CRPS-I: PREVENTION OF CHRONIC PAIN

Anne Louise Oaklander MD PhD

Departments of Neurology and Pathology, Mass. General Hospital & Harvard Medical School

Funded by NINDS (R01NS42866, R01NS052754, K24NS059892), RSDSA, Mayday Fund, nonprofit foundations and grateful patients

No commercial sponsors, no conflicts of interest

Lab contributors:

Julia Rissmiller MD, Lisa Gelman MD, Jennifer Brown MD, Isabelle Decosterd MD, Ralph Gott MS, Isin Unal-Cevik MD PhD, Sandra Siegel PhD, David W. Chen, MD, Jeung Woon Lee PhD, Ezekiel Fink, MD, Heather Downs BS

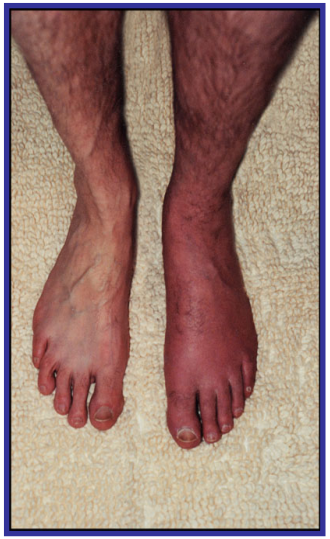
Complex Regional Pain Syndrome (CRPS)

1994 IASP Diagnostic Criteria:

1. A noxious event or cause of immobilization
2. Continuing or disproportionate pain, allodynia, or hyperalgesia
3. Edema, changes in skin blood flow, or abnormal sweating in the region of pain at some time in course
4. No other condition that could otherwise account for this degree of pain and dysfunction

CRPS-II refers to patients with known nerve injury (replaces causalgia)
CRPS-I refers to patients without known nerve injury (replaces reflex sympathetic dystrophy)
The phenotype is the same, the response to treatment is the same

Merskey H, Bogduk N eds. IASP Press, 1994



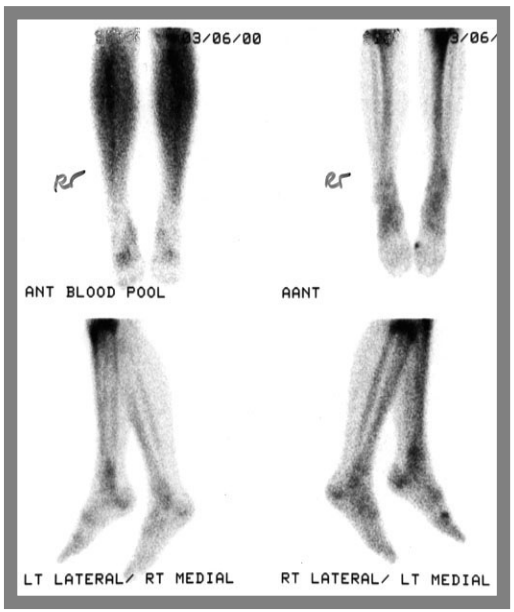
CRPS is a "pain plus" syndrome that affects the originally injured limb

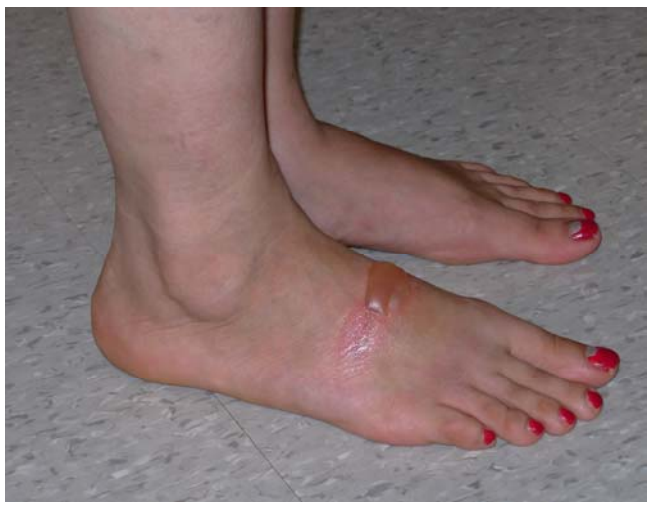
Signs and symptoms worse distally

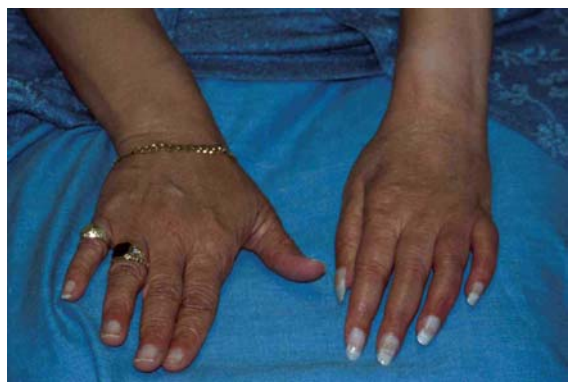
Microvascular dysregulation causes color and temperature asymmetry, edema

