Biology of Peripheral Nerve Injury: clinical view

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NHS SCOTLAND

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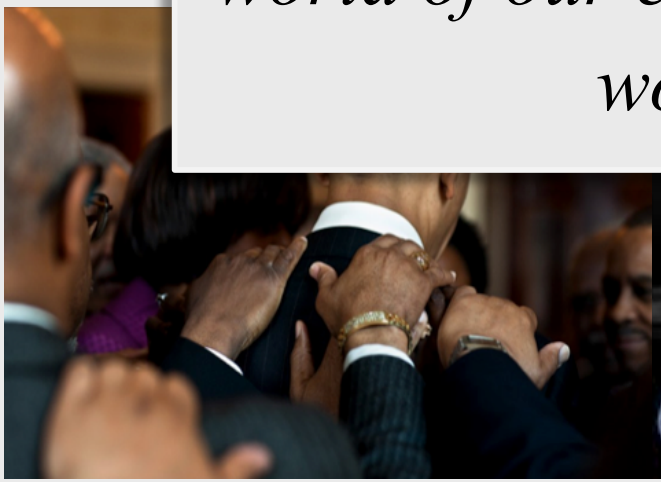
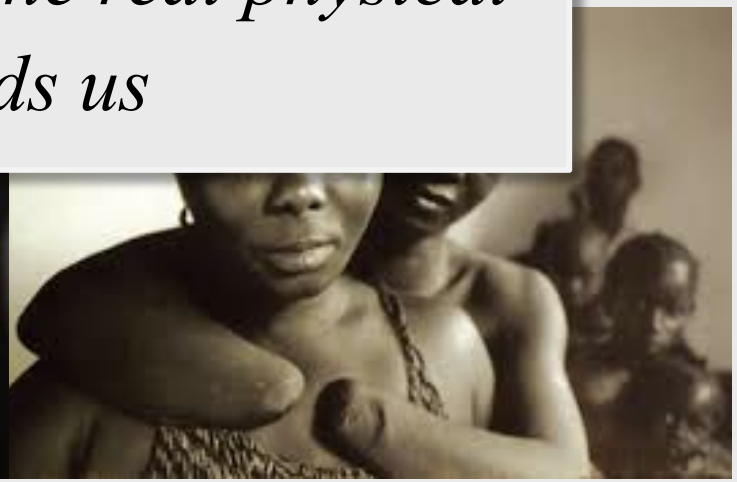
The Peripheral Nerve System

afferent & efferent determination of reality



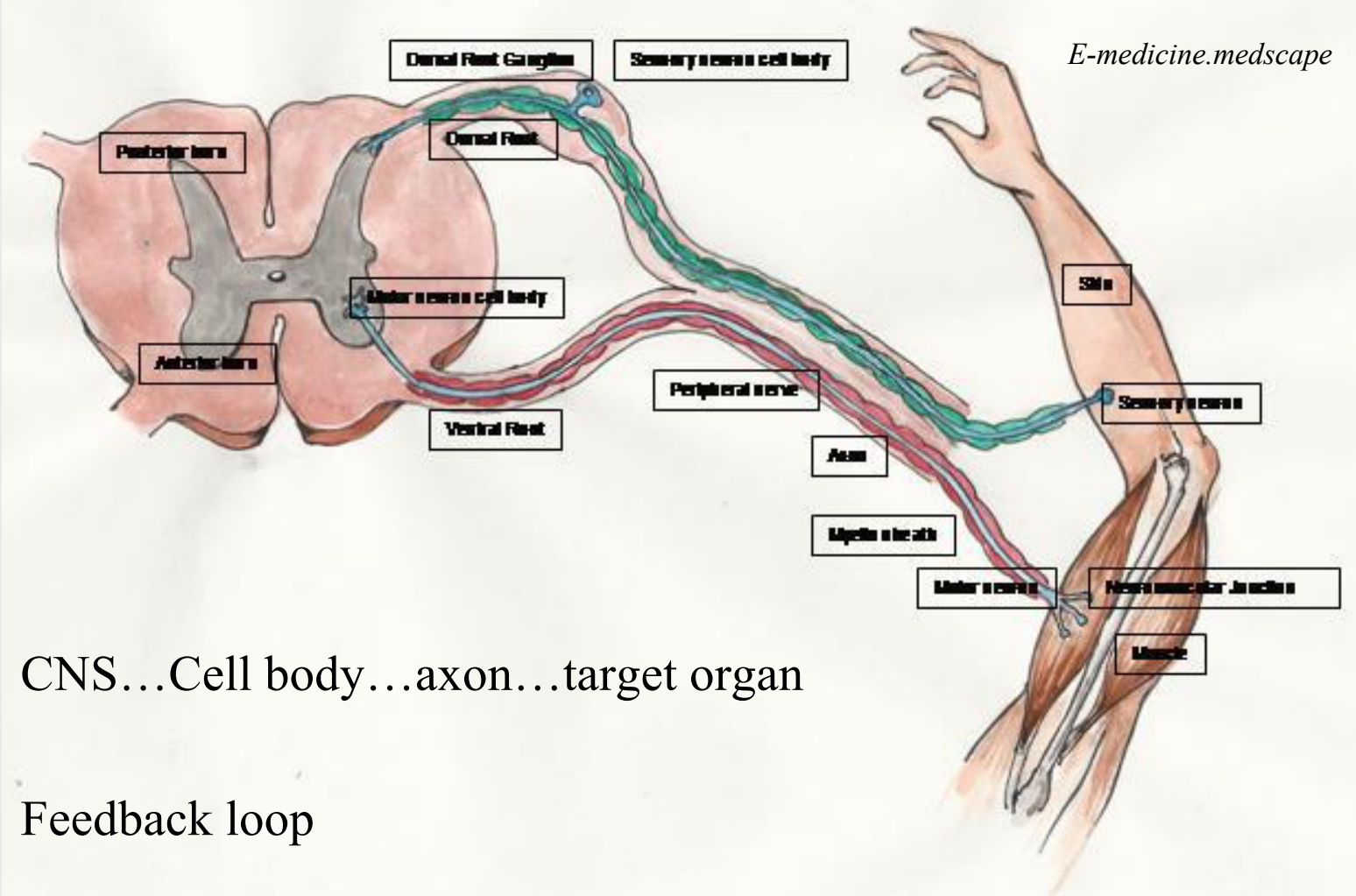

Peripheral nerve system links the virtual world of our consciousness to the real physical world that surrounds us





Peripheral Nerve System

Boils down to input & output

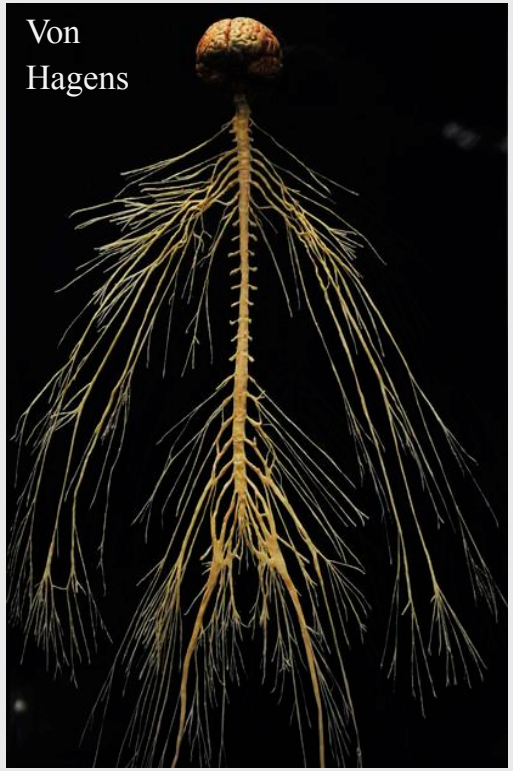


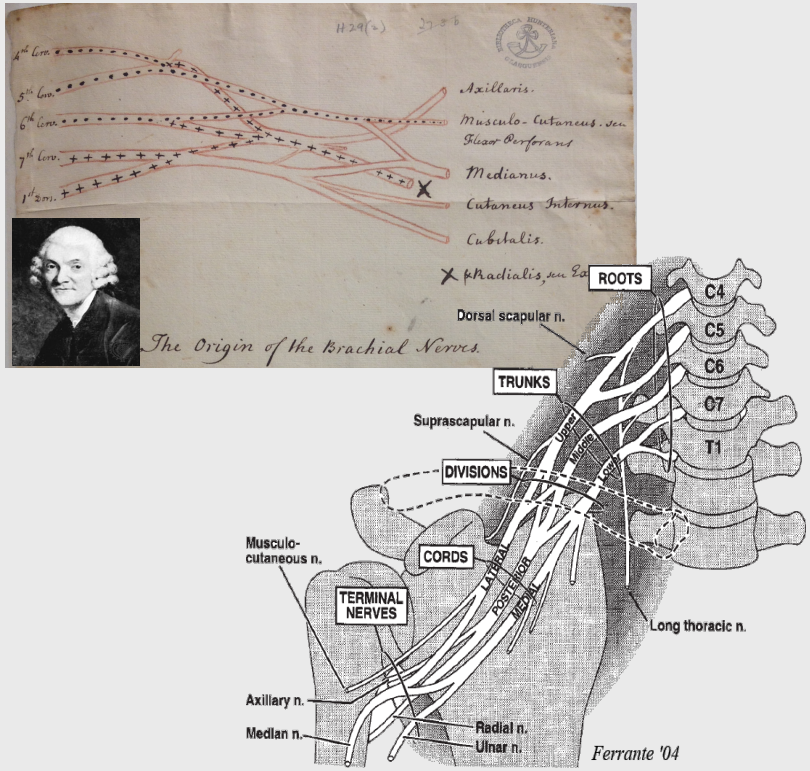
CNS…Cell body…axon…target organ

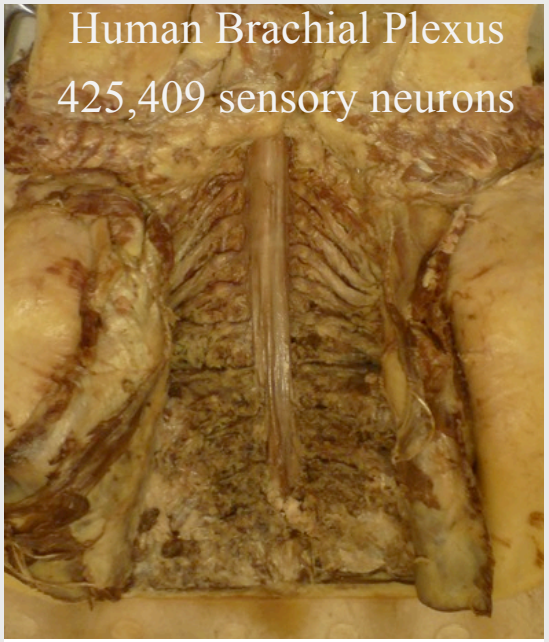
Feedback loop

Gross Anatomy

Roots, plexuses & terminal nerves







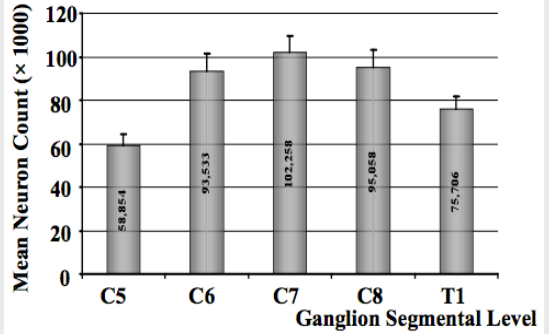


Figure 3: Mean neuron counts (+/- standard deviation) for C5-T1 dorsal root ganglia (n=10)

