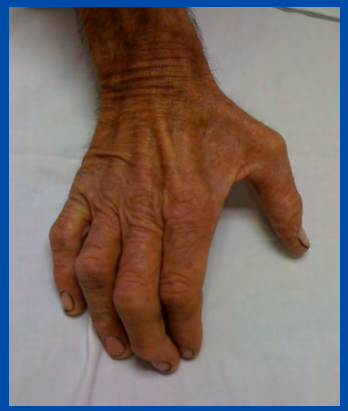
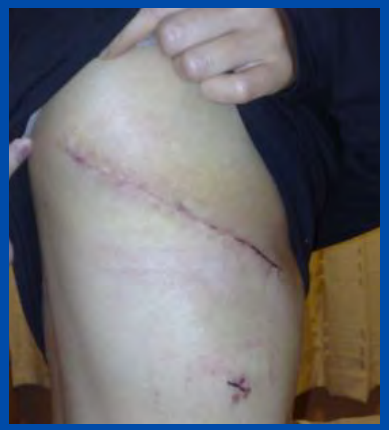
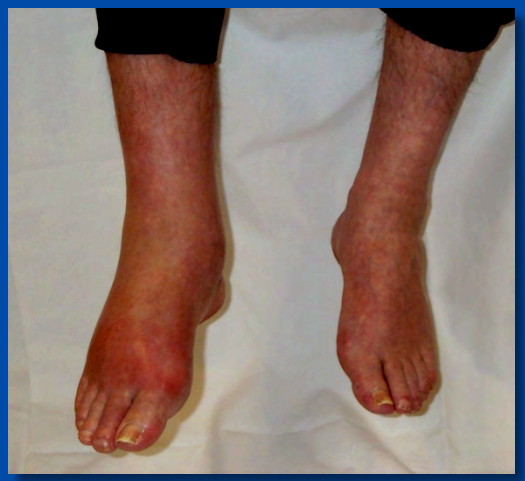
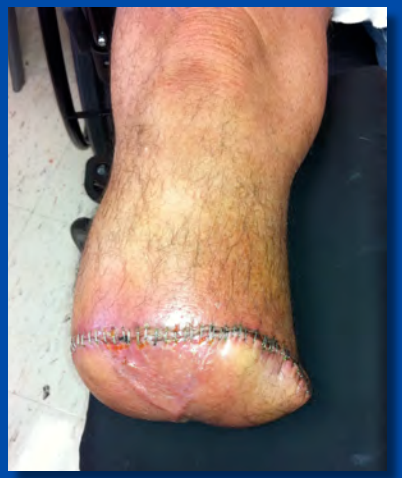








Google Images

Pain Society of the Carolinas 2015: Nerve Injury and Neuropathy

Thomas Buchheit, MD
Associate Professor
Director of Pain Medicine
Department of Anesthesiology
Duke University Medical Center
Durham VAMC

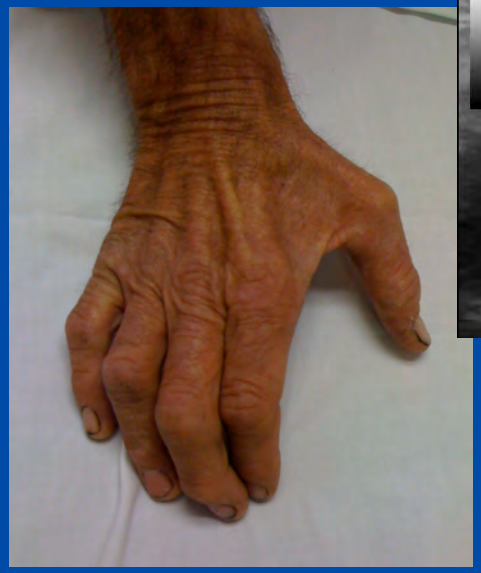
Disclosures

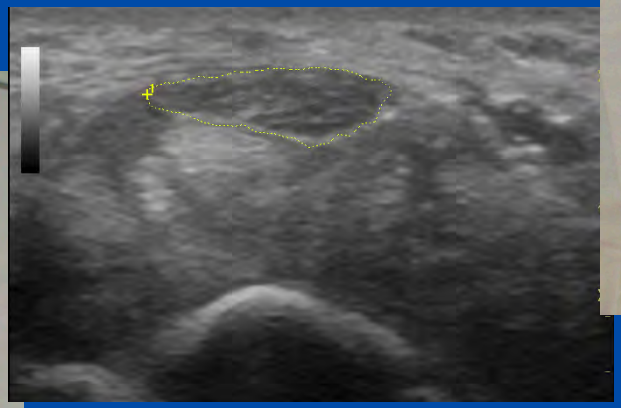
- Consulting:
  - Bioventus
  - DARA Bioscience
  - Thar Pharmaceuticals
- Research funding:
  - Department of Defense: CDMRP DM102142

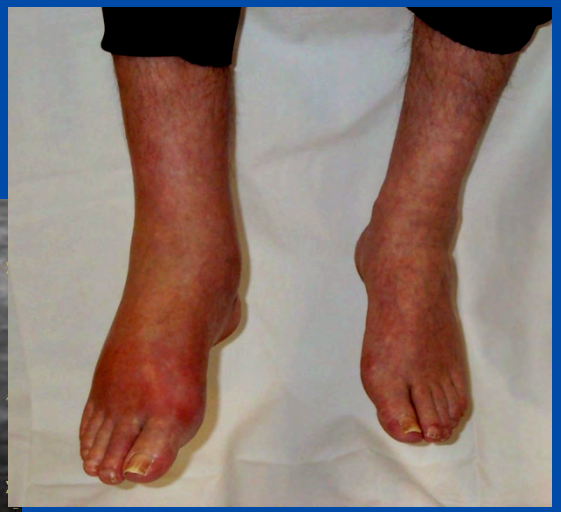
Outline

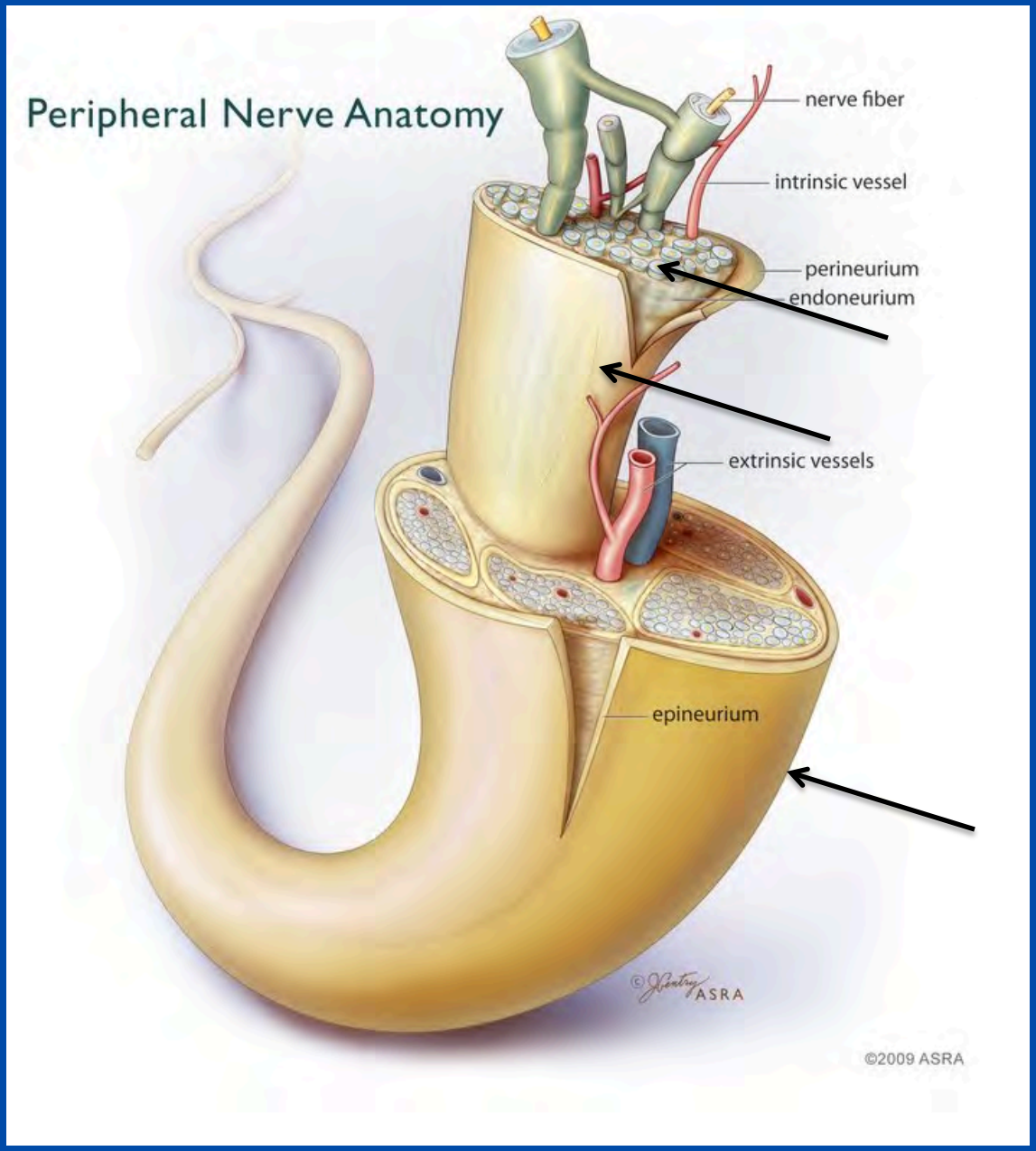
- Anatomy and imaging
- Physiology of nerve injury
- Current Therapies
- Future directions

Anatomy:
Types of Nerve Injury







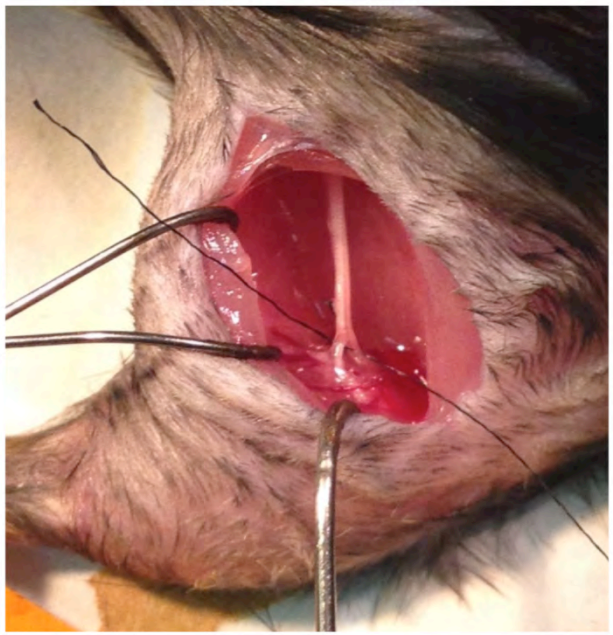

Peripheral Nerve Anatomy
nerve fiber
intrinsic vessel
perineurium
endoneurium
extrinsic vessels
epineurium
ASRA
©2009 ASRA

