

Diabetic Neuropathy: Pathogenesis and Treatment

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American Neurological Association

American Neurological Association

2013 Annual Meeting – Oct. 13-15 – New Orleans

Scientific symposia

Stroke – MS – Epilepsy – Neuro-repair – Public Policy*

Special Interest Group Symposia

18 Different Topics

Career Development

Junior Faculty through

Department Chairs

*President William J. Clinton - Keynote Speaker





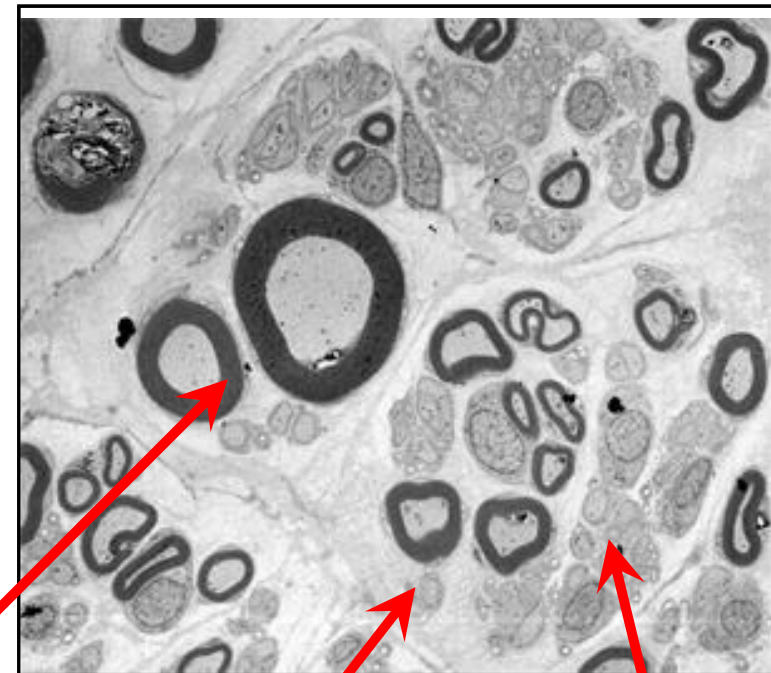
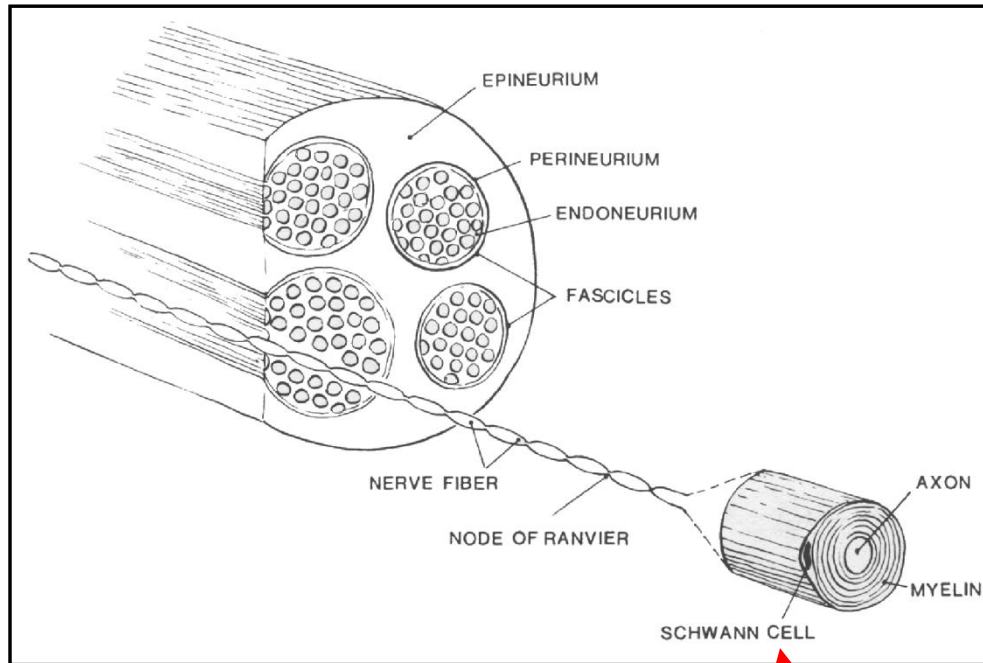
Peripheral Neuropathy: Pathogenesis and Treatment

Goals of Today's Presentation are:

- 1. Overview of basic nerve anatomy and clinical neuropathy (www.pnrd.umich.edu)**
- 2. Diabetic neuropathy: Introduction to diabetes and diabetic neuropathy?/ Clinical studies lead to new mechanisms on pathogenesis**
- 3. Treatment paradigms for painful diabetic neuropathy**

