Complex Regional Pain Syndrome

David V. Dent, DO, MPH
Assistant Professor of Anesthesiology
Program Director, Pain Medicine Fellowship
Dartmouth-Hitchcock Medical Center; Lebanon, NH
Geisel School of Medicine at Dartmouth;

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Disclosures

- 1. I have nothing to disclose
- 2. There is no commercial support for today's activity.

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Objectives

- Definition of Complex Regional Pain Syndrome (CRPS)
- History of CRPS
- Clinical Presentation of CRPS
- Diagnostic Criteria
- Diagnostic Tests
- Treatment

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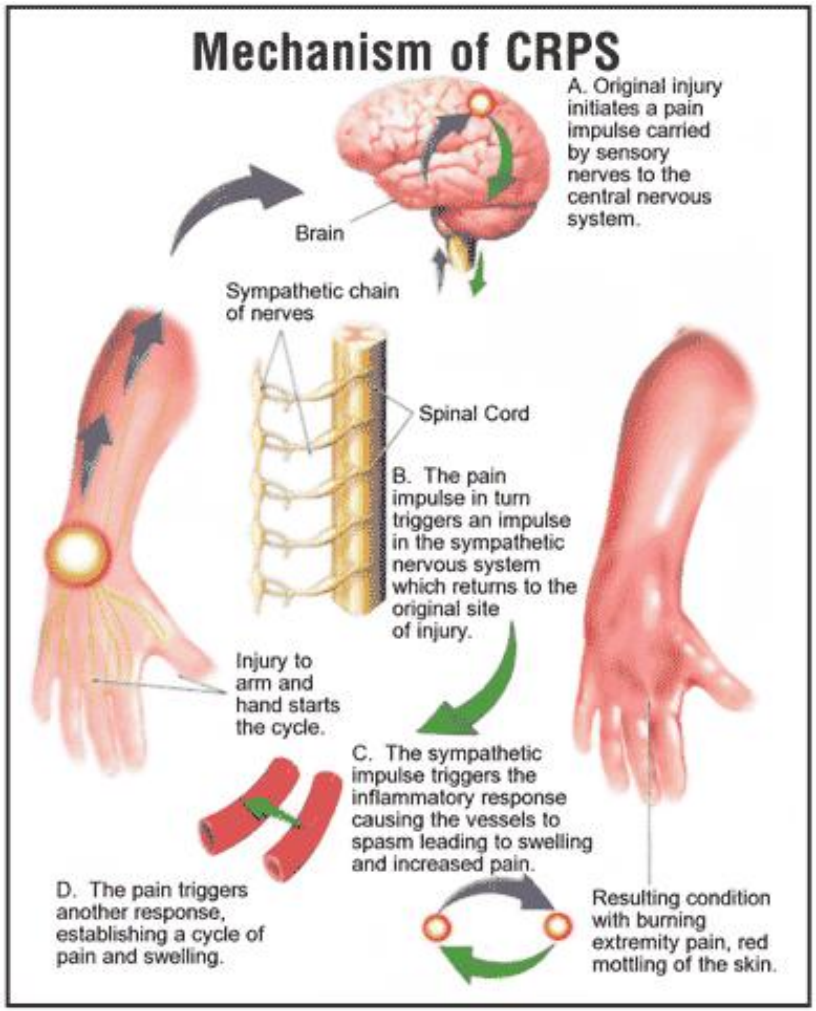
What is CRPS?

- Complex: Varied and dynamic clinical presentation
- Regional: Non-dermatomal distribution of symptoms
- Pain: Out of proportion to the inciting events
- Syndrome: Constellation of symptoms and signs



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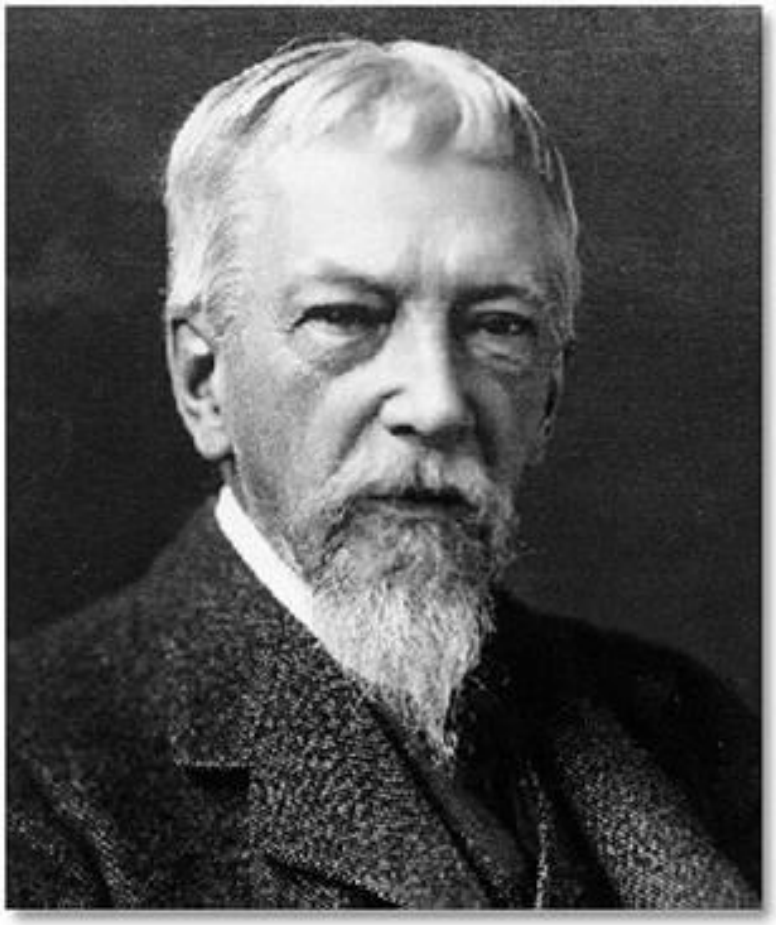
Long History (Dating back to the American Civil War)

- Weir Michell,
  - A physician during the American Civil War
- Observed a chronic pain syndrome in soldiers who suffered from traumatic nerve injuries
- Symptoms included:
  - Hypersensitivity
  - Swelling
  - Color change
  - Trophic changes
- Michell named the syndrome - Causalgia



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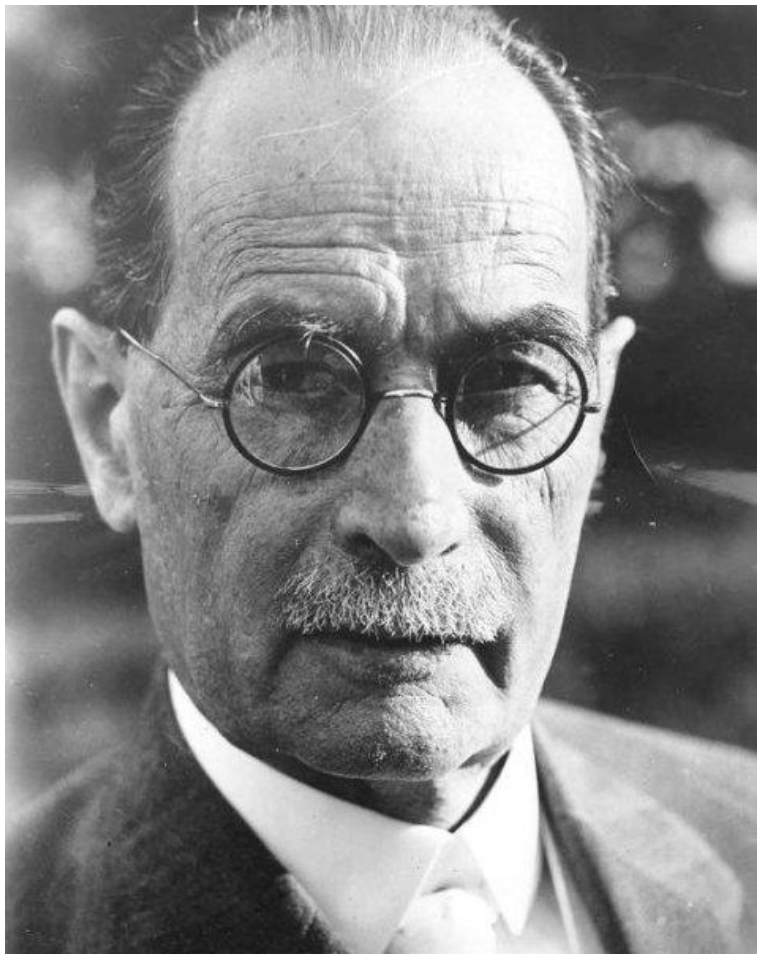
History (early 20th century)

- Paul Sudeck
  - German Surgeon
- Observed muscle atrophy and bony demineralization as a complication of infected limbs
- Sudeck's Atrophy: Patchy osteoporosis in affected extremity shown on x-ray



