Peripheral Nerve Segment Defect Repair

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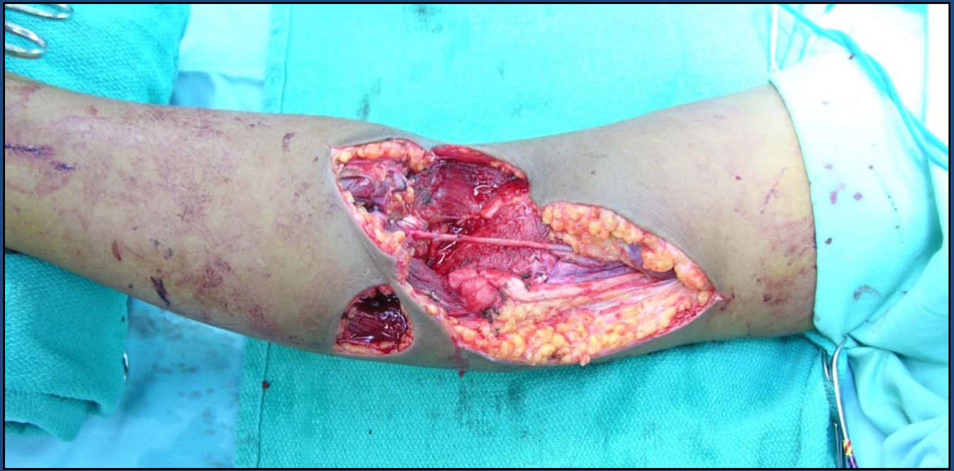
Disclosures

- I own stock in Orthovative, LLC a startup orthopaedic device company
  - This company has nothing to do with nerve repairs or nerve repair technology

Peripheral Nerve Injury: The Problem

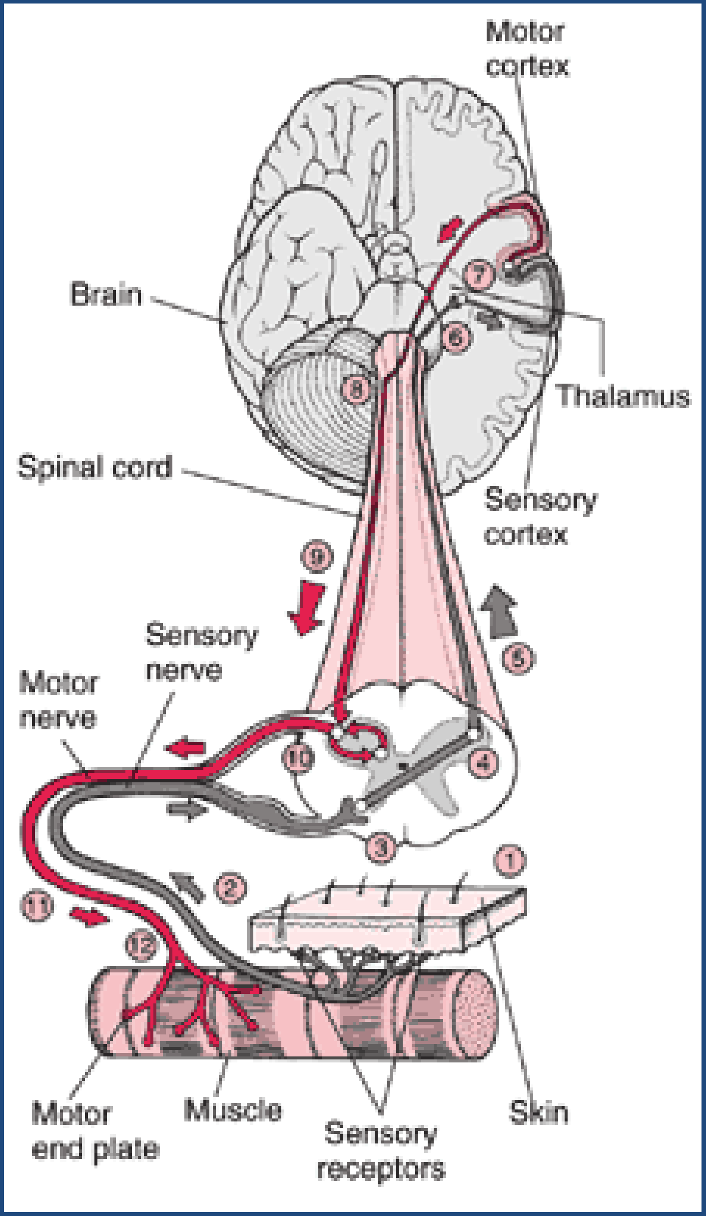
- 2-3% of trauma patients suffer a major nerve injury
  - 31,000,000 ED traumas/yr
- 100,000 digital amputations per year in the US
  - ~30% are suitable for replantation
- Nerve injury and aging
  - 50% of patients over 50 will not achieve any functional recovery after nerve repair



Nervous Control of Skeletal Muscle

Motor Control

Sensory Input



Merck Manual

Peripheral nerve injury

Common Injuries to Motor Nerves

- Brachial plexus injuries
- Carpal tunnel syndrome
- Ulnar nerve entrapment
- Thoracic Outlet syndrome
- Laceration, contusion
- Stretch & Traction
- Thermal

Peripheral nerve injury

- Complete transection
- Crush
- Ischemia

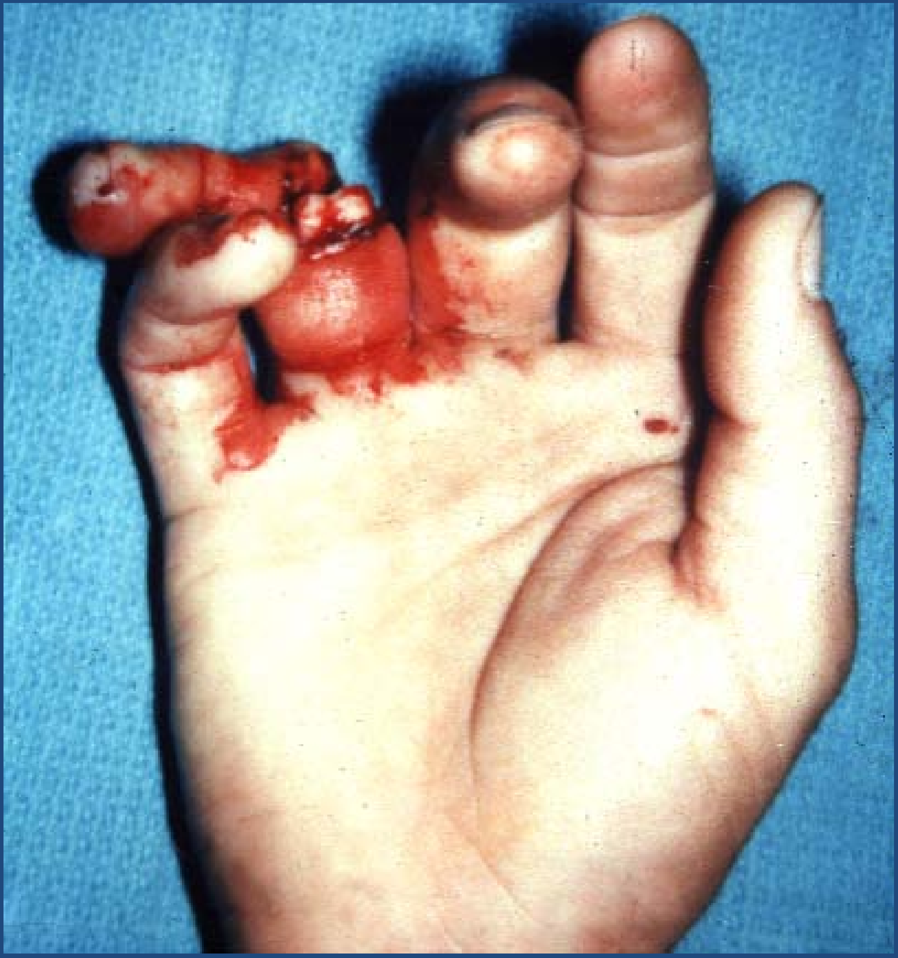
Challenges of nerve injury

- Problems:
  - Size of nerve – Vascular supply
    - 1 mm
  - Distance to target organ
  - Selectivity of re-innervating nerve fibers
  - Time to re-innervation of target – specifically muscle
  - Size of nerve gap

- State of Research

Peripheral nerve injury

What happens with Nerve Injury?