No Disclosures

Peripheral Nervous System

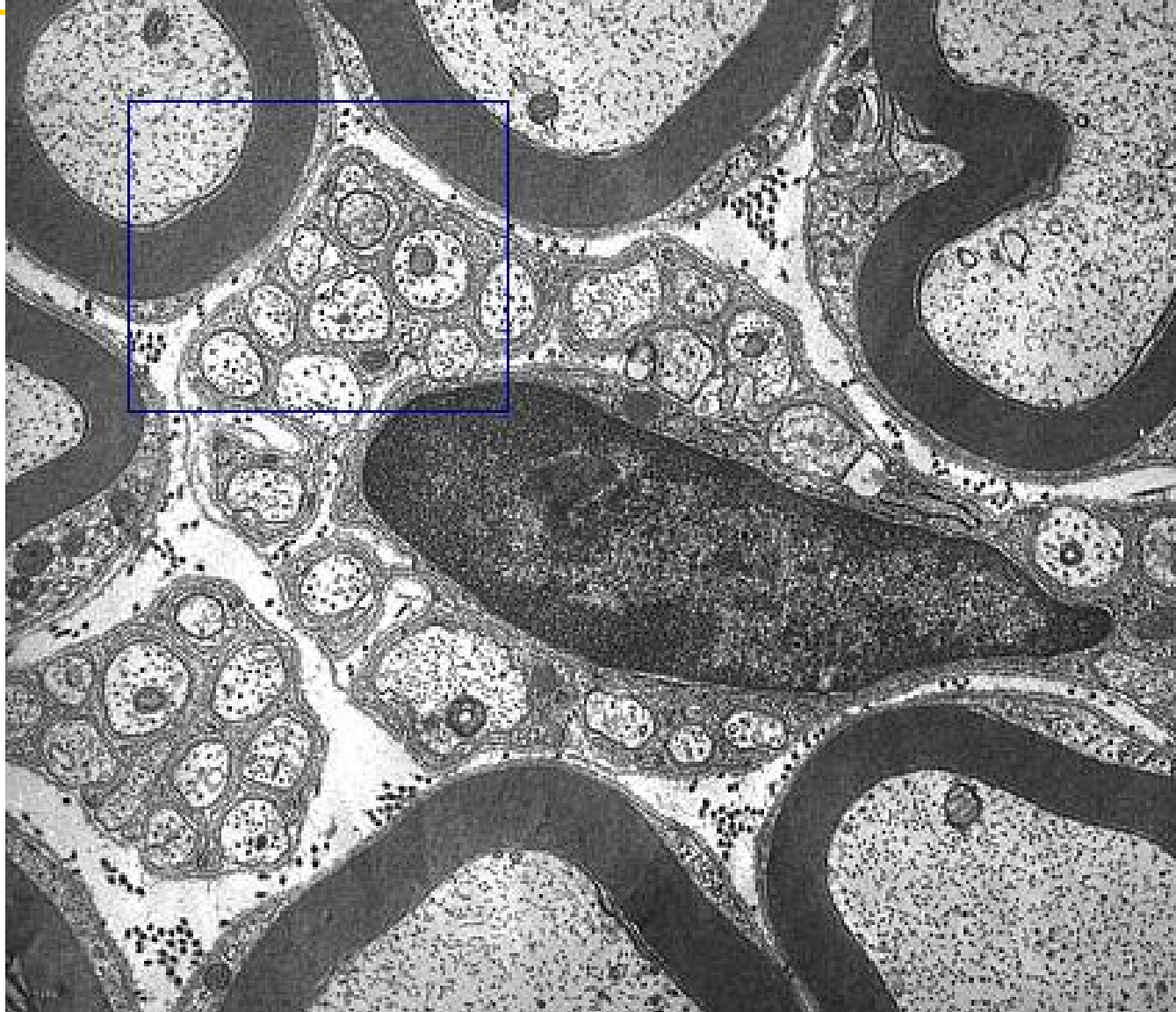


**Large
myelinated
fibers**

**Small
myelinated
fiber**

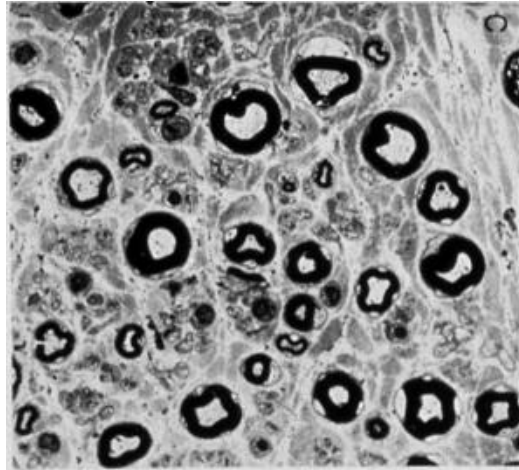
**Unmyelinated
fibers**

Unmyelinated Axons: Most Abundant Axon in the PNS

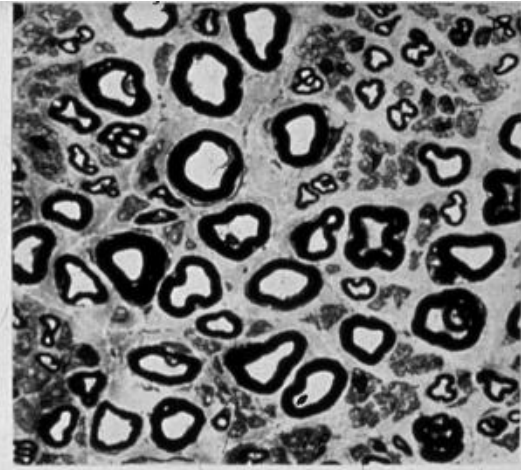


Axonal Loss of all Fiber Types in Neuropathy

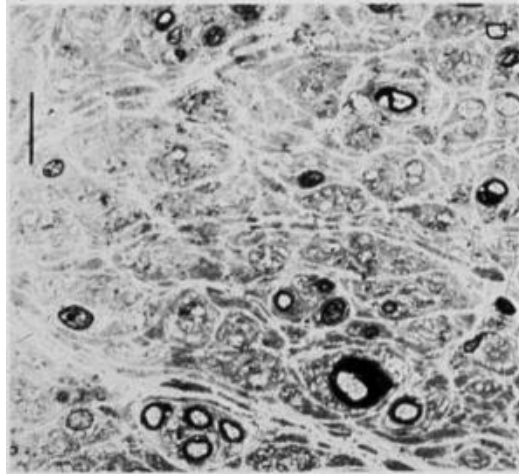
Mild



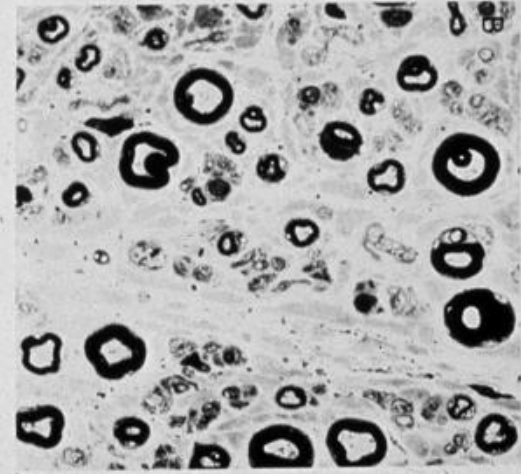
Normal



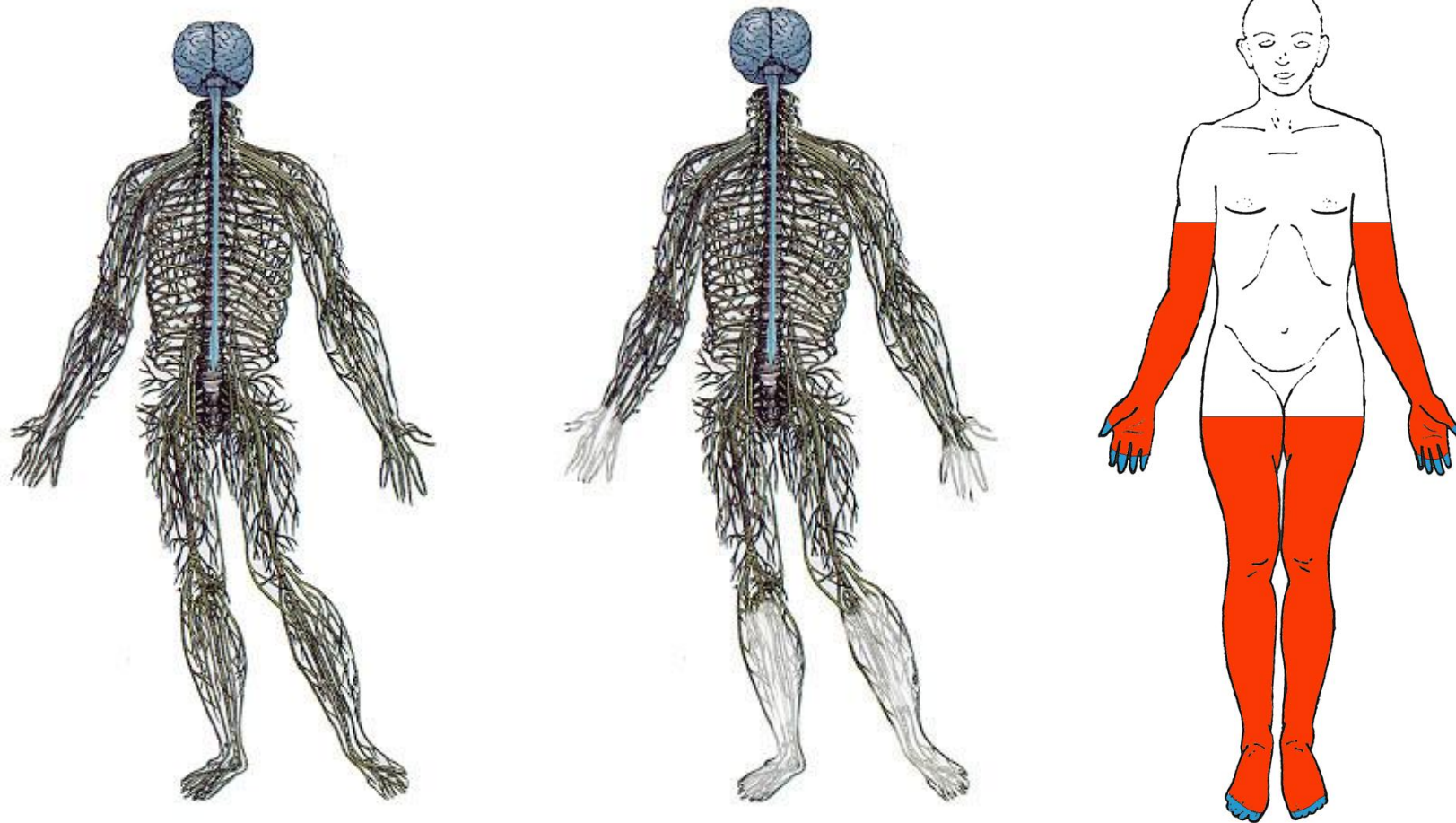
Severe



Moderate



Neuropathy: Distal to Proximal Axonal Loss





