Spinal Cord and Nerve (Somatic and Autonomic) Anatomy and Evaluation

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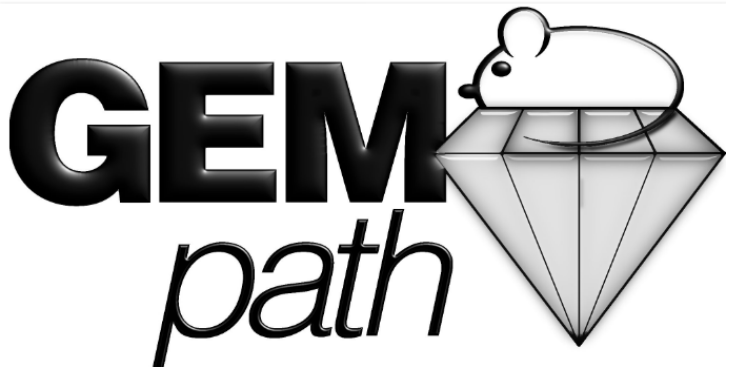


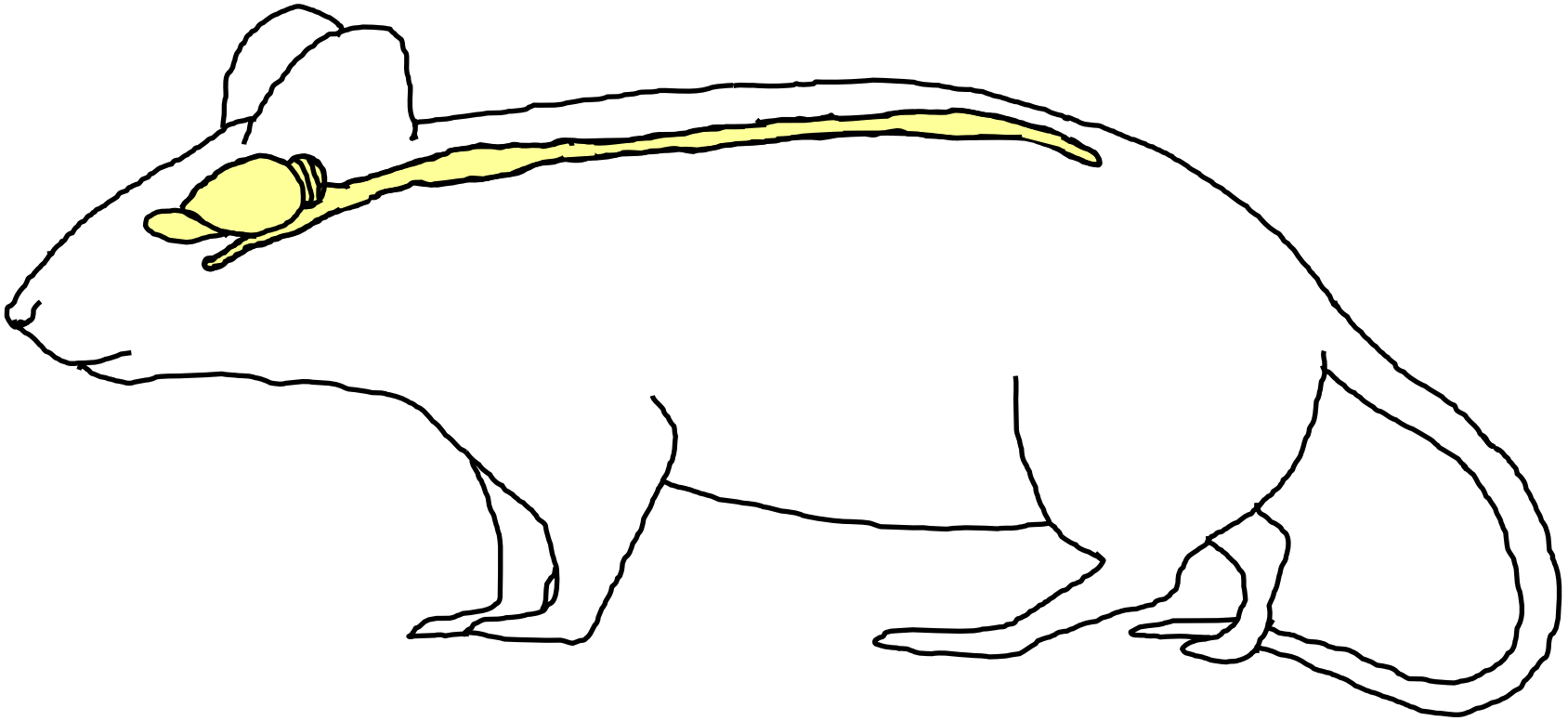
Session Objectives

- **Provide a broad (though brief) anatomic review for the spinal cord, ganglia, and nerves**
- **Review recommended practices for collecting and processing spinal cord, ganglia, and nerves**
- **Explore the principal structural lesions and artifacts that occur in the spinal cord, ganglia, and nerves**

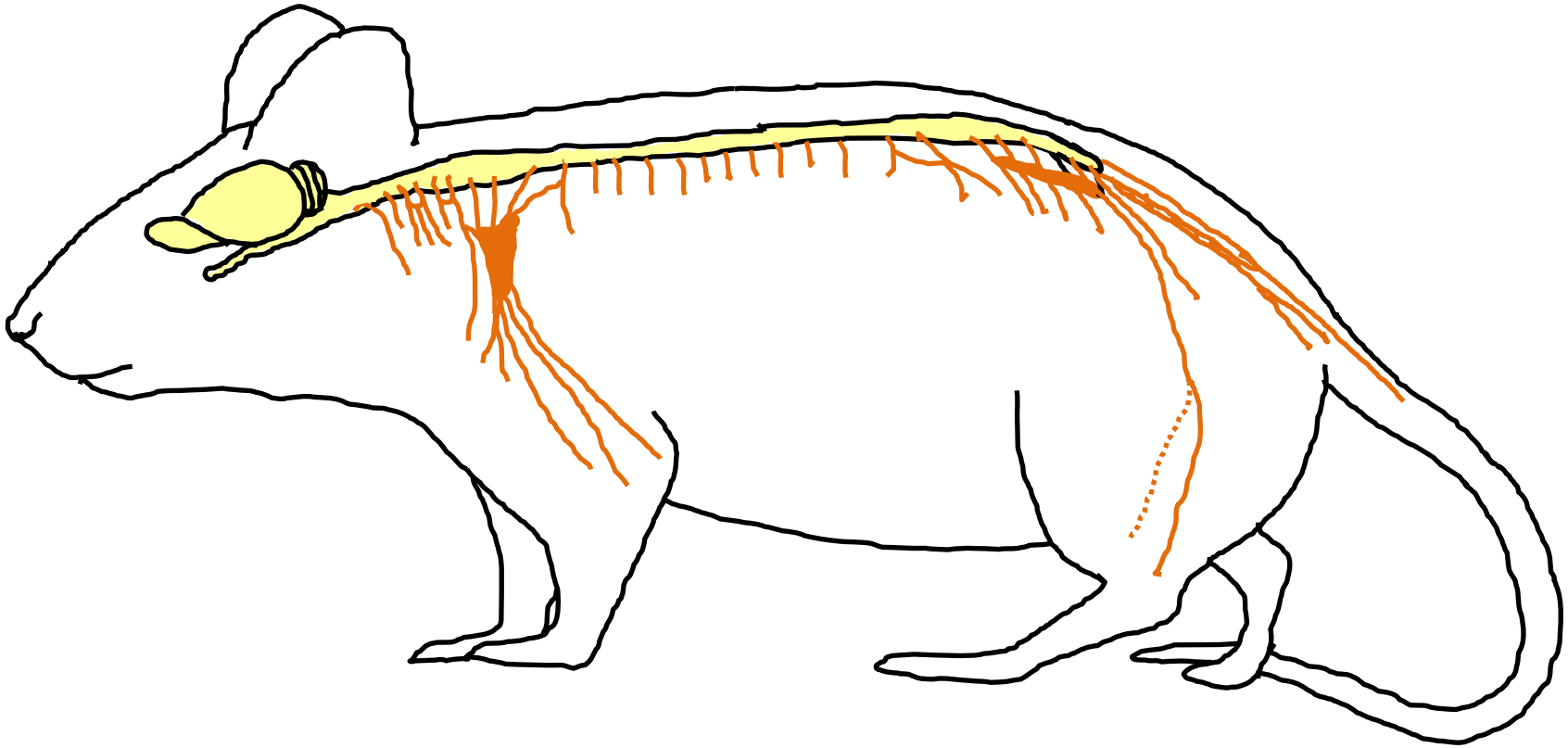
Part I:

Anatomy of the Spinal Cord and Peripheral Nervous Systems

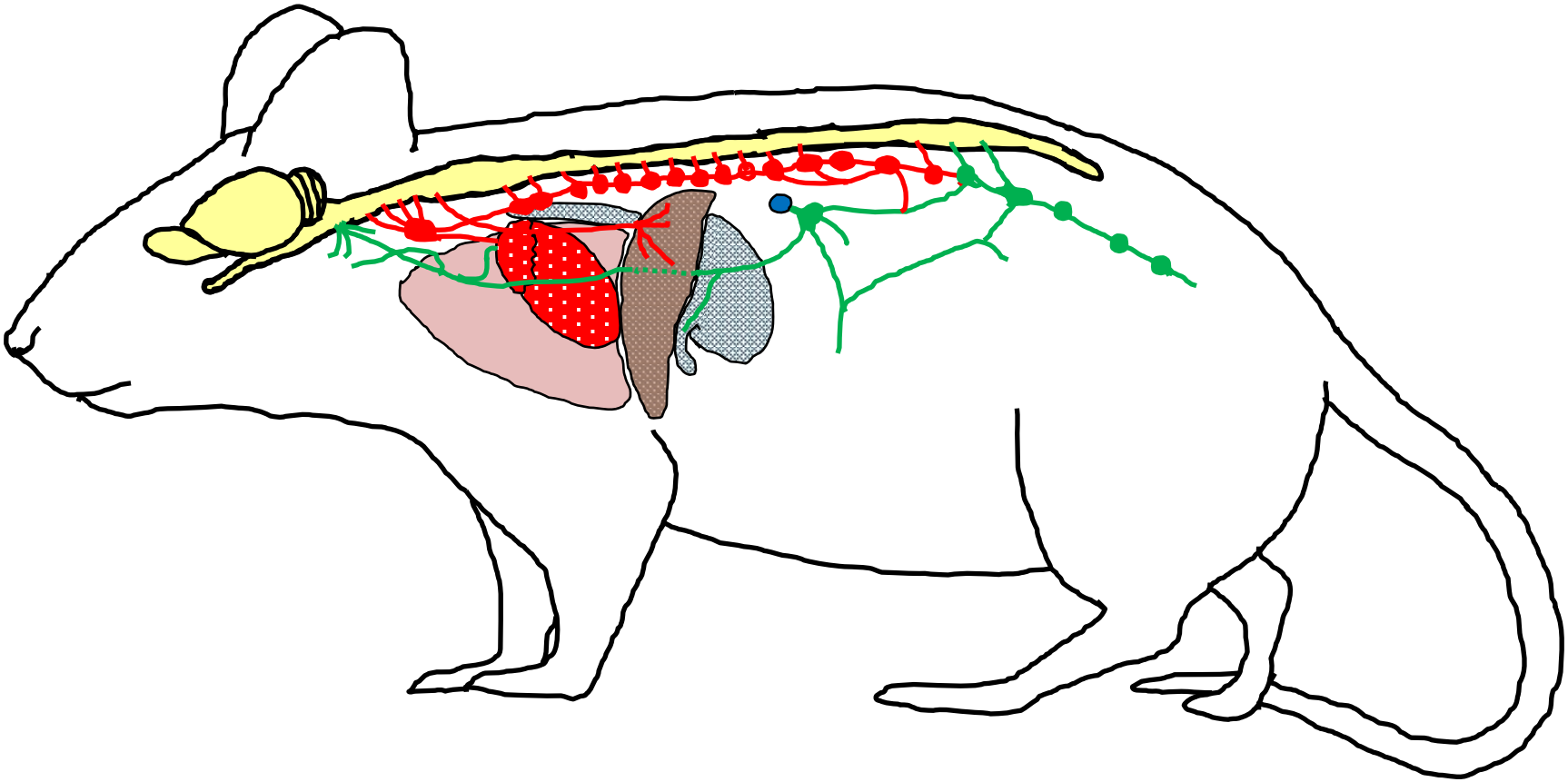
Organization of the Central Nervous System



Distribution of the Somatic Peripheral Nervous System



Distribution of the Autonomic Peripheral Nervous System



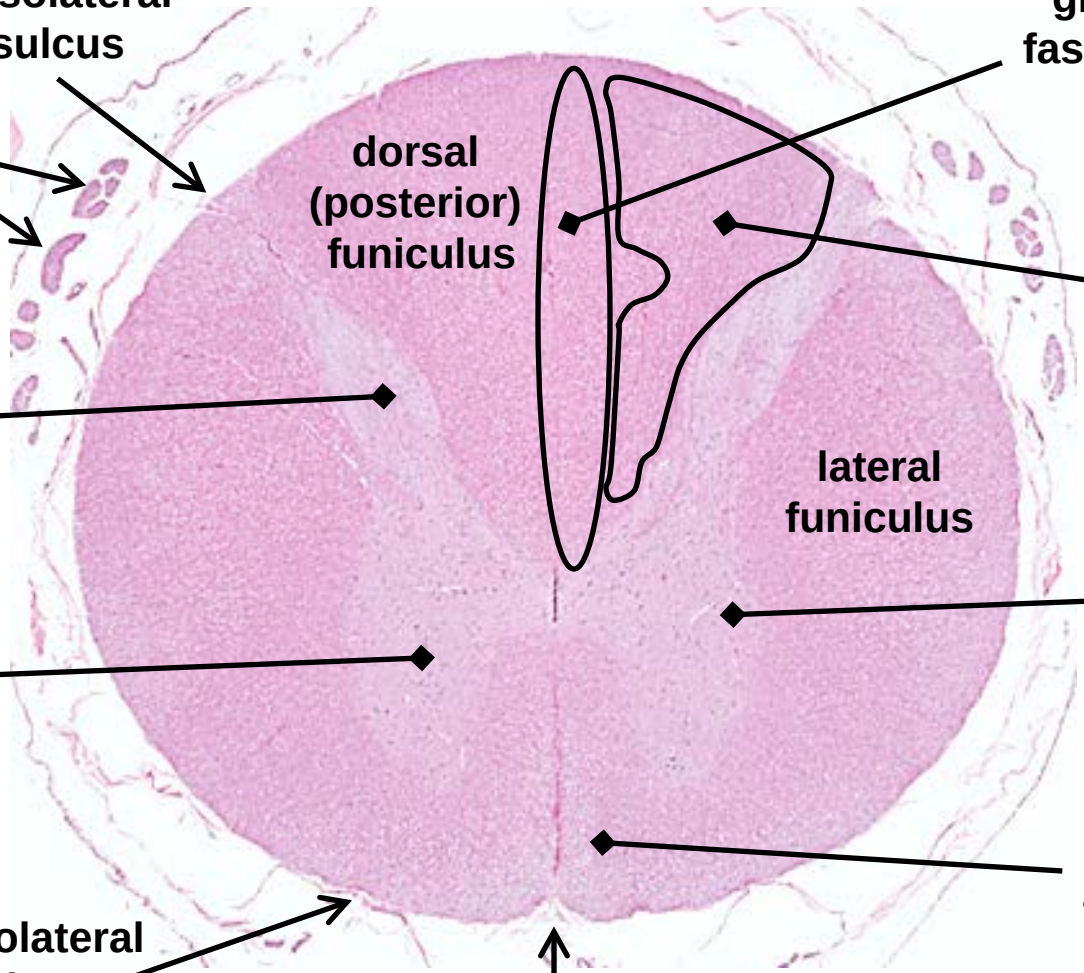
Spinal Cord – Regional Differences

Cervical

Lumbar

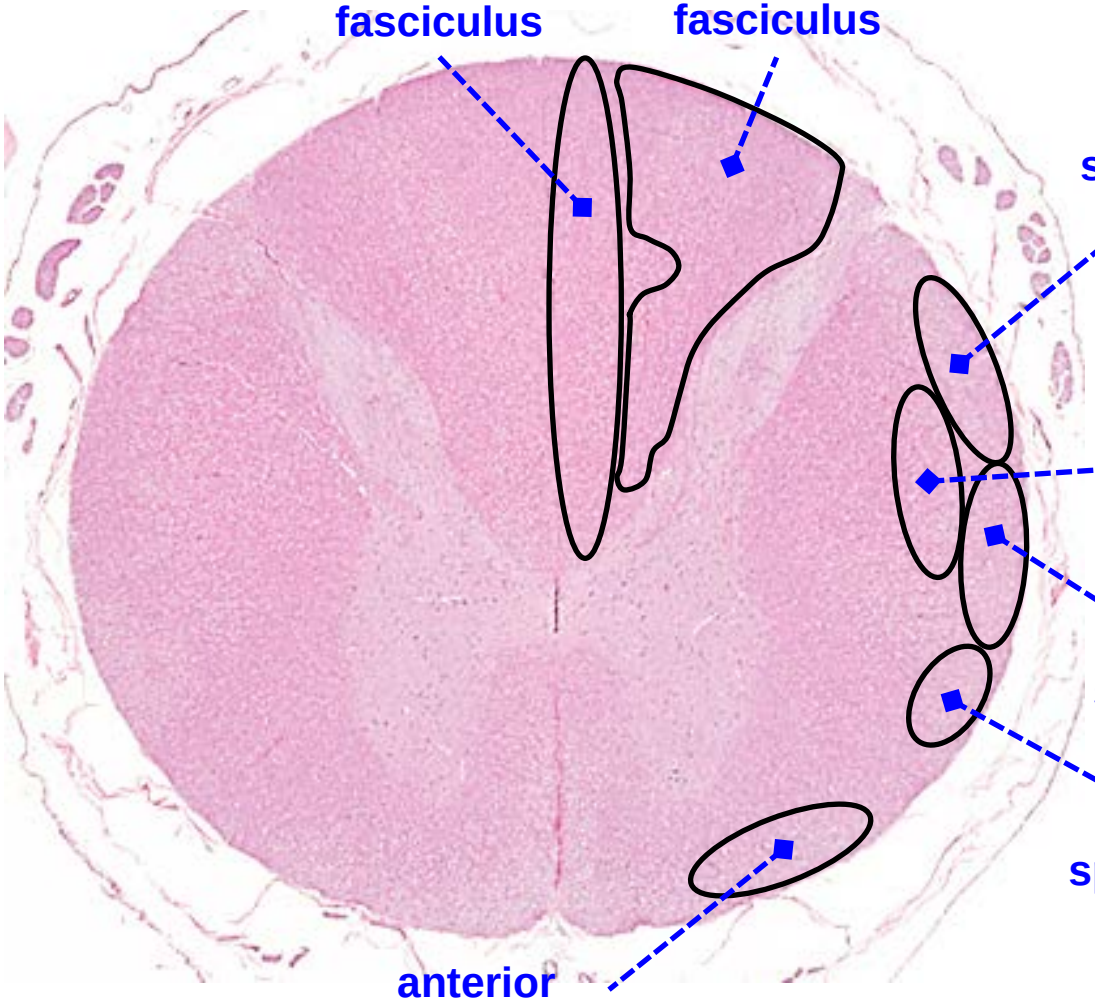
Toxicol Pathol **40: 624-636, 2012**

Spinal Cord – Landmarks (Cervical)



