

# Complex Regional Pain Syndrome

Managing a poorly understood condition

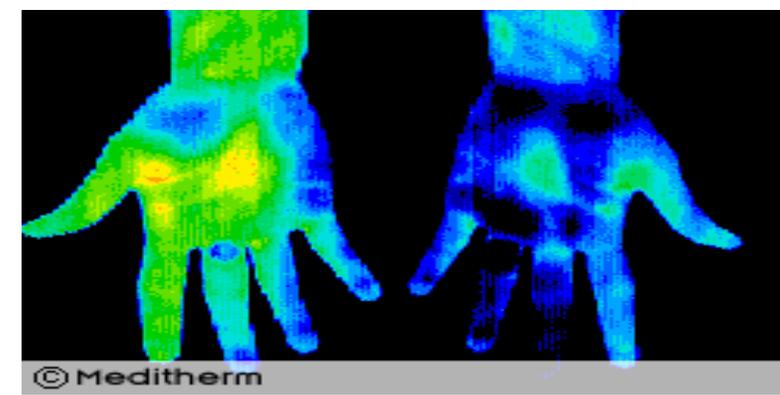
Andrew Friedman MD

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# CRPS



- Hypersensitivity to touch
- Swelling
- Changes in skin temperature
- Changes in skin color
- Continuous burning or throbbing pain usually in hand or foot
- Changes in skin texture
- Changes in hair or nail growth
- Motor symptoms
- Abnormal sweating

# History

- Ambroise Pare treated King Charles ix for smallpox by lance. Subsequently the King developed progressive atrophy and contracture of the limb





# History

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- Described in Civil War after battlefield injuries
  - Trauma to limb, amputation, immobilization
  - Heart attack or stroke

Various names over the years:

- **Causalgia**—Mitchell's original term
- **Sudek's atrophy**—1900. Sudek noted spotty osteopenia and suggested abnormal inflammatory response
- **RSD**—Coined in 1946 after work suggesting sympathetic dysfunction
- **CRPS**—IASP term defined in 1994
- Budapest Criteria--2007

# CRPS

- CRPS I—most common (90%). Previously referred to as RSD
- CRPS II—Involves distinct nerve injury. Previously “causalgia”

# CRPS Epidemiology

- Incidence 5-26:100,000
- Female to Male 3:1
- Peak incidence ages 35-50
- Major or minor injury
- Immobilization
- Described after MI, Stroke
- CRPS I>>>CRPS II
- 44% CRPS follows fracture
  - Radial, tibial, foot
- Upper extremity>Lower extremity
- CRPS II 1-5% after peripheral nerve injury
  - Barron 2005

# Symptoms/Signs

- Hypersensitivity to touch
- Swelling
- Changes in skin temperature
- Changes in skin color
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- Motor symptoms
- Abnormal sweating



**Table. Budapest Criteria for CRPS**

All of the following statements must be met:

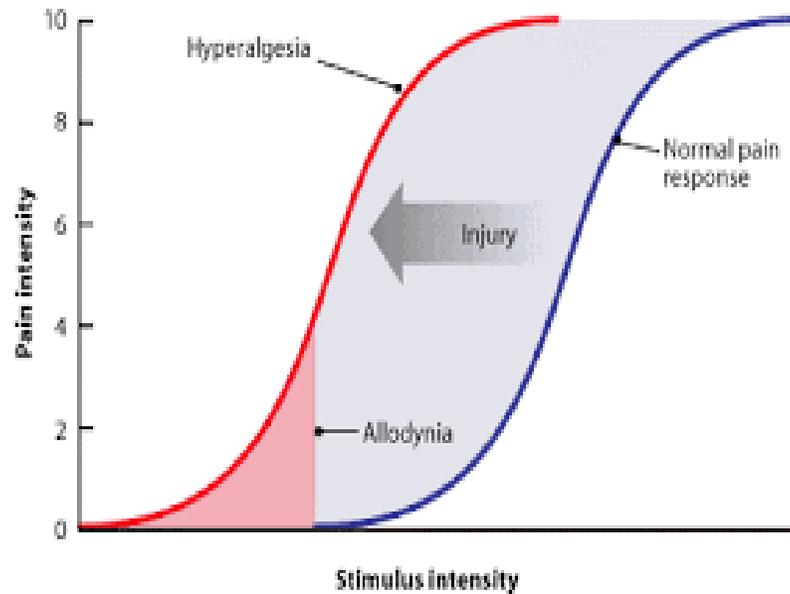
- The patient has continuing pain that is disproportionate to any inciting event
- The patient has a least 1 sign in 2 or more of the categories below
- The patient reports at least 1 symptom in 3 or more of the categories below.
- No other diagnosis can better explain the signs and symptoms.

