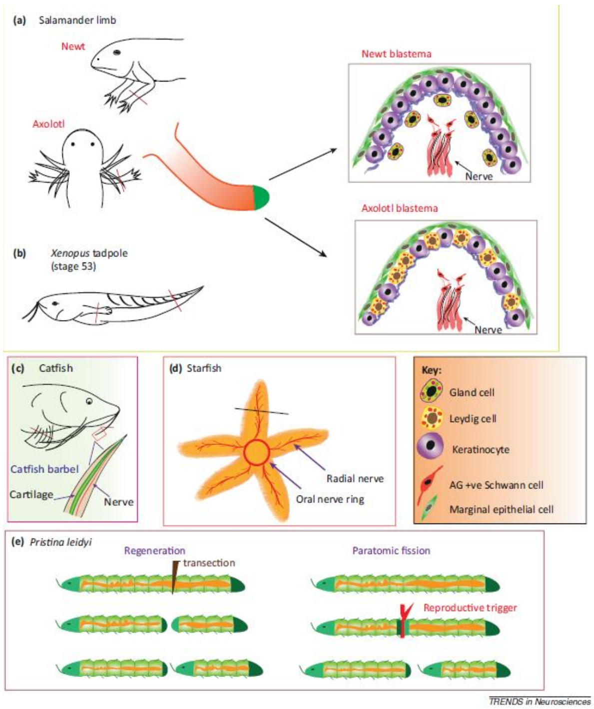
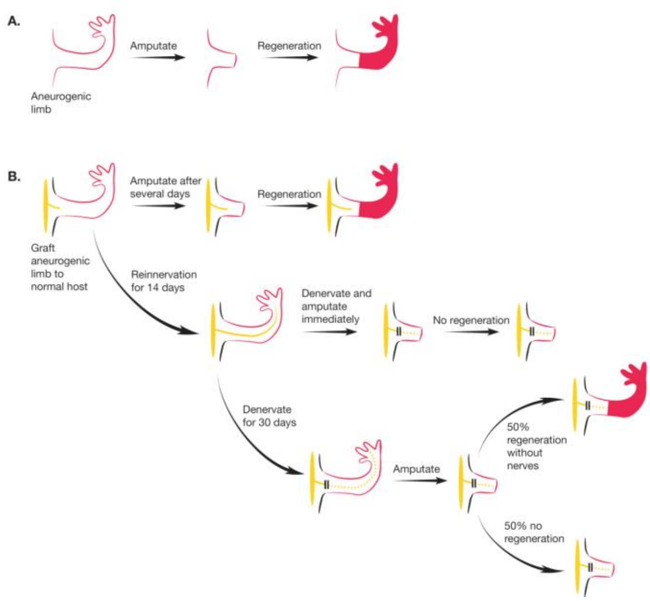
Peranan syaraf pada regenerasi

Epimorphic regeneration
Nerves and salamander limb regeneration

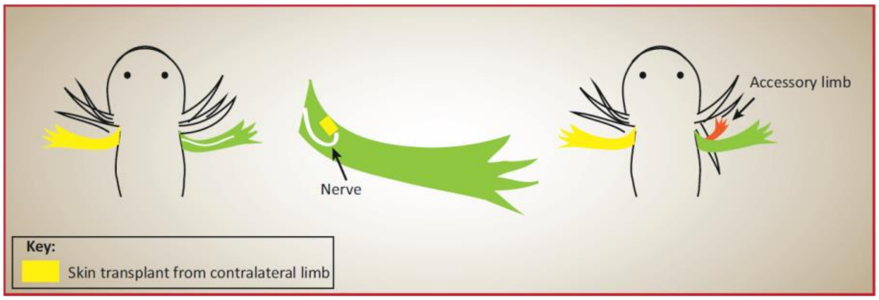
- Limb denervation at the level of the brachial plexus appears to inhibit neither WE formation by cell migration nor generation of the initial cohort of blastemal progenitors.