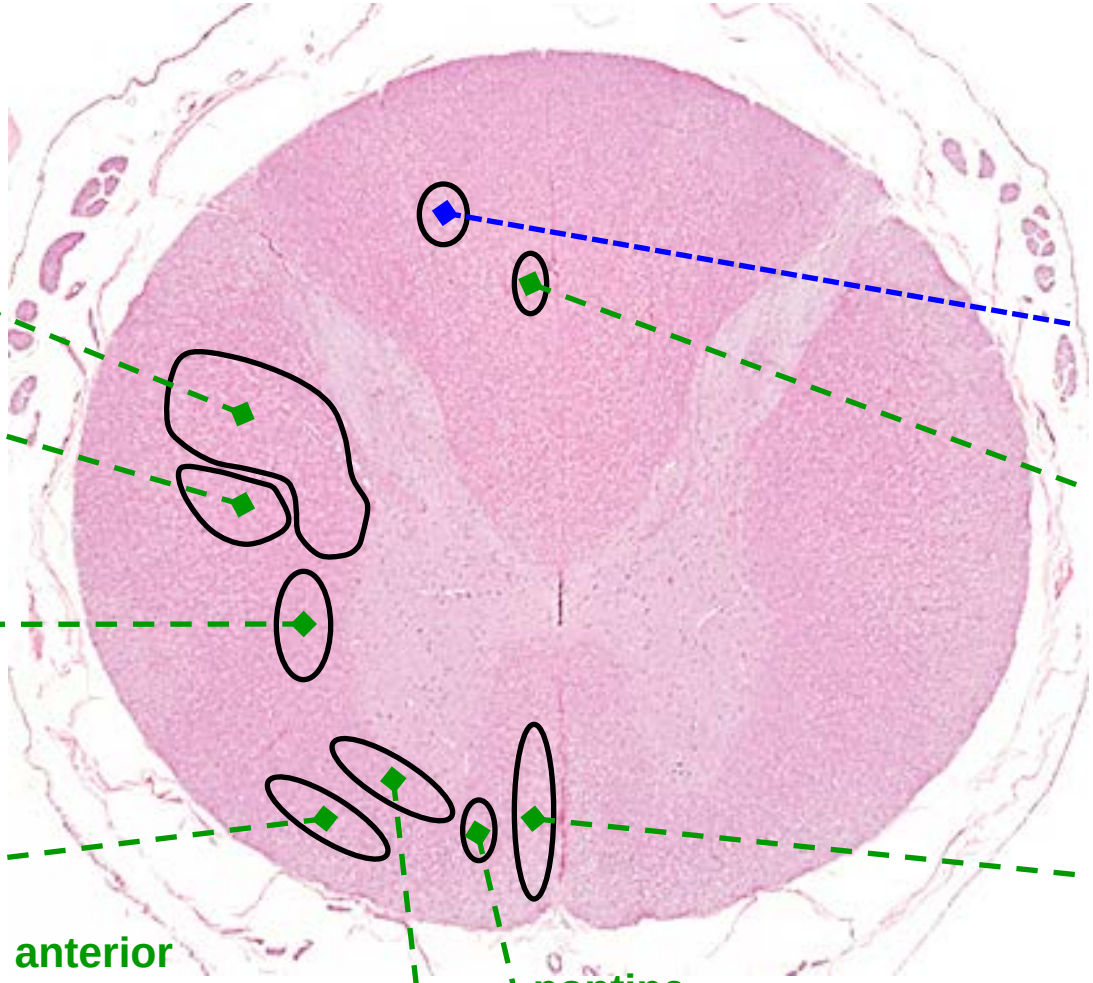
Toxicol Pathol 40: 624-636, 2012

Spinal Cord – Ascending Tracts



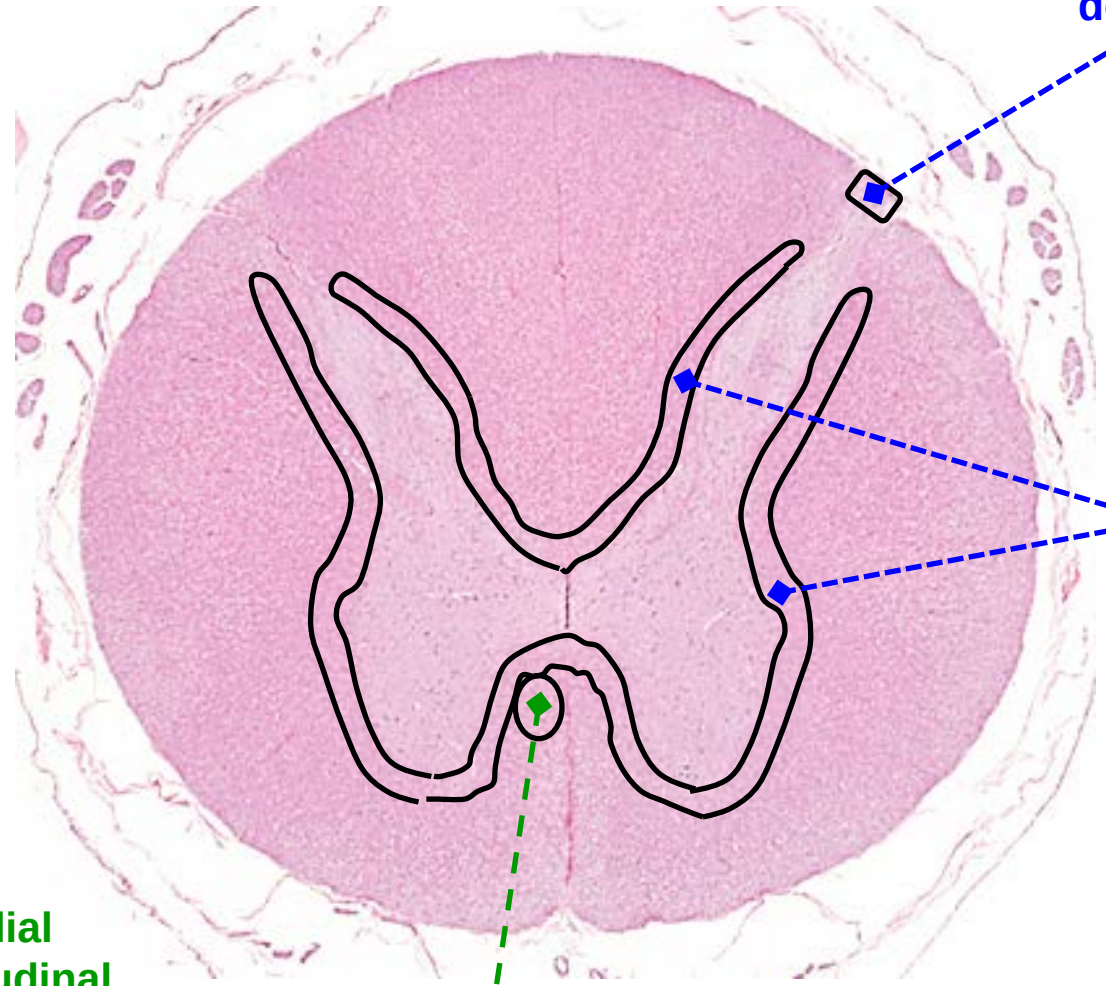
Toxicol Pathol 40: 624-636, 2012

Spinal Cord – Descending Tracts



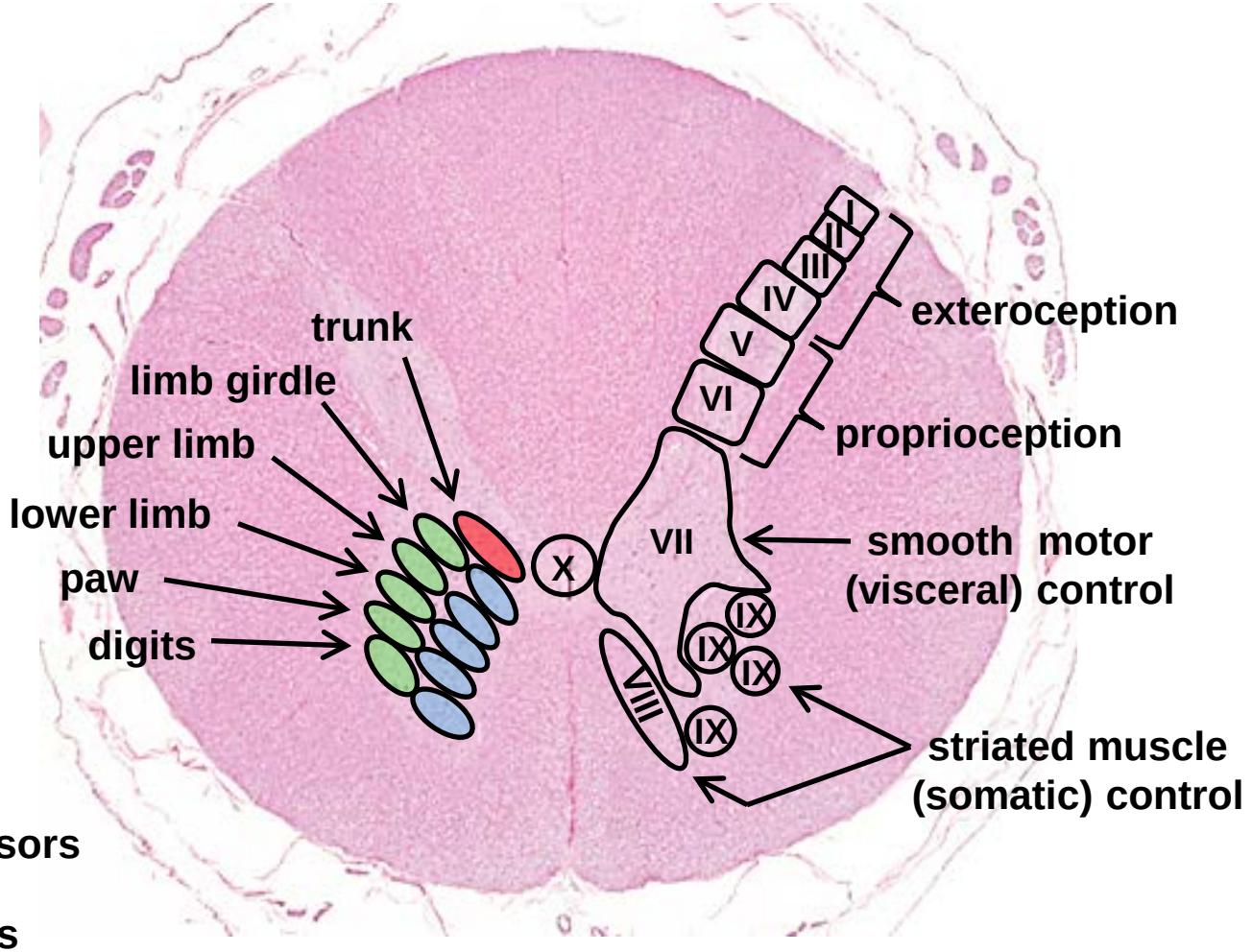
Toxicol Pathol 40: 624-636, 2012

Spinal Cord – Bidirectional Tracts



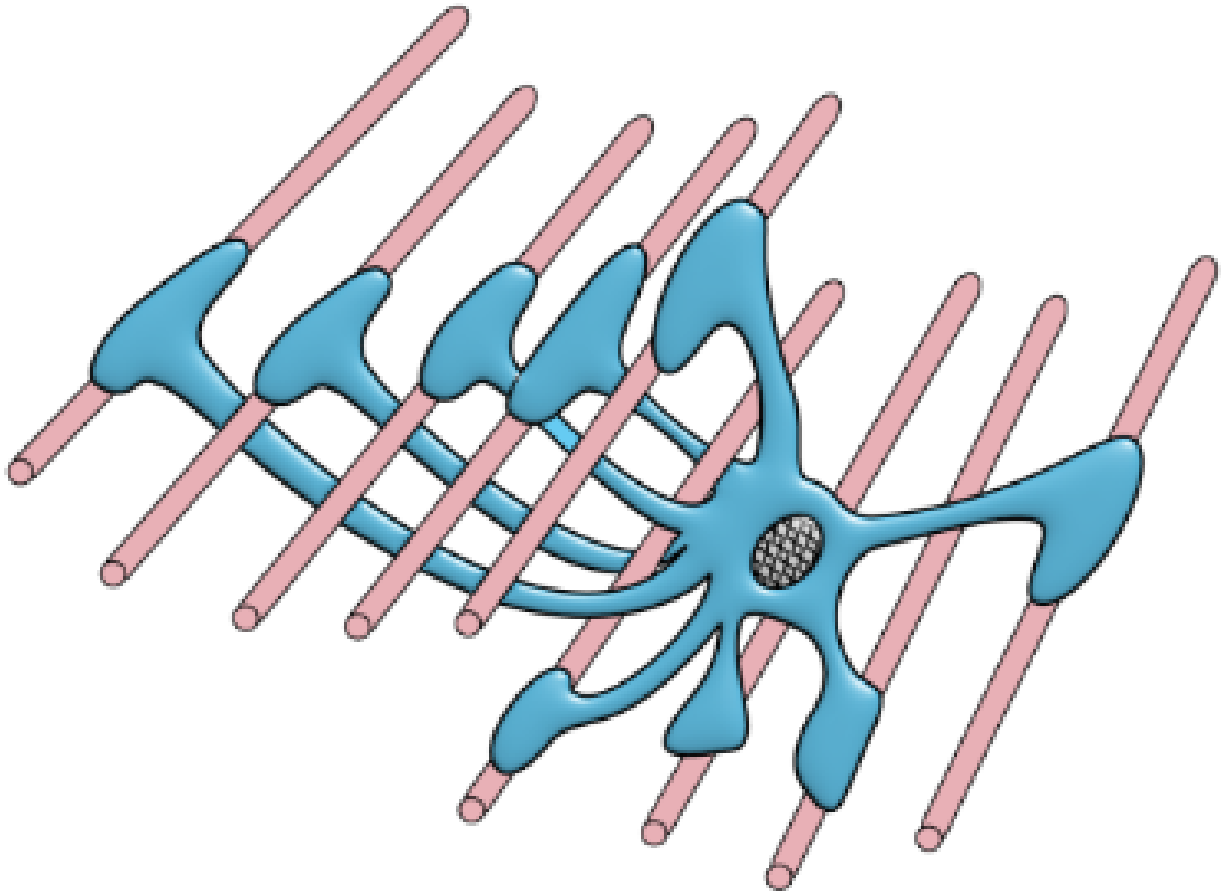
Toxicol Pathol 40: 624-636, 2012

Spinal Cord – Gray Matter Domains



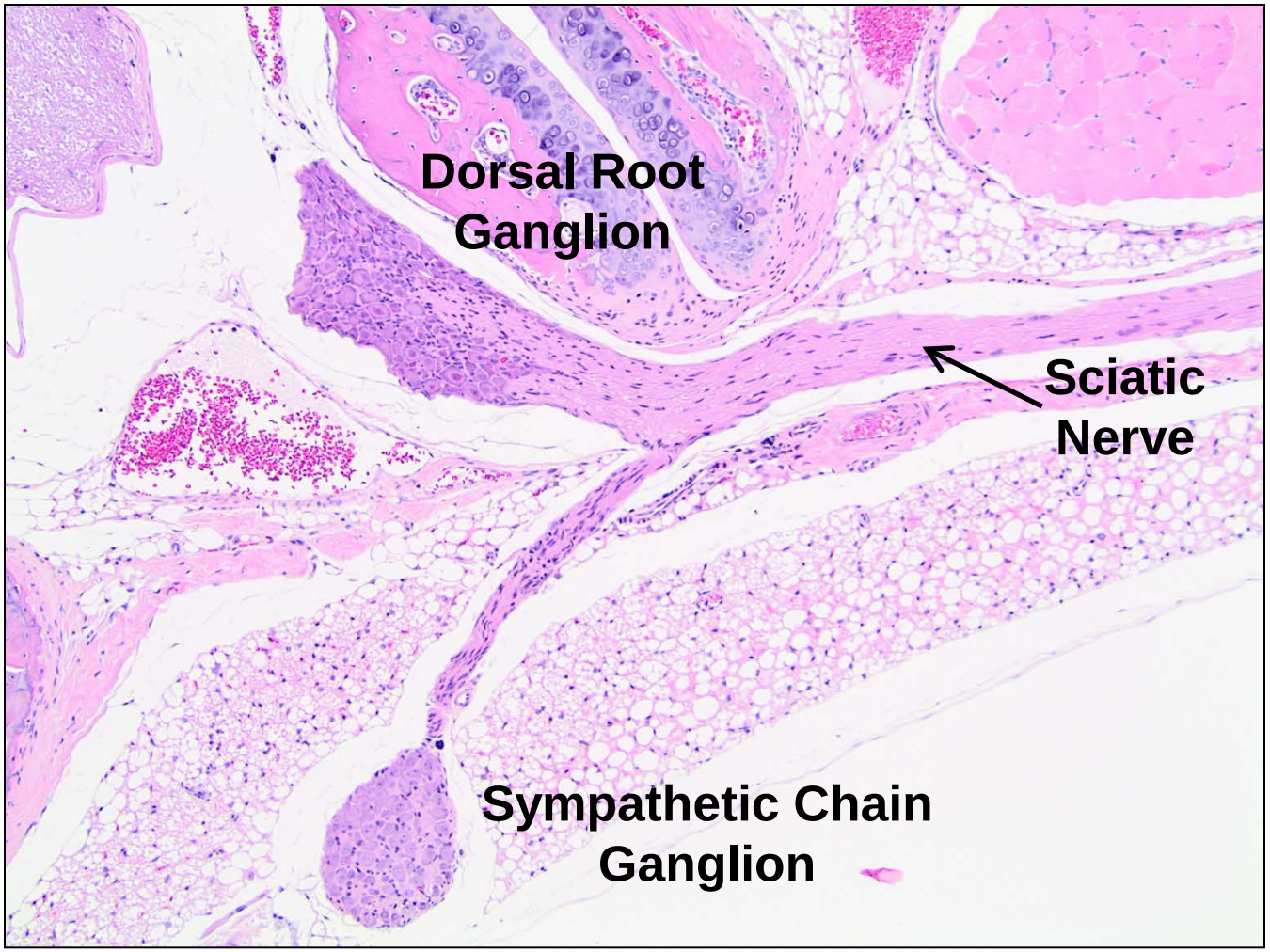
Toxicol Pathol 40: 624-636, 2012

Primary Oligodendroglial Function



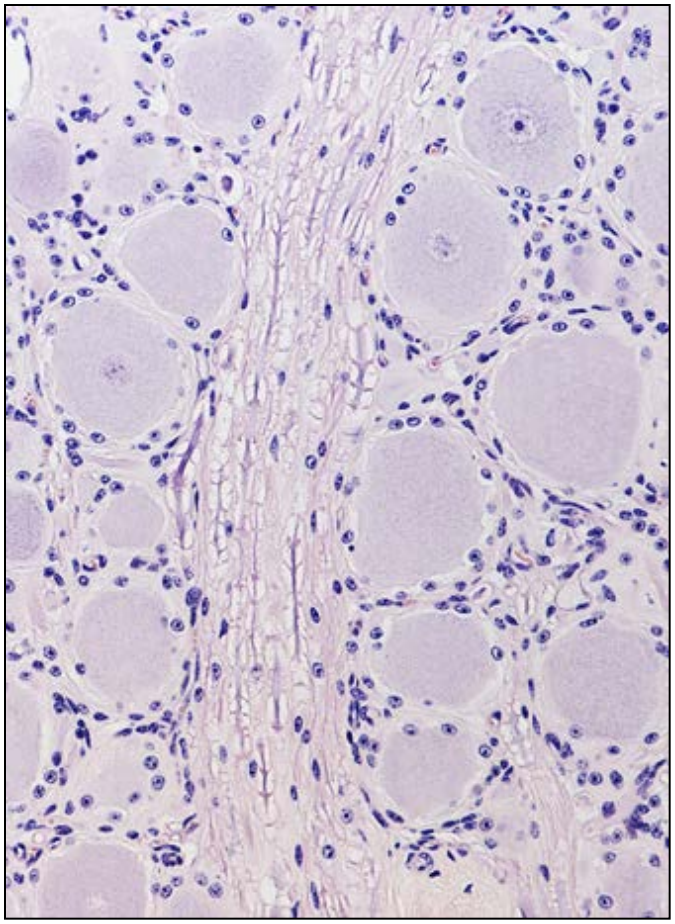
***Fundamental Neuropathology for Pathologists and Toxicologists*, Ch 23, 2011**
(courtesy Dr. G. Krinke)