Peripheral nerve injury

Motor Control – Peripheral Nerve transmission

Nodal conduction (saltatory)

120-200 meters/sec

Nodes of Ranvier – 1 micron wide

- separate Schwann cells
- 1871: Louis-Antoine Ranvier (1835-1922) "noeuds de Ranvier"

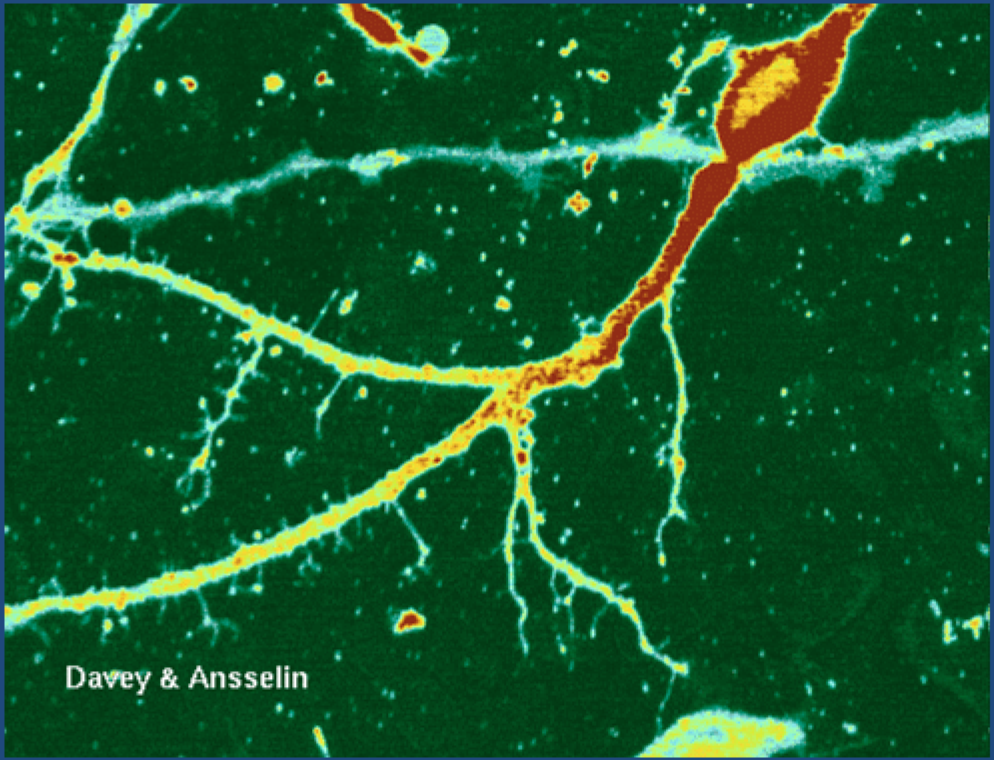
Peripheral nerve injury

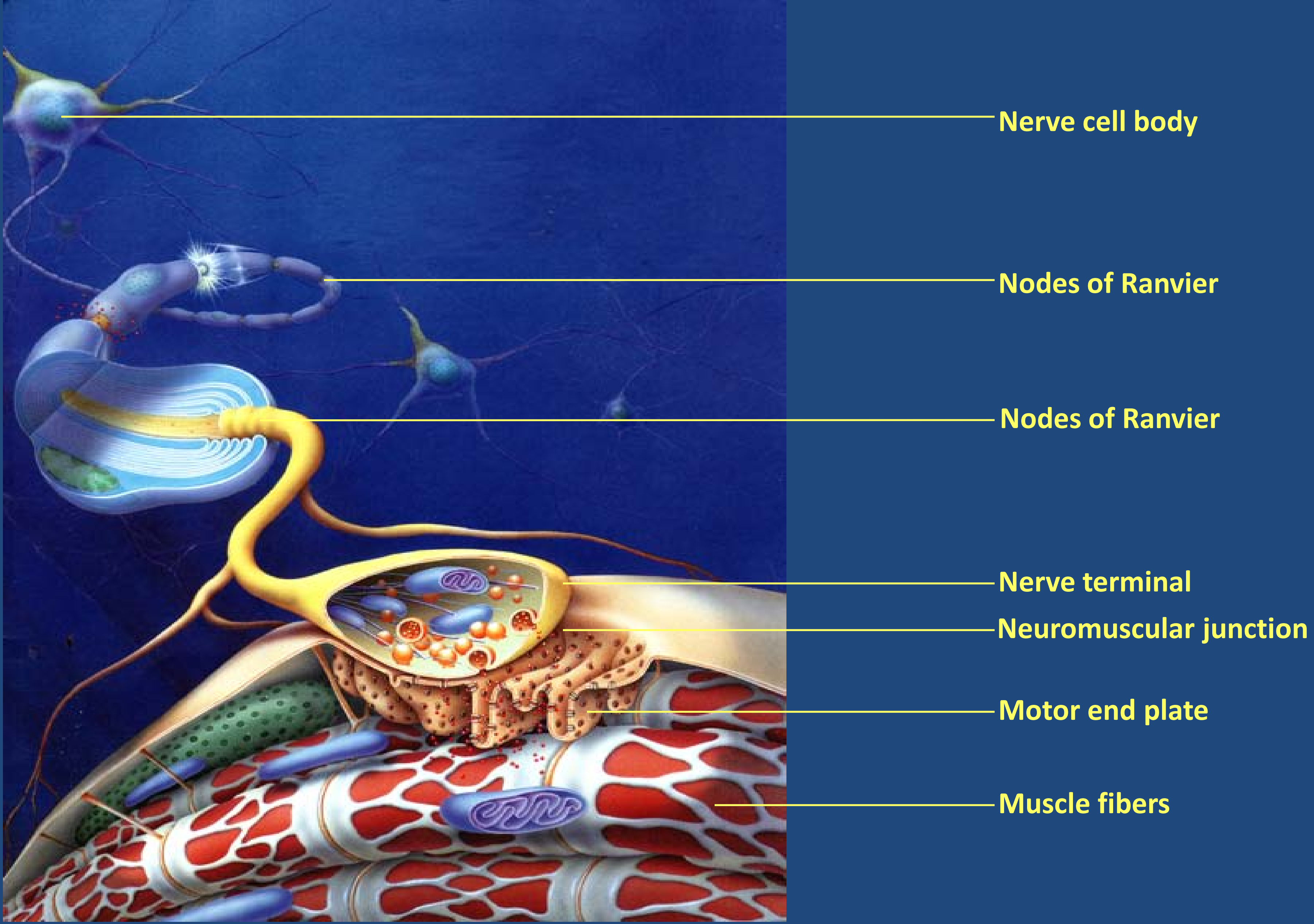
Schwann Cells (Specialized glial cells)

- up to 500 per neuronal axon

-Provide insulation by the envelopment of the nerve with lipid-rich myelin sheath.