May have focal bone bone and joint changes

May have changes in muscle, skin, hair, nails



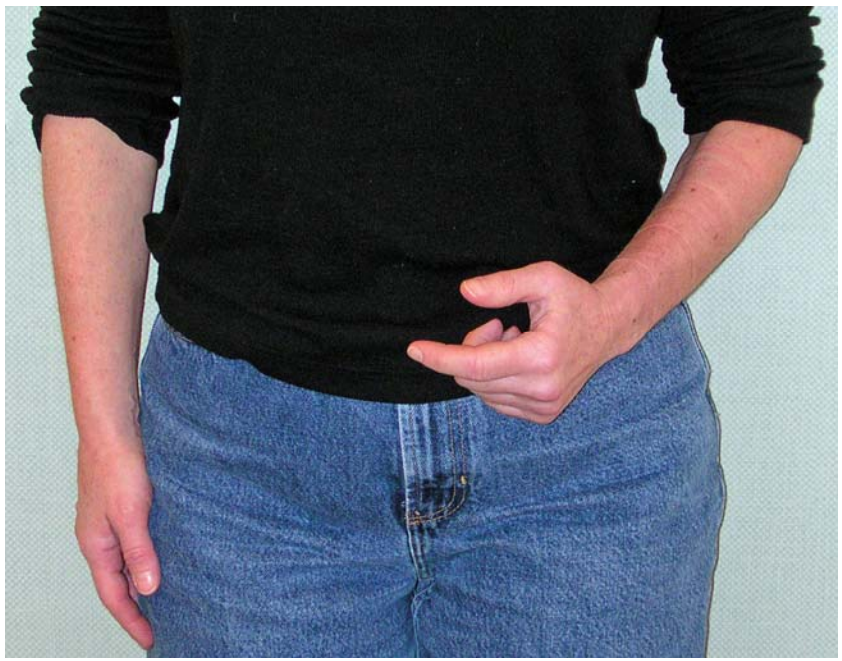




Some CRPS patients have movement disorders

Distal tonic dystonia is common

Strong female predominance among CRPS/dystonia patients



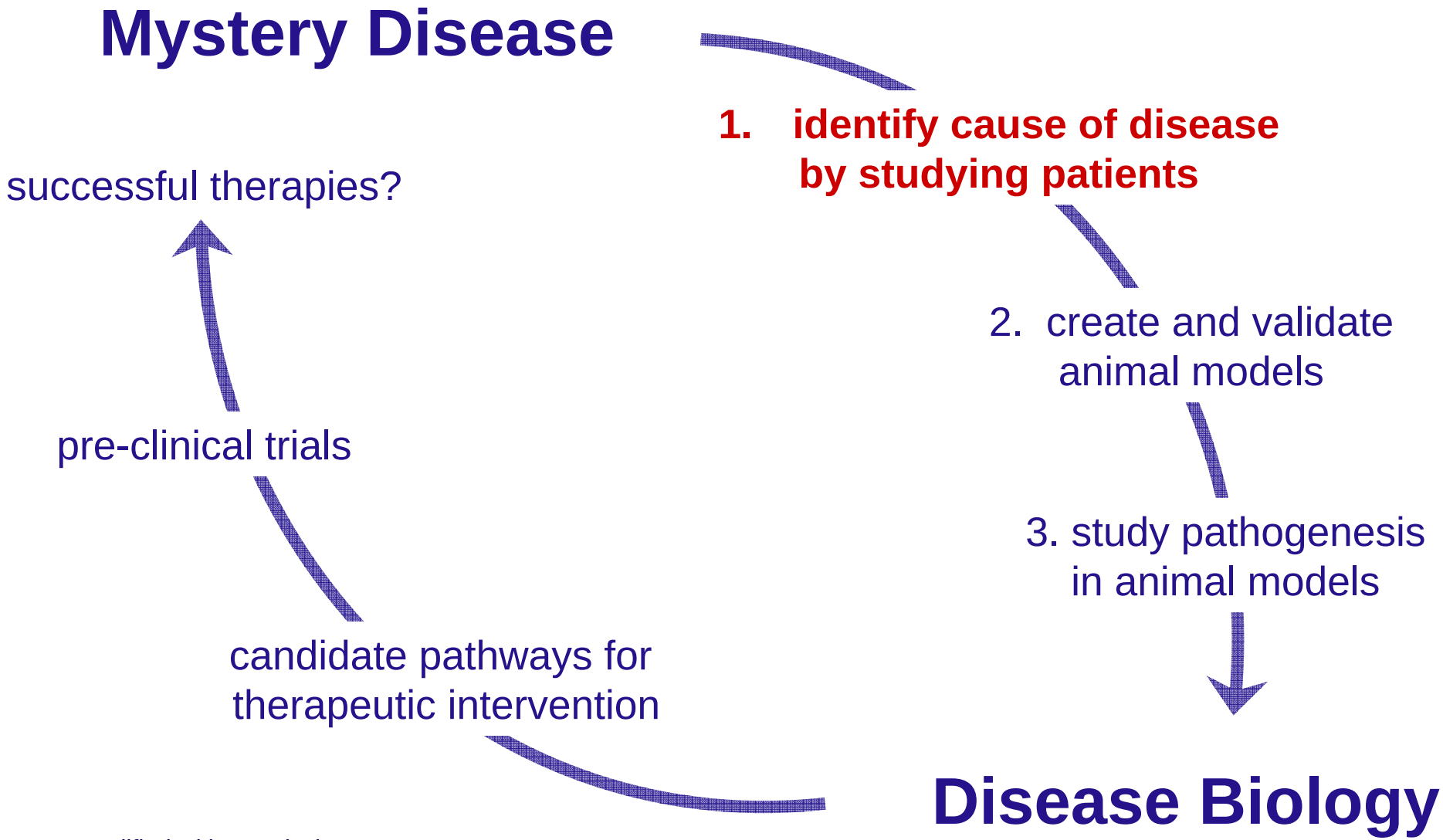
Also weakness, muscle atrophy tremor, incoordination

CRPS epidemiology

- **CRPS is a rare complication of trauma**
- **Rare in the elderly**
- **Strong female predominance (75-80%)**
- **Limb fractures a common cause**
  30% of Colles wrist fractures or tibial fractures develop CRPS
- **Evidence does not support consecutive phases** (Veldman 1993)
- **Children and teenagers almost always recover (Berde, Wilder)**
- **"Classical" cases are the most severe end of a spectrum. Mild cases are common in the community; and often resolve on their own (Sandroni 2003)**

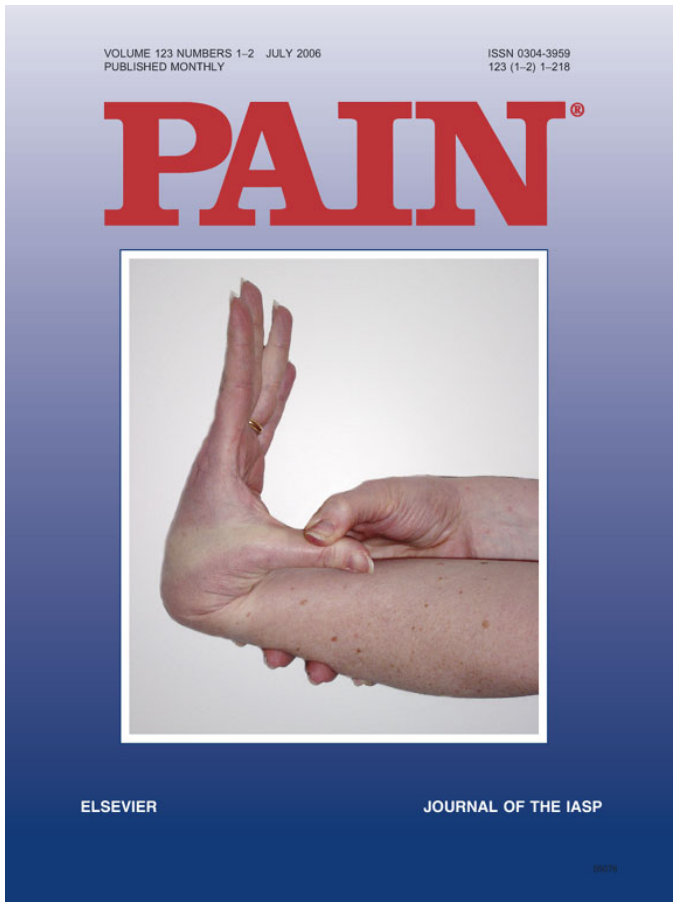
CRPS long viewed as a “Mystery Disease”

- Ill-defined constellation of symptoms
- Diverse causes – mostly traumatic
- No clear pathology or pathophysiology
  Thought psychogenic by many, even today
- Symptom relief only treatment option, elusive
- No FDA-approved drugs for CRPS
- No pharmaceutical-sponsored or large trials



modified with permission
from H. Zoghbi

Genetics: CRPS is a complex disorder



HLA-DQ1 associated with CRPS-I
(van de Beek, 2000)

CRPS-I associated with Ehlers-Danlos, a collagen mutation that causes joint hyperflexibility
(Stoler & Oaklander, 2006)

EDS patients may have more trauma, more surgeries, nerves more vulnerable to stretch, penetration

Can GWAS provide target leads?