Ganglia

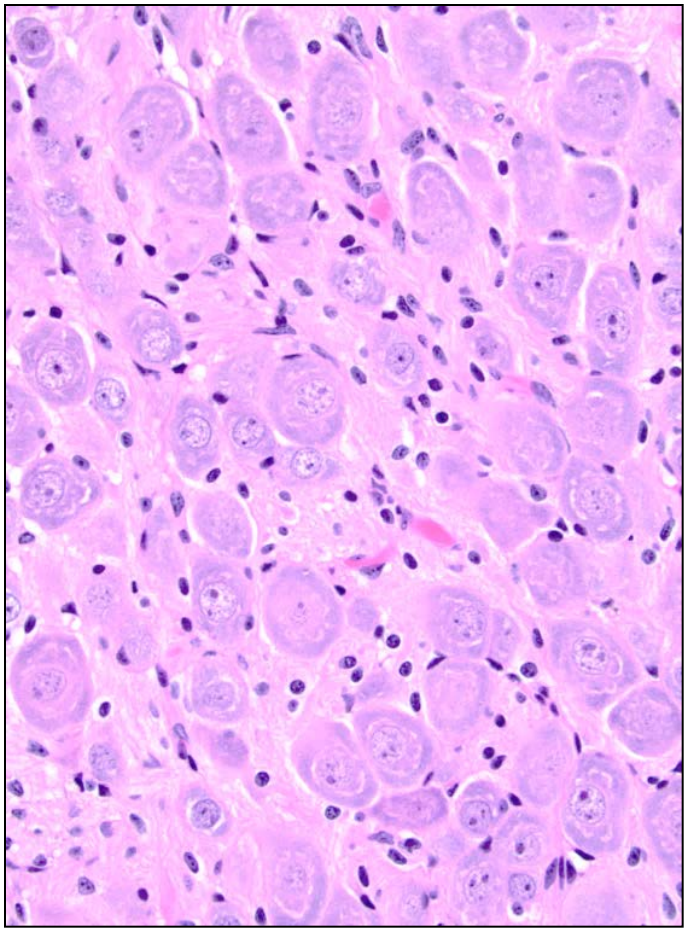

Dorsal Root Ganglion
Sciatic Nerve
Sympathetic Chain Ganglion

Ganglia

Dorsal Root Ganglion

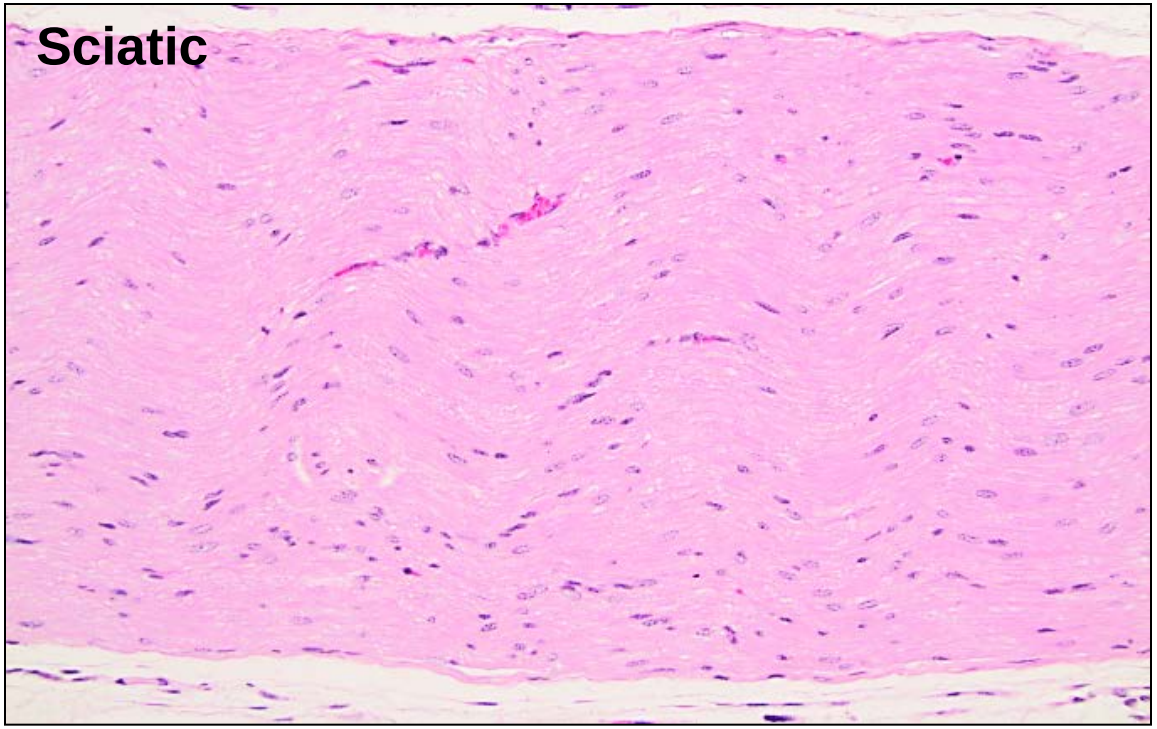


Autonomic Ganglion

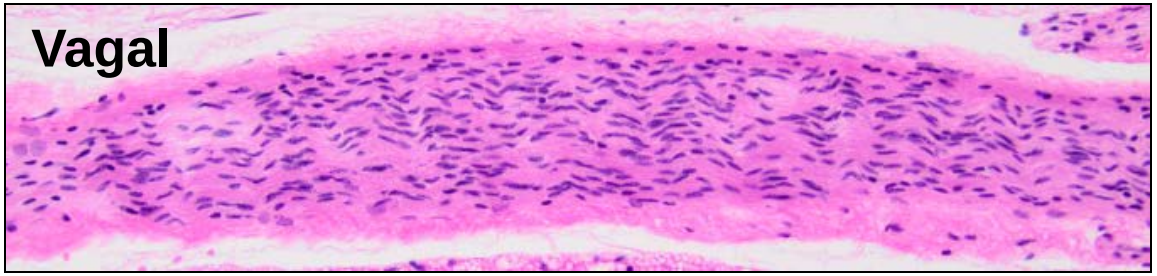


Nerve Form Depends on Function

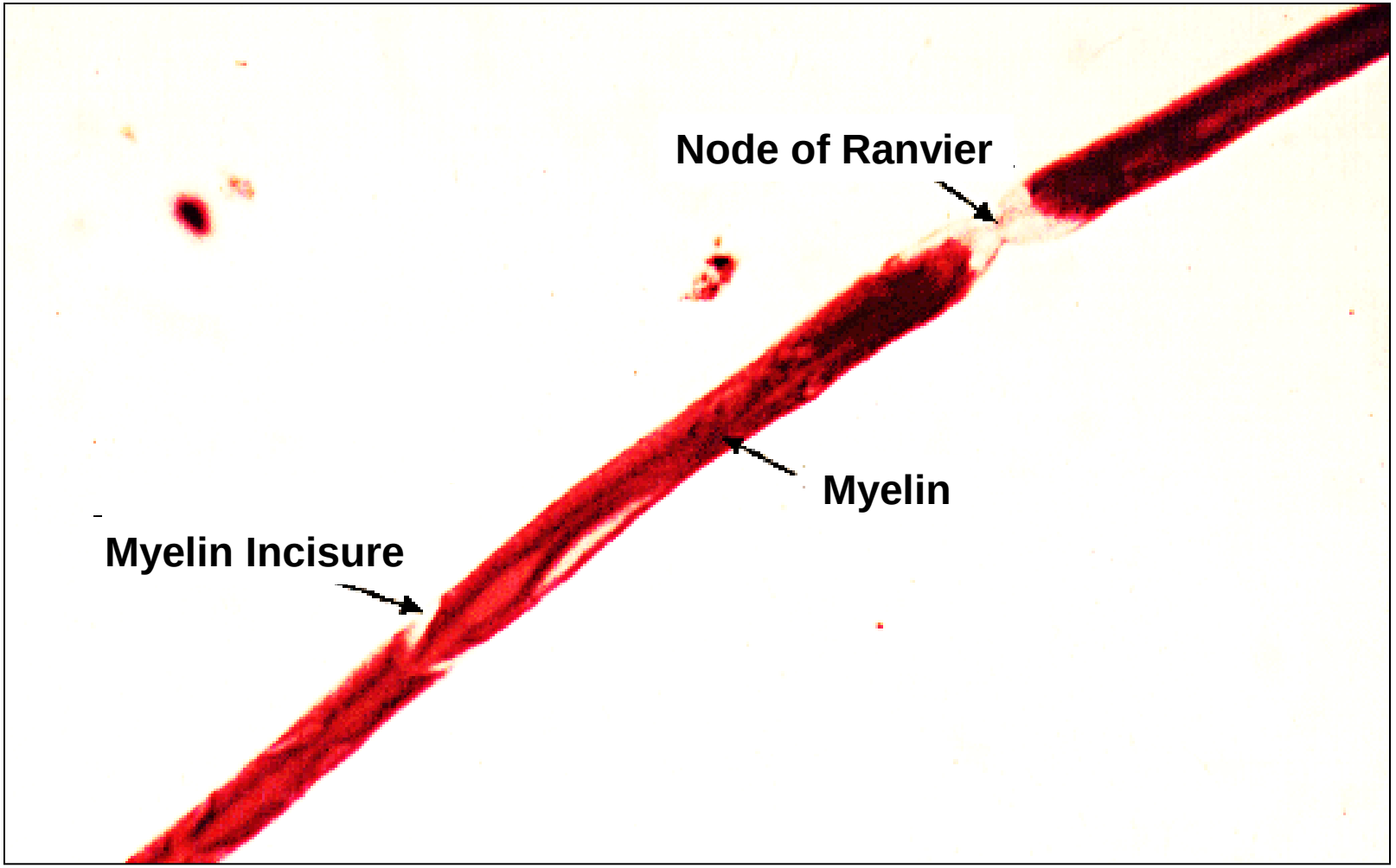
Myelinated (somatic n.)



Non-myelinated (autonomic n.)



Nerve Fiber – Longitudinal Anatomy



http://education.med.nyu.edu/Histology/courseware/modules/nervous-sy/nervous.46.html

Nerve – Cross Section Anatomy

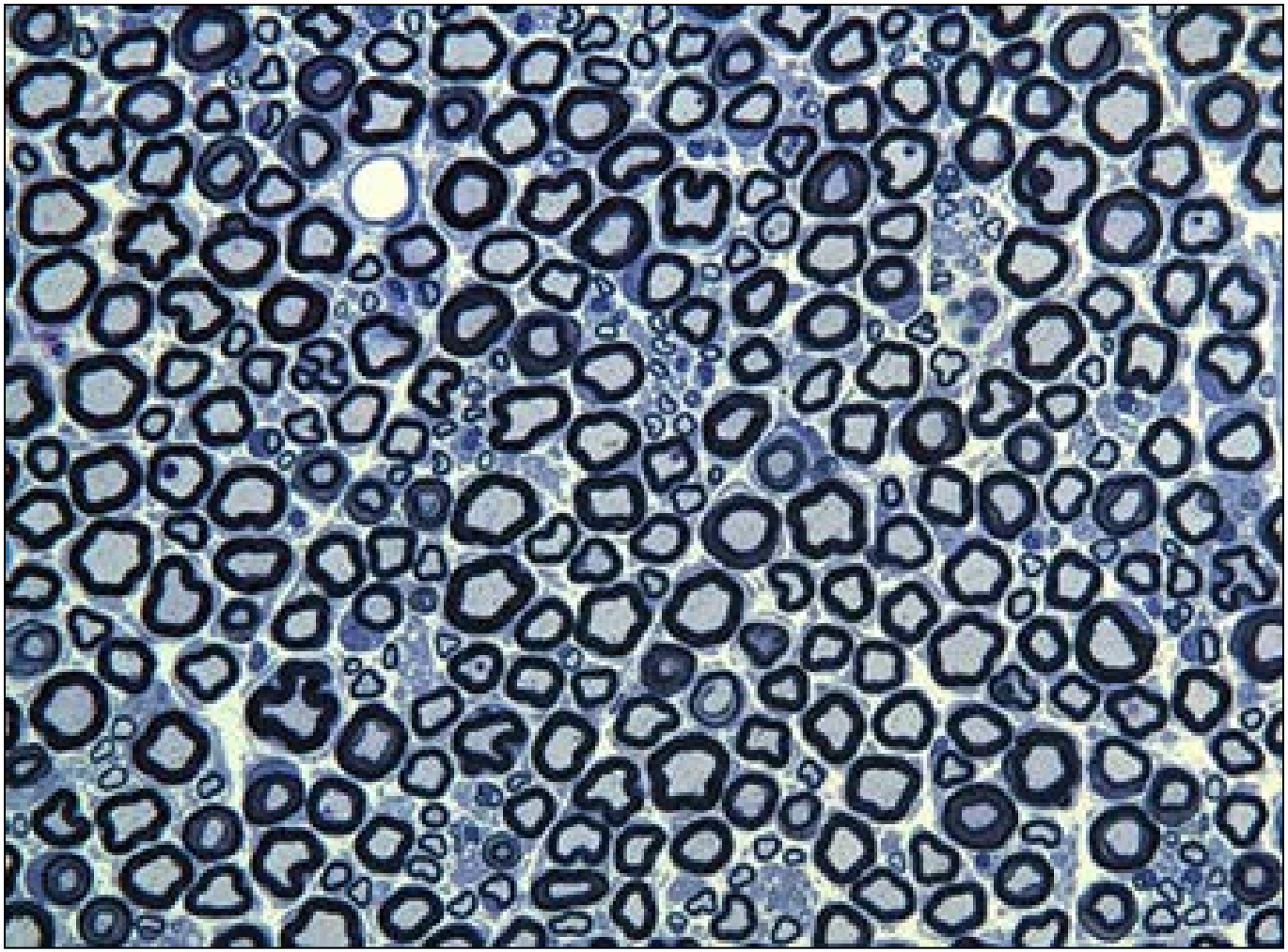


Image courtesy Dr. W. Valentine

Nerve – Special Features

Arrows
myelin (Schmidt-Lanterman) incisures

Asterisks
axon fluting

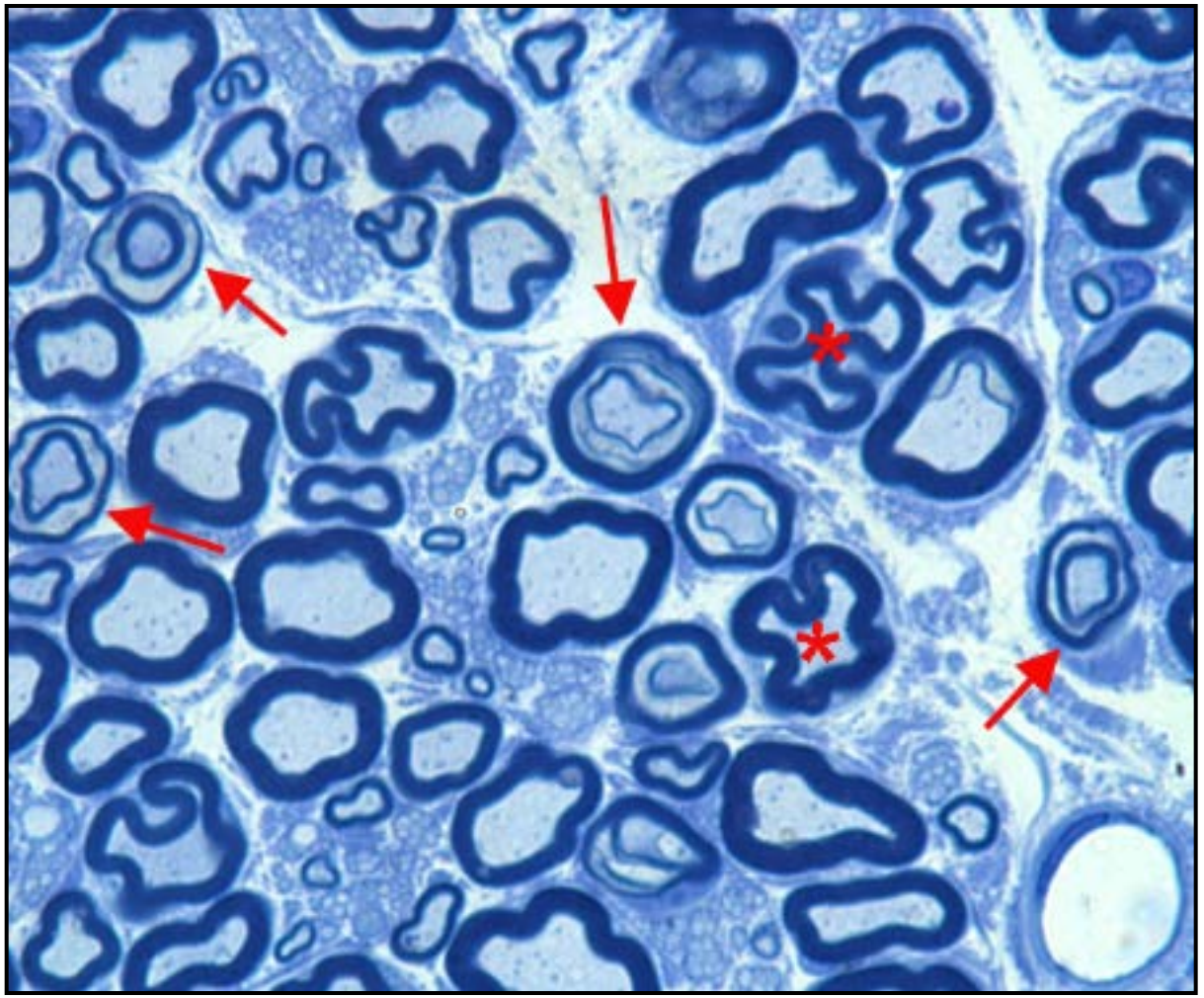


Image courtesy Dr. W. Valentine

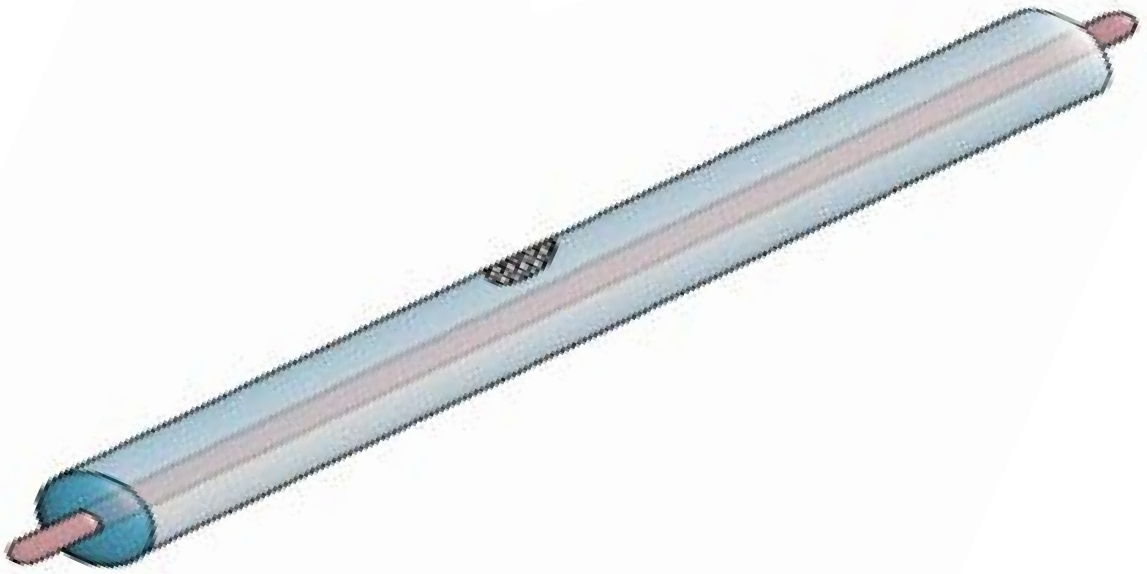
Myelinated Axon: Ultrastructure

Adult rat (control)

myelinated nerve fiber

Image courtesy Dr. W. Valentine

Primary Schwann Cell Function



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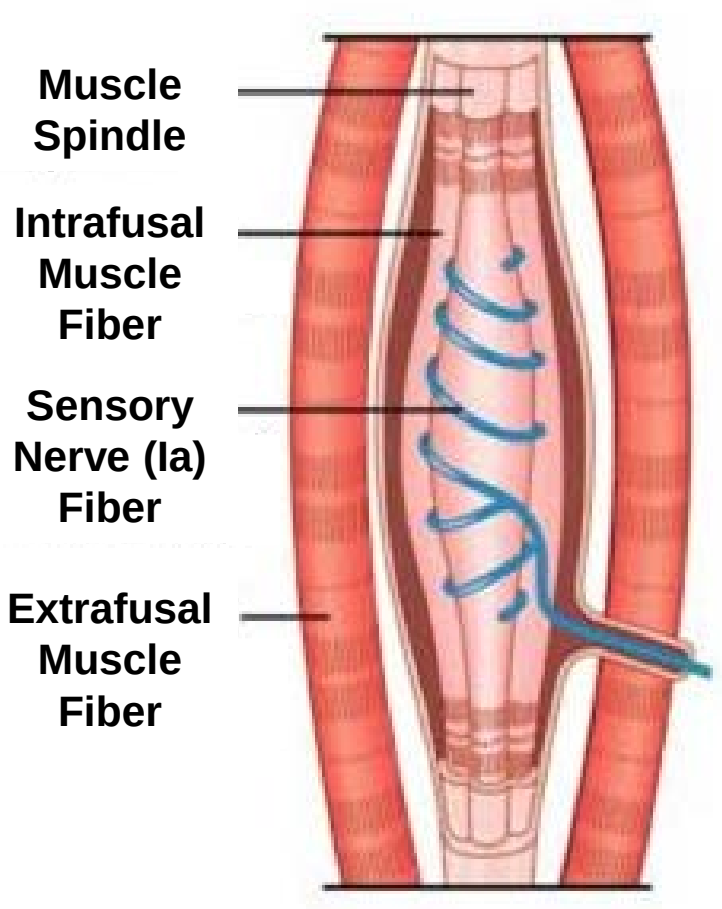
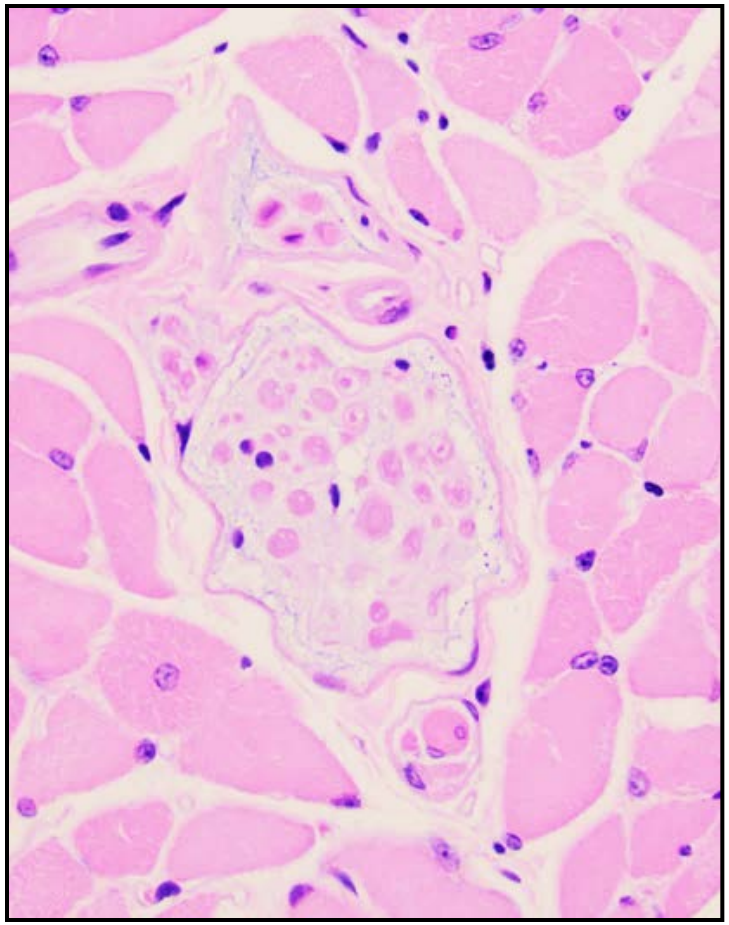
(courtesy Dr. G. Krinke)

