COMPLEX REGIONAL PAIN SYNDROME

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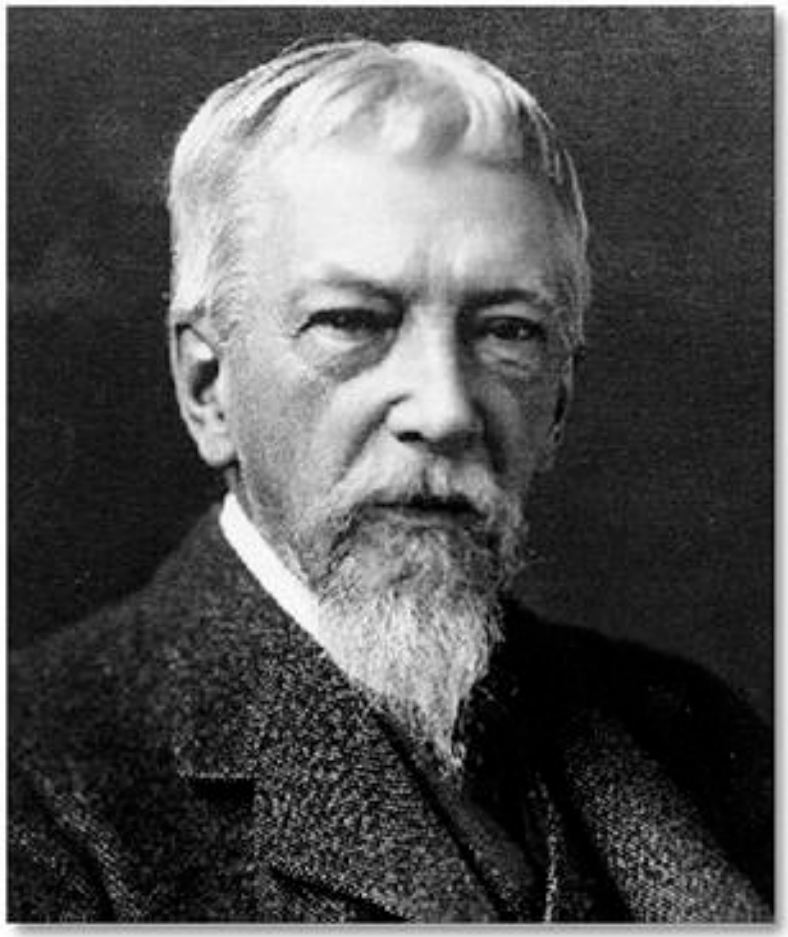
Nov 6, 2019

COMPLEX REGIONAL PAIN SYNDROME

- History
- Epidemiology
- Definition & Taxonomy
- Causes
- Clinical Presentation
- Diagnostic Tests
- Pathophysiology
- Treatments

1864 - Colonel Weir Mitchell, MD
“severely painful dystrophic syndrome following ballistic injuries” in Civil War soldiers: Causalgia



History

- Paul Sudeck
- Suggested that the signs and symptoms of RSD may be caused by an exaggerated inflammatory response to injury or operation of an extremity.
- Sudeck's Atrophy: Bone loss associated with RSD

Rene Leriche

Sympathetic nervous system dysfunction as a cause of pain.

Therapeutic surgical sympathectomy

John Bonica

- The syndrome much as we know it today
  - Promoted the term RSD
  - Described 3 stages

Epidemiology

- CRPS I: 21 per 100,000
- CRPS II: 4 per 100,000

- Female-to-Male ratio: 3:1
- Any age, but middle age predominates
  - Median 42 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

Clinical Presentation

- Precipitating event:
  - CRPS I
    - Minor trauma, contusion, sprain or strain
    - Fracture (especially colles fx)
    - Post surgical
    - Immobilization
    - Less frequently: CVA, spinal cord injury
  - CRPS II
    - Documented peripheral nerve injury and concordant focal deficits (but the signs and symptoms of CRPS are not limited to the same distribution as the affected nerve.)

Clinical Presentation

- Usually an extremity(65%) , but any part of the body can be affected.
- CRPS may progress and spread to other extremities over time.

Clinical Presentation

- PAIN, PAIN, 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. Worst distally.
  - Severe mechanical and thermal allodynia, hyperalgesia, and hyperpathia

Clinical Presentation Time Course

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

CRPS Stage 1 (Acute)

Immediately after injury--3 months

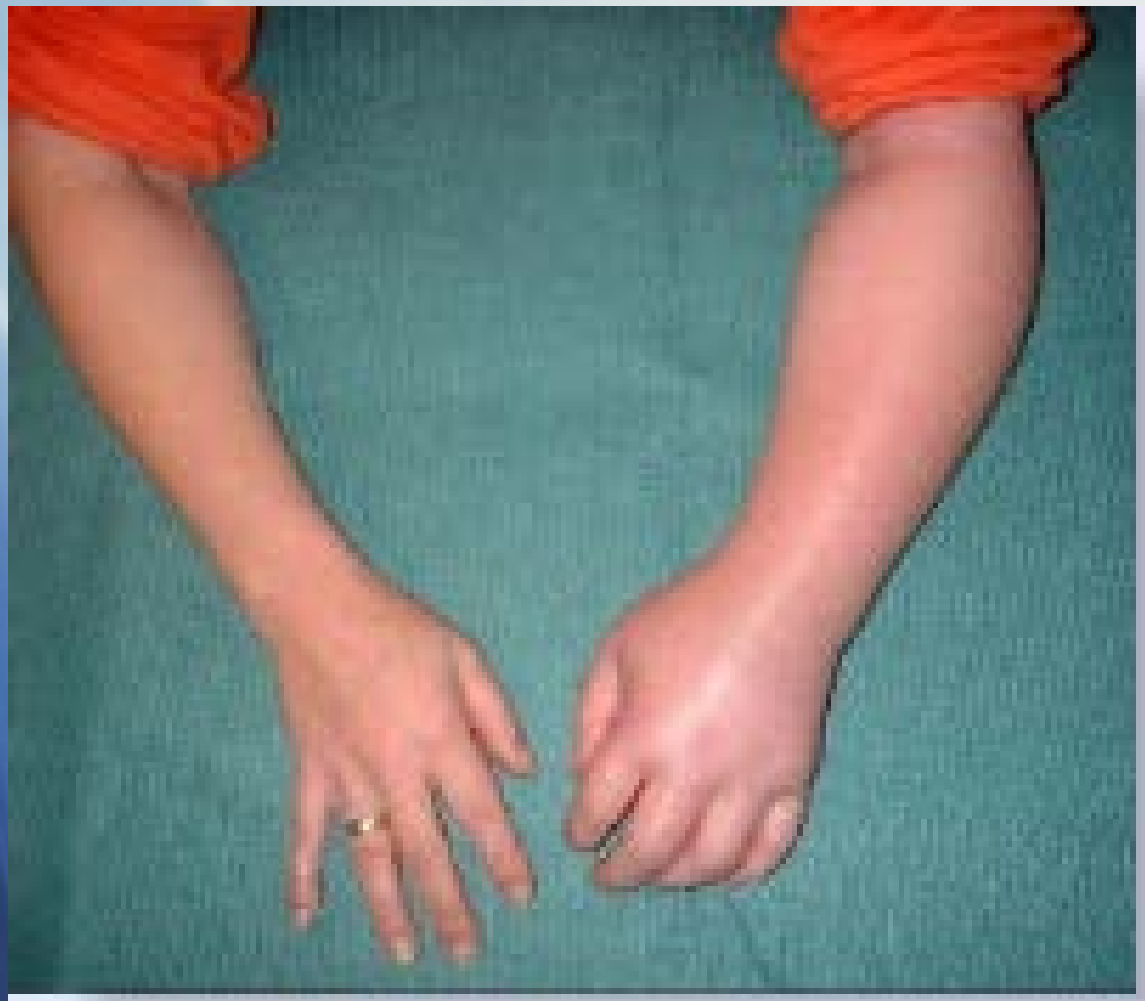
MOST LIKELY TO BE REVERSED AND CURED

- SKIN: Red, warm, swollen, dry, inflamed. Later color may change to mottled and colder with marked hyperhydrosis. Changes back and forth especially with painful use.
- DISTRIBUTION: Pain is not compatible with a single peripheral nerve, trunk, or root lesion.
- SYMPATHETIC:
  - VASOMOTOR: Disturbances occur with variable intensity, producing altered color and temperature. Hyperemic ⟷ Mottled
  - SUDOMOTOR: Dry ⟷ Hyperhydrosis
- MOTOR: Decreased ROM, weakness
- X-RAYS: Normal
- BONE SCAN: Increased uptake

Clinical Presentation

- Autonomic (Sympathetic) Abnormalities
  - Vascular
    - Hot, swollen, erythemetous
    - Cold, blanched
    - Mottled
  - Sudomotor
    - Hyperhydrosis
    - Hypohydorosis

Stage 1 (Acute)



