

**Research Design Considerations for Clinical Trials of
Pre-Emptive Analgesia and the Secondary Prevention of
Chronic Pain**

Chronic Neuropathic Low Back Pain

Prepared for:
IMMPACT XI
6 June 2009
Arlington, Virginia

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University of Rochester

Overview

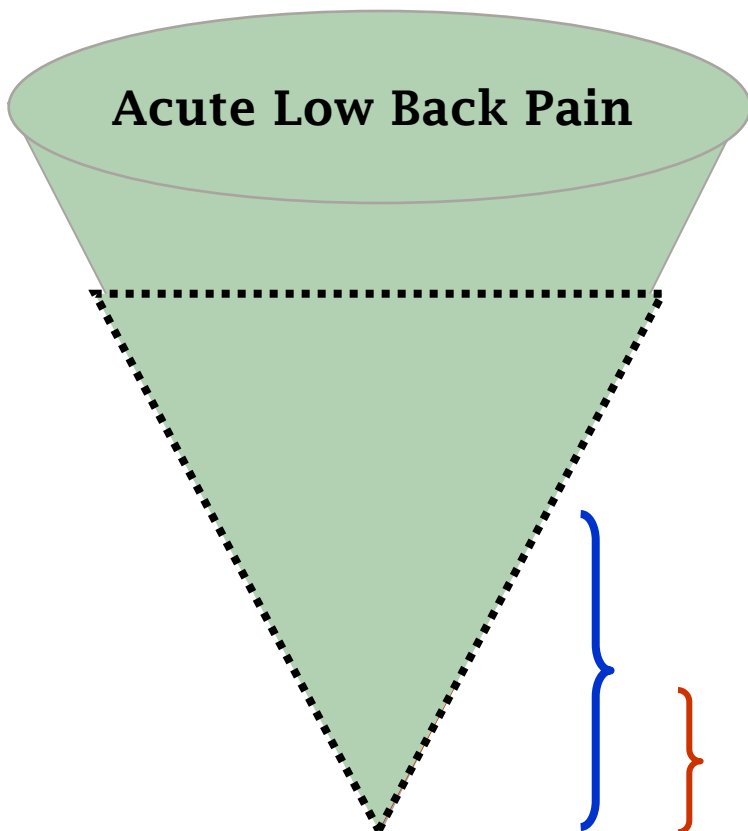
The Radicular Hypothesis

Two Condition-Specific Approaches

Prevention: Post Spine Surgery Neuropathic Pain Syndromes

Preemption: Neurogenic Intermittent Claudication

The Relapsing / Remitting Burden of Low Back Pain



17.4 million US adults will have an episode of severe acute low back pain



5.7 million will have low back pain of moderate intensity one year later



3.5 million will have substantial activity limitation related to low back pain

Proposed Core Measures for Evaluating Low Back Pain Treatment

IMMPACT

- **Pain**
- **Physical Functioning**
- **Rating of Improvement and Satisfaction with Treatment**
- **Symptoms and Adverse Events**
- **Participant Disposition (adherence to treatment and premature withdrawal)**

Deyo et al

- **Pain Symptoms**
- **Back-related Dysfunction (RMDQ or Oswestry)**
- Generic Well Being (SF-12/EQ 5D)**
- Disability (social role): absenteeism/productivity**
- Satisfaction with Care**



Tailored Approach

Specific Neuropathic
CLBP Clinical Condition

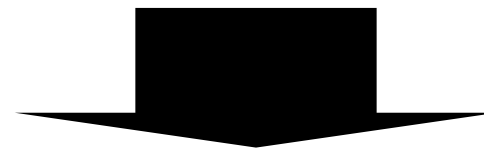


- Discrete Onset
- Reproducible Clinical Phenomenology
- Characterized Tempo
- Natural History / Epidemiology
- Plausible Neuro Localization

Tailored Designs
Pain and Function



- Improved Walking/Standing Tolerance
 - Reduced Pain Intensity
- } NIC
- Modify Symptom Free Interval
 - Attenuate Chronic Pain Intensity
- } PSPS



Bridge Two Literatures

Is neurogenic intermittent claudication an example of Dr. Woolf's second scenario?

(Reversible Plasticity Following Sensitization)

Are the acute structural interventions undertaken by Krishna examples of the "change of mindset" that he calls for or more of the same?

Does the measurement of pain and function with treadmill testing represent a composite measure of the type Dr. Raja suggests?

Does parsing the post-laminectomy syndrome as done here meet the bar for specificity of post-surgical syndrome study population that Dr. Kehlet suggests is required?

Does the relapsing-remitting background here further complicate the question of time horizon of measurement raised by Dr. Gilron?

How do new pains and new co-morbid conditions associated with the primary surgical indication, as raised by Dr. Katz, modulate the intensity of the pain? How do new therapies aim to attenuate?

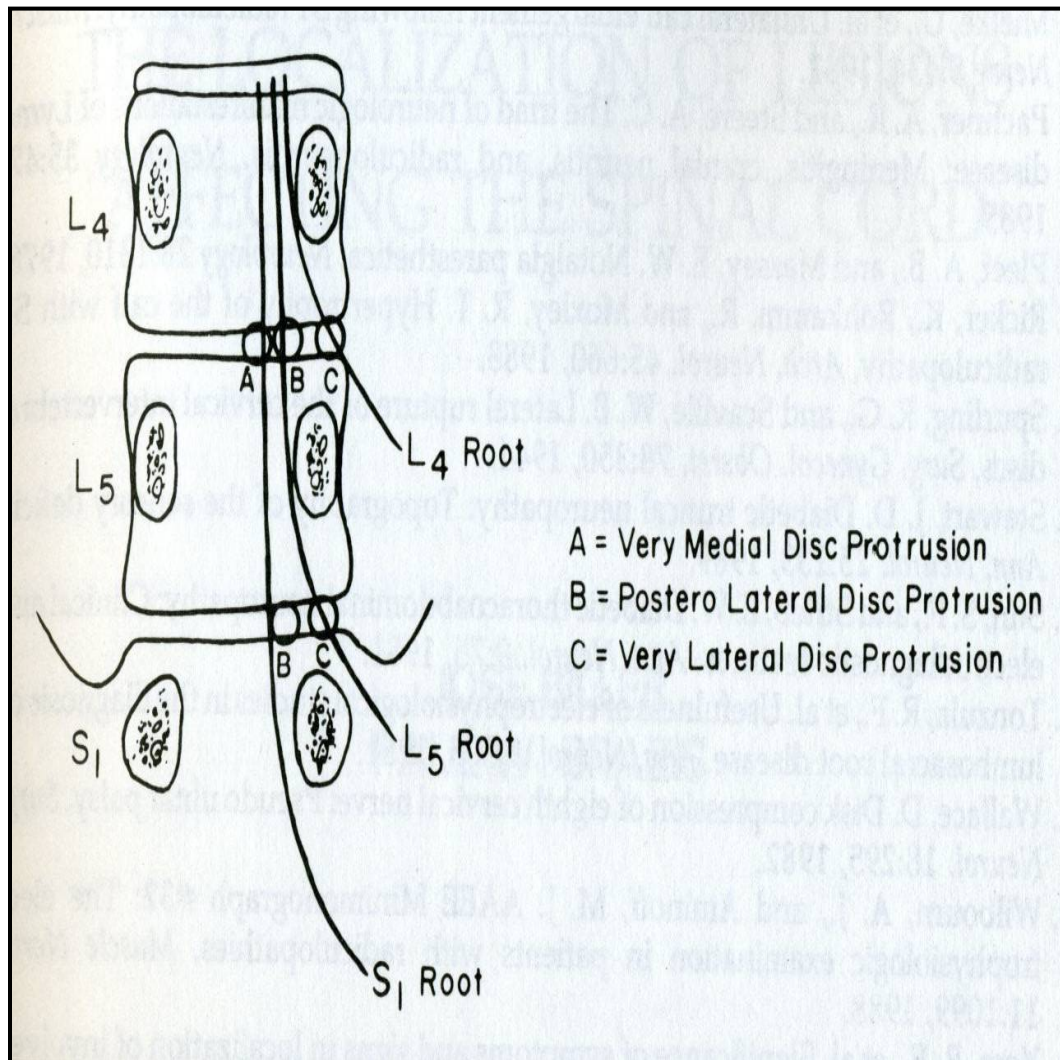
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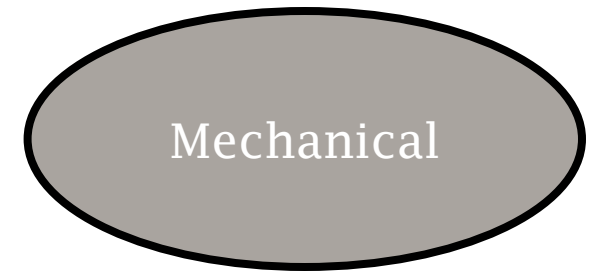
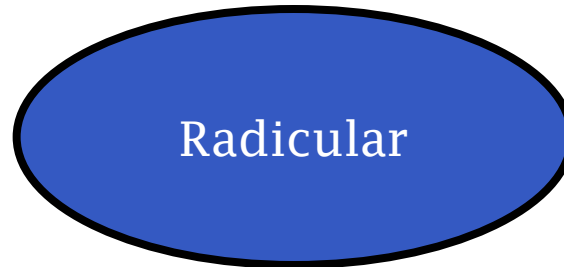
Preemption: Neurogenic Intermittent Claudication