The Endoneural Environment

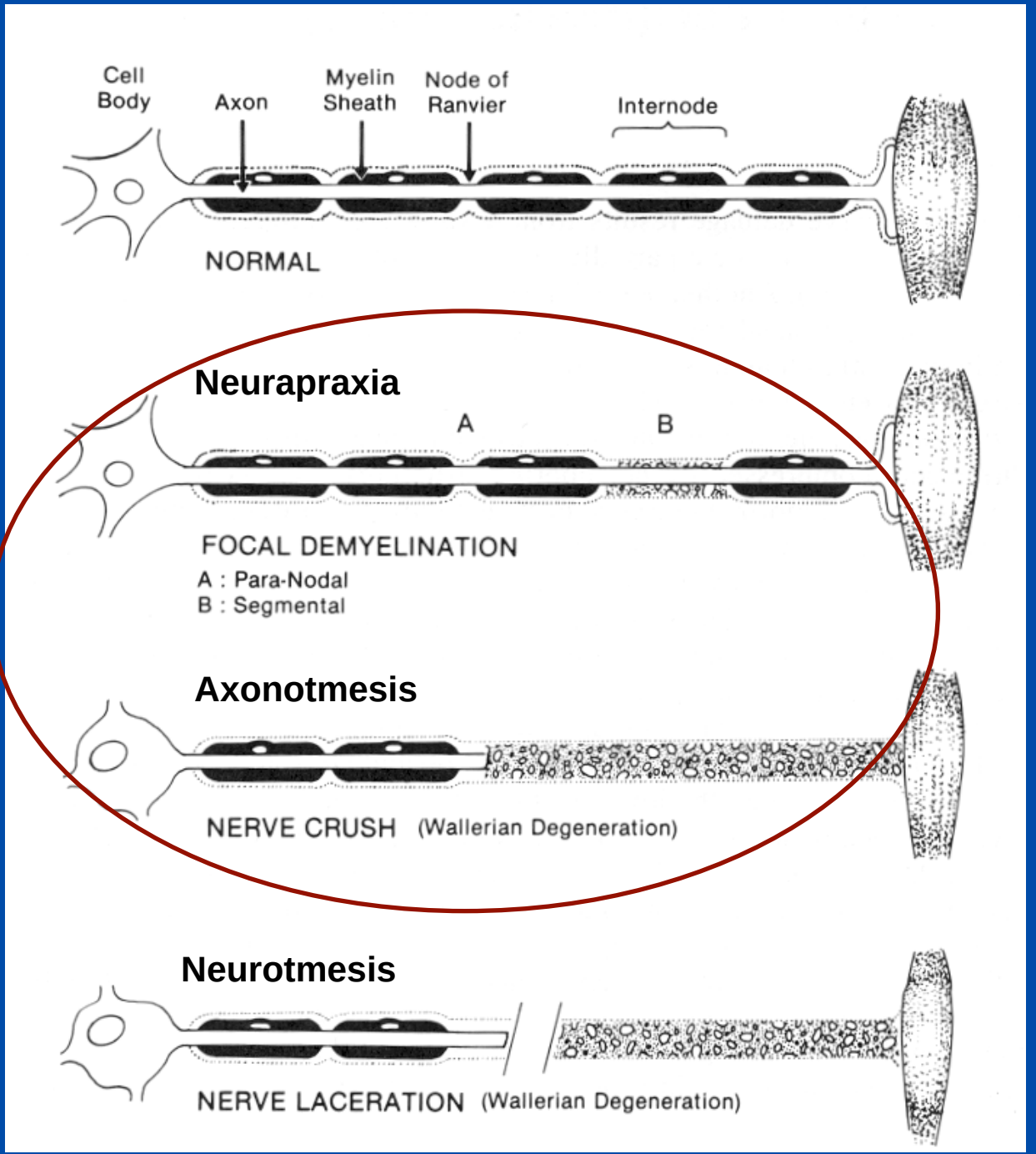
- Regulation occurs within the perineurium
  - Relatively impermeable
  - Sensitive to intrafascicular injection
  - Permeability altered by Schwann cell, macrophage and mast cell activity
- Neuropathies can be considered perturbations of endoneurial homeostasis

Mizisin: Homeostatic regulation of endoneurial microenvironment. Acta Neuropathol. 2011. 121:291

Nerve Response to Injury



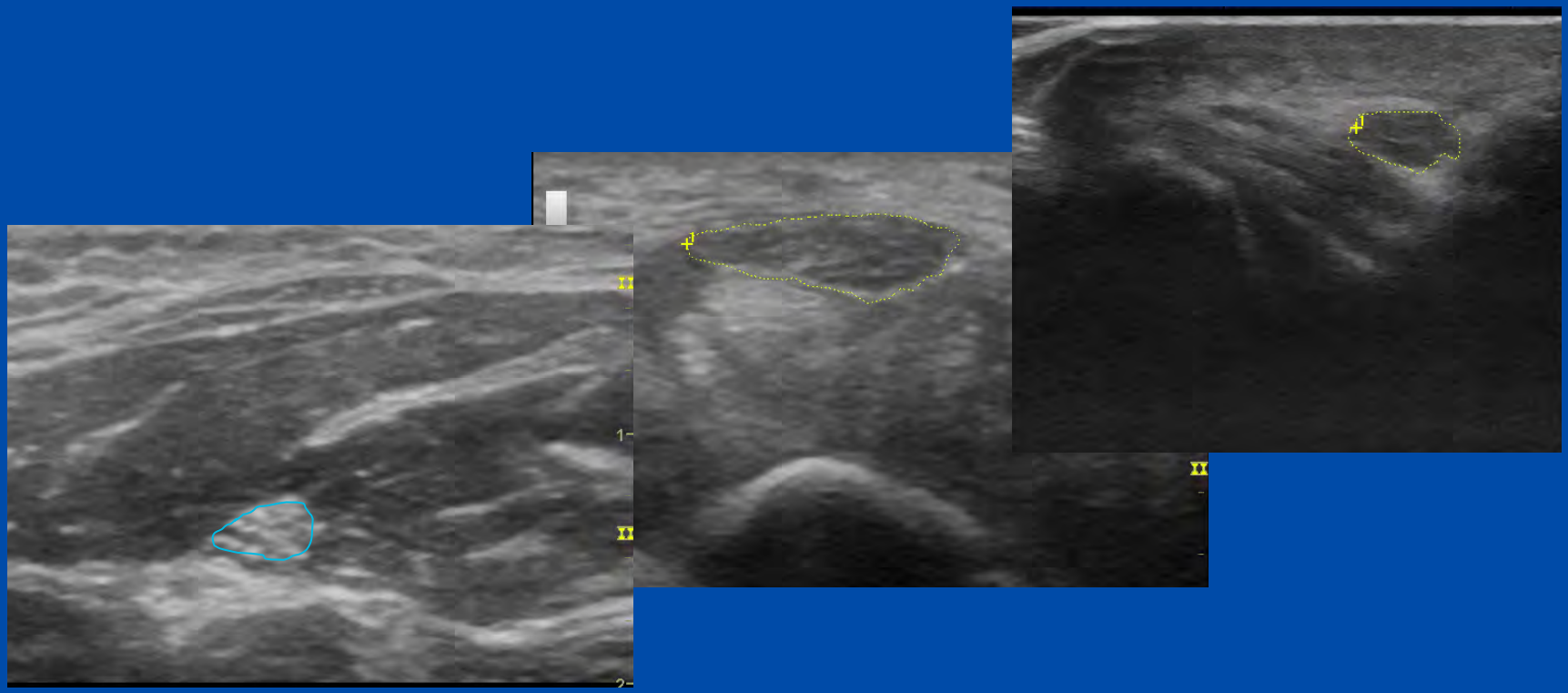
Stewart: Focal Peripheral Neuropathies
2nd, Ed.'93, Praven press



Degrees of Injury

- Neurapraxia: Temporary nerve dysfunction
  - Most patients will see recovery within 3 months or less
- Axonotmesis:
  - Wallerian degeneration
    - axonal and myelin degeneration distal to point of injury
  - Preserved epineurium and basal lamina
- Neurotmesis:
  - Complete division of a peripheral nerve and connective tissue structures
    - Will not regenerate along original channels
    - May form neuroma at transection site

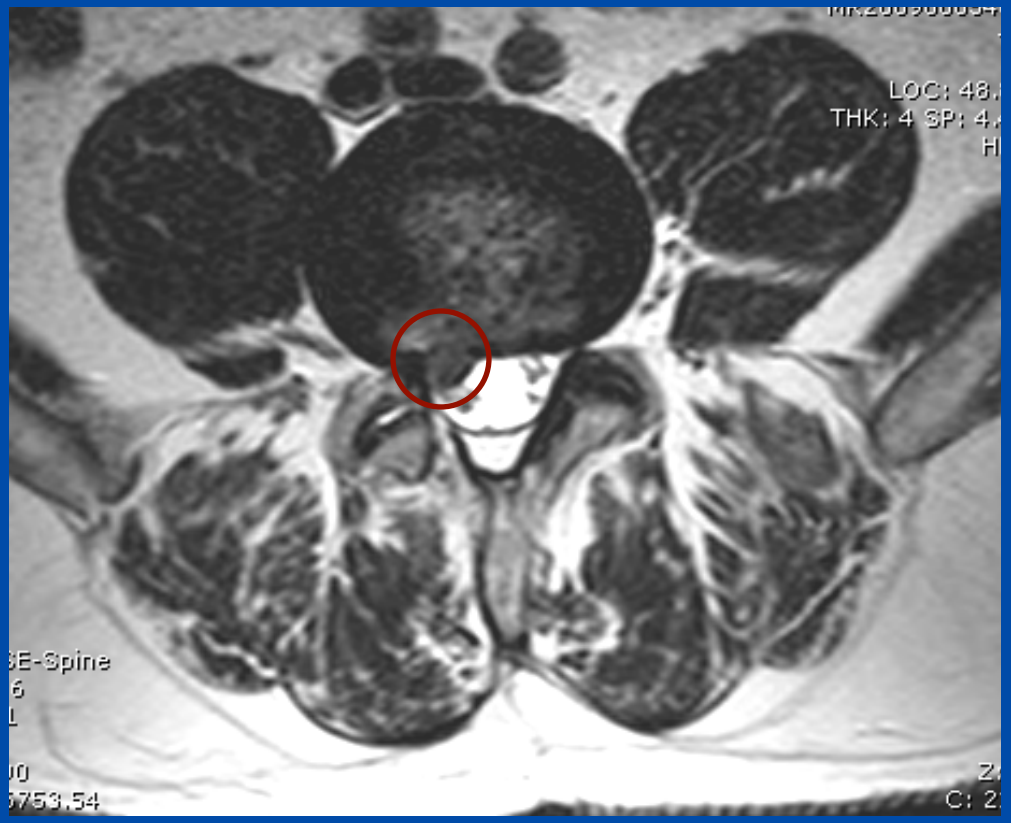
Compression Neuropathies:
Peripheral Nerve