Examples of nerve-dependent regeneration in various phyla. (a) Regeneration of the forelimb in the newt and larval axolotl. After amputation of the limb, regeneration proceeds by formation of a blastema (green). The panel on the right shows diagrammatic illustrations of the blastema. In the newt, anterior gradient (AG) protein is expressed in Schwann cells at the end of the nerve and in gland cells underlying the wound epithelium [7]. In axolotls, Leydig cells of the wound epithelium, in addition to Schwann cells, express AG. (b) Xenopus tadpoles are capable of limb regeneration until metamorphosis at stage 53. Tail amputation results in regeneration of the spinal cord, as well as a full-length tail. (c) The catfish can regenerate its sensory barbels after injury. The barbel is supported by a cartilaginous core and nerves run along the axis of the tissue to the sensory receptors. (d) In starfish the oral nerve ring is critical for arm regeneration. Each arm of the starfish is innervated by radial nerves, which radiate from the oral nerve ring. (e) Regeneration of the worm Pristina leidyi occurs after transection, as well as after paratomic fission [58]. Favourable environmental conditions trigger fission at the middle of the body. A fission zone containing a presumptive head and tail forms before fission, and scission of the body occurs through the mid-plane (red). After transection of the worm, the anterior segment regenerates a tail, whereas the posterior fragment regenerates a new head.

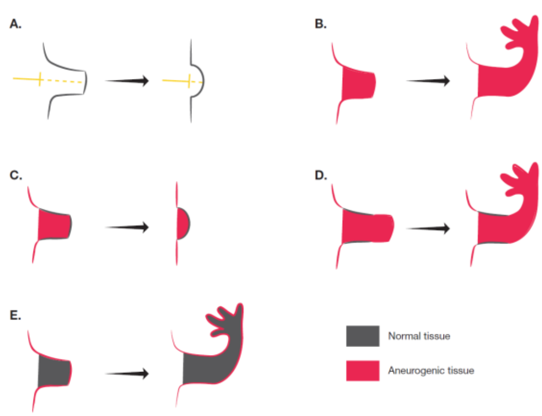


Experiments on the regeneration of aneurogenic limbs. *(A)* After amputation, an aneurogenic limb regenerates completely. *(B)* After grafting an aneurogenic limb onto a normal host, the grafted limb regenerates if amputated several days after grafting. If the grafted limb is allowed to become innervated for 14 days and is amputated immediately after denervation, it does not regenerate, whereas if it remains denervated for 30 days, it may recover the ability to regenerate. (Based on Thornton and Thornton's [1970] experiments.)

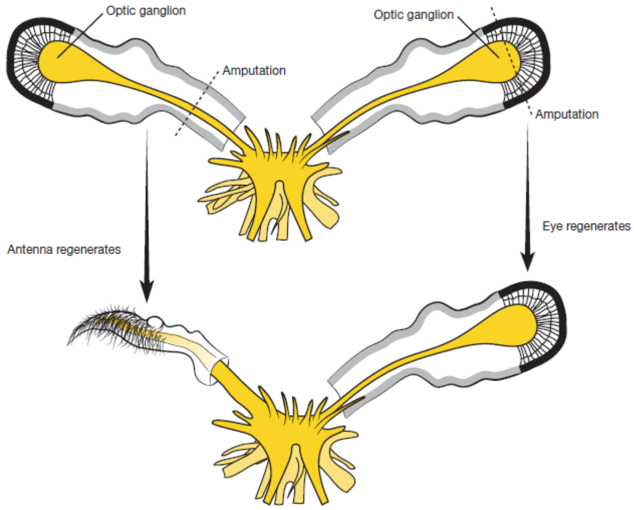


TRENDS in Neurosciences

Formation of ectopic limbs in axolotls. If a large nerve branch is transected and the cut end is deflected under a skin wound in the regenerative territory, this can induce formation of a limb or other appendage, depending on the location of the wound [72]. Deflection of the nerve under normal skin does not induce a limb, but if the nerve is positioned at the margin of the wound, the regenerating axons interact with the WE formed at that location. The preferred method for production of accessory limbs in axolotls involves transplantation of a skin patch (yellow) from the contralateral limb to create a local axial disparity [61,73].