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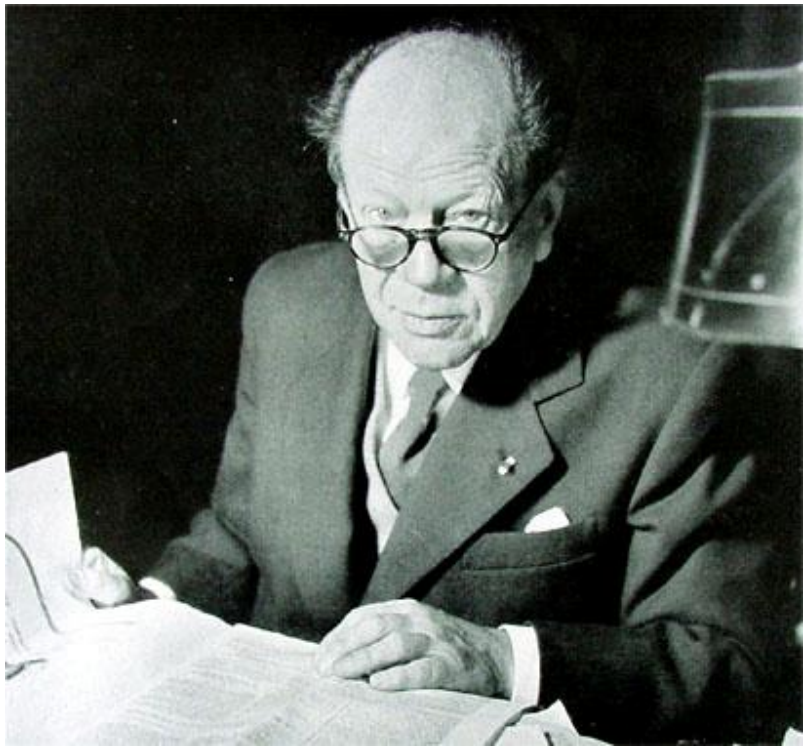
History (World War 1)

- Rene Leriche
  - French military surgeon
- Treated several WW1 soldiers with nerve injuries
- Described sympathetic nervous system dysfunction as a cause of pain
- Tried to alleviate the pain with Surgical Sympathectomy



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History

- Terminology and classification of CRPS has been in flux
- **1994**-IASP (International Association for the Study of Pain) introduced the terminology ‘Complex Regional Pain Syndrome’
  - Diagnostic criteria
  - Lacked specificity
  - Resulted in over diagnosis
- **2003**-Budapest Criteria
  - Improved specificity
- Recently-Modified Budapest Criteria (**2007**)
  - Criteria we use today

IASP Clinical Diagnostic Criteria for CRPS[4]

1. Continuing pain that is disproportionate to any inciting event
2. At least 1 symptom in 3 of the 4 following categories:
   - A. Sensory: reports of hyperesthesia and/or allodynia
   - B. Vasomotor: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   - C. Sudomotor/edema: reports of edema and/or sweating changes and/or sweating asymmetry
   - D. Motor/trophic: reports of decreased range of motion and/or motor dysfunction and/or trophic changes
3. At least 1 sign at time of evaluation in 2 or more of the following categories:
   - A. Sensory: evidence of hyperalgesia and/or allodynia
   - B. Vasomotor: evidence of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   - C. Sudomotor/edema: evidence of edema and/or sweating changes and/or sweating asymmetry
   - D. Motor/trophic: evidence of decreased range of motion and/or motor dysfunction and/or trophic changes
4. No other diagnosis better explains the signs and symptoms

Diagnostic Criteria: Budapest Clinical Criteria

- Continuing pain, which is disproportionate to any inciting event
- For the clinical diagnosis of CRPS, the patient must report at least one **symptom** in **3** of the following four categories:
  - **Sensory**: Reports of hyperesthesia and/or allodynia
  - **Vasomotor**: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
  - **Sudomotor/edema**: Reports of edema and/or sweating changes and/or sweating asymmetry
  - **Motor/trophic**: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

Diagnostic Criteria: Budapest Clinical Criteria

- For the clinical diagnosis of CRPS, the patient must display at least one **sign** at the time of evaluation in **2** of the four following categories:
  - **Sensory**: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
  - **Vasomotor**: Evidence of temperature asymmetry (>1°C) and/or skin color changes and/or asymmetry
  - **Sudomotor/edema**: Evidence of edema and/or sweating changes and/or sweating asymmetry
  - **Motor/trophic**: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
- **Also, there is no other diagnosis that better explains the signs and symptoms**

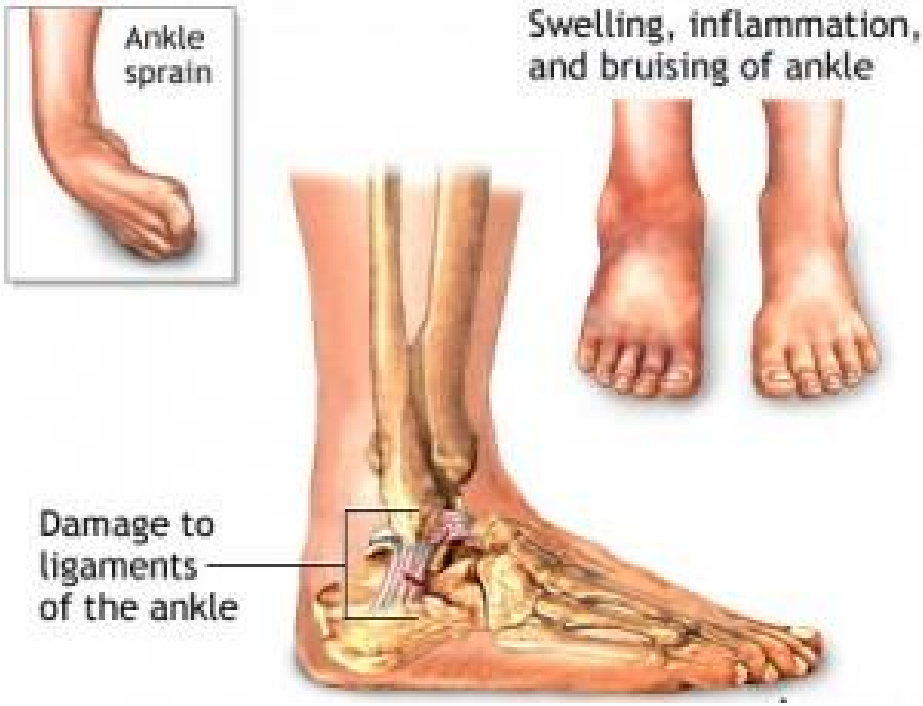
Epidemiology (relatively rare)

- CRPS Type I: 21 per 100,000 (about the same rate as Non-Hodgkin Lymphoma in the US)
- CRPS Type II: 4 per 100,000

- Female-to-Male ratio: 3:1
- Any age, but middle age predominates
  - Mean: 37-50 years
- Onset 9 – 85 years of age
- CRPS occurs in about 1-2% of patients who have had fractures and in approximately 2-5% of patients after peripheral nerve injuries
- Arm: 60% of cases, Leg: 40% of cases

CRPS 1 – Precipitating Event

- Minor trauma, contusion, sprain or strain
- Fracture (especially colles fx)
- Post surgical
- Immobilization
- Less frequently: CVA, spinal cord injury



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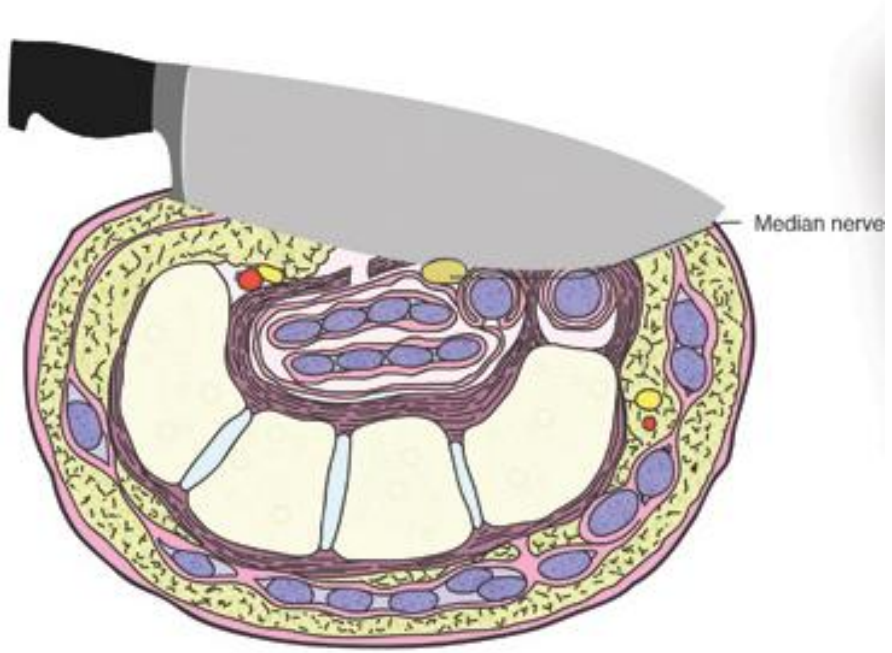
CRPS 2 – Precipitating Event

- Documented peripheral nerve injury
- Concordant focal deficits:
  - Signs and symptoms not limited to the same distribution as the affected nerve
- Signs and symptoms of both CRPS 1 and CRPS 2 are clinically indistinguishable



