I. RESPONSE OF THE NEURON TO INJURY
   A. All neurons react similarly
   B. Principles
      1. If cell body damaged, the neuron dies and is not replaced by cell division in mature brain.
      2. If axon damaged or severed, again, the neuron is often lost, but there is a good chance of regeneration, primarily in the PNS. Occasionally, there is regrowth of axons in the CNS.

II. GLOSSARY OF GLIAL CELLS
   A. Astroglia – in adult, thought to block regeneration, especially "reactive" astroglia in scars near injury site; in the immature nervous system, they support axon growth.
   B. Myelin-forming cells: oligodendroglia (oligodendrocytes) in CNS, Schwann cells in PNS.
      Dichotomy in CNS vs. PNS: oligodendrocytes are inhibitory to axon regrowth in adult CNS regeneration; Schwann cells are growth supportive - as a growth surface and by releasing growth factors.
   C. Microglia (resting) and macrophages (active) - cells of immune system. Like astroglia, not clear whether they aid in growth support as well as phagocytose; not well-understood.

III. DEGENERATION
   A. Cytological signs.
      1. Immediate
         a. Synaptic transmission off
         b. Cut ends pull apart and seal up, and swell because, within the axon, axonal transport carries molecules and organelles both anterogradely and retrogradely
         c. Degeneration of the axon terminal or synaptic ending; accumulation of neurofilaments and vesicles.
         d. Glia normally surround terminal but, after axotomy, help to pull terminal away from target cell.
      2. Days to weeks
         a. Myelin breaks up and leaves debris (hard to degrade).
         b. Axon itself undergoes Wallerian degeneration
         c. Chromatolysis - cell body swells; Nissl substance and eccentric nucleus.
   B. Severing the axon causes degenerative changes in the injured neuron and in the cells that have synaptic connections with that neuron.
      1. Visual system model
      2. Classical use of this approach – transynaptic degeneration - to trace neural circuitry.

IV. REGENERATION
   A. Neurons in the PNS can regenerate their axons. How?
      1. Schwann cell helps in regeneration of cut distal axon; the postsynaptic cell, if not injured, can provide trophic factors
      2. Axon distal to cut degenerates but Schwann tubes remain and are rebuilt.
      3. Axons sprout in many directions, some find Schwann cell tubes of the distal stump.
      4. Macrophages clean up degenerated myelin and debris.
B. Neurons in the CNS have a limited capacity to regenerate axons. Why? Growth is impeded by the negative elements in the environment and by the lack of intrinsic growth proteins. *PNS neurons cannot grow in the CNS.*

1. Extracellular growth-promoting molecules, such as laminin, have limited or different distributions in adult CNS compared to developing brain; there is a correlation between levels of proteoglycans and success of regeneration.
2. Growth factors/neurotrophins have different spatial distributions and activity in mature CNS
3. Intracellular growth-promoting molecules, e.g., GAP-43, a membrane-associated protein involved in signal transduction at the growing tips of axons, are at low levels compared to developing CNS
4. Factors on oligodendrocytes inhibit axon growth in the mature CNS
5. Glial cells, including astroglia and microglia, proliferate near a wound, and unlike immature forms, block axon growth in mature CNS; role of microglia unclear, however.

Thus, upon injury to the CNS, there is an imbalance of growth-promoting and growth-inhibiting factors, in favor of the latter. Adult CNS neurons can regrow, but the environment is inhospitable.

V. EXPERIMENTAL STRATEGIES TO PROMOTE REPAIR/RECOVERY OF FUNCTION IN CNS

A. Therapeutic strategies/principles

1. Implants: Peripheral nerve bridges or artificial tubes, to implement nerve regrowth
2. Cellular transplants
   a. Fetal tissue, or stem cells, to replace dead or injured neurons
   b. Cell lines/transfected cells that produce growth factors
   c. "Good" glia: olfactory ensheathing glia (OEG)
3. Gene transfer via retroviruses, injection of RNA, anti-sense oligonucleotides; transgenic mice
4. Direct delivery of growth factors
5. Application of "neutralizing" activity (e.g. antibodies) to combat inhibitory glia/myelin
6. Combinations of strategies

B. Recent advances in molecular mechanisms of regeneration

1. Vaccination to combat myelin
2. “Prime” cells with neurotrophins or cyclic nucleotides: neurons become insensitive to myelin proteins and regenerate
3. Identification of a gene underlying Wallerian degeneration
4. Microglia can help regeneration in the eye
5. Signals that travel from injury site back to the nucleus…how?
6. Molecules that increase, decrease during degeneration and regeneration: Information from microarrays.
7. Identification of oligodendrocyte-/myelin-derived growth inhibiting factors: MAG (myelin-associated glycoprotein), NOGO, OMgp (Oligodendrocyte myelin glycoprotein), their receptor(s) (NogoR), and co-receptors (p75).

C. Bottom line: what can work in humans? The case of Christopher Reeves: use/exercise/stimulation
References (Reviews)
Filbin, MT  2003  Myelin-associated inhibitors of axonal regeneration in the adult mammalian CNS.  Nat Rev Neurosci 4: 1-11..

Relevant reading: Chapters 2 and 55 in Principles