Muscle Spindle Apparatus

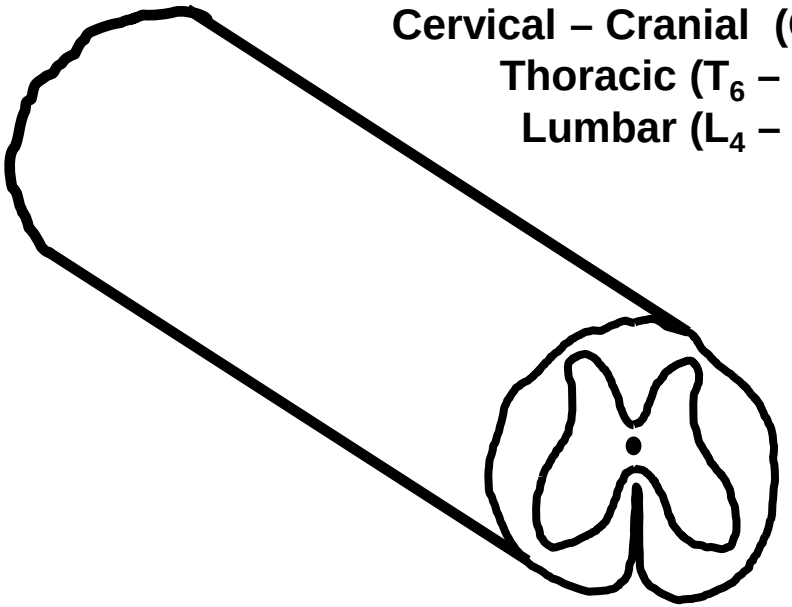




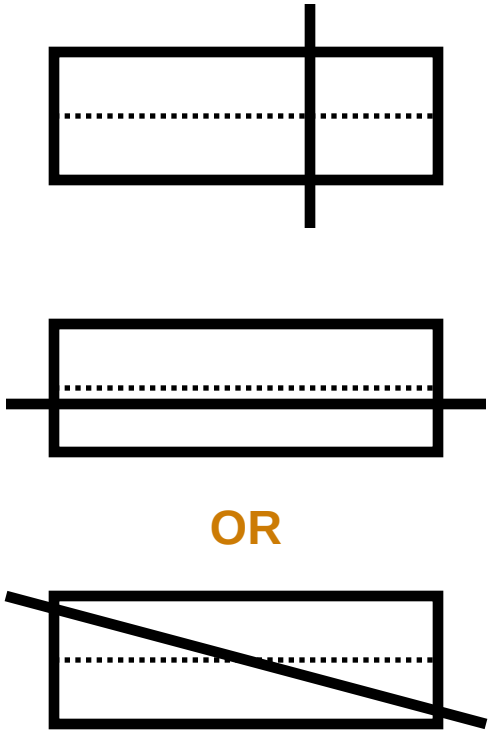
Part II:

Recommended Practices for Collecting and Processing Spinal Cord, Ganglia, and Nerves

STP Best Practices for Sampling Spinal Cord in General Toxicity Testing



Cervical – Cranial (C_1)
Thoracic (T_6 – T_8)
Lumbar (L_4 – L_5)

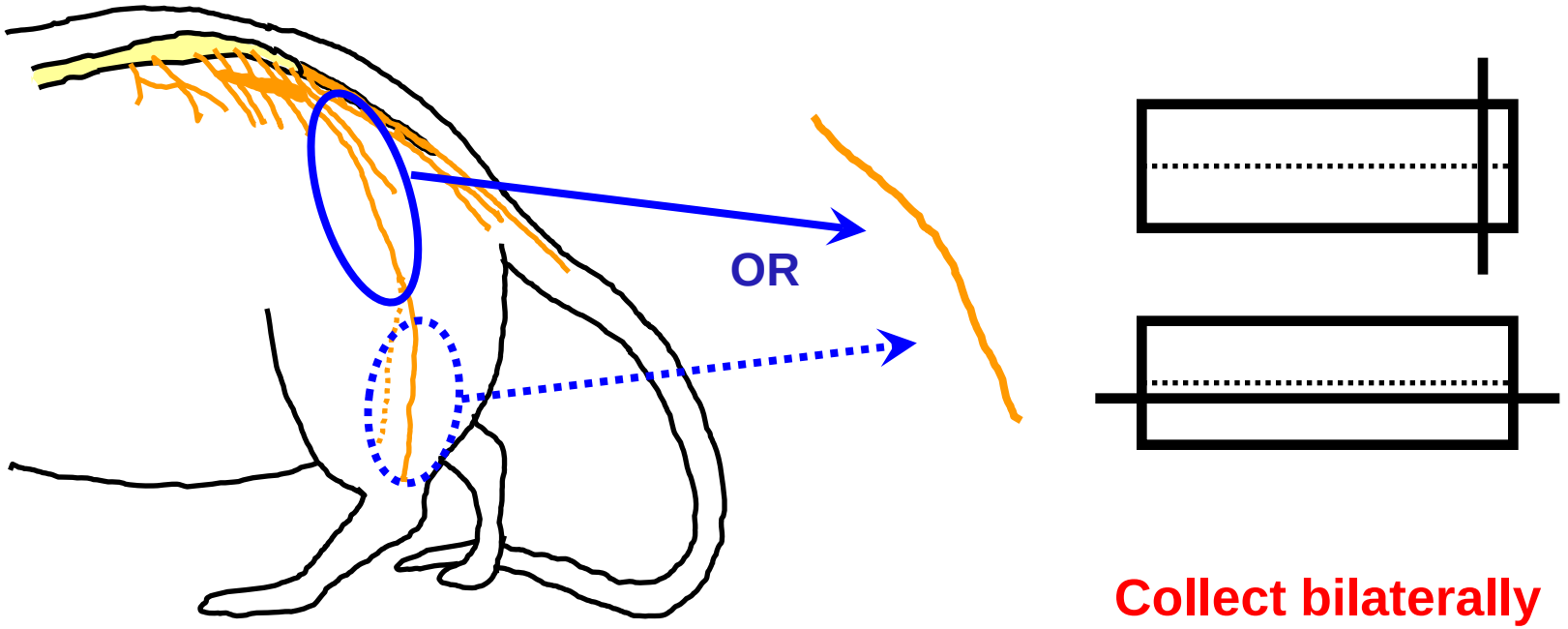


Toxicol Pathol 41: 1028-1048, 2013

STP Best Practices for Sampling Ganglia in General Toxicity Testing

- **No neurotoxic potential – hold ganglia in wet tissue**
- **Somatic neuropathy – multiple dorsal root ganglia**
  - **Signs: abnormal movement, circling, difficulty walking, lameness of unknown origin, generalized muscle weakness**
  - ***In situ* (rodent only) or isolated (rodent or non-rodent)**
  - **Sample: at least 2 for each of cervical and lumbar intumescences**
- **Autonomic neuropathy – more autonomic ganglia**
  - **Signs: abnormal gastrointestinal motility, heart rhythm, micturition, salivation, or vascular tone, and/or formation of sperm granulomas**
  - **Sample: multiple parasympathetic (e.g., caudal [“nodose”]) and sympathetic (e.g., cranial cervical, cervicothoracic, celiac) ganglia**

STP Best Practices for Sampling Nerves in General Toxicity Testing

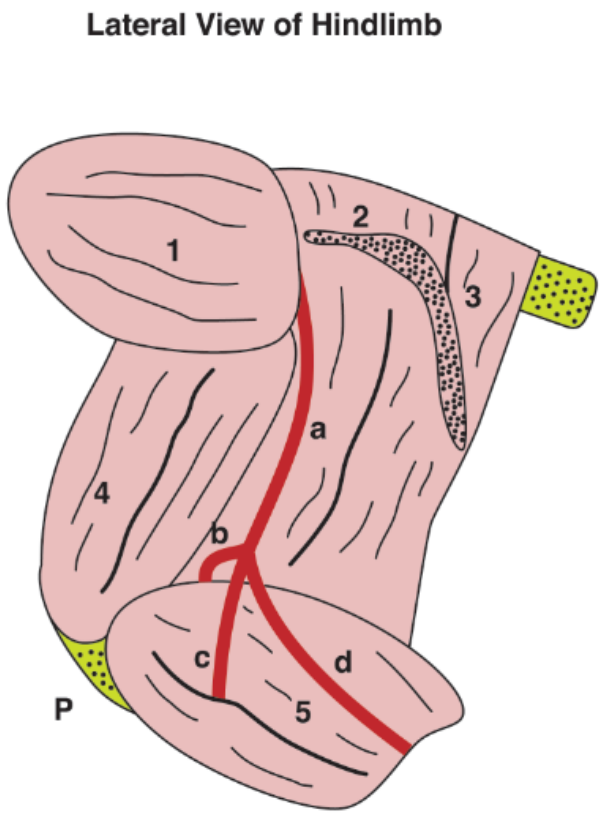


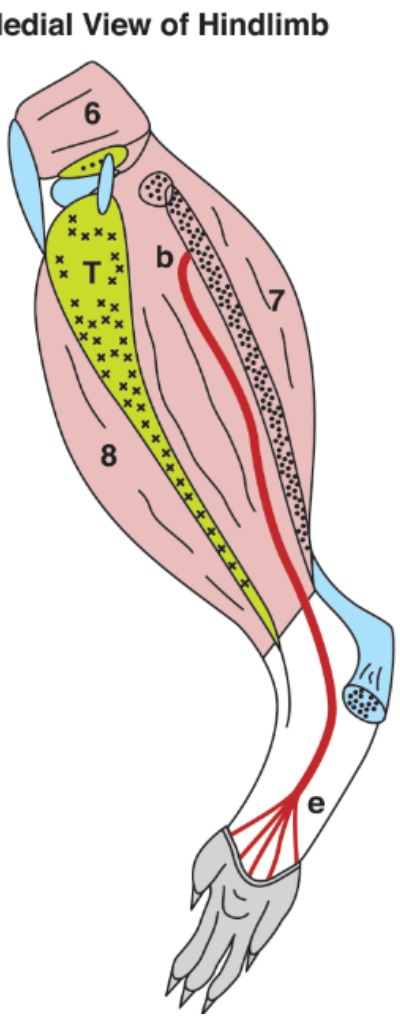
Collect bilaterally

Process unilaterally

Toxicol Pathol 41: 1028-1048, 2013

Sampling Additional Nerves for Dedicated Neurotoxicity Testing





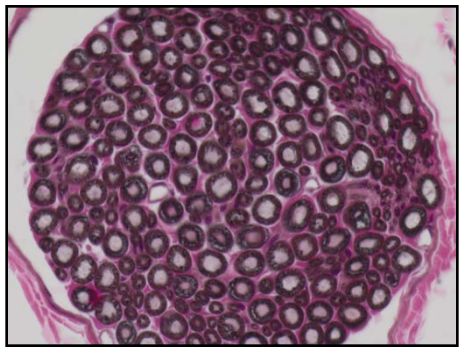
Nerve Options

a = Sciatic
b = Tibial
c = Common peroneal
d = Lateral sural
e = Plantar

Toxicol Pathol **34: 296, 2006**

Fixatives for Nerves

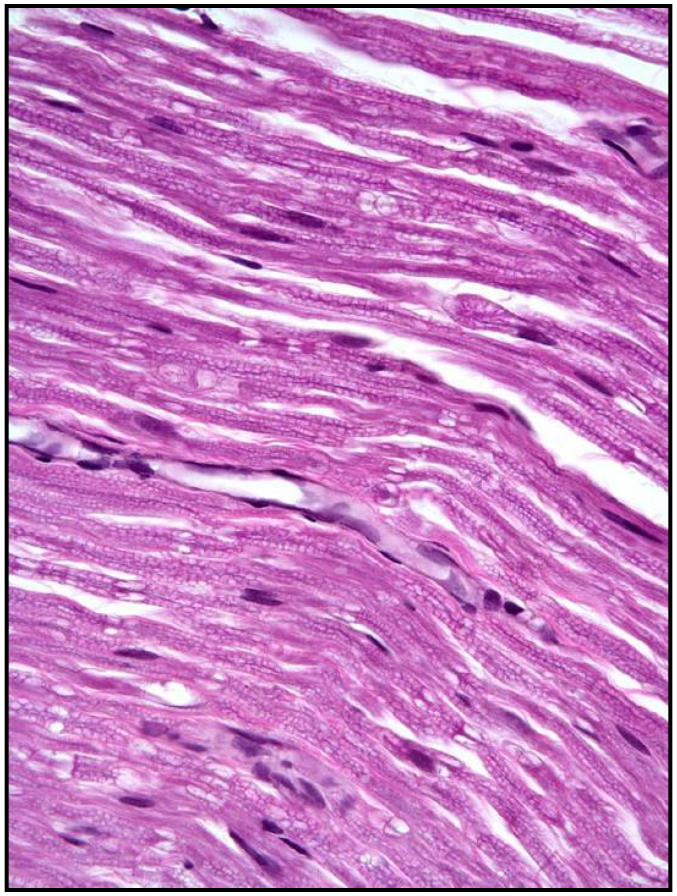
- **Routine studies – formaldehyde (4%)**
  - Neutral buffered 10% formalin (NBF) or paraformaldehyde
  - Commercial NBF often contains stabilizers (e.g., methanol)
- **Special studies**
  - High-resolution nerve analysis
    - Post-fixation in osmium tetroxide
    - Rationale: stabilizes myelin
  - Electron microscopy
    - Perfusion fixation with modified Karnovsky's solution (mixtures of paraformaldehyde and glutaraldehyde)
    - Avoid stabilizers (which promote myelin vacuolation)
    - Rationale: provides better preservation of subcellular features

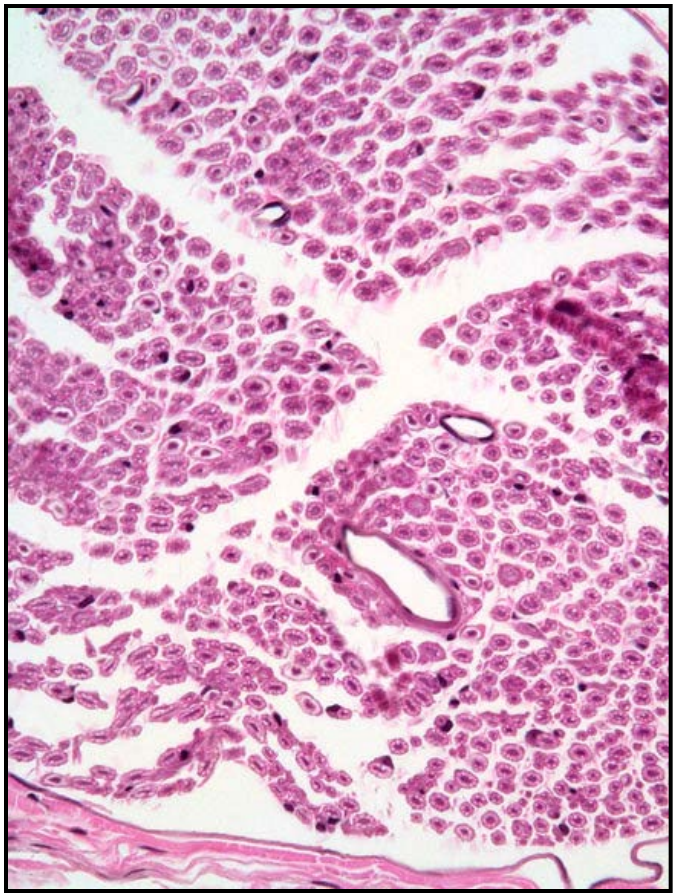


Embedding Nerves

- **Paraffin**
  - **Advantages: rapid and routine procedure in most histology facilities**
  - **Disadvantages: delicate neural structures (especially nerves) may be insufficiently supported by soft wax**
- **Plastic – required by some regulatory agencies**
  - **Advantages: provides better support for delicate neural structures**
  - **Disadvantages: employs neurotoxic reagents, necessitates special equipment and trained personnel, low throughput**
  - **NOTE: for optimal resolution, the medium should be a "hard plastic" (e.g., epoxy resin) and not a "soft plastic" (e.g., glycol methacrylate)**

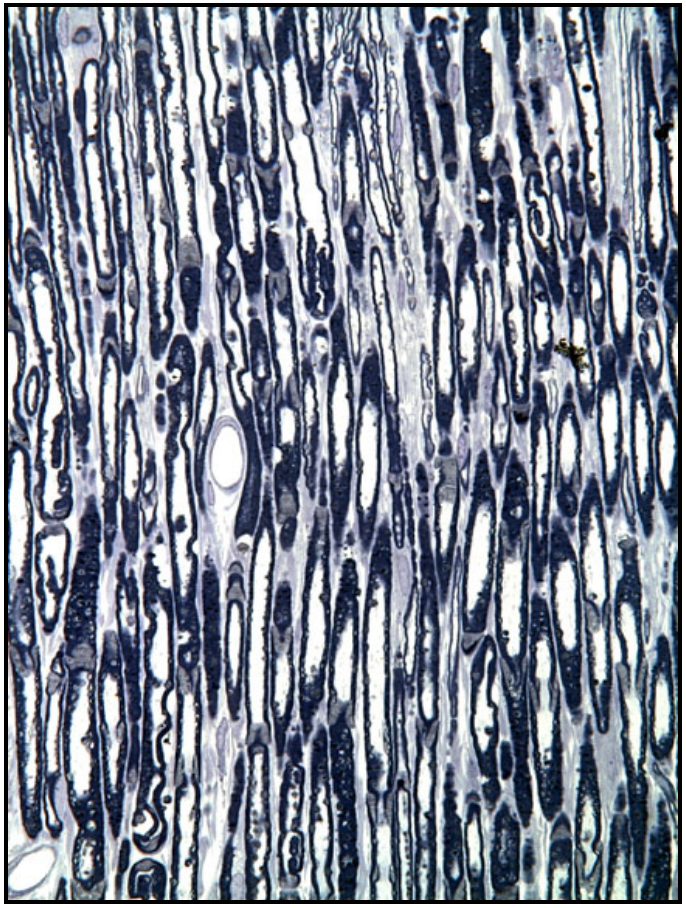
Paraffin Embedding (H&E)

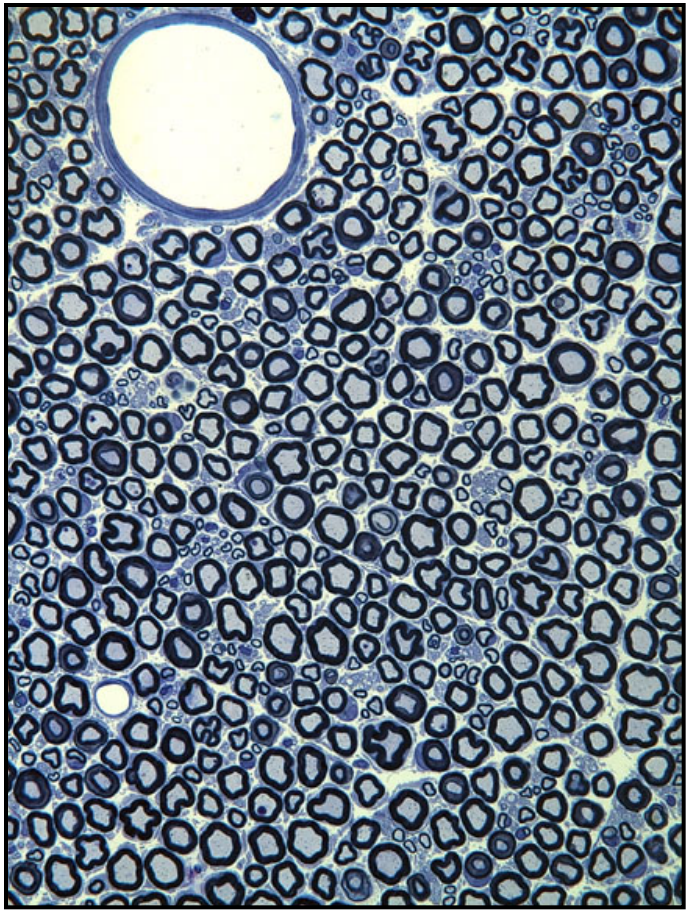




Images courtesy Dr. W. Valentine

Resin Embedding (Toluidine Blue)





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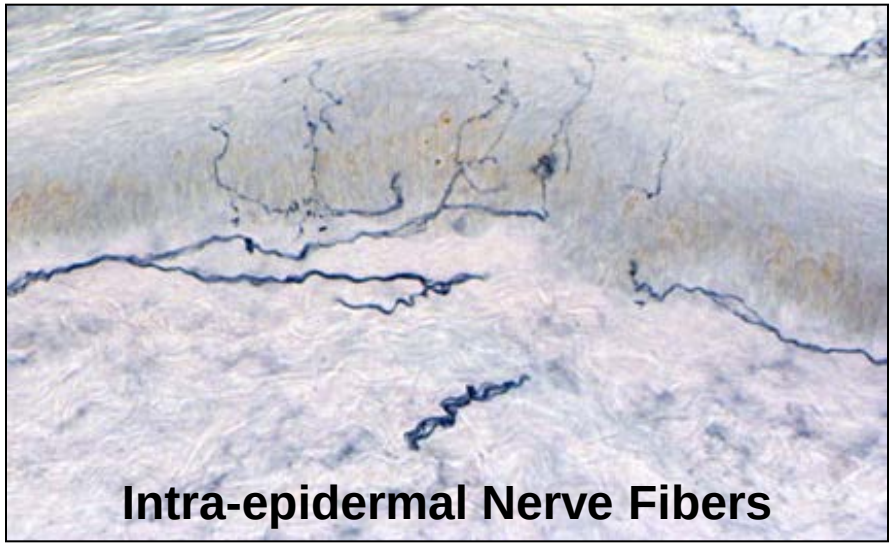
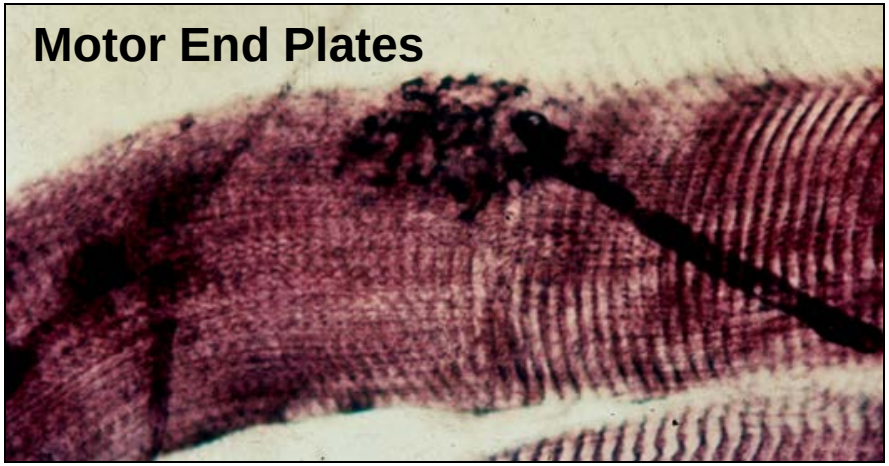
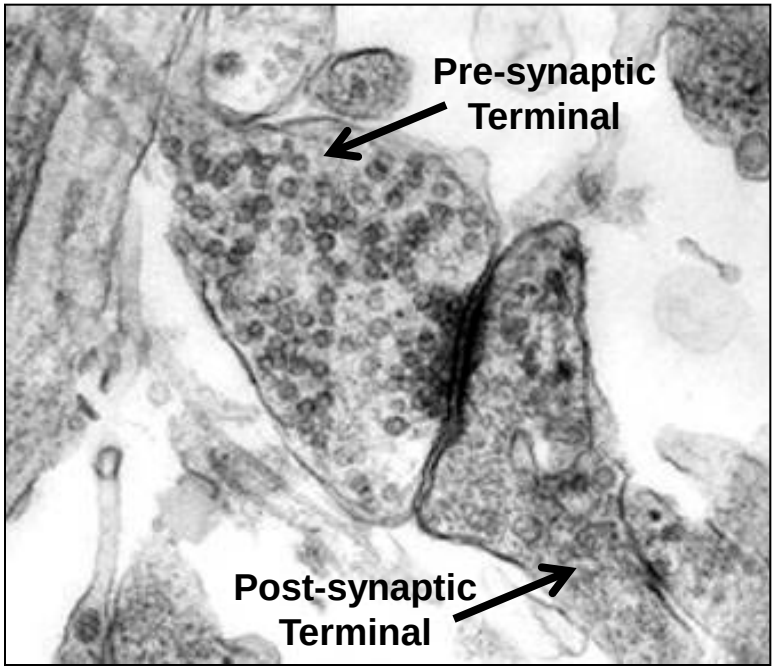
(courtesy Dr. W. Valentine)