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Clinical Presentation

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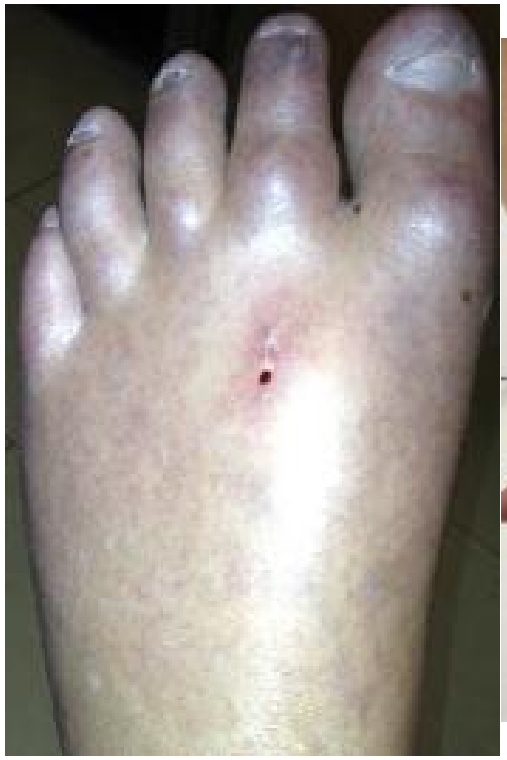
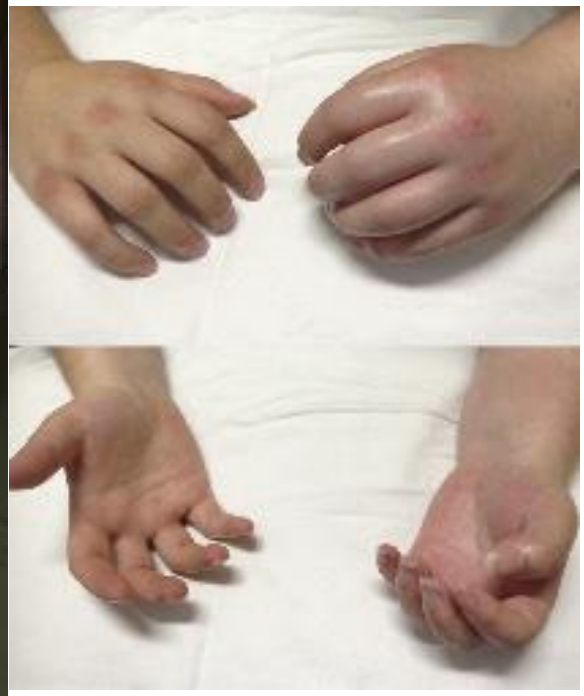
Clinical Presentation

- Distribution
  - Usually an Extremity: 65%
  - Ratio of upper: lower extremity=1-2:1
  - CRPS may progress and spread to other extremities over time





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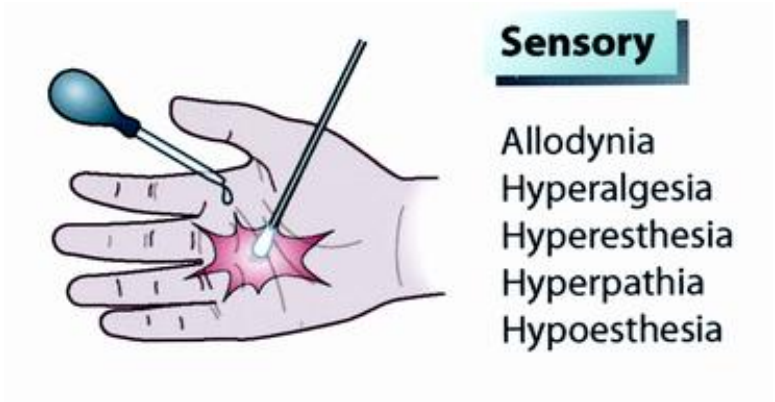
Clinical Presentation

1. Pain:
   - Spontaneous, constant, burning, aching, throbbing
   - Disproportionate to the injury and persists beyond normal or expected recovery period
   - Asymmetrical and not in the distribution of a peripheral nerve.

Clinical Presentation

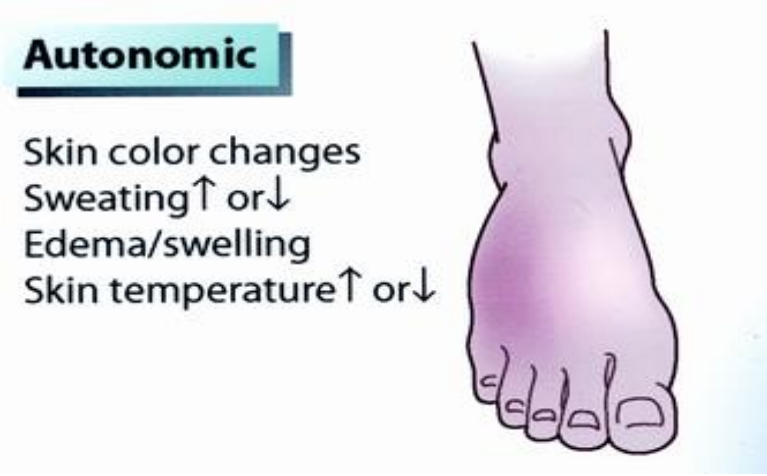
2. Sensory Changes
   - Hyperalgesia
     - Heightened sensitivity to pain
   - Allodynia
     - Experience of pain from a non-painful stimulation
   - Hyperesthesia
   - Pain disproportionate to inciting event

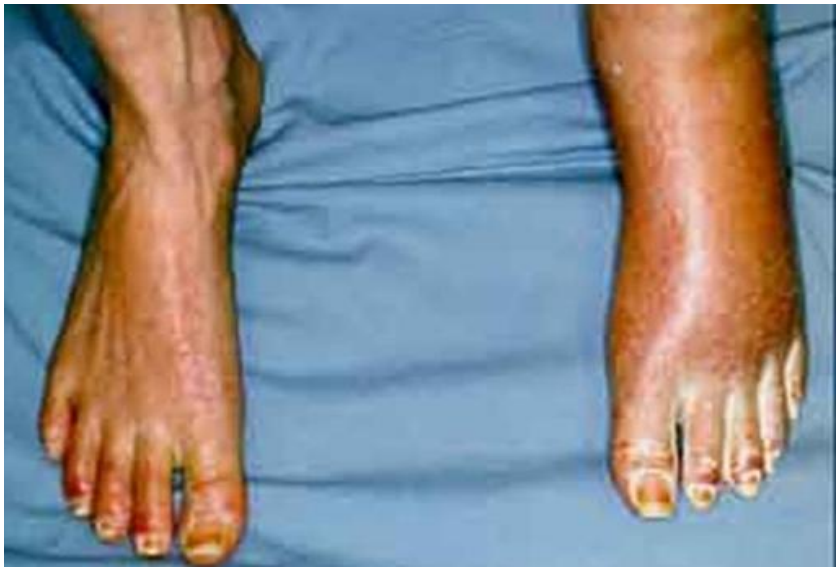


Clinical Presentation

3. Autonomic Abnormalities:

- Vascular
  - Hot, swollen, erythematous
  - Cold, blanched
  - Mottled
- Sudomotor
  - Hyperhidrosis
  - Hypohidrosis





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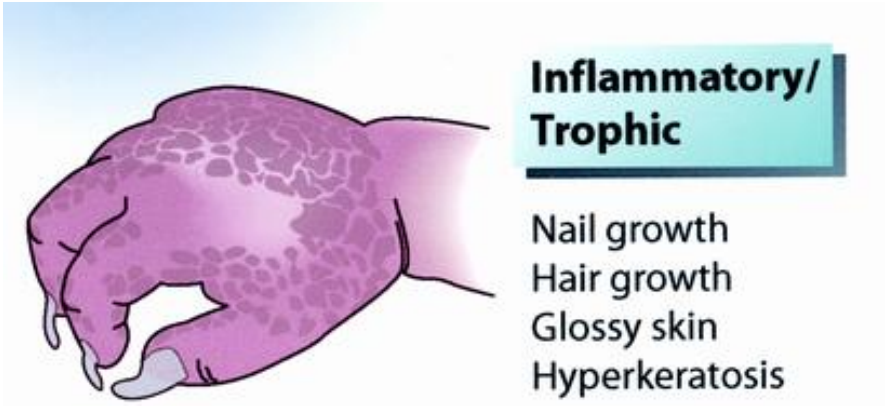
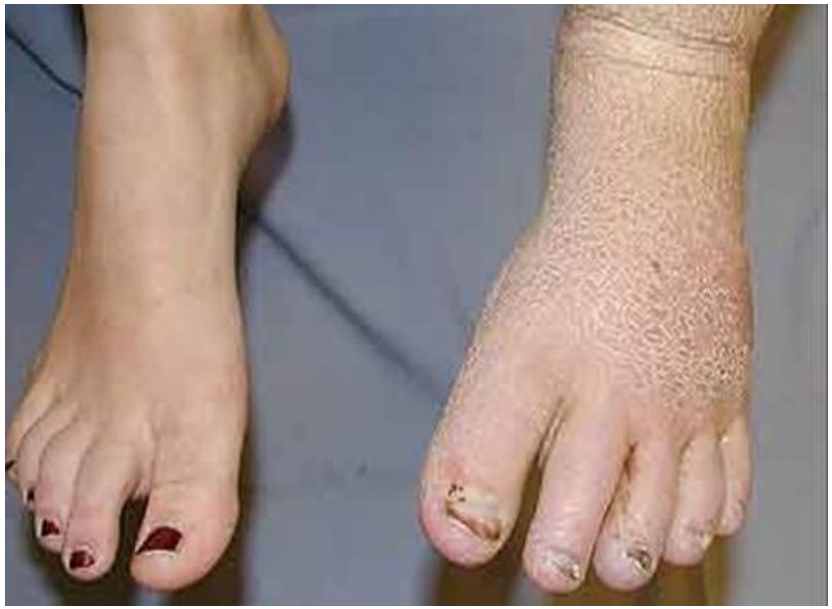
Clinical Presentation