Peripheral Neuropathy: Clinical Challenges and Opportunities

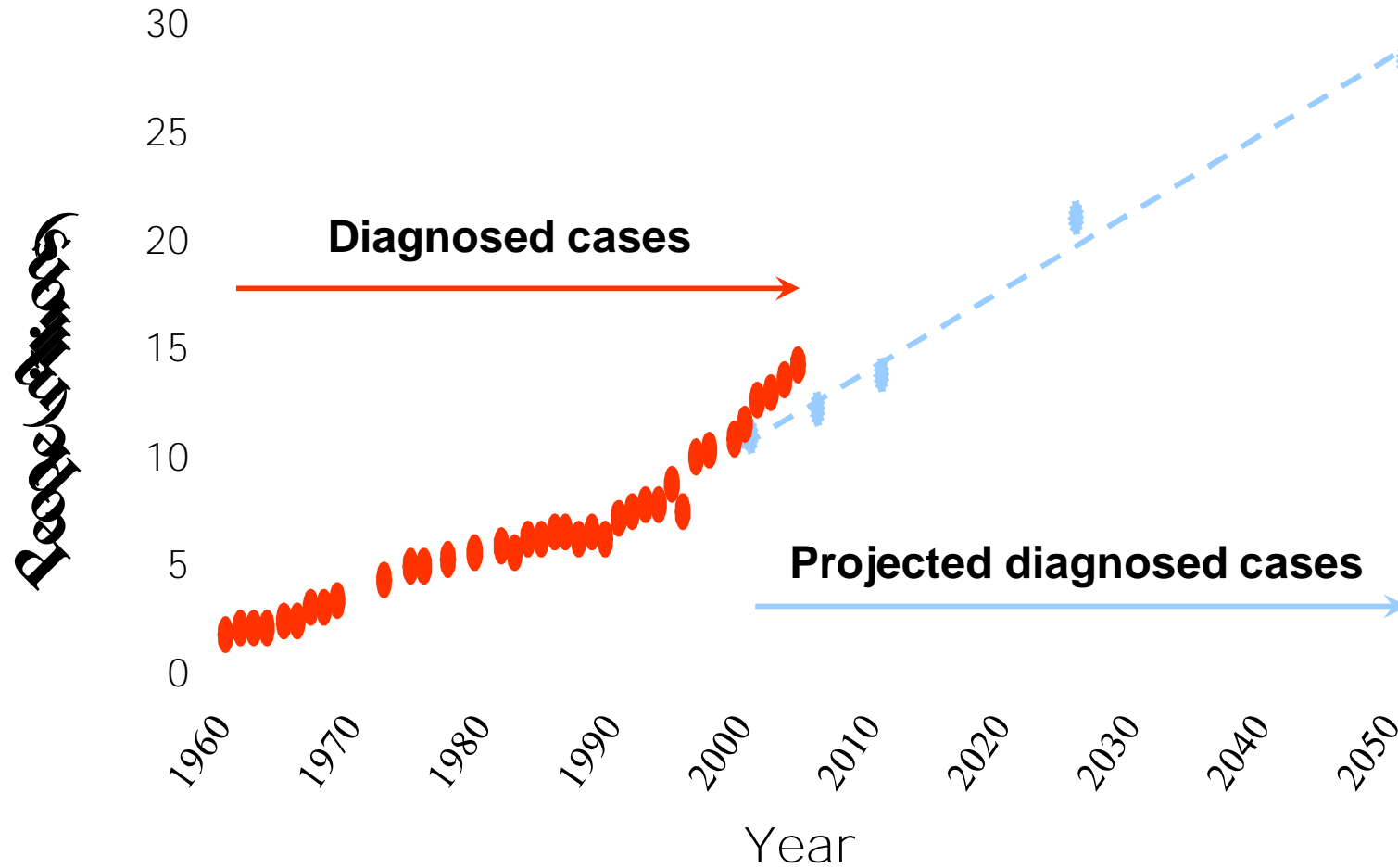
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The Neuropathy Epidemic: Diabetes is the Most Common Cause

- The most common cause of neuropathy in the Europe, USA, China and India **is type 2 diabetes**
- World Health Organization: 371 million people worldwide have diabetes and 50% have diabetic neuropathy
- The number is accelerating at an alarming rate
- **DIABETIC NEUROPATHY IS A SERIOUS WORLDWIDE EPIDEMIC**

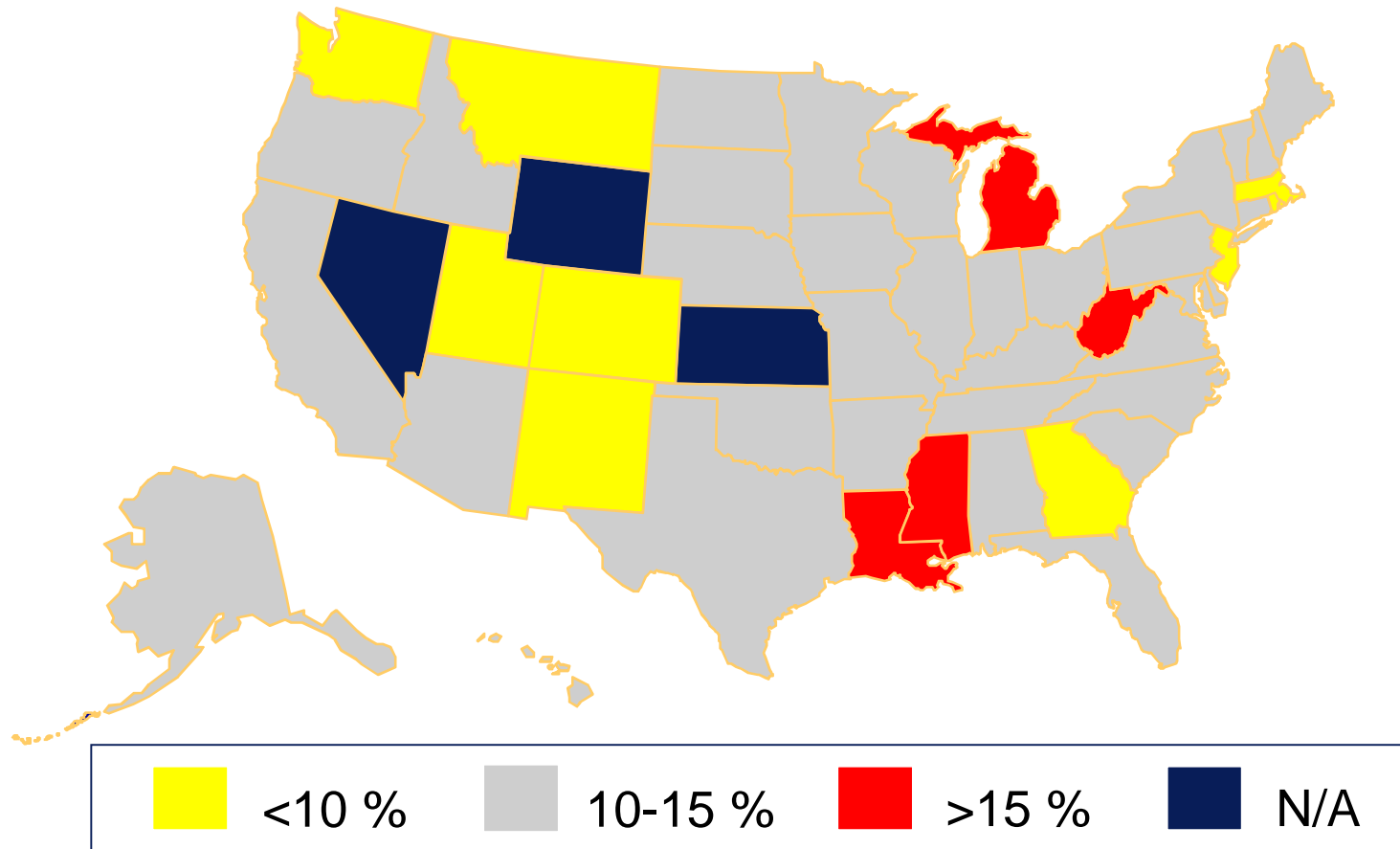
Diabetes Epidemic in the U.S.A.