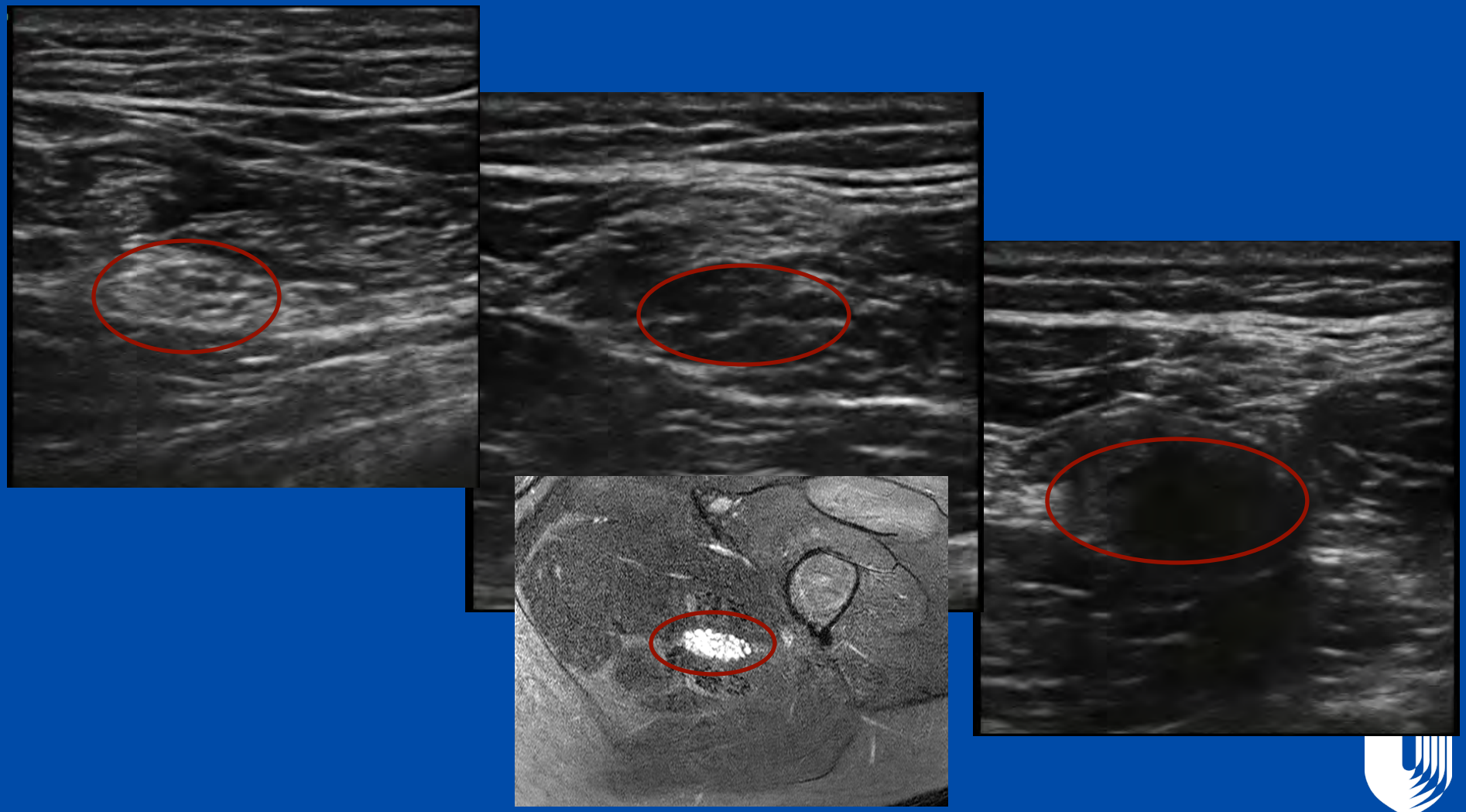
EMG Findings in CTS

- Most common compressive mononeuropathy (1-5% of population)
- Edema and thickening of vessel walls in the endoneurium
- Myelin thinning and fibrosis seen
  - Motor nerve conductions slow
  - Sensory fibers more sensitive to compression than motor fibers
- Axon loss can be seen in advanced cases

Compression Neuropathies:
Proximal Nerve/DRG



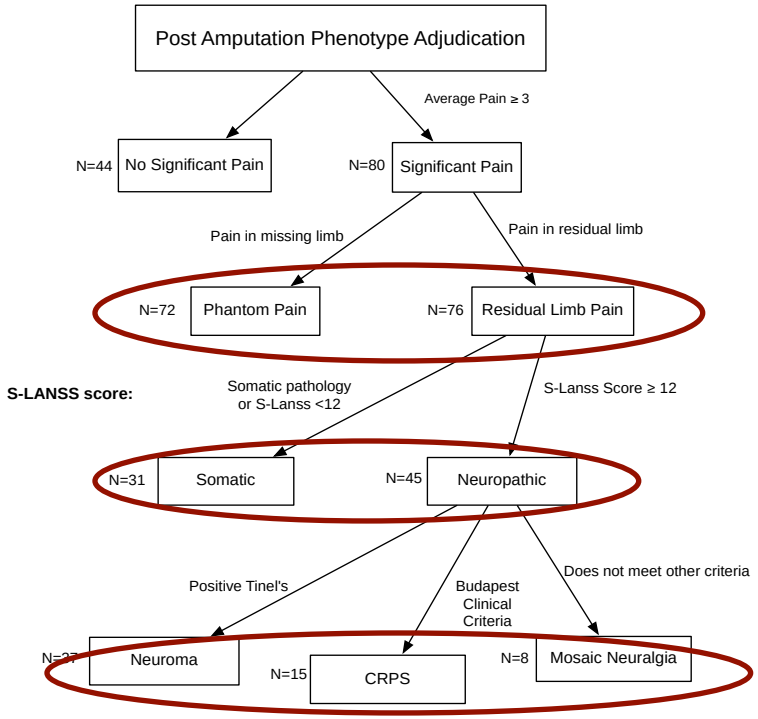
Transection Neuromas



Original

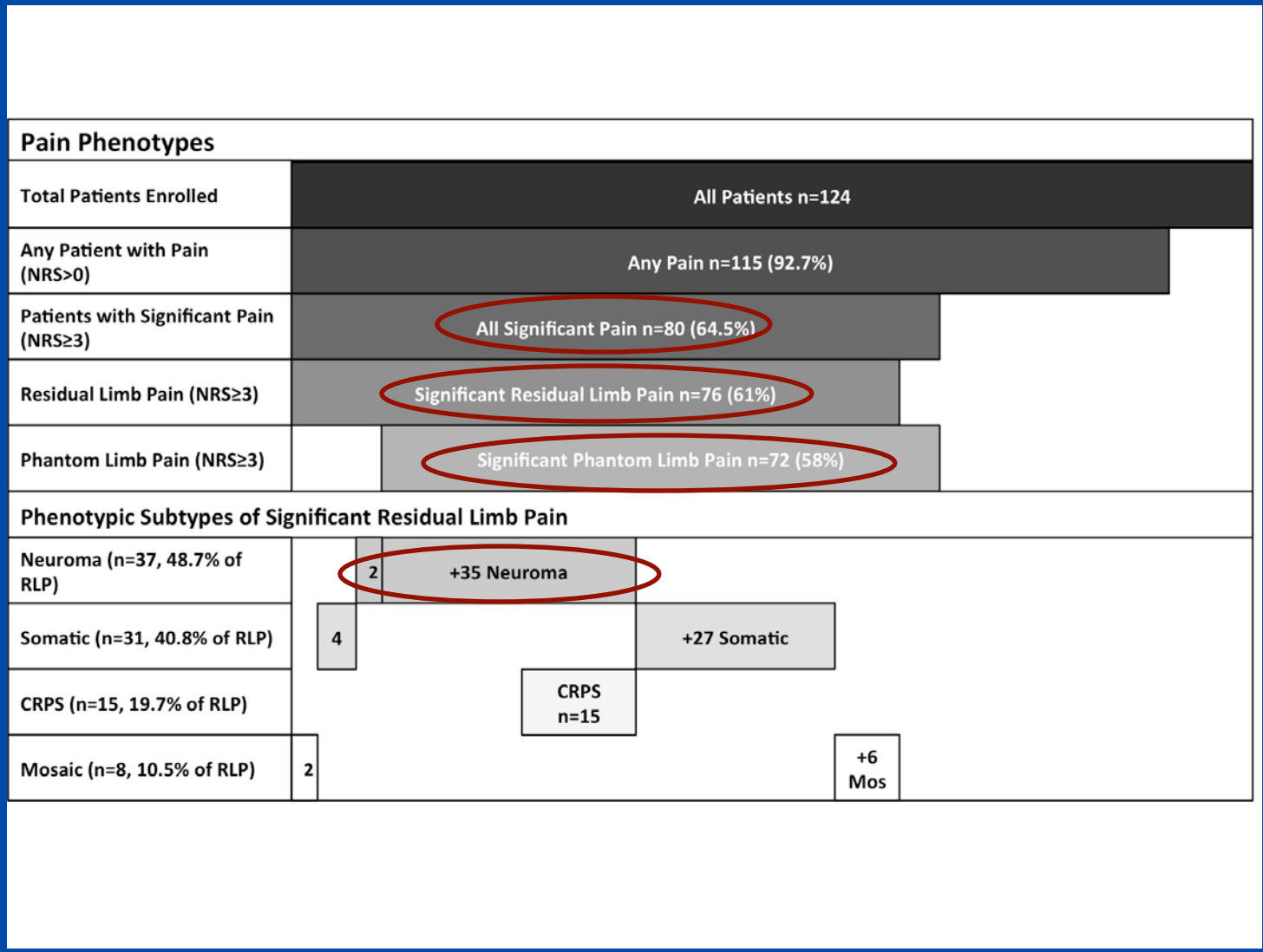
Pain Phenotypes and Associated Clinical Risk Factors Following Traumatic Amputation: Results from Veterans Integrated Pain Evaluation Research (VIPER)

Figure 1. Phenotype Adjudication Algorithm



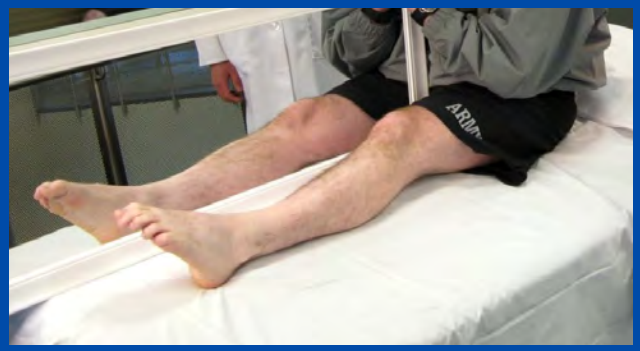
Buchheit T, and Van de Ven T,. Pain Phenotypes and Risk Factors Following Traumatic Amputation:. Pain medicine 2015

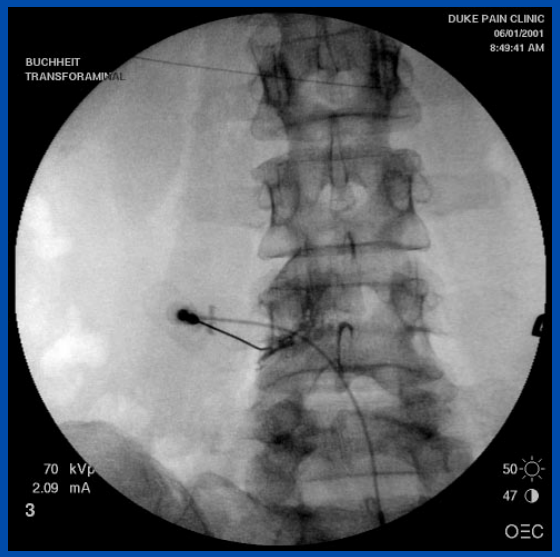
Pain Phenotype Results

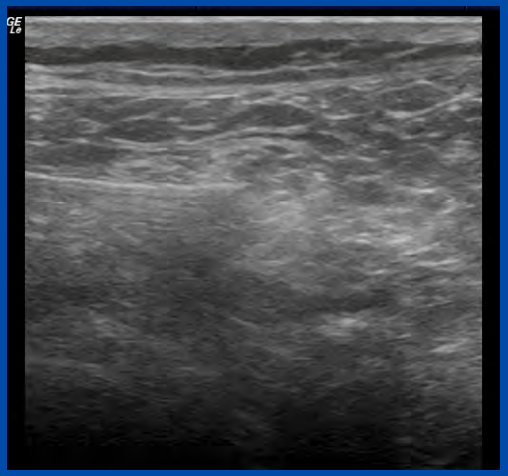


Buchheit T, and Van de Ven T,. Pain Phenotypes and Risk Factors Following Traumatic Amputation:. Pain medicine 2015

Is Phantom Pain a Central of a Peripheral Problem?