4. Motor Impairments:
   - Weakness of the extremity,
     - Normal EMG until late in the disease
   - Tremor
   - Dystonia

Clinical Presentation

5. Trophic Changes:
   - Nail growth
   - Loss of function: muscle, joint and tendon atrophy, contractures and fibrosis
   - Hair changes (coarse hair, loss of hair)
   - Skin--thin and glossy, loss of elasticity, ulceration.
   - Osteoporosis





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Clinical Presentation-Time Course

- Three stages:
  - Stage 1 (acute)
  - Stage 2 (dystrophic)
  - Stage 3 (atrophic)

Stages of CRPS Type 1

Stages	Symptoms	Time Frame
Acute stage	◗ Affected limb swollen, red, burning ◗ Increased diaphoresis of affected limb ◗ All symptoms are near the site of original injury	Within weeks of injury
Dystrophic stage	◗ Skin of limb is cool and diaphoretic ◗ Sudek's atrophy of bone on X-ray ◗ Pain occurs throughout limb, not just at site of injury	Within months of injury
Atrophic stage	◗ Skin becomes pale and shiny ◗ Atrophy of muscle and bone in the affected limb ◗ Pain may be constant even with treatment	For years after injury

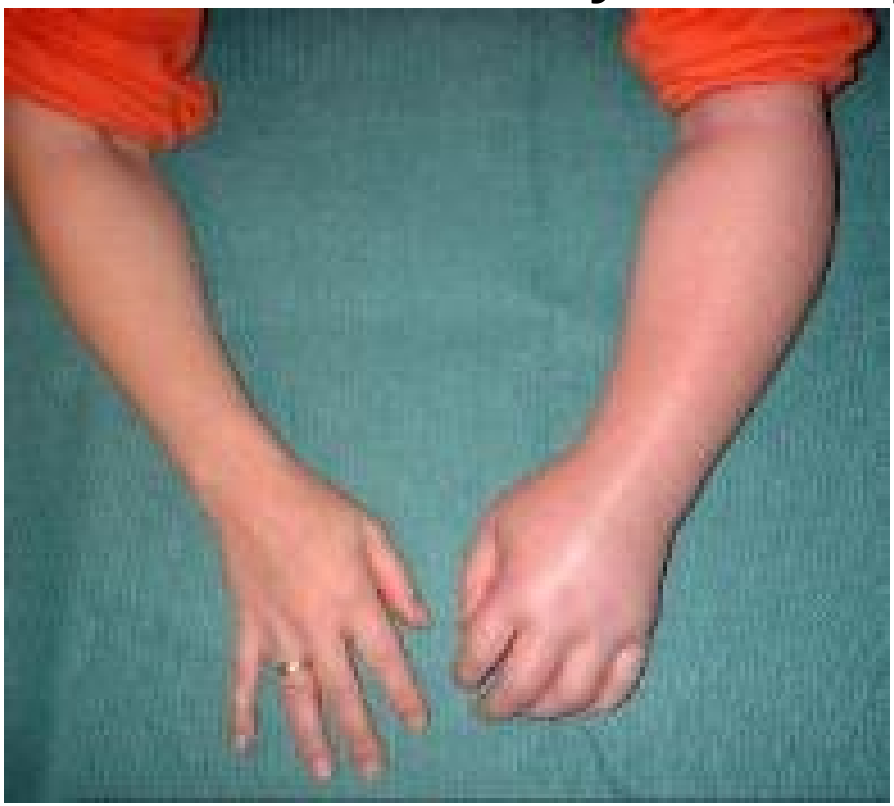
CRPS Stage 1-Acute

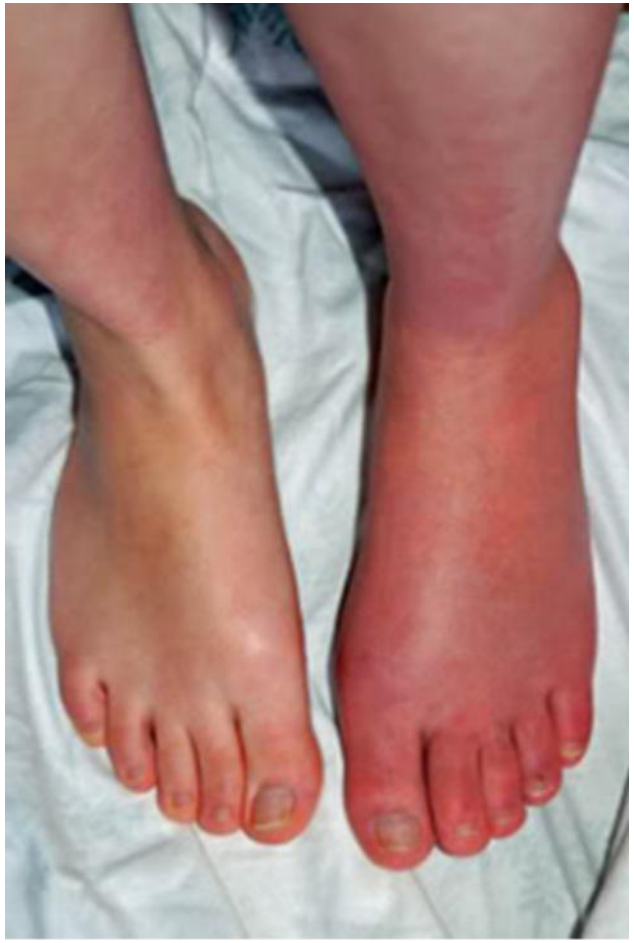
Immediately after injury – 3 months

- SKIN: Red, warm, swollen, dry, inflamed.
- DISTRIBUTION: Pain is not compatible with a single peripheral nerve, trunk, or root lesion
  - Limited to site of injury
- VASOMOTOR: Altered color and temperature.
- SUDOMOTOR: Hyperhidrosis
- MOTOR: Decreased ROM, weakness
- X-RAYS: Normal
- BONE SCAN: Increased uptake
- Most likely to be reversed and cured

CRPS Stage 1-Acute

Immediately after injury – 3 months





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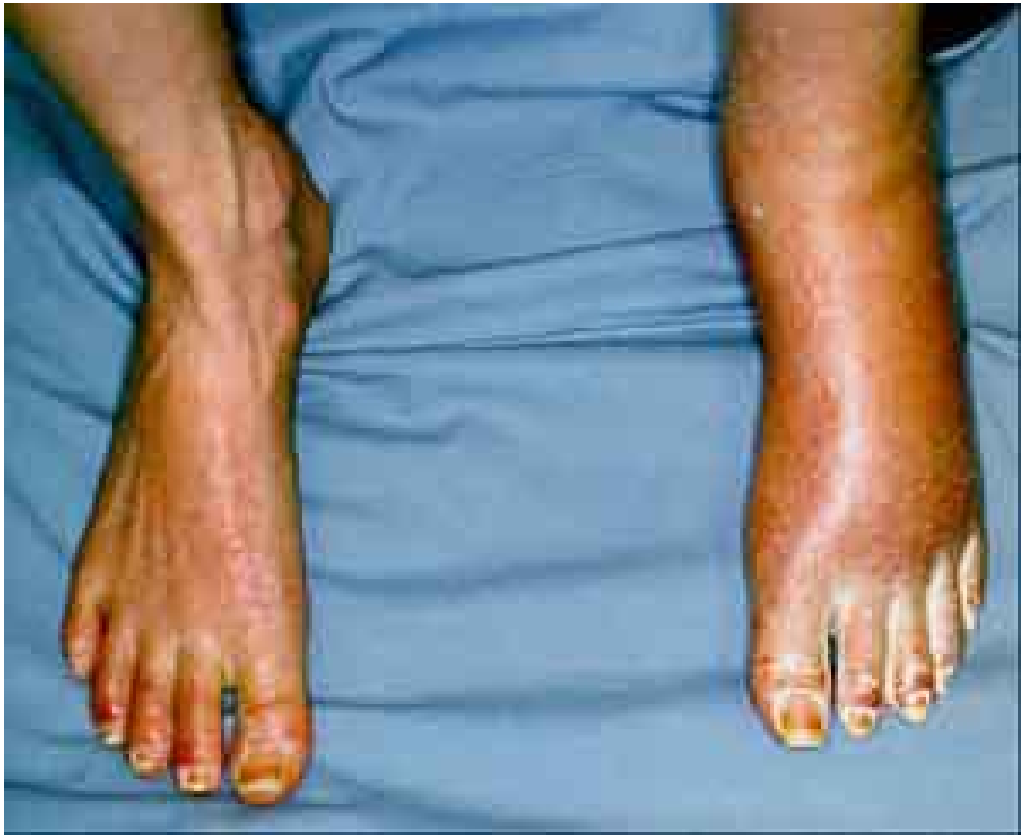
CRPS Stage 2-Dystrophic