Special Methods for Nerve Analysis



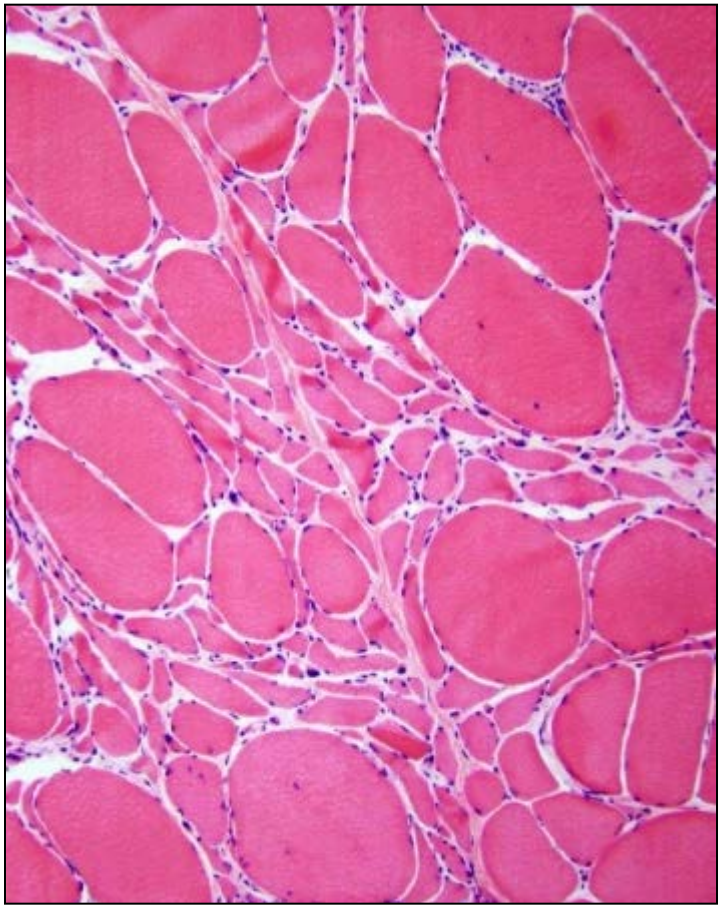


Synapses

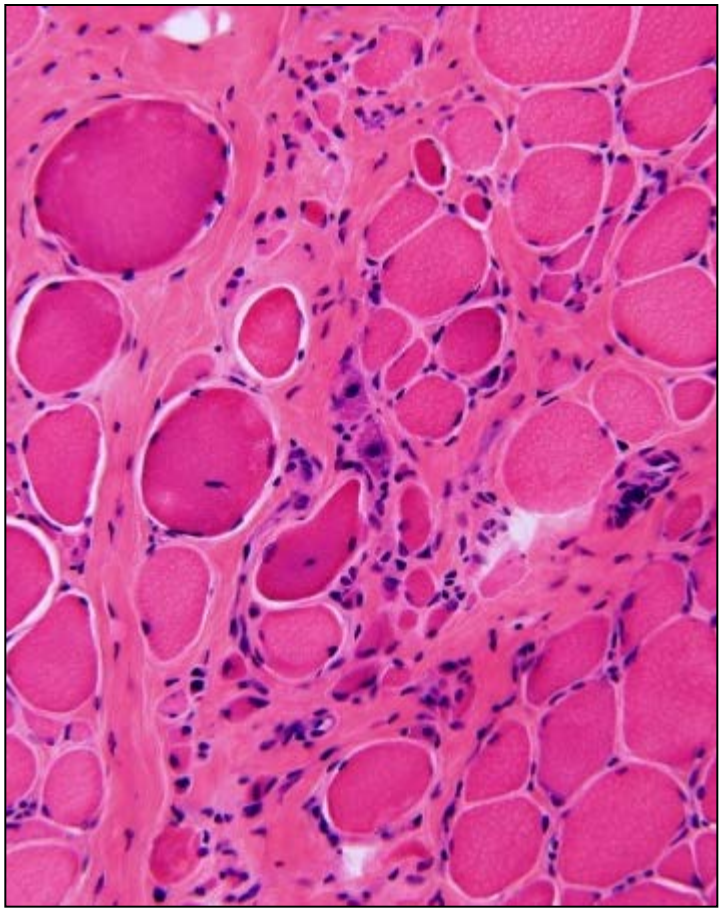


Denervated Effector Organs

Neurogenic



Myopathic



http://www.slideshare.net/gliageek/pathology-of-skeletal-muscle-presentation

Part III:

Analysis of Spinal Cord, Ganglia, and Nerves

Macroscopic Changes: Spinal Cord

- **Cavity**
  - **Hydromyelia – widened central canal**
  - **Syringomyelia – cyst formation within spinal cord tissue**
- **Discoloration**
  - **Gray or tan**
    - **Inflammation**
    - **Necrosis (“malacia”)**
    - **Neoplasm (commonly lymphocytic)**
  - **Red = hemorrhage (± necrosis)**
- **Swelling**
  - **Cell accumulation (inflammation or neoplasm [ependymal, glial, or hematopoietic])**
  - **Fluid accumulation (typically in myelin)**

Microscopic Changes: Spinal Cord Neurons

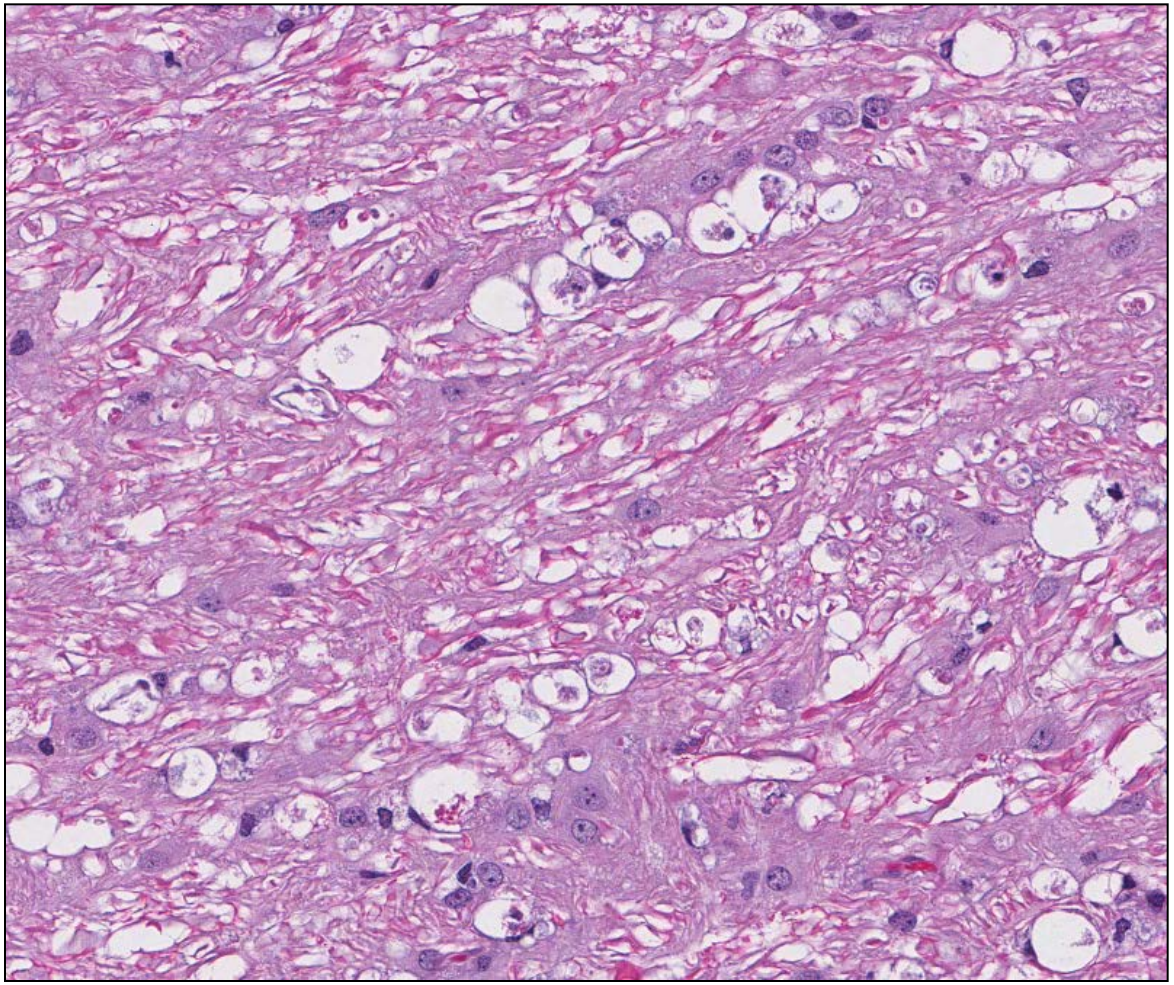
- **Degeneration (irreversible)**
  - **Swelling (of axons) – “spheroids”**
  - **Loss – axon fragmentation and axonophagia**
  - **Vacuolation**
- **Hemorrhage (reversible)**
- **Infiltration (non-neural cells)**
  - **Inflammatory cells**
  - **Neoplastic cells**

Microscopic Changes: Spinal Cord Glia

- **Degeneration (reversible in principle) – swelling**
- **Proliferation**
  - **Hyperplasia (reversible in principle)**
  - **Neoplasia**
- **Swelling (reversible in principle) – edema**
  - **Intracellular – metabolic imbalance**
    - **Cell body – cytotoxic edema**
    - **Cell processes – astrocyte (perivascular) foot processes**
  - **Extracellular**
    - **Transependymal – ependymal barrier failure**
    - **Vasogenic – altered vessel integrity**
  - **Intramyelinic**

Degeneration: Spinal Cord Axons

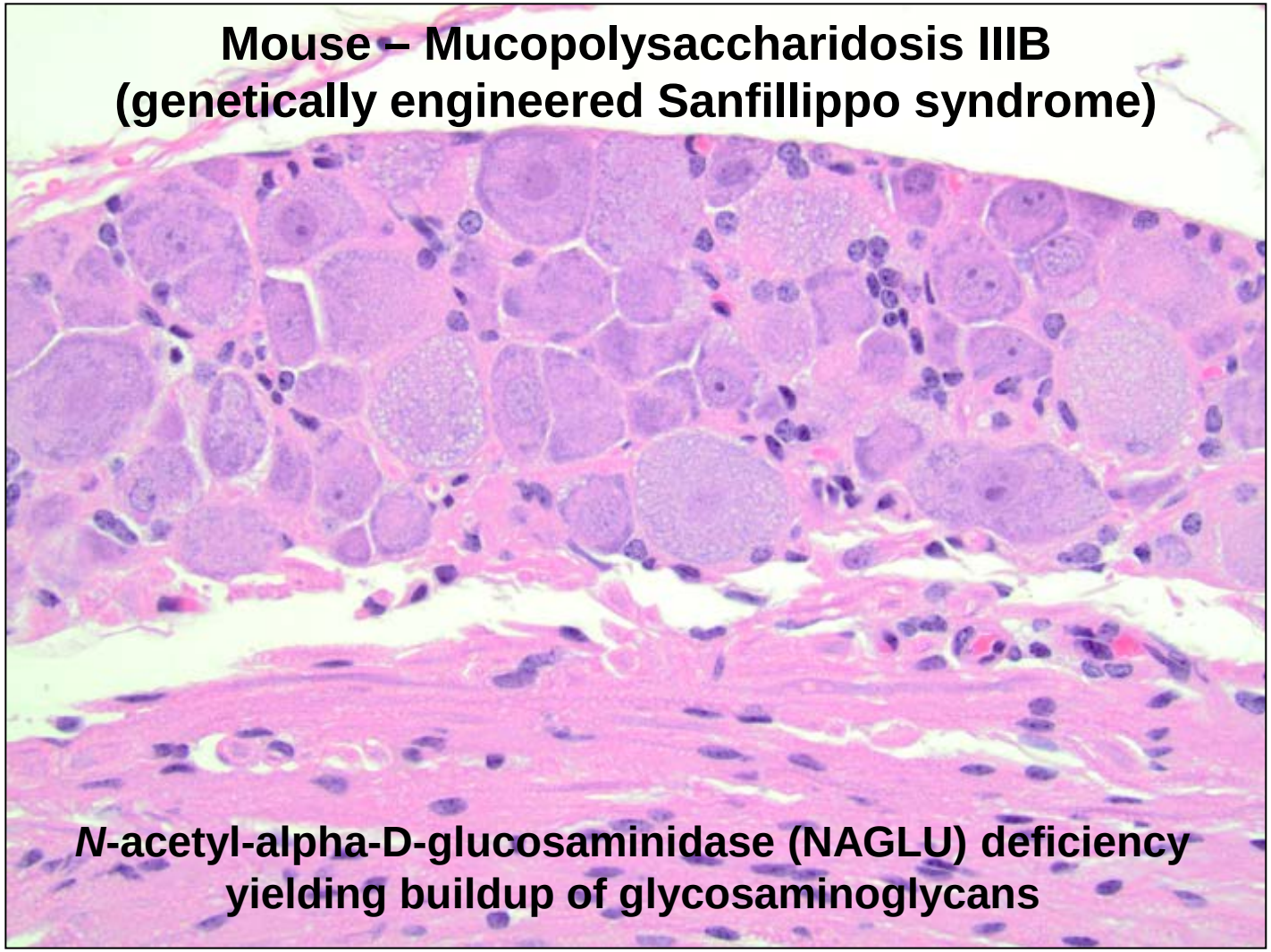
Adeno-associated virus serotype 9 (AAV9) viral vector



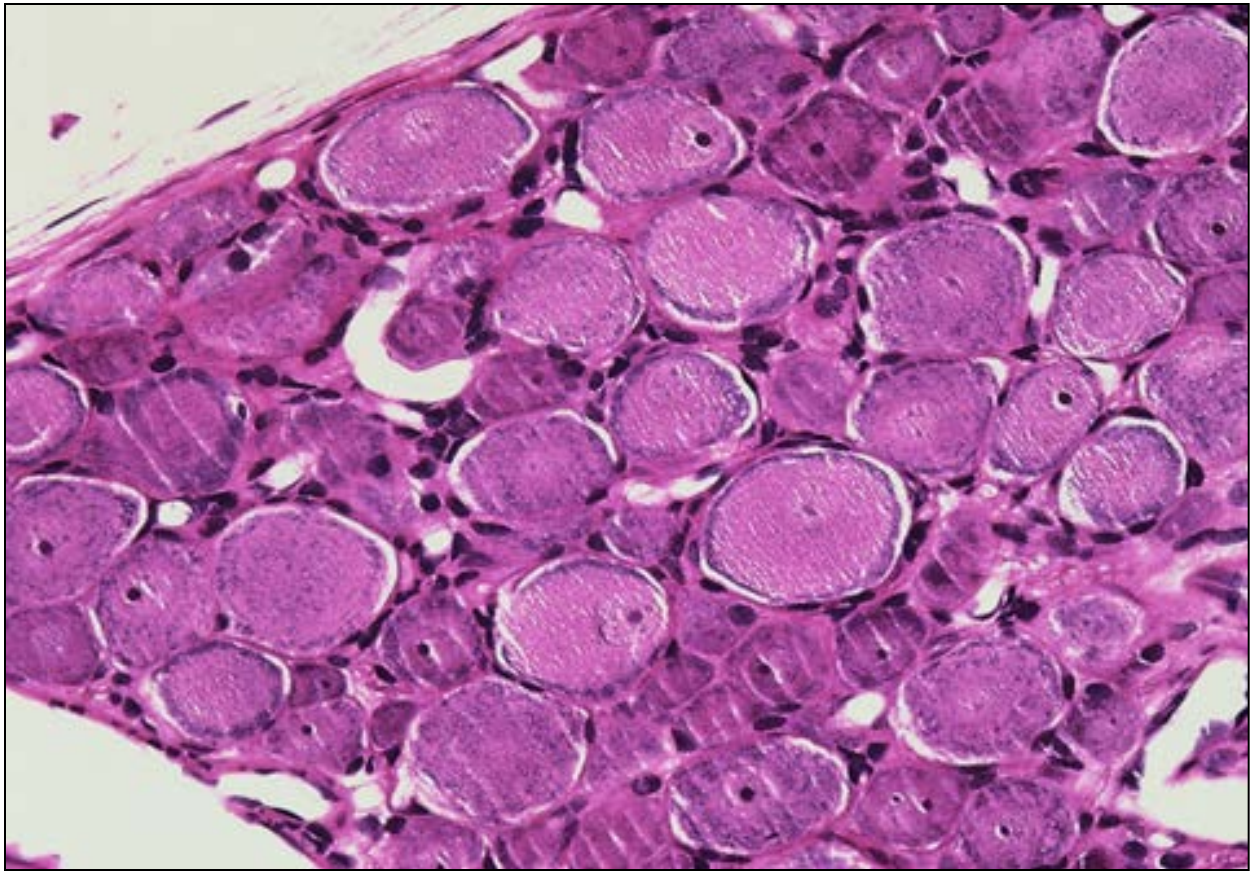
Microscopic Changes: Ganglia (PNS)

- **Accumulations (typically irreversible in practice)**
  - **Metabolic or structural byproducts**
  - **Viral inclusions (infectious agents, especially rabies)**
- **Degeneration (reversible in principle)**
- **Death (irreversible)**
  - **Destructive phase – apoptosis or necrosis**
  - **Resolution phase – neuronophagia**
- **Infiltration**
  - **Non-neoplastic cells – inflammation**
  - **Neoplastic cells – usually lymphoma**
- **Proliferation – satellite cell hyperplasia**