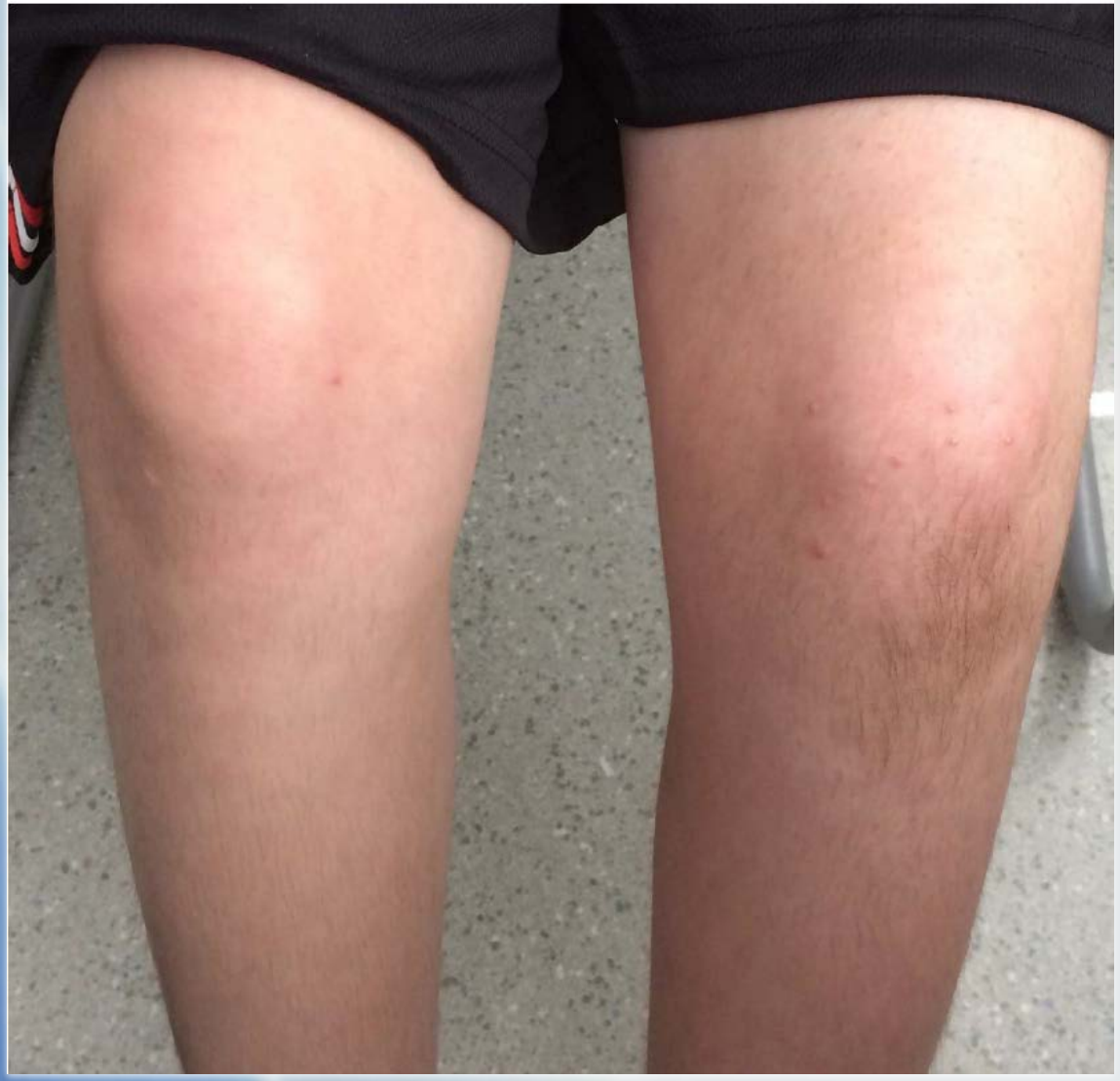
Clinical Presentation

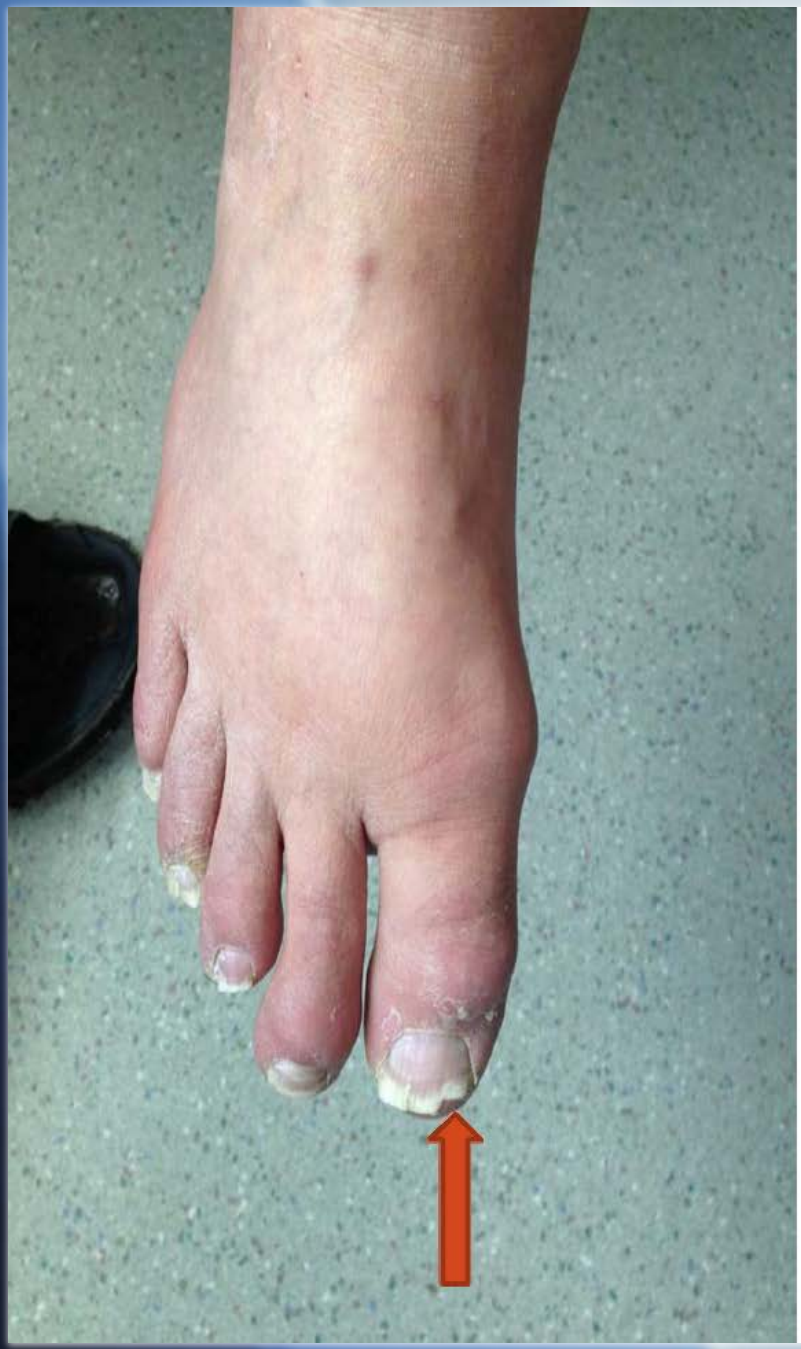
- Motor
  - Diffuse weakness of the extremity, but normal EMG/NCS until late in the course of the disease.
  - Tremor
  - Dystonia occasionally

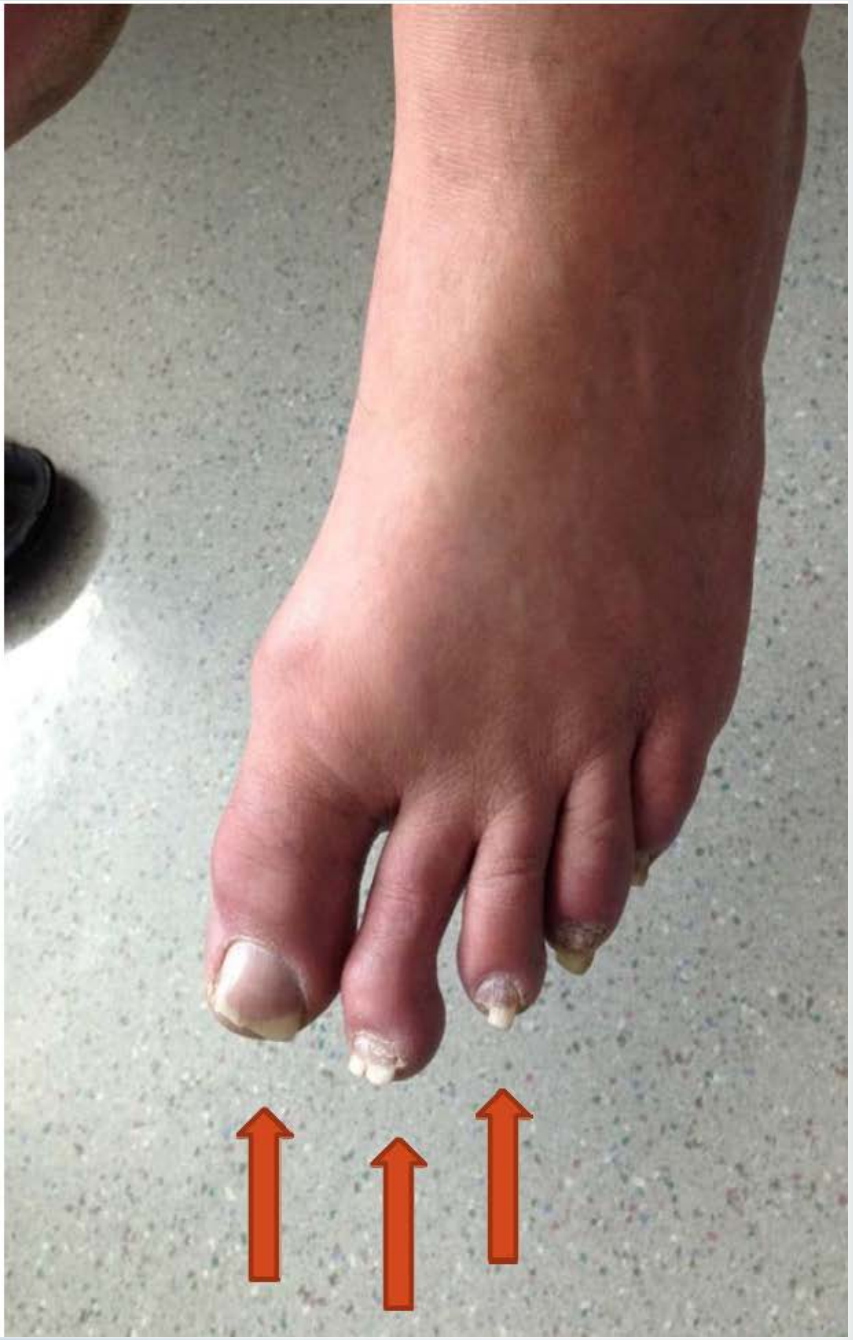
Clinical Presentation

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

Hair growth







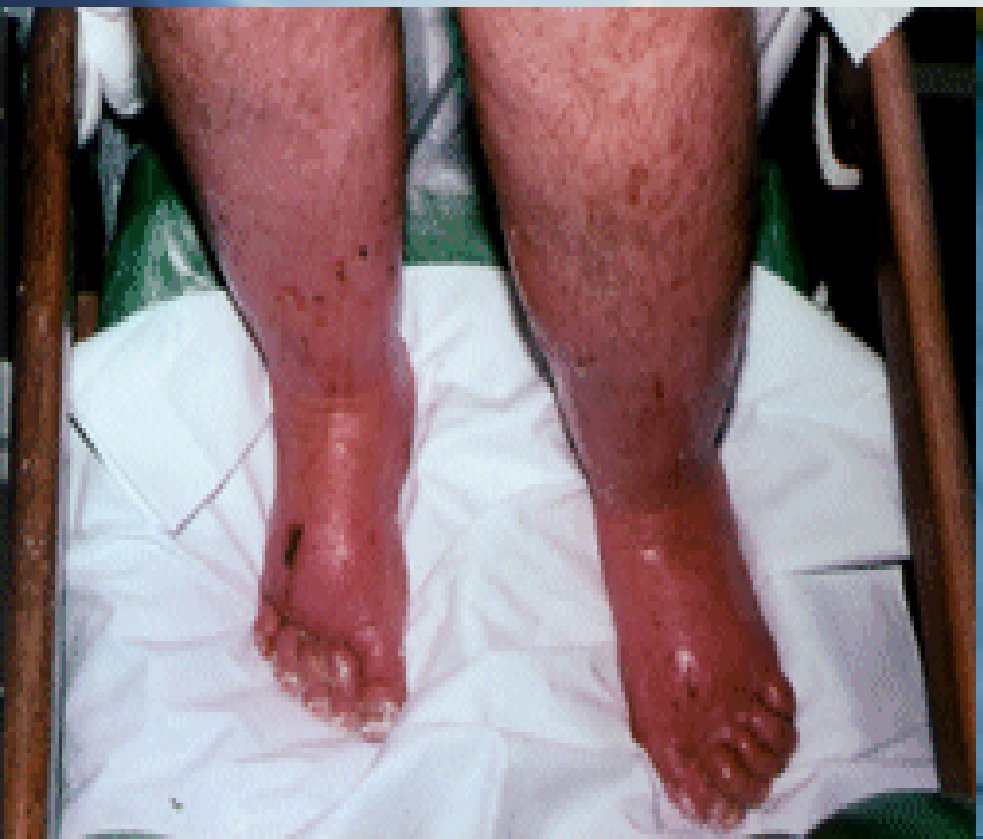
CRPS Stage 2 (Dystrophic)

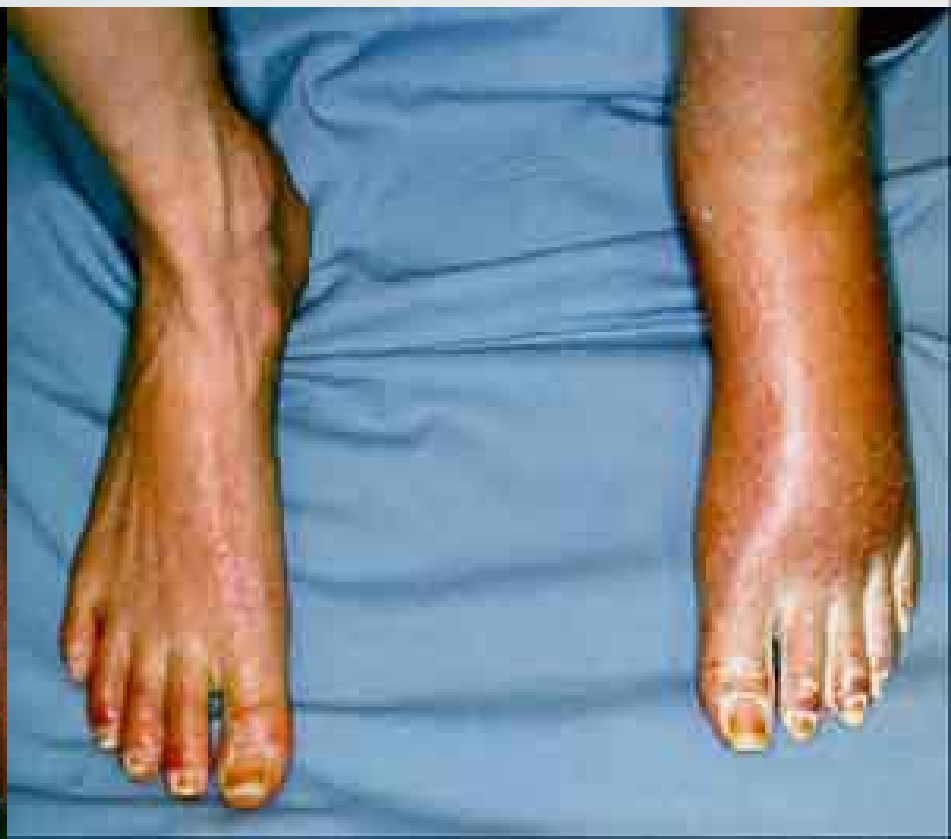
- Pain remains SEVERE. Same characteristics as Stage 1.

