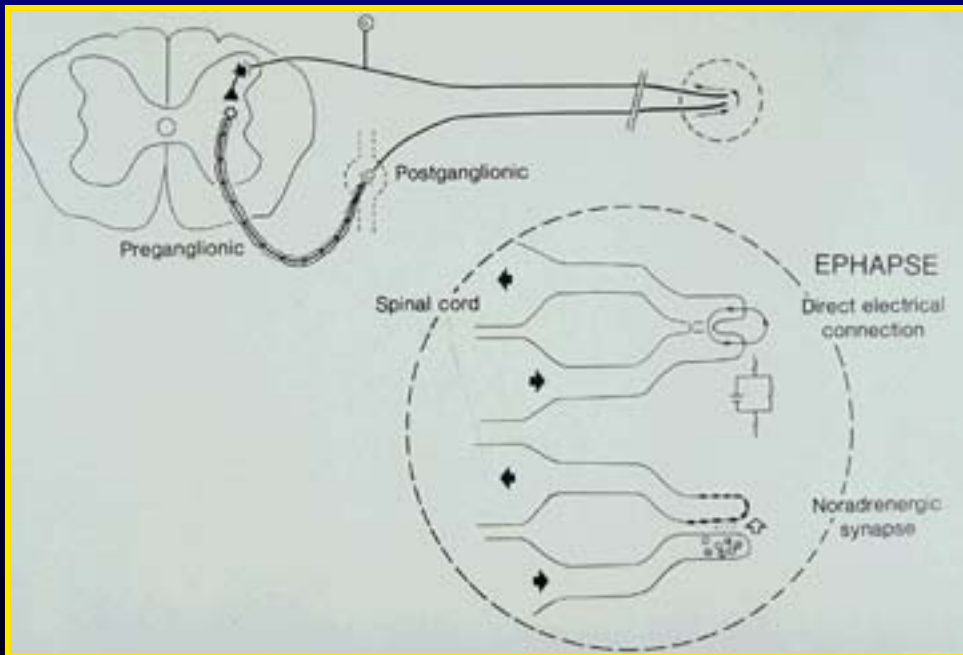


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# Nerve Injury



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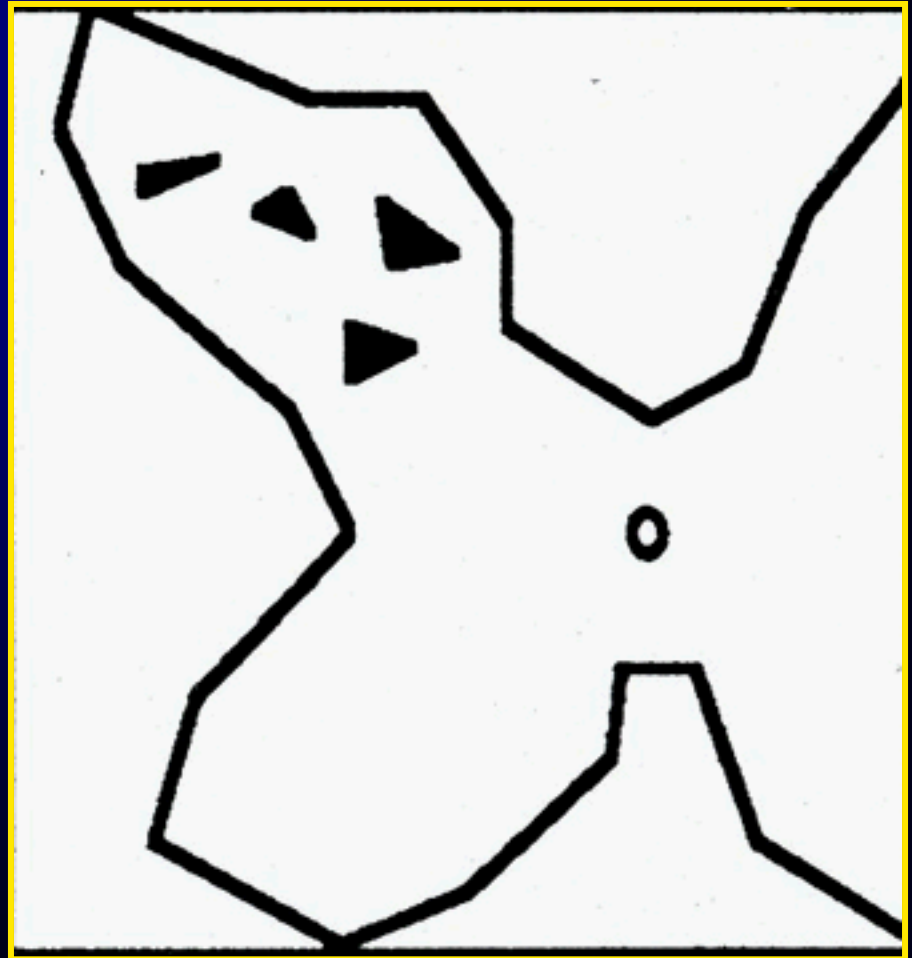