The reality of spine surgery is that only 5% of patients have foot drop . . . I began to realize I was a pain management doctor.

-Neurosurgery
KOL

The Prevailing Chronic Low Back Pain Paradigm



Localization

Nerve Root

Non-neural
tissue

Pain Mechanism

Neuropathic

Nociceptive
(instability)

Treatment

Surgical
Decompression Anti-
neuropathic agents

Fusion / Bracing
Anti-
inflammatory

Challenges to the *Radicular-as-Neuropathic* Hypothesis

· CLBP are Mixed Pain States

- Mechanism
- Localization
- Temporal Horizon

· Negative Clinical Trials of Agents with Efficacy in Other Neuropathic Pain Conditions

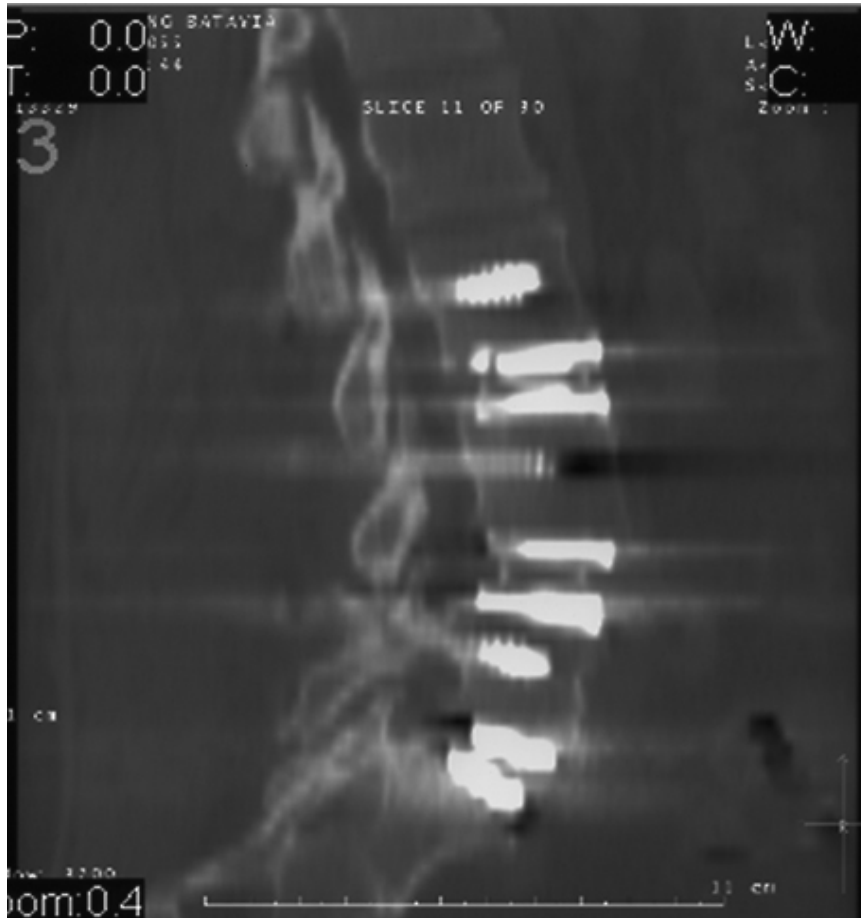
- - Topamax
- - Pregabalin
- - Unpublished

Distal, lateralized leg pain
Reflex Change
Weakness/Atrophy
Sensory Dysfunction
Allodynia?

· Clinical Relevance

- Primacy of physical signs / fixed neurologic deficits
- Patients' sciatica explanatory Model

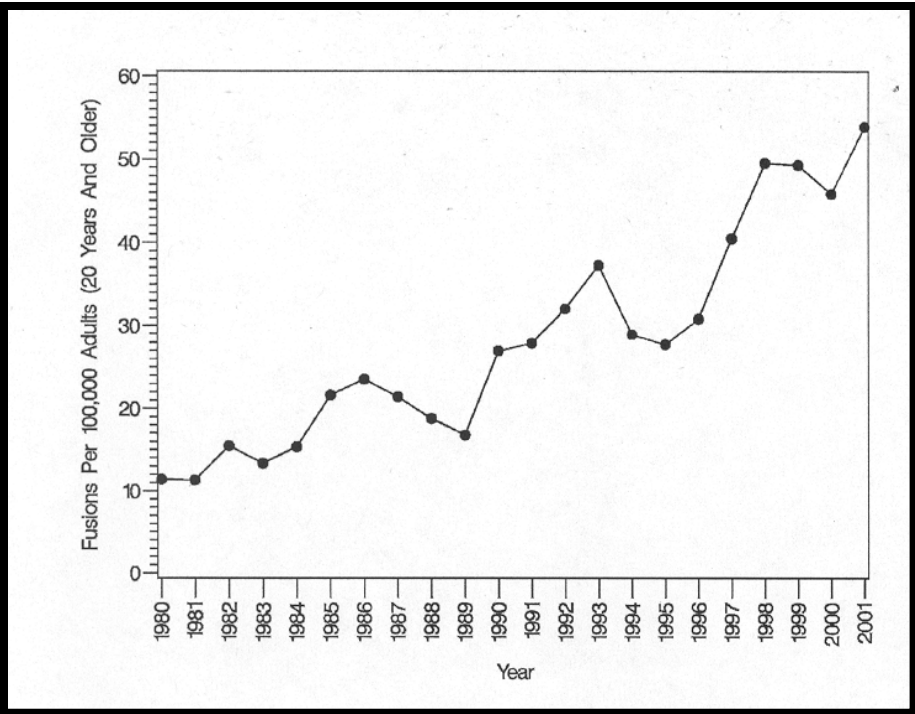
Recurrence of Primary Surgical Problem, Induction of Chronic Neuropathic Pain, or Both?