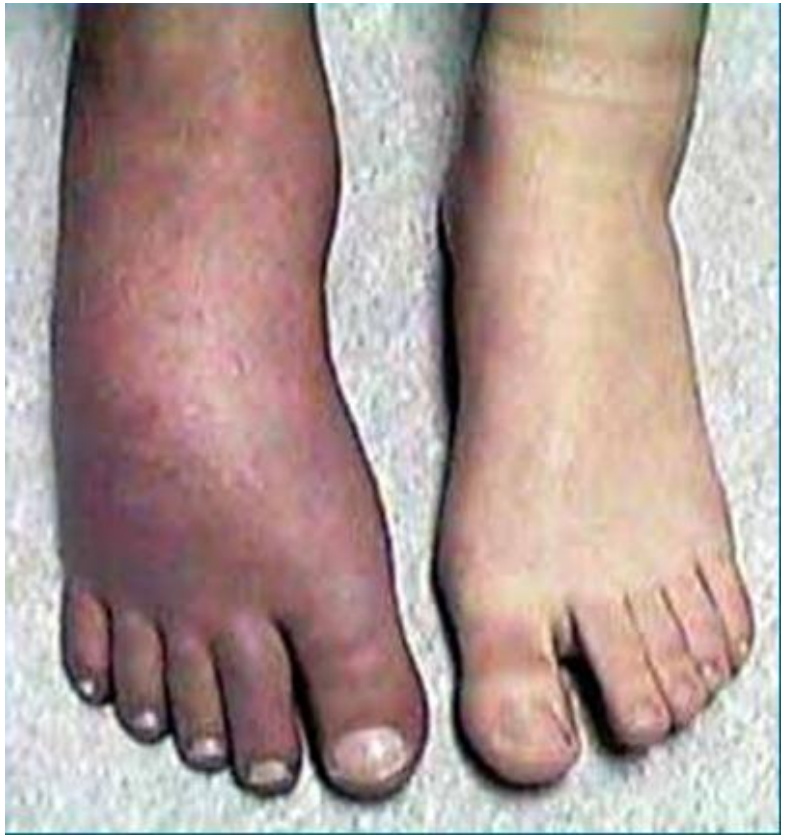
6 weeks – 1 year

- SKIN:
  - Cool, moist, tight/shiny, swelling, coarse/sparse hair, brittle nails, discolored, edema
- SYMPATHETIC:
  - VASOMOTOR: Mottled/cyanotic
  - SUDOMOTOR: Hyperhidrosis
- MOTOR: Weakness, decreased ROM
- BONE SCAN: No longer helpful.

CRPS Stage 2-Dystrophic

2-3 months – 1 year





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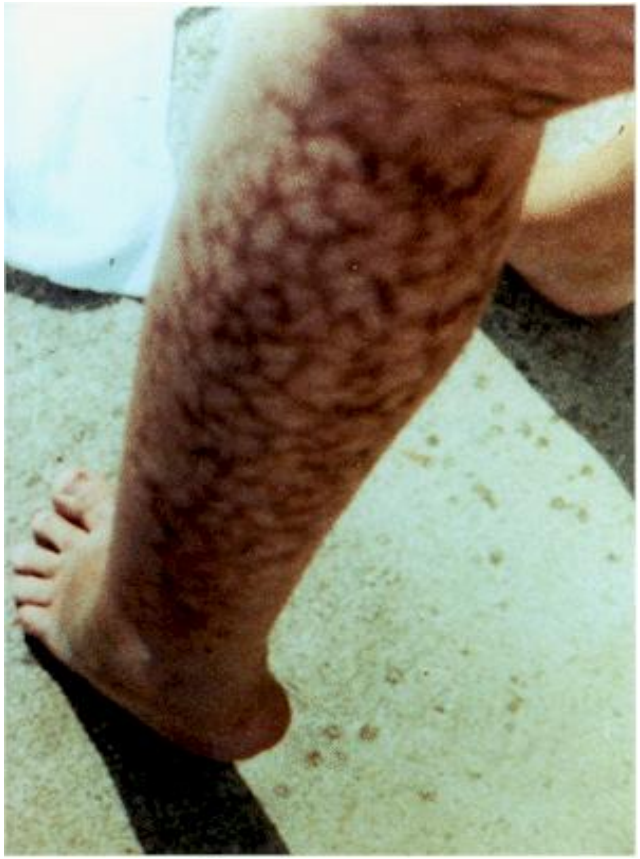
CRPS Stage 3-Atrophic

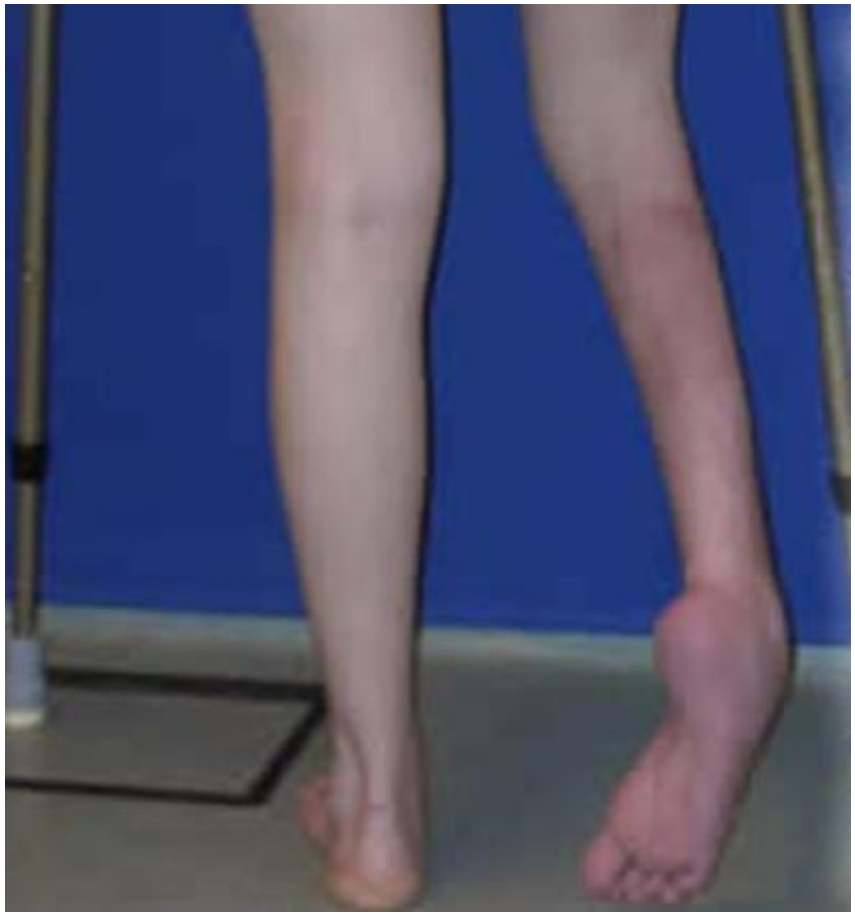
6 month – Forever???

- Pain is somewhat decreased (but still debilitating)
  - Less at rest, worse with passive motion
- SKIN: Atrophy, “waxy”, very thin, ulcerations, brittle nails
- SYMPATHETIC:
  - VASOMOTOR: Cold, intermittently cyanotic/mottled
- MOTOR: Decreased ROM, weakness, muscle & tendon atrophy, contractures, dystonia, tremor.
  - Nonfunctional limb.
- X-RAYS: Diffuse patchy osteoporosis
- Changes are irreversible, poor outcomes, permanent disability

CRPS Stage 3-Atrophic

6 month – Forever???





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Diagnostic Tests

There is **no** test validated for CRPS diagnosis

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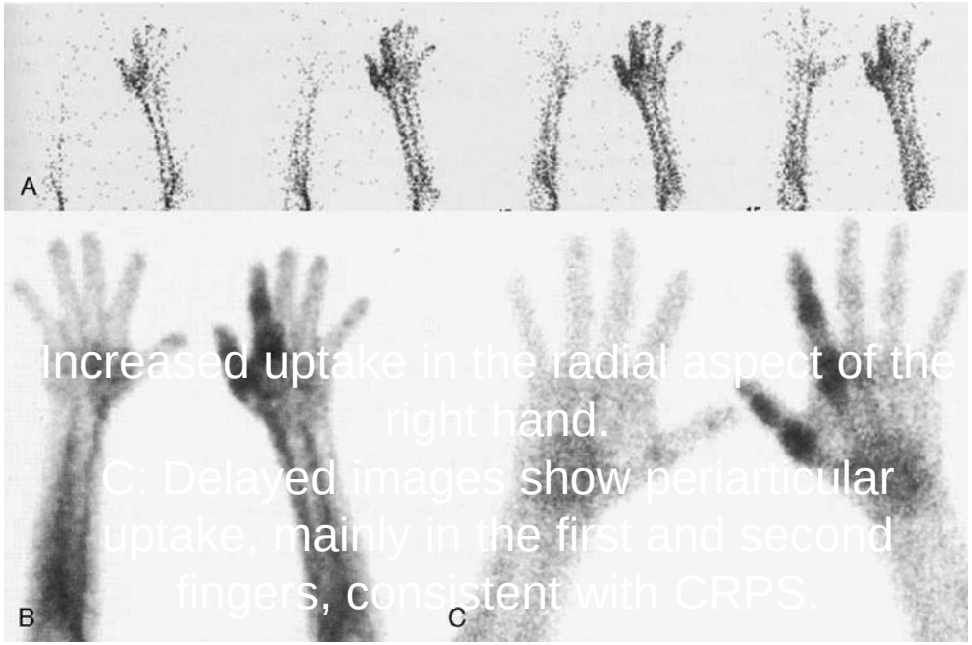
Diagnostic Tests: Three Phase Bone Scintigraphy

- **Only** in acute stage
  - During the first year
- Scan is considered positive if flow is asymmetric in scan 1, 2, and/or 3
- Increased blood flow to the CRPS-affected area
- Suggestive and supportive of the diagnosis of CRPS, **but not** diagnostic
  - Useful to rule out other pain syndromes



Increased uptake in the radial aspect of the right hand.
C: Delayed images show periarticular uptake, mainly in the first and second fingers, consistent with CRPS.