Data for 1960-2004 from the National Health Interview Survey, NCHS, CDC.

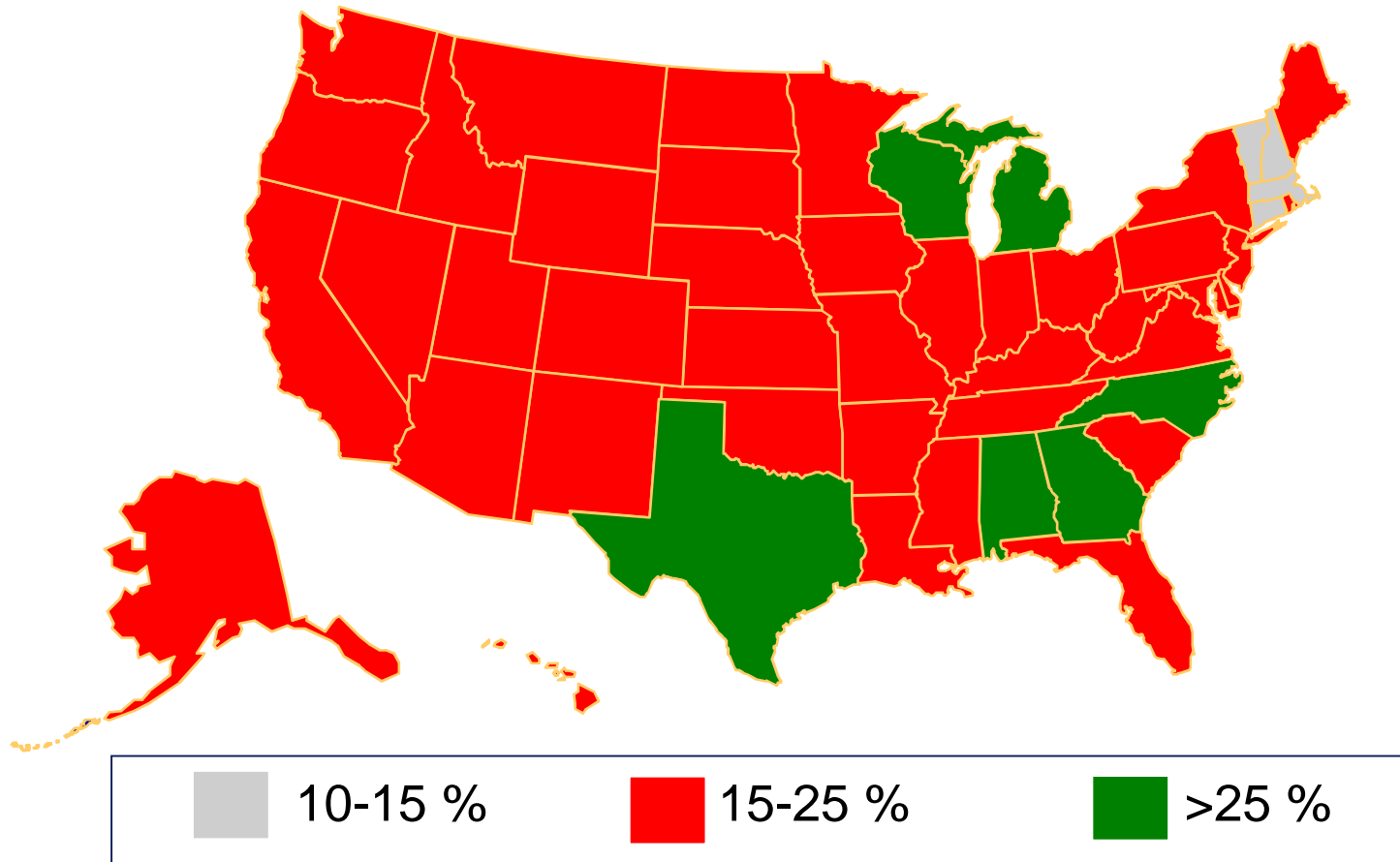
Projected data for 2000-2050 from Boyle JP, et al, *Diabetes Care* 24:1936-1940, 2001.

*Prevalence of Obesity** *Among U.S. Adults in 1991*



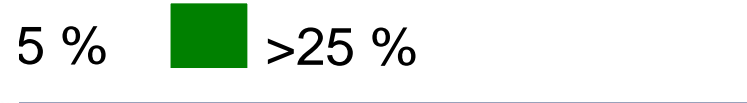
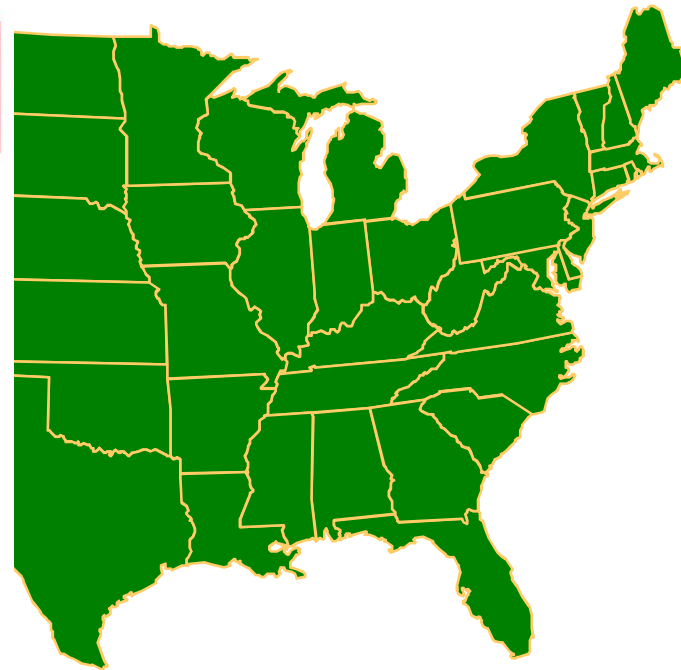
(*Approximately 30 pounds overweight)

*Prevalence of Obesity** *Among U.S. Adults in 2005*



(*Approximately 30 pounds overweight)