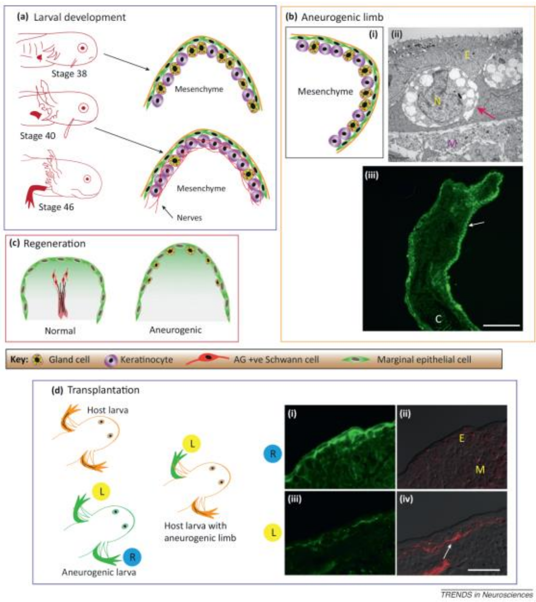
Exchange experiments between normal and aneurogenic limbs. *(A)* If a normal limb is denervated and then amputated, it regresses. *(B)* An amputated aneurogenic limb regenerates. *(C)* If an amputated aneurogenic limb is covered with normal skin and then amputated, the wound is covered by normal epidermis, and regeneration fails to occur. *(D)* If the proximal part of an aneurogenic limb stump is covered by normal skin, but a thin cuff of aneurogenic skin remains at the end of the stump, the wound epidermis is derived from aneurogenic epidermis, and limb regeneration occurs. *(E)* If the stump of an amputated aneurogenic limb is filled with mesoderm from a normal limb, then limb regeneration occurs. (Based on Steen and Thornton's [1963] experiments.)



Regeneration of an antenna instead of an eye in the shrimp Palinurus. If the eyestalk is amputated distal to the optic ganglion (right), an eye regenerates. If the level of amputation is proximal to the optic ganglion (left), an antenna regenerates. (After Herbst [1896].)

- aneurogenic limb tissues themselves produce the trophic substance➔ after amputation there is sufficient trophic substance to support regeneration.
- The criteria for a successful trophic substance candidate :
  - presence in the blastema,
  - reduction after denervation,
  - possession of a mitogenic effect for blastemal cells,
  - ability to substitute for nerves in supporting regeneration, and
  - ability to block regeneration after its removal (Brockes, 1984).
- Important trophic substance :
  - fibroblast growth factor-2,
  - glial growth factor,
  - substance P, and
  - transferrin

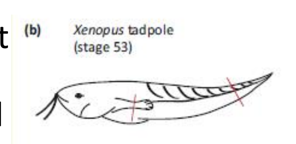
The aneurogenic limb

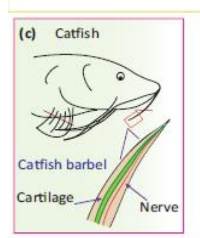


Limb development and regeneration in the presence and absence of nerves in the spotted salamander Ambystoma maculatum. (a) During normal development of the limb, nerves enter the limb bud after stage 38, and by stage 46 the number of unicellular glands in the epidermis that express anterior gradient (AG) has markedly decreased [34]. (b) During aneurogenic development, the number of glands (ii, red arrow) remains high, as determined by electron microscopy(i, ii), and overall AG expression in the epidermis is also high, as detected by staining with antibodies to AG (iii, green fluorescence, arrow) [34]. (c) The consequence of this difference for limb regeneration is that the normal blastema has an early wound epithelium (WE) that lacks AG expression whereas the aneurogenic WE is positive for gland cells. (d) After transplantation of a left aneurogenic limb in place of a normal limb, the control right limb from the donor aneurogenic larva maintains high AG expression in the epidermis (i, green fluorescence) in the absence of nerves, as detected by staining with antibodies to acetylated tubulin (ii, red fluorescence), whereas AG downregulation its observed in its transplanted counterpart (iii) after innervation (iv) [34]. Scale bars: bii, 5 mm; biii, 100 mm; di–iv, 50 mm. Abbreviations: C, cartilage; E, epidermis; M, mesenchyme; N, nucleus.