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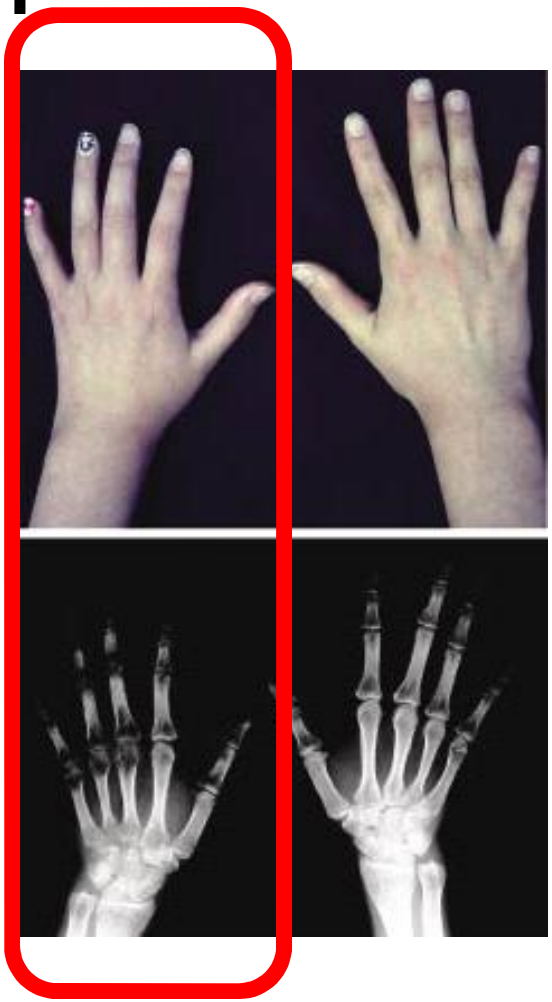
Diagnostic Tests: Plain Radiographs

- During Stage 1 of CRPS:
  - Normal x-rays
- ◈ **Late findings** only with atrophic stage showing bone loss and patchy osteoporosis
- Demineralization with disuse and loss of function of the CRPS-affected area increases with time



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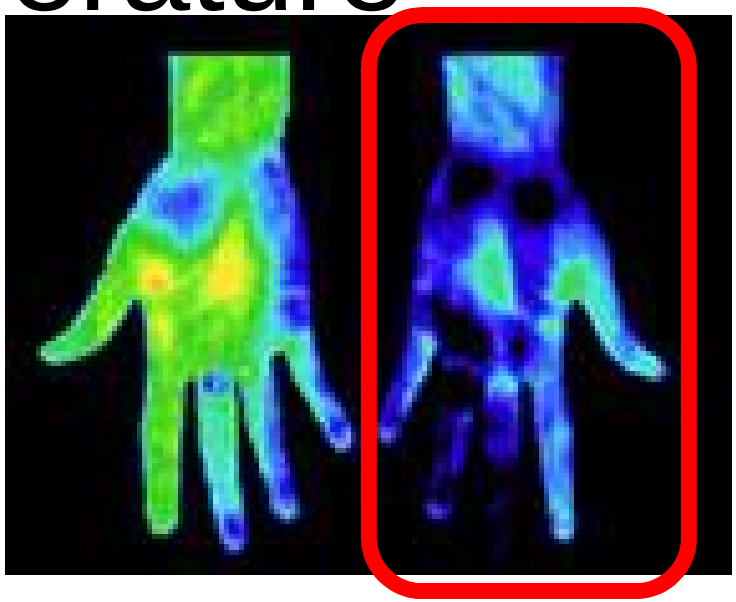
Diagnostic Tests: Skin Temperature

- Thermography may show asymmetry.
- Affected limb is warmer than normal in acute stage and later becomes cooler
- **<u>Controversy</u>** over the effectiveness of thermography in diagnosing CRPS



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Treatment/Management

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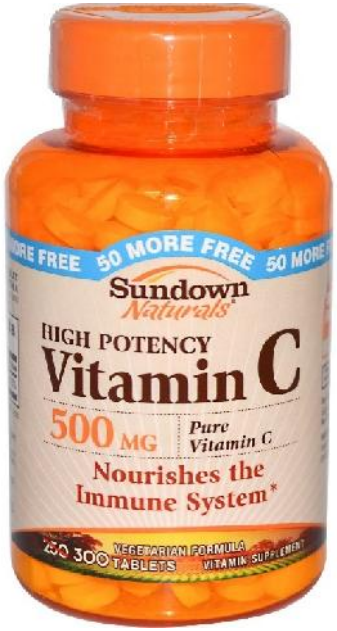
Treatment: Prevention

Best treatment of CRPS:
Prevention

1. Vitamin C following fracture or surgery appears to reduce the risk of developing CRPS
   - MOA: Unknown
   - Little risk from use
   - Dose: 500 mg Daily for 50 days
2. Early Mobilization
   - No high quality data confirming benefit



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Can Vitamin C Prevent Complex Regional Pain Syndrome in Patients with Wrist Fractures?

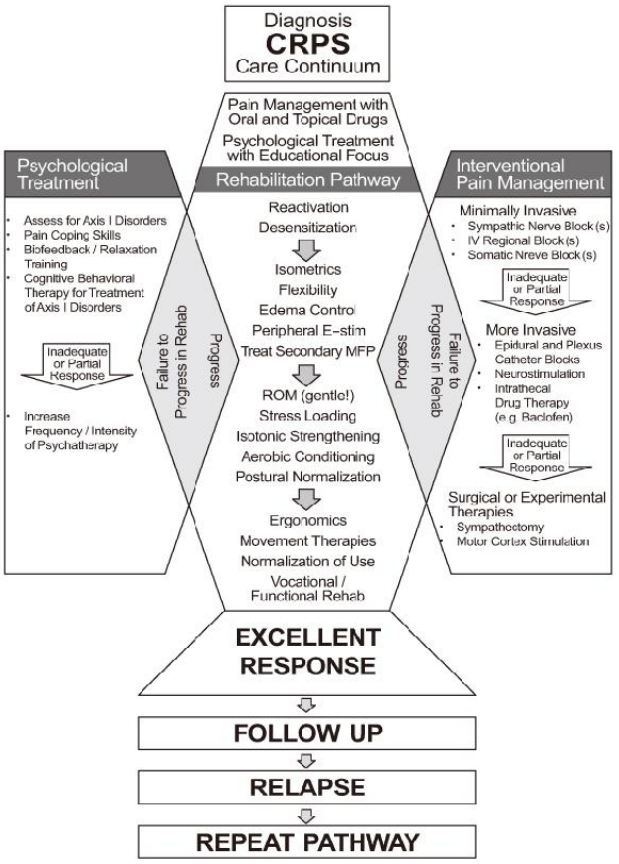
A Randomized, Controlled, Multicenter Dose-Response Study

By P.E. Zollinger, MD, W.E. Tuinebreijer, MD, PhD, MSc, MA, R.S. Breederveld, MD, PhD, and R.W. Kreis, MD, PhD

- Background: CRPS is treated symptomatically.
  - A protective effect of vitamin C has been reported previously.
  - A dose-response study was designed to evaluate its effect in patients with wrist fractures.
- Methods: A double-blind, prospective, multicenter trial, 416 patients with 427 wrist fractures were randomly allocated to treatment with placebo or treatment with 200, 500, or 1500 mg of vitamin C daily for fifty days.
- Conclusions: Vitamin C reduces the prevalence of complex regional pain syndrome after wrist fractures. A daily dose of 500 mg for fifty days is recommended

Treatment Goals

- Relief of pain
- Return of function
- Prevent or slow progression
- A multiisciplinary approach that simultaneously addresses these domains is optimal
- 3 domains of treatment
  - Rehabilitation
  - Psychological treatment
  - Pain management