No.	Category	Signs/Symptom
1	<b>Sensory</b>	Allodynia (pain to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement) and/or hyperalgesia (to pinprick)
2	<b>Vasomotor</b>	Temperature asymmetry and/or skin color changes and/or skin color asymmetry
3	<b>Sudomotor/edema</b>	Edema and/or sweating changes and/or sweating asymmetry
4	<b>Motor/trophic</b>	Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair/nail/skin)

Based on reference 3.

# Allodynia

- Pain experienced with stimuli that are not usually painful
  - 70-80% of patients



# Washington State L&I Diagnostic Criteria

- <http://www.lni.wa.gov/ClaimsIns/Files/OMD/MedTreat/ComplexRegionalPain2011.pdf>
- Positive bone scan can substitute for one as one of the positive physical exam findings

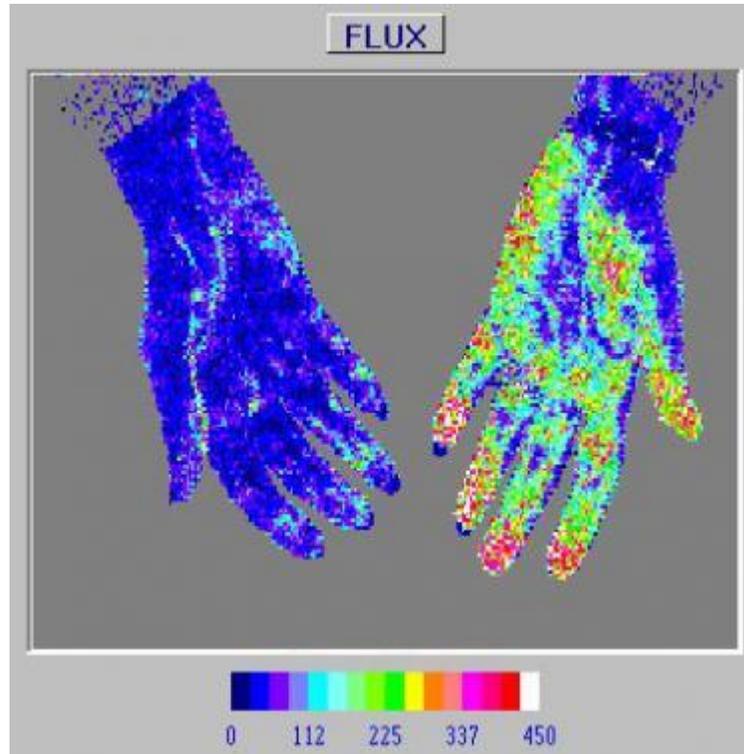
# Evolution of CRPS over time

- Typically, CRPS I is subdivided into the following 3 phases:
  - Acute stage - Usually warm phase of 2-3 months
  - Dystrophic phase - Vasomotor instability for several months
  - Atrophic phase - Usually cold extremity with atrophic changes
- This classic description is highly variable. “spreading” CRPS debated. Contiguous, random and mirror image spreading described.

# Differential Diagnosis

- Nerve injury
- DVT
- Occult fracture
- Arterial insufficiency
- Raynaud's phenomenon
- Plexopathy
  - Pancoast tumor
- Acute neuropathy
- Infection
- Erythromelalgia
- Somatoform disorder
- Factitious disorder