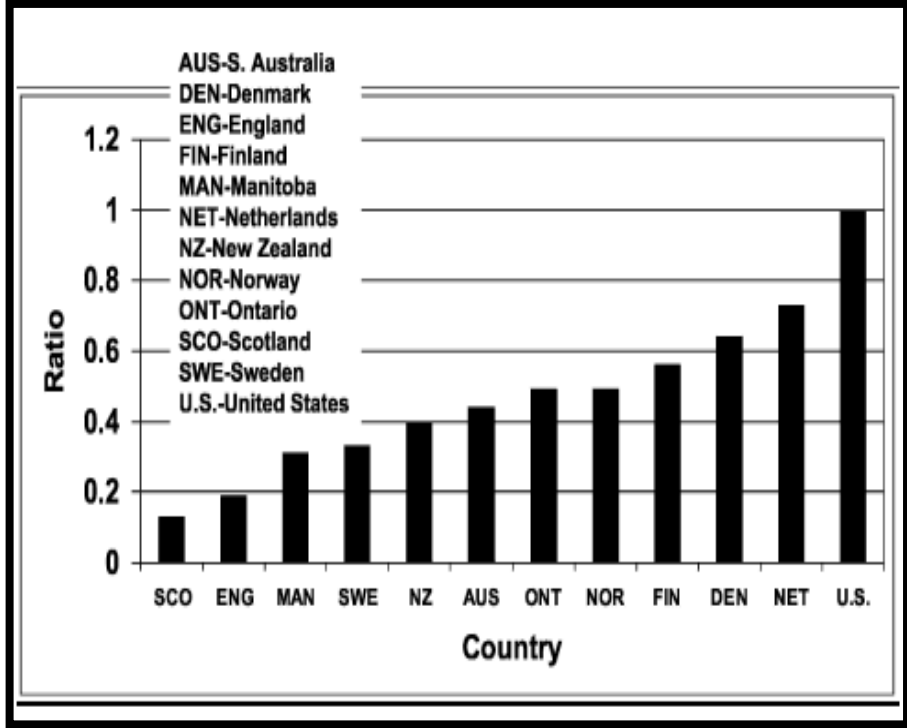
What is the time horizon of interest?

What is the differential diagnosis of the symptom free interval?

Surging Rates of Instrumented Lumbar Surgery in the US



220% increase in rates of lumbar fusion surgery from 1990-2001



US Rate of Lumbar Surgery compared with other industrialized nations



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Surgical versus Nonsurgical Therapy for Lumbar Spinal Stenosis

James N. Weinstein, D.O., M.S., Tor D. Tosteson, Sc.D., Jon D. Lurie, M.D., M.S.,
Anna N.A. Tosteson, Sc.D., Emily Blood, M.S., Brett Hanscom, M.S.,
Harry Herkowitz, M.D., Frank Cammisa, M.D., Todd Albert, M.D.,
Scott D. Boden, M.D., Alan Hilibrand, M.D., Harley Goldberg, D.O.,
Sigurd Berven, M.D., and Howard An, M.D., for the SPORT Investigators*

Recurrent Neurogenic
Claudication
Non-Surgical Treatment
Surgical Non-Responders

“The creation of a limited, fixed protocol for nonsurgical treatment was neither clinically feasible nor generalizable. . . We did not assess the effect of surgery versus any specific nonsurgical treatment.”

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The Advantages of Studying Post Lumbar Surgery Neuropathic Pain Syndromes

Clinical Factors

- Rising Incidence
- Discrete Onset
- Leading reason for referral to chronic pain management centers
- Motivated Stakeholders

Research Factors

- Ample Enrollment
- Characterize Patient, Risk Factors, and Nerve Injury
- Easy to Standardize
- Motivated Stakeholders

Persistent Neuropathic Pain Following Lumbar Surgery has a Unique Differential Diagnosis

Lack of Reduction in Pain Intensity

- Wrong Patient
- Wrong Lumbar Segment
- Insufficient Removal of Herniated Disc /
- Inadequate Decompression
- Unrecognized second Disc Herniation/Pathology
- Nerve Root Trauma

Recurrence of Pain

- Recurrence of Disc Herniation
- New Disc Herniation
- Epidural Fibrosis
- Arachnoiditis
- Symptomatic OA/
Adjacent Level Disease
- Secondary Spinal Stenosis
- Microinstability
- Macroinstability
- Spondylolisthesis

Post PLIF (Posterior Lumbar Interbody Fusion) Neuralgia: An Illustration of Limitations of Current Study Designs

Single surgeon

Consecutive Series

Two years of Undifferentiated CLBP unresponsive to “Conservative Management”

Diverse Intra/Post Op Insults:

Implant subsidence, pseudarthrosis, epidural bleeding, dural tears, donor site pain, nerve root injury

Inclusion Criteria:

Multiple Structura, Etiologies, DJD + /- modic change, Grade 1-III listhesis, Post Lami/Discectomy Pain, Broad Based Disc Prolapse

Limitations of Current Study Designs

- 20 - cage/ 206 + cage (n=226); 44 years old; median duration 60 months
- Subtotal facetectomy in first 103 /123 total superior facetectomy /156 single level
- Neuralgia = leg pain (patient report)
- “Patients were considered to have post PLIF neuralgia if they complained of severe radiculopathy which was not present before surgery.”
- 16 cases of neuralgia
- “Sensory in all but one patient”
- Conjoint nerve root, relative stenosis (48 hours + post op), misplaced screw (<48 hours post op), loose posterior arch (<48 hours post surgery), graft subsidence (6 months)

What is the Differential Diagnosis of Poor Perioperative Pain Control in the Patients?

QuickTime™ and a
decompressor
are needed to see this picture.

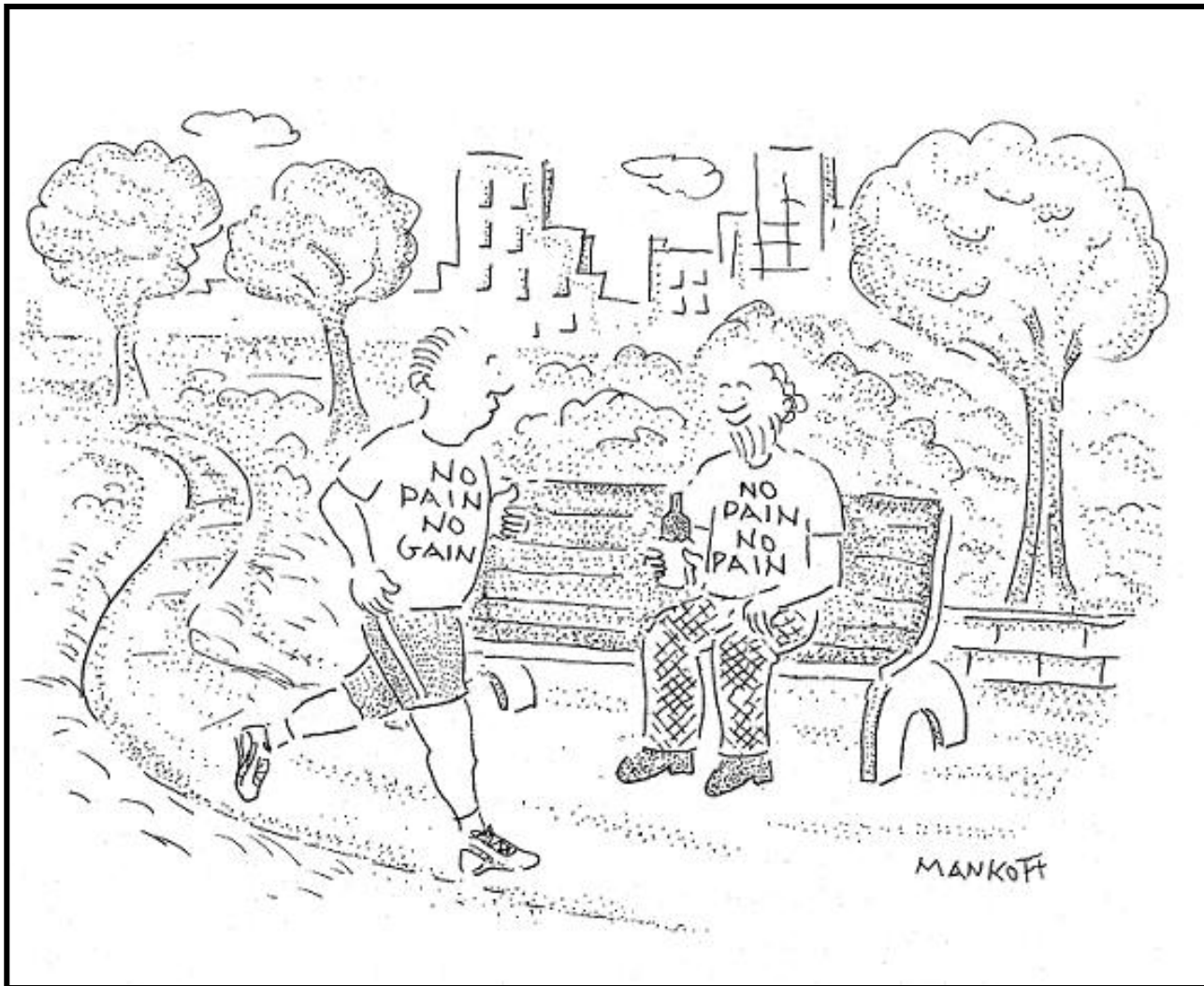
QuickTime™ and a
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Must bridge Pathoanatomy and Pathophysiology

Arachnoiditis Prevention Literature

What is the clinical significance of postoperative fibrosis to persistent and recurrent pain of moderate to severe intensity?