CRPS Stage 2 (Dystrophic)
6 weeks--1 year

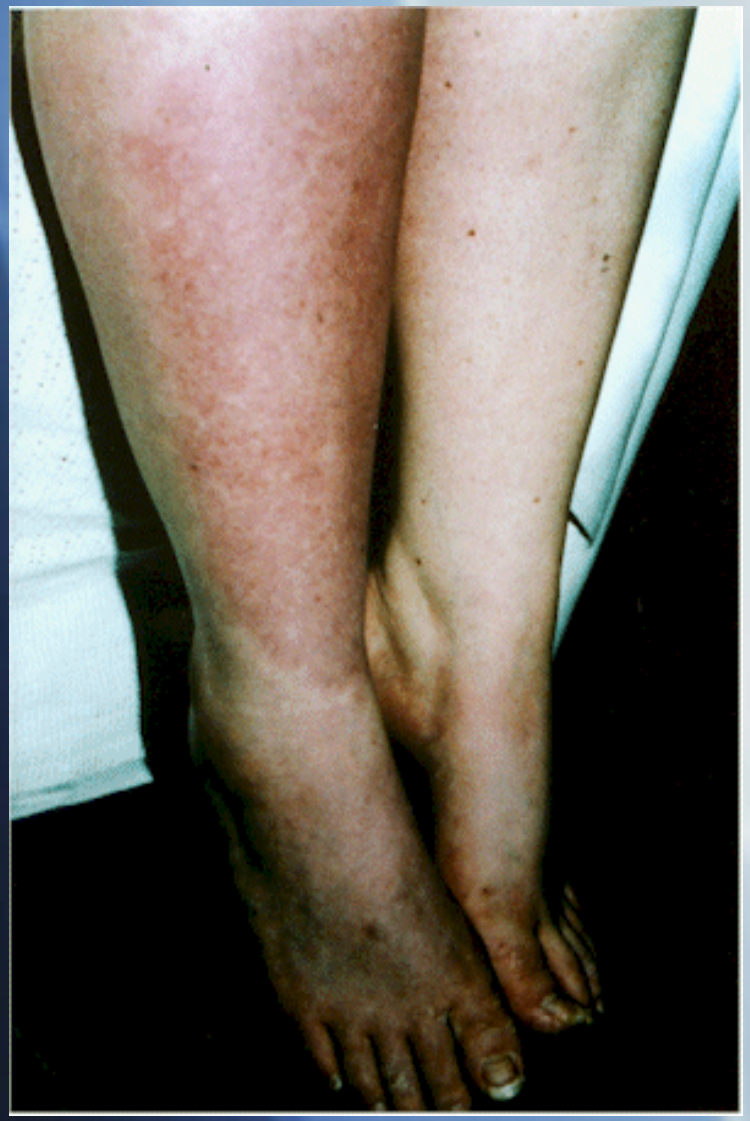
- SKIN: Cool, moist, tight/shiny, swelling, coarse/sparse hair, brittle nails, discolored, edema
- SYMPATHETIC:
  - VASOMOTOR: Mottled/cyanotic
  - SUDOMOTOR: Hyperhydrosis
- MOTOR: Weakness, decreased ROM
- BONE SCAN: No longer helpful.

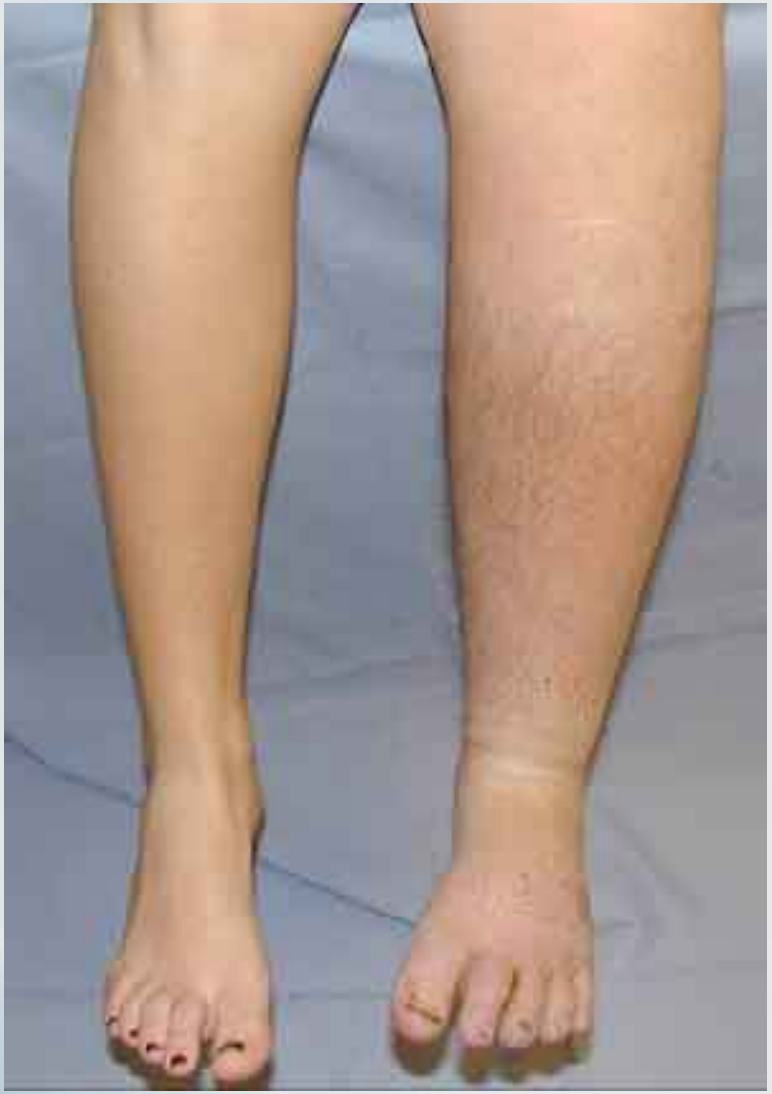
Stage 2 (Dystrophic)





Stage 2 (Dystrophic)



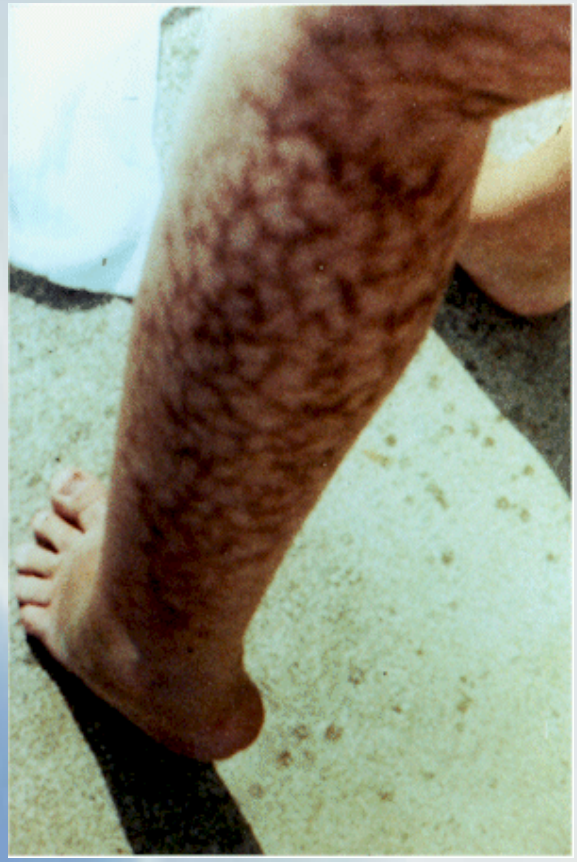


CRPS Stage 3 (atrophic)
6 months--Forever?

- Pain is somewhat decreased (but still debilitating)
  - less at rest, worse with passive motion
- Changes are irreversible, poor outcomes, permanent disability
- 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 (Sudeck’s Atrophy)

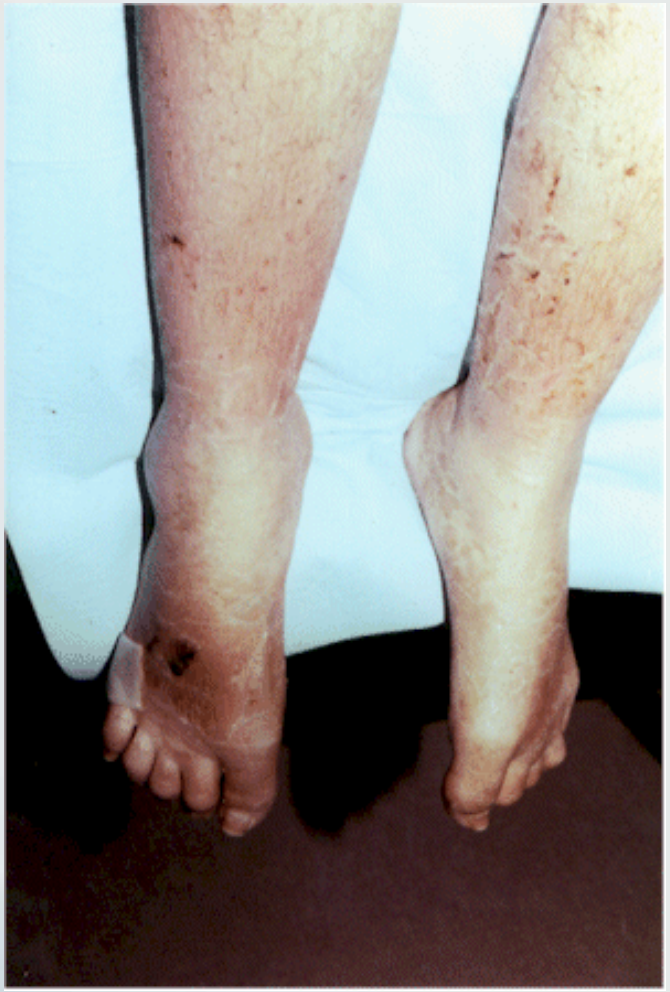
Atrophic Stage 3

Severe Mottling



Atrophic Stage 3

Contractures
Skin Ulceration
Migratory/progressive



CRPS I Diagnostic Criteria - IASP

- 1. The presence of an initiating noxious event or a cause of immobilization.
- 2. Continuing pain, allodynia or hyperalgesia with which the pain is disproportionate to the inciting event.
- 3. Evidence at some time of edema, changes in skin blood flow or abnormal sudomotor activity in the painful region.
- 4. The diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.
  - note: *Criteria* 2,3 *and 4 are necessary for a* ***diagnosis*** *of complex regional pain syndrome.*

- ***International Association for the Study of Pain: Diagnostic Criteria for Complex Regional Pain Syndrome with 1997 ICD Codes***
- *Merskey* H, ***Bodguk*** N, *eds. Classification of chronic pain, descriptions of chronic pain syndromes* ***and*** *definitions of pain terms. Id ed. Seattle: IASP Press, 1994:40-3.*

CRPS II (Causalgia) - IASP

1. The presence of continuing pain, allodynia or hyperalgesia **after a nerve injury**, not necessarily limited to the distribution of the injured nerve.
2. Evidence at some time of edema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain.
3. The diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

note: *All three criteria must be satisfied.*

International Association for the Study of Pain: Diagnostic Criteria for Complex Regional Pain Syndrome with 1997 ICD Codes

Merskey H, ***Bodguk*** N, *eds. Classification of chronic pain, descriptions of chronic pain syndromes* ***and*** *definitions of pain terms. Id ed. Seattle: IASP Press, 1994:40-3.*

Diagnostic Criteria

Table. Budapest Criteria for CRPS

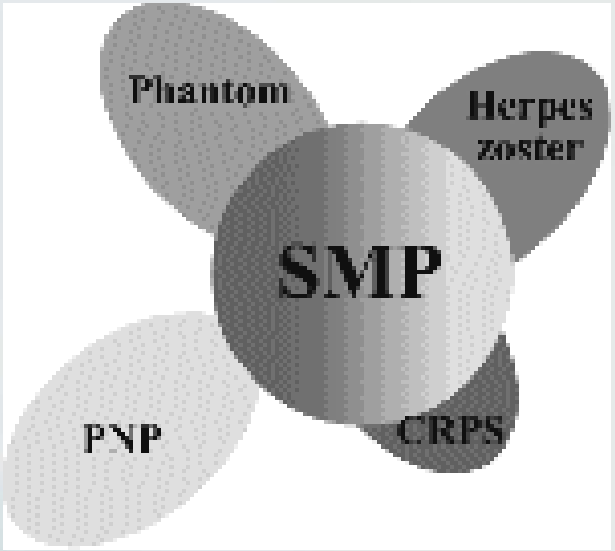
All of the following statements must be met:

- 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.