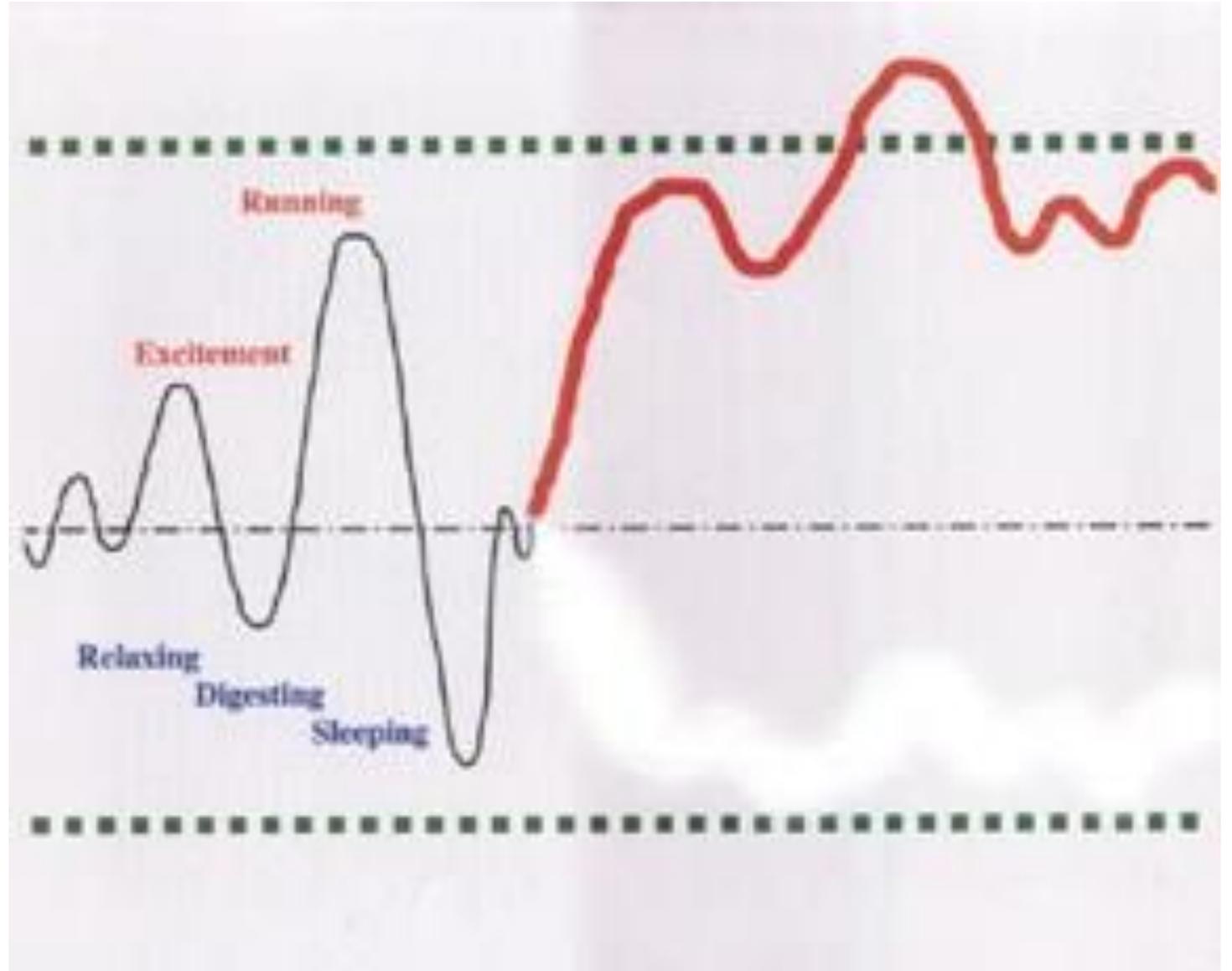
# Theories of pathophysiology in CRPS



- Sympathetic
- Neurological maladaptation
- Inflammatory
- Behavioral
- Primary bone disease