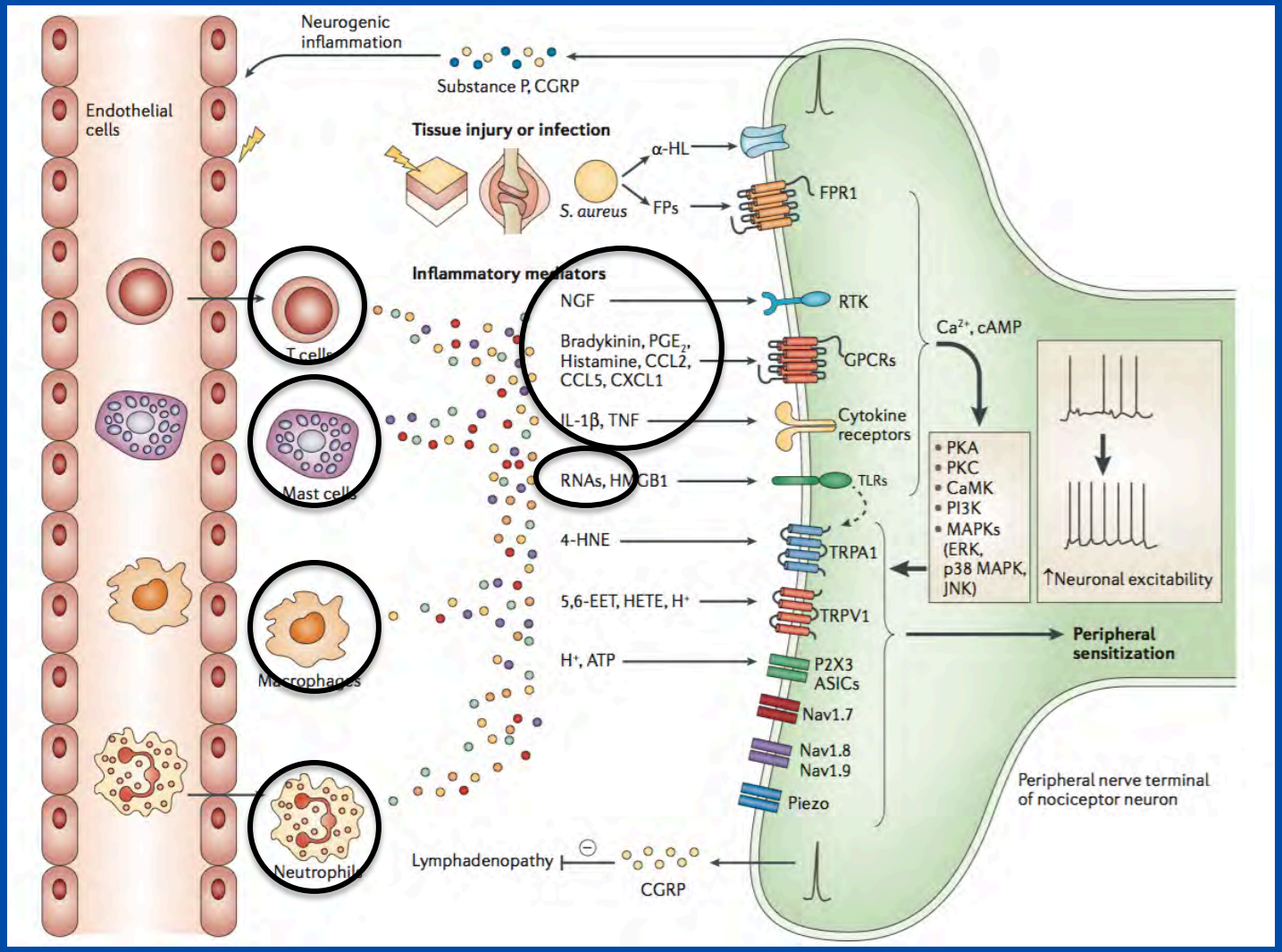






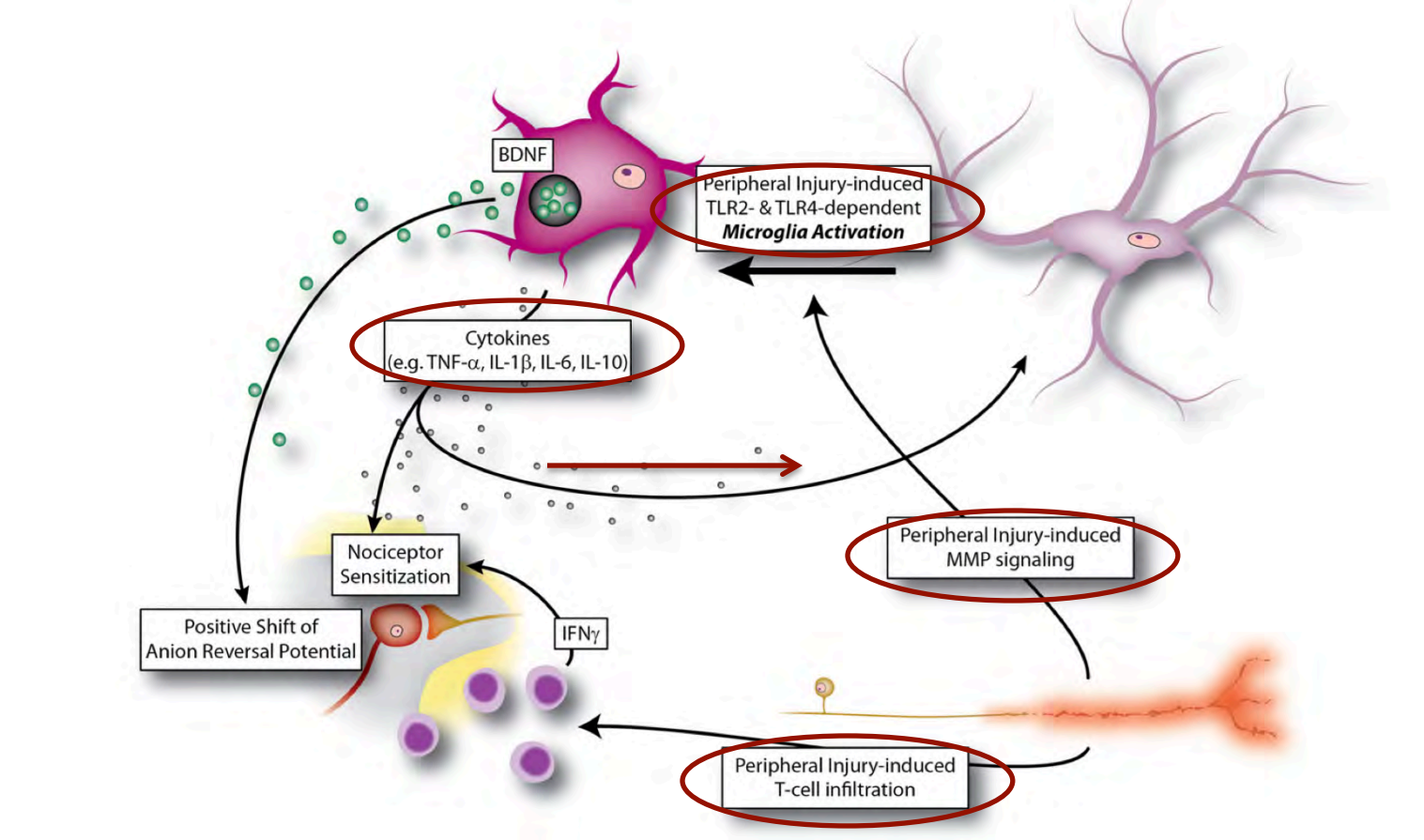
Physiology of Nerve Injury

Neuroinflammatory Mechanisms



Ji RR et al. Emerging targets in neuroinflammation-driven chronic pain. Nature. 2014;13:533–548.

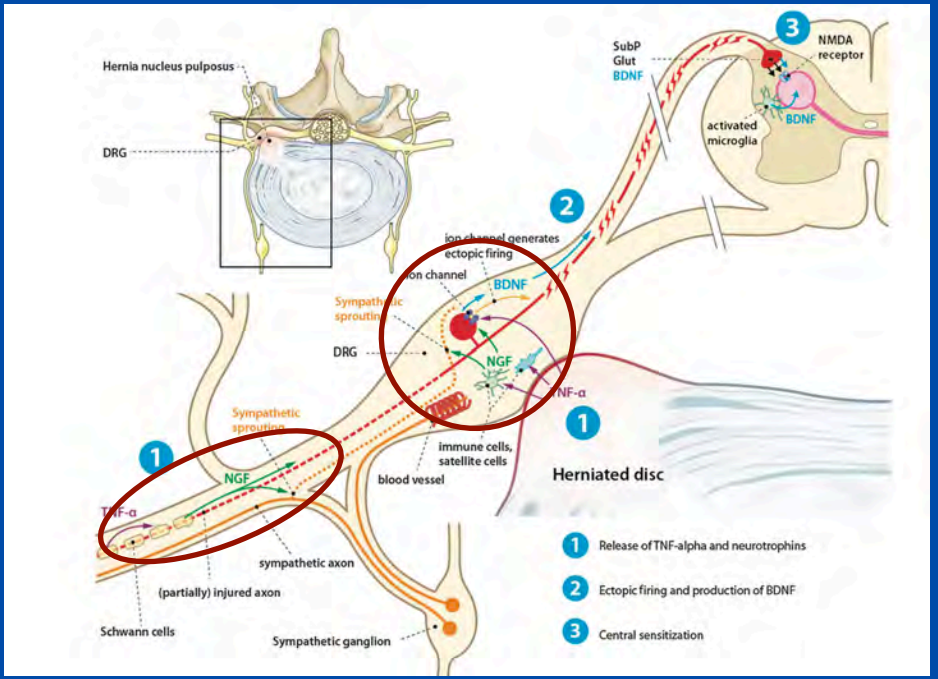
Neuroinflammatory Mechanisms



Von Hehn, Baron and Woolf: Deconstructing the neuropathic pain phenotype. Nature 2012

Neuroinflammatory Mechanisms in Disc Herniation

- TNF and other cytokines are released by Schwann cells at site of injury and DRG
- After peripheral nerve injury:
  - 25% of ectopic activity at peripheral axon
  - 75% at DRG



Van Boxem K, Huntoon M, Van Zundert et al. Pulsed Radiofrequency. RAPM 2014;39:149–159.