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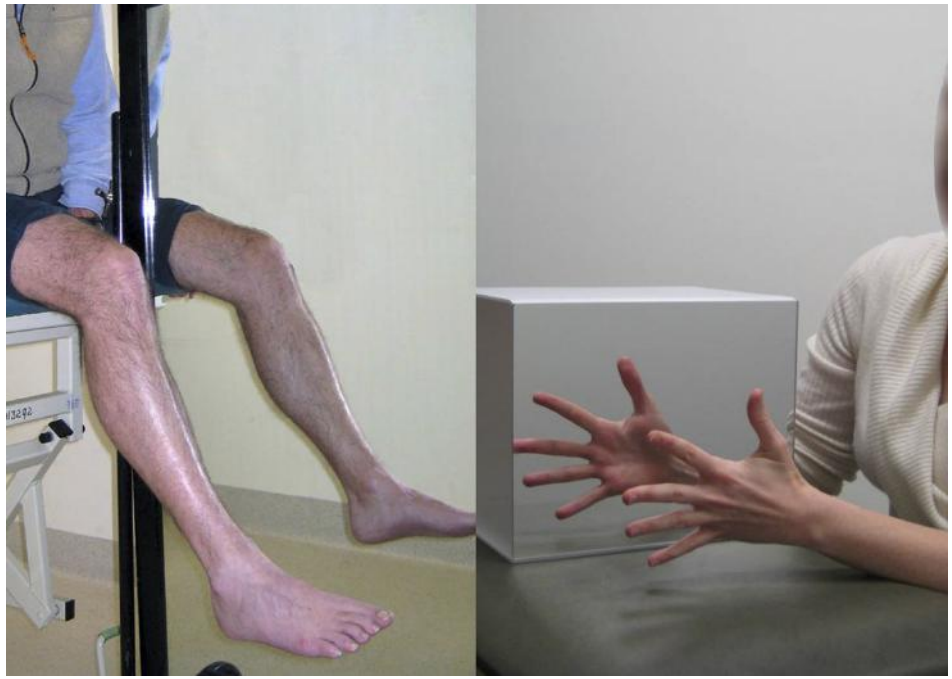
Treatment: Physical and Occupational Therapy

- Graded motor imagery
  - Strongest Evidence??
  - Decrease pain and swelling
- Pain-exposure physical therapy:
  - Reduce pain avoidance behaviors
- Self-administered tactile and thermal desensitization with the aim of normalizing touch perception
- Mirror visual feedback
- Functional movement techniques:
  - Improve motor control and awareness of affected limb position
- Principles of stress loading



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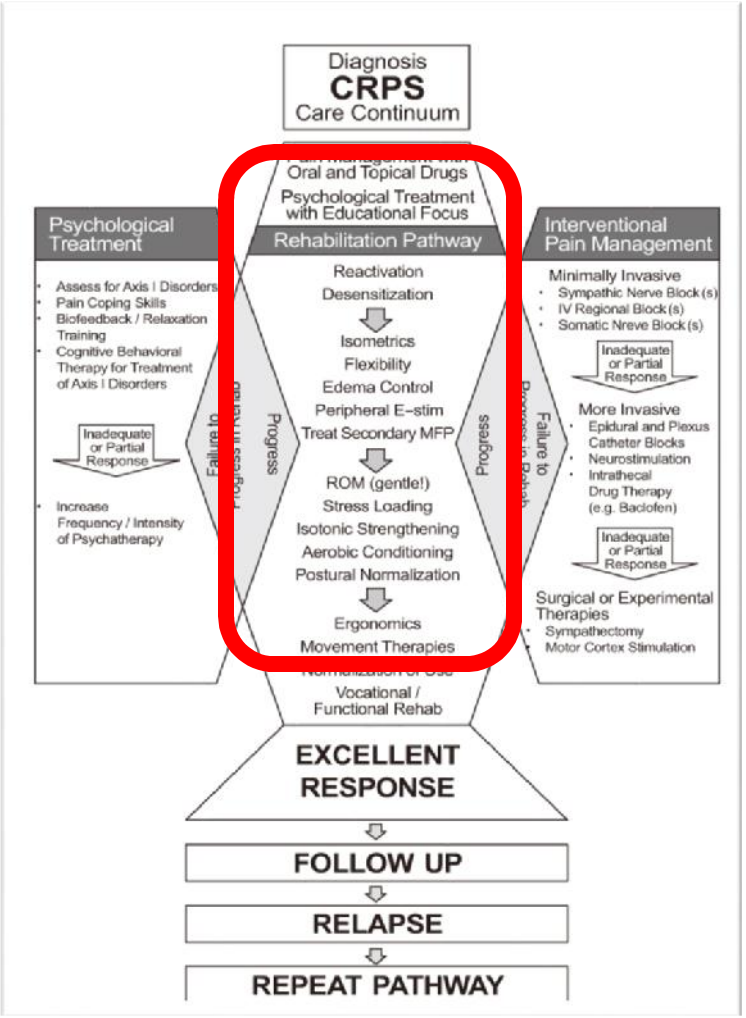
Treatment: Physical and Occupational Therapy

- Physical therapy
  - All stages of disease
- Begin before limitation of movement
  - Maintain range of motion
  - Prevent contractures
- Resting splints
  - Used with a goal of preventing progressive joint contractures
  - Effectiveness of splinting is uncertain



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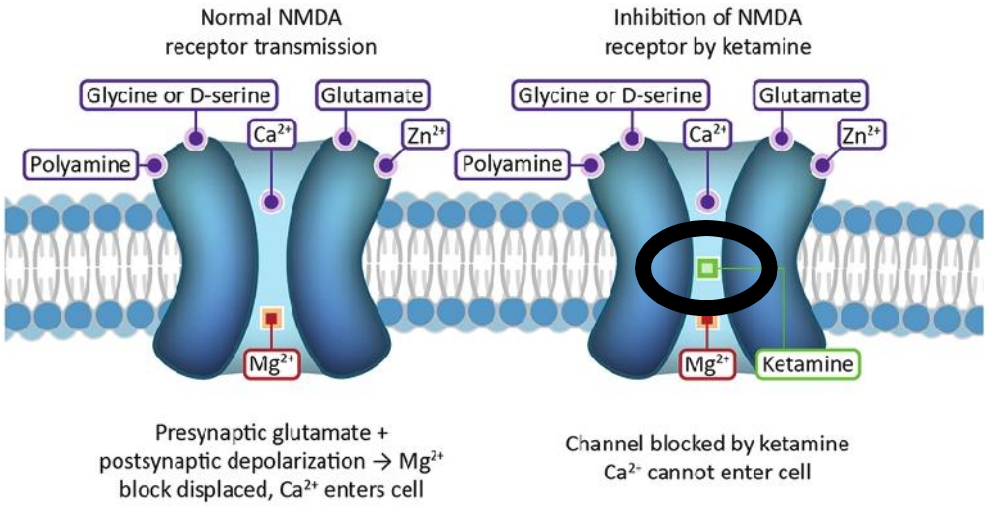
Treatment: Pharmacologic

- Pharmacologic approaches
  - Multiple treatment modalities
  - Reduce pain so that patients can tolerate physical therapy
- Nonsteroidal anti-inflammatory drugs
- Membrane stabilizers
- Antidepressants
- Calcitonin
- Bisphosphonates
- Vasodilators
- NMDA receptor antagonists
- Topical Ointment
- Opioids

Treatment: Ketamine

- MOA:
  - Non-competitive antagonist of the NMDA receptor
  - Receptor channel needs to be open to enter and exert it's action
- Metabolism:
  - Hepatic via hydroxylation and N-demethylation
  - Active metabolite: Norketamine is 33% as potent as parent compound (greater conversion to norketamine occurs after oral administration)



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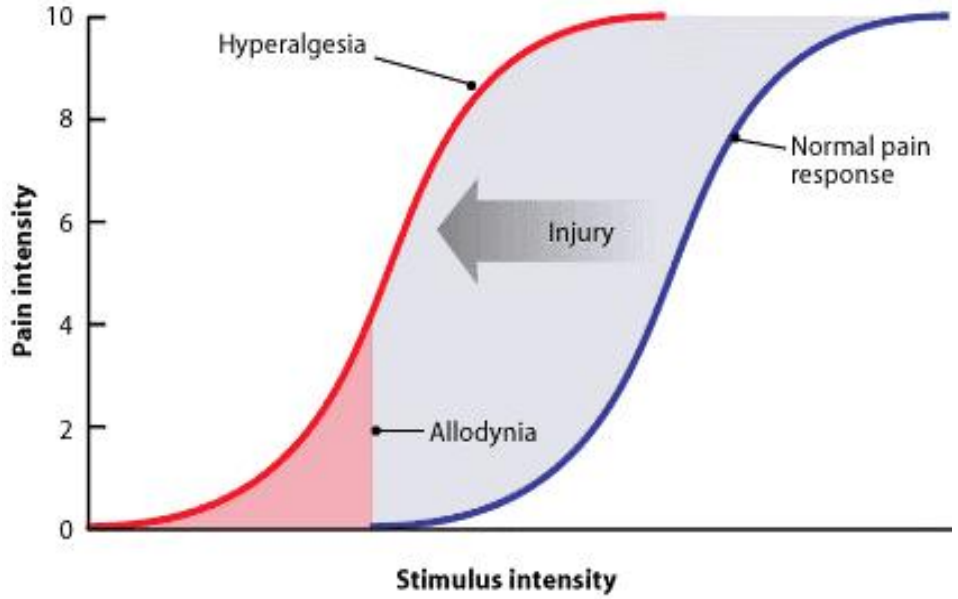
Treatment: Ketamine

Activation of NMDA receptors has been associated with hyperalgesia, neuropathic pain, and reduced functionality of opioid receptors

1. Hyperalgesia and neuropathic pain:
   - Amplification of response, leading to a heightened level of pain
2. Reduced function of opioid receptors:
   - Decrease in the opioid receptor's sensitivity
     - Translates to opioid tolerance as patients will require higher doses of opioids to achieve the same therapeutic effects

NMDA antagonists may have a role in these areas of pain management



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Pain Physician. 2005;8:175-179, ISSN 1533-3159

PROSPECTIVE CASE SERIES

MULTI-DAY LOW DOSE KETAMINE INFUSION FOR THE TREATMENT OF COMPLEX REGIONAL PAIN SYNDROME

Michael E. Goldberg, MD, Richard Domsky, MD, Denise Scaringe, MD, Robert Hirsh, MD, Jessie Dotson, MSN, Imran Sharaf, MD, Marc C. Torjman, PhD, and Robert J. Schwartzman, MD

- Background: Current literature supports the effectiveness of ketamine in blocking central sensitization through its effects on the NMDA receptor. Recent treatment with anesthetic doses of ketamine in severely ill patients with generalized CRPS prompted our interest in a lower dose therapy.
- Methods: Patients diagnosed with CRPS by a single neurologist were assigned to receive a 10-day outpatient infusion of ketamine
- Conclusions: A four-hour ketamine infusion escalated from 40-80 mg over a 10-day period can result in a significant reduction of pain with increased mobility and a tendency to decreased autonomic dysregulation.