Accumulation: Metabolic Byproducts



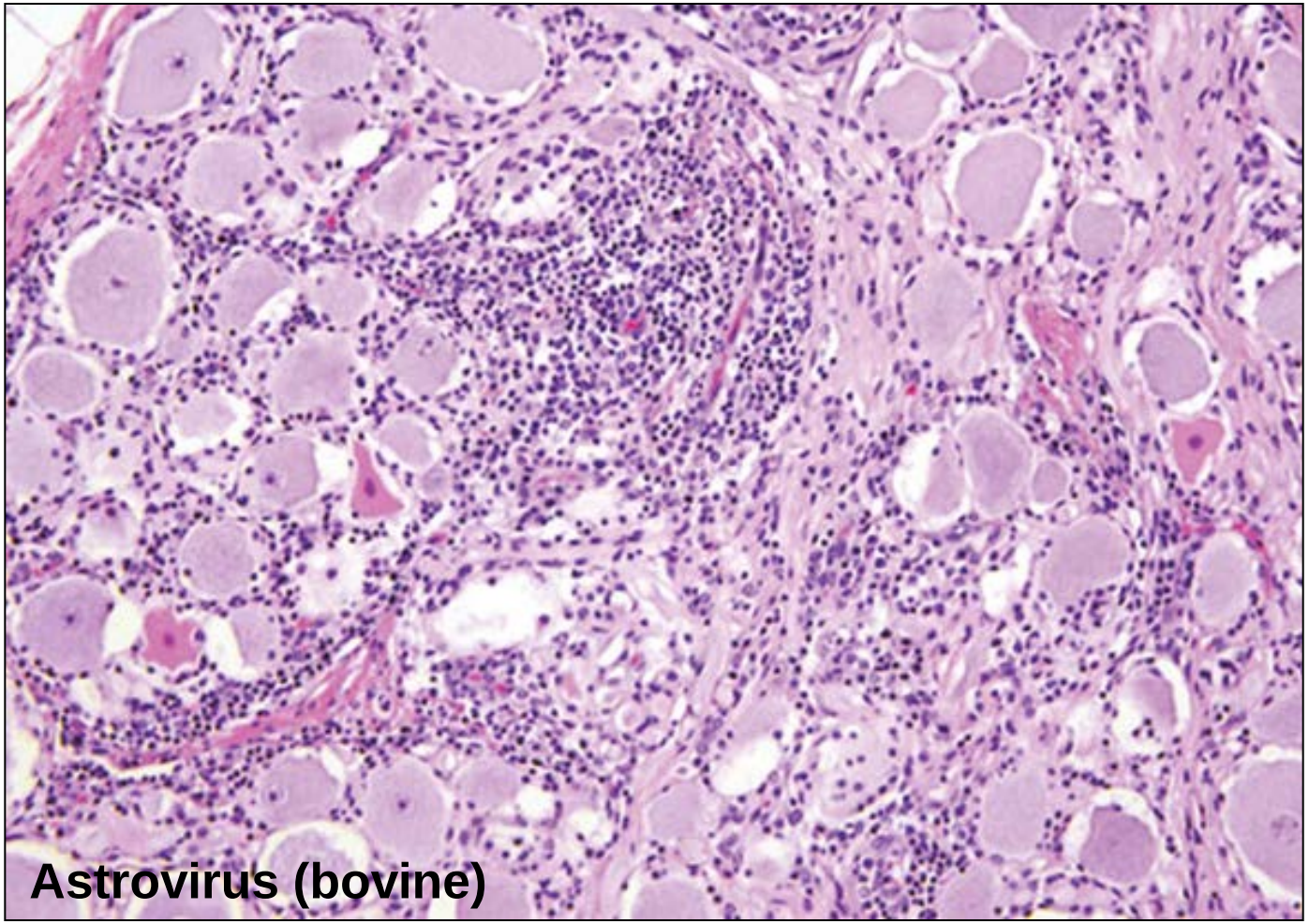
Degeneration: Axonal Reaction



Rat – acrylamide polyneuropathy

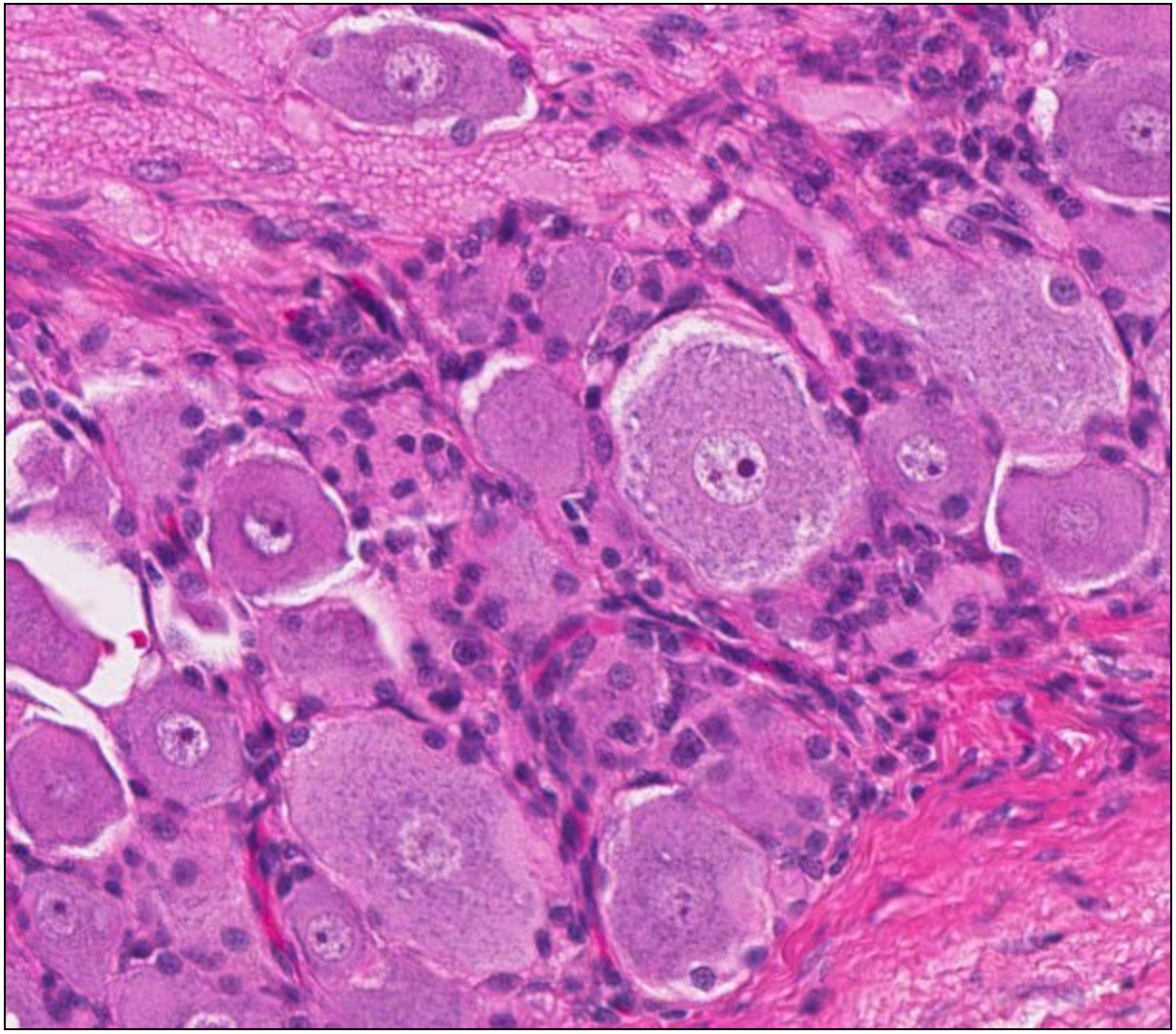
Image courtesy Dr. G. Krinke

Infiltration: Ganglionic Inflammation



http://wwwnc.cdc.gov/eid/article/19/9/13-0682-f5

Proliferation: Satellite Cell Hyperplasia



Macroscopic Change: Nerve Enlargement

Lymphoma

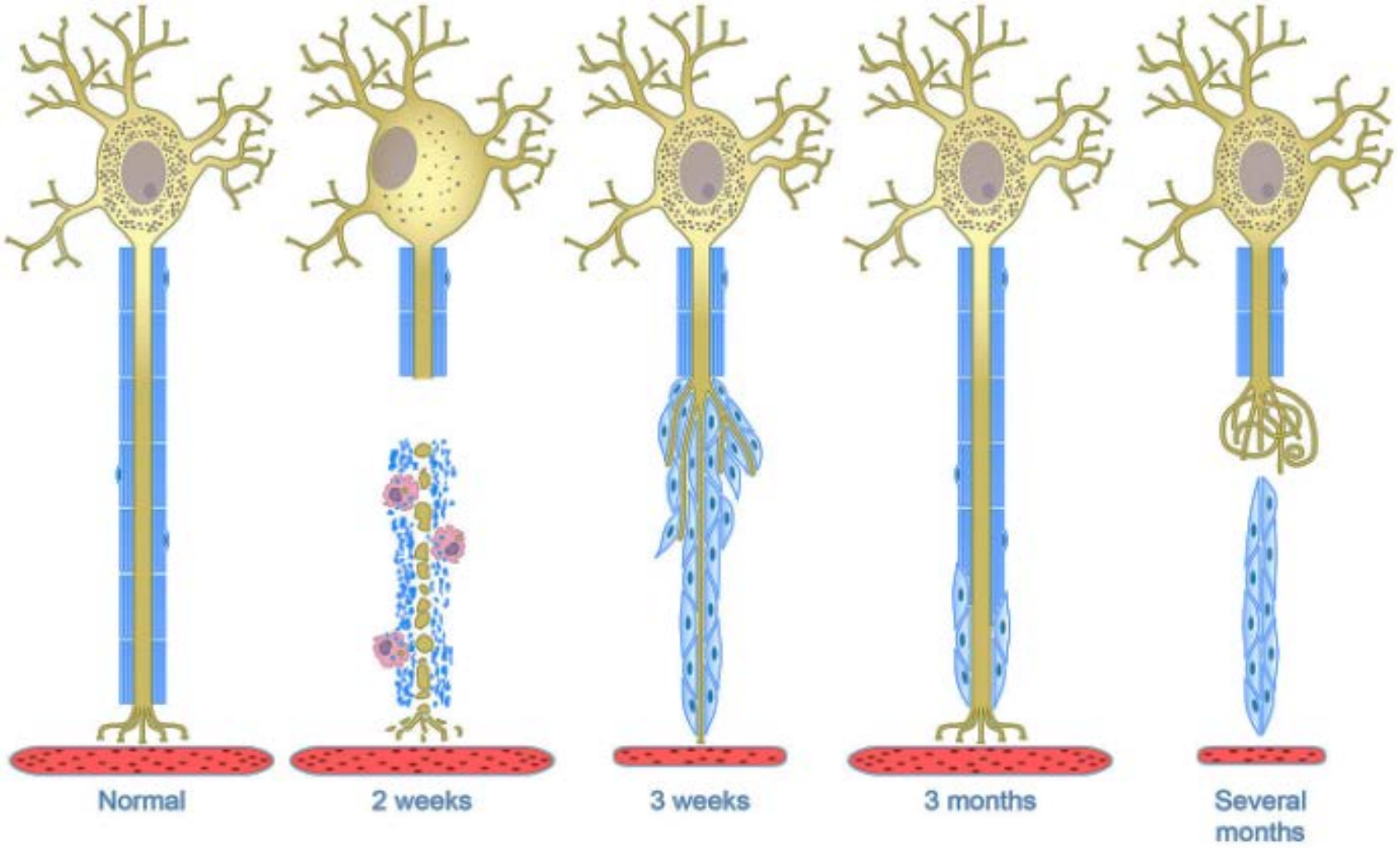
Cauda equina filled with neoplastic lymphocytes (cat infected with feline leukemia virus)

Image courtesy Dr. S. Krakowka

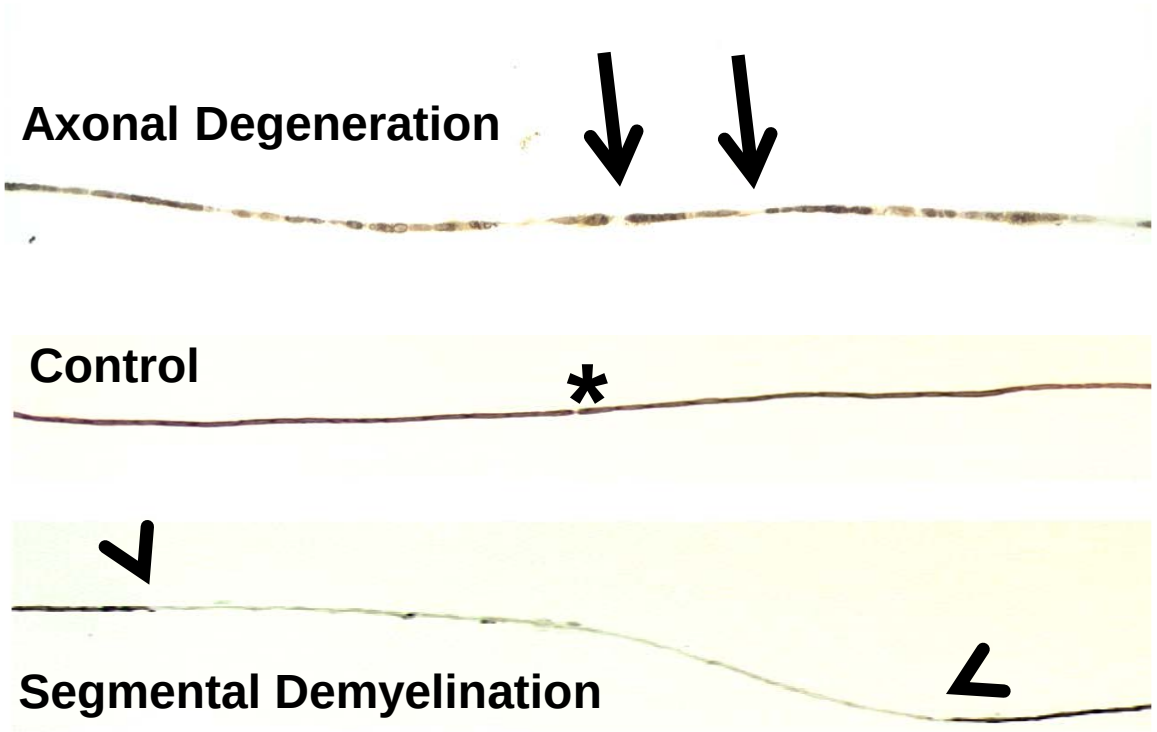
Microscopic Changes in Axons (PNS)

- **Accumulation (reversible) – swelling (chronic)**
- **Degeneration (irreversible) – primary axon injury**
  - **Swelling (transient)**
  - **Axon fragmentation**
  - **Axonophagia – “digestion chambers”**
- **Restoration – axon sprouting**

Degeneration: Primary Axonal Injury



Microscopic Lesions: Nerve Fibers



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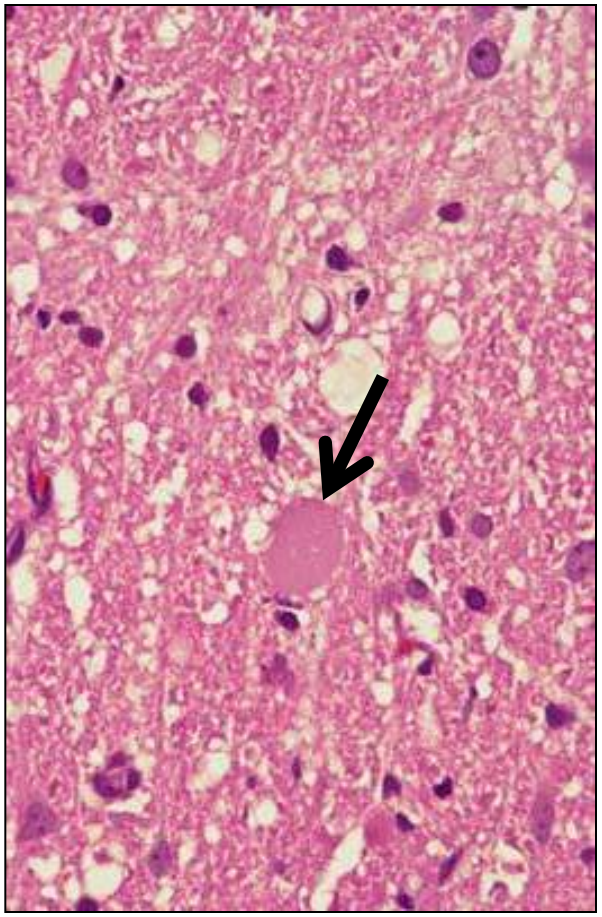
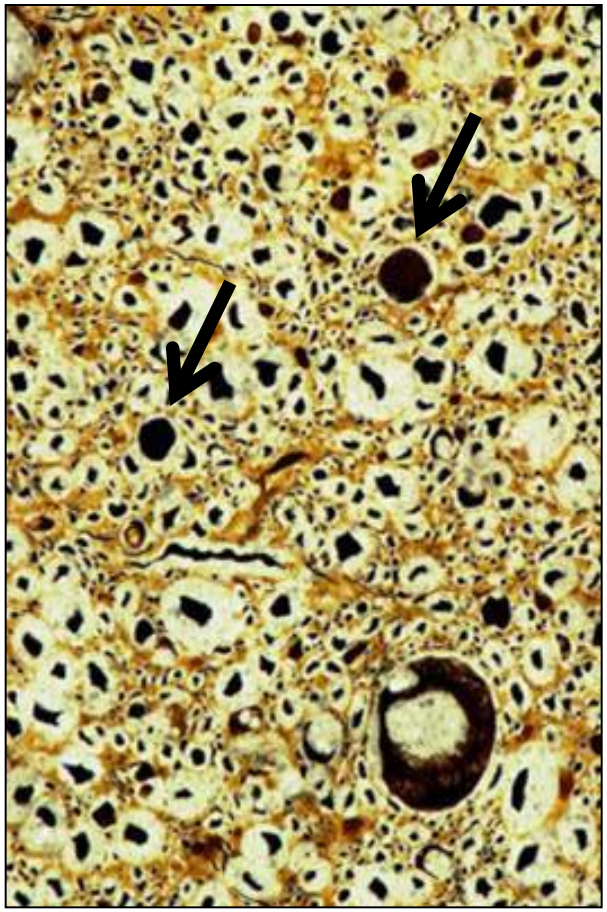
(courtesy of Dr. W Valentine)

Accumulation: Axonal Swelling

Hematoxylin and Eosin



Bielschowsky's Silver



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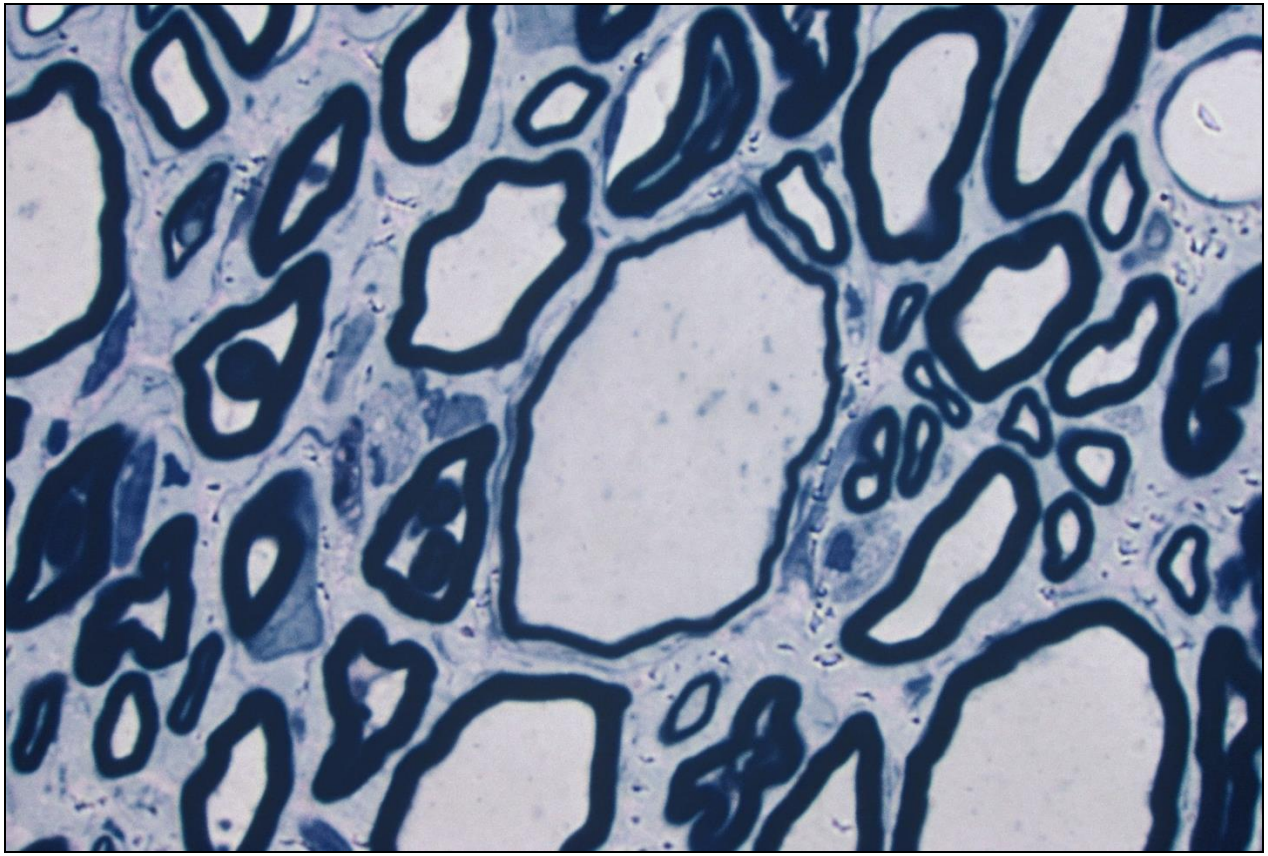
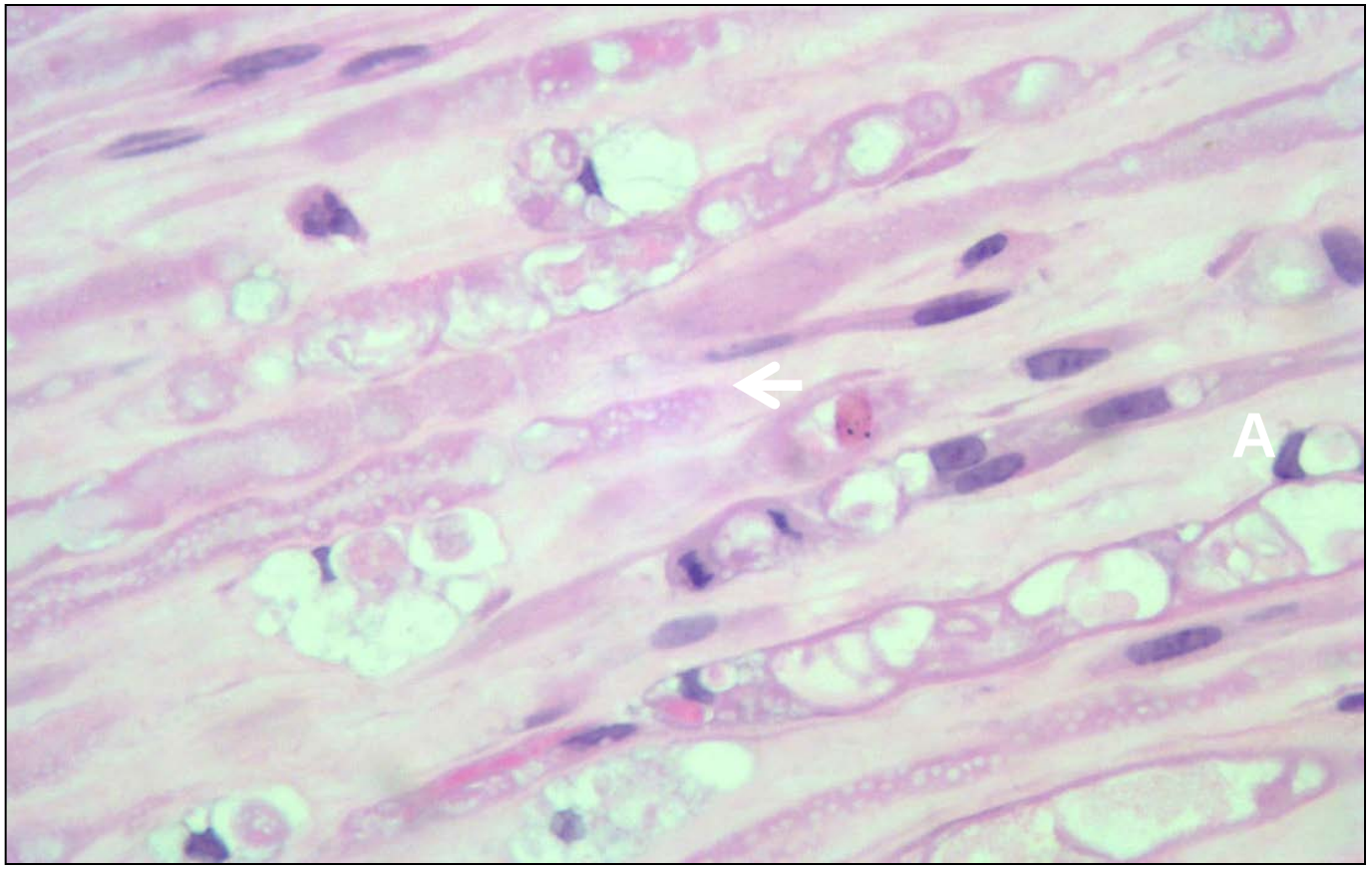
Accumulation: Axonal Swelling