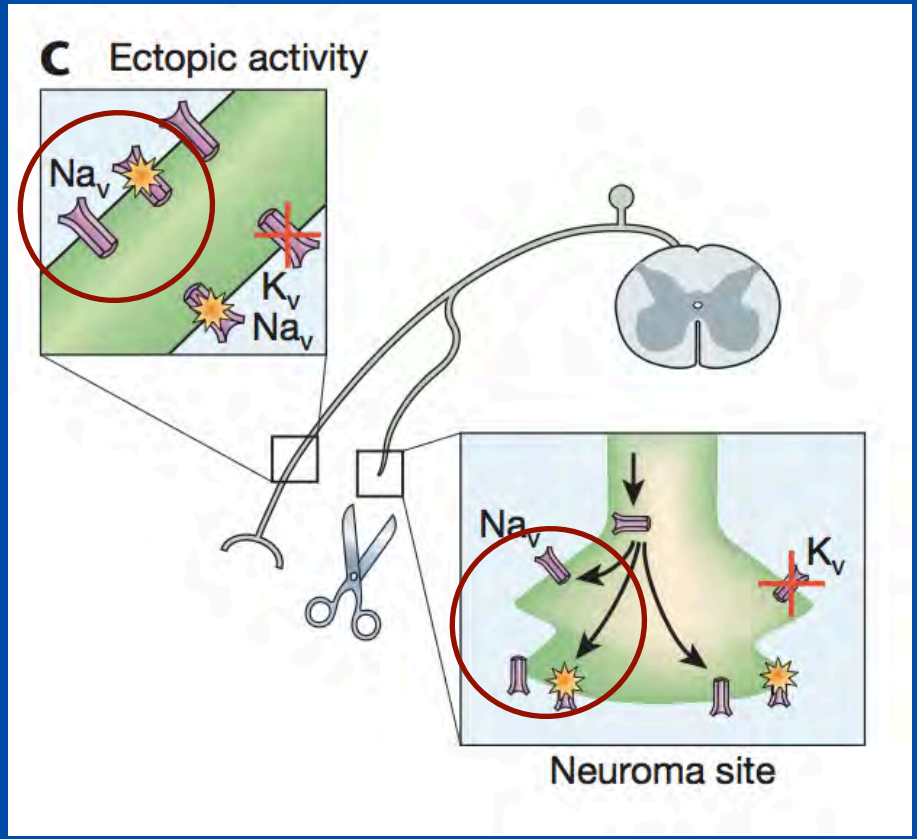
Inflammation-Driven Phenotypic Change

- Macrophage infiltration and cytokine release at site of axonal injury and DRG
  - Microglial activation
    - Microglia number increase by 2-4 fold in dorsal horn
  - Astrocyte activation persists for months

Ramer et al: Wallerian degeneration neuropathic pain and sympathetic sprouting in DRG. Pain. 1997; 72: 71-78
Raghavendra V et al Anti-hyperalgesic and morphine-sparing actions of propentofylline following nerve injury. Pain 2003:104:655-64
Gao Y-J, Ji R-R. Chemokines, neuronal-glial interactions, and central processing of neuropathic pain. Pharmacol Ther 2010:126;56-68

Neuroma Ectopic Activity

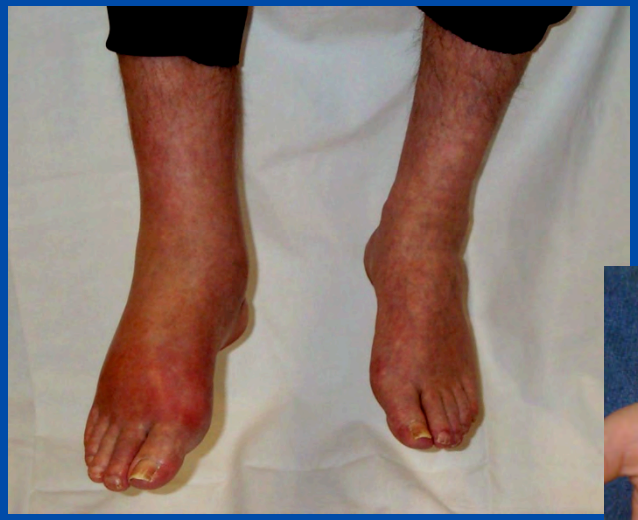
- Injury leads to:
  - Mechanical sensitivity
    - Focal demyelination of A-fibers at site of injury
  - Ectopic activity
    - Proliferation of Nav 1.7 and 1.8 channels at injury and DRG
  - Catecholamine sensitivity
    - Sympathetic sprouting at DRG

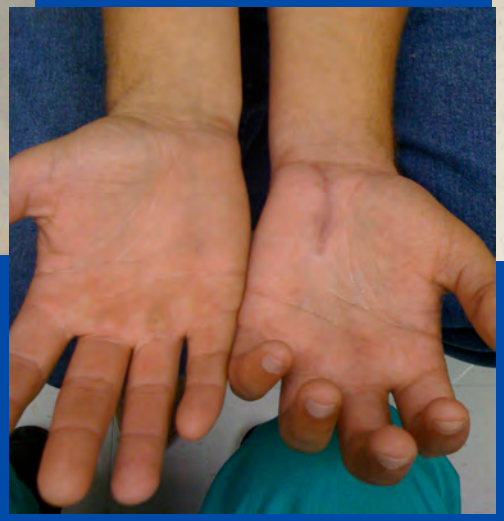


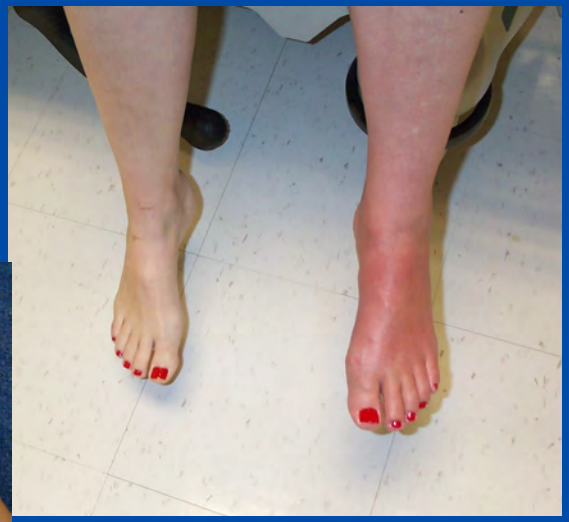
Blumberg. Discharge afferent fibers from neuroma. Pain. 1984. P 335-53.
Amir. Ectopic spike in neurons. J Neurosci. 2005 25(10) 2576-85.

Scholz and Woolf: Can we conquer pain. Nature Neuroscience. Nov 2002

Neuroinflammatory Mechanisms in the Clinic







Common Immune-Associated Neuropathic Pain Syndromes

- Myelinopathies:
  - Autoimmune Neuropathies (Guillain-Barré)
  - Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Multiple sclerosis
- CRPS

CRPS: Inflammatory Mechanism

- Serum concentrations of IL-6, and TNF-alpha are elevated
- Joint fluid demonstrates increased protein and neutrophils
- Cytokine inhibitors improve symptoms, especially in early warm CRPS
  - Animal model of fracture/casting
    - Demonstrates inflammatory changes that do not occur in soft tissue injury
- Improved CRPS symptoms in patients treated with IVIG, DMARDs, and bisphosphonates

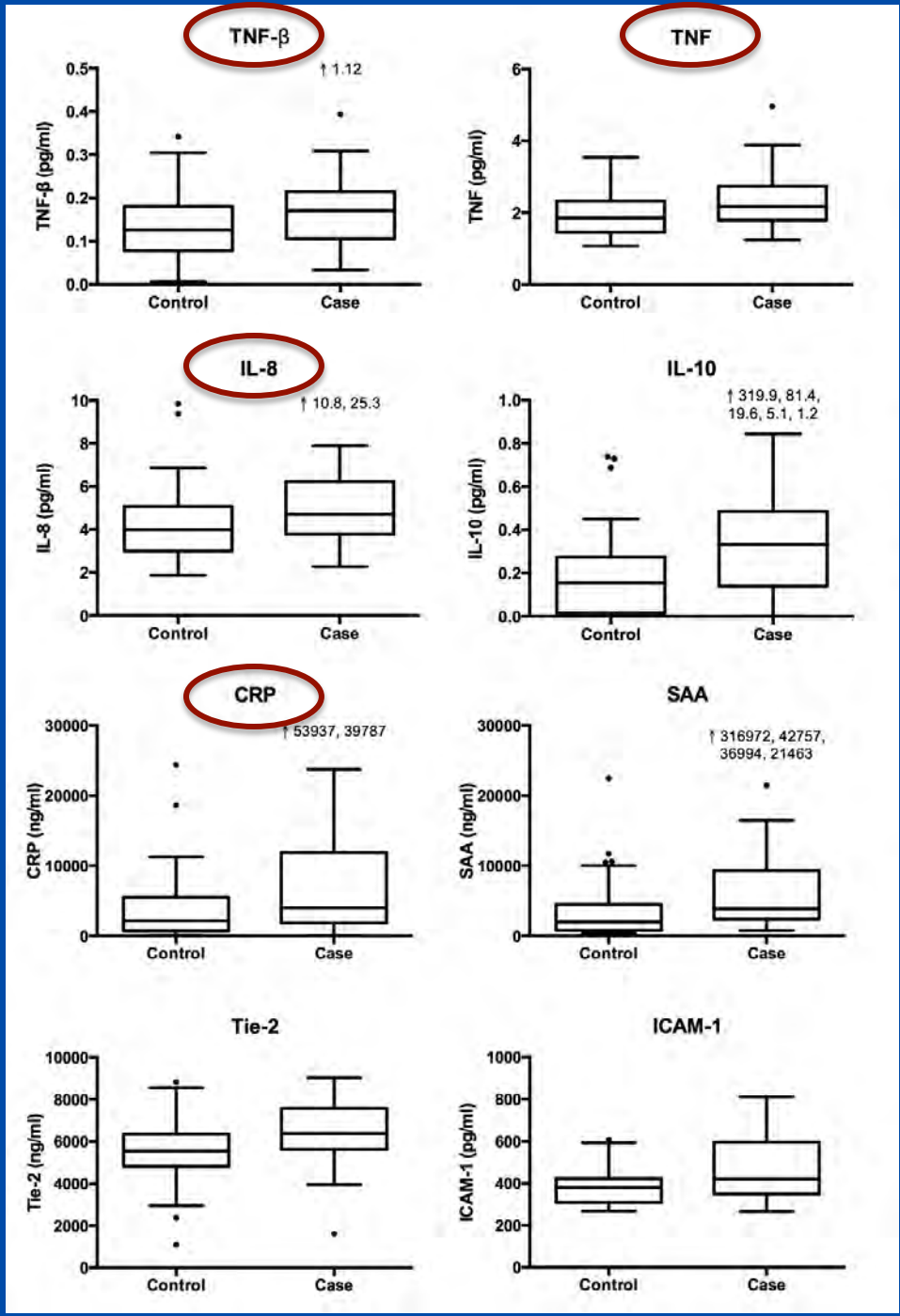
Wasner et al: CRPS– diagnostic, mechanisms, CNS involvement, and therapy. Spinal Cord 2003 (41) 61-75.
Li W-W, and Clark JD. Autoimmunity contributes to sensitization in complex regional pain syndrome. Pain 2014;155:2377–2389.