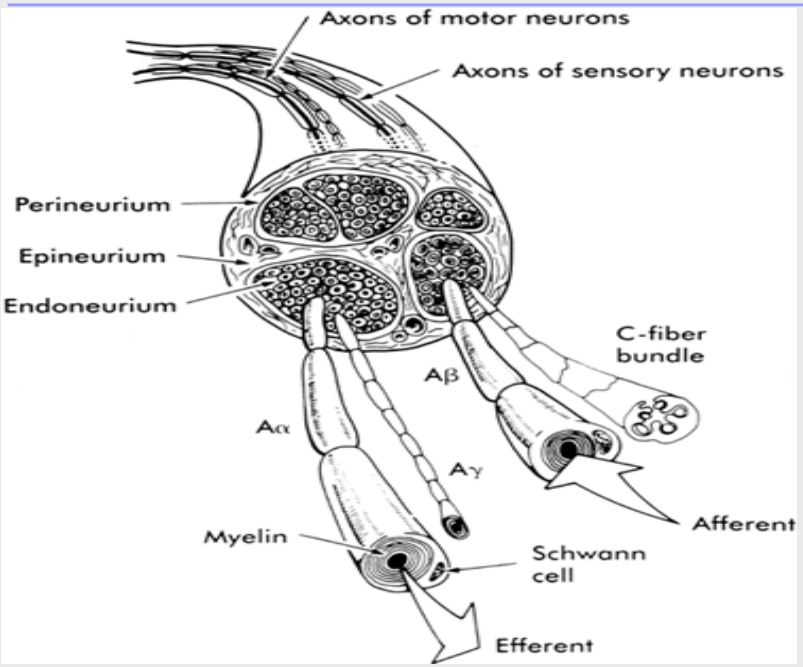
Dermatome/myotome vs. nerve territories

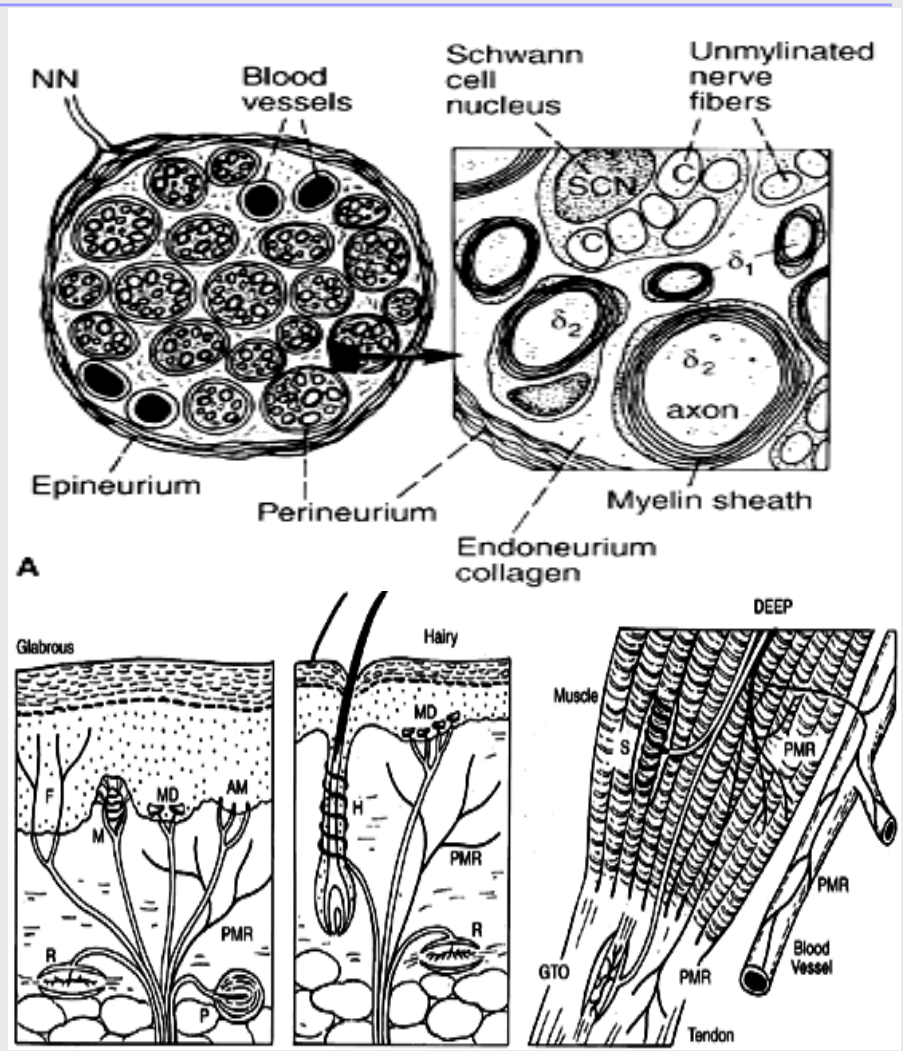
Long distances

Segregated fascicular anatomy

Microscopic Anatomy

Schwann cells, Protection & Fascicular Anatomy





Mechanical protection

Fascicular anatomy

Endoneurial tubes

Specialised target organelles

Neuron

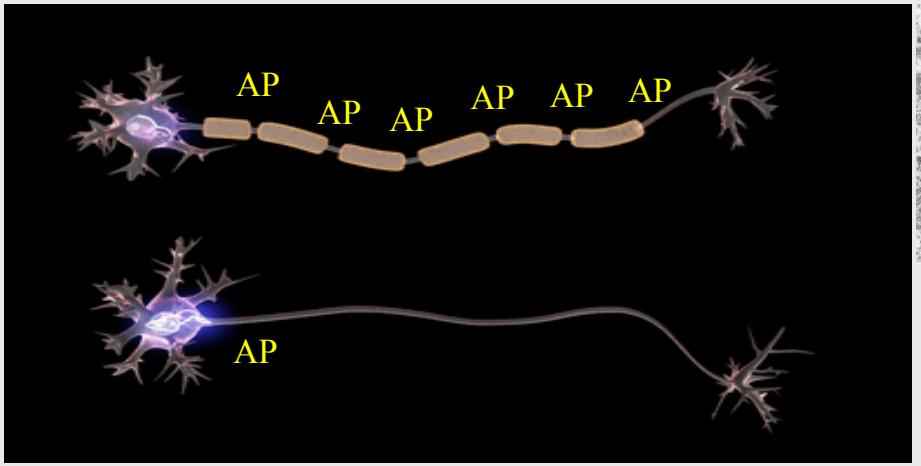
Metabolic hub + projections

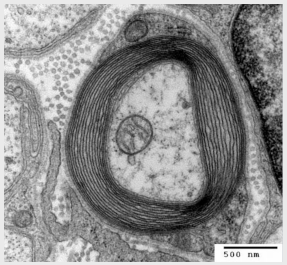
Cell body + Schwann cells exists to support axon

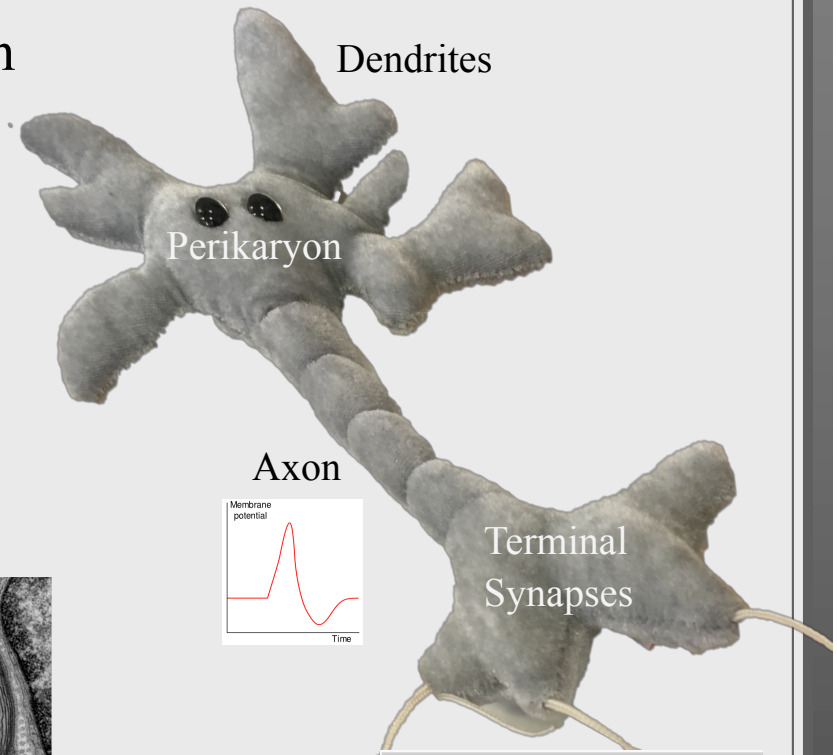
Axon exists to:

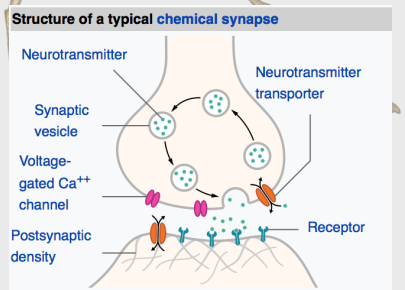
- Conduct: action potential
- Transport: trophic factors & control growth (OBPI)
- +/- regenerate