Anuran and fish regeneration

- Limb regeneration in Xenopus during the early stages of larval development is independent of nerves, and only shows a denervation effect at the end of larval life
- Spinal cord ablation does not affect the early steps of regeneration ➔ regeneration of the spinal cord may be a step that is critical for subsequent regeneration





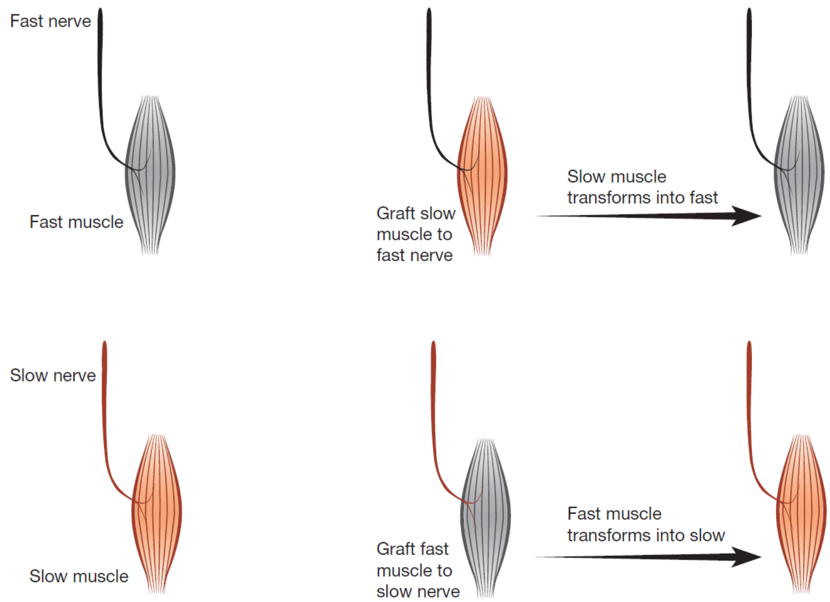
TISSUE REGENERATION

- In the absence of motor innervation, intact muscles lose their ability to contract voluntarily and undergo progressive atrophy over weeks and months.
- After damage, skeletal muscle fibers regenerate to nearly normal structure and function if they are adequately vascularized and innervated. In the absence of a nerve supply, the regeneration of skeletal muscle fibers is severely compromised

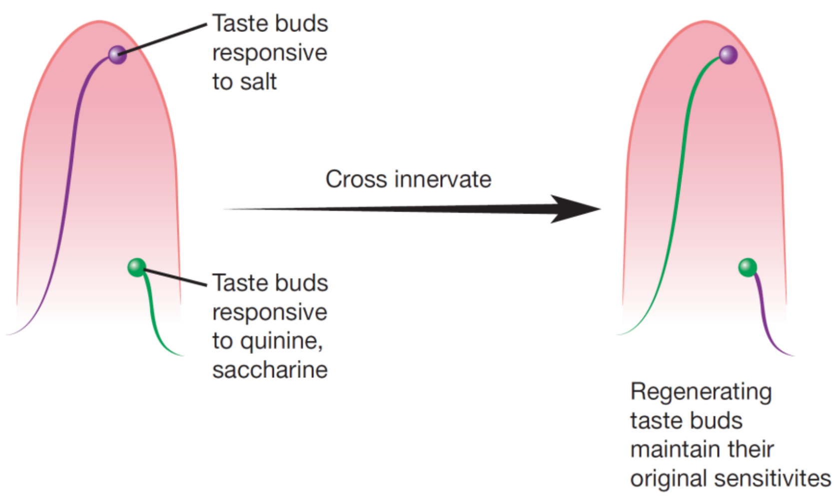
- In contrast to epimorphic processes,
  - denervation has little observable effect on the initial stages of muscle regeneration.
  - The degeneration of damaged muscle fibers, in both the intrinsic and phagocyte-mediated phases → independently of innervation.
  - The activation of satellite cells, their proliferation, and their fusion into multinucleated myotubes do not require the mediation of nerves.