Neuroinflammation in non-CRPS Neuropathy

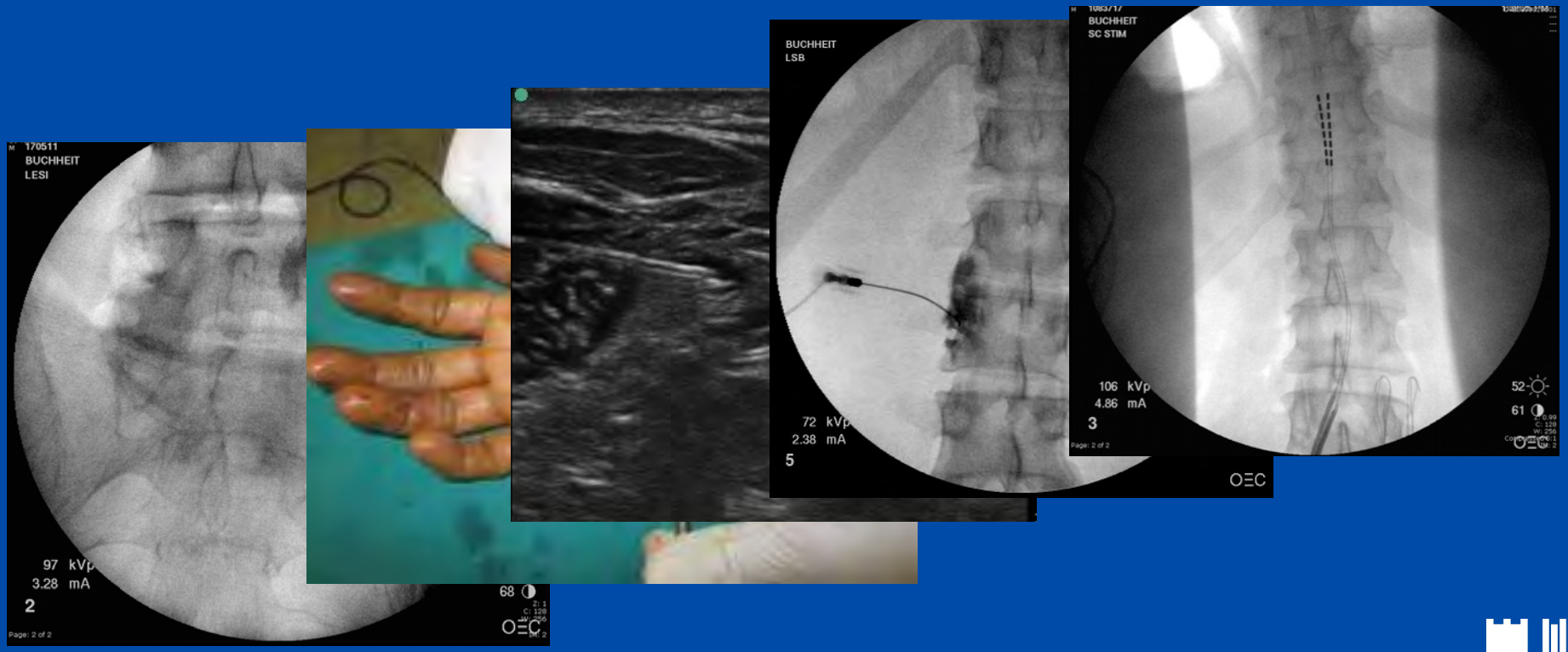
- Small fiber neuropathy:
  - Skin biopsy demonstrates increased gene expression of IL-1β, TNFα, IL-6, IL-8

Uceyler et al. Elevated proinflammatory cytokine expression in skin in small fiber neuropathy. Neurology. 2010 Jun 1;74(22):1806-13

Are there differences in systemic cytokine levels in patients with persistent pain after amputation?

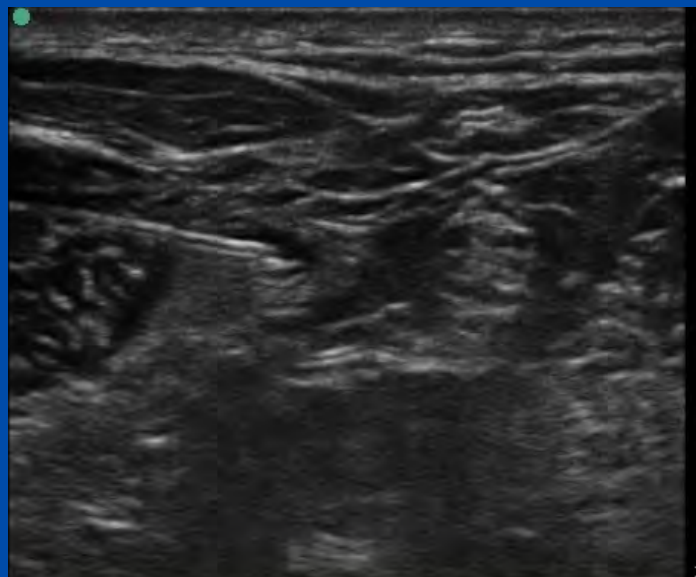


Current Therapies



Smith and Gomez: Local injection therapy of neuromata.J Bone Joint Surg 52A: 71, 1970
Martinez: Efficacy of minocycline after discectomy. An RCT. Pain 2013: 154: 1197

Neurolytic Therapies

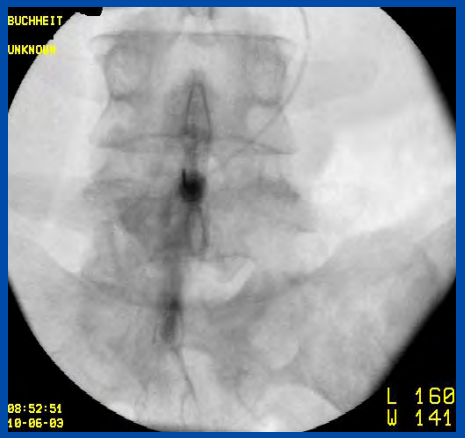


Neurolytic Therapies for Neuroma and Nerve Injury Pain

- Radiofrequency Lesioning
- Cryoneurolysis
- Chemical Neurolysis
  - 2 observational trials demonstrating significant improvement in treatment of amputation neuromas

Kirvela O: Treatment of painful neuromas with neurolytic blockade. *Pain.* May 1990;41(2):161-165.
Gruber et al: Sonographically guided phenol installation of stump neuroma: Amer J. Roentgenology. 190 (5): 1263-9, 2008.

Prevention in an Amputation Injury Model



Preventive Analgesic in Amputation Injury

- Ketamine:[1]
  - No significant difference in the incidence of phantom pain at 6 months (47% phantom pain in ketamine and 71% in control group, p=0.28)
- Gabapentin[2]:
  - No effect when started on POD #1 and continued 30 days at 2,400mg/d
- Memantine[3]:
  - No effect when 20mg/day memantine compared with placebo

1. Hayes C et al. Perioperative intravenous ketamine infusion for the prevention of persistent post-amputation pain: a randomized, controlled trial. Anaesth IntensiveCare2004;32:330 – 8
2. Nikolajsen L. A randomized study of the effects of gabapentin on postamputationpain.Anesthesiology2006;105:1008 –15
3. Nikolajsen L, Gottrup H, Kristensen AG, Jensen TS. Memantine in the treatment of neuropathic pain after amputation: a randomized, double-blinded, cross-over study. Anesth Analg 2000;91:960 – 6

Preventive Trials for Post-amputation Pain

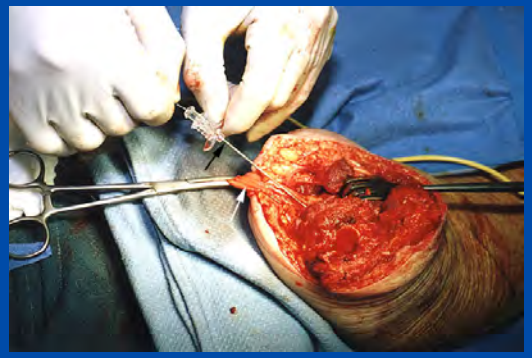
- 2010 systematic review
  - 11 studies of epidural and perineural catheter use
    - Good evidence for efficacy in treating acute postoperative pain
    - No robust evidence that preventive techniques reduce the incidence of chronic pain

Ypsilantis: Pre-emptive analgesia for chronic limb pain after amputation for peripheral vascular disease: A systematic review. Ann Vasc Surg 2010; 24:1139-46

Preventive Trials:
Is Duration of Therapy Important?

- Longer-term perineural catheter use:
  - Borghi 2010
    - Average catheter duration 30 days
    - 84% pain free at 12 months

Borghi et al: Prolonged peripheral neural blockade after amputation. 2010 .Anes Analg 111 (5) 1308-1305.