Nerve Injury → Dorsal horn “dark staining” neurons

Reduced dorsal horn GABA/  
Glycine

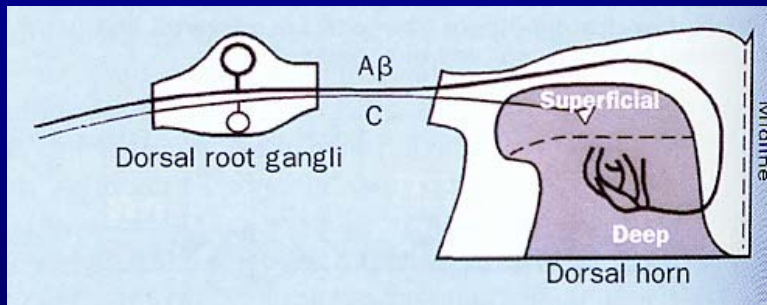


Tactile Allodynia  
(reflects ongoing role of tonic  
or evoked inhibition of large  
afferent evoked dorsal horn  
Excitation, which is read out  
as a “painful state”)

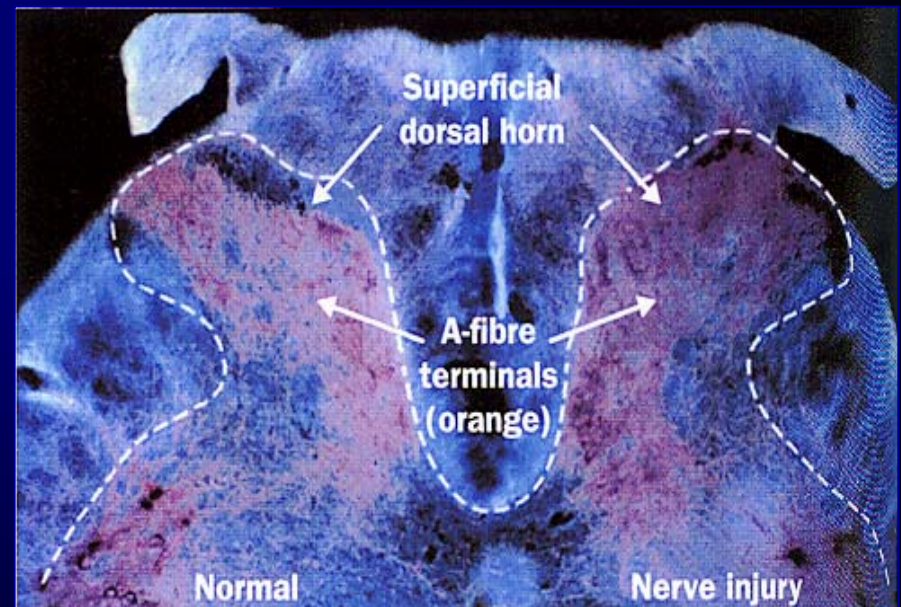
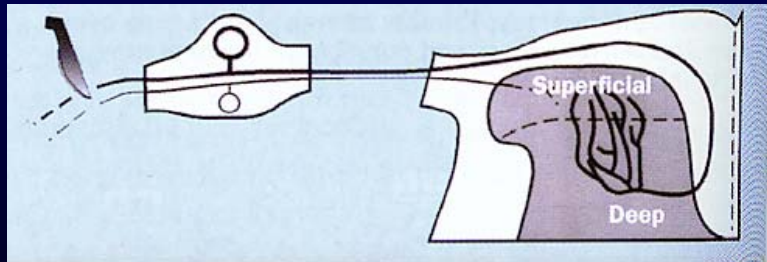


# Nerve Injury → Dorsal Horn Sprouting

Normal terminations of primary afferents in the dorsal horn



After nerve injury, C-fiber terminals atrophy and A-fiber terminals sprout into the superficial dorsal horn