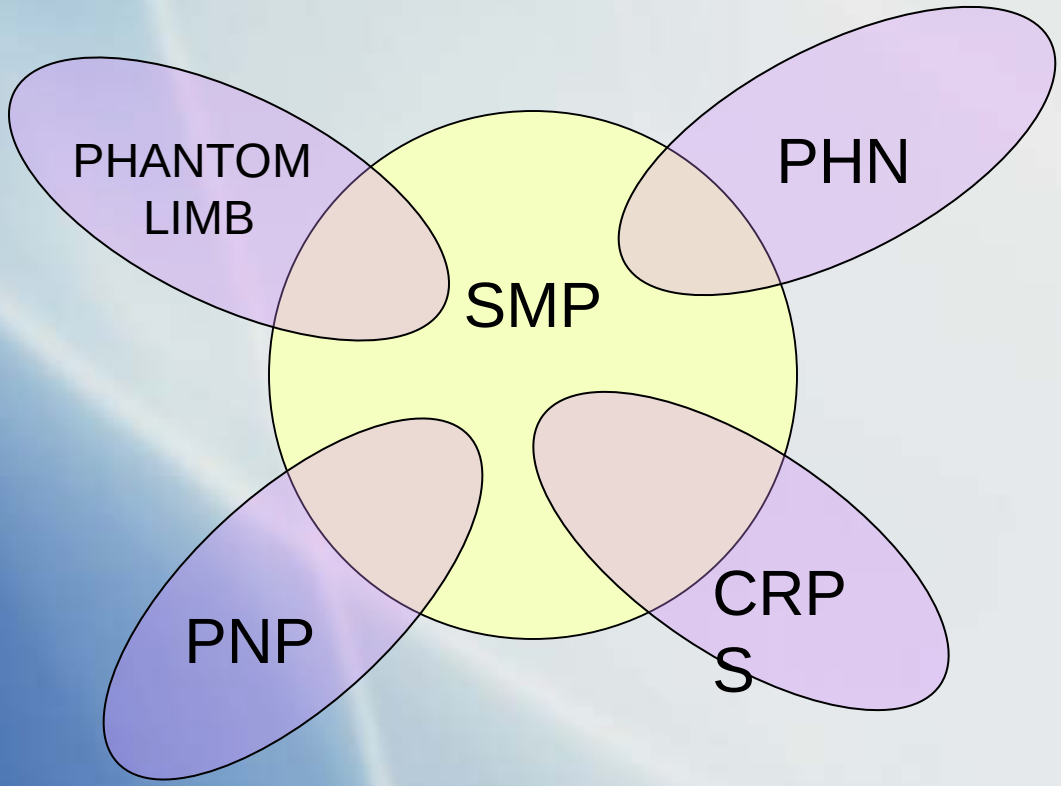
No.	Category	Signs/Symptom
1	**Sensory**	Allodynia (pain to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement) and/or hyperalgesia (to pinprick)
2	**Vasomotor**	Temperature asymmetry and/or skin color changes and/or skin color asymmetry
3	**Sudomotor/edema**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

Diagnostic Tests
Sympathetic Blockade

- Sympathetically Maintained Pain
  - Previously synonymous with CRPS
  - Sympathetic block was deemed diagnostic for CRPS.
  - Now considered a symptom of underlying neuropathic pain sydromes, including, but not exclusively, CRPS.

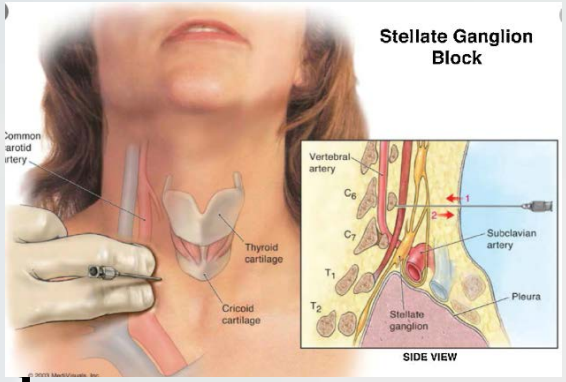


SYMPATHETICALLY MAINTAINED PAIN

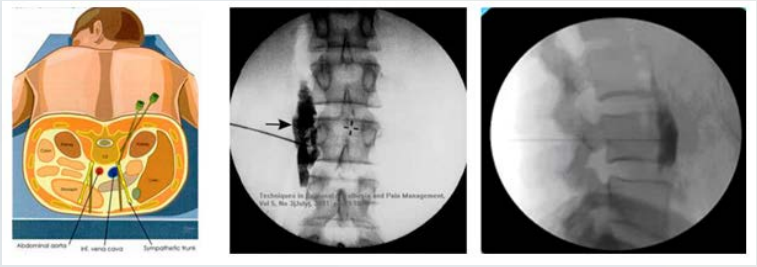


Diagnostic Tests:Sympathetic Blockade

- Stellate Ganglion Block



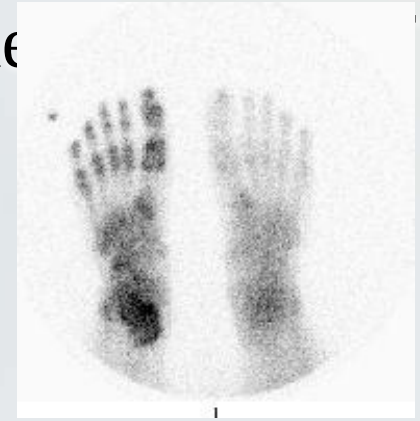
- Lumbar Sympathetic Block



A successful block (increase in temperature, for example) that results in pain relief helps confirm a diagnosis of CRPS in the presence of other consistent clinical findings.

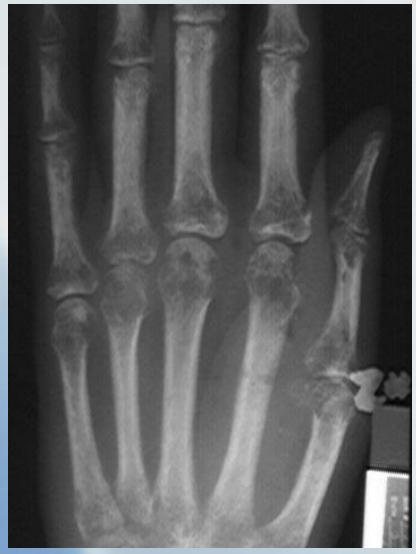
Diagnostic Tests

- Three Phase Bone Scintigraphy
  - Only in acute stage
  - Hyperperfusion
  - Suggestive and supportive of the CRPS, but not diagnostic



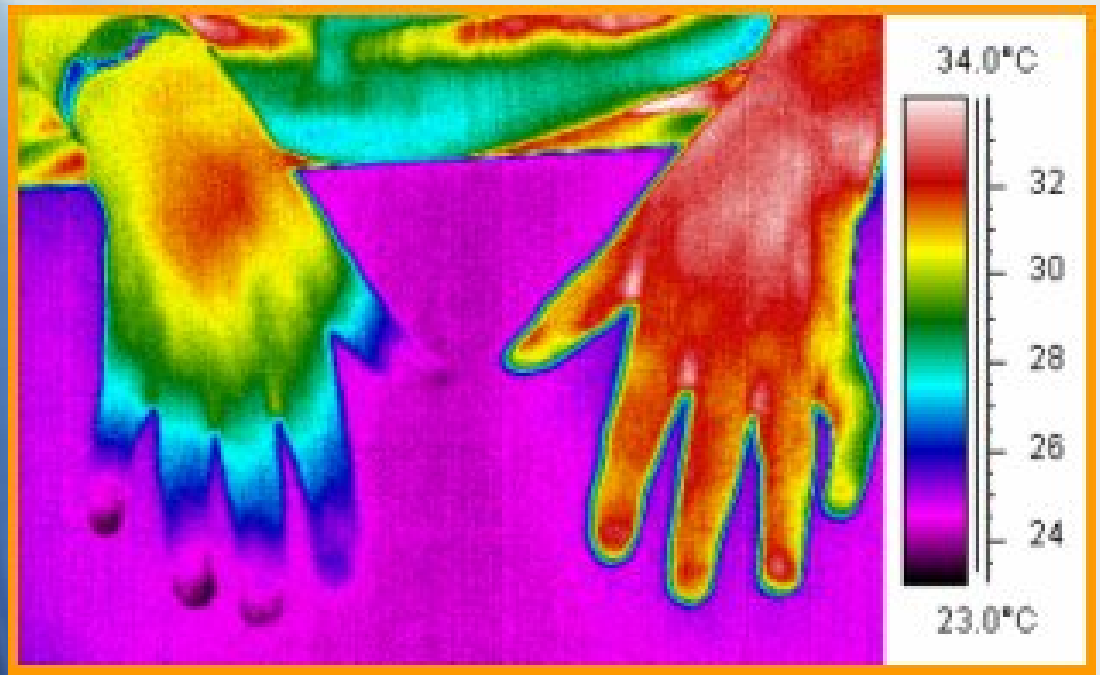
Diagnostic Tests

- Plain Radiographs
  - Late findings only with atrophic stage showing bone loss and patchy osteoporosis



Diagnostic Tests
Skin Temperature

Thermography may show asymmetry. Affected limb is warmer than normal in acute stage and later becomes cooler. Not a readily available procedure.