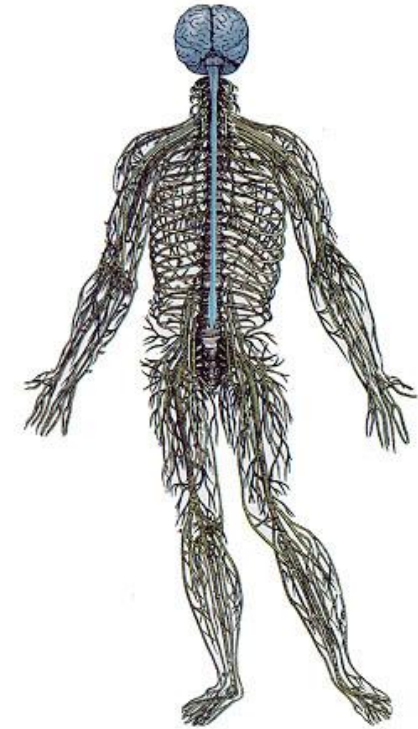
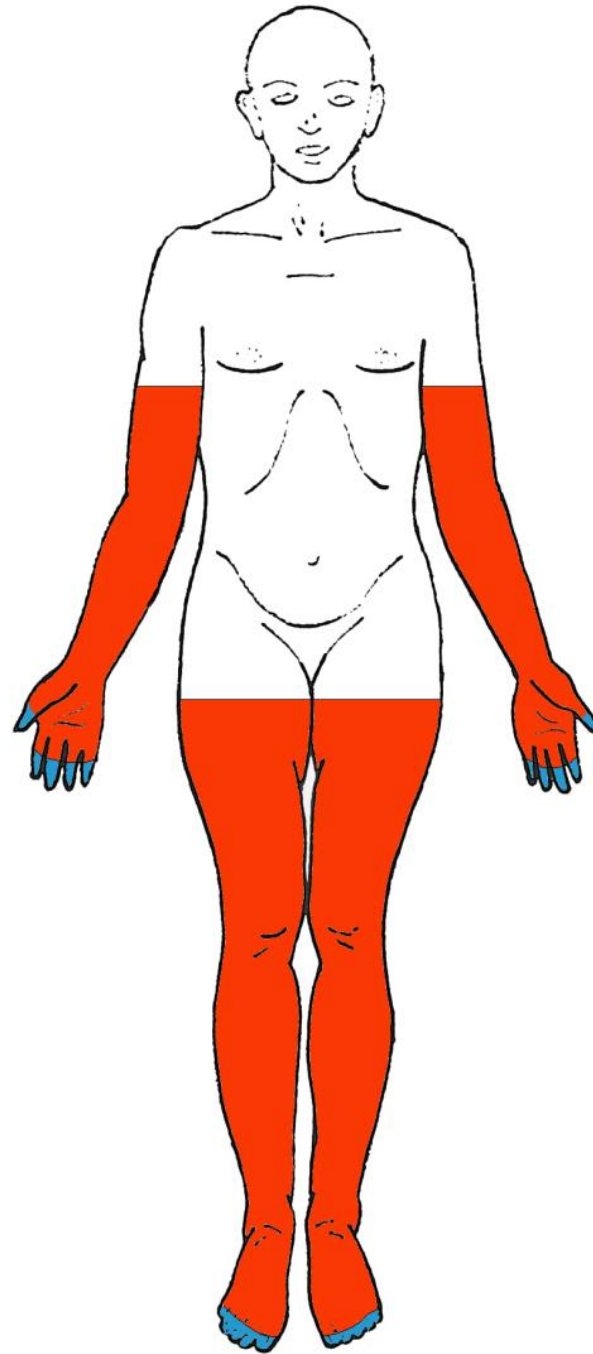
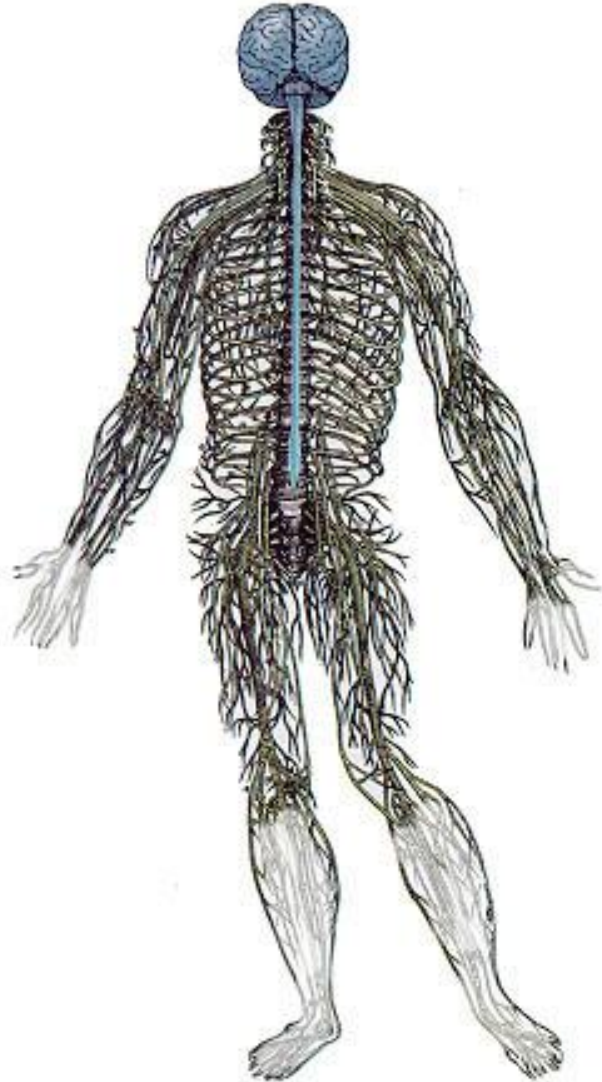
Prevalence of Obesity* Among U.S. Adults in 2010



pounds overweight)

Diabetes in USA &

uropathy



Diagnosis of Diabetic Neuropathy

- **History**
- **Examination**
 - **Inspection**
 - **Sensation: pin, light touch (small fiber); vibration, proprioception (large fiber)**
 - **Ankle reflexes**
 - **Strength (esp distal foot musculature)**
 - **Clinical pearl: this is a symmetric disorder**

Diabetic Neuro





University of Michigan
He

Injury is Painless and Dangerous



Andrew Boulton M.D.



Peripheral Neuropathy: Clinical Challenges and Opportunities

- Overview of basic nerve anatomy and clinical neuropathy (www.pnrd.umich.edu)
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Glucose Control Impacts Neuropathy In Patients with Type 1 Diabetes

Trial	Pts	Years	Effect
Dahl-Jorgensen	45	2	Yes
Holman et al	74	2	Yes
DCCT	1,441	5	Yes
Reichard et al	102	7.5	Yes
Linn et al	49	5	Yes

Callaghan *et al.*, Cochrane Reviews, 2012



Glucose Control Alone Does NOT Impact Neuropathy in Type 2 Diabetics

Trial	Pts	Years	Effect
UKPDS	3,867	10	No*
Azad et al	153	2	No
Gaede et al	160	8	No
Duckworth et al	1,791	5.6	No
Ismail-Beigi et al	10,251	3.7	No

Callaghan *et al.*, Cochrane Reviews, 2012

Type 2 Diabetes: UKPDS

- 3867 patients received intensive therapy (sulfonylurea, insulin or metformin) or conventional therapy (diet)
- 7.0% versus 7.9% over at least a 10 year period
- Using bioesthiometer as a measure of neuropathy, **there is no effect** at year 10 on intensive control