Rat – *N*-hexane (γ-diketone) polyneuropathy

Image courtesy Dr. G. Krinke

Degeneration: Axonal Fragmentation



Rat – Acrylamide polyneuropathy

Image courtesy Dr. M.T. Butt

Degeneration: Digestion Chamber

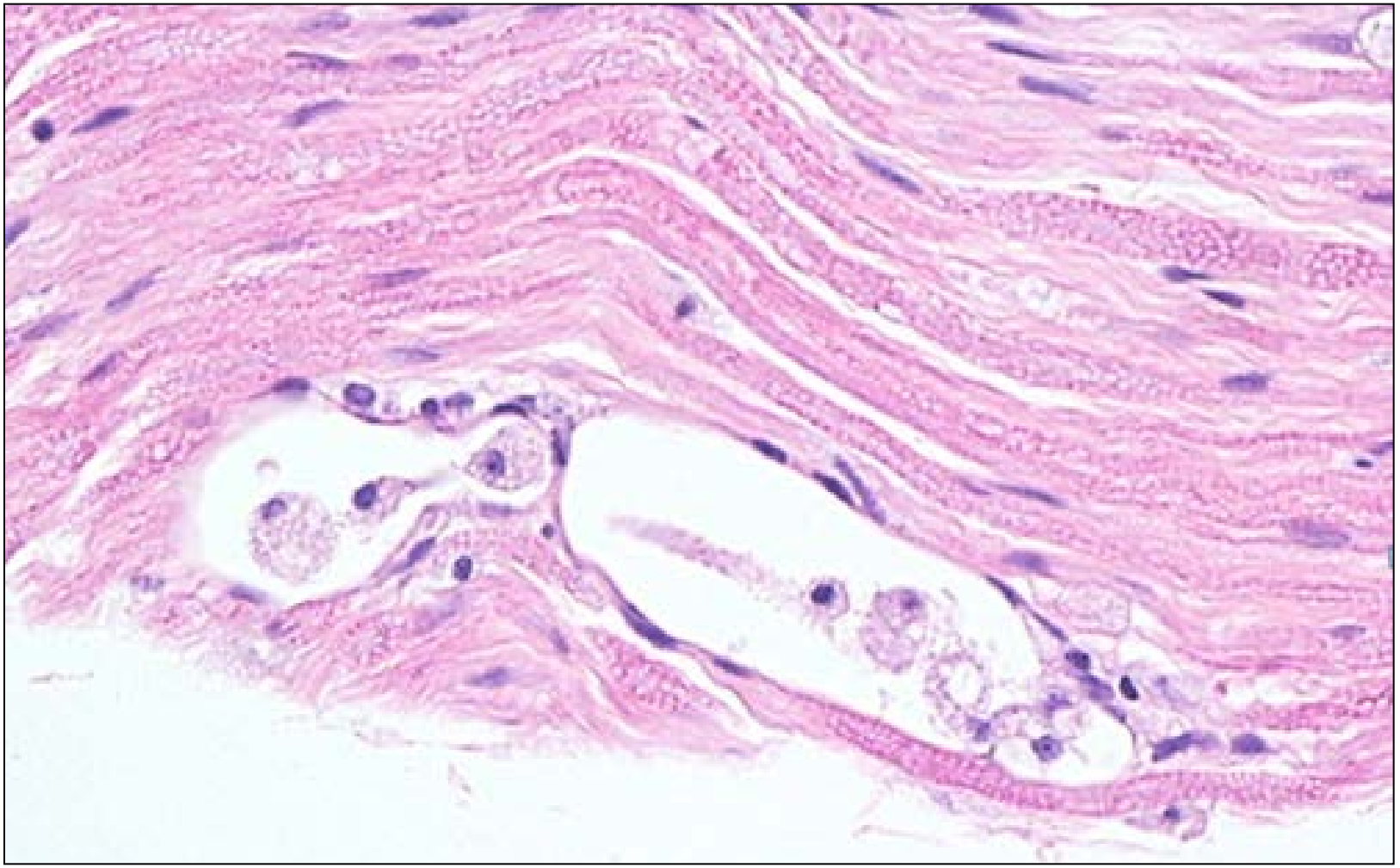
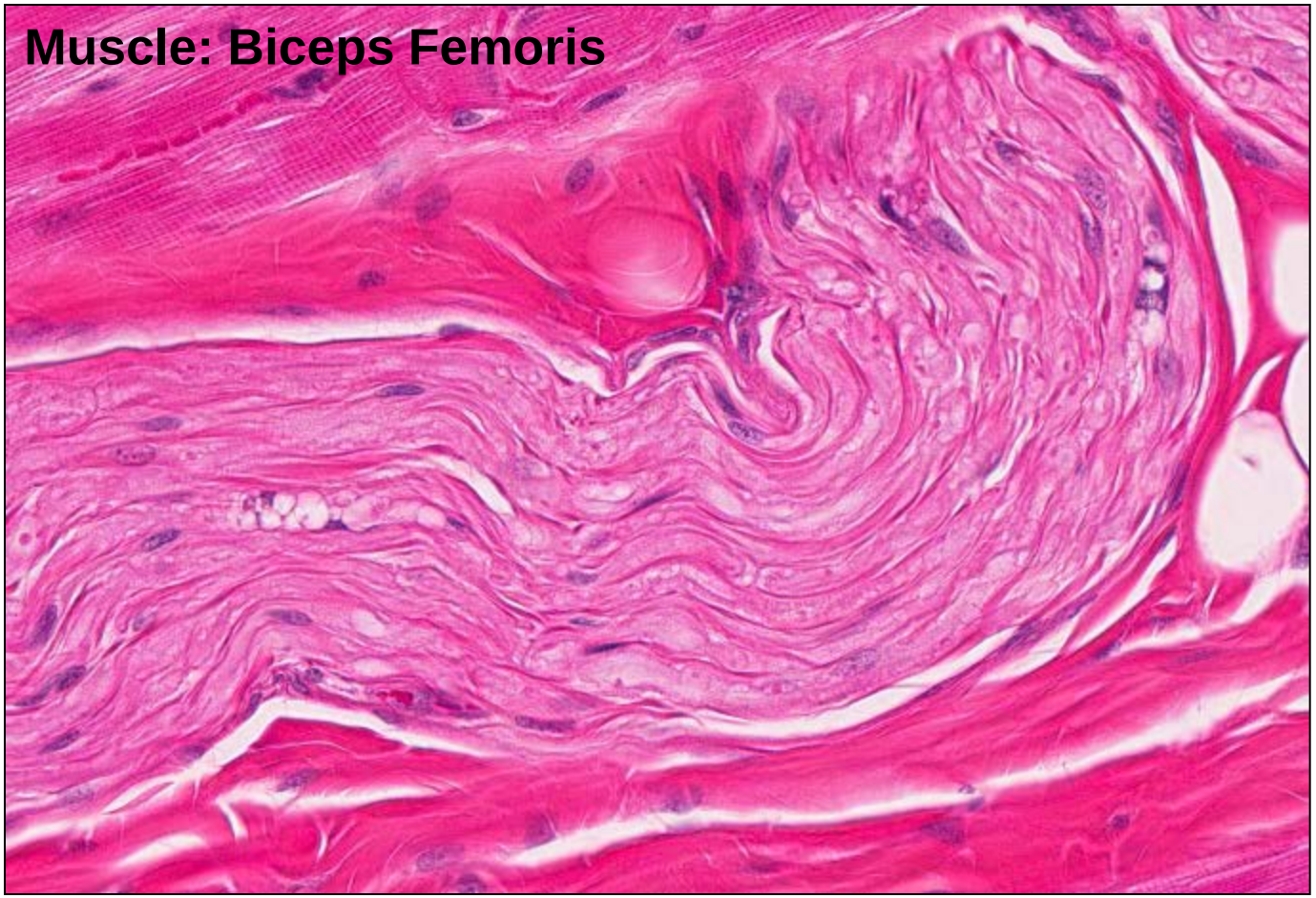


Image courtesy of Dr. G. Krinke

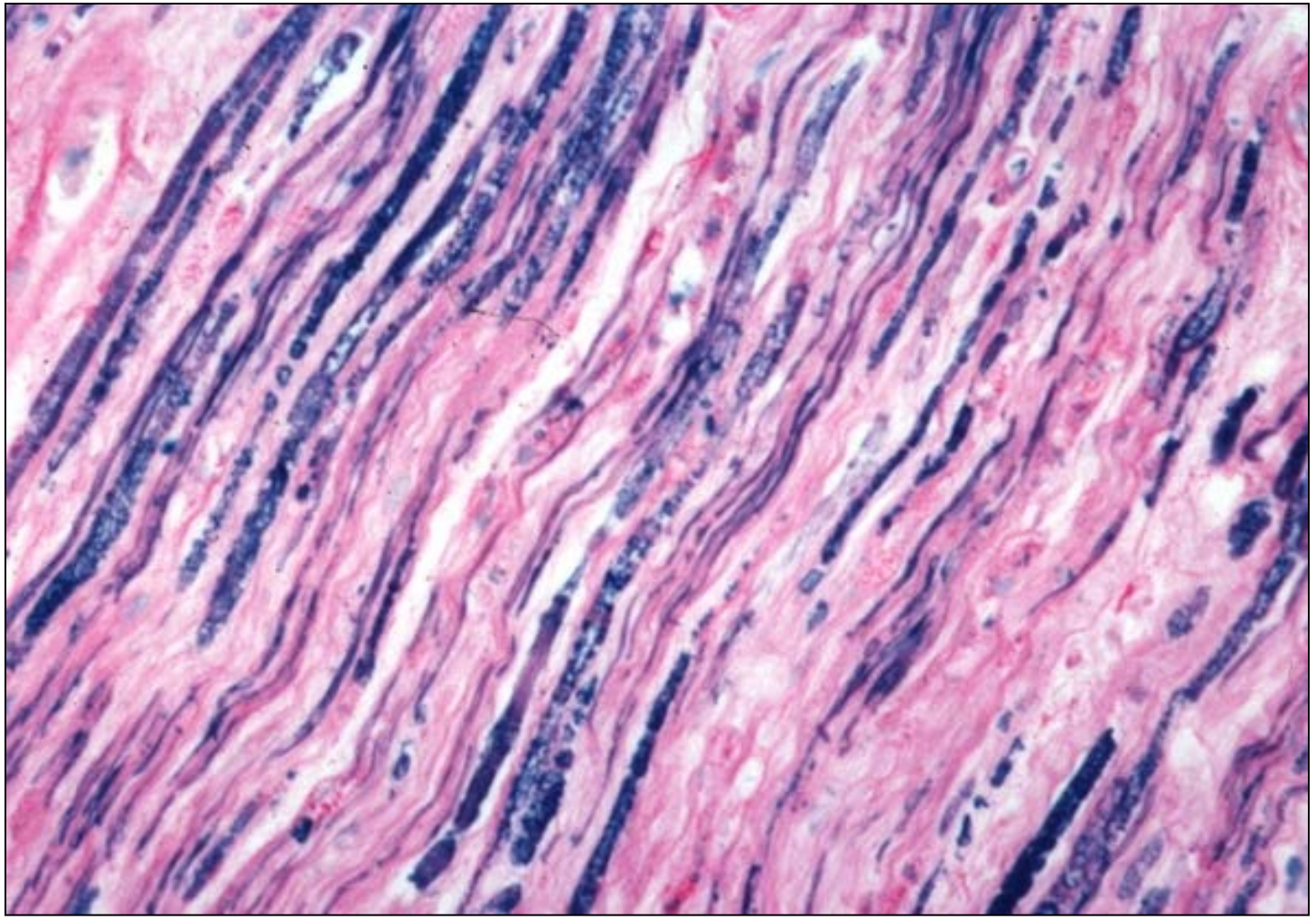
Nerve Fiber Degeneration in Effector Organs



Microscopic Changes in Glia (PNS)

- **Degeneration (reversible in principle)**
  - **Primary – axons are intact**
  - **Secondary – axons are damaged first, Schwann cells later**
- **Proliferation**
  - **Non-neoplastic – hypertrophy and hyperplasia**
  - **Neoplastic**

Degeneration: Primary Demyelination



http://peir.path.uab.edu/library/picture.php?/5880

Degeneration: Primary Demyelination

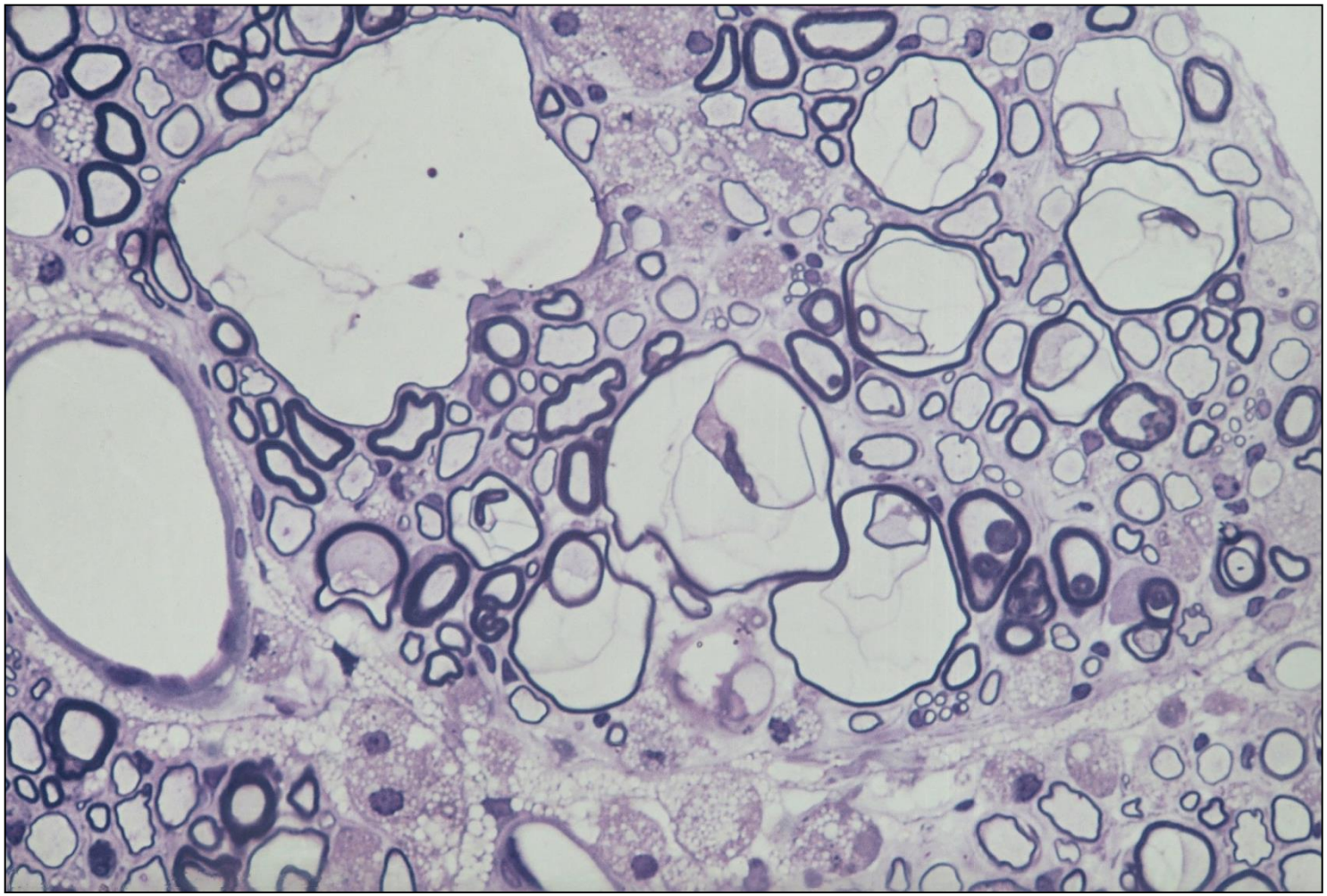
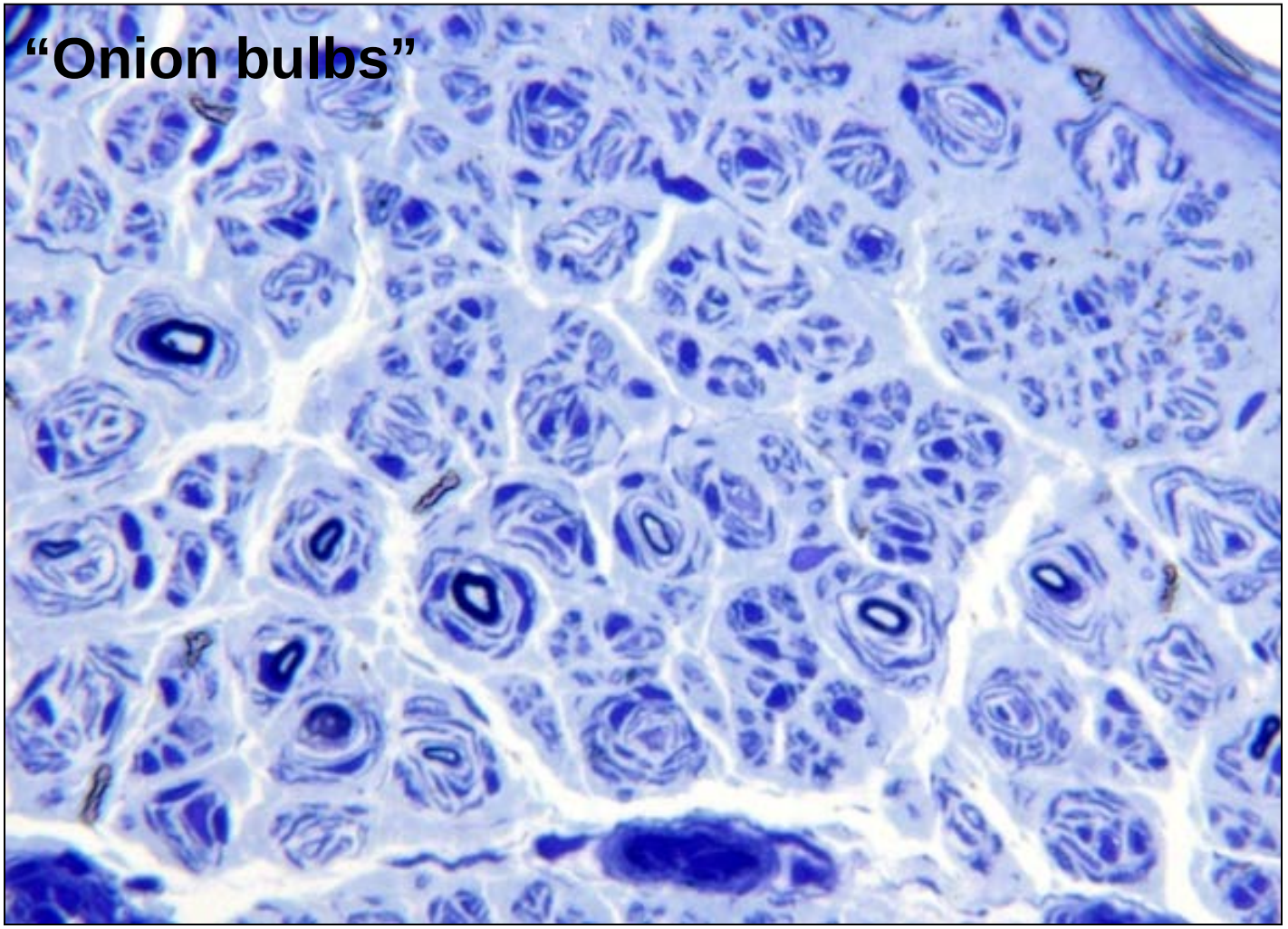