Cholinergic transmission at nmj





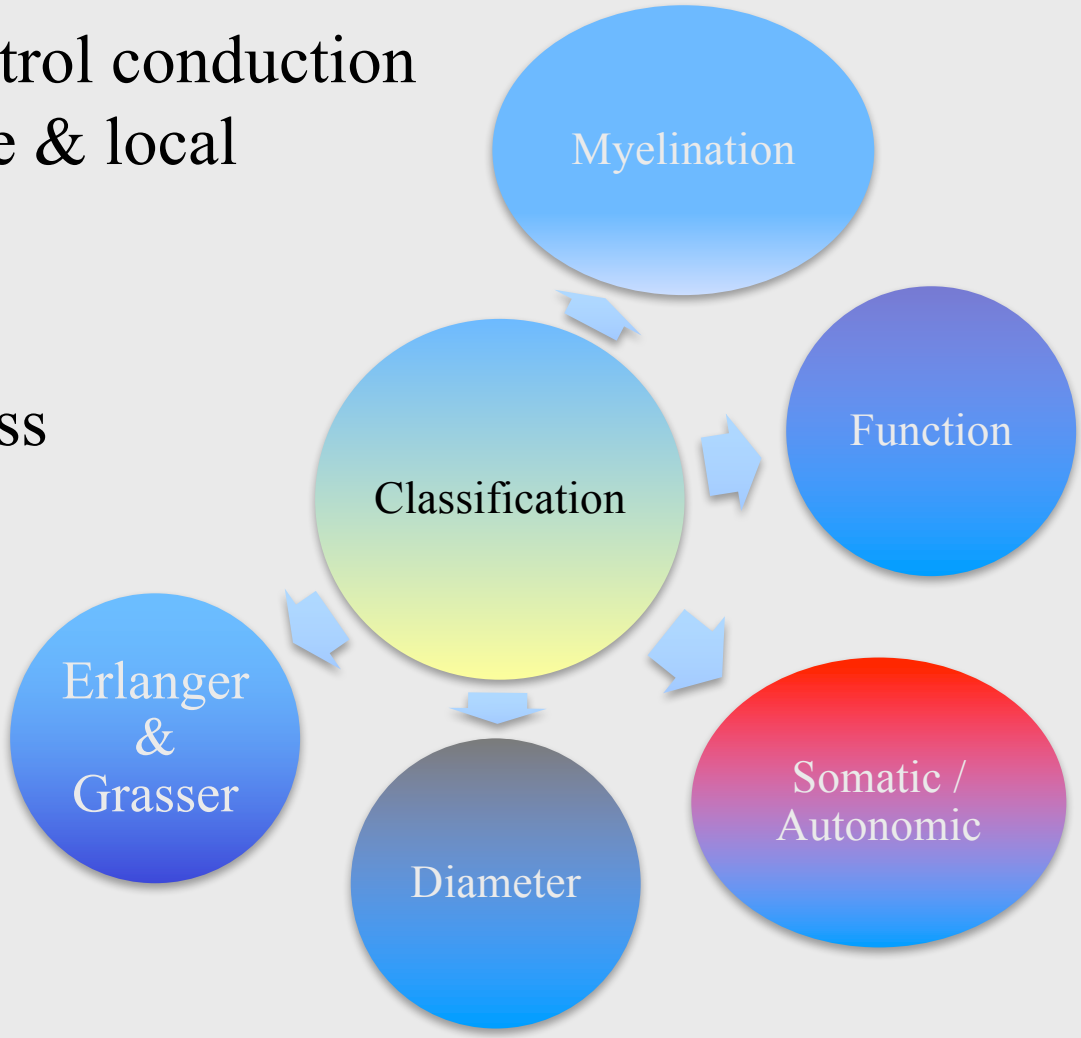




Neuron Classification

Myelination & diameter control conduction velocity, ischaemia tolerance & local anaesthetic sensitivity

Faster the conduction, the less ischaemia tolerant the fibre



Unified Classification of Nerve Injury:

Progressive destruction of AP conduction mechanism

Physiological conduction block:

- *Type A: intraneural circulatory arrest, metabolic ionic failure*
- *Type B: intraneural oedema, metabolic ionic failure*

Neurapraxia *(Sunderland 1)*: local conduction block, myelin damage

Axonotmesis *(Sunderland 2/3)*: loss of axonal continuity

Neurometsis:

- *Sunderland 3 – loss of axonal & endoneurial continuity*
- *Sunderland 4 – loss of axonal, endoneurial & perineurial continuity*
- *Sunderland 5 – loss of axonal, endoneurial, perineurial & epineurial continuity*

[After Lundborg 2004]

Grade of injury – is repair needed?

Physiological conduction block:

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[After Lundborg 2004]

Mechanism of injury –

what repair will be needed?

Inflammatory

Metabolic

Compression

- *acute*
- *chronic*

Sharp injury

Traction

Neoplastic infiltration +/- DXT

Nerve Injury

~100 years and we're doing the same thing

SUTURE OF THE BRACHIAL PLEXUS IN BIRTH PARALYSIS OF THE UPPER EXTREMITY.

By ROBERT KENNEDY, M.A., M.D., D.Sc.,

298 THE BRITISH MEDICAL JOURNAL] SUTURE OF BRACHIAL PLEXUS. [FEB. 7, 1903.

operative intervention has certainly been fully justified; and in consideration of the hitherto unsatisfactory prognosis of these cases and of the safety of modern surgical procedure, I think that operation is the right course to follow in all cases which do not very early show spontaneous improvement.

Benefit of plexus repair at ~2 months ages

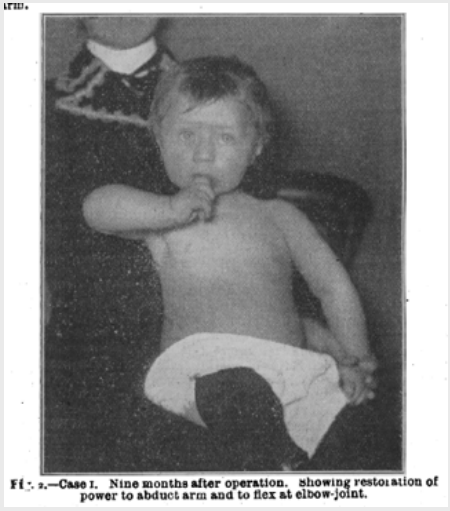


Fig. 2.—Case I. Nine months after operation. Showing restoration of power to abduct arm and to flex at elbow-joint.

Later reported electrophysiology, diagnostic & operative repair work on 38 Glaswegians..., and Subsequently on numerous macaques

NERVE WOUNDS

SYMPTOMATOLOGY OF PERIPHERAL NERVE LESIONS CAUSED BY WAR WOUNDS

1917

BY

J. TINEL

ANCIEN CHEF DE CLINIQUE ET DE LABORATOIRE DE LA SALPÊTRIÈRE

PREFACE BY

PROFESSOR J. DEJERINE

2. Suture.—Nerve suture is indicated in all cas ruption of nerve fibres where no satisfactory regener

The most effective suture is that which produces the best contact with a minimum of traumatism for the nerve trunk. Speaking generally, it is astray (Nageotte). Rather than incur this risk, it is better to leave between the segments a space of one or even two millimetres, easily filled in by the neuroglial proliferation.

3. Nerve grafting.—When the distance between the segmer nerve trunk is too great to permit of direct suture, *the only operation is nerve grafting*, as recommended by J. and A. Dej Mouzon.

This consists in uniting the segments of the interrupted nerve by the interposition of fragments removed from a sensory nerve. The musculo-

All other grafting processes are more or less defective.

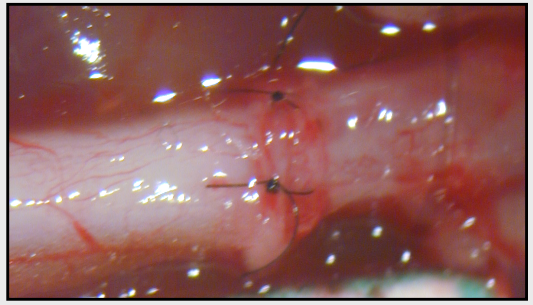
Defective operations.—All that we have said about the main p of nerve regeneration is sufficient to show how illogical and ineffe certain methods once strongly recommended.

All lateral sutures must be condemned that do not make co the axis-cylinders of the central end and the empty sheaths of t pheral end; lateral implantations, sutures by division into two upper segment, transplantations of one nerve into the other, a especially transplantations of a motor nerve into a sensory one ar always useless and often mischievous operations.

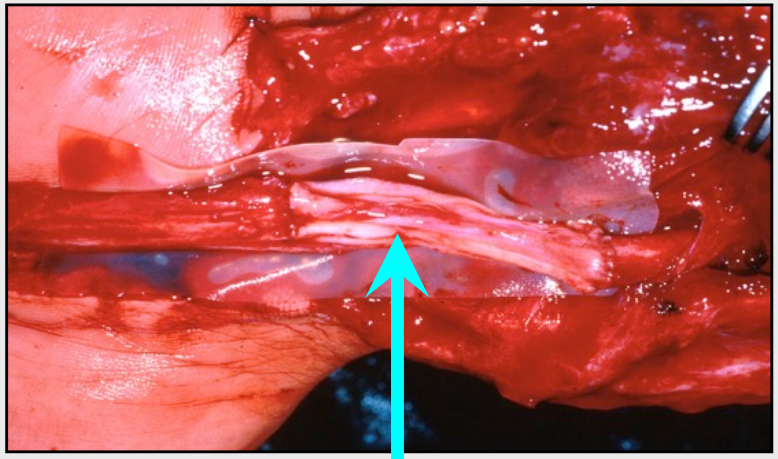
Specified nerve repair, grafting, impact of tension, and defective operations.