- CRPS is a complex disease (genes + environment)
- Strong environmental influence (injury) obscures genetic influence
- Clear genetic risk for post-traumatic neuralgia
- Devor, Evidence for heritability of pain in patients with traumatic neuropathy PAIN, 2004
- Rare and usually transient phenotype – not enough patients
- Phenotyping difficult – no definition, no tests, no markers

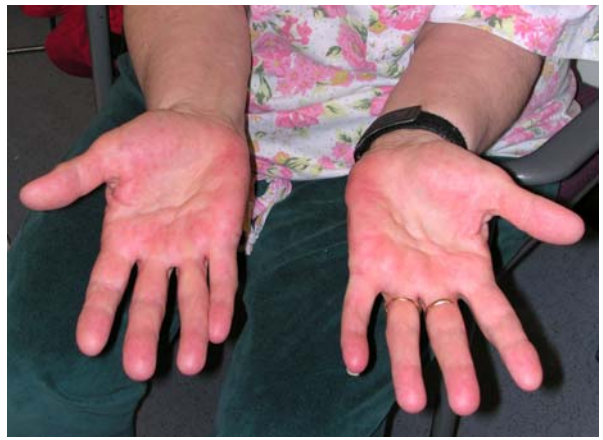
New EMR epidemiology is more useful

- **Retrospective** EMR study of 600,000 Dutch patients found incidence 26.2 per 100,000 person/years (4x higher than Mayo study). Sex ratio of 3.4:1 and fracture as most common precipitant (44%)
  de Mos et al, PAIN 2007

- **Prospective** EMR study of comorbidities prior to CRPS onset linked CRPS with nerve injury, asthma, migraine, osteoporosis, NOT with somatization or psychiatric disease
  de Mos et al, PAIN 2008

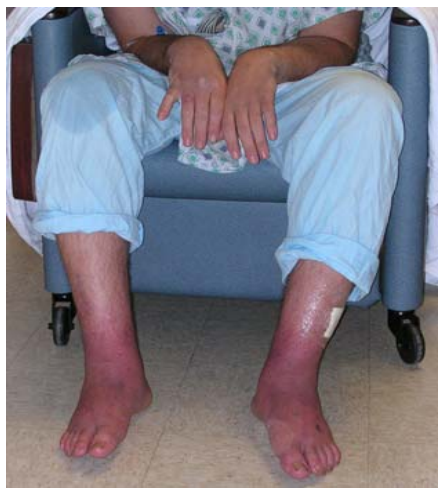
CRPS-I likely a small-fiber predominant nerve injury

- Small-fiber polyneuropathies cause CRPS-like phenotype
- Same phenotype caused by nerve injuries in CRPS-II
- Neuro exam of CRPS-I patients usually reveals nerve injuries



Novak, Autonomic impairment in painful neuropathy *Neurology*, 2001

Adult onset erythromelalgia: the small-fiber polyneuropathy phenotype that most resembles CRPS Oaklander, Anesthesia & Analgesia, 2007



Why might nerve injuries go unrecognized in CRPS-I?

- CRPS patients not examined by nerve specialists
  - de Mos, Referral and treatment patterns for complex regional pain syndrome in the Netherlands. *Acta Anaesthesiol.Scand.*, 2009
- Injuries to small-fibers difficult to diagnose
  - Do not cause weakness, muscle atrophy, or reduced reflexes
  - EMG/NCS do not detect small fiber function
  - Function usually preserved after partial nerve injuries
- Patients with other diseases are commingled
  - Inflammation/infection (eg cellulitis)
  - Small-fiber polyneuropathies
  - Peripheral arterial disease
  - Deep vein thrombosis
  - Plexopathy

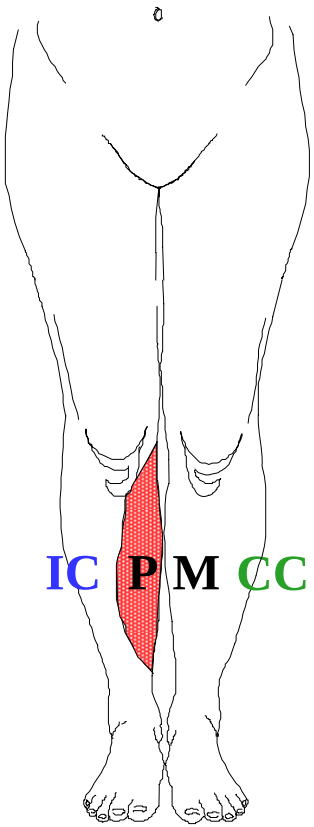
Pathological study of CRPS-I tissues shows chronic subtle axonal degeneration, worse in small-fibers

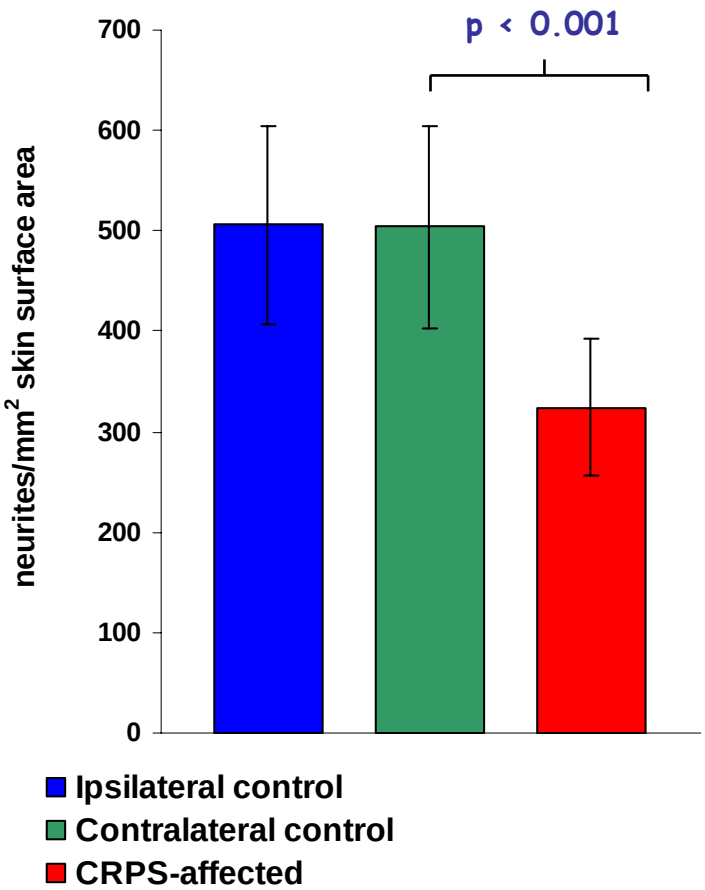
van der Laan, et al.
Complex regional pain syndrome type I (RSD): pathology of skeletal muscle and peripheral nerve. *Neurology*, 1998