University of Michigan
Health System

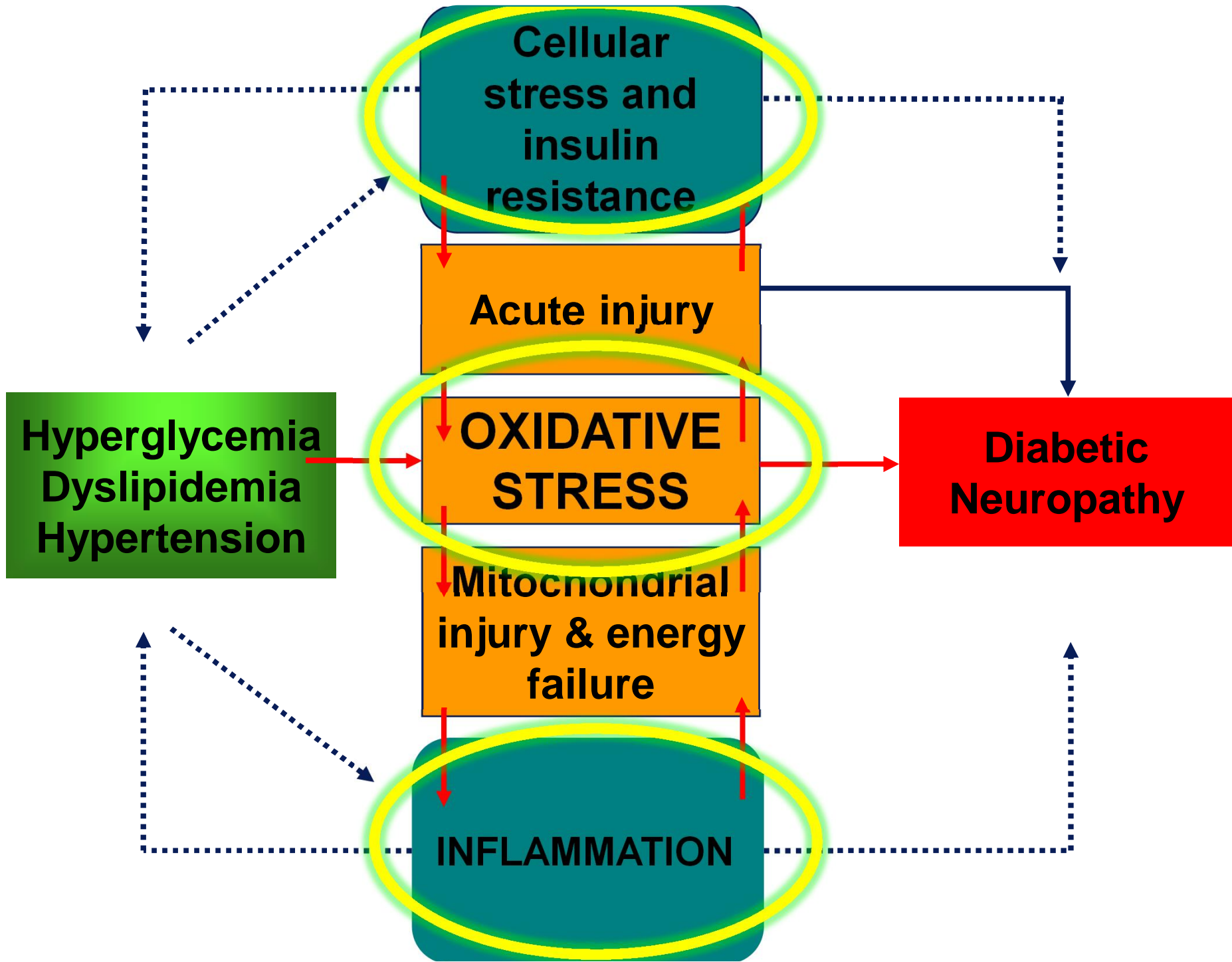
Amputation in the 1800's in England





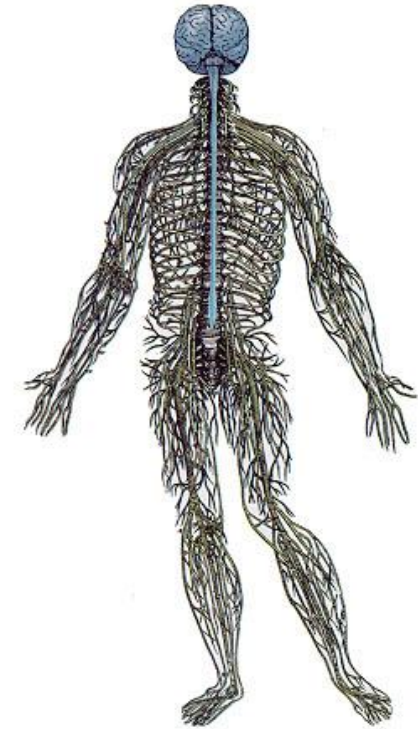
Clinical Studies Reveal a New Mechanism: Metabolic Syndrome Leads to Neuropathy

**CURRENT HYPOTHESIS:
HYPERLIPIDEMIA, HYPERTENSION,
OBESITY & HYPERGLYCEMIA UNDERLIE
DIABETIC NEUROPATHY IN
TYPE 2 DIABETES**



Treatment of Diabetic Neuropathy in USA & Worldwide

- **For type 1 diabetes and neuropathy: glucose control**
- **For type 2 diabetes and neuropathy: glucose, lipid, blood pressure control are all needed**
- **There is no drug universally accepted to prevent the onset or progression of diabetic neuropathy**
- **Commonly used: antioxidants, vitamin supplements and aldose reductase inhibitors without clear evidence**





Peripheral Neuropathy: Clinical Challenges and Opportunities

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First Line Pharmacological Treatment For Neuropathic Pain

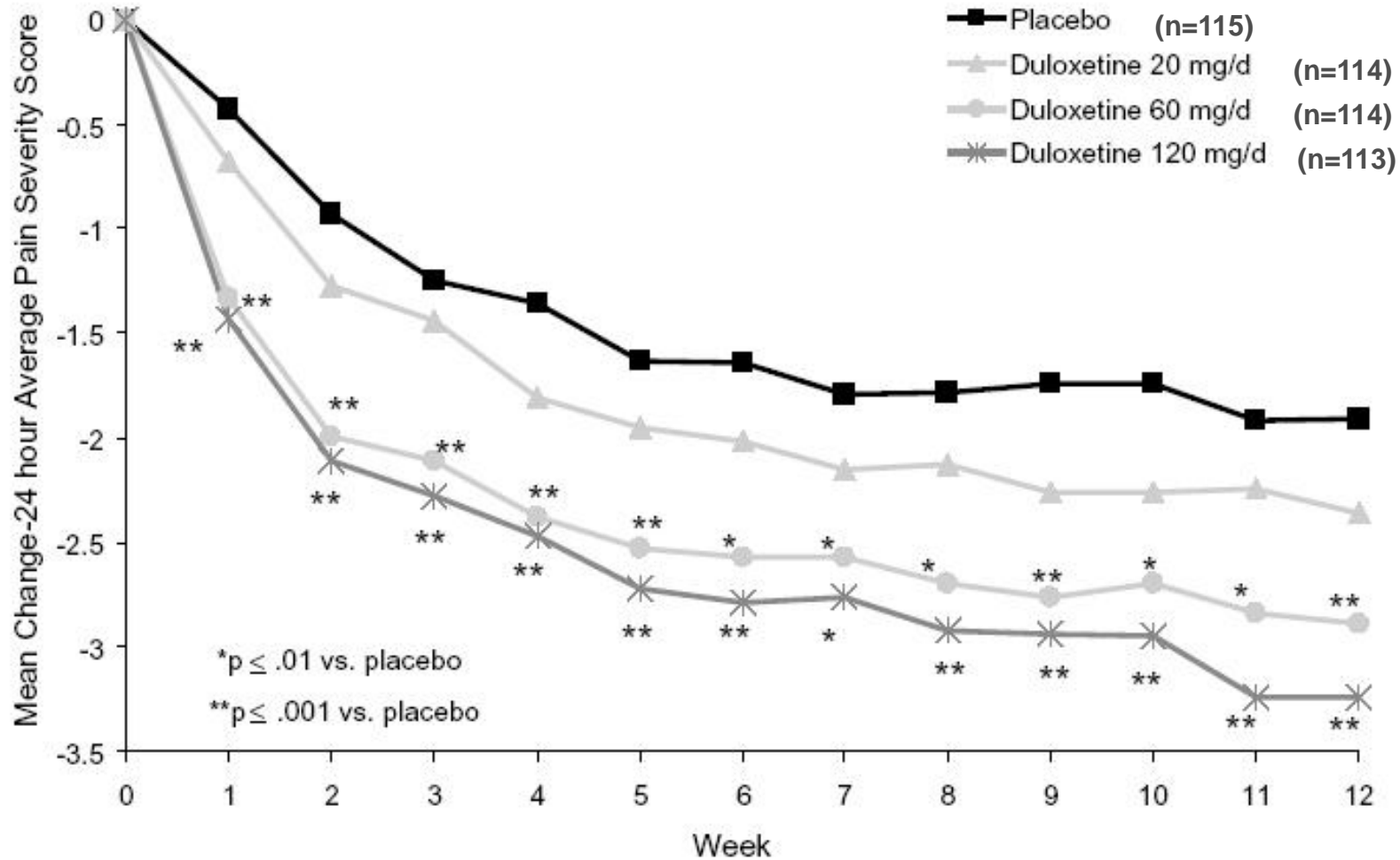
- **Duloxetine or pregabalin (only 2 drugs with FDA approved indications) with Class 1 and 2 evidence per the AAN**
- **Gabapentin**
- **Tricyclic antidepressants**
- **Tramadol**



Duloxetine

- **Norepinephrine and serotonin reuptake inhibitor**
- **60mg QD or BID**
- **Randomized clinical trial**
- **Efficacy at one week**
- **Open label extension 1 year safe and ongoing benefit**