-Potentiate conduction

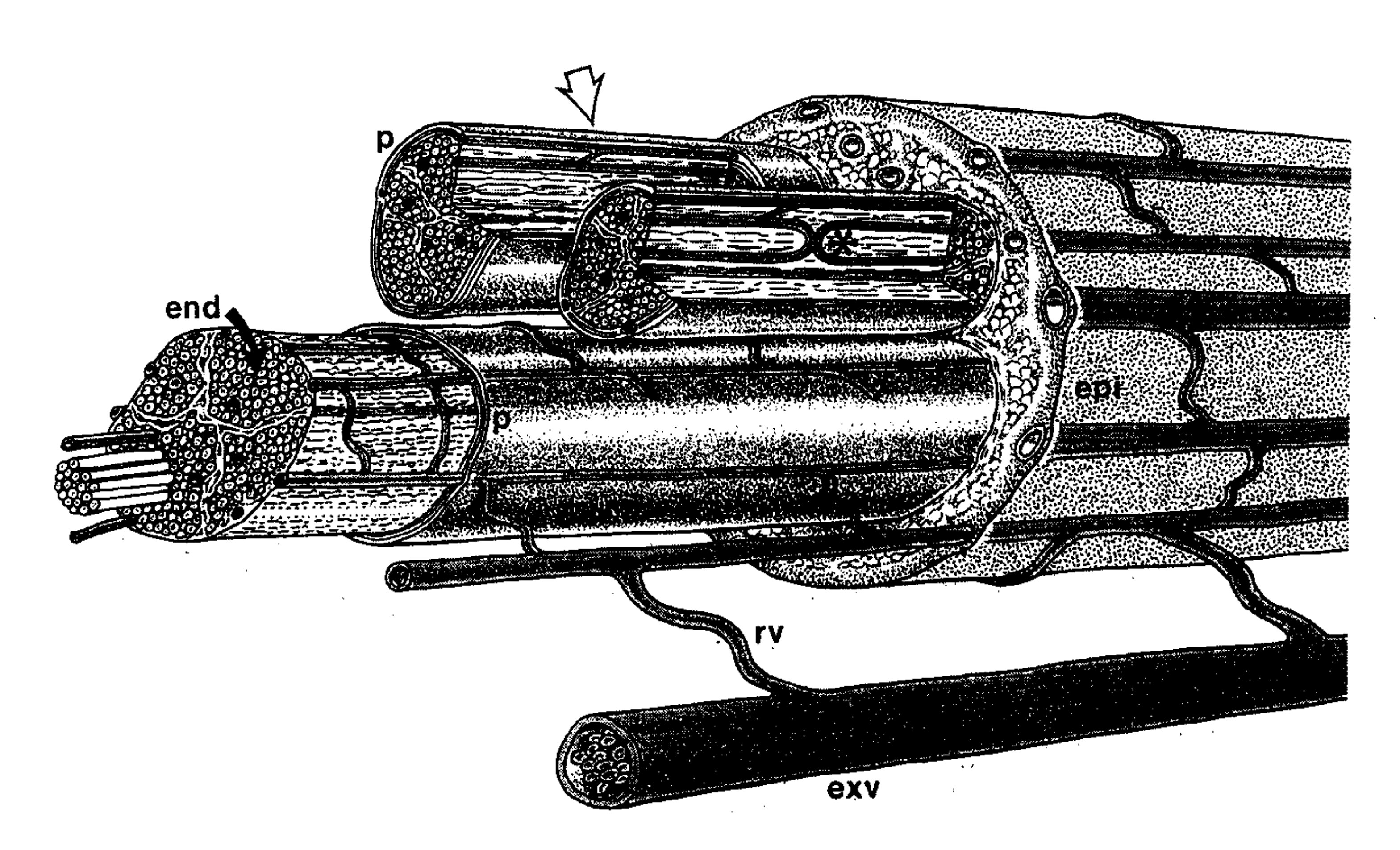




William J. Germann and Cindy L. Stanfield, Principles of Human Physiology, Interactive Physiology

Peripheral nerve injury

Neurovascular system

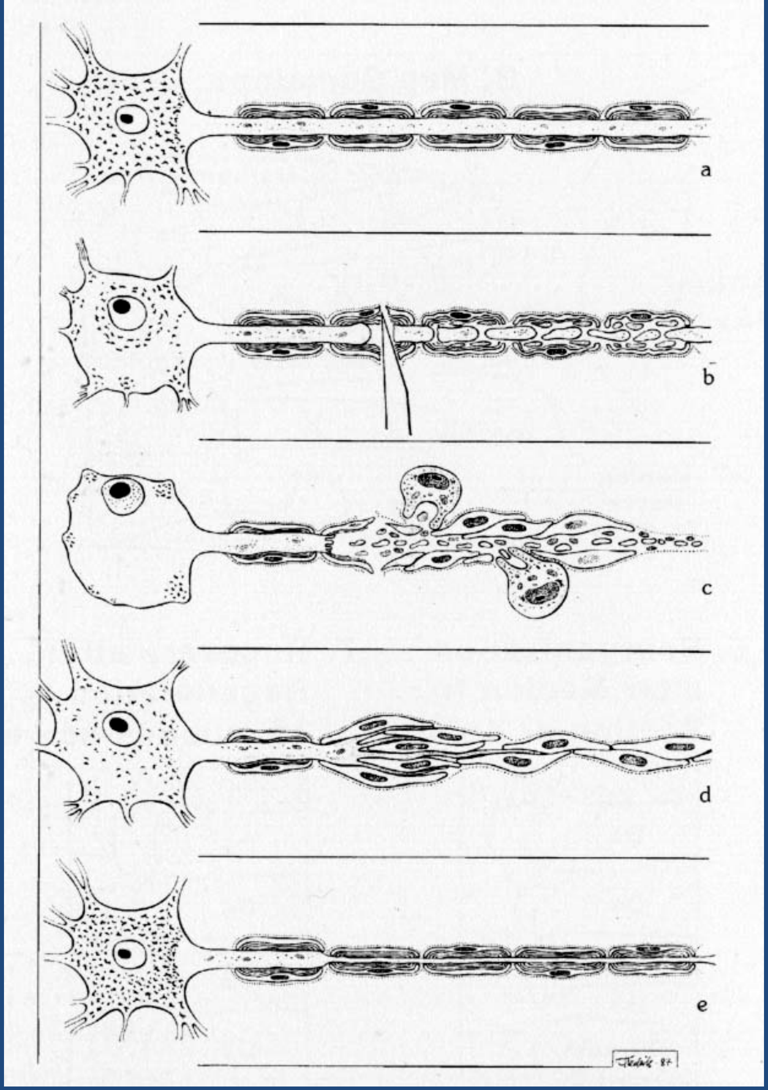


AAOS – Orthopaedic Basic Science

Response of Peripheral Nerve to Injury

DISTAL SEGMENT:

- Rapid disintegration occurs- Wallerian degeneration
- Myelin disintegrates and is phagocytised by Schwann cells & macrophages
- Empty axon tubules rapidly cleared in anticipation of regenerating axons