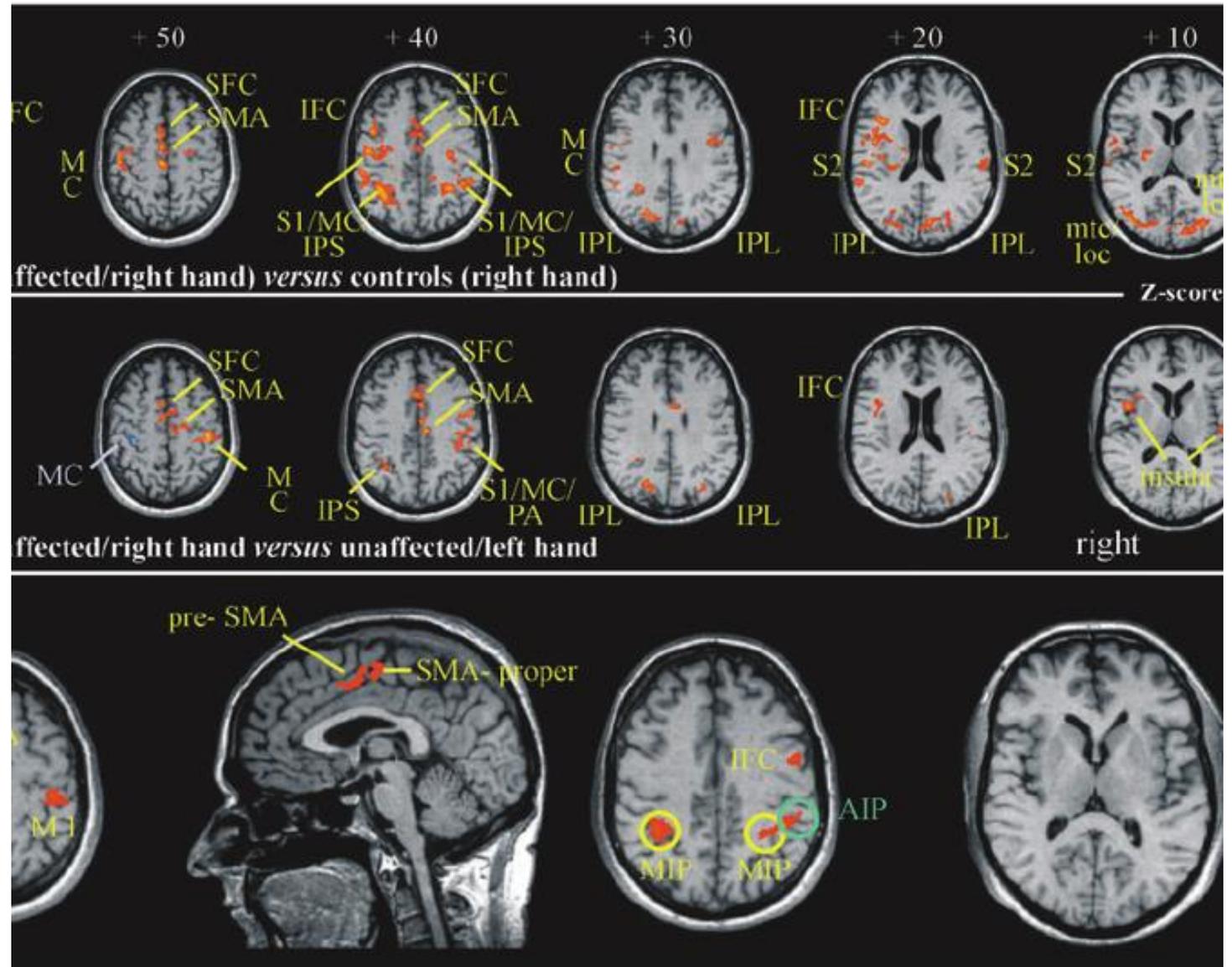
# Pathophysiology

- Autonomic dysregulation
- Distinct from autonomic dysreflexia
- Rationale for sympathetic blockade in CRPS
- Catecholamine levels **lower** in limbs with CRPS



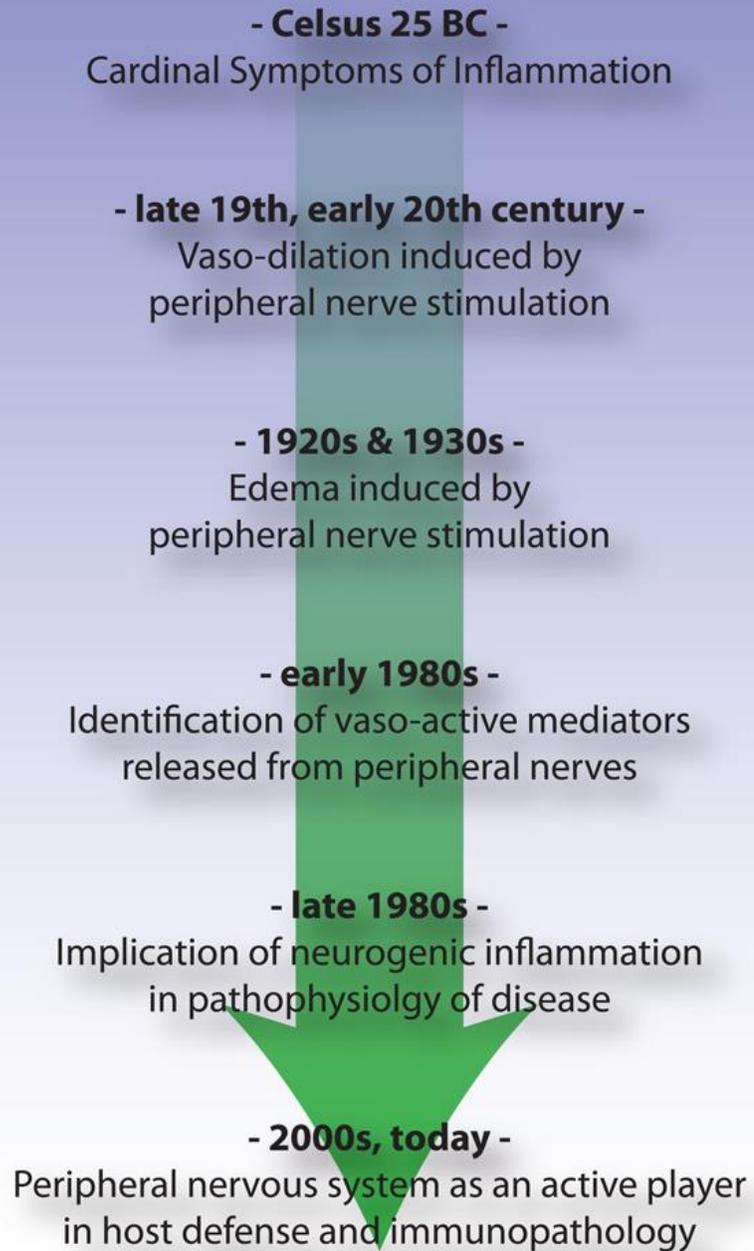
# Maladaptive Neuroplasticity

- Spinal—aka windup
  - Increased mRNA for alpha receptors in DRG following injury
- Brain—changes in cortical sensory areas and limbic areas