Surgical Strategies for reconstruction

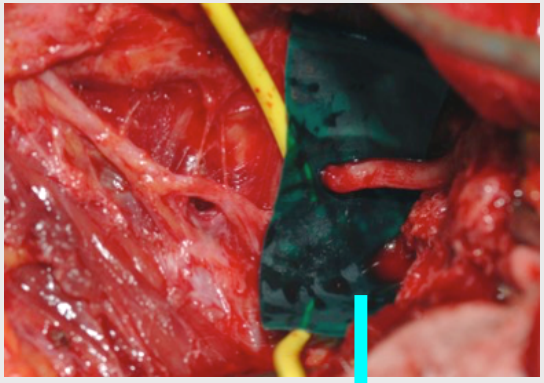
4 main surgical strategies



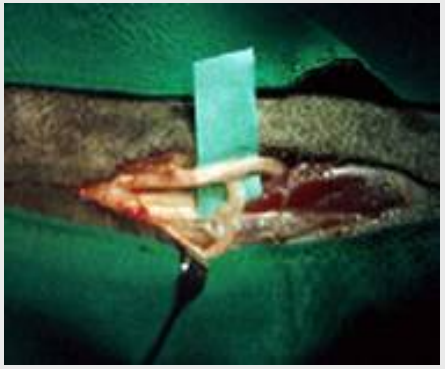
direct neurorraphy



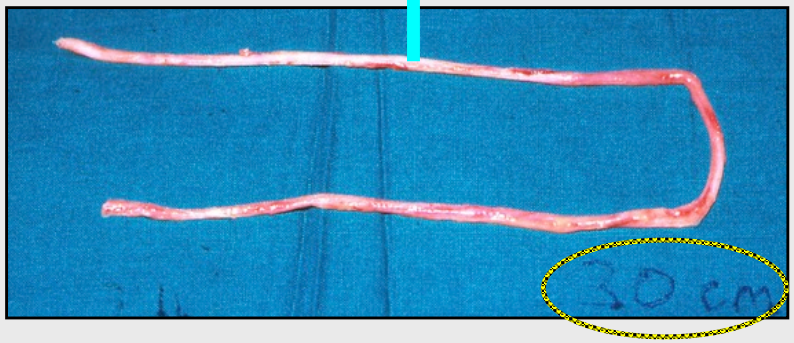
nerve graft repair

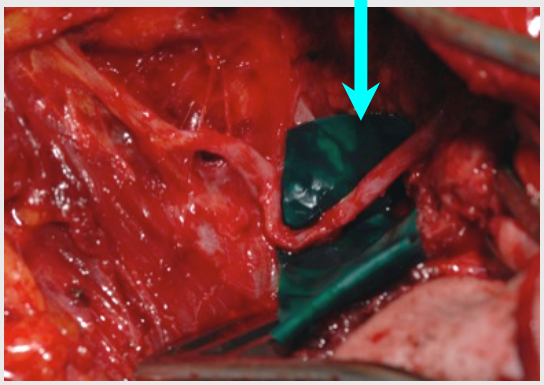


nerve transfer



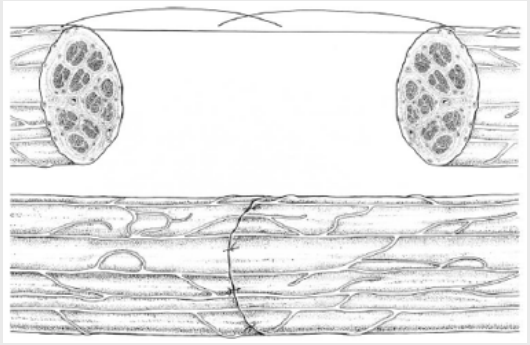
[end-side repair]



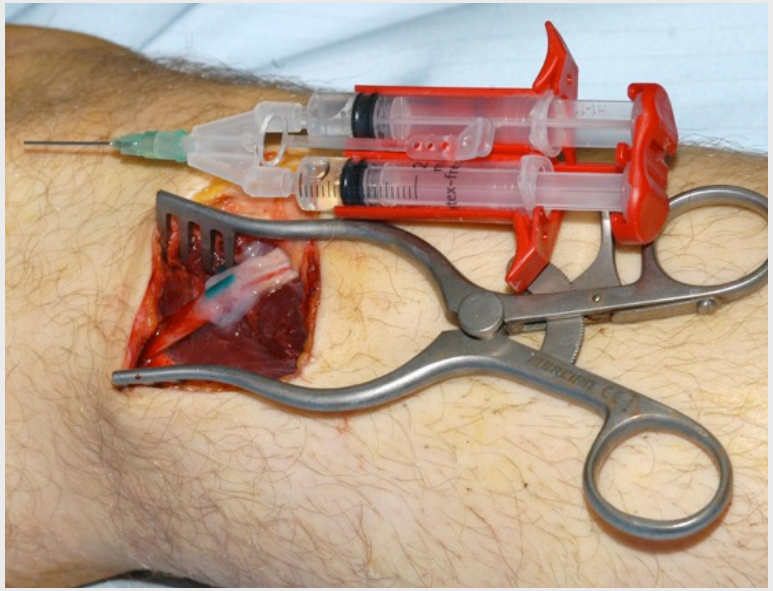


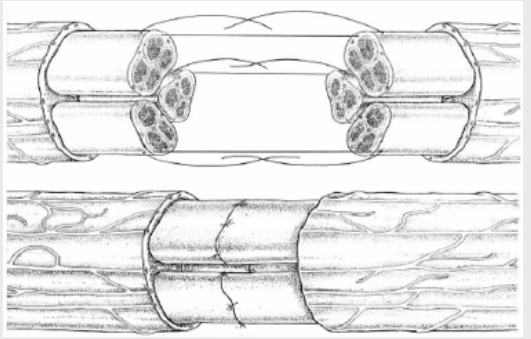
Surgical techniques for nerve repair

3 main techniques

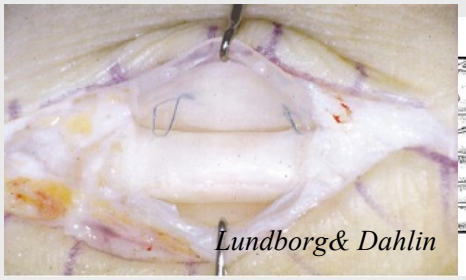


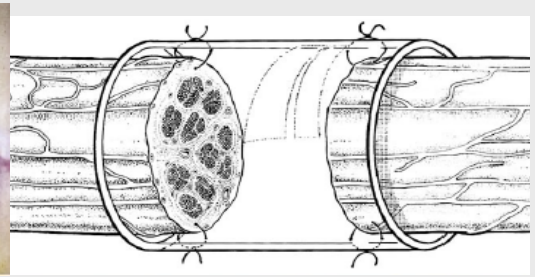
Epineurial repair

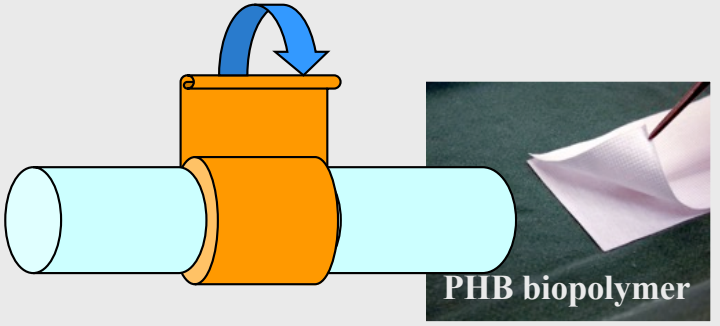




Fascicular repair



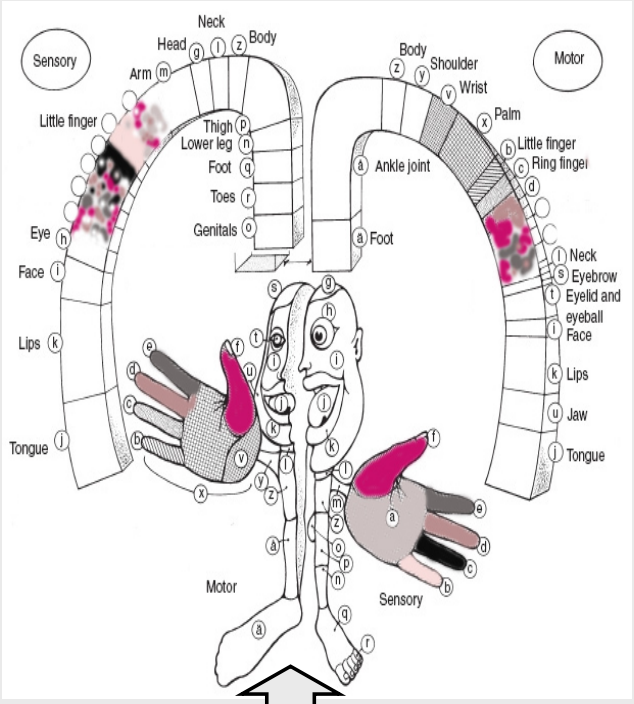


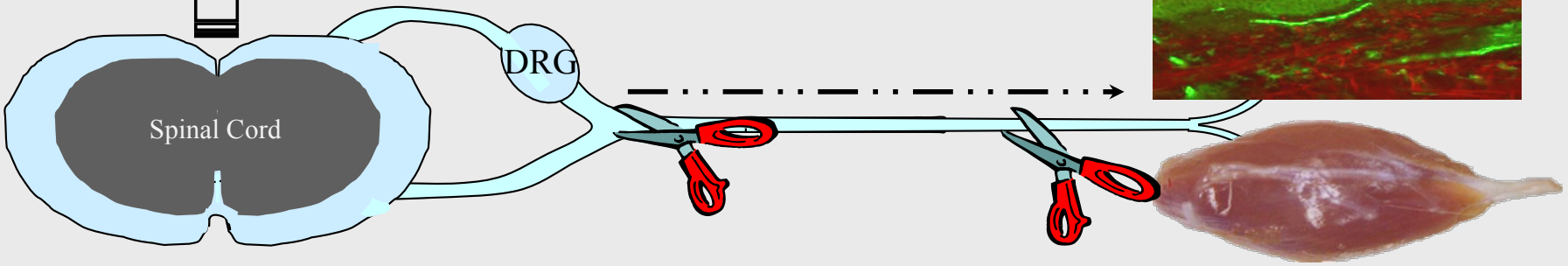


entubulation / wraparound repair gives axons self-determination?

Neurobiology of peripheral nerve injury:

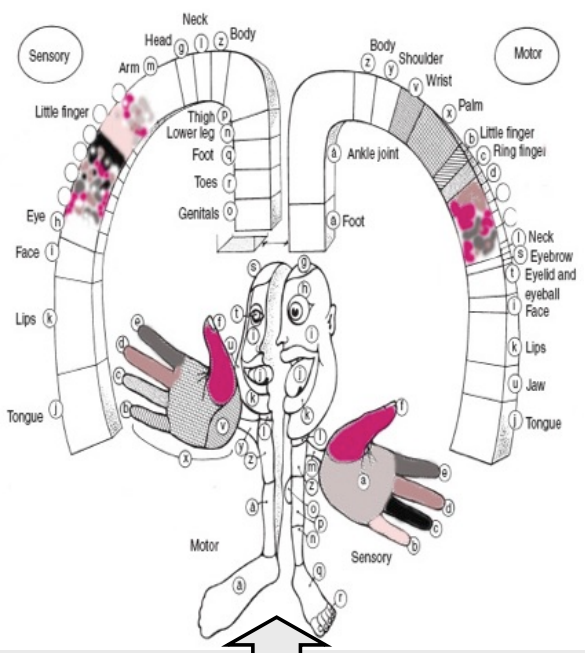
what actually matters?