Molnar, 2004
Lundborg

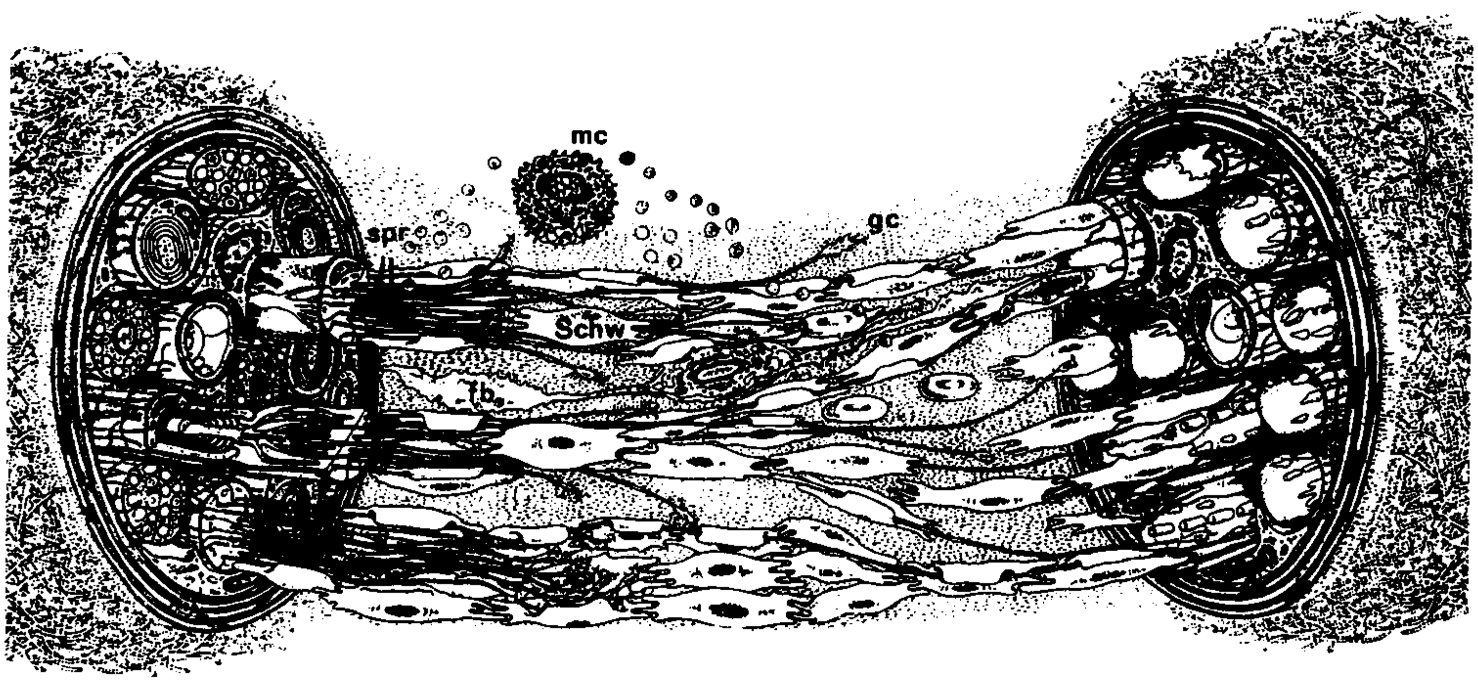
Response of Peripheral Nerve to injury

PROXIMAL NERVE SEGMENT:

- Axons degenerate for a distance of one or several internodal segments
- A single nerve fibre will sprout into a regenerating unit containing many nerve fibres
- Axon regenerate rate average: 1.0-1.5mm/day
- Axons that make connection with peripheral targets mature and myelinate, the rest disappear

Peripheral nerve injury

Axonal recovery and re-growth



Lundborg

Peripheral nerve injury repair

Nerve injury repairs

Paul of Aegina – 625-690: importance of approximation of nerve ends

Hueter – 1871: primary epineural nerve repairs

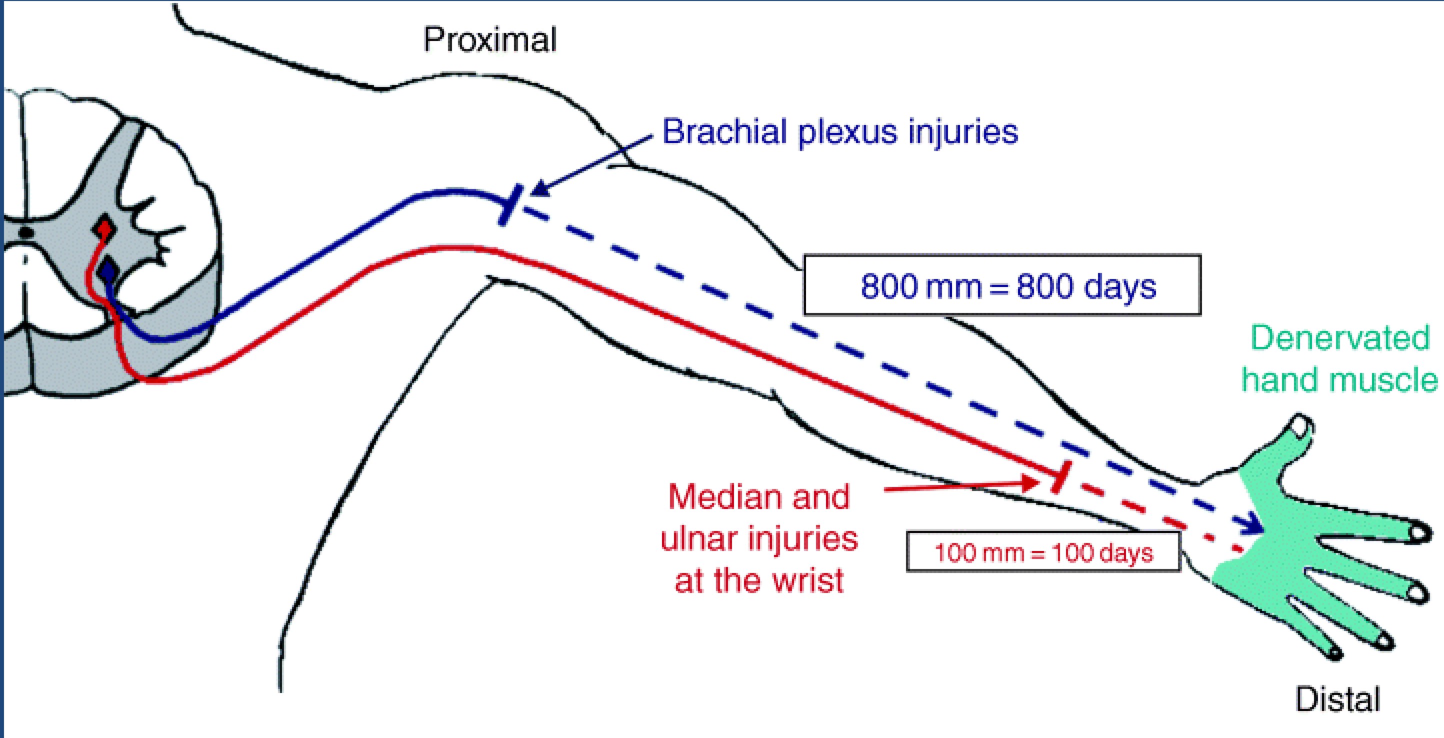
Loebke – 1884: bone shortening to reduce tension

Ortho Res Center: Cleveland Clinic

Peripheral nerve injury

Nerve growth following injury

– rate of 1 mm/day

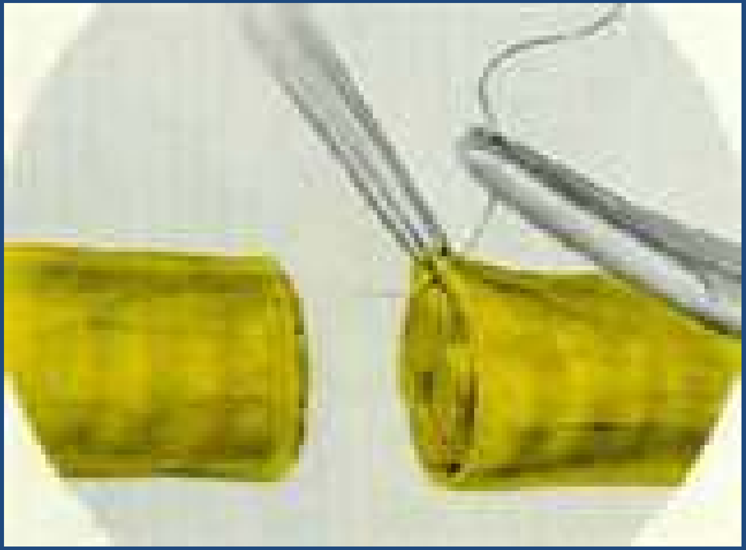


Gordon et al. JPNS 2003

Peripheral nerve injury

- Several types of nerve repairs - microsurgical
  - Primary (end-to-end)

- "Tension Free"
  - Grafts
  - External fixator



Wheeless online

Management of Peripheral Nerve Defects: External Fixator Assisted Primary Neurorrhaphy



Ruch et al. Bone and Joint Surg (Am), 2004; 86-A(7)

"The Use of Hinged External Fixation to Facilitate Primary Neurorrhaphy in Lower Extremity Injuries"