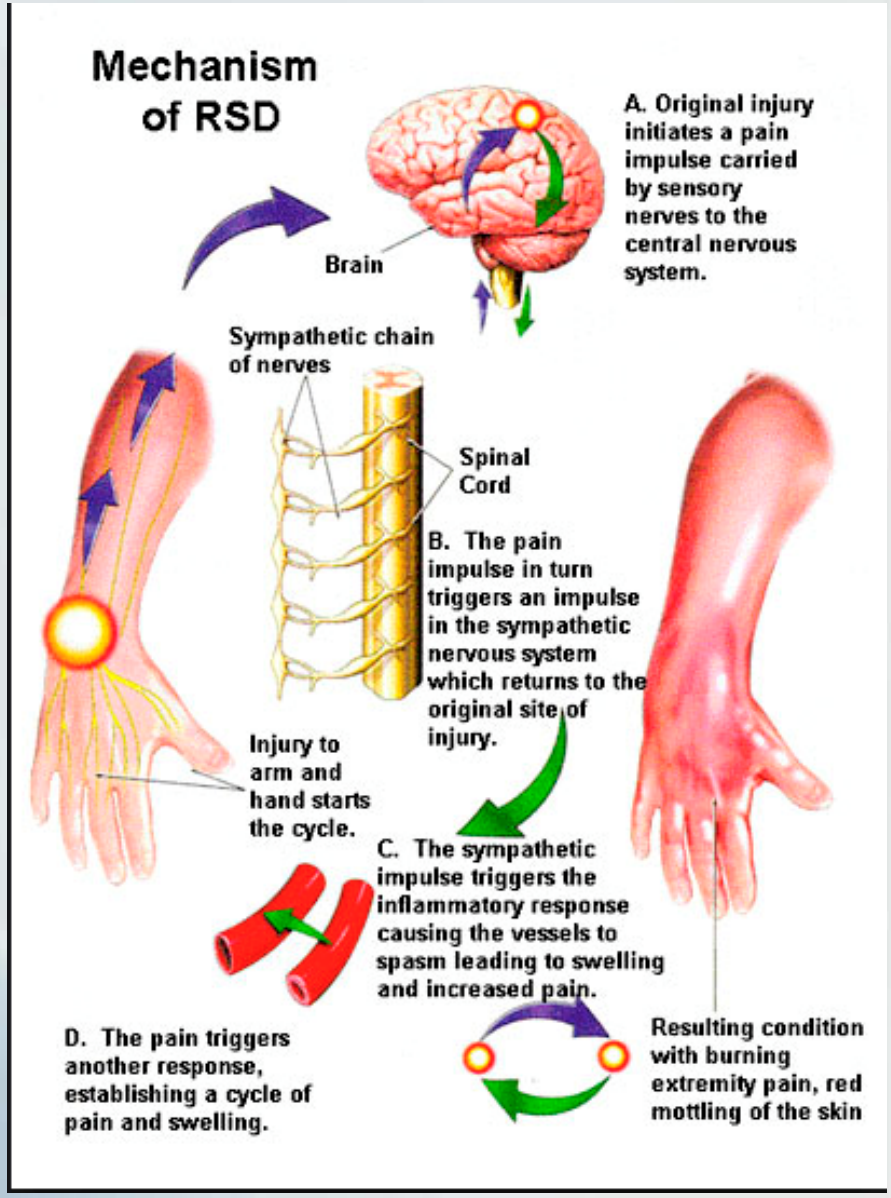


Diagnostic Tests

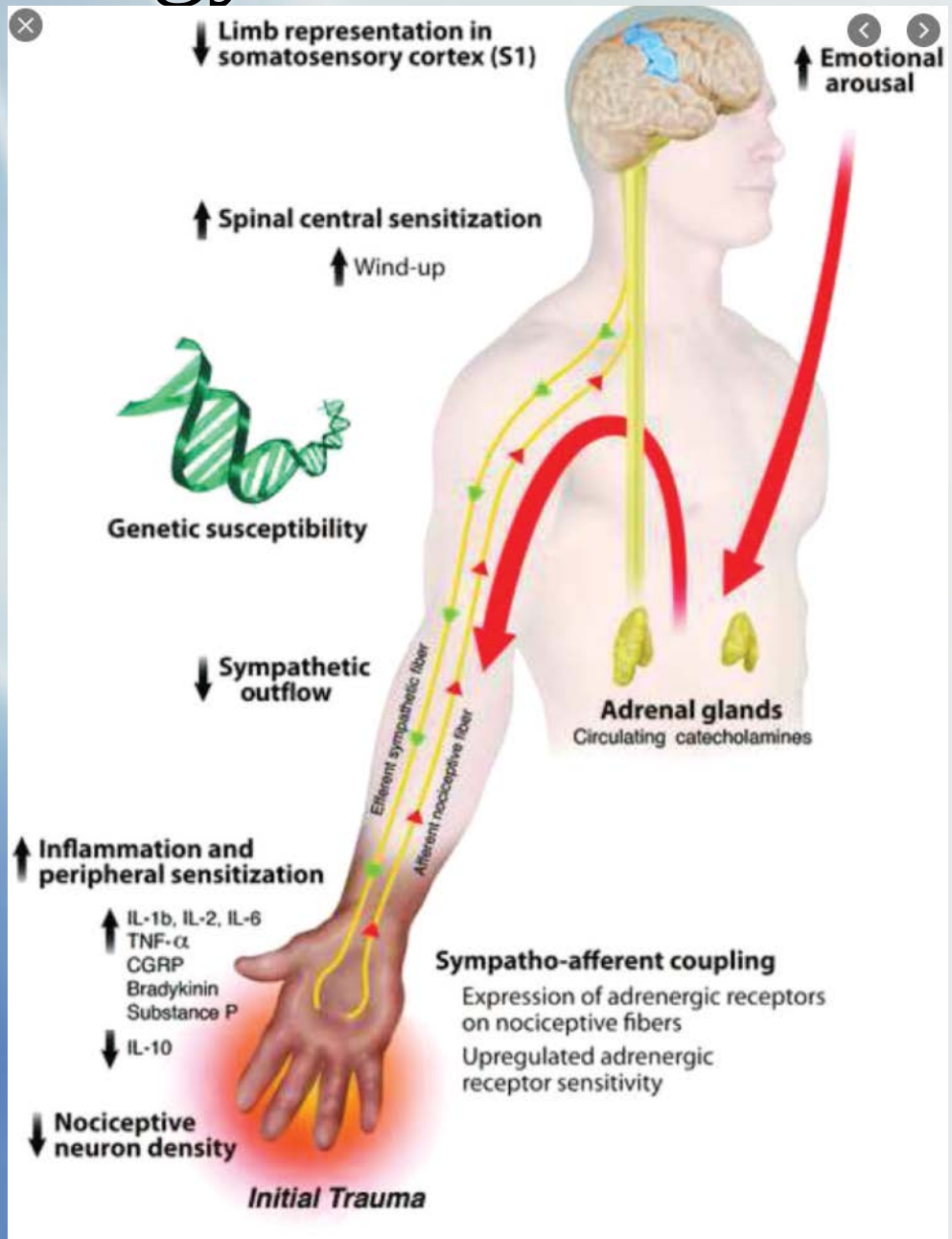
- Quantitative Sensory Testing: Rarely available and no specific profile for CRPS
- QSART: Quantitative Sudomotor Axon Reflex Test of autonomic function. Rarely available

Pathophysiology

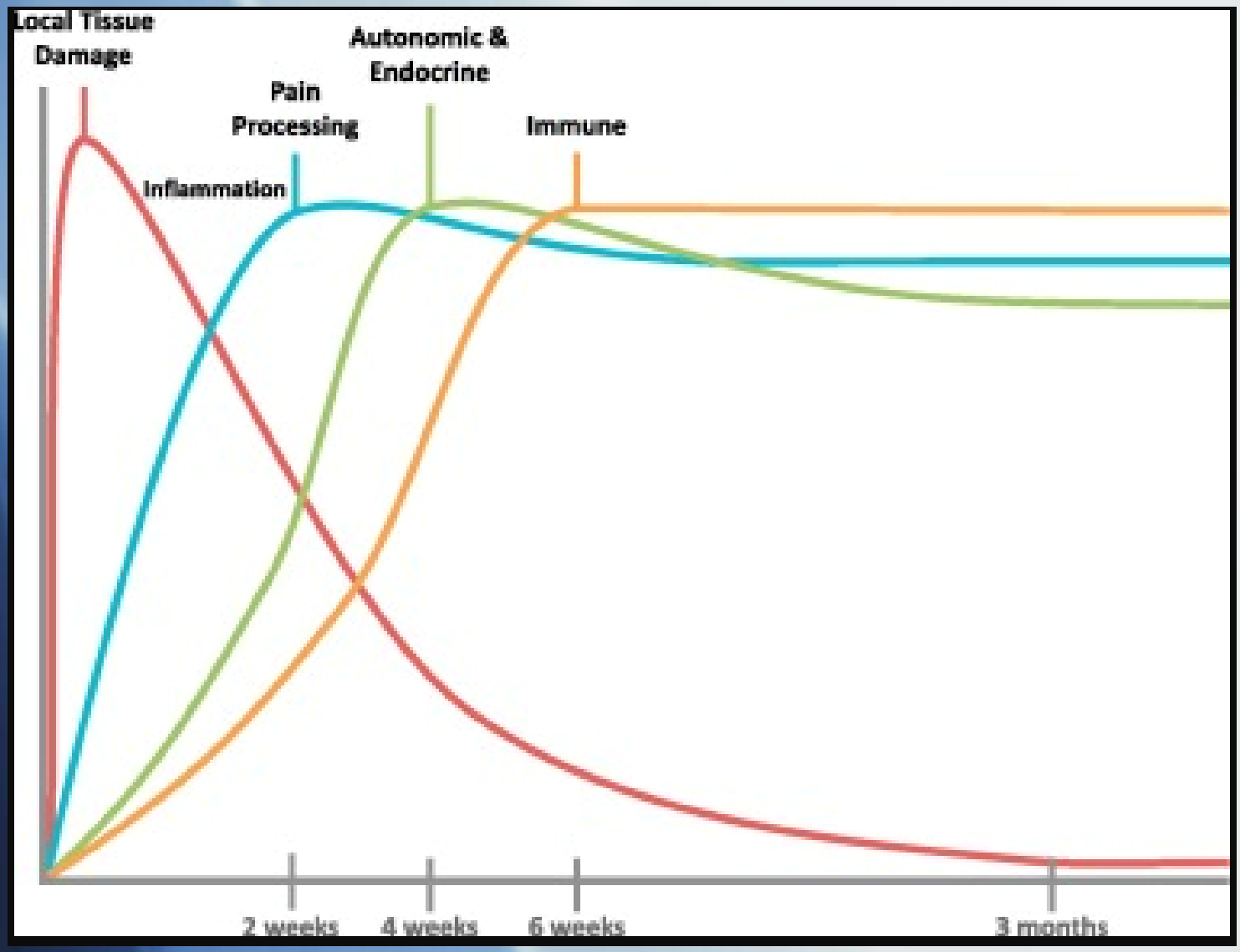
- NOT KNOWN!
- What we do know:
  - Neurogenic Inflammation
  - (acute stage)