Albrecht, et al.
Pathologic alterations of cutaneous innervation and vasculature in affected limbs from patients with complex regional pain syndrome. *PAIN*, 2006

Oaklander, et al.
Evidence of focal small-fiber axonal degeneration in complex regional pain syndrome-I (reflex sympathetic dystrophy). *PAIN*, 2006

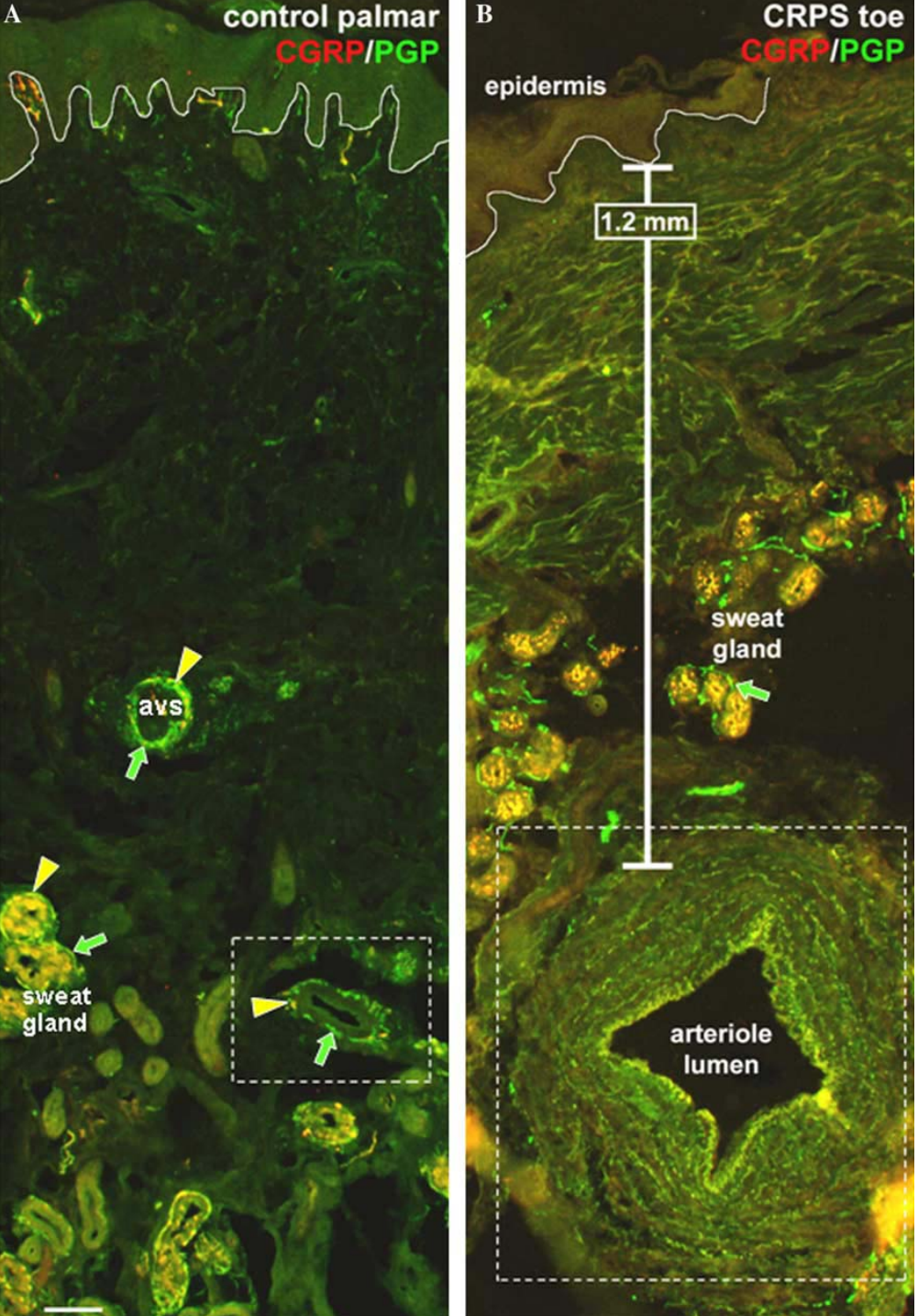
PGP9.5^{+} skin biopsies from 18 CRPS-I patients showed 29% fewer small-fiber nerve endings in painful CRPS-affected area





Oaklander et al. PAIN, 2006

A control group of 7 symptom-matched osteoarthritis subjects who also had severe leg pain, edema, and disuse had no IENF loss, suggesting specific association with CRPS



- Study of skin from amputated limbs of 2 end-stage patients
- Sweat glands and blood vessels are denervated and hypertrophied in CRPS-I skin
- Similar to changes seen in diabetic small-fiber polyneuropathy
- Likely causes other CRPS symptoms

Albrecht et al, PAIN, 2006

Trauma seems to sometimes preferentially damage small nociceptive axons

- **Lack of myelin and saltatory conduction increases axonal energy needs**

- **Thin axons have high surface to volume ratio more axolemma, less axonal transport**

Sciatic transection in adult rats causes death of 37% of DRG cells by 32 weeks. Loss is earlier in and more severe in small, dark cells with unmyelinated axons than in large, light cells with myelinated axons
Tandrup et al. *J Comp Neurol, 2000*

Cutting or crushing rat sciatic nerve does not reduce myelinated sensory axons in dorsal roots ... Unmyelinated axons were reduced by 50%
Coggeshall et al. *Neuroscience*, 1997

Chronic CRPS may have different mechanisms than early CRPS

- Neurogenic microvascular dysregulation can cause chronic distal limb (and nerve) ischemia
- Injury to primary afferents triggers secondary changes in post-synaptic targets and network, including cortical plasticity
- Tertiary patient changes – inactivity, deconditioning, disuse and neglect syndrome, depression, poverty

3 opportunities to prevent chronic CRPS

A. Preventing the original trauma
   Preventing added iatrogenic trauma
   - Unnecessary surgeries (knee arthroscopy)
   - Tight casts, IVs, needlesticks

C. Preventing trauma/nerve injury from triggering early CRPS

D. Secondary intervention with disease-modifying treatment to prevent early CRPS from lingering into chronic CRPS

A few small placebo-controlled trials for early CRPS suggest disease-modifying effect, steroid trials have the best results of any

Treatment	Efficacy	Trial (methods score)
Oral corticosteroids	Yes	Christensen, 1982 (71),
	Yes	Braus et al., 1994 (51)
Calcitonin	Yes	Gobelet et al., 1992 (80)
	No	Bickerstaff, 1991 (82)

Supportive, non-placebo controlled trials of bisphosphonates, free-radical scavengers (including vitamin C)

from: Kingery, A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. *Pain* 73, 1997

Small, placebo-controlled trials of interventional treatments mostly negative, mean duration 3.5 weeks