Ruch et al. *J Orthop Trauma* 2002

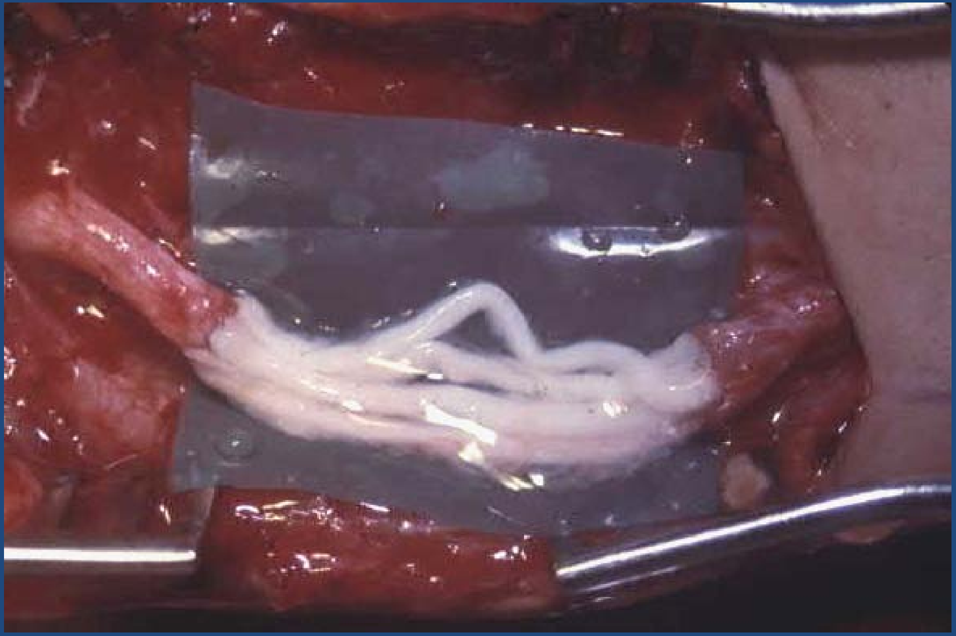
- 4 patients with tibial or sciatic nerve defects
- Articulated external fixators were slowly extended
- Good motor and sensory outcomes

Conclusions

- Outcomes superior to traditional repair techniques
- No joint contractures
- Useful for injuries near the joint

Peripheral nerve injury

- Several types of nerve repairs
  - –Cable (interfasccicular nerve graft) = autograft
    - Permits adequate perfusion of nerve
  - – Morbidity at donor site
- "Tension Free"
- Gold Standard



Autograft

- Autograft: most common donor nerves
  - *Sural nerve: 40cm each side*
  - *Lateral Antebrachial Cutaneous Nerve,*
  - *Medial Antebrachial Cutaneous Nerve,*
  - *Posterior Interosseous Nerve*
- Morbidity

Current State of Research

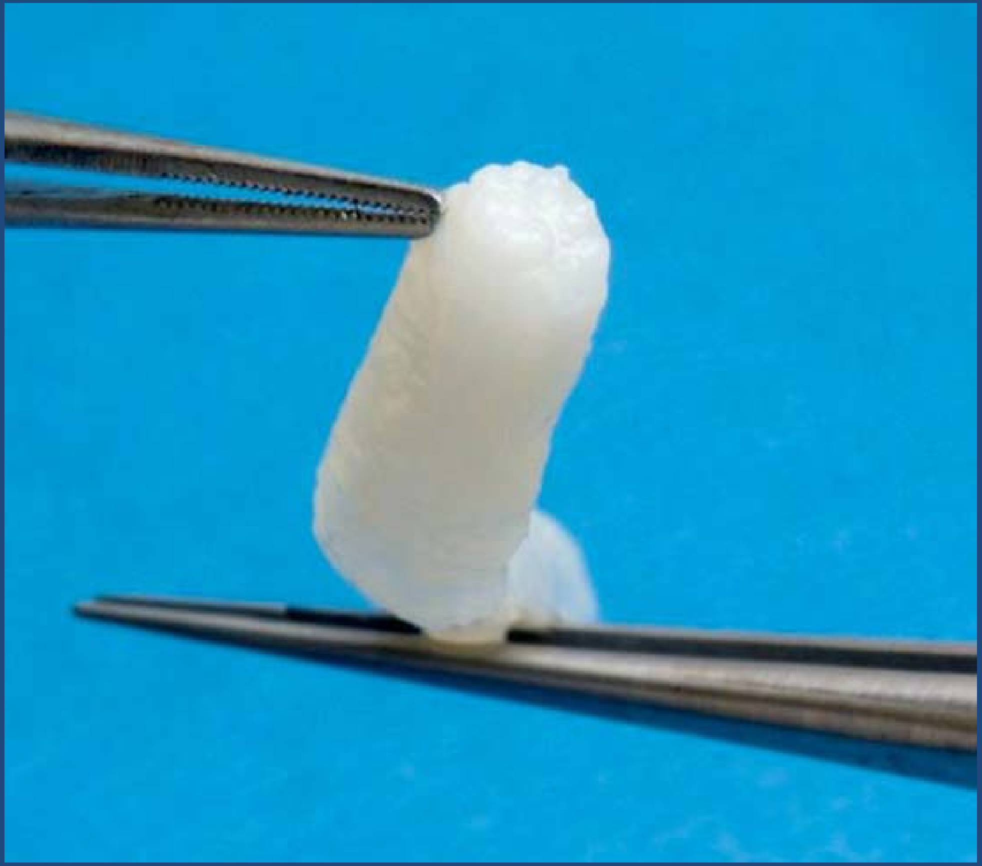
- Autografts – less than 3 cm
- Allografts – 70 mm (7 cm) – width of dollar bill
- Nerve guides – less than 3 cm
    - Matrix – cellular attachment
        - Filaments/haptic structures
    - Matrix + trophic factors
        - Mechanism of release - nanoparticles, microspheres
    - Electrical

Peripheral nerve injury

- Several types of nerve repairs

Nerve allograft

- Commercially available
- 7 cm nerve gap
- “Tension Free”