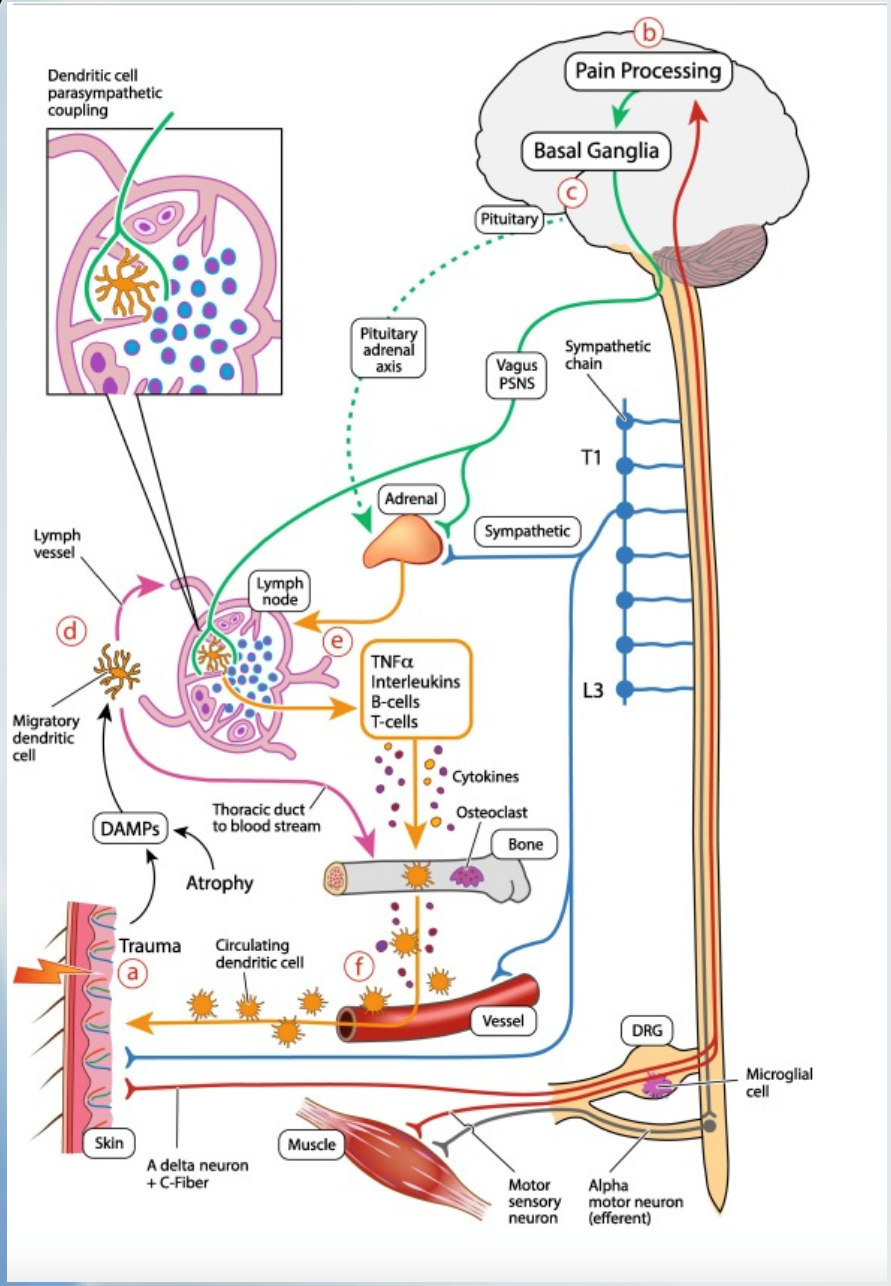
Pathophysiology



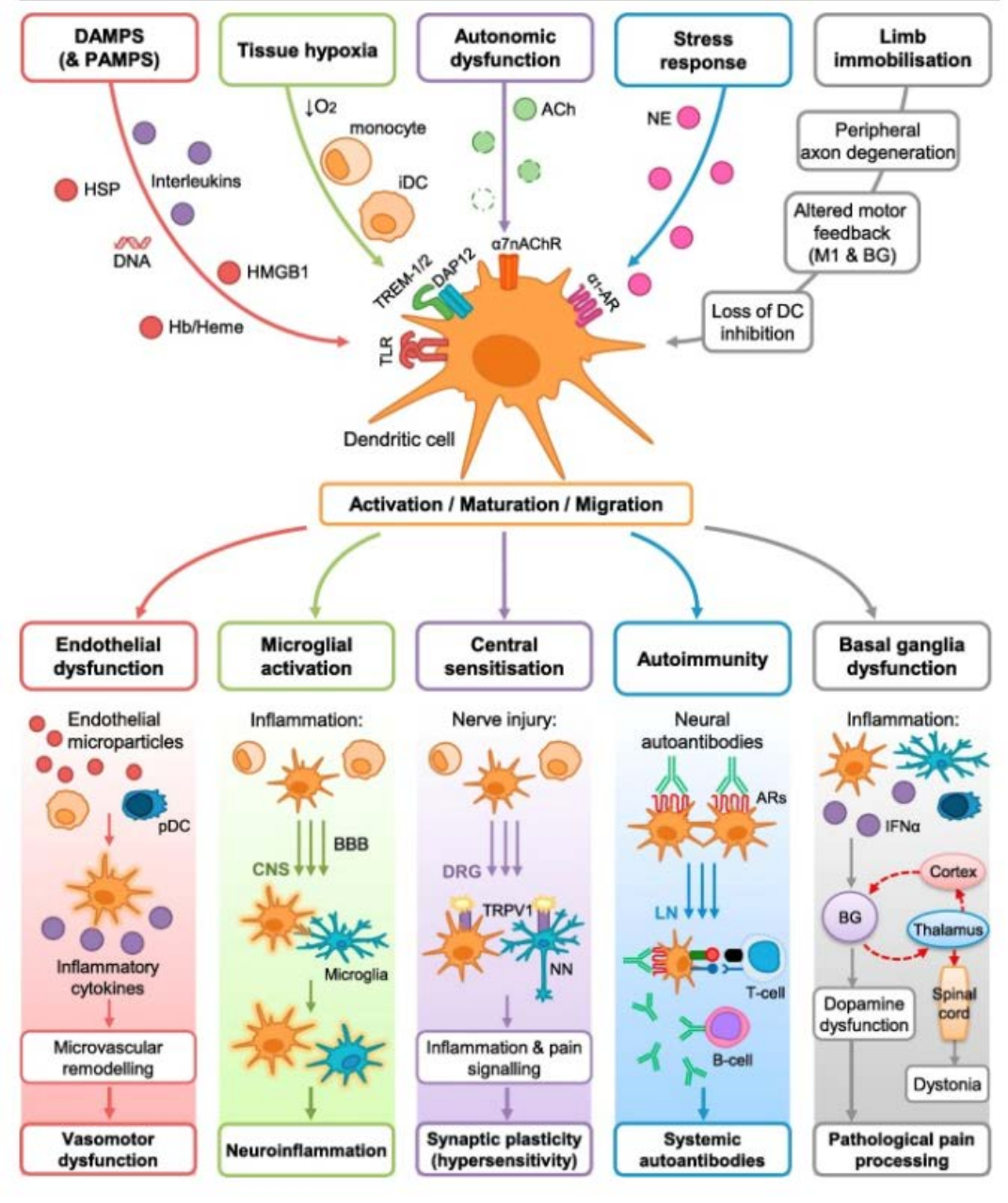
Pathophysiology



Pathophysiology



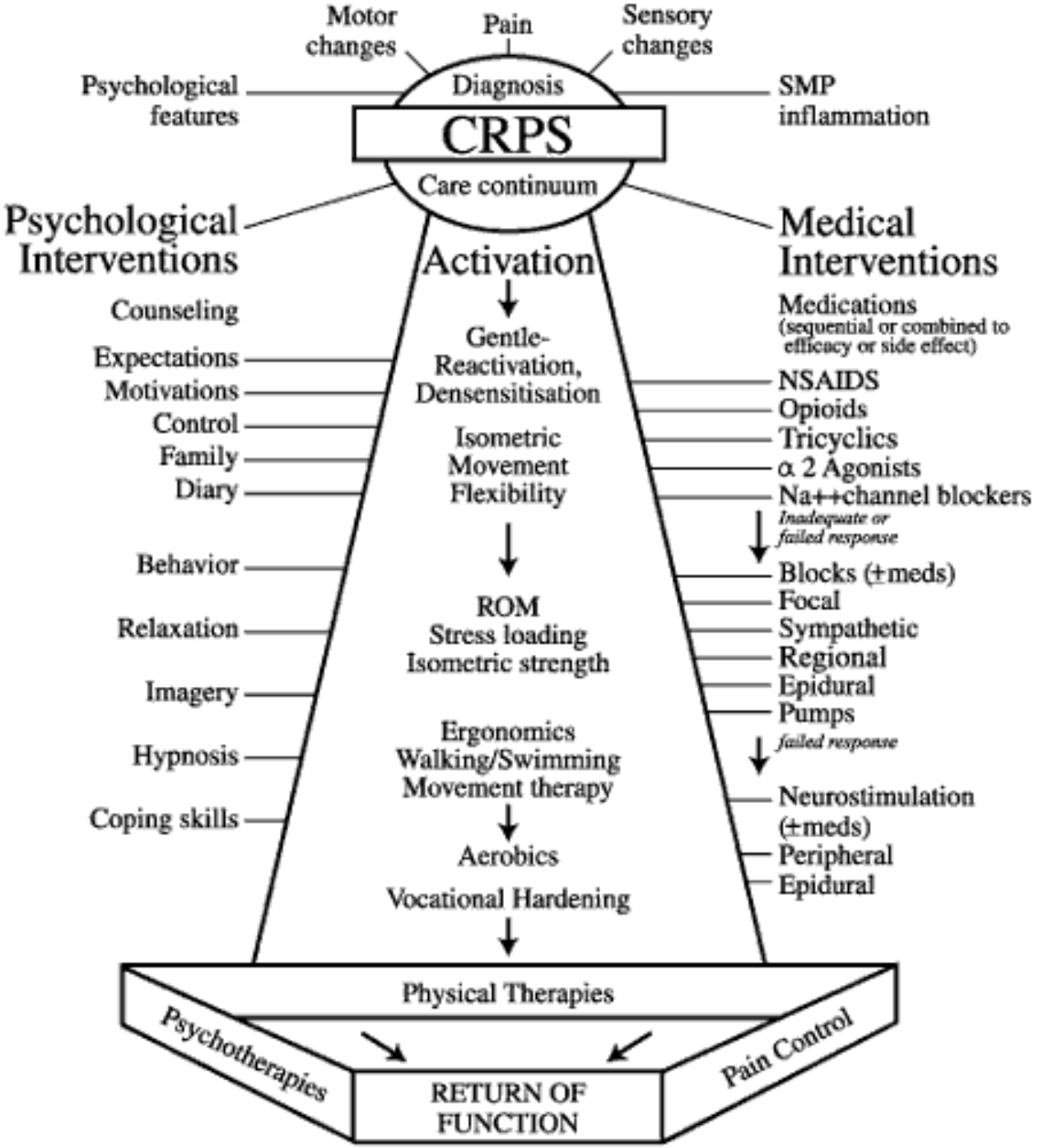
Pathophysiology



Treatment Goals

- Relief of pain
- Return of function
- Prevent or slow progression

EARLY TREATMENT = IMPROVED OUTCOME


Motor changes
Pain
Sensory changes
Psychological features
Diagnosis
SMP inflammation
CRPS
Care continuum
Psychological Interventions
Activation
Medical Interventions
Counseling
Expectations
Motivations
Control
Family
Diary
Behavior
Relaxation
Imagery
Hypnosis
Coping skills
Gentle-Reactivation, Densensitisation
Isometric Movement Flexibility
ROM Stress loading Isometric strength
Ergonomics Walking/Swimming Movement therapy
Aerobics
Vocational Hardening
Medications (sequential or combined to efficacy or side effect)
NSAIDS
Opioids
Tricyclics
α 2 Agonists
Na++channel blockers
Inadequate or failed response
Blocks (±meds)
Focal
Sympathetic
Regional
Epidural
Pumps
failed response
Neurostimulation (±meds)
Peripheral
Epidural
Physical Therapies
Psychotherapies
Pain Control
RETURN OF FUNCTION

Physical Therapy

- In the acute stage PT is the most important factor in reversing the syndrome.
- Later, it can improve pain & function and help prevent progression and migration.
- Aggressive PT may only be possible with treatment of pain: pain meds, sympathetic and/or somatic blockade.

Physical Therapy - two types

- Pain Focused: Patients who have recently developed CRPS – PT should focus more on pain

- Time based: Patients who have had CRPS for a while (Chronic) – PT should be more time based

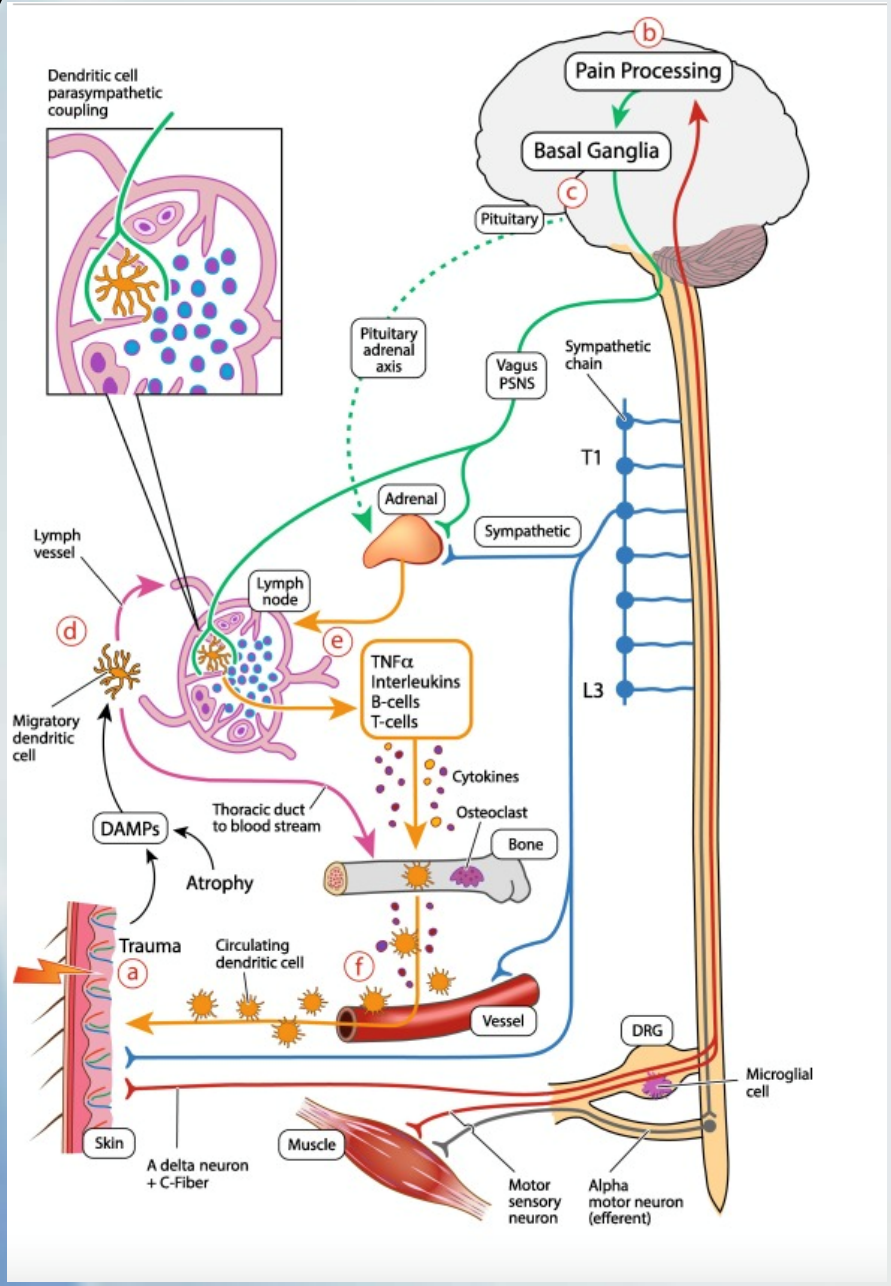
Medications

- NSAIDs-Mild to moderate pain
- Opioids-Not Effective for severe neuropathic pain. Beware of all issues related to chronic opioid use.
- Steroids-effective in acute (inflammatory) stage.
- Gabapentin and Pregabalin-moderately Effective

Opioids and CRPS and Glia

- Opioids taken chronically have been shown to increase glial cell activation
- Glia play a key role in developing tolerance to opioids.
- Increased tolerance to opioids leads to increasing the dose of opioids which, in turn, cause further glial cell activation
- Similarly, drugs that decrease glial cell activation also increase the effectiveness of opioids.

Pathophysiology



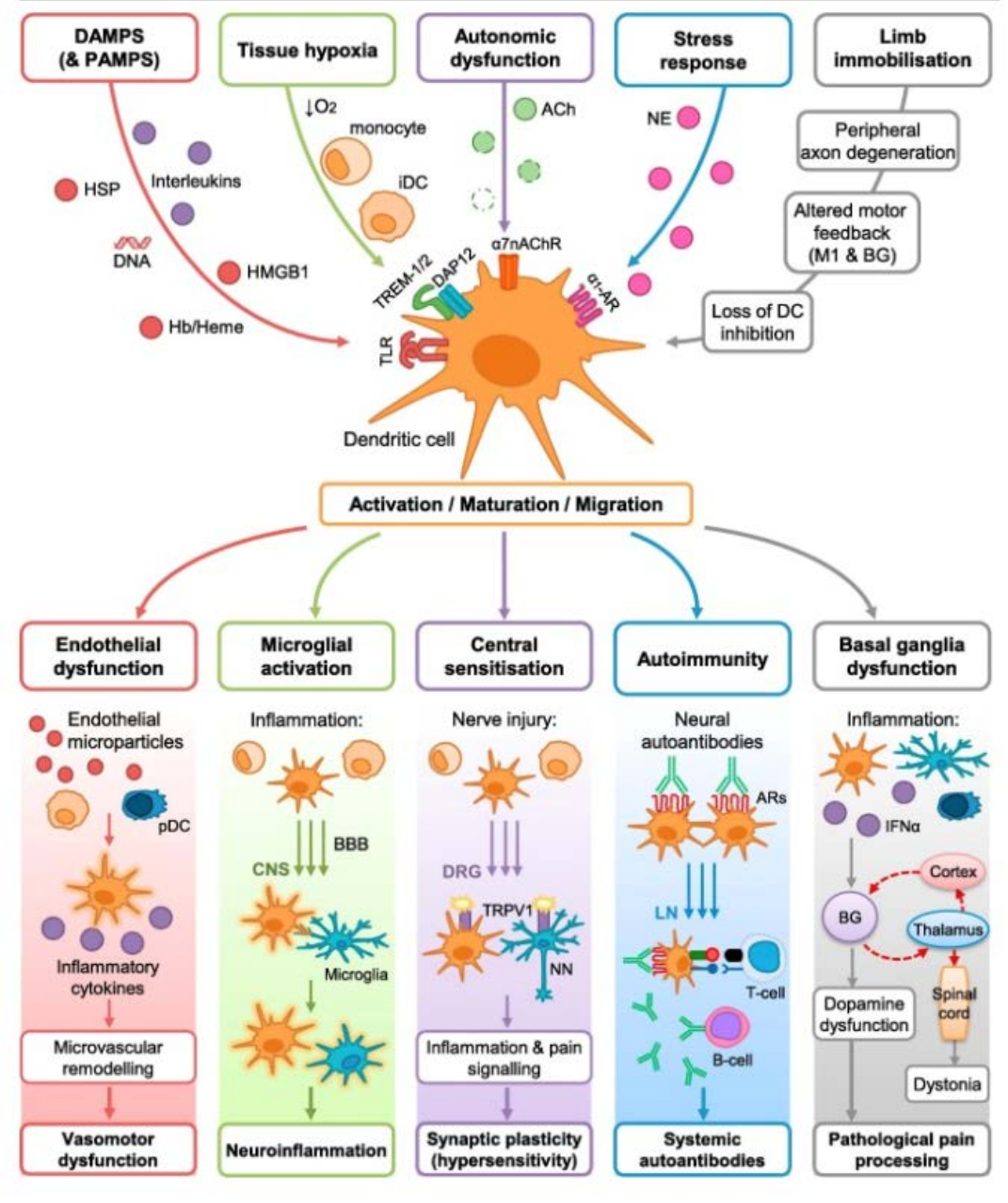
Central Sensitization: Glia

- Activated glial cells release chemicals (cytokines) that cause nerve inflammation
- Treatments used towards de-activating glia maybe useful for managing CRPS
- Treatments that we know of are: medications and exercise /Physical Therapy
- Opioids / narcotics increase glial cell activation

BROWN

Milligan ED, Watkins LR (2009) Pathological and protective roles of glia in chronic pain. Nat Rev Neurosci 10:23–36

Pathophysiology



Central Sensitization: Activated Glial Cells

- Glial cells make up 70% of all the cells in our Central Nervous System
- Under normal circumstances, they remain dormant and are part of the nervous system's immune function
- In CRPS with Central Sensitization, these glial cells are activated.
- Activated glia release certain chemicals (Cytokines) that cause nerves to become inflamed
- Glial cells are an important link between the nervous system and the immune system and inflammation and pain

BROWN

Milligan ED, Watkins LR (2009) Pathological and protective roles of glia in chronic pain. Nat Rev Neurosci 10:23–36

Glial cell attenuators

- Drugs that decrease glial cells activation are still in experimental stages, but there are some that are used clinically
- Pentoxyfilline
- Tetracyclines - Minocycline, Doxycycline
- Ibudiblast – Used for the last 20 years in Japan and Korea for asthma and stroke. Glial cell attenuator. Neuroprotective.