Image courtesy Dr. G. Krinke

Degeneration: Chronic Demyelination



http://frontalcortex.com/?page=qod&topic=pathology&qid=021409131

Proliferation: Schwann Cell Hyperplasia

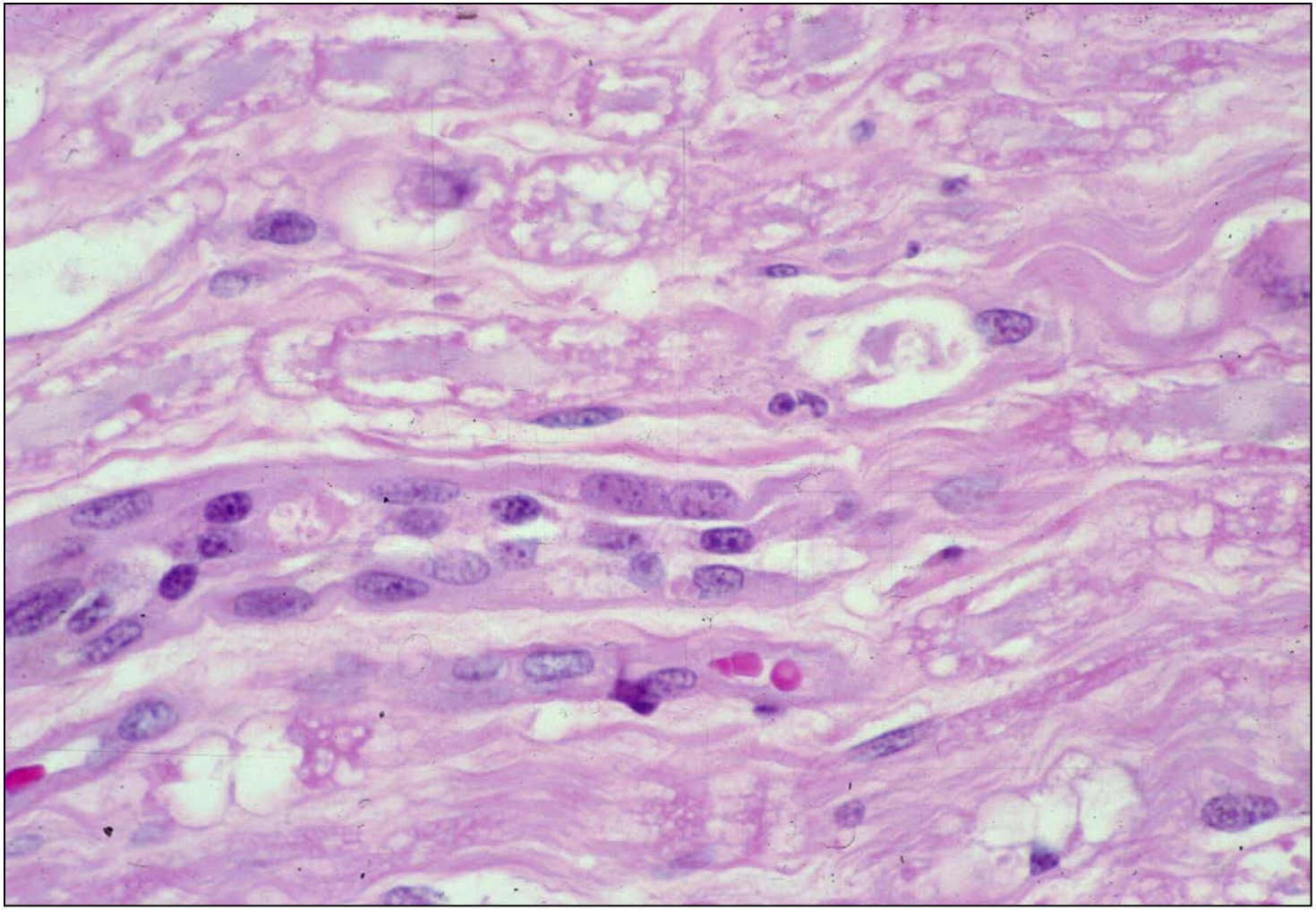
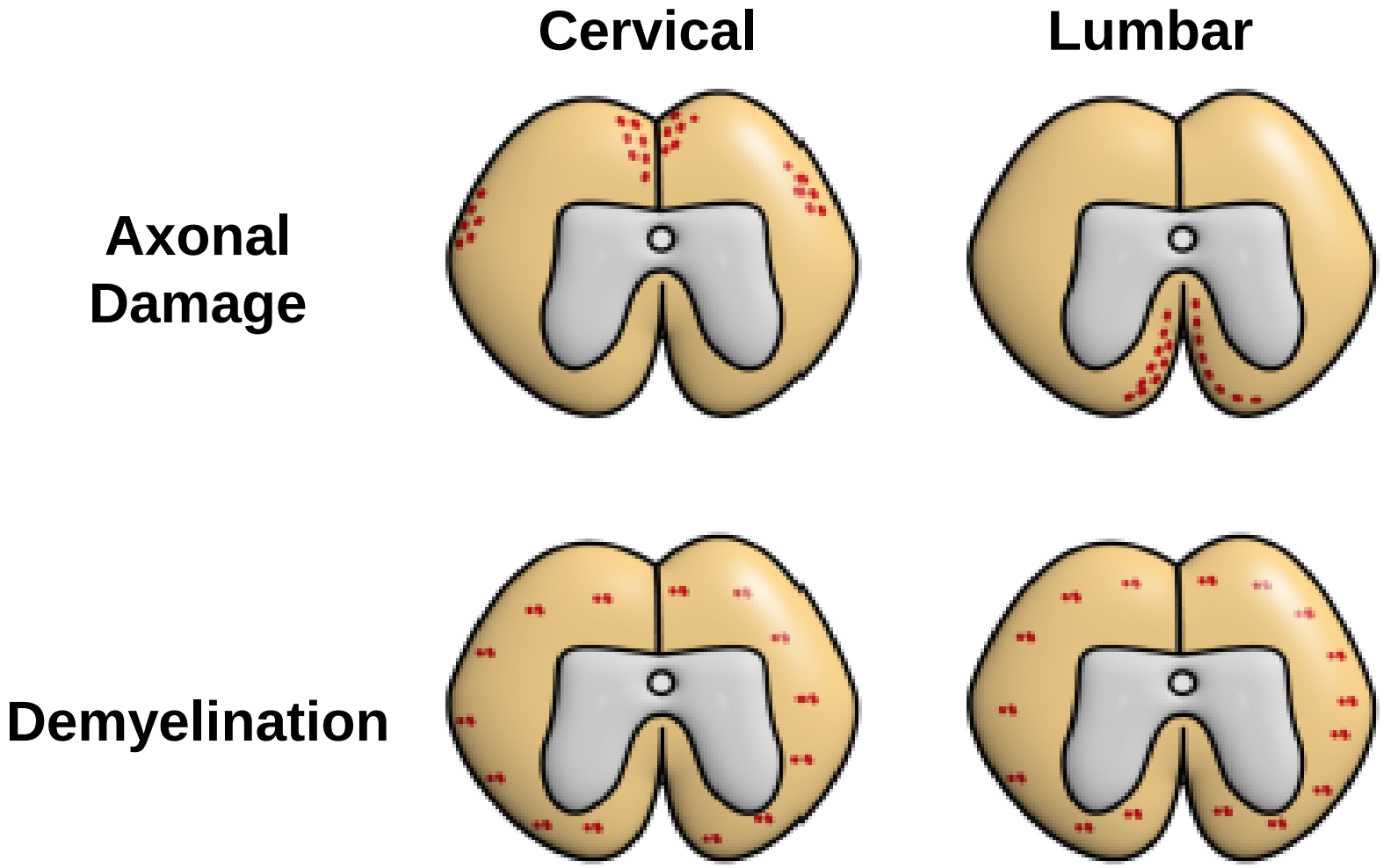


Image courtesy Dr. M. Oglesbee

Impact of PNS Injury on CNS Integrity



Fundamental Neuropathology for Pathologists and Toxicologists, Ch 23, 2011
(courtesy Dr. G. Krinke)

Part IV:

Common Artifacts in the Peripheral Nervous System

Neuron Necrosis (Ganglion)

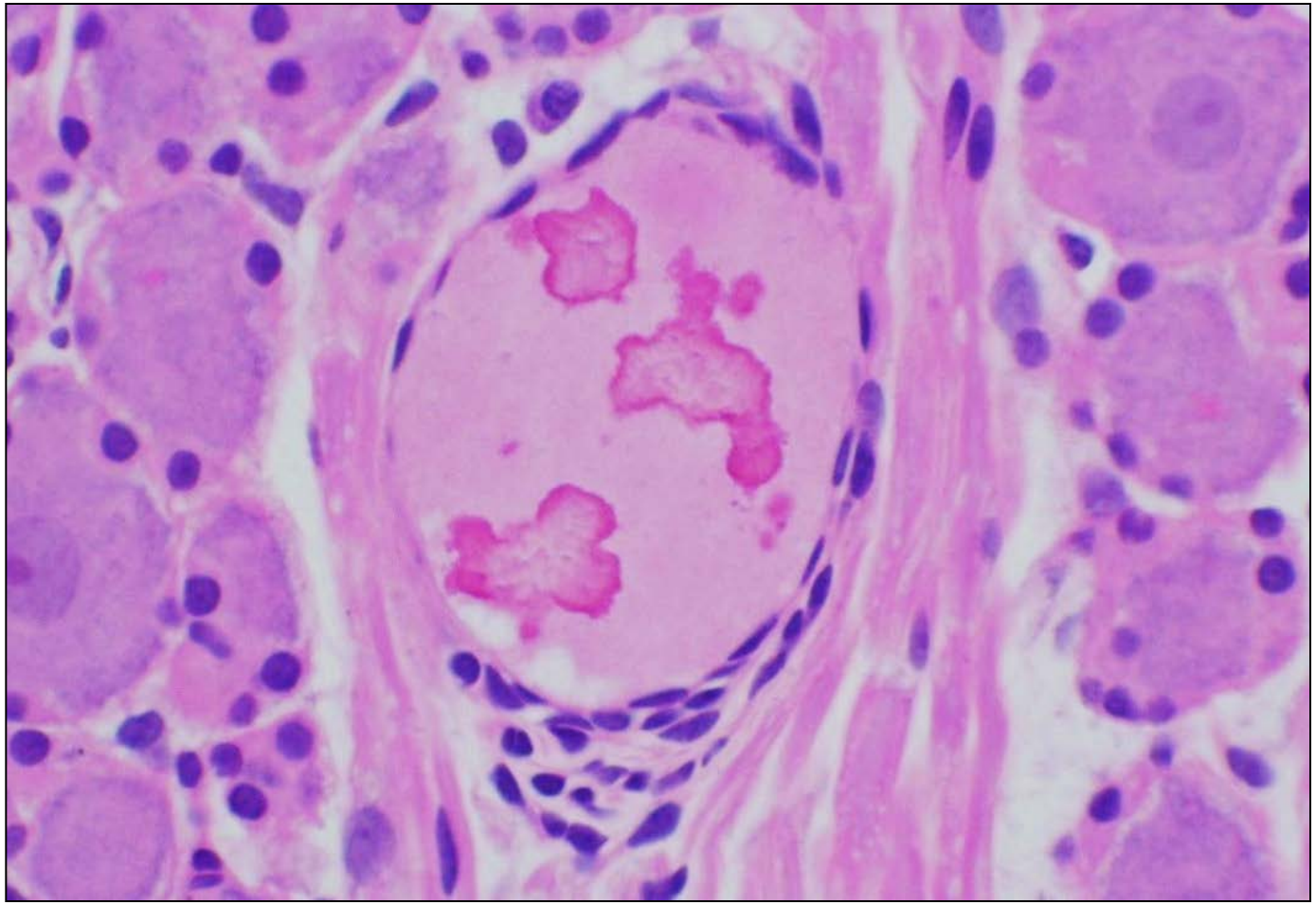
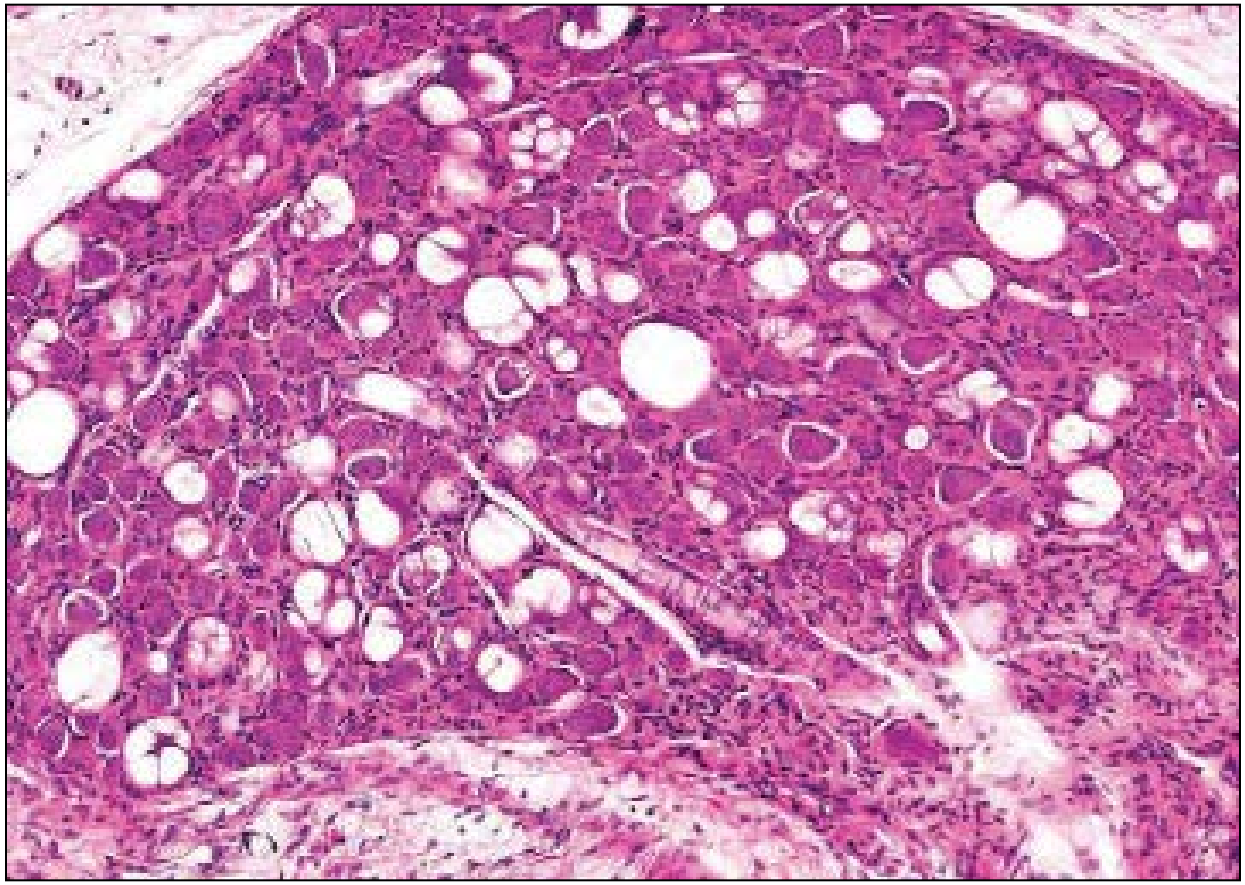


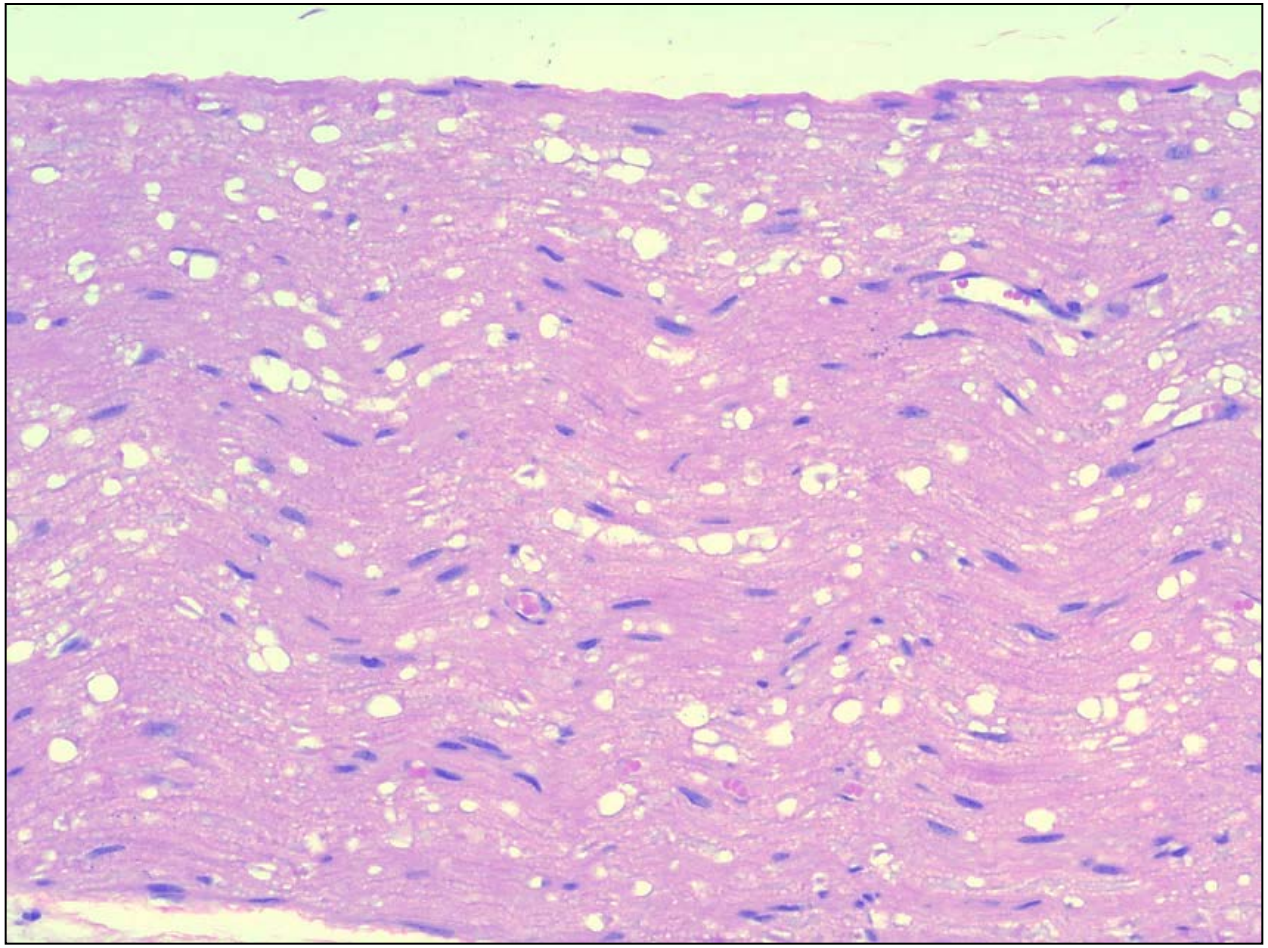
Image courtesy of Dr. M. Butt

Neuron Vacuolation (Ganglion)



***Toxicol Pathol* 40: 87S, 2012**

Myelin Bubbles



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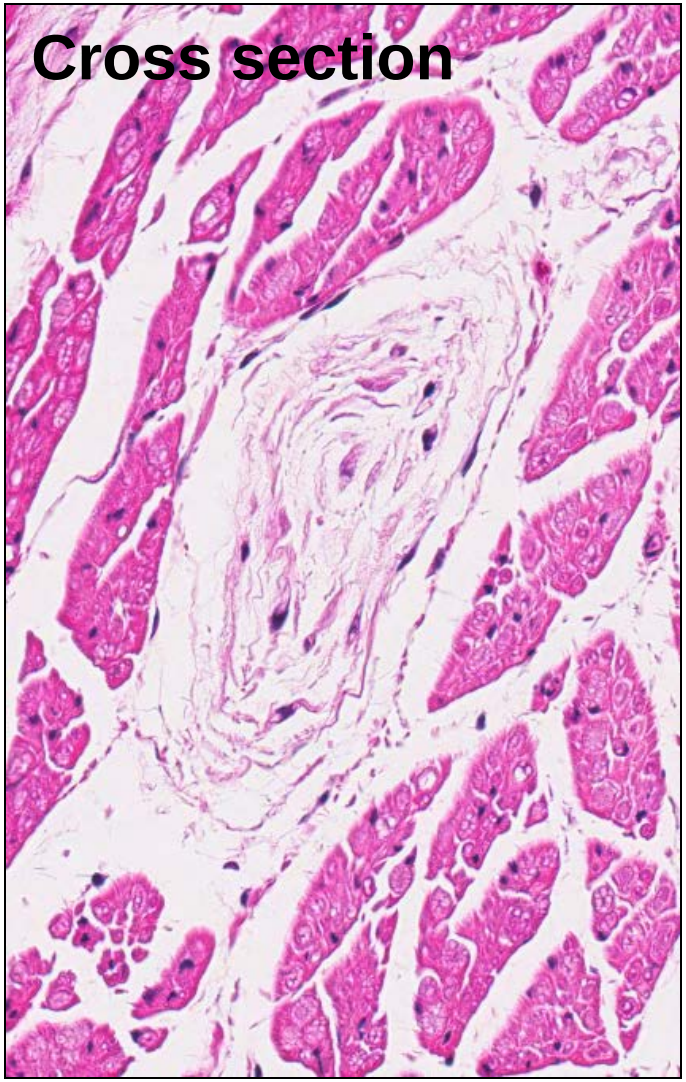
Renaut Bodies



Lessons Learned

- **Know the lay of the land.** Know the key features of spinal cord, ganglionic, and nerve anatomy.
- **Garbage in, garbage out.** Badly prepared specimens (especially PNS) may be difficult to interpret.
- **Learn to discriminate authentic from artifact.** Learn to distinguish genuine lesions from handling effects.
- **Don’t be a hero.** Get assistance from an experienced neuropathologist.