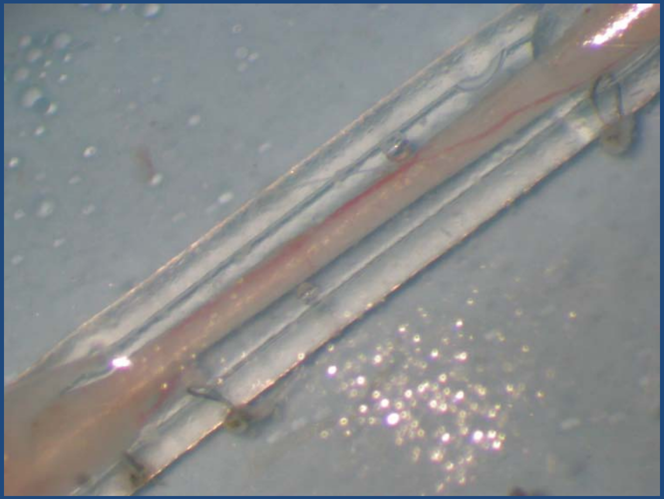


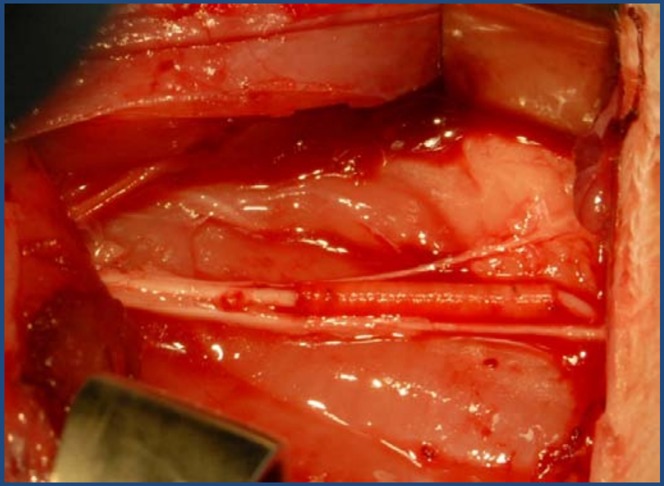
Peripheral nerve injury

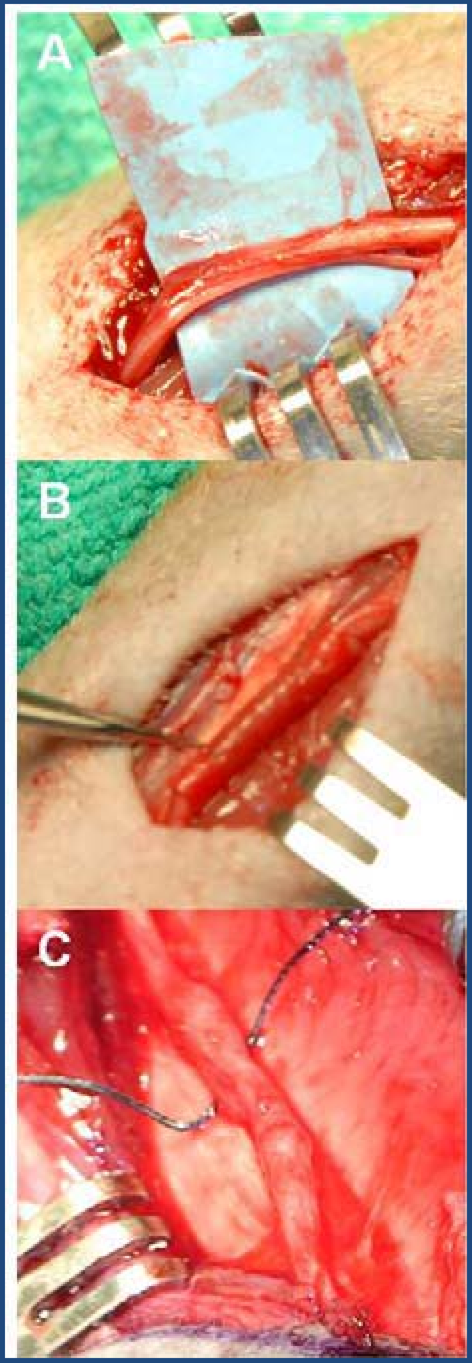
- Several types of nerve repairs

Nerve conduit

- Commercially available
- "Tension Free"







Nerve guide for nerve repair

Non-human Primates - pictured

Mice

Rats**

Rabbits

Keratin – other fillers

Trophic factors

Other - channels, nanotech

Nerve guides/growth factors

Polycaprolactone nerve Guide

Double-Walled GDNF Microspheres: Marra (Pitt)

Silk nerve guide: Kaplan (Tufts)

Polycaprolactone nerve guide

PLGA – VEGF microspheres : Wang, Windebank (Mayo)

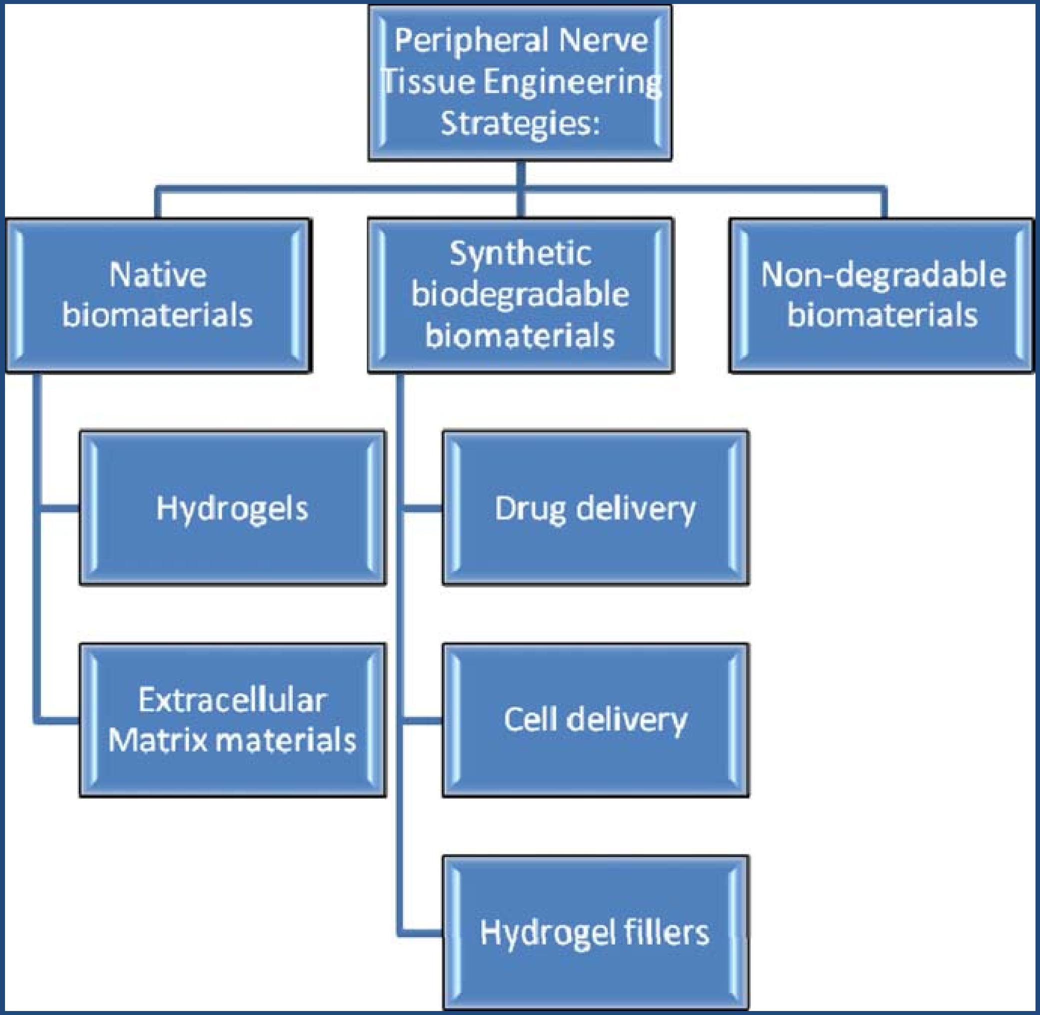
Collagen nerve guide: VanDyke (WFU)

Keratin

Hydrogel use in nerve guides

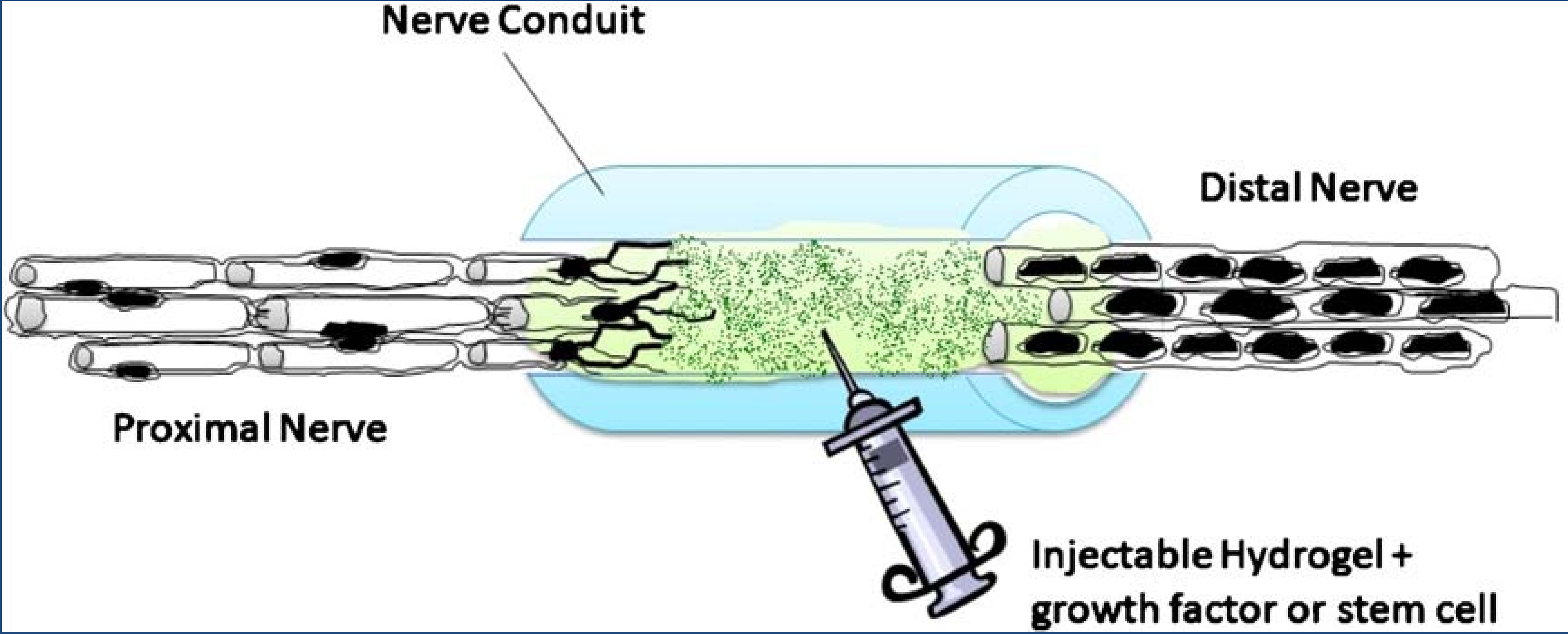
Hydrogel use strategy in peripheral nerve regeneration.