Drug	Route		Trial (methods score)
Guanethidine	Intravenous regional block	Yes	Glynn et al., 1981 (54)
		No	Rocco et al., 1989 (68),
		No	Blanchard et al., 1990 (71),
		No	Jadad et al., 1995 (68),
		No	Ramamurthy et al., 1995 (83)
Reserpine	Intravenous regional block	No	Rocco et al., 1989 (68),
		No	Blanchard et al., 1990 (71)
Droperidol	Intravenous regional block	No	Kettler, Abram, 1988 (44)
Atropine	Intravenous regional block	No	Glynn et al., 1993 (72)
Bretylium	Intravenous regional block	Yes	Hord et al., 1992 (57)
Ketanserin	Intravenous regional block	Yes	Hanna and Peat, 1989 (48)
	Intravenous	No	Bounameaux et al., 1984 (45)
Clonidine	Epidural	Yes	Rauck et al., 1993 (59)
Phentolamine	Intravenous	Yes	Raja et al., 1991 (41)
		No	Verdugo, Ochoa, 1994 (52)

from: Kingery, A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. *Pain* 73, 1997

When to consider disease-modifying treatments

1. **Use immediately post-trauma after high-risk traumas (eg radial head fx)**

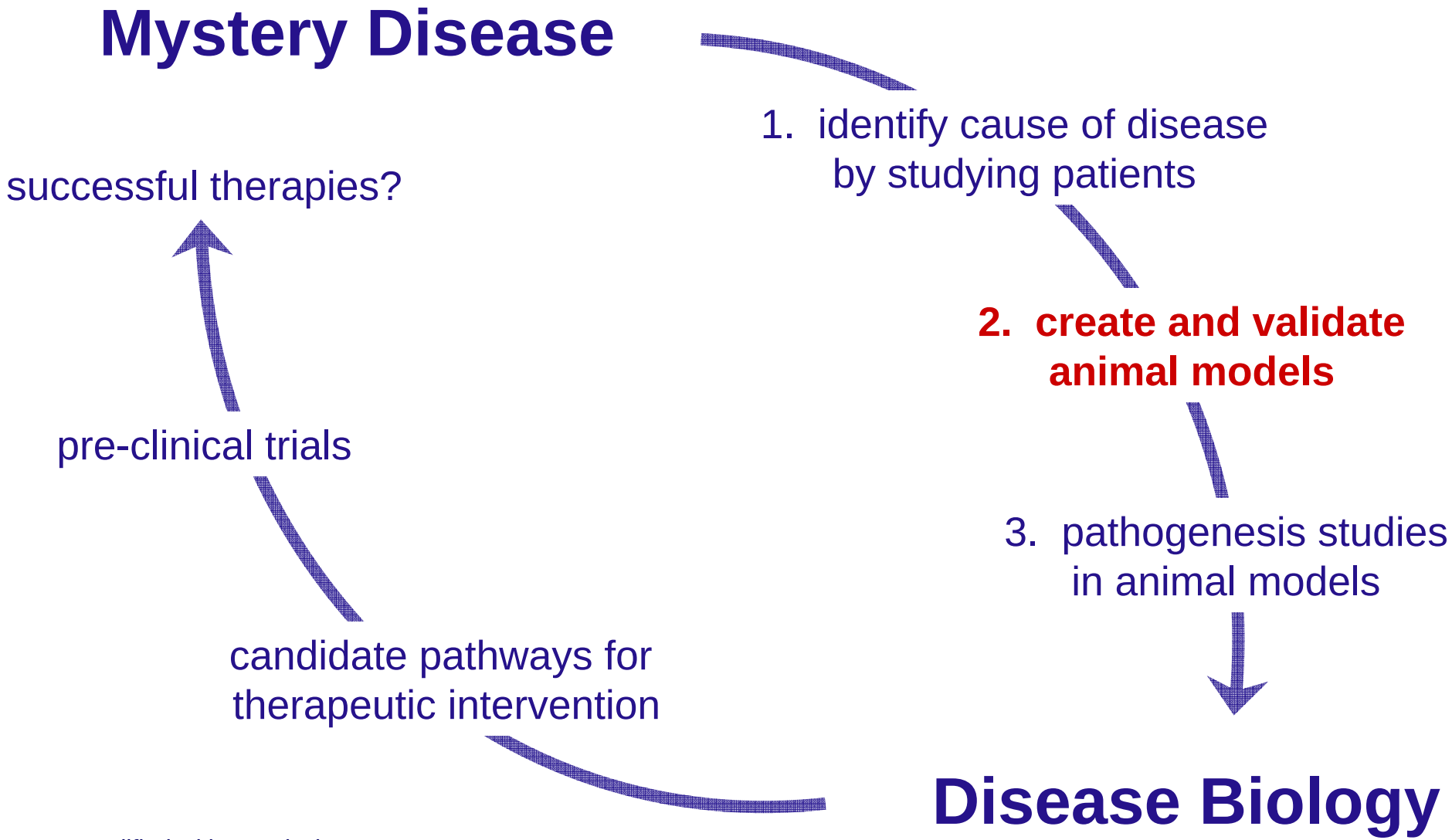
2. **Use immediately post-trauma to high-risk patients (need to define)**

3. **Use within first weeks after trauma to patients with early CRPS to reduce risk of prolonged CRPS**

   D. Bowsher. The effects of pre-emptive treatment of postherpetic neuralgia with amitriptyline: a randomized, double-bind, placebo-controlled trial. *J Pain Symptom Manage* 13:, 1997

4. Use in patients with chronic CRPS to speed healing

They may not be drugs (rehabilitation, neural stimulators, mirror therapy, hyperbaric oxygenation)



modified with permission
from H. Zoghbi

3 animal models of CRPS-I based on different CRPS causes:

Chronic post-ischemia pain (CPIP)

Coderre, Xanthos, Francis, Bennett, PAIN, 2004

O-ring on hindlimb of anesthetized rat for 3 h causes severe distal ichemia. Pain behaviors last at least 4 weeks in 70% of CPIP rats.