Peripheral nervous system

Dynamic living tissues with complex injury response



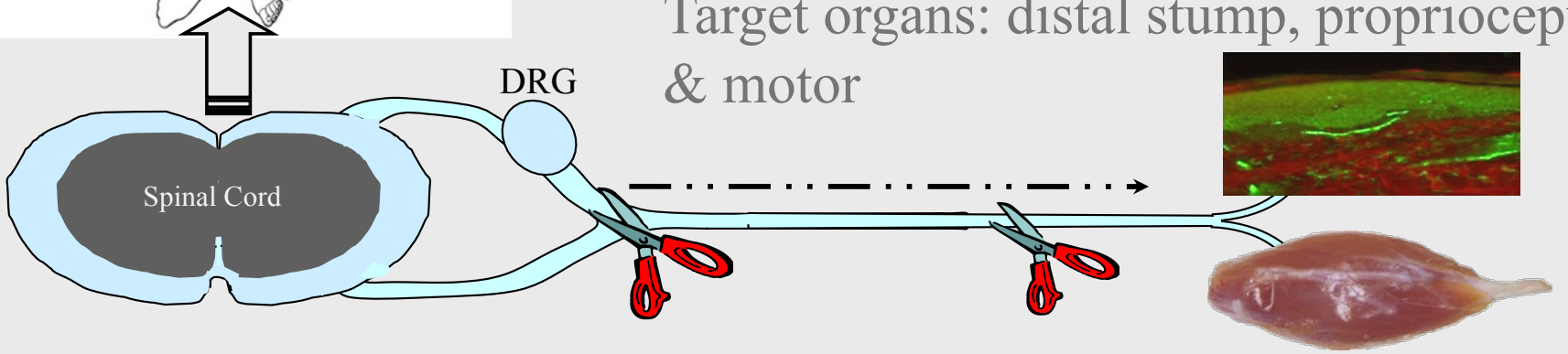
Sensory & motor neuron changes

CNS events

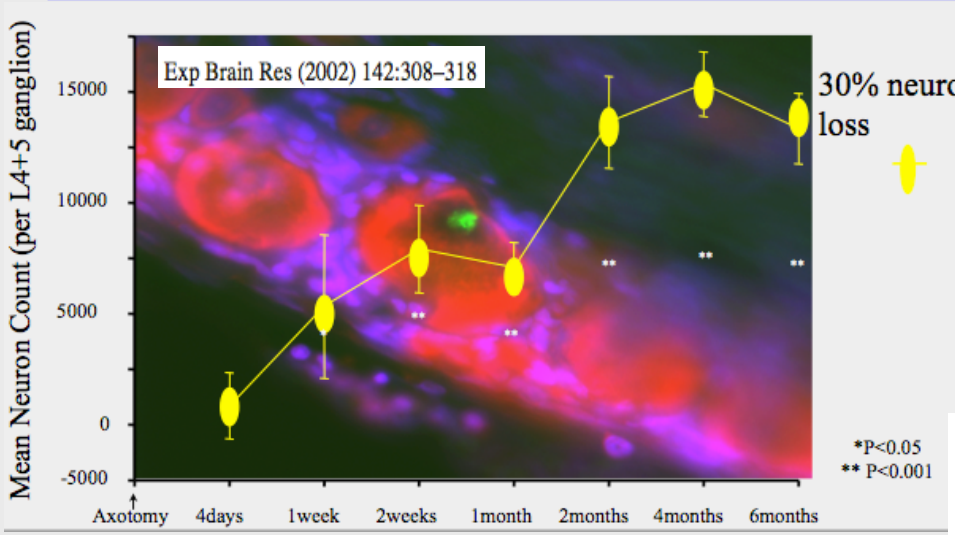
Repair site

- Proximal stump
- Neurosythesis
- Distal stump entry zone

Target organs: distal stump, proprioceptive & motor



Nerve transection causes neuronal death: *a brief therapeutic window exists*



Sensory neurons:

20-70% cell death

large myelinated ones more resistant

starts in <24 hours, complete in 2 months

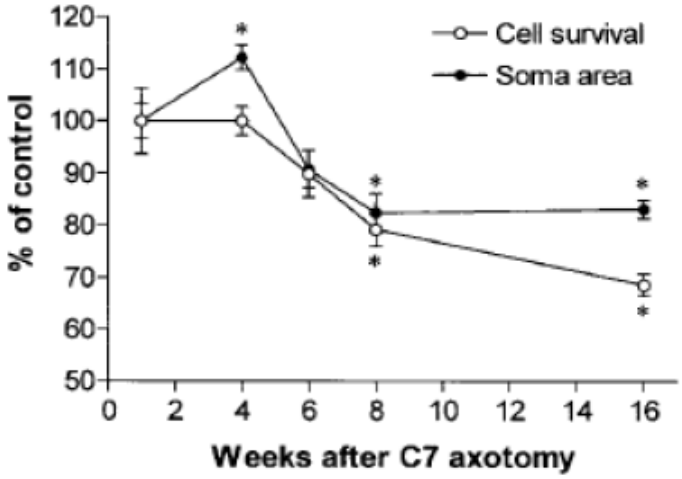
From: Ma J., Novikov L.N., Wiberg M., Kellerth J.O. "Delayed loss of spinal motoneurons after peripheral nerve injury in adult rats: a quantitative morphological study" Exp.Brain Res. 2001;139(2):216-223. Publisher – Springer Verlag, DOI 10.1007/s002210100769

Motorneurons:

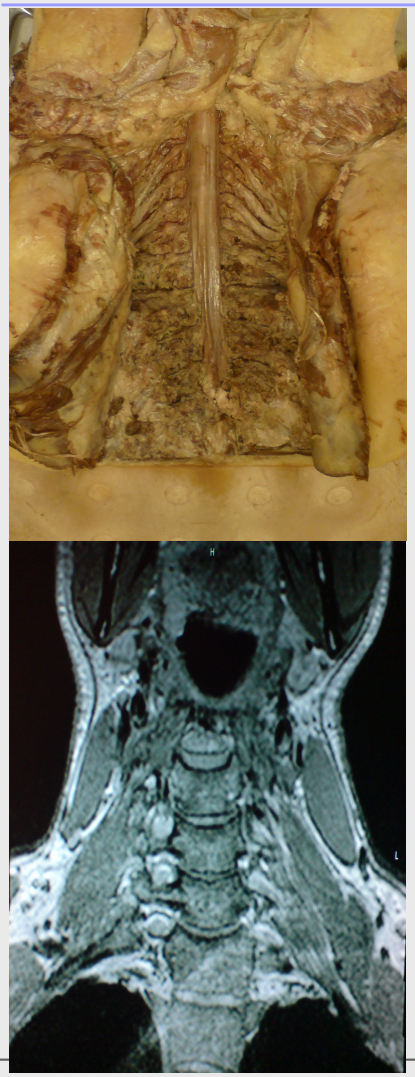
30-50% cell death (proximal injury)

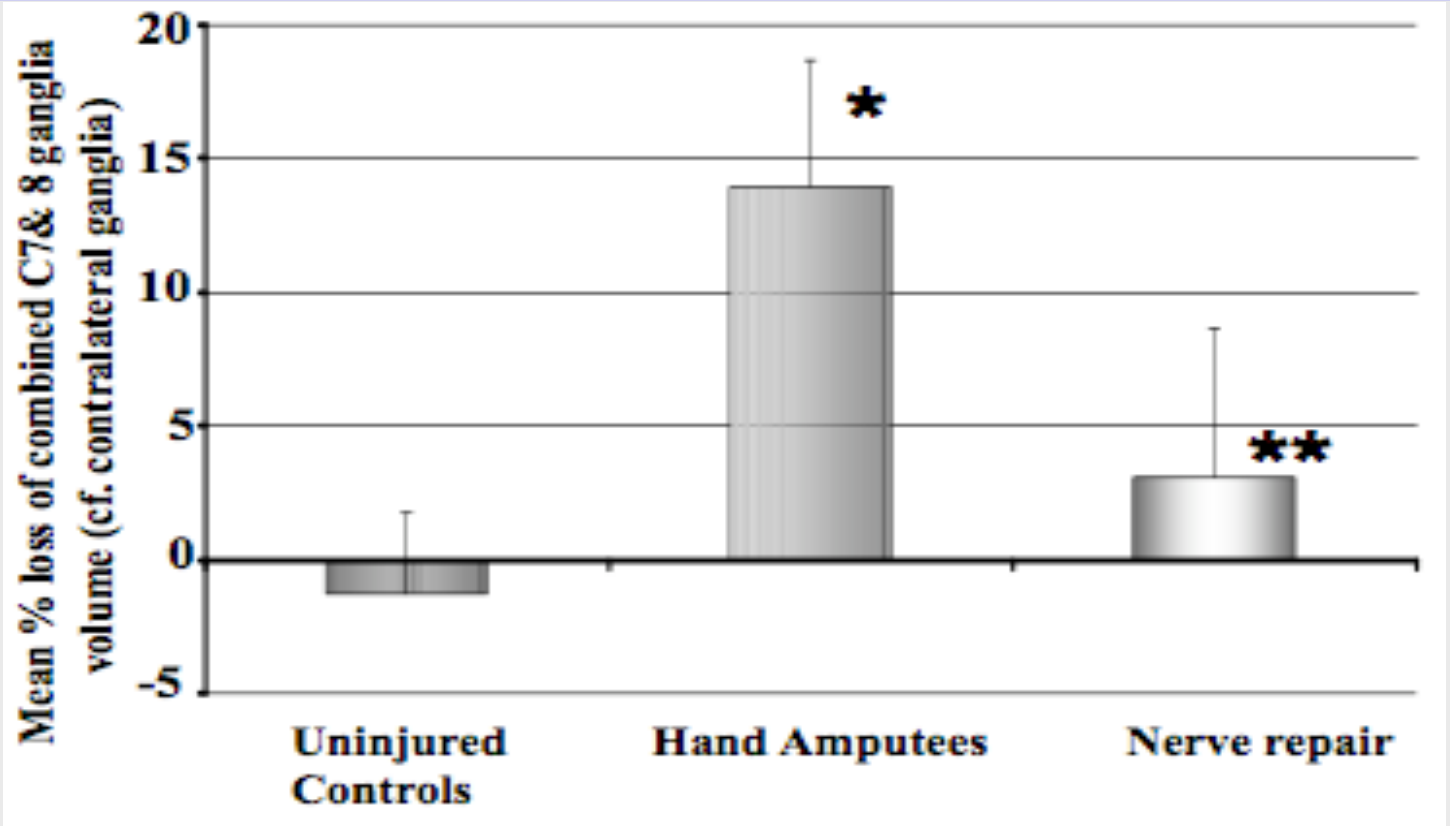
starts in 2-4 weeks, complete in ~3 months

some necrose



Neuronal death is restricted by **early** nerve repair



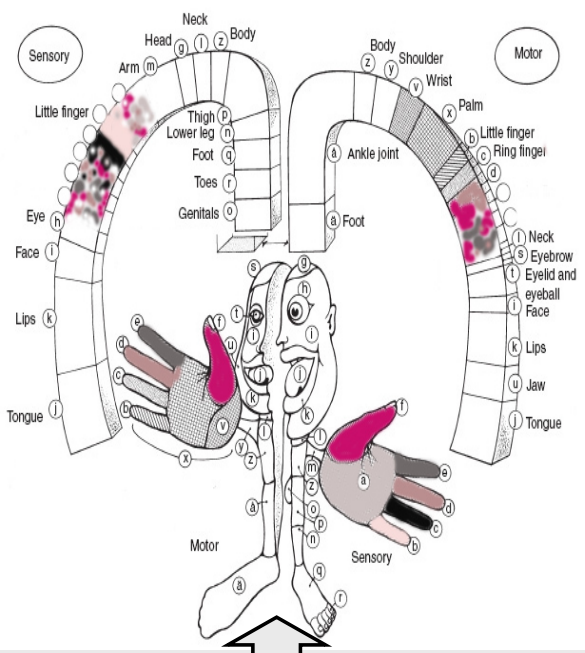


DRG volume loss after nerve transection (*p<0.001 vs controls)