1. Autografts (eg fat, ligament, bone)
2. Manufactured Biomaterials (Gel foar, silastic membrane, surgicel, Avitene, TachoComb, Gortex, ADCON-L)
3. Topic fibroblast inhibitors (urokinase, TPA, mitomycin- C)
4. Intraoperative Co₂ laser
5. External Beam Radiation



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Neurogenic intermittent claudication associated with lumbar spinal stenosis has a distinctive clinical signature.

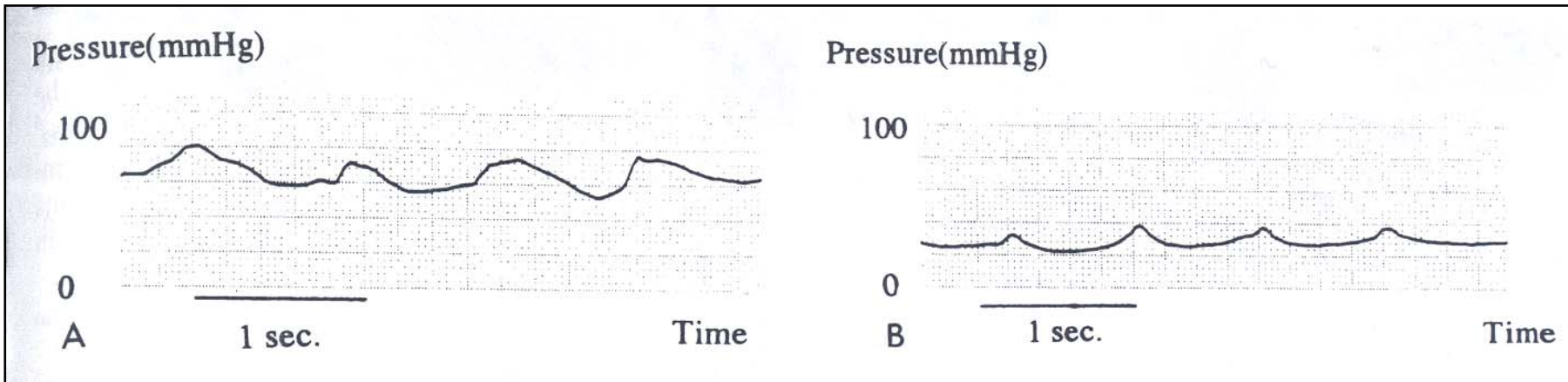
Cardinal Features

Anatomic Distribution	Lumbar and leg(s)
Temporal Pattern	Progressive
Key Exacerbating Factor	Standing and walking
Key Alleviating Factor	Postures that reduce the lumbar lordosis

Epidural pressure is elevated in patients with lumbar spinal stenosis when walking.

Simple walking

Walking with lumbar flexion



Peak values
82.8+/-14.2

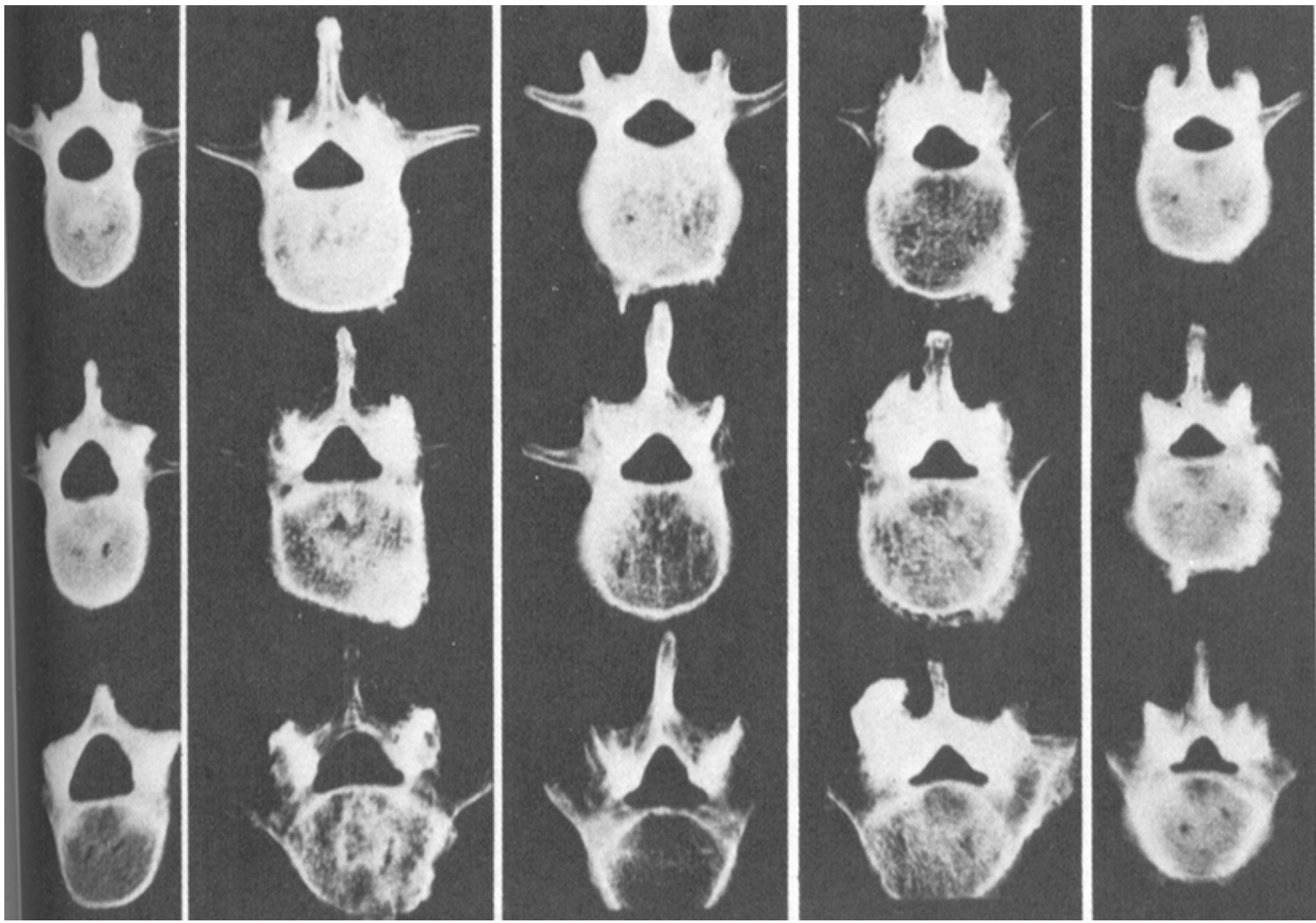
Peak values
34.2+/-4.9

There was no statistical difference between simple walking in normal individuals and walking with lumbar flexion in patients with lumbar spinal stenosis