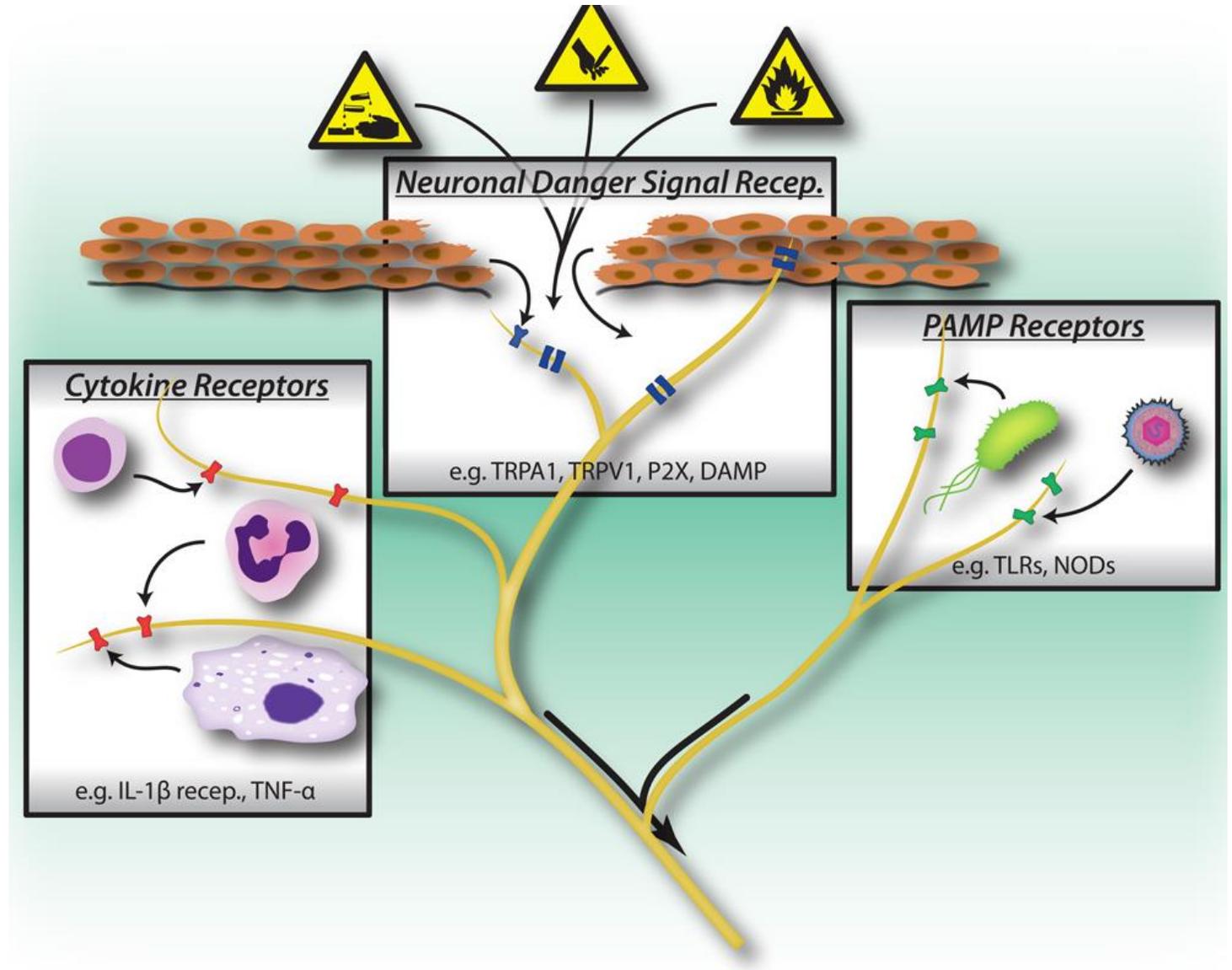
# Pathophysiology

## Aberrant inflammation



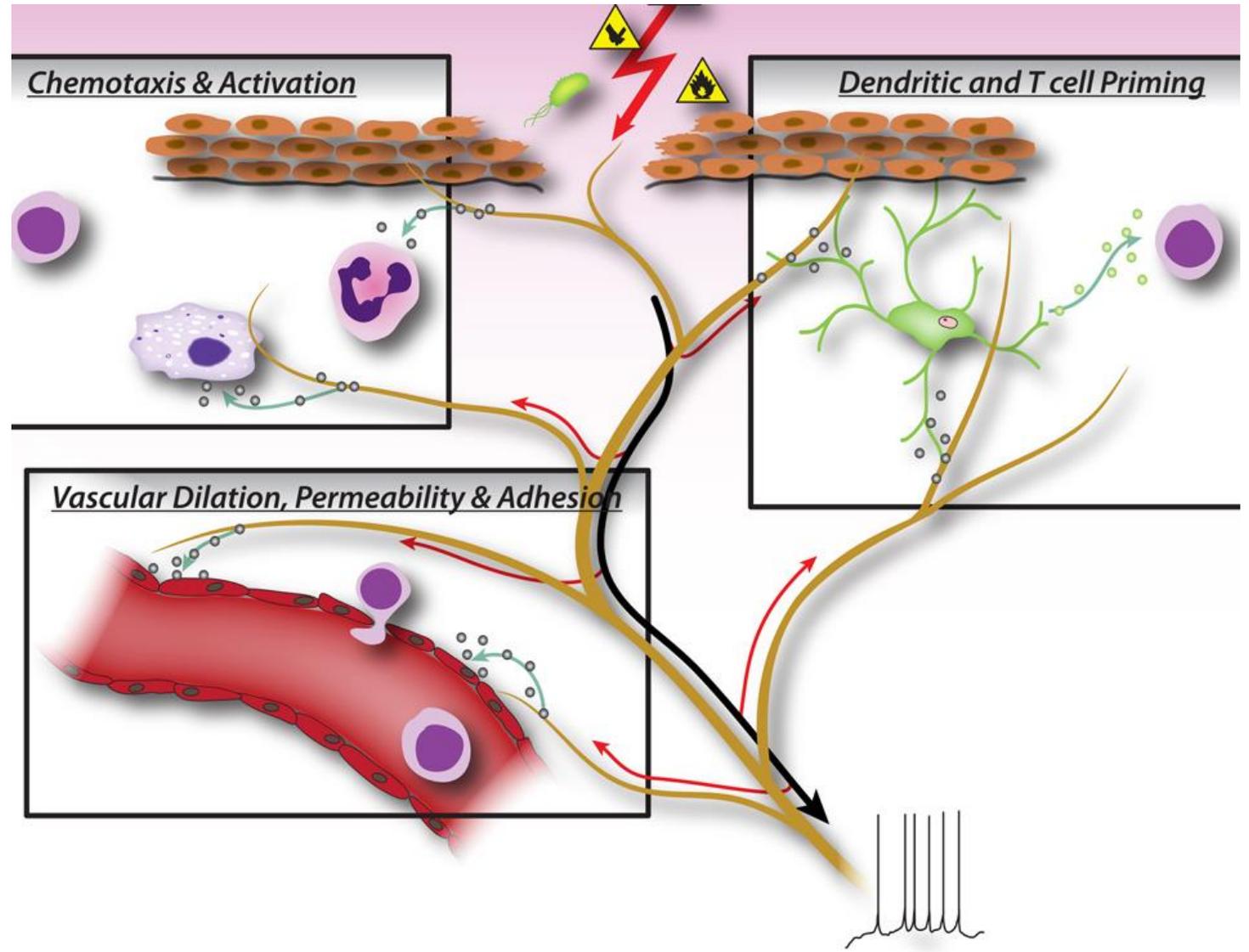
# Neurogenic Inflammation

- Nervous system and immune system are interconnected
- Rapid behavioral response to injury
- Rapid immune response to injury
  - Chiu Nature NS 2012