Loss reduced by nerve repair (**p<0.01vs. amputees)

Peripheral nervous system

Dynamic living tissues with complex injury response



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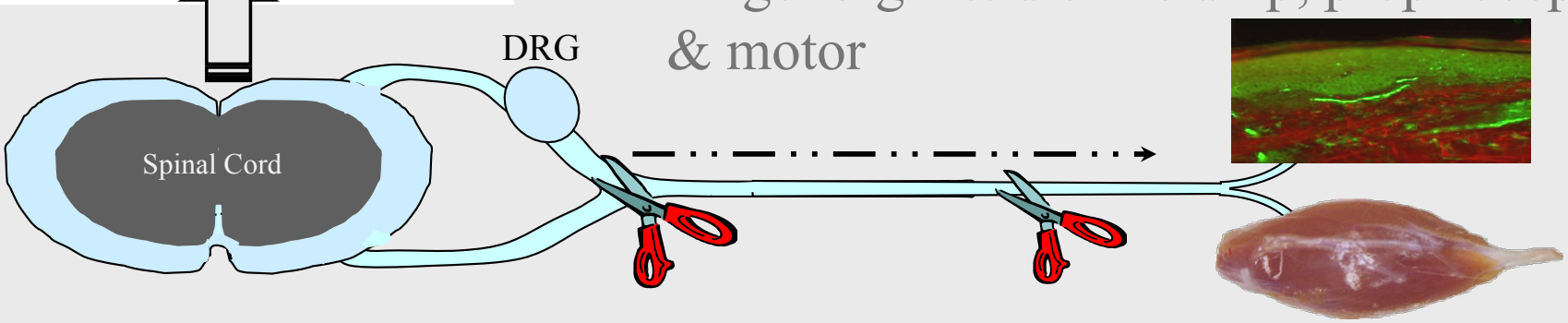
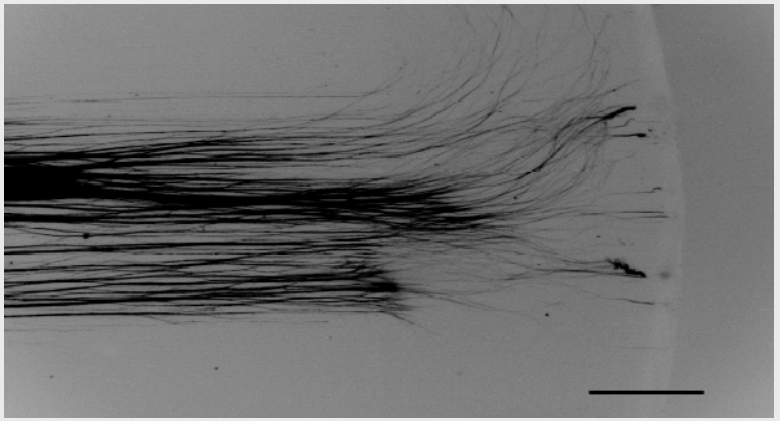


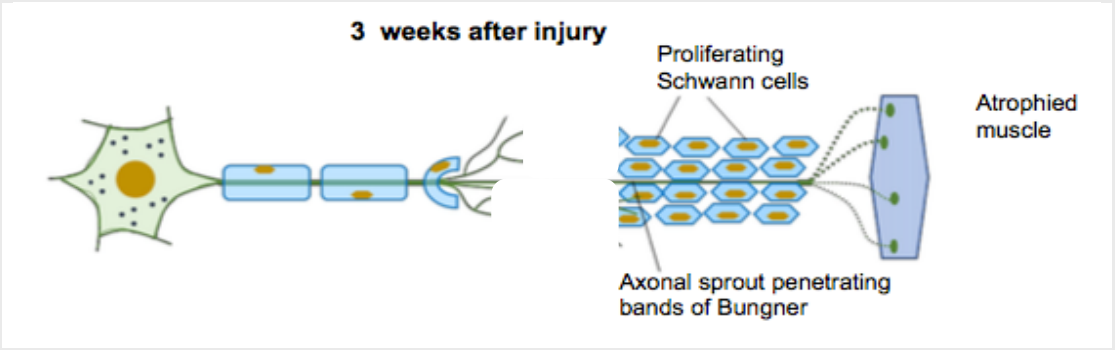
Repair Site – axons exit the proximal stump

Cellular response: inflammatory, SC, vascular

Outgrowth from proximal stump:

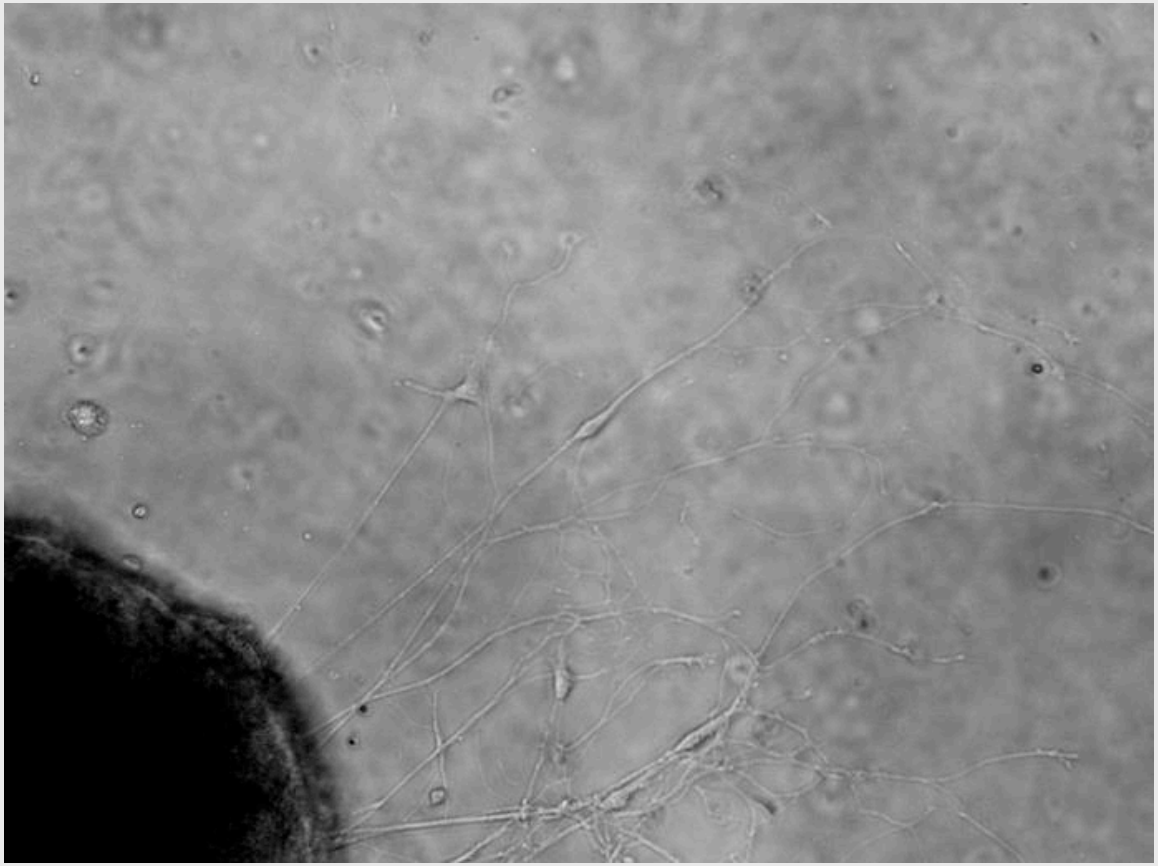
- "staggered" outgrowth over 4 weeks
- multiple processes
- competitive dieback
- neuroma





Repair Site

outgrowth from proximal stump takes ~ 3 weeks



DRG explant, 24-60 hours in vitro
NGF(20ng/ML) NAC (50µg/ML) 10% FBS, 37C on flat substrate