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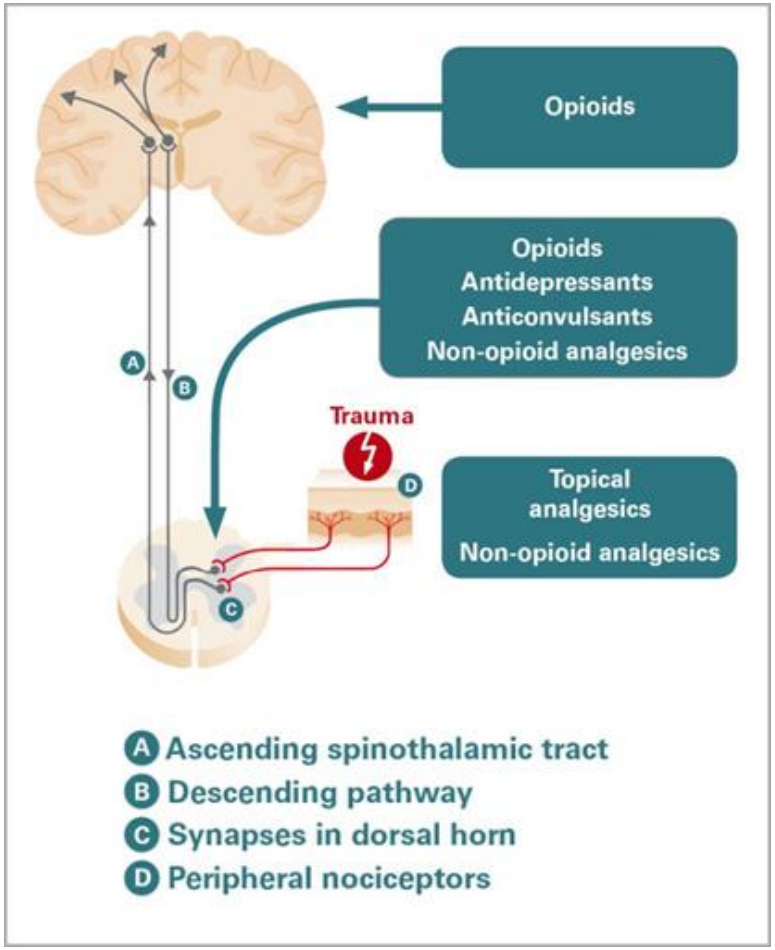
Treatment: Opioids

- Opioid use for neuropathic pain and CRPS:
  - Controversial
- Considered if pain is affecting physical therapy participation
- Low dose opioids may be justified in select cases when other approaches have failed
  - Escalating the dose can result in the risk outweighing the benefit



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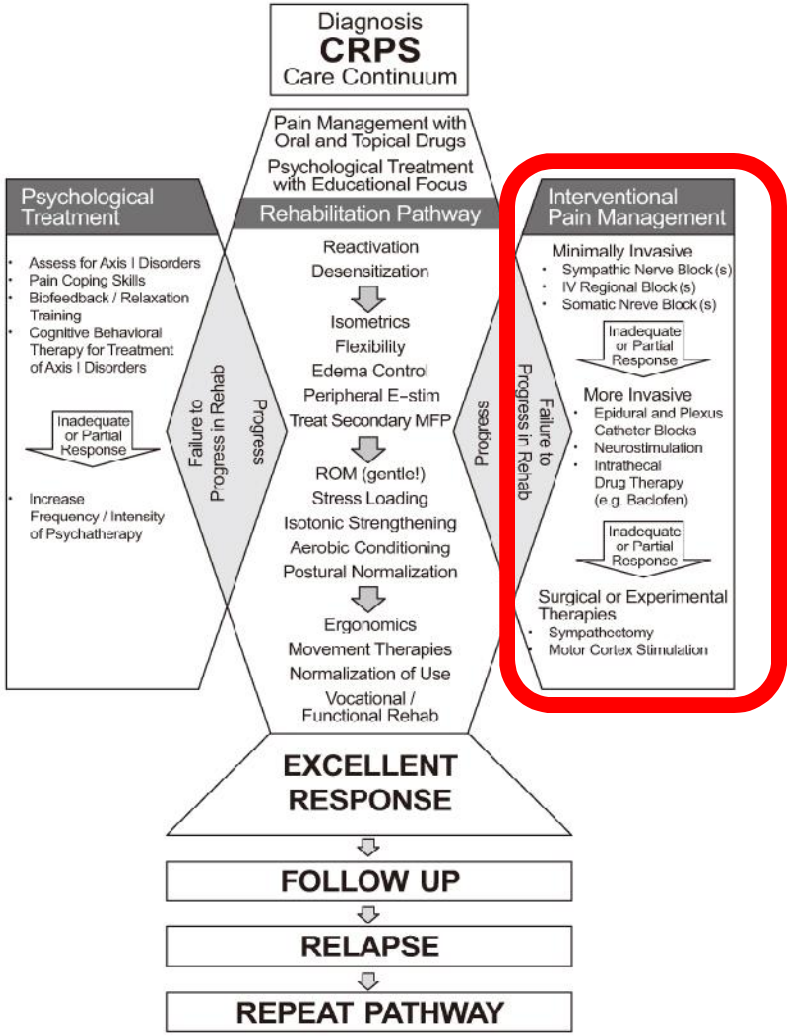
Treatment: Interventions

Patients receiving noninvasive therapy who are not improving are candidates for increasingly invasive interventions

- Trigger/tender point injections
- Regional sympathetic nerve block
- Spinal cord stimulation
- Epidural clonidine
- Chemical or mechanical sympathectomy



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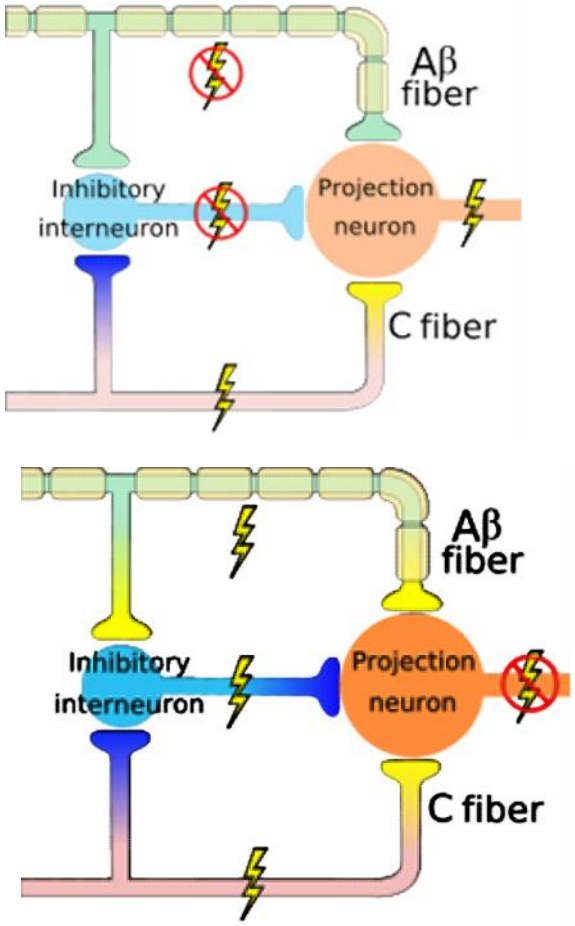
Treatment: Spinal Cord Stimulation

How it works?

- Based on the Gate Theory
- Stimulation reduces the pain because the electrical current interrupts the pain signal prior to reaching the brain
  - Does not eliminate the source of pain, it simply interferes with the signal to the brain



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Prognosis

- Uncertain
- **Highly variable** rates of poor and favorable outcomes
- A substantial proportion of patients have some degree of **prolonged disability**
- **Litigation and work-related compensation** issues can complicate the clinical course
- Recurrence of CRPS is not uncommon
  - Younger patients
  - Cold exposure
  - Trauma
  - Surgery to affected limb
  - Emotional trauma

Key Messages

- Diagnosis of exclusion
- Cause is uncertain
- No specific treatment
- Rehabilitation is the key treatment
- Other treatments are aimed to facilitate the above in a multidisciplinary approach

Thank you!

Questions?

David.V.Dent@hitchcock.org

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