BROWN

Watkins LR, Maier SF (2003) Glia: a novel drug discovery target for clinical pain. Nat Rev Drug Discov 2:973–985

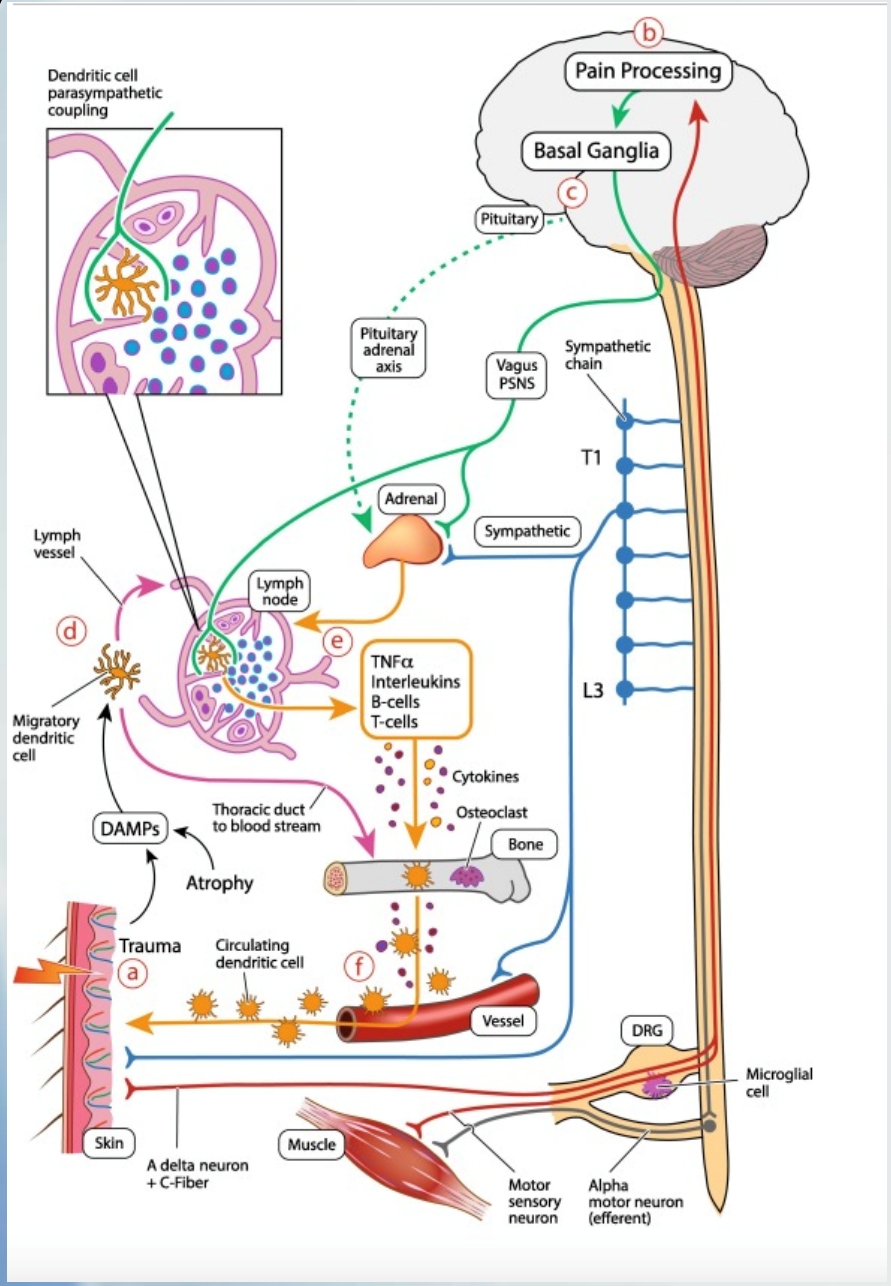
Low Dose Naltrexone

LDN

Low Dose Naltrexone (LDN) 1

- Competitive antagonist of opioid receptors
- Clinically used for 30 years for addiction
- Suppressive effects on the CNS microglia, which….
- Attenuates production of pro-inflammatory cytokines and neurotoxic superoxides (chemicals that cause inflammation)

Pathophysiology



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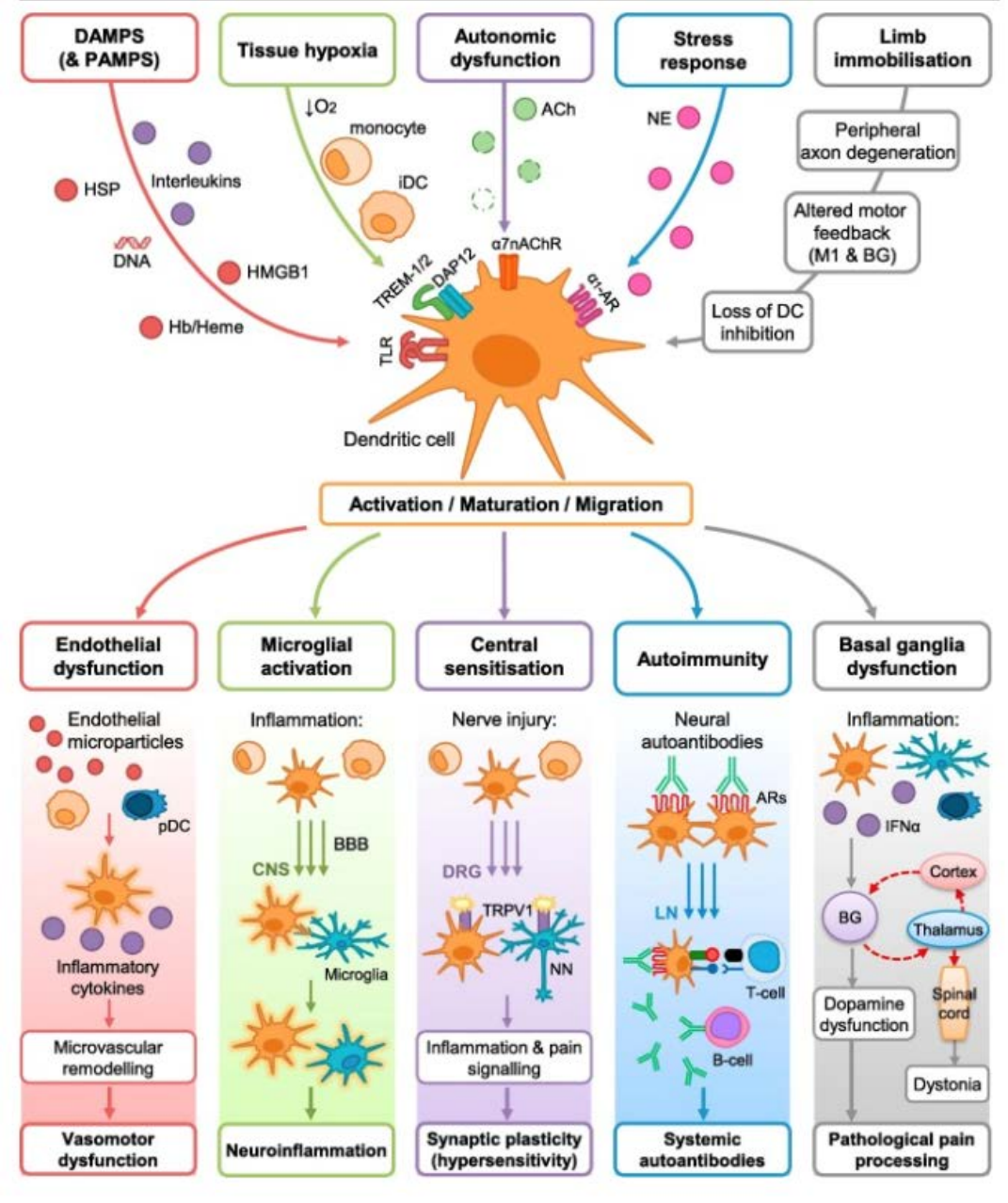


Low Dose Naltrexone (LDN)

- There are several theories as to how LDN may work.

1. Transiently blocks opioid receptor leading to positive feedback production of endorphins (Zagnon)
2. LDN increases production of OGF (opioid growth factor) as well as number of and density of OGF receptors by intermittently blocking the opiate receptor. Increased in OGF repairs tissue and healing.
3. Naltrexone blocks the effect of TLR4 (Toll Like receptors) which decreases glial cell activation

Low Dose Naltrexone (LDN)

- Dose can vary anywhere between 1.75mg to 4.5mg
- May cause insomnia, mild headaches initially.
- Patients report increased physical activity, flare ups not as acute, better tolerance to pain.
- Recommend a trial of at least 12 weeks
- To avoid all opioids or tramadol.

Medications

- Tricyclics-Effective for a variety of neuropathies
- Sodium channel blockers-IV lidocaine, Lidoderm, mexilitene, lamotrigine.
- Calcitonin (intranasal)-Effective in acute stage.
- NMDA blockers-Ketamine
- DMSO (topical)- Free radical scavenger. Questionable benefit
- Topical Clonidine- α_2-agonist: prevents release of catecholamines? Maybe helpful.

Ketamine

- NMDA as a mediator of chronic pain
- Ketamine “coma” (Germany & Mexico)

Ketamine

- CRPS - activation and proliferation of NMDA receptors
- Strong NMDA Receptor blocker
- One of the safest anesthetic drugs
- Powerful analgesic even at low doses
- Poor absorption when administered orally.
- Effective as IV or submucosal (Troche)

Correll GE, Maleki J, Gracely EJ, Muir JJ, Harbut RE. Subanesthestic ketamine infusion therapy: a retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. Pain Medicine 2004;5(3):263-75.