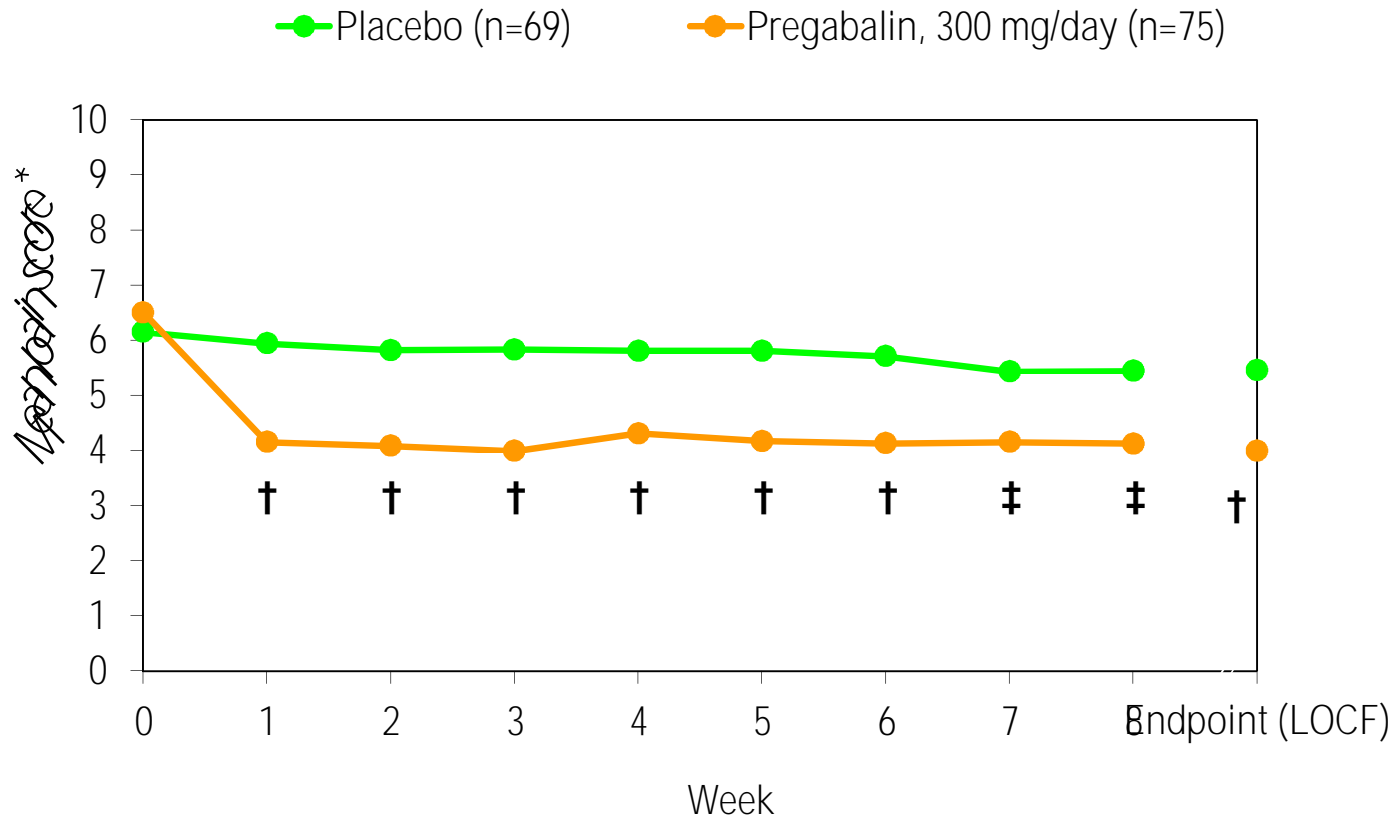
Duloxetine in Diabetic Peripheral Neuropathy



Duloxetine: Adverse Events

- **Nausea**
- **Somnolence**
- **Dizziness**
- **Constipation**
- **Dry mouth**
- **Hyperhidrosis**
- **Decreased appetite**
- **Anorexia**
- **Weakness**

Pregabalin: Effect on Mean Weekly Pain Scores in DPN



* Least squares means calculated from the model.

† $P \leq 0.01$; ‡ $P \leq 0.0001$.

LOCF=last observation carried forward.



Pregabalin: Adverse Events

- **Dizziness**
- **Somnolence**
- **Peripheral edema**
- **Headache**
- **Infection**
- **Dry mouth**

Gabapentin

- **Multicenter, randomized, double-blind, 8 week, placebo-controlled, parallel design trial in 165 pts titrated up to 3600 mg/day**
- **Average daily pain score dropped from 6.4 to 3.9 on GBP compared to a drop from 6.5 to 5.1 for placebo (P < 0.001)**
- **Most common adverse events on GBP were dizziness and somnolence**

Gabapentin

- **Start low 100-300 mg QHS**
- **Increase Q 1-7 days**
- **If no improvement at 1800mg/day stop**
- **If partial improvement can titrate further to 3600mg/day**
- **Adequate trial 3-8 weeks**



Painful Polyneuropathies: Tricyclic Antidepressants

- **Efficacy established in a number of small cross-over, placebo-controlled clinical trials***
- **Analgesic effect independent from effect on mood**
- **Start low and go slow. Usual dose range between 50-150 mg/day**
- **Analgesia starts to occur after a week and reach maximum efficacy after 3 weeks**



Painful Polyneuropathies: Tricyclic Antidepressants

- **Tertiary amines are metabolized to secondary amines (fewer side effects)**
- **Amitriptyline to nortriptyline**
- **Imipramine to desipramine**
- **Use the secondary amines if possible**



Painful Polyneuropathies: Tricyclic Antidepressants

- **Avoid or use cautiously with history of MI, glaucoma, urinary retention, autonomic neuropathy, or in the elderly with risk of falls**
- **Consider ECG for patients with cardiac history**
- **Adequate trial 6-8 weeks**
- **Wean off slowly or change to another antidepressant**

- **Weak serotonin norepinephrine reuptake inhibitor. Weak u opioid agonist**
- **In randomized, controlled trials the optimum dosage self selected by patients was 250 mg/day**
- **PDN study NNT 3.4**
- **Avoid if history of drug abuse, seizures, ?on bupropion**
- **Trial 4 weeks**



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No Disclosures



Largest College Football Stadium in the USA: 115,000 Football Fans!





Thank You! efeldman@umich.edu



University of Michigan Medical Center, Ann Arbor, Michigan



Second Line Treatment: Painful Diabetic Polyneuropathy

- **Other antidepressant agents**
- **Other anti-epileptic agents**
- **Topical therapies**



SSRIs and Peripheral Diabetic Neuropathy

- **Paroxetine small RCT significant improvement over placebo**
- **Citalopram small RCT significant improvement over placebo**
- **Fluoxetine no improvement**
- **Overall – modest benefit**

Sindrup SH, et al. *Pain*. 1990;42:135-144.

Sindrup SH, et al. *Clin Pharmacol Ther*. 1992;52:547-552.

Max MB, et al. *NEJM*. 1992;326:1250-1256.



*Anticonvulsant Drugs and Neuropathic Pain**

First-generation

- **Carbamazepine †**
- **Divalproex sodium ‡**
- **Phenytoin †**
- **Valproic acid ‡**
- **Clonazepam ‡**
- **Phenobarbital ‡**

Second-generation

- **Gabapentin †**
- **Pregabalin †**
- **Lamotrigine †**
- **Levetiracetam ‡**
- **Oxcarbazepine †**
- **Tiagabine ‡**
- **Topiramate ‡**
- **Zonisamide ‡**

* Not approved by the FDA for this use.

† Published randomized controlled trials.

‡ Clinical anecdotes and/or published case series.

Topiramate in Painful Diabetic Neuropathy

- **3 multicenter, randomized, placebo-controlled clinical trials in PDN were negative**
- **1 multicenter trial (323 pts) positive**
- **Initiating therapy: 25-50 mg\|d qhs for one week**
- **Maintenance dose: 100-200 mg bid**
- **Titration: 25-50 mg qd**
- **SE: Ataxia, Cognitive difficulties, dizziness, weight loss, kidney stones**

Raskin P, et al. *Neurology* 2004;63(5):865-73.

Thienel U, et al. *Acta Neurol. Scand* 2004;110(4):221-31.



Capsaicin and Painful Diabetic Neuropathy

- **4 studies, 299 patients, 0.075% strength of capsaicin**
- **Neuropathy: No effect**
- **Diabetic Neuropathy: Significant effect**
- **Postherpetic Neuralgia: Significant effect**

Capsaicin Study Group. Arch Intern Med. 1991;151:2225-2229.