Repair Site

attempt to cross the repair site

Vascularisation

Schwann cell migration into repair site

Cues to direct neurite / axonal growth

- tropic vs. trophic factors
- μ / η topographic
- adhesion molecules

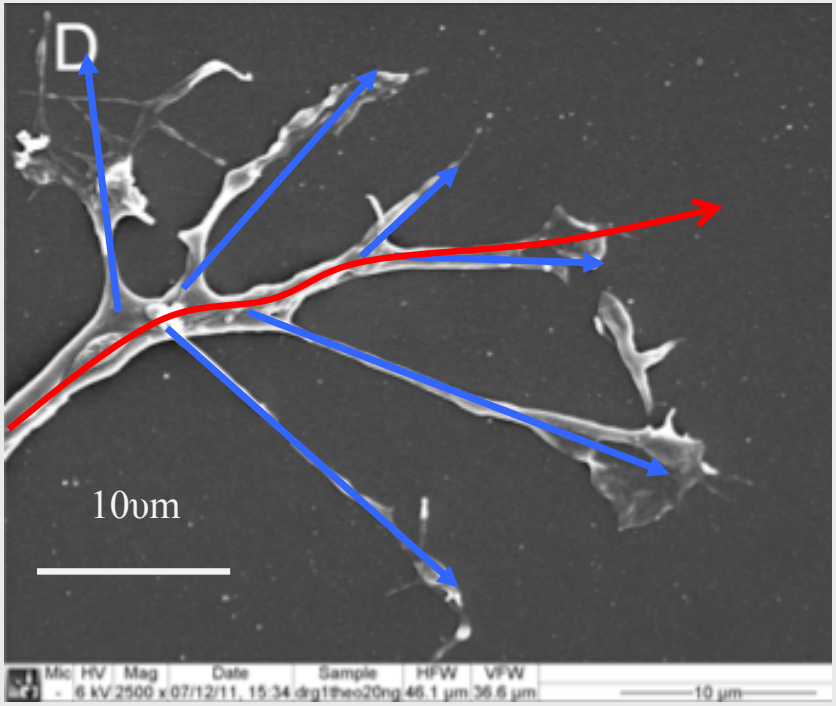
Avoid scar interposition

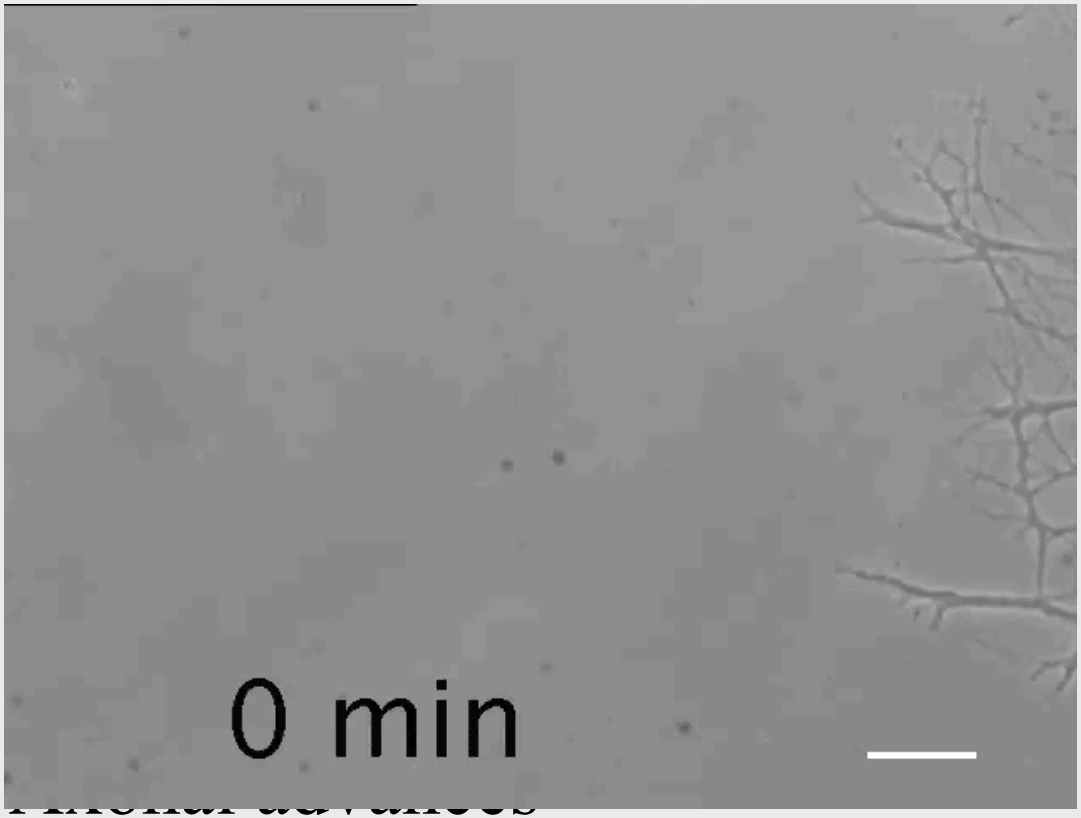
Tension impairs regeneration

Lundborg 2004

Repair Site

attempt to cross repair





~3/52 to reach distal nerve

≤50% of fibres get lost

NGF(20ng/ML) NAC (50µg/ML) 10% FBS, 37C on flat glass. Scale bar 50µm.

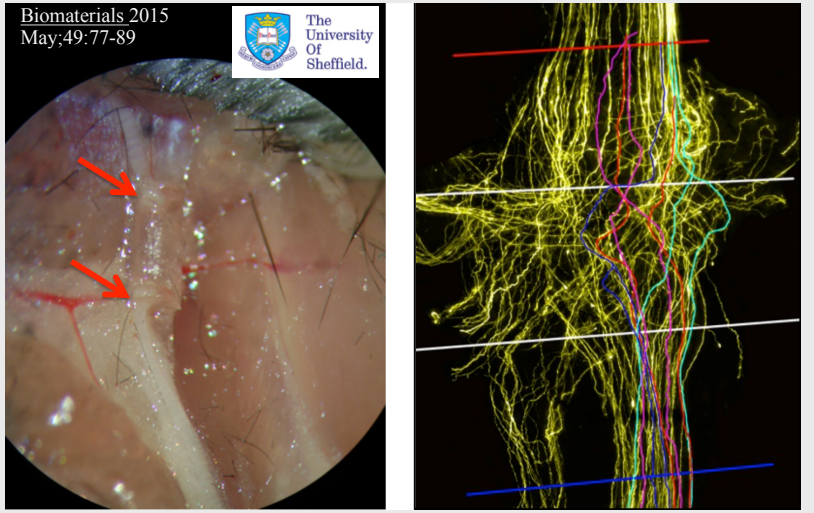
Repair Site

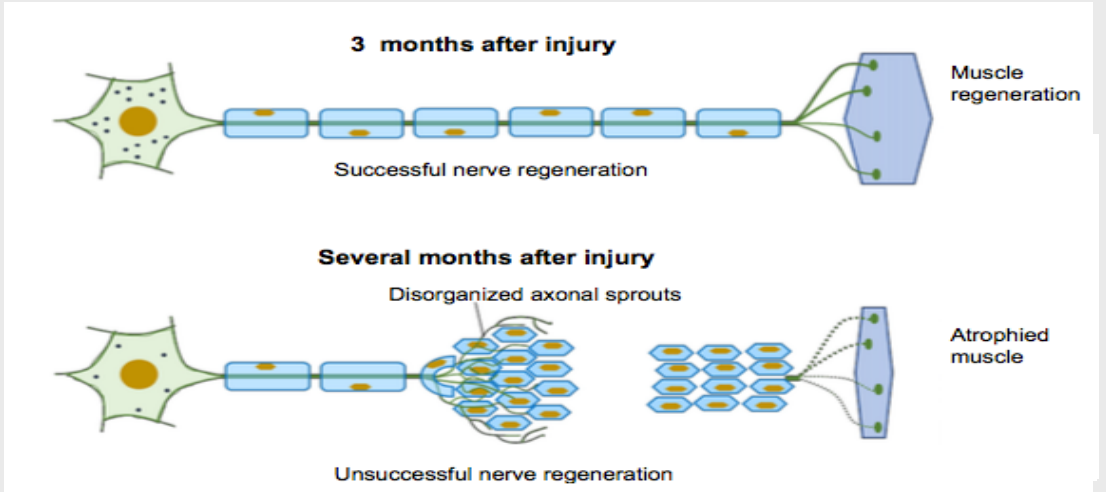
axons must exit the repair

Guidance cues: tropism, contact, others?

Entry to distal stump:

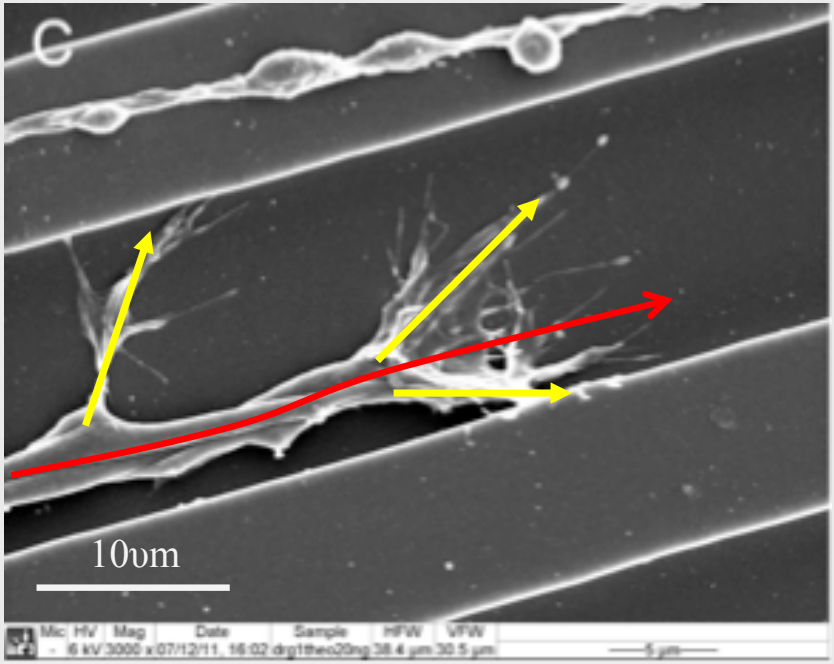
- Bands of Bungner
- axon/SC interaction
- competitive dieback
- **sensorimotor mismatch**
- **topographical specificity**
- **+/- neuroma**

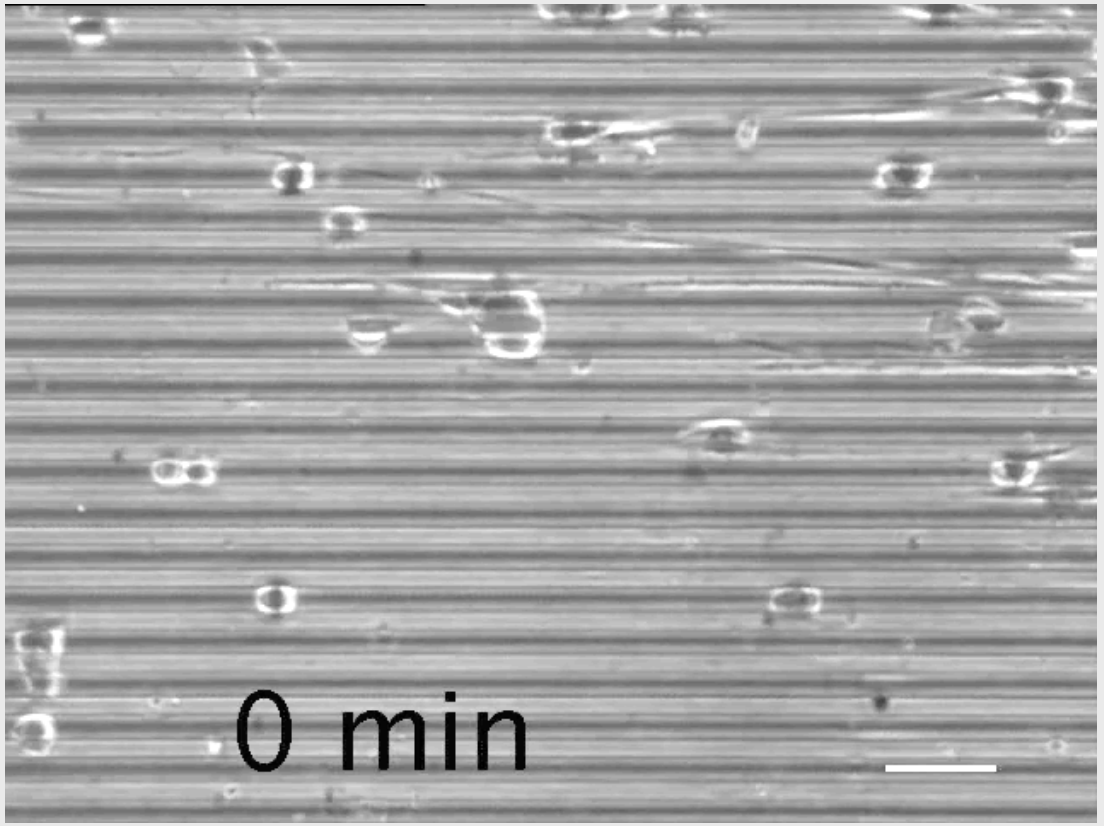




Growth down distal nerve

better with guidance / support from distal nerve





~1mm/day

6-18 months to complete regeneration

Then brain needs to reformat

10% FBS, 37C
on 12.5μm width 5μm depth microgrooved 30s plasma treated PDMS. Scale bar 50μm.