L3

L4

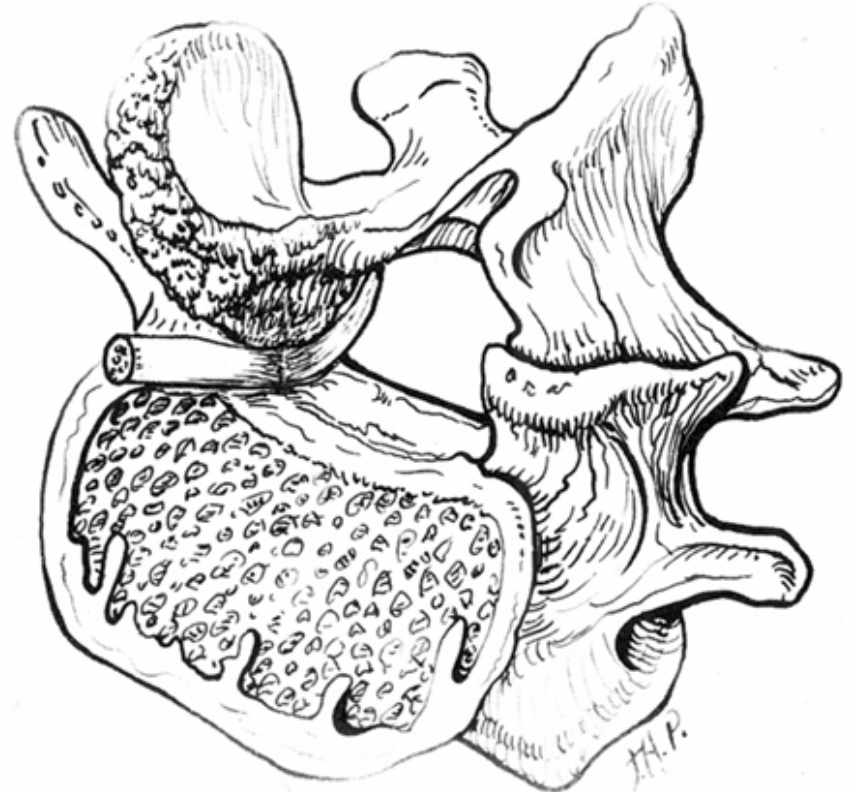
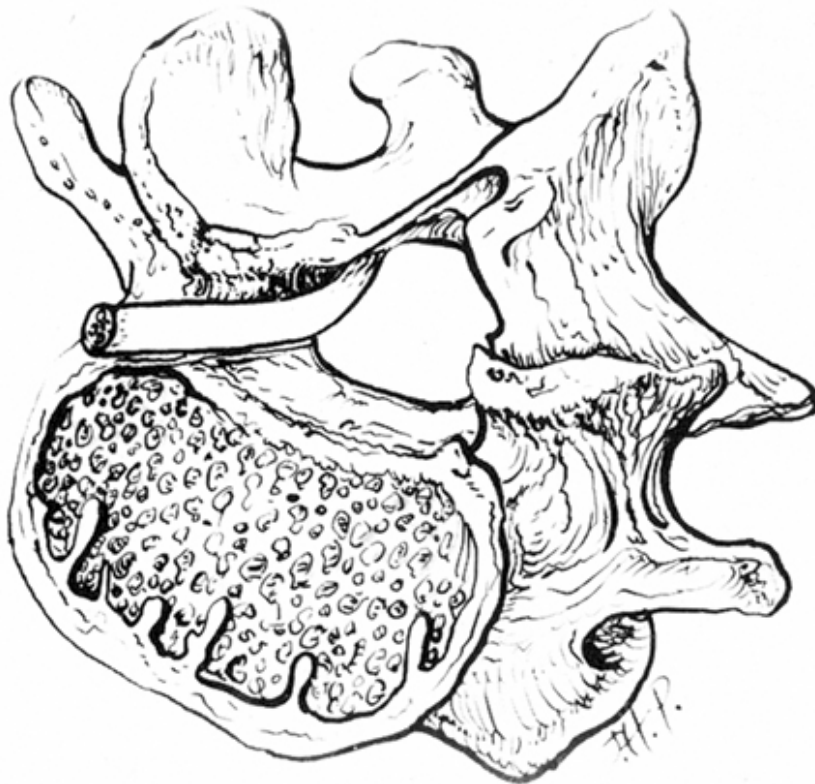
L5



Lateral Recess

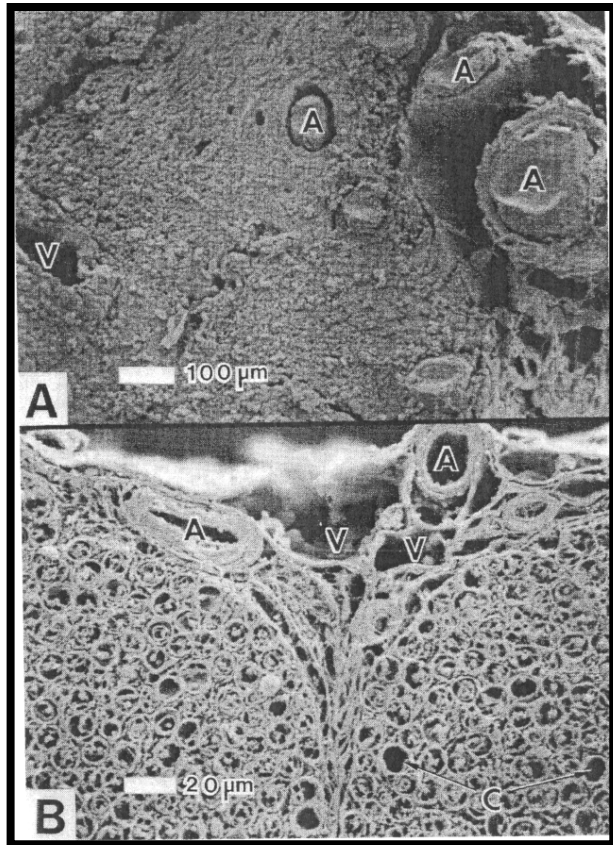
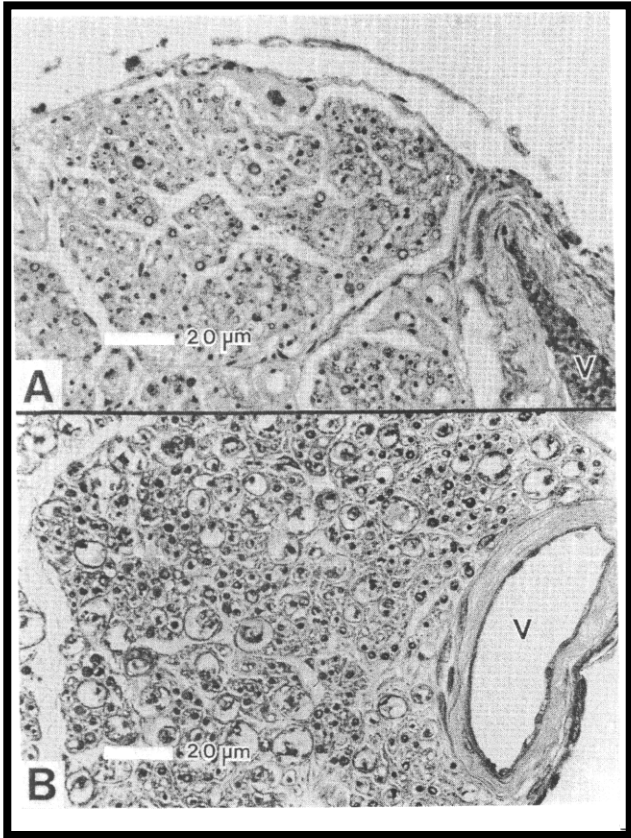
Facet Hypertrophy

Facet Hypertrophy in the lateral recess



Ventral-to-dorsal diameter of the lateral recess varies from 3 to 5 mm. A lateral recess of 3mm may be associated with symptoms of lateral recess stenosis.