Lin Y-C, Marra K –
Biomed Matl. 7 - 2012



Addition of factors to Guide

Incorporation of fillers, cells or growth factors within a nerve guide.



Lin Y-C, Marra K – Biomed Matl. 7 - 2012

Clinically and Experimentally Implemented Design Criteria for Nerve Guidance Conduits

Materials	Clinical (C) or experimental (E)	Design criteria implemented	References
Biopolymers			
Collagen	C (NeuraGen)	Bio, Deg, Phys	33
	E	Bio, Deg, Anis, Phys	37
	E	Bio, Deg, Pro, Phys	106
Fibrin	E	Bio, Deg, Pro, Phys	38
Fibrin (matrix)	E	Bio, Deg, Phys, Supp	107
Gelatin	E	Bio, Deg, Phys	39
Keratin	E	Bio, Deg, Phys	40,41,90
Silk	E	Bio, Deg, Phys, Supp	87

Bio, biocompatibility; Deg, degradation/porosity; Anis, anisotropy; Pro, protein modification/release, Phys, physical fit; Supp, support cells

Nectow et al. 2012, Tiss. Eng. 18(1)

Clinically and Experimentally Implemented Design Criteria for Nerve Guidance Conduits

Materials	Clinical (C) or experimental (E)	Design criteria implemented	References
Synthetic polymers			
PCL	C (Neurolac)	Bio, Deg, Phys	15
PGA	C (Neurotube)	Bio, Deg, Phys	20,34
Poly (hydroxybutyrate)	E	Bio, Deg, Pro, Phys	46
Poly (D,L-lactide)	E	Bio, Deg, Anis, Phys	47
PLGA	E	Bio, Deg, Phys	48
	E	Bio, Deg, Phys, Supp	63

Bio, biocompatibility; Deg, degradation/porosity; Anis, anisotropy; Pro, protein modification/release, Phys, physical fit; Supp, support cells; Elec, electrically conducting.

Nectow et al. 2012, Tiss. Eng. 18(1)

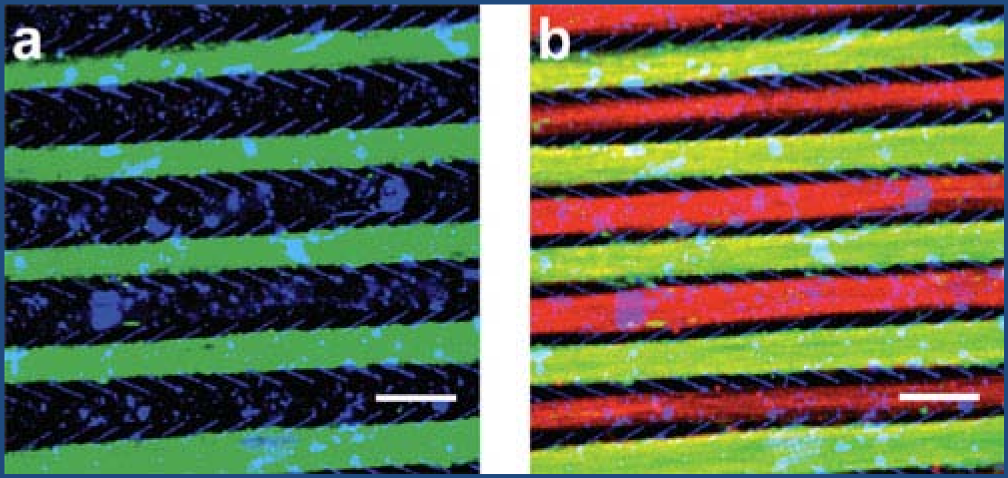
Growth Factors Utilized for Peripheral Nerve Repair

Growth Factor(s)	*Delivery Methods*	*Repair Site*	*Outcomes*
NGF	Nanofibers & Conduits	Rat Sciatic Nerve	Mature Nerve Fibers, ↑ Functional Recovery ↑ Nerve conduction velocities, Prevention of connective tissue ingrowth
GDNF	Microspheres	Rat Sciatic Nerve	↑ Gastrocnemius twitch force ↑ Improved Tissue Integration Nerve Fibers across entire area of regeneration
GDNF or BDNF	Transfection into Neural Stem Cells (NSC)	Rat Sciatic Nerve	↑ Myelination from GDNF NSC & BDNF NSC ↑Size of Regenerated Tissue from GDNF NSC & BDNF NSC ↑Blood Vessels from GDNF NSC ↑ Functional Gait from GDNF NSC & BDNF NSC
NGF & GDNF	Collagen tube impregnation	Rat Sciatic Nerve	↑ Early (2-week) regeneration
BMP-2	Injection	Rabbit Facial Nerve	Denser axons, Thicker axons ↑ Tau Protein
IGF-1	Injection	Rat Sciatic Nerve	↑ Functional Recovery Faster sensory recovery ↑ G-ratios

M.C. Tupaj – Tufts Dissertation -2012

Additional nerve guide modifications

- Physical guides for axon growth
  - Fibers
  - Channels
- Electrical potentials
  - Internal
  - Exogenous
- Combinations
  - Nanowires



Outcomes of Nerve Repair

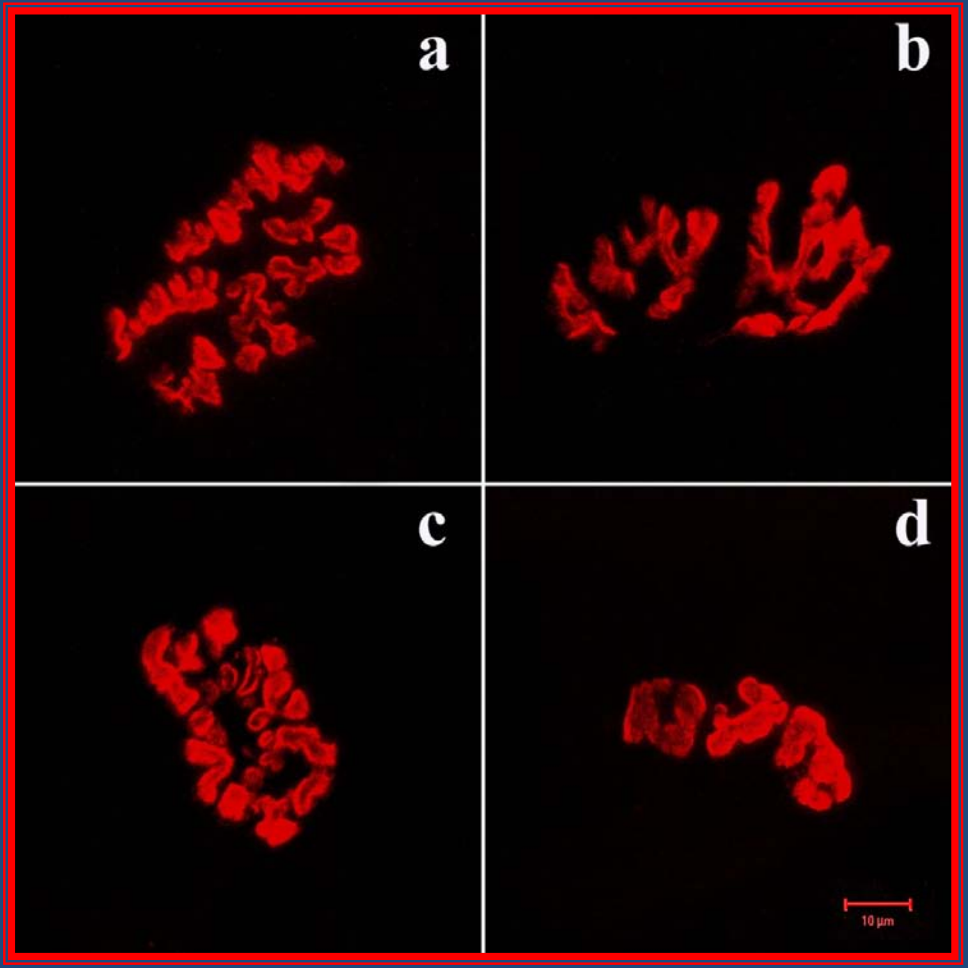
- **<u>Functional</u>** outcomes – motor
  - Gait
  - Muscle force generation
  - Compound motor action potential
  - Dexterity - pinch