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PLOS ONE

Effect of Delayed Peripheral Nerve Repair on Nerve Regeneration, Schwann Cell Function and Target Muscle Recovery

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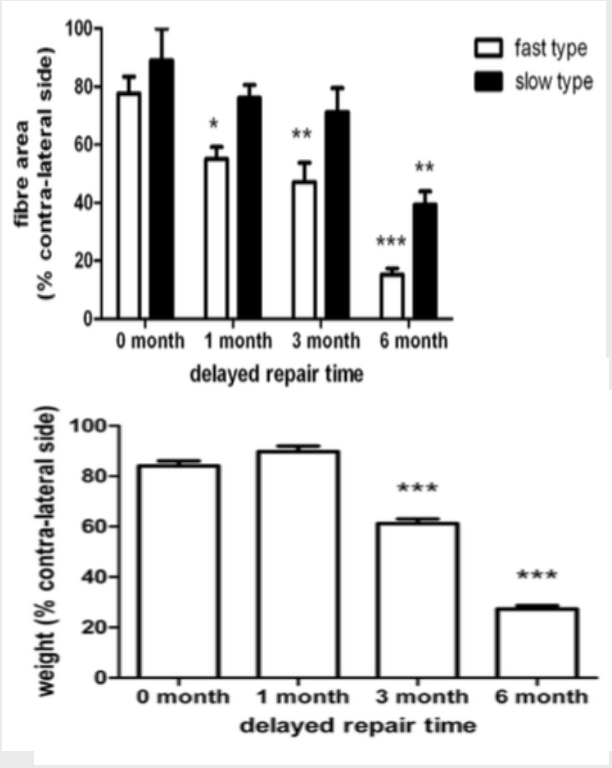
Rat sciatic nerve, repair delayed 0-6 months

Between 1&3 months:

- MN numbers fell
- Axons arrested at the repair site & lose structure
- Schwann cell death & phenotypic deterioration
- Distal stump fibrosis
- Muscle wasting, fiber atrophy, nmj loss,
- *Distal stump change critical to loss of reinnervation*



Early plexus repair improves motor outcome in ABPI

Journal of Plastic, Reconstructive & Aesthetic Surgery (2009) 62, 472–479

The influence of pre-surgical delay on functional outcome after reconstruction of brachial plexus injuries☆

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Department of Plastic and Reconstructive Surgery, St James's University Ho

Summary It has been proposed that delayed surgery after traumatic brachial plexus injury may adversely affect functional outcome.

In this study the influence of pre-surgical delay on the outcome of brachial plexus reconstruction was examined retrospectively. All patients who underwent surgery for traumatic brachial plexus injury in the Leeds Plastic and Reconstructive Surgery unit (UK), between 1987 and 2002, were identified.

Of the 110 patients identified, 27 had nerve grafting to the upper trunk to restore shoulder and biceps muscle function. Postoperative functional outcome was evaluated in this subgroup of patients. The 27 patients were divided into three groups: surgery <2 weeks ($n = 10$), 2 weeks to 2 months ($n = 10$) and >2 months ($n = 7$) following injury. The efficacy of nerve grafting was correlated to pre- and postoperative biceps strength, which was assessed using the British Medical Research Council (MRC) Motor Grading Scale. In all patients the preoperative elbow grade was M0.

The results showed that in the <2 weeks, 2 weeks–2 months and >2 months delay groups, the mean postoperative elbow MRC grades were 4.2 ± SD 1.0, 3.8 ± SD 0.8 and 1.1 ± SD 1.7, respectively. Functionally better results were obtained with early surgery. When surgery was delayed beyond 2 months there was no significant difference between mean pre- and postoperative elbow grades.

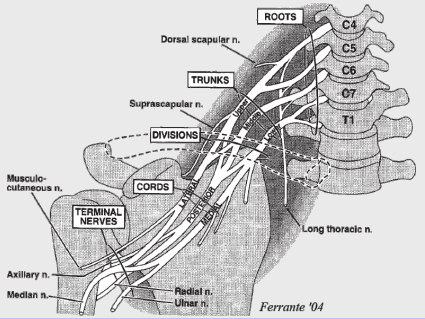
We therefore believe that early exploration and reconstruction of adult traumatic brachial plexus injuries minimises the pernicious adverse effects of delay attributable to recent findings of the neurobiological effects of axonal damage.

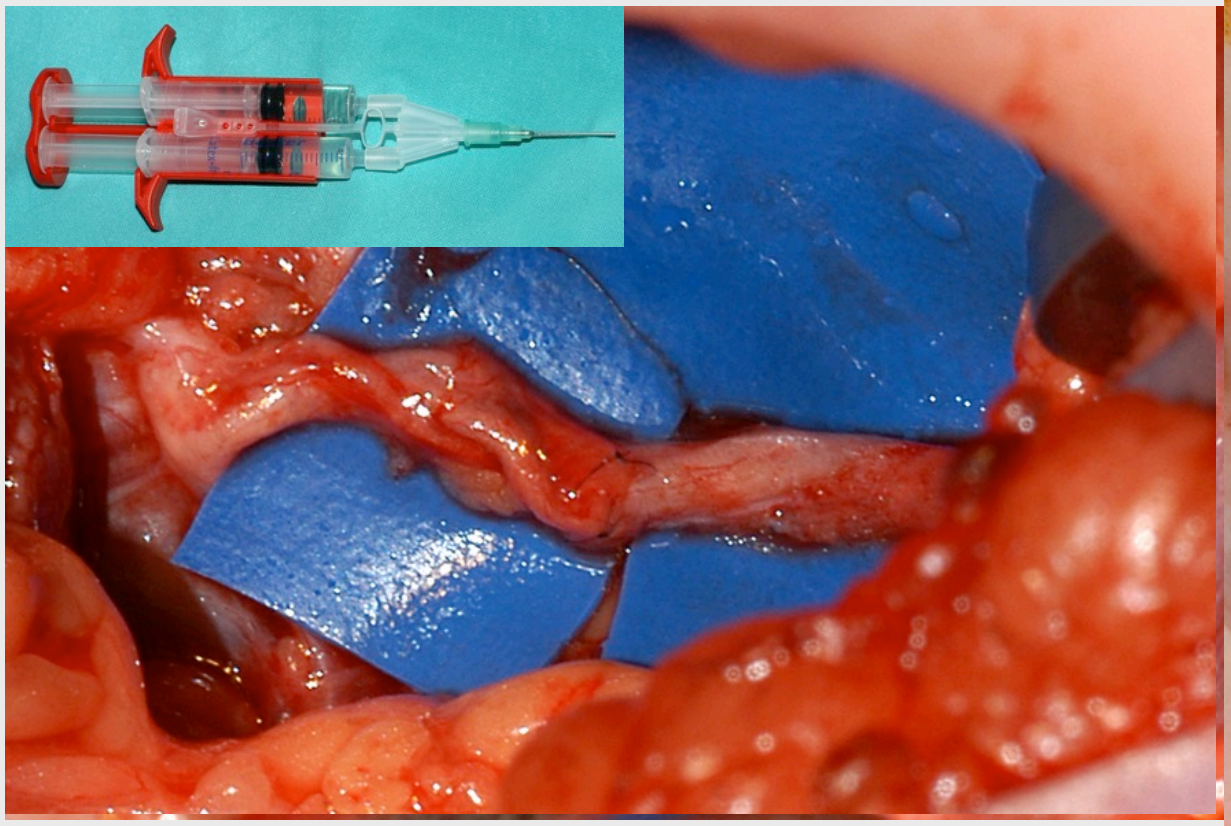
N=27 upper trunk

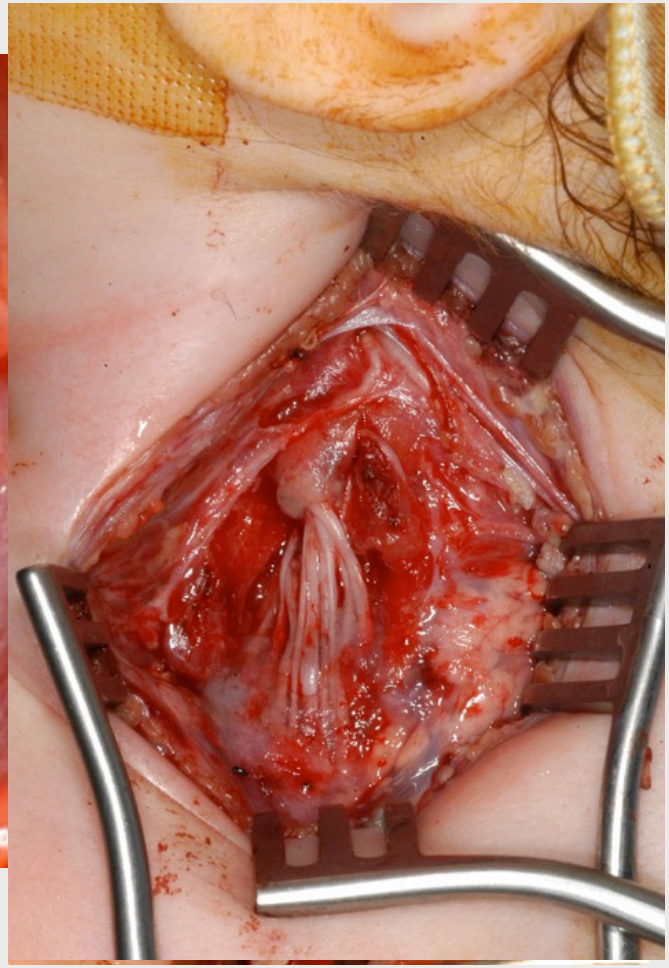
<2 vs. 2weeks-2months vs. >2 month presurgical delay

Early surgery best

Reconstruction Upper trunk graft & nerve transfer







Neurobiology Conclusions

Urgent reconstruction

Optimise the soft tissues

Promote the biology

- avoid ischaemia – tension free, don't over tighten the repair
- rotational alignment
- select from repairs, grafts & transfers

Counsel - pain, timecourse, cold, never regain normal function