Are these the nerve lesions needed to make this a lesion of the nervous system fitting with the emergent description of neuropathic pain.



Compressed S1 root

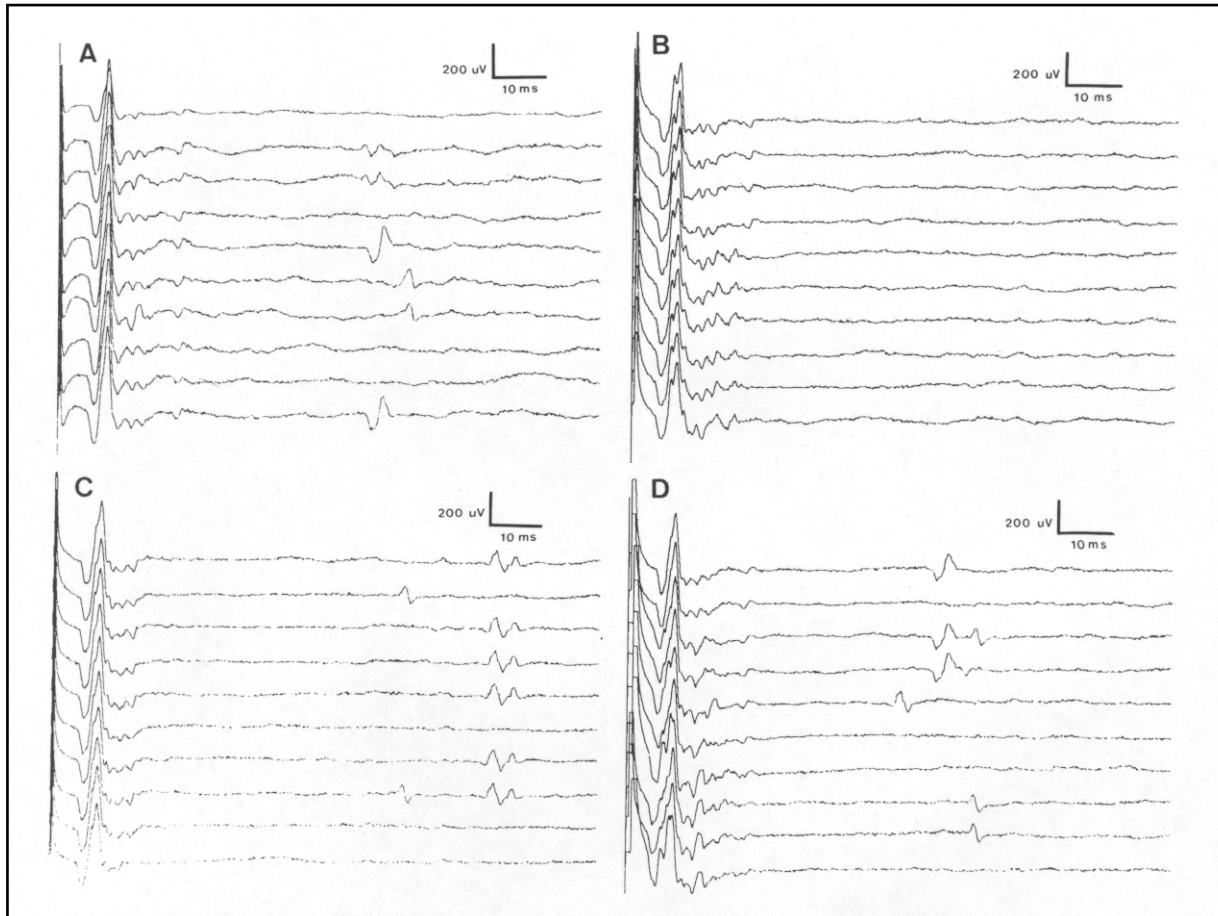
Normal nerve root

Loss of nerve fibers, especially large myelinated type with a mixture of degenerating and regenerating fibers in addition to adhesive changes of the pia-arachnoid.

Motor Dysfunction correlated with F waves. What about the pain?

F waves @
rest left
posterior
tibial nerve

10 minutes
post exercise



30s Post
exercise

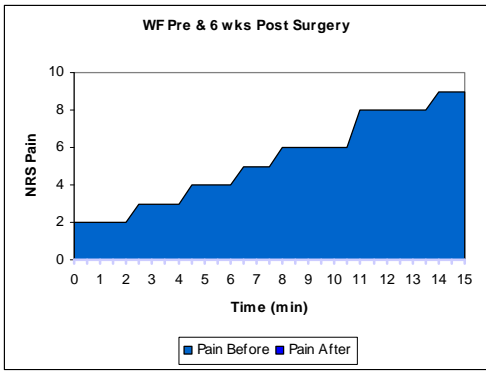
15 minutes
post exercise

F waves from the left posterior tibial nerve of a patient with intermittent claudication and spinal stenosis with focal weakness and depressed reflexes after exercise

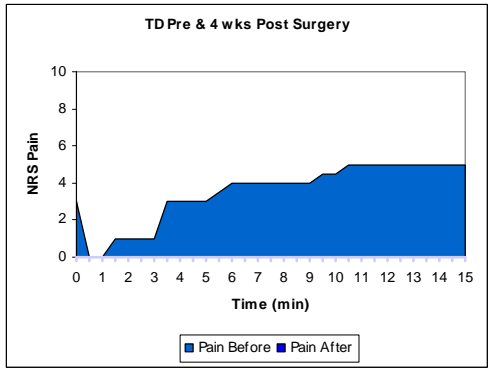
Treadmill Testing To Improve Treatment Matching