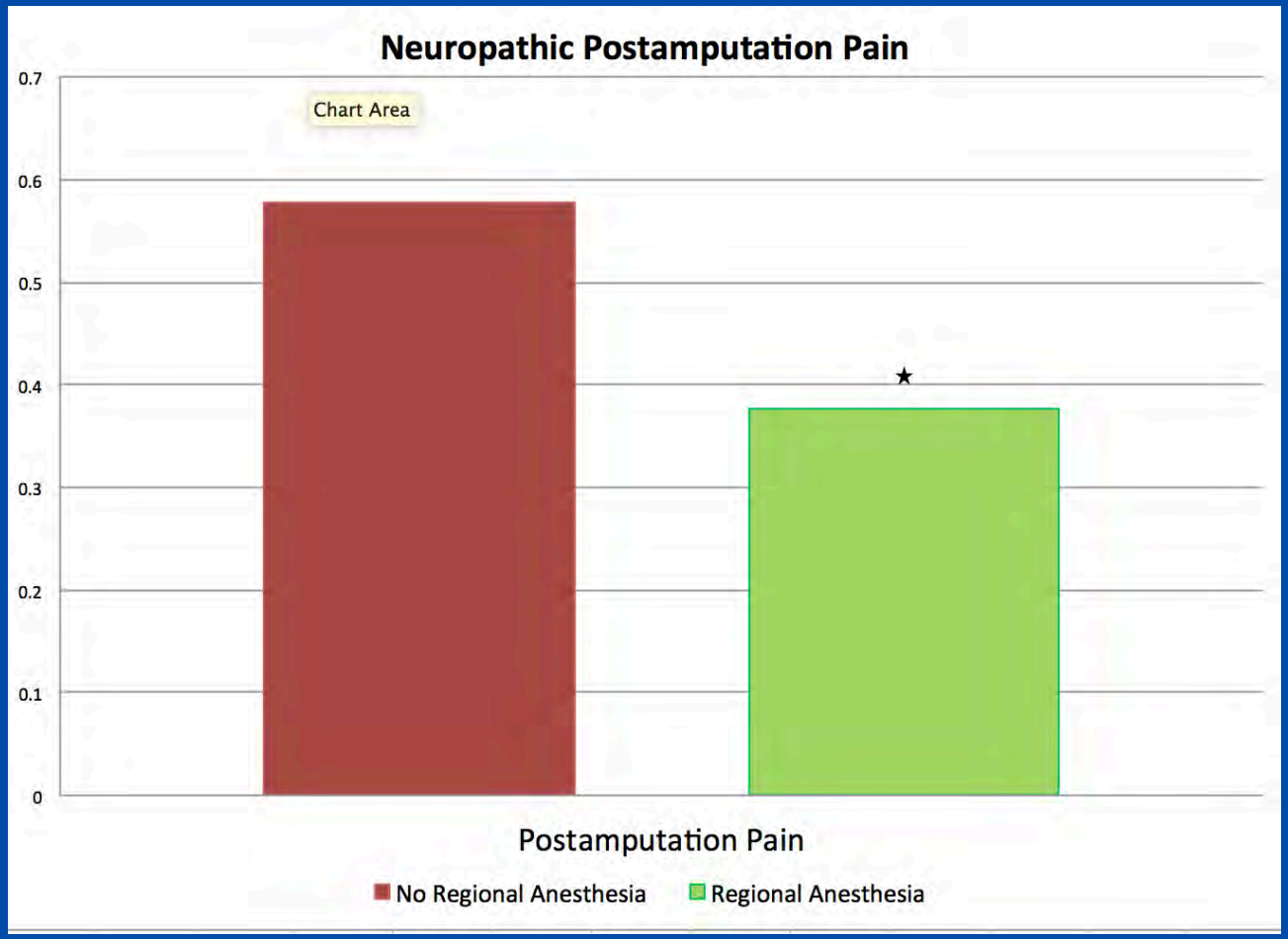
Risk Factors for Post-amputation Pain

	Chronic Pain (cases)	Phantom Pain (cases)	RLP (cases)	RLP-Somatic (cases)	RLP-Neuropathic (cases)	RLP-Neuroma (cases)	RLP-CRPS (cases)	RLP-Mosaic (cases)	Neuropathic Pain (All)
	OR (CI) [p]	OR (CI) [p]	OR (CI) [p]	OR (CI) [p]	OR (CI) [p]	OR (CI) [p]	OR (CI) [p]	OR (CI) [p]	OR (CI) [p]
Clinical Factor									
PCS	13.39 (1.73-103.87)	6.20 (0.34-112.49)	3.05 (0.16-59.29)	0.48 (0.15-1.50)	2.71 (0.87-8.45)	2.47 (0.85-7.14)	1.82 (0.53-6.20)	1.08 (0.20-5.85)	3.78 (1.28-11.18)
[p value]	***[0.0016]****	[0.1876]	[0.5676]	[0.194]	[0.0735]	[0.0899]	[0.3474]	[1.0000]	***[0.0103]****
PTSD-M	10.08 (1.28-79.14)	1.72 (0.20-15.14)	2.31 (0.12-45.15)	0.19 (0.04-0.89)	6.92 (1.44-33.17)	6.67 (1.71-26.04)	7.13 (1.98-25.70)	0.58 (0.07-5.12)	9.28 (2.01-42.88)
[p value]	***[0.0099]****	[1.0000]	[1.0000]	***[0.0373]****	***[0.0088]****	***[0.0038]****	***[0.0029]****	[1.0000]	***[0.0010]****
PHQ-9	2.40 (0.94-6.13)	9.13 (0.51-164.62)	4.46 (0.23-86.00)	0.38 (0.13-1.09)	3.53 (1.22-10.19)	3.72 (1.36-10.15)	4.59 (1.42-14.91)	0.71 (0.13-3.79)	4.46 (1.81-10.99)
[p value]	[0.055]	[0.0520]	[0.3036]	[0.0624]	***[0.0142]****	***[0.0081]****	***[0.010]****	[1.0000]	***[0.0006]****
Regional Catheter	0.63 (0.30-1.33)	5.00 (0.58-42.80)	1.96 (0.19-19.70)	1.24 (0.50-3.12)	0.91 (0.37-2.25)	1.42 (0.58-3.51)	2.09 (0.67-6.49)	0.20 (0.02-1.71)	0.44 (0.21-0.92)
[p value]	[0.227]	[0.142]	[1.0000]	[0.6423]	[0.8397}	[0.4443]	[0.2034]	[0.142]	***[0.0269]****

Table 4: Clinical risk factors for development of post-amputation chronic pain subtypes.

The odds-ratios for development of chronic pain (all types), neuropathic pain, phantom limb pain, all types of residual limb pain, somatic residual limb pain, residual limb pain from presence of neuroma, complex regional pain syndrome, mosaic neuropathic residual limb pain and all neuropathic residual limb pain are reported above with p-values in brackets. Factors associated with significant risk of a specific pain subtype (p-value <0.050) are marked with an asterisk and italicized. The data presented in the final column include total patients with neuropathic pain regardless of case or control status.

Incidence of Chronic Pain with Regional Catheter Post-Injury



Future directions

We can’t (and shouldn’t?) prevent inflammation after injury.

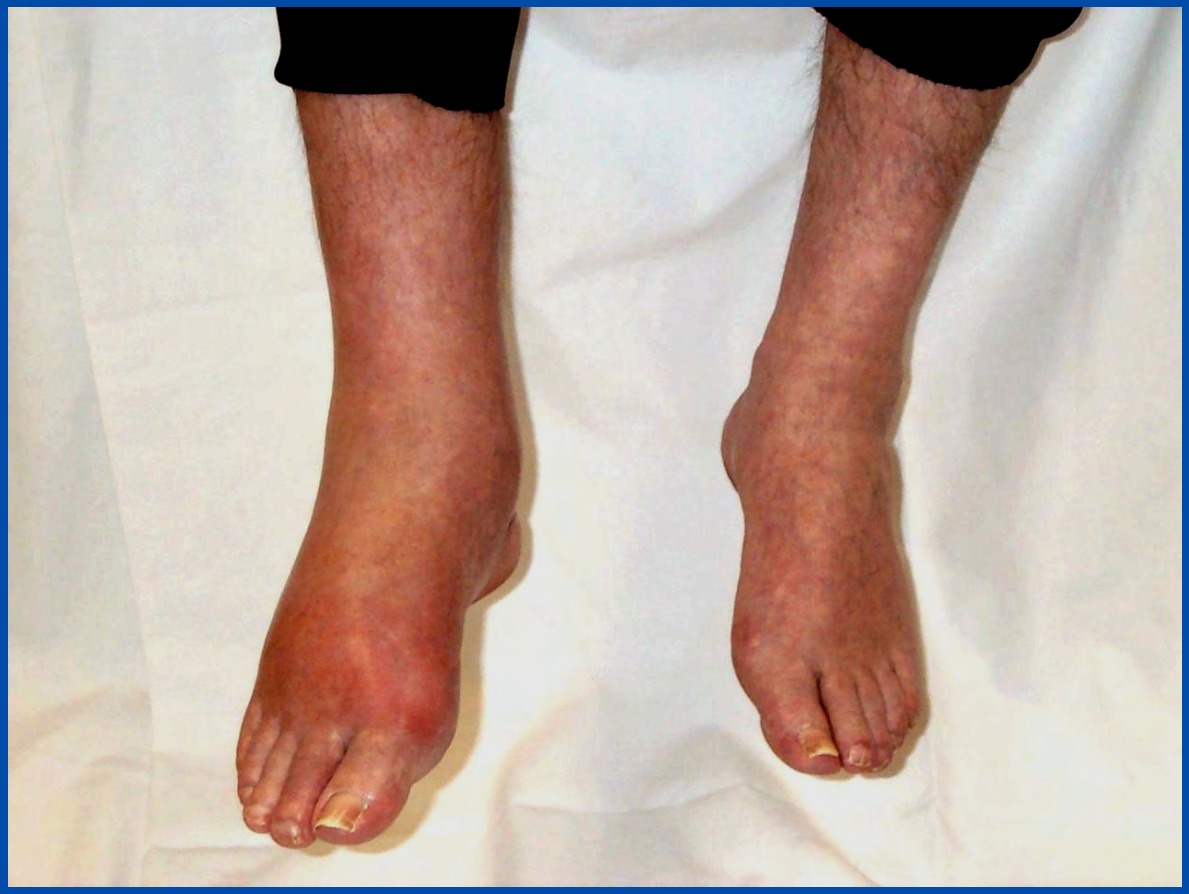
Can we facilitate recovery and resolution?

Future Treatments

- Immune modulation
  - IVIG
  - Bisphosphonates
  - Cytokine inhibitors
    - Positive pilot data for etanercept use for neuromas
- Epigenetic intervention
- Novel pathway discovery
  - Wnt, NOD

Dahl E, Cohen SP. Perineural injection of etanercept as a treatment for postamputation pain. Clin J Pain. 2008 Feb;24(2):172-5

Why aren’t we treating the inflammatory component of CRPS routinely?



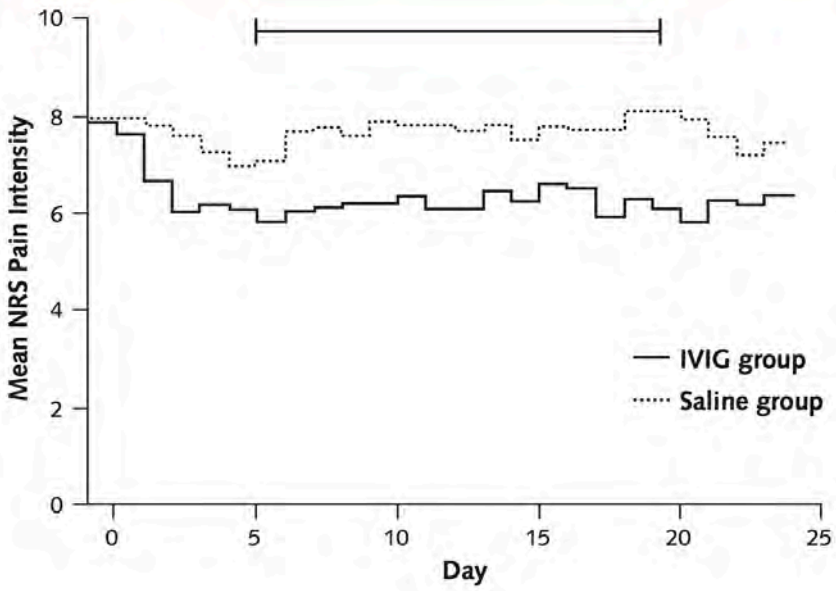
ARTICLE | Annals of Internal Medicine

Intravenous Immunoglobulin Treatment of the Complex Regional Pain Syndrome

A Randomized Trial

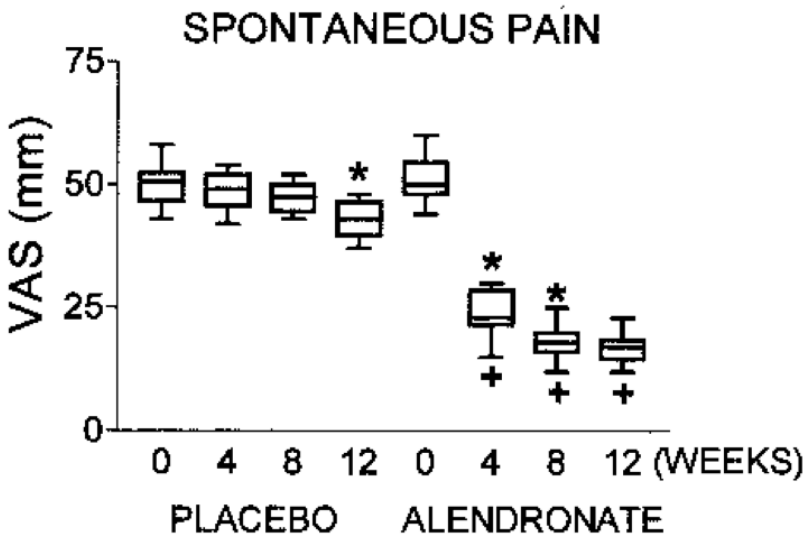
Andreas Goebel, MD, PhD; Andrew Baranowski, MD; Konrad Maurer, MD; Artemis Ghiai, RGN; Candy McCabe, PhD; and Gareth Ambler, PhD