## Antidromic Actions— wound healing and immune defense

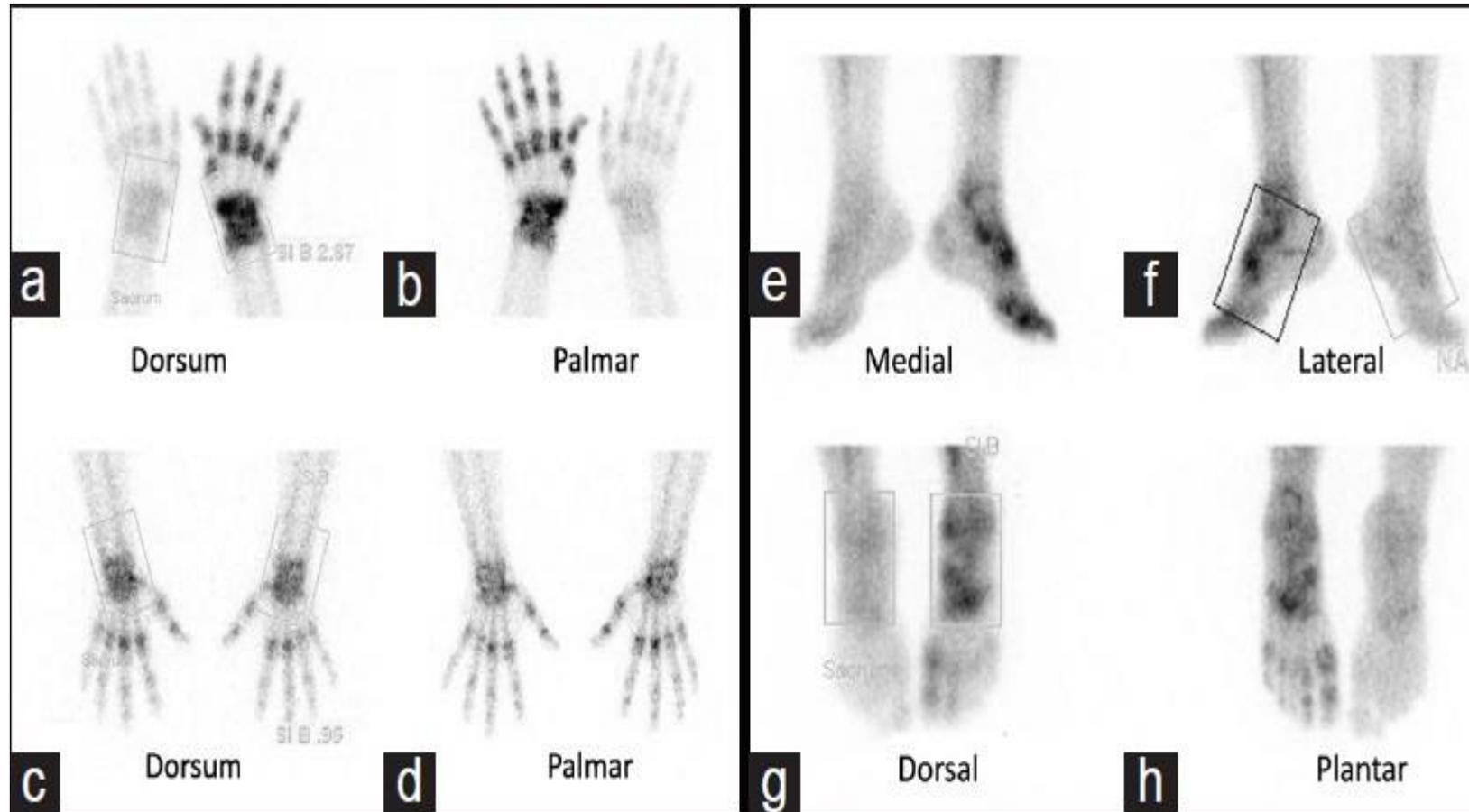
- **CGRP**—vasodilation
- **SP**—Increases capillary permeability and recruits immune cells
- Denervation of joint attenuates synovitis in RA
- Sensory neurons implicated in allergic pulmonary dz, colitis, psoriasis



# Diagnostic studies

- Blood tests—primarily to r/o alternative processes
- Xray—osteoporosis or periarticular bone loss
- Bone scan—specific pattern of periarticular uptake
- MRI—similar periarticular pattern of marrow changes
  - MRI may have higher sensitivity but lower specificity than bone scan

# Imaging studies



# Prevention

- Early mobilization—reduced incidence of CRPS after stroke
- Vitamin C 500mg/day for 50 days
  - Reduced incidence of CRPS following radial, foot and ankle fx
    - Zollinger
      - RCT after wrist fracture Lancet 1999
      - RCT and dose response study JBJS 2007

# Treatment of CRPS--Systematic Reviews

- Forouzanfar T, Köke AJ, van Kleef M, Weber WE. Treatment of complex regional pain syndrome type I. *Eur J Pain*. 2002. 6(2):105-22. [Medline].
- Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. *Pain*. 1997 Nov. 73(2):123-39. [Medline].
- Perez RS, Kwakkel G, Zuurmond WW, de Lange JJ. Treatment of reflex sympathetic dystrophy (CRPS type 1): a research synthesis of 21 randomized clinical trials. *J Pain Symptom Manage*. 2001 Jun. 21(6):511-26. [Medline].