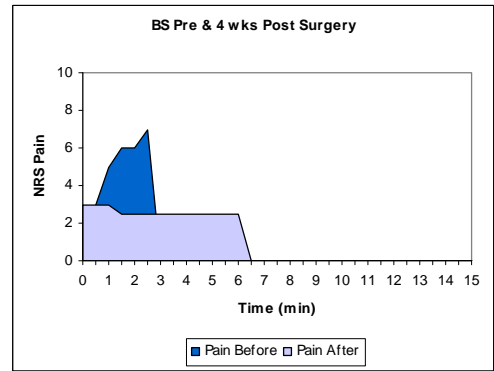
Patient A



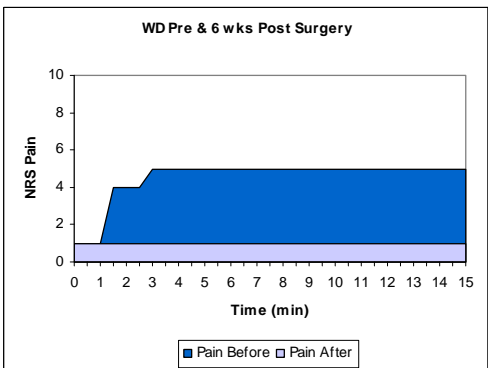
Patient B



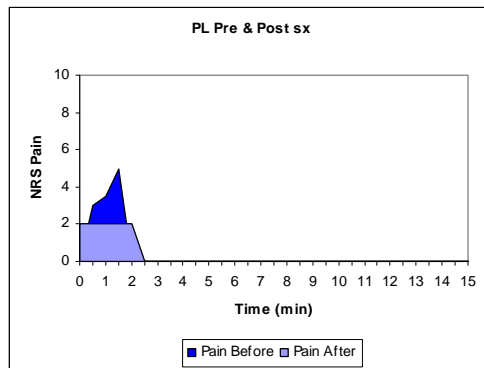
Patient C



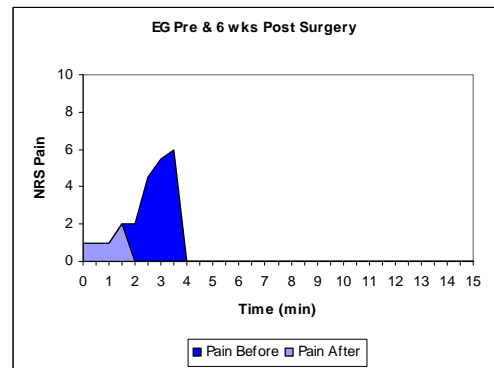
Patient D



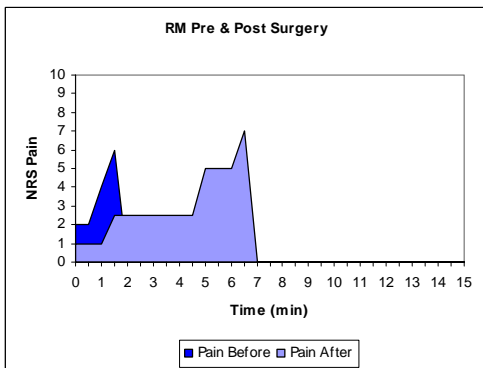
Patient E



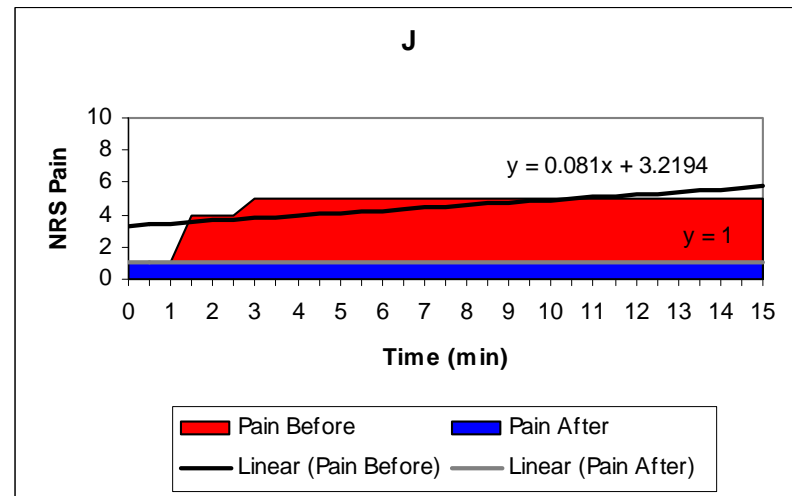
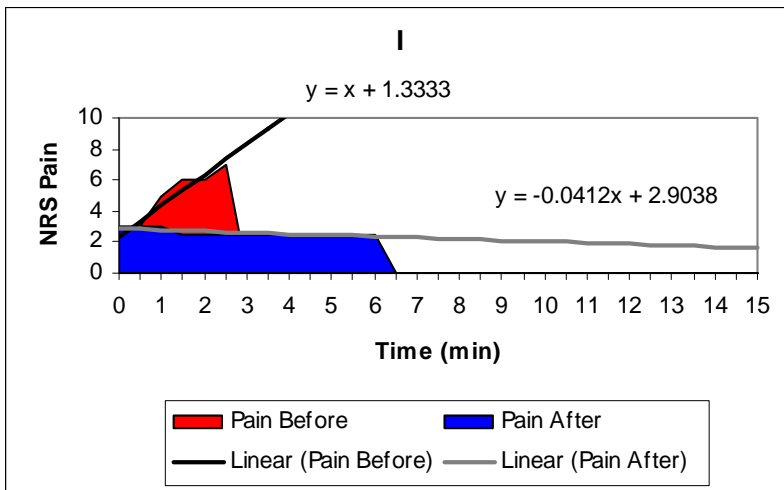
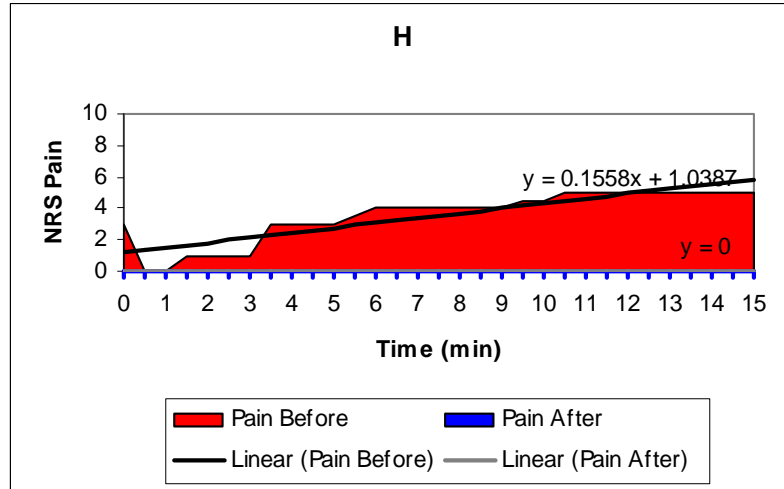
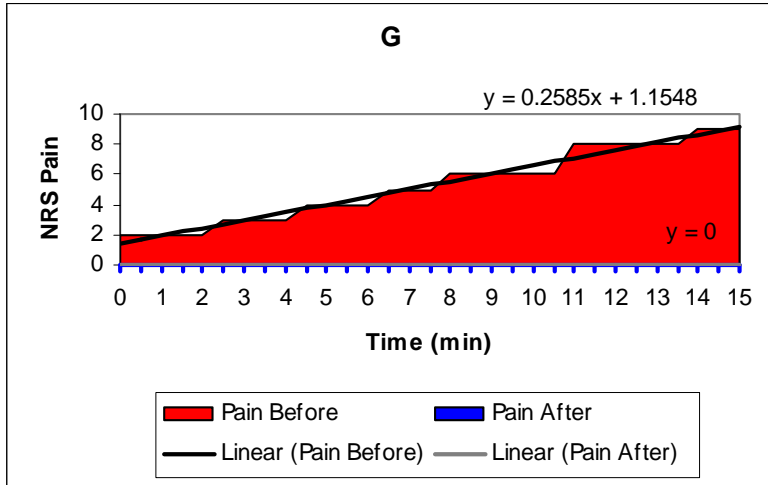
Patient F