Bernstein JE, et al. J Am Acad Dermatol. 1989;21:265-270.

Low PA, et al. Pain. 1995;62:163-168.



Data Considered for Pregabalin Schedule V Designation

- **Studied in an at-risk population**
 - Recreational sedative/hypnotic users (n=15)
 - Subjective ratings: “good drug effect,” “high,” “liking”
 - Pregabalin (450 mg single dose) received these ratings to a degree similar to diazepam (30 mg single dose)
- **Reports of euphoria**

	Percent of Patients	
	Pregabalin	Placebo
All pregabalin	4.0	1.0
Painful DPN	2.0	0.0
PHN	1.0	0.0
Epilepsy	0.8	0.3

- **Adverse events following abrupt/rapid discontinuation**

	Percent of Patients	
	Pregabalin	Placebo
Insomnia	2.4	0.7
Headache	2.1	1.5
Nausea	1.8	1.1
Diarrhea	1.2	1.0

Examples of Scheduled Products

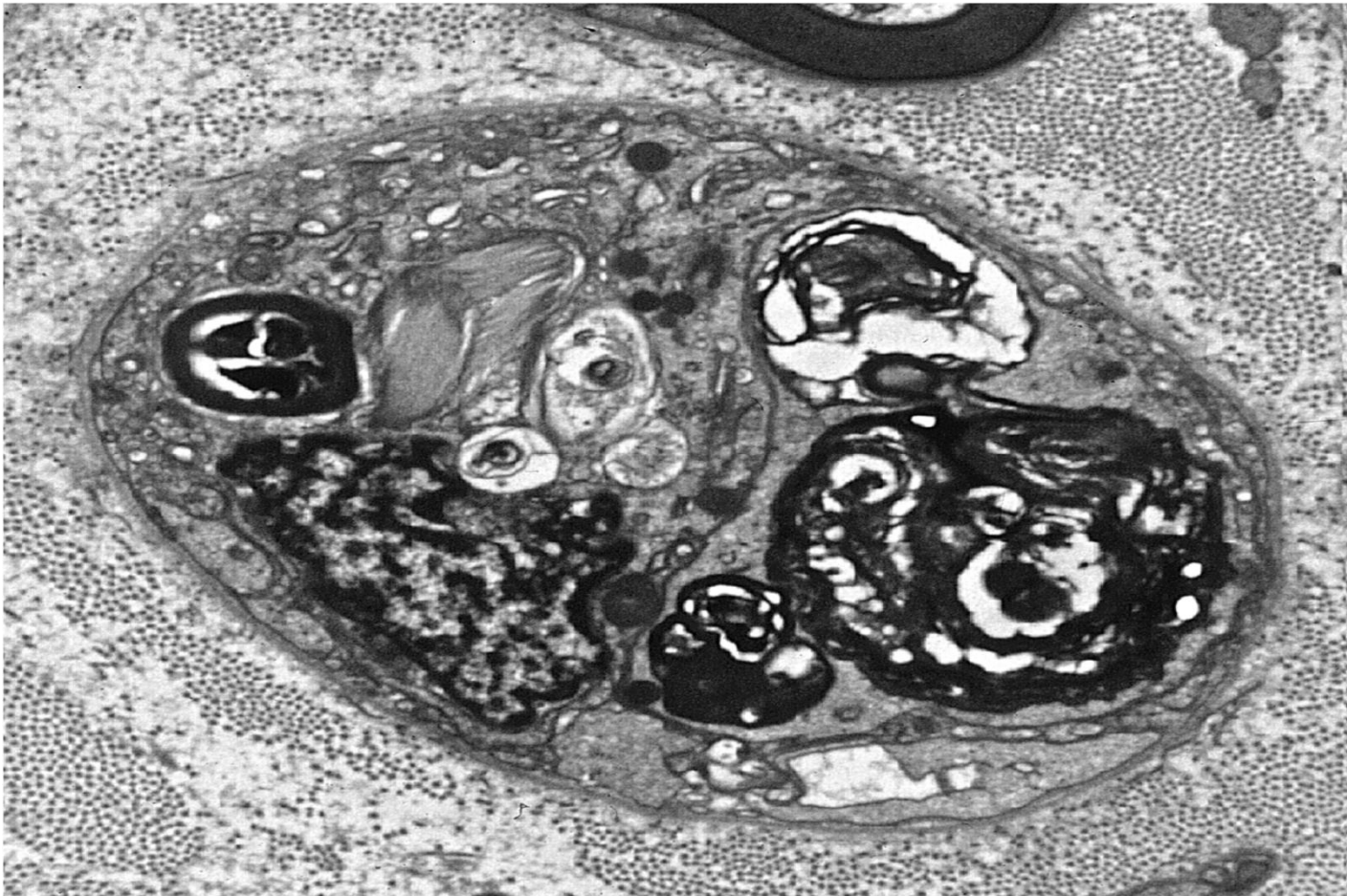
Schedule	Examples	Medical Use(s)
C-I	Heroin	None
C-II	Adderall® Ritalin® Morphine OxyContin®	Attention deficit disorder with hyperactivity; narcolepsy Moderate to severe pain Moderate to severe pain
C-III	Tylenol® with codeine Vicodin®	Mild to moderately severe pain Moderate to moderately severe pain
C-IV	Ambien® Xanax® Valium® Phenobarbital	Short-term treatment of insomnia Anxiolytic Anxiolytic Sedative; anticonvulsant
C-V	Robitussin® with codeine Lomotil®	Cough preparation Antidiarrheal

WW2

Need to make consistent with newer version. Dave/Andy/Ashley to send.

William Watkins, 06/06/2005

Axons Degenerate in Neuropathy: Human Sural Nerve Biopsy





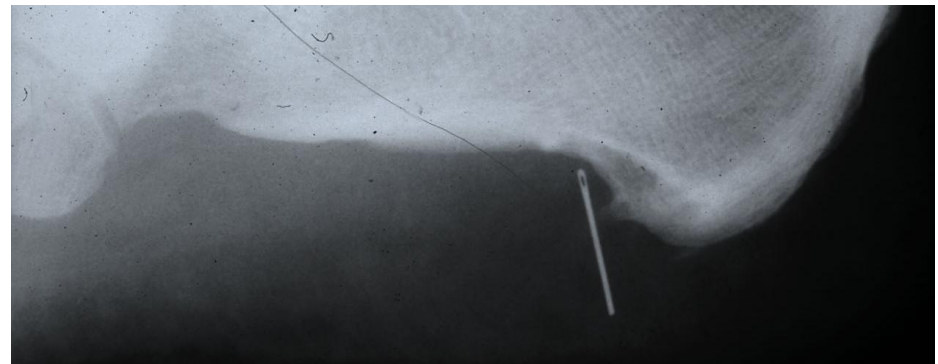
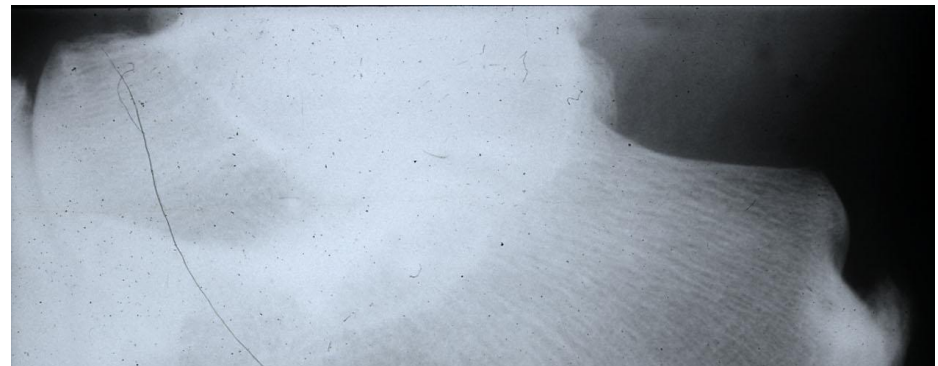
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