Peripheral nerve injury

Factors affecting recovery = Challenges

- Length of delay before repair
  - 6-12 months
  - Changes in the target organ
- Age
  - Compromised in aging population
- Health (e.g. Diabetes)

Peripheral nerve injury



Peripheral nerve injury

Factors affecting recovery = Challenges

– Size of nerve gap

– Co-morbidities

  - multi-trauma

Others?

Focus areas for the Future

- Improve functionality
- Tissue engineering/regenerative medicine
- Halt target organ changes – increase temporal window for re-innervation
- Increase gap repair capabilities
- Improve outcomes for patients over 25

People who work on this

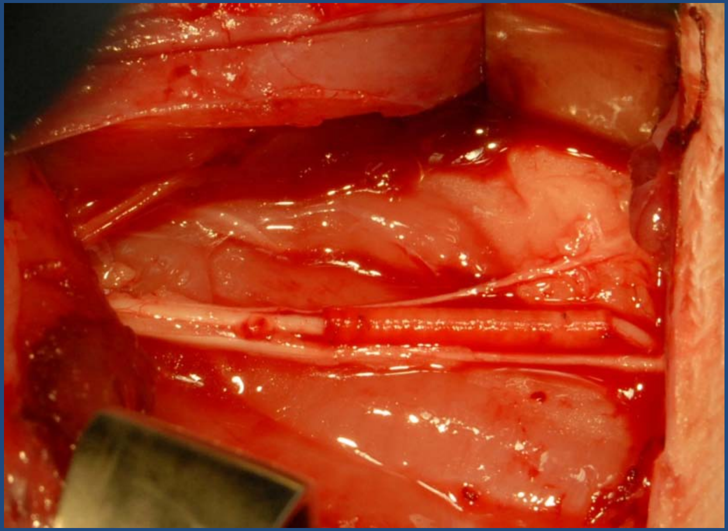
- Lauren Pace
- Mark Van Dyke
- Peter Apel
- Johannes Plate
- Zhongyu Li
- L Andrew Koman

Supported by

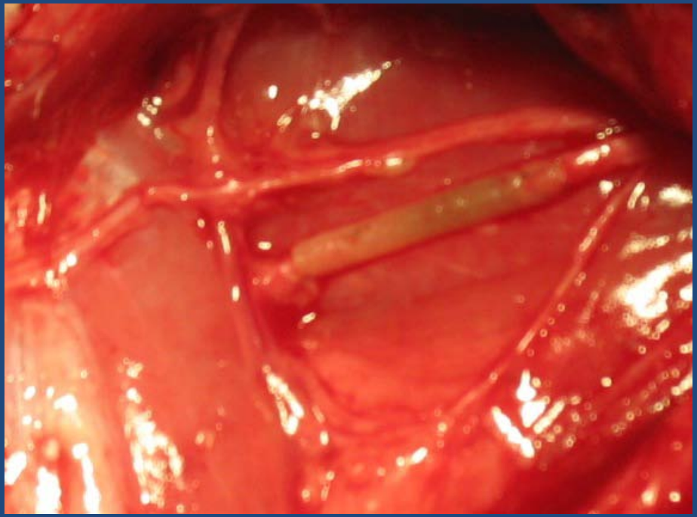
- AFIRM
- ASSH
- Errett Fisher Fdn
- CDMRP

Thank you

Nerve Regeneration Through a Keratose-Filled Conduit: A Study in Rabbits



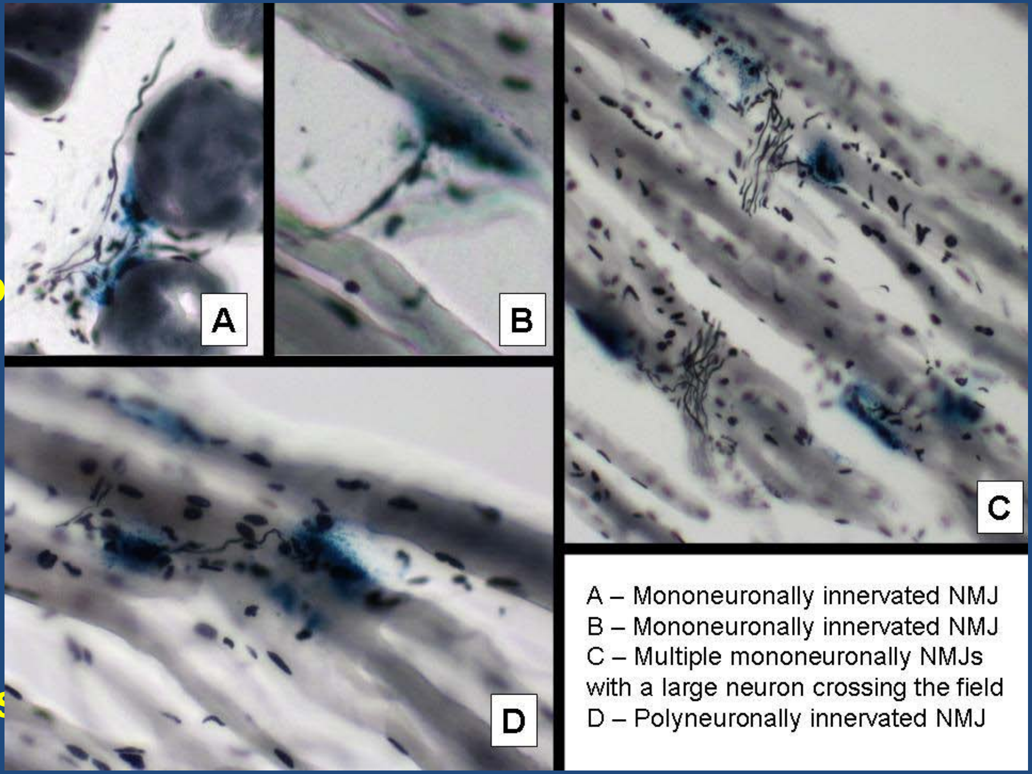
- Primary Site: WFIRM
- Preliminary studies underway
  - Techniques
  - Methodology
- Pilot study – To begin in January
  - To determine 'critical gap'



- Full study
  - 3 groups
    - Sural nerve autograft
    - Empty
    - Keratose
  - n=10 for each group

Nerve Regeneration Through a Keratose-Filled Conduit: A Study in Rabbits

- Outcome measures
  - Electrophysiology of neuromuscular unit
  - Muscle force generatio
- Rate of reinnervation
  - Serial NMJ histology
  - Thick sections (40μm)
  - Light microscopy
    - Silver stain
    - Acetylcholinesteras stain



- Nerve histomorphometry
- Muscle phenotype changes

Peripheral nerve injury

Following nerve injury

- Gap-43 – soma as well as distal nerve trunk (axons only, not in dendrites)
- Nerve Growth factors
- CAP 23