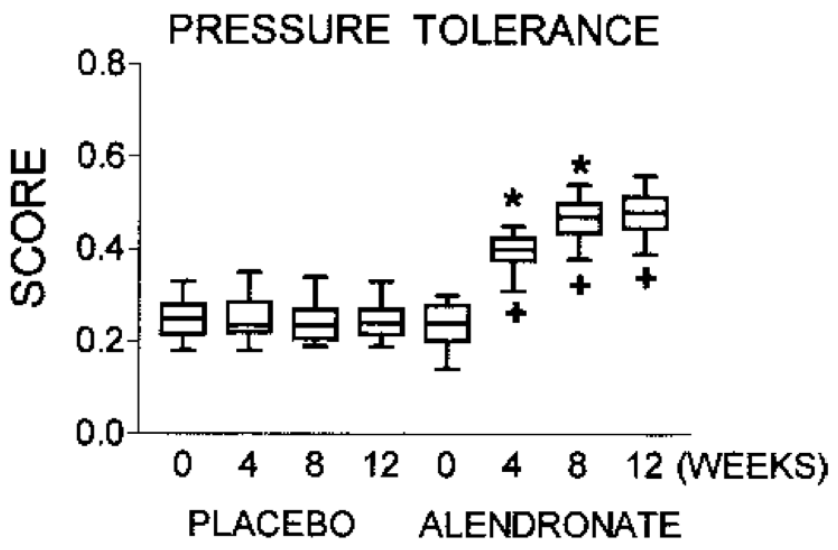
Figure 2. Mean pain intensity for each day after the infusion.



Role of Alendronate in Therapy for Posttraumatic Complex Regional Pain Syndrome Type I of the Lower Extremity

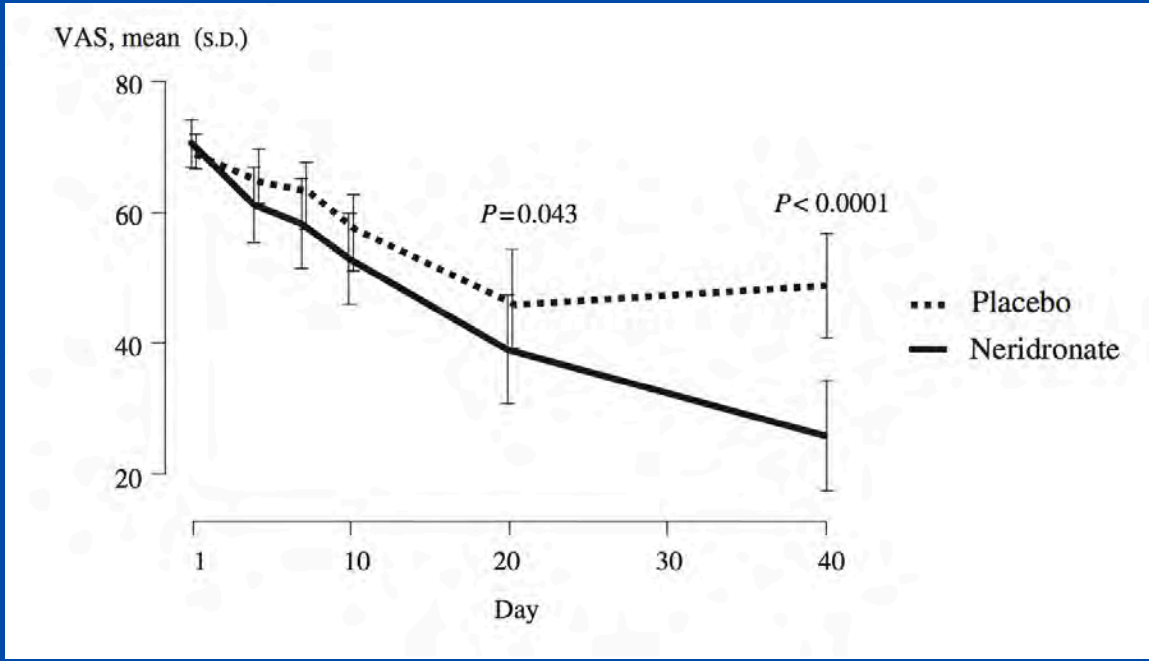
Daniel-Henri Manicourt, Jean-Pierre Brasseur, Yves Boutsen, Geneviève Depreseux, and Jean-Pierre Devogelaer





Treatment of complex regional pain syndrome type I with neridronate: a randomized, double-blind, placebo-controlled study

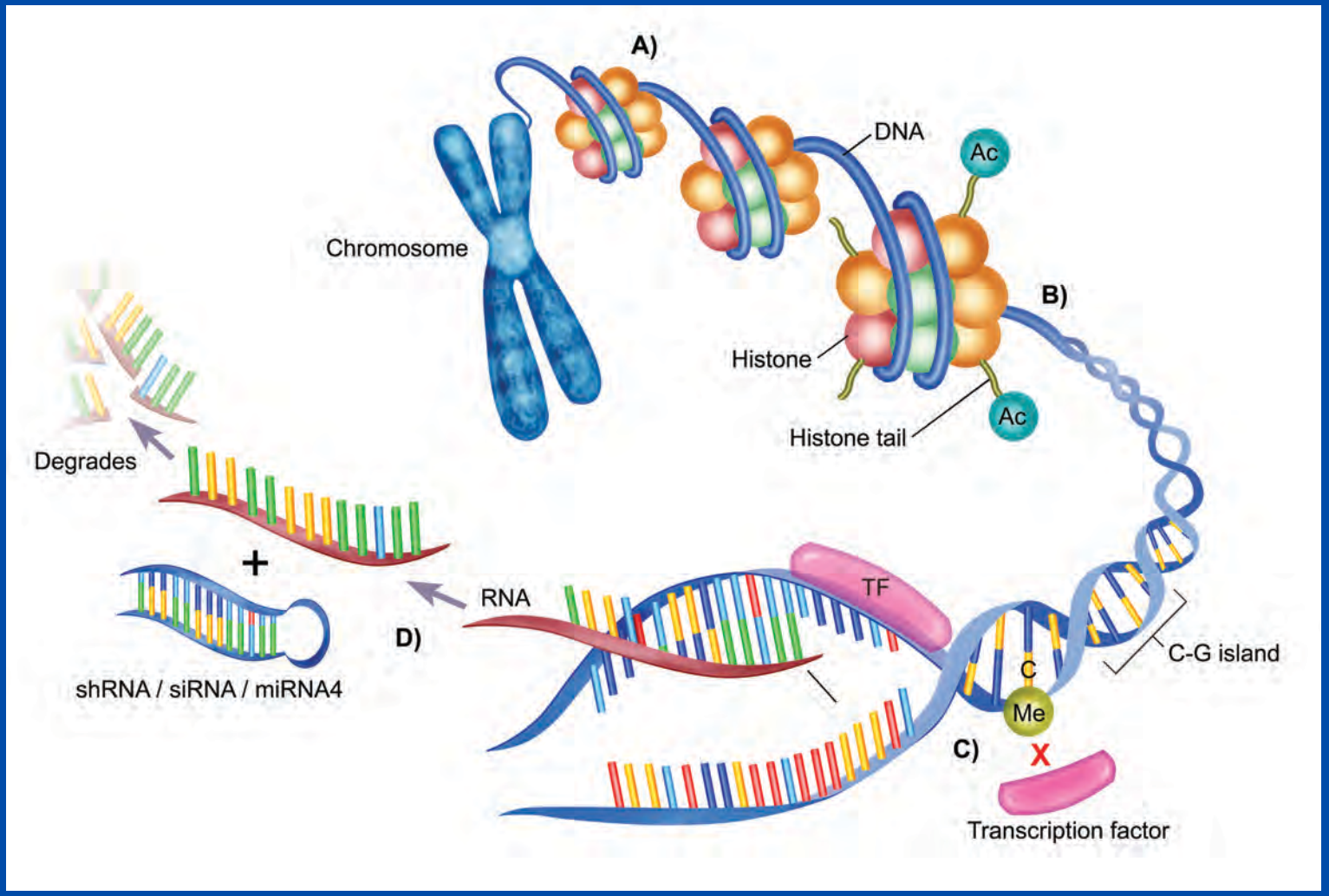
Massimo Varenna[1], Silvano Adami[2], Maurizio Rossini[2], Davide Gatti[2], Luca Idolazzi[2], Francesca Zucchi[1], Nazzarena Malavolta[3] and Luigi Sinigaglia[1]



What causes these inflammatory and expression changes after injury?

Epigenetic Modifications

Epigenetic Mechanisms



Buchheit T, Van de Ven T, Shaw A. Epigenetics and the transition from acute to chronic pain. Pain medicine 2012;13:1474–1490.

Can we alter gene expression?

Epigenetics Mechanism	Drug	Action	Clinical Use	Comments
Histone Deacetylase Inhibitor	Valproic Acid	Inhibits Class I and II HDAC	Seizures, Pain	Effective for migraine prophylaxis
	Givinostat	Inhibits Class I and II HDAC	Juvenile idiopathic arthritis	Effective in human arthritis trial
	Tricostatin A (TSA)	Inhibits Class I and II HDAC	Laboratory only	Produces analgesia in animal models. Enhances μ-opioid receptor transcription
	Suberoylanilide hydroxamic acid (SAHA)	Inhibits Class I HDAC	Laboratory only	Produces analgesia in animal models
DNA Methylation	Glucosamine	Prevents demethylation of IL-1β gene promoter	Arthritis pain	Common clinical use. Effect on IL-1β reduces inflammatory cytokine production
	Valproic Acid	Induces demethylation of Reelin promoter	Seizures, Pain	Reelin modulates NMDA function and pain processing
	L-methionine	Induces methylation at glucocorticoid receptor promoter gene	Dietary Supplement	Alters experimental stress response. Used as dietary supplement for arthritis
RNA Interference	SiRNA targeted to NMDA receptor subunits	Gene silencing of NR1 and NR2 subunits of NMDA	Experimental	Produces analgesia in animal models
	SiRNA to P2X3	Gene silencing of P2X3	Experimental	Produces analgesia in animal models. No observed neurotoxicity with intrathecal use
	SiRNA to TNF-α	Gene silencing of TNF-α	Experimental	Produces analgesia in animal models

Conclusions

- Proper diagnosis (better phenotyping) is a precursor to improving therapies
- Neuroinflammation is a part of most neural injury pain states regardless of injury site
- Preventive techniques may be effective with longer duration of therapy
- “Next generation” therapies will likely include immune modulation and epigenetic intervention