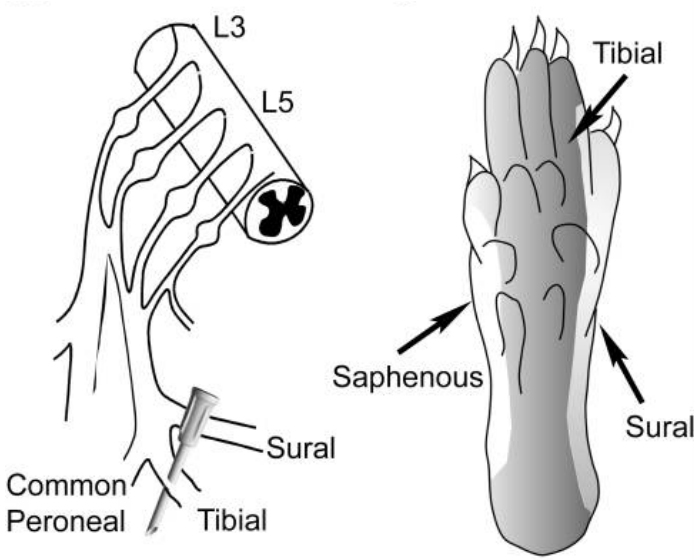
BUT all axons below o-ring degenerate, does not model partial axonal losses of CRPS-I patients

Kingery rat tibia-fracture model *PAIN*, 2008

Tibia fracture and 4 weeks of casting causes hindpaw warmth, edema, allodynia, and regional osteopenia. It causes primary sensitization, up-regulates local NGF, neuropeptide, and cytokines, and spinal cord Fos

BUT this lesion does not reduce hindpaw innervation, does not model partial axonal losses of CRPS-I patients

Needlestick DNI:



We injure one distal sciatic branch with a single needlestick

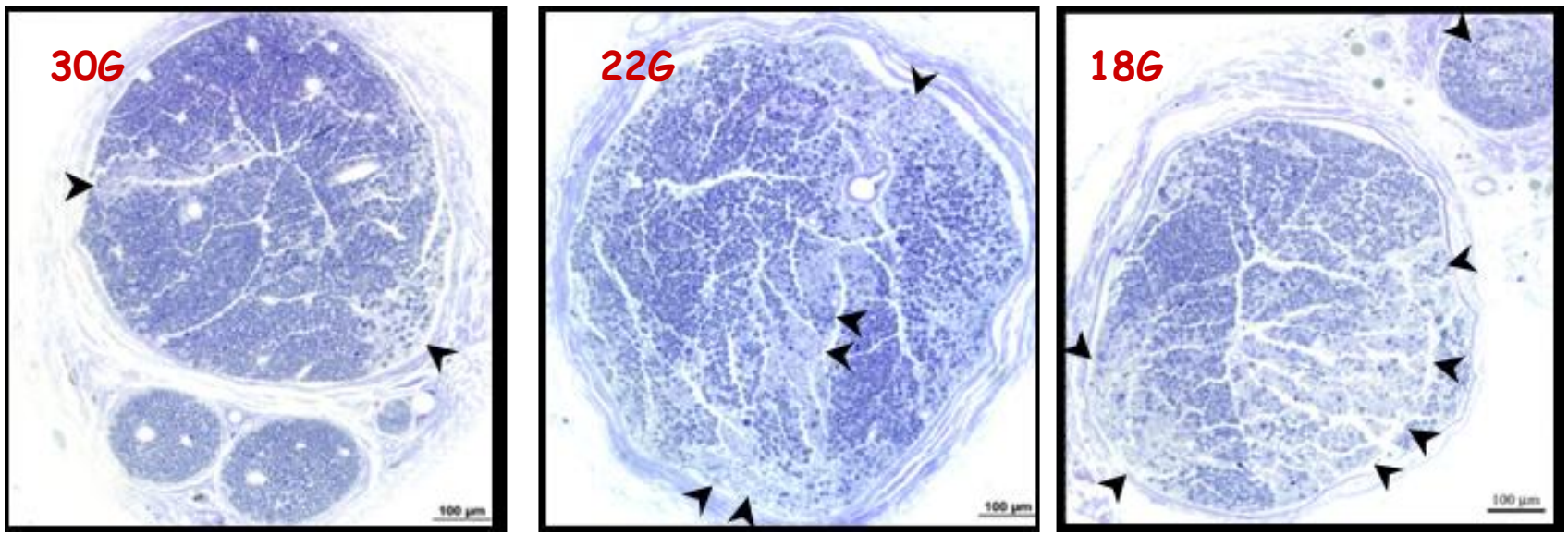
Pre-mortem: **pain behaviors** measured on plantar hindpaws

Post-mortem: **tissues** gathered for biological testing

Half of rats develop long-lasting CRPS-like phenotype, half recover quickly from surgery (normal phenotype)

Anesthesia & Analgesia, 2007

Severity of distal axonal loss after 18g needlestick closely models the 29% average epidermal axon losses of CRPS-I patients



Skin from ipsilesional hindpaw shows mean loss of PGP9.5^{+} axons:

0% after 30G-needlestick

15% after 22G-needlestick

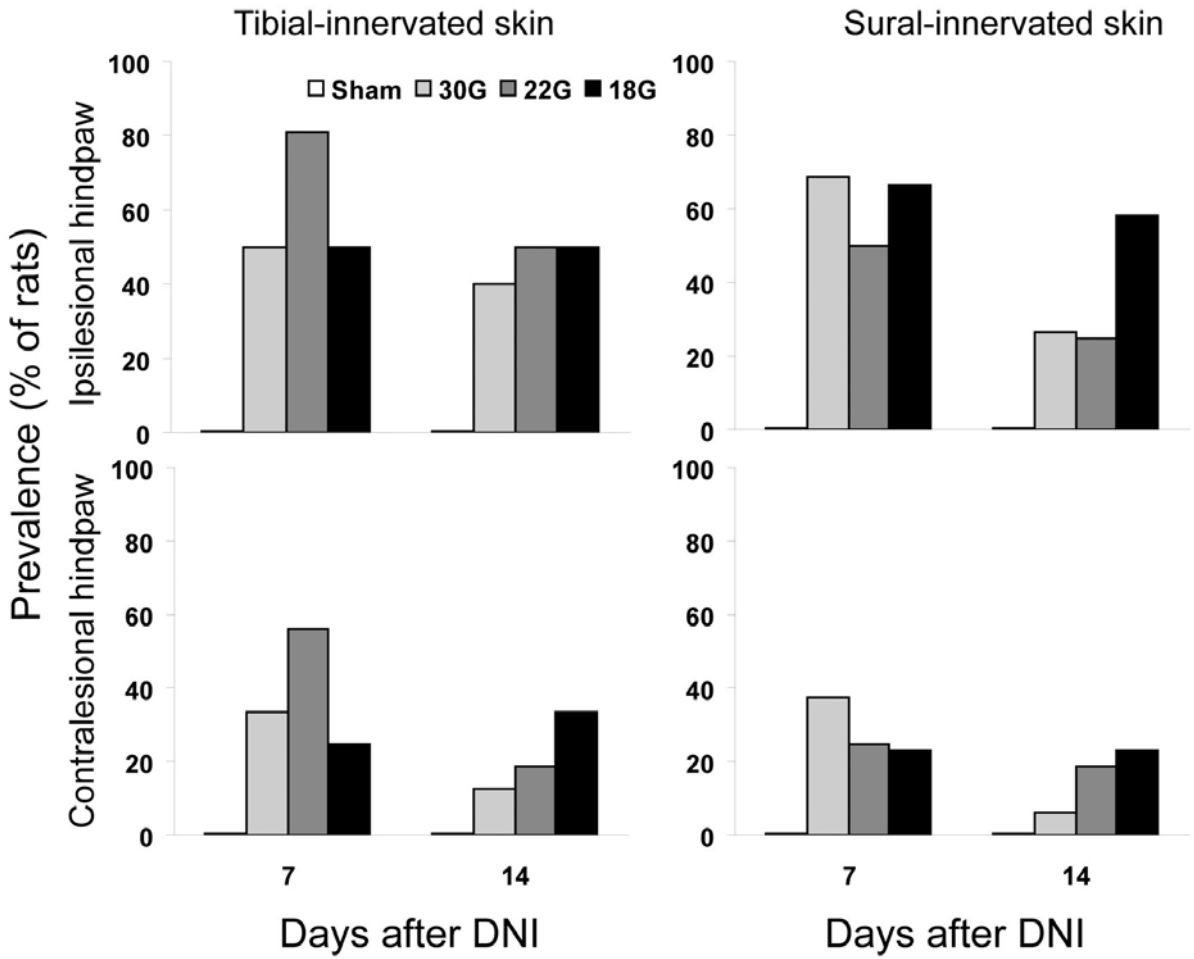
26% after 18G-needlestick

Anesthesia & Analgesia, 2007

Risk of developing evoked pain after needlestick is independent of lesion size

One tibial-nerve needlestick can cause hindpaw mechanical allodynia (≥ 51% drop in vF threshold)

Allodynia develops intraterritorially, extraterritorially, contralesionally

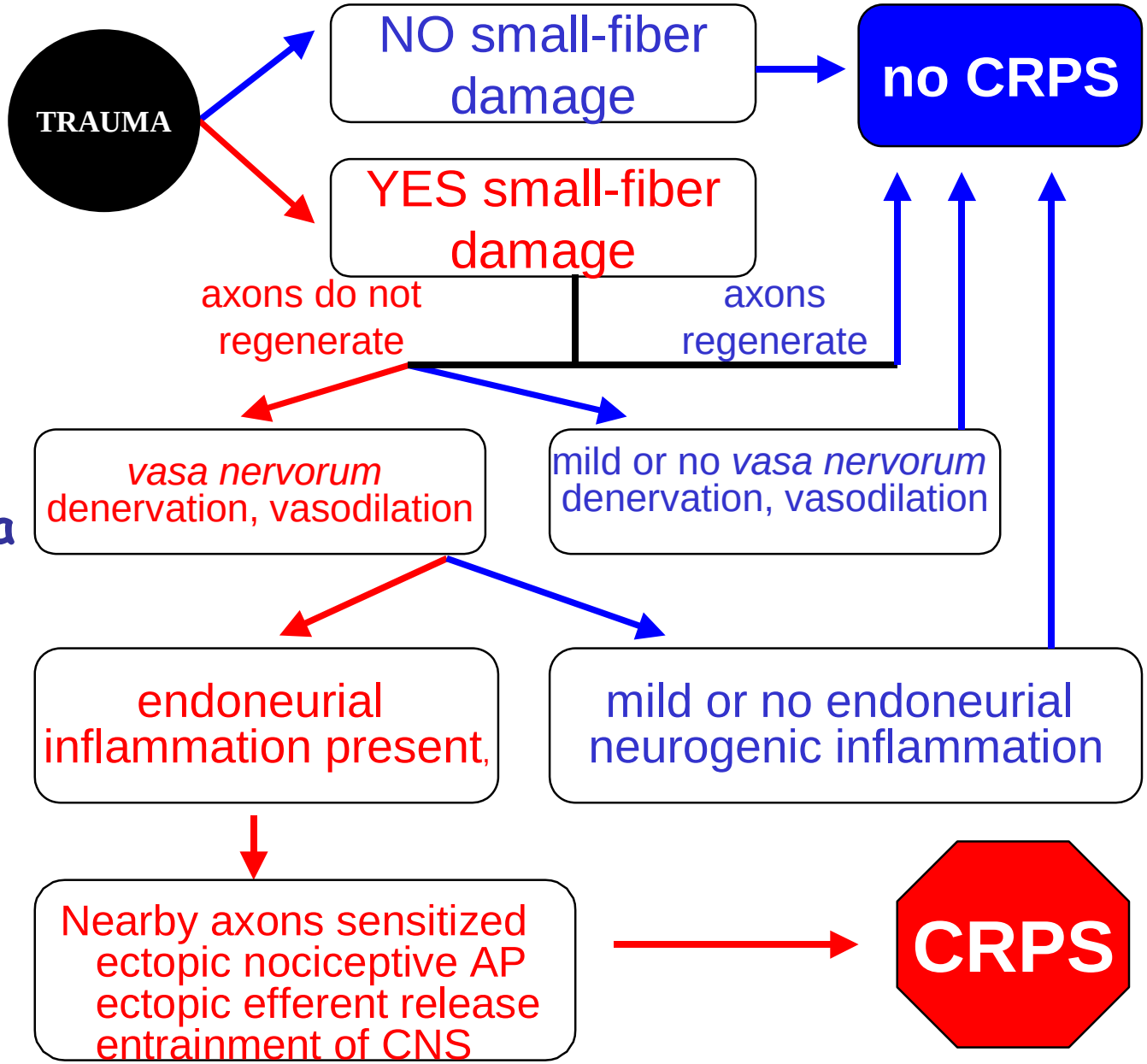


Anesthesia & Analgesia, 2007

CONCLUSION:

Development of CRPS-I may require several "hits"

Neurogenic edema and inflammation within injured nerves may help magnify DNI into CRPS



Consider pooling CRPS and PTN for clinical trials

- CRPS microvascular dysregulation fluctuates from day to day and hour to hour
- CRPS regresses through PTN during healing
- Patients with PTN and CRPS respond to the same treatments
  Rehab, medications and augmentative neurostimulation
- Consider classifying CRPS a "pain-plus" syndrome where patients may need treatment for neuralgia + other problems

Autoimmunity - A new player in CRPS?

- CRPS rare in elderly (c/w natural history of resolution)
  elderly have reduced inflammatory response
- 75-80% female sex ratio
  women more prone to autoimmunity
- Comorbidity with asthma
- Limited evidence of autoantibodies against PNS in CRPS patients
  Blaes, Autoimmunity in complex-regional pain syndrome. *Ann N Y.Acad.Sci*, 2007
- Corticosteroids effective in aborting chronic CRPS, what about NSAIDS?