Patient G



Surgical Patient Ambulation and Pain Assessment Over Time



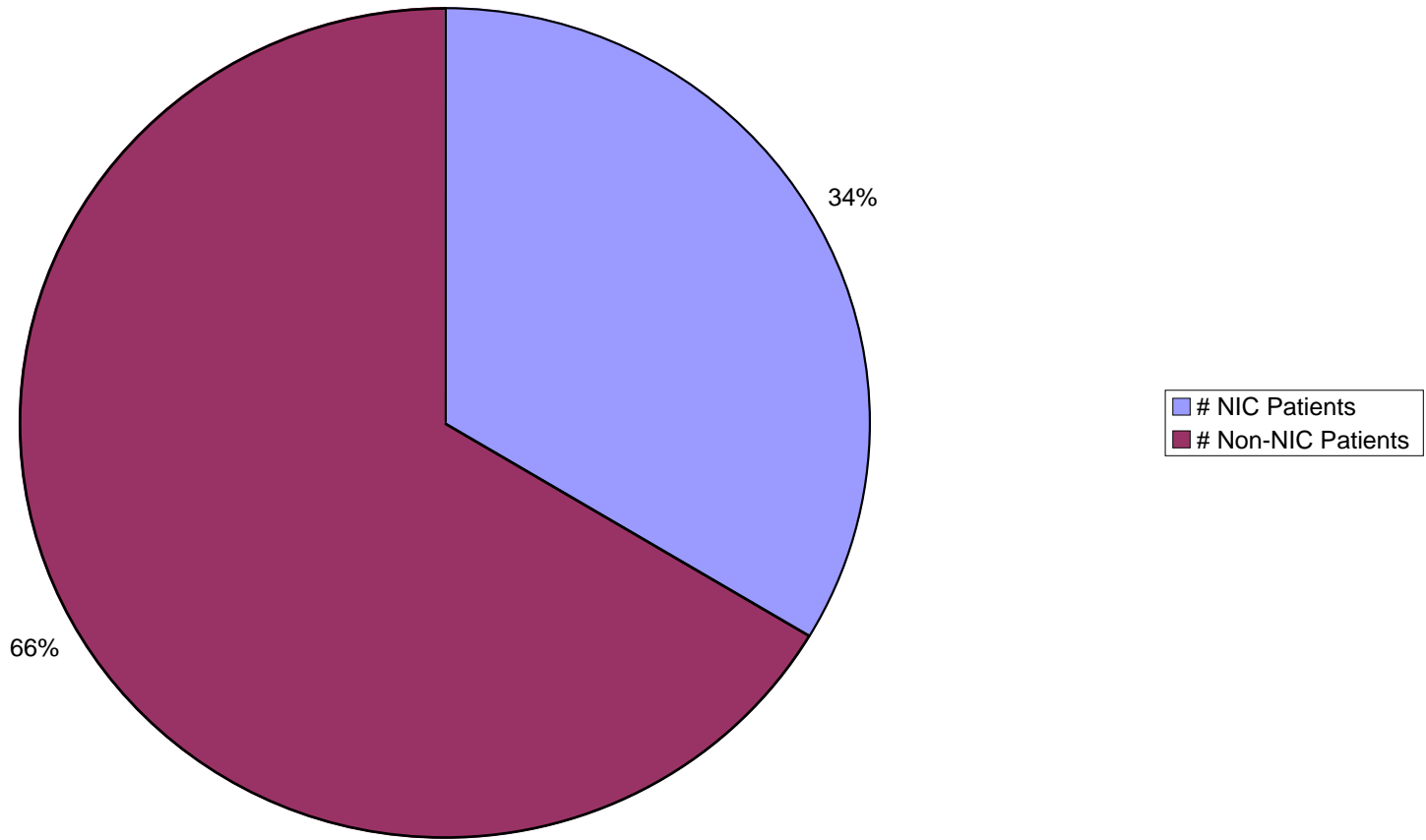
**Neural compressive
lumbar radiculopathy**

**Neurogenic intermittent
claudication**

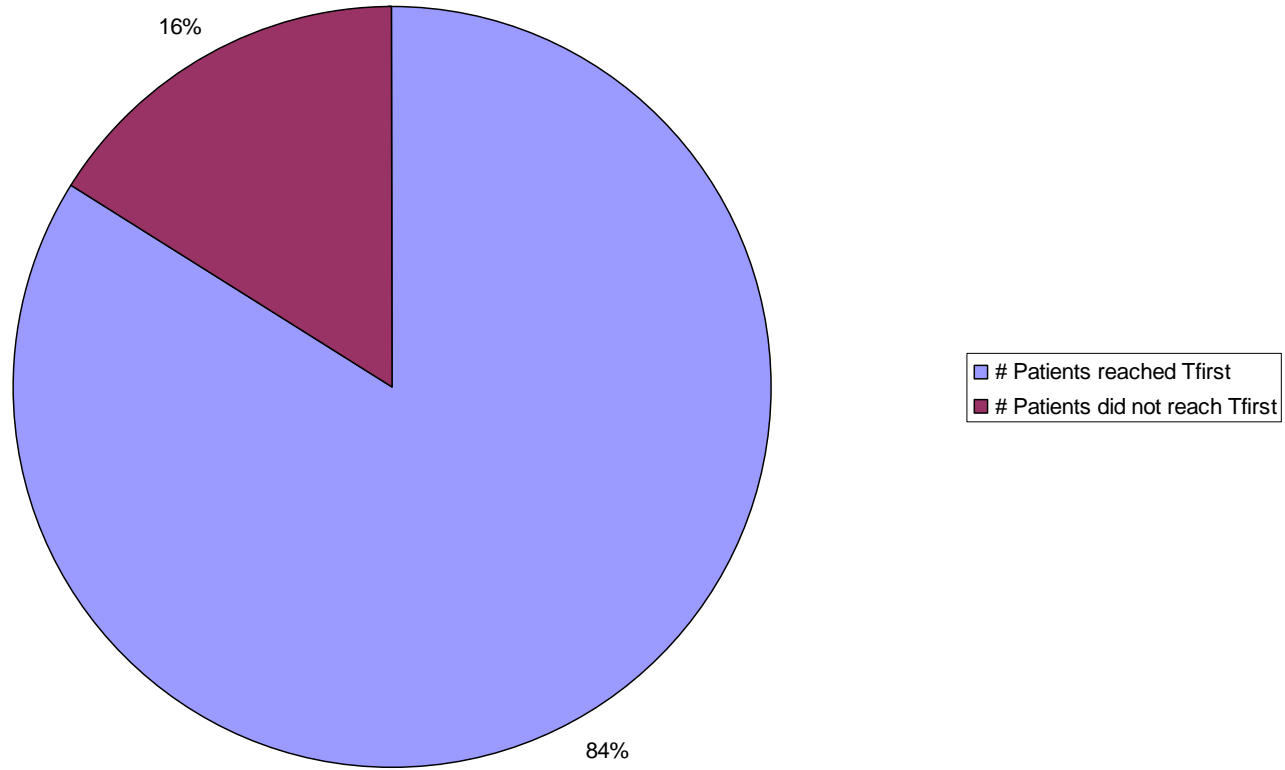
**Mechanical lumbar
joint dysfunction**



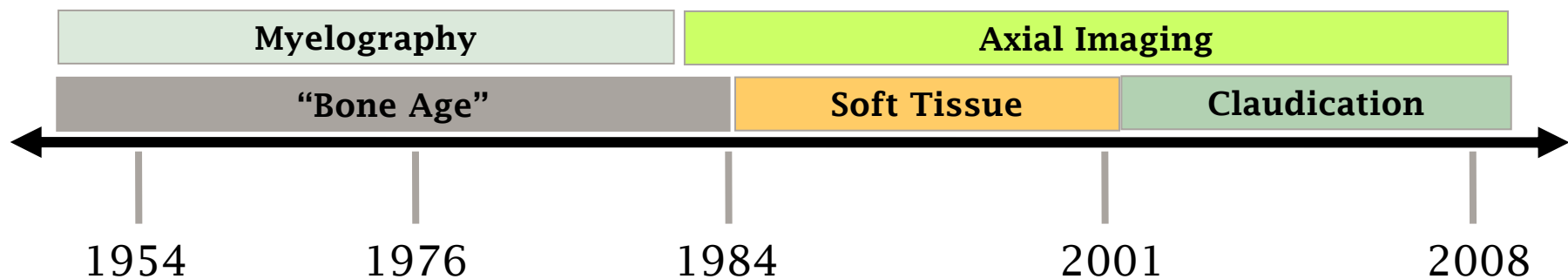
Percentage of Neurogenic Intermittent Claudication (NIC) vs Non Neurogenic Intermittent Claudication Patients Assessed by Treadmill Testing



Total Number of Patients Reached Time to First Pain of Moderate Intensity (NRS >4, Tfirst) as Assessed by Treadmill Testing



The Evolution of the Concept of Neurogenic Intermittent Claudication





Tailored Approach

Specific Neuropathic
CLBP Clinical Condition

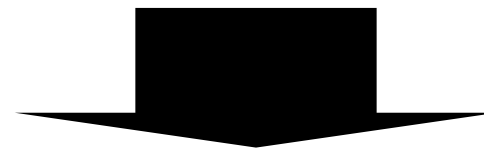


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Nikki Murray
Bob Dworkin
Mike McDermott
Web Pilcher
Paul Maurer
Jason Huang
Tom Rodenhouse
Ed Vates
Kevin Walter
Jason Schwalb
Shirley Rast
Julie Ortega
Jeremy Sinkin
Beth Anderson
Babak Jharomi
Howard Silberstein
Bernard Ravina
Alan Friedman

US Department of
Education
Endo
Pharmaceuticals
Pfizer
Rochester
Neurosurgery
Partners
Excellus

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