# Treatment--corticosteroids

- Several low quality studies in 1970s and 1980s
- Suggest benefit within first 12 weeks of onset
- Unlikely benefit at later stages

# Treatment

- **Calcitonin**

- Goberlet Pain 1992

- **Bisphosphonates**

- Adami S, Fossaluzza V, Gatti D, Fracassi E, Braga V. Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. *Ann Rheum Dis*. 1997 Mar. 56(3):201-4. [Medline].
- Varenna M, Zucchi F, Ghiringhelli D, Binelli L, Bevilacqua M, Bettica P. Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome. A randomized, double blind, placebo controlled study. *J Rheumatol*. 2000 Jun. 27(6):1477-83. [Medline].
- Manicourt DH, Brasseur JP, Boutsen Y, Depreseux G, Devogelaer JP. Role of alendronate in therapy for posttraumatic complex regional pain syndrome type I of the lower extremity. *Arthritis Rheum*. 2004 Nov. 50(11):3690-7. [Medline].

# Treatment

- TCAs—no studies
- Opioids—no studies
- NSAIDs—no studies
- IV lidocaine—low quality studies
- Topical lidocaine—low quality studies
- Gabapentin—weak evidence for benefit
- Oral sympatholytics—case reports only
- Clonidine—weak evidence

# Sympathetic blocks

- Up to 70% of patients report some immediate relief
- Systemic review: “literature inadequate to draw any conclusions”
  - Cepeda MS, Carr DB, Lau J. Local anesthetic sympathetic blockade for complex regional pain syndrome, Cochrane Database Syst Rev. 2005. 4:CD004598.

# IV Regional Blocks

- Guanethidine—7 trials showed little analgesia
- Bretylium—one trial suggested superiority to lidocaine
- Droperidol, reserpine, atropine—no clear benefit

# IV infusions

## Ketamine

--2004 Uncontrolled study-- 76% of 33 patients improved

Correll GE. *Pain Med.* 2004 Sep. 5(3):263-75

--2009 60 patients five days IV ketamine v. placebo. No sustained difference  
in pain or improvements in function

Sigtermans MJ, *Pain.* 2009 Oct

--2009 RCT 10 days of iv ketamine vs. placebo showed improvement in pain  
parameters

Schwartzman T, *Pain.* 2009 Dec 15.

# Spinal Cord Stimulation

- Kemler —36 patients comparative study. Described improvement in pain and economic benefits at 6 mo and 1 yr.
  - NEJM 2000
- 3 year retrospective study of two different types of SCS systems in 101 patients suggests that newer systems may offer more benefit.
  - **Poree** L, Krames E, Pope J, Deer TR, Levy R, Schultz L. Spinal cord stimulation as treatment for complex regional pain syndrome should be considered earlier than last resort therapy. *Neuromodulation*. 2013

# Psychological Interventions

- Single blind study of CBT resulted in significant improvements in pain and function in both adults and children
  - Lee BH, Scharff L, Sethna NF, McCarthy CF, Scott-Sutherland J, Shea AM. Physical therapy and cognitive-behavioral treatment for complex regional pain syndromes. *J Pediatr.* 2002 Jul. 141(1):135-40.
- Graded exercise and exposure to movement therapy resulted in reduced pain and pain-related disability
  - de Jong JR, Vlaeyen JW, Onghena P, Cuypers C, den Hollander M, Ruijgrok J. Reduction of pain-related fear in complex regional pain syndrome type I: the application of graded exposure in vivo. *Pain.* 2005 Aug. 116(3):264-75

# Physical therapy

- Patients with better pain control and support are more likely to benefit from therapy
- Sustained attention to injured limb may be part of maladaptive process.
- Protocol involving mirror therapy, motor planning activities reduced disability in CRPS
  - Moseley CL. Is successful rehabilitation of complex regional pain syndrome due to sustained attention to the affected limb?. *A randomised clinical trial, Pain.* 2005. 114:54-61.



# Treatment Recommendations—L&I 2011

- Treatment should include elements of the following:
- Physical therapy (PT) or occupational therapy (OT)
- Medication for pain control
- Psychological or psychiatric consultation and therapy
- Sympathetic blocks
- Multidisciplinary Program for Pain Management

# 2011 L&I Guideline

- The Department will not authorize the following interventions for CRPS:
- Sympathectomy--no effect/no improvement in function
- Spinal cord stimulation non-covered benefit; see Health Technology Assessment2010:[http://www.hta.hca.wa.gov/documents/adopted\\_findings\\_decision\\_scs\\_102510.pdf](http://www.hta.hca.wa.gov/documents/adopted_findings_decision_scs_102510.pdf) )
- Ketamine infusions --no effect/no improvement in function, serious adverse events

# Treatment Principles WA LNI Guideline



- 1. Establish an early and accurate diagnosis
- 2. Exclude common masquerading conditions
- 3. Avoid over diagnosis
- 4. Evaluate whether patient is recovering normally
- 5. Refer to specialty care early if CRPS suspected or patient is not recovering normally.