Factors that are important in getting the best out of a ketamine infusion

- How long does the ketamine stay in the body i.e. how long are the receptors blocked
- How much is needed to keep most of the receptors blocked
- Minimize trauma while delivering the infusion
- Ketamine infusions are good only if done in conjunction with other therapies, especially exercise

DMSO 50% - Dimethyl Sulphoxide

- Topical use only.
- Particularly helpful for 'warm' CRPS
- CRPS less than 1 year - three month course of DMSO applied 5 times topically every day
- CRPS more than 1 year – One month trial course of DMSO everyday.
- If trial helps, then continue

Vitamin C

- Natural antioxidant
- There are several studies that have shown that Vitamin C can prevent CRPS after a fracture
- Vitamin C 500 mg for 45 days to 50 days was shown to prevent development of CRPS
- ? Any value to using it in established CRPS, certainly helpful in prevention

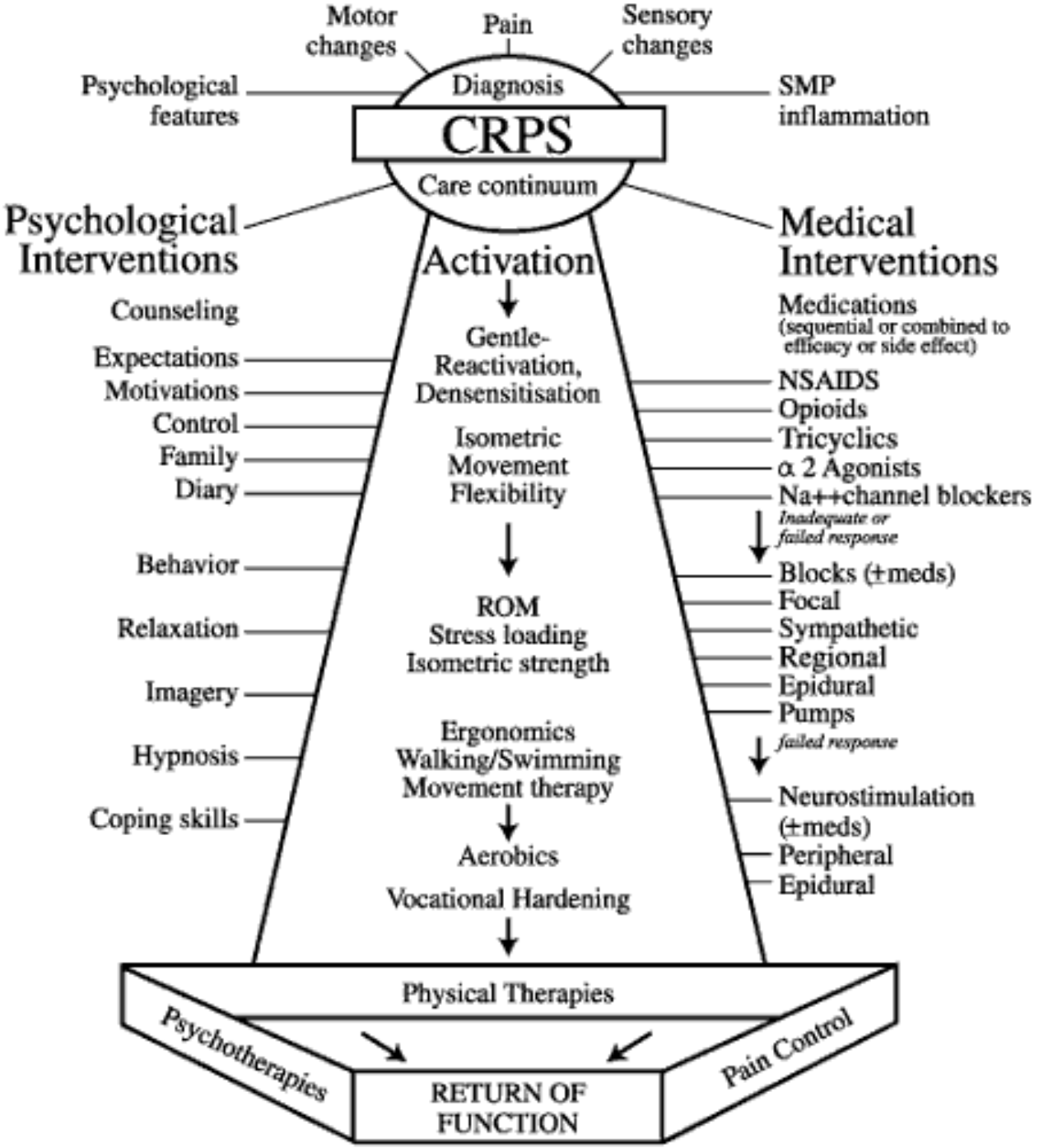
Sympathetic Blockade

- Lumbar sympathetic block
- Stellate ganglion block
- IV regional with guanethidine

If effective, sympathetic blockade often gives relief well past the duration of the block.

Repeated blocks can be reverse the course of the disease.

Very helpful in facilitating PT.


Motor changes
Pain
Sensory changes
Psychological features
Diagnosis
SMP inflammation
CRPS
Care continuum
Psychological Interventions
Activation
Medical Interventions
Counseling
Expectations
Motivations
Control
Family
Diary
Behavior
Relaxation
Imagery
Hypnosis
Coping skills
Gentle-Reactivation, Densensitisation
Isometric Movement Flexibility
ROM Stress loading Isometric strength
Ergonomics Walking/Swimming Movement therapy
Aerobics
Vocational Hardening
Medications (sequential or combined to efficacy or side effect)
NSAIDS
Opioids
Tricyclics
α 2 Agonists
Na++channel blockers
Inadequate or failed response
Blocks (±meds)
Focal
Sympathetic
Regional
Epidural
Pumps
failed response
Neurostimulation (±meds)
Peripheral
Epidural
Physical Therapies
Psychotherapies
Pain Control
RETURN OF FUNCTION

Psychology (Psychiatry)

- Earlier anxiety progresses to severe depression. (Pain, loss of work and self worth, financial loss, family breakdown, pain behavior, medication dependence and abuse)
- Medical treatment of depression
- Counseling, set realistic goals and expectations, behavioral & cognitive therapies, biofeedback, hypnosis.

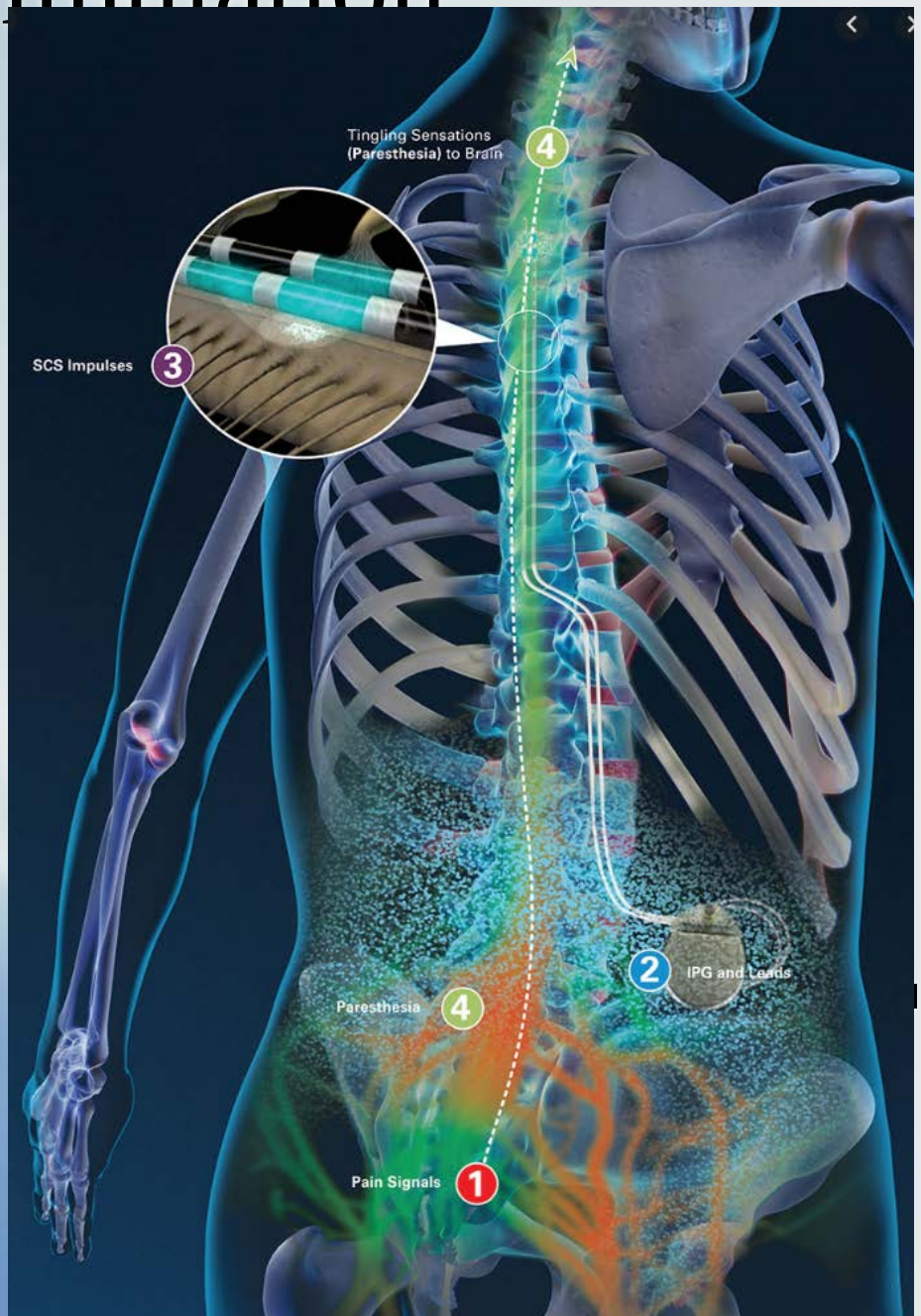
Continuous Infusion

- Tunneled epidural catheter. Patients who have a good but short duration response to sympathetic block or for sympathetic independent pain.
  - May be left in place for several weeks.
  - Titrate local anesthetic to sympathetic or somatic block with minimal motor block.
  - Physical therapy every waking moment!

Spinal Cord Stimulation

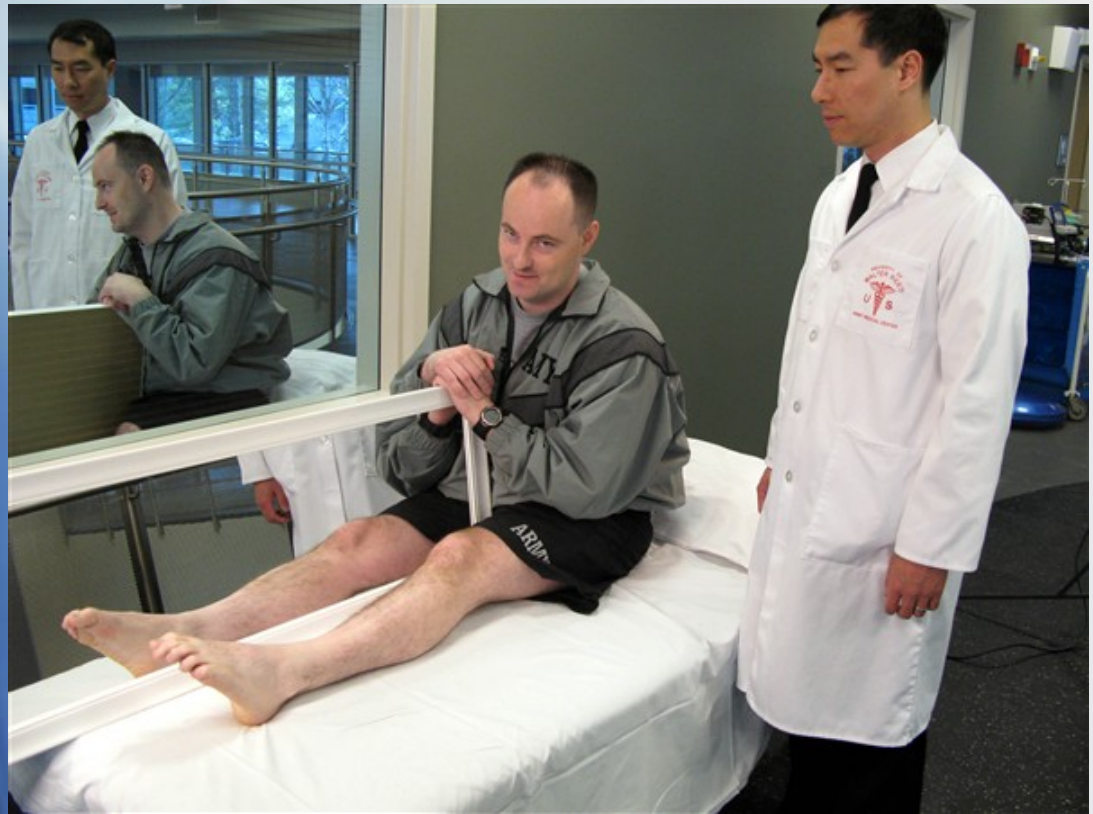
- Permanently implanted for control of chronic neuropathic pain
- Tunneled percutaneous leads for several weeks in the acute stage for therapeutic reversal for the disease. More and more frequently used.

Spinal Cord Stimulation



Mirror Therapy

The brain wants congruence between motor intention, peripheral sensory input and visual input. Mirror therapy “restores” this relationship.



The Future

- Education for earlier detection and aggressive treatment.
- Better understanding of the pathophysiology for development of specific, targeted therapies.

Stages	Duration	Signs & Symptoms
Stage I	Usually last two to six weeks but may last up to six month	Skin changes: Initially warm and dry, later cold and cyanotic. Mottling of the skin Sweat changes: Hyperhydrosis Temperature changes: Usually increase Edema: Non pitting Pain: Usually not significant, tenderness and hyperesthesia may happen
Stages II	Starts two to six week after initial injury and may last up to three to six month	Skin changes: Cool, pale, mottled cyanotic and a shiny appearance Sweat Changes: Hyperhydrosis Temperature: Usually decrease Edema: Extensive edema with a indurated and brawny character. Pain: Diffuse, constant, burning, and increased by stimuli. Hyperesthesia, Hyperalgesia and allodynia may also be present
Stage III	Starts six to eight months after the initial injury, last for unpredictable period.	Skin changes: Irreversible atrophy Fat and Muscles changes: Irreversible atrophy Temperature changes: Decrease Joint changes: Decrease range of motion and decrease strength. Pain: Intractable, Hyperesthesia, Hyperalgesia and allodynia may also be present X-rays Findings: Diffuse demineralization.