Nerve Injury → Spinal Glutamate Release

- Increased spontaneous activity of primary afferent
- Loss of inhibitory neurons
- Activation of immediate early genes
- Phosphorylation of channels and receptors

LONG TERM/PERSISTENT CHANGES IN FUNCTION

Nerve Injury →

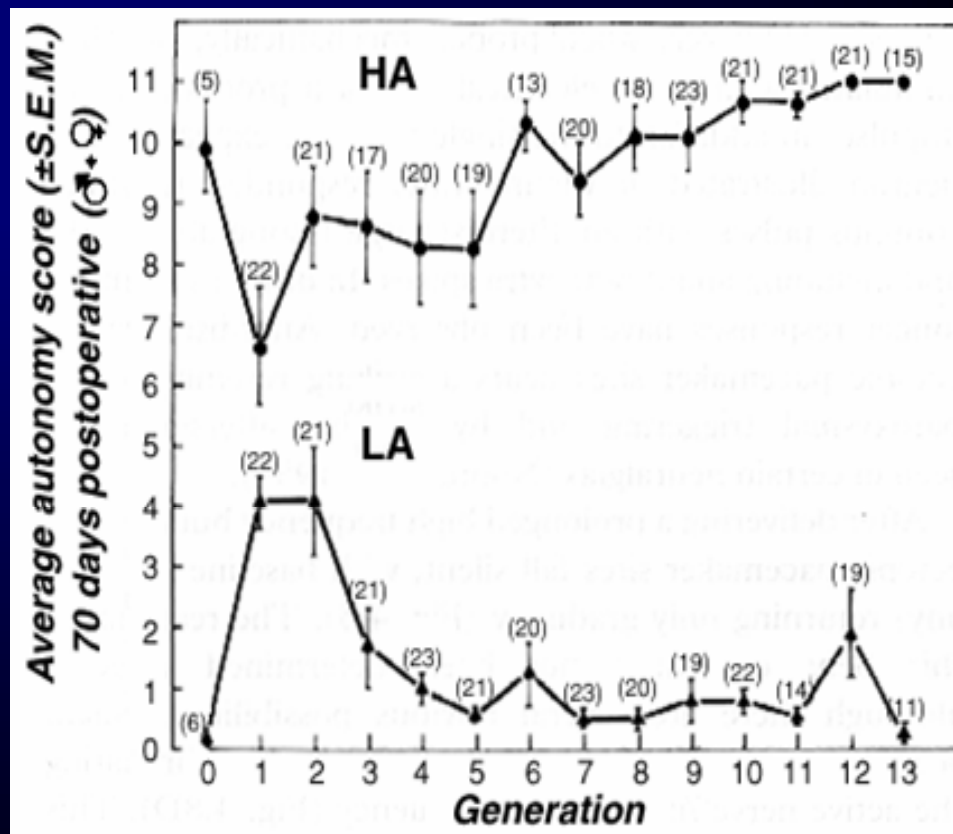
Activation of non neuronal cells  
(astrocytes, spinal microglia)

•Increased spinal expression of COX, NOS, glutamate transporters, proteinases

LONG TERM/PERSISTENT CHANGES IN FUNCTION

# Why Me?

- Why, after identical lesions, does one develop CRPS while another has no pain problem at all?
  - »
- Genetic predisposition
  - Women with certain HLA profiles seem predisposed to CRPS
  - Familial frequency reported by Griep and Thomas
  - Genetic traits of autonomy in rats
- Disuse
- Psychological factors
  - No good evidence



# Summary

- CRPS has an extremely complex pathophysiology involving sensory, motor and autonomic abnormalities
- It is unknown as to how the autonomic abnormalities and inflammatory processes affect the pain and sensory/motor abnormalities
- It is unknown if and how the syndrome can be prevented

# Suggested Reading

- Baron R, Raja SN. Role of adrenergic transmitters and receptors in nerve and tissue injury related pain. Malmberg AB, Chaplan SR (eds.). Mechanisms and Mediators of Neuropathic Pain. 2002, Birkhauser Verlag Basil/Switzerland. 153-174
- Sommer C. Cytokines and Neuropathic Pain. Hansson PT, Fields HL, Hill RG, Marchettini P. (eds.) IASP Press, Seattle, 2001, 37-62
- Baron R, Binder A, Schattschneider J, Wasner G. Pathophysiology and treatment of complex regional pain syndrome. Dostrovsky JO, Carr DB, Koltzenburg M. (eds.). IASP Press, Seattle, 2003, 683-704