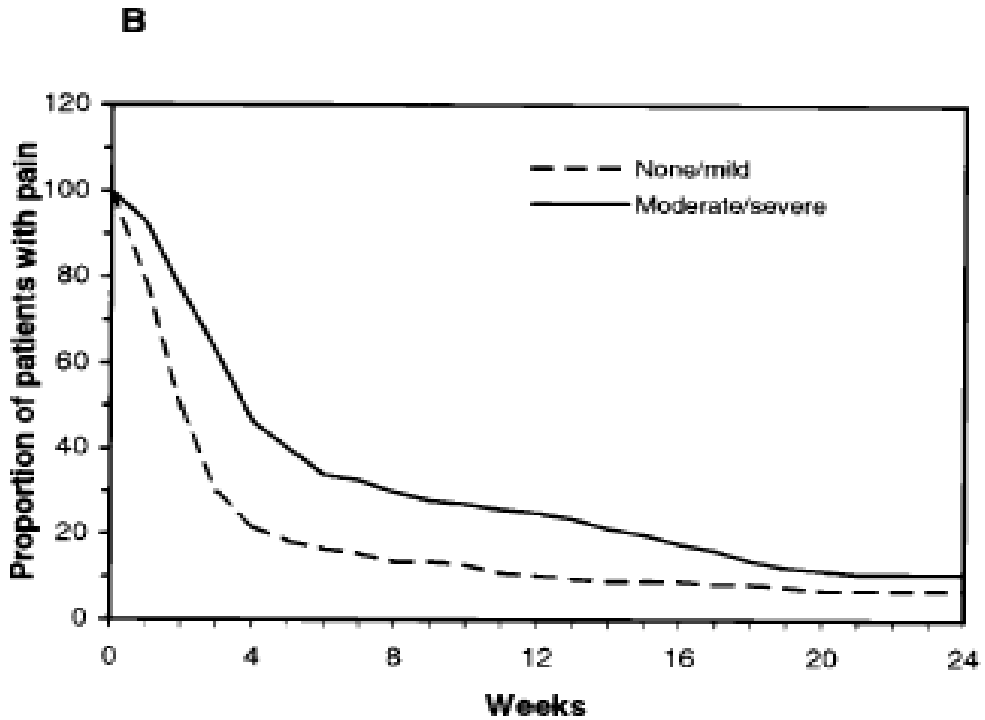
Consider removing blockers of normal healing

- Children under age 5 do not develop neuropathic pain after nerve injuries **ADD CITATION;** older kids and teens develop acute but not chronic CRPS
- We evaluate non-recovering CRPS patients to find out why
  - FOCAL INHIBITORS
    - nerve ischemia from microvascular dysregulation
    - ongoing nerve compression, traction, aberent regeneration (neuroma)
  - SYSTEMIC INHIBITORS
    - of vascular perfusion (SMOKING, atherosclerosis) Tesfaye NEJM 2005
    - of axonal regeneration (DM, thyroid, vit deficiency or excess, hep C)
- We encourage use and rehabilitation
  - To help reverse cortical plasticity
  - To lessen secondary sources of pain; deconditioning, obesity, depression
  - To improve perfusion of damaged tissues and nerve

CRPS (and PTN) are monophasic insults that usually resolve on their own, like shingles Why? Strong evolutionary pressures against pain persistence after injury

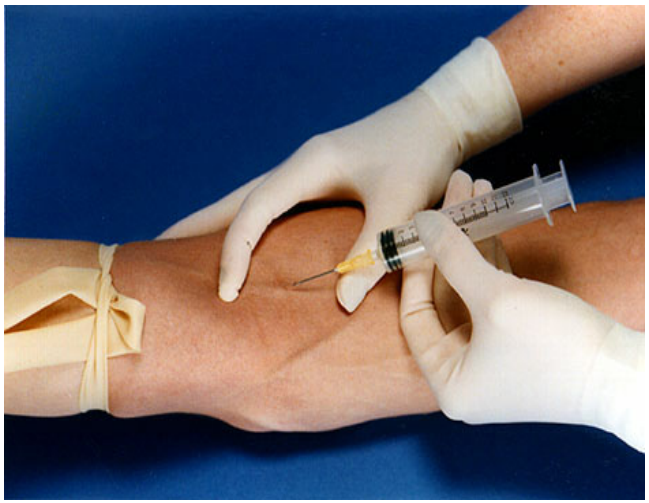
- A 33-year old subject with CRPS for almost 5 months had severe pain and IENF loss (3% of control).
- She requested re-biopsy 9 months later for symptom resolution; this showed recovery of IENF to 95% of control, raising the question of whether recovery from CRPS is associated with successful axonal regeneration

Oaklander, PAIN 2006



Whitley RJ, J Infectious Diseases, 1998

Best CRPS research subjects: Needlestick



Horowitz. Venipuncture-induced causalgia: anatomic relations of upper extremity superficial veins and nerves, and clinical considerations. *Transfusion*, 2000

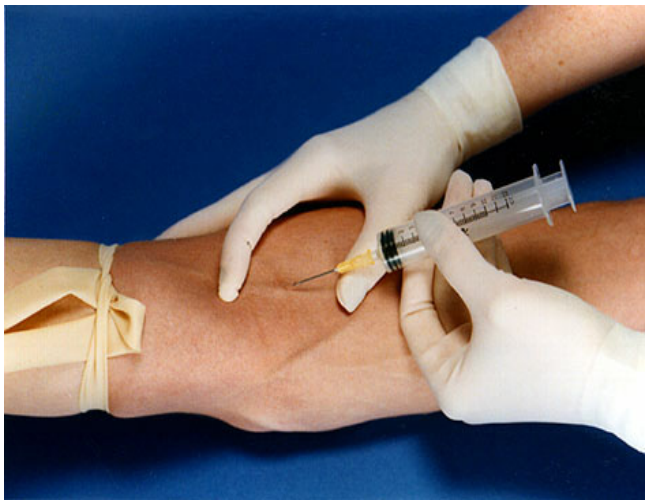
Horowitz. Venipuncture-induced neuropathic pain: the clinical syndrome, with comparisons to experimental nerve injury models. *Pain*, 2001

Horowitz. What happens when cutaneous nerves are injured during venipuncture? *Muscle Nerve*, 2005.

- Stereotyped location - medial or lateral cutaneous nerve of forearm
- Stereotyped wound – needle diameter
- Stereotyped effect - only axotomy
- Samples entire population
- Samples mostly healthy people without pre-procedure pain
- Definite time of onset
- Normal phenotype is no pain; abnormal phenotype easy to define
- Highly organized collaborative group already established (Red Cross)
- Patients seeking treatment, available for treatment trials
- Subjects have already donated DNA!
- Models many iatrogenic and military injuries
- Rodent model already established

Siegel, Needlestick distal nerve injury in rats models symptoms of complex regional pain syndrome. *Anesth Analg*, 2007

Drawbacks of needlestick nerve-injury model



Newman & Waxman. Blood donation-related neurologic needle injury: evaluation of 2 years' data from a large blood center. *Transfusion*, 1996

Newman. Venipuncture nerve injuries after blood donation. *Transfusion*, 2001

Newman, et al. Adverse effects in blood donors after whole-blood donation: a study of 1000 blood donors interviewed 3 weeks after whole-blood donation. *Transfusion*, 2003

- A rare lesion; in 1/6300 blood donations (patients who filed reports)
- Most injuries mild, may not meet full CRPS criteria
- Rapid recovery for most

- Politically difficult; Red Cross adverse to publicizing complications

Summary of new CRPS science

- CRPS has gone from "mystery pain" to predominantly neuropathic pain
- Evidence of distal nerve injury (DNI) in CRPS-I patients merges the subtypes
- These DNI disproportionately affect small-fibers
- Severity of nerve injury may not be major risk factor for CRPS development; likelihood of developing neurogenic inflammation may be more important