- The ability of electric stimulation to maintain the mass of denervated muscle
- the main neurotrophic effect on regenerating skeletal muscles is the transmission of contractile impulses, rather than an effect mediated by chemical growth or maintenance factors.

- A number of other regenerating tissues are influenced by nerves.
- For some, the neural effects are indirect : wound healing → is slower and less complete in denervated areas for others, a direct influence of the nerve on the regenerating end organ exists.



If a fast muscle is cross transplanted into the site of a slow muscle and is innervated by the slow nerve, it regenerates into a slow muscle and vice versa. (Based on Gutmann and Carlson [1975].)

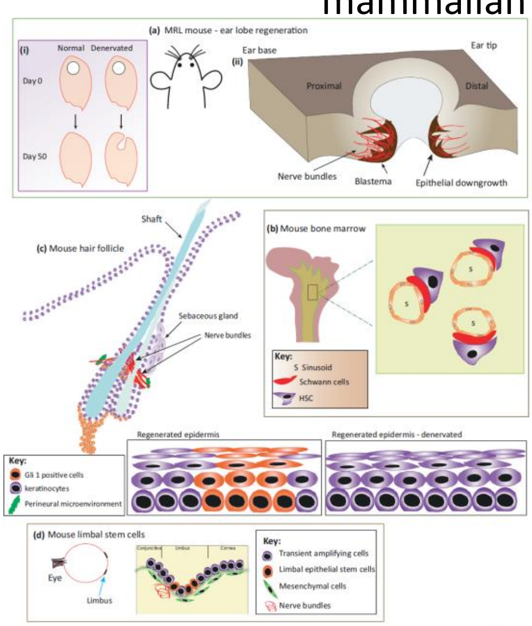


(B) In the rat tongue, if the nerves supplying anterior and posterior taste buds are switched, the original sensitivities of the taste buds are retained. (Based on Oakley [1967].)

Comparison of Neural Requirements and Influences among Three Systems of Regeneration

Amphibian limb	Skeletal muscle	Mammalian taste buds
Nerves needed for the initiation of regeneration. (insect limbs possibly an exception)	Nerves not needed for the initiation of regeneration	Nerves needed for initiation of regeneration.
Nerves not required for later regeneration, but growth is retarded.	Nerves required for final functional differentiation	Nerves required throughout the regenerative process.
Quantity and not type of nerve is important.	Type of nerve is critical (motor nerve needed)	Type of nerve is important (but some sensory can substitute for gustatory).
Neural effect mediated through some type(s) of trophic factor. Electric impulses ineffective.	Neural effect mediated by electric impulses.	Nerve effect mediated through putative trophic factor. Electric impulses ineffective.
Neural input can be replaced by defined molecules (e.g., transferrin).	Neural input can be replaced by defined electric impulses.	No substitutes found for direct innervation.

Nerves, mammalian regeneration, and mammalian niches



Innervation and mammalian regeneration. (a) Regeneration of the pinna in the Murphy Roths Large (MRL) mouse. (i) Injury induced by an ear punch is completely healed by day 50 in the presence of normal innervation [37]. Transection of the nerves to the ear lobe prior to ear punch results in abnormal wound healing and necrosis of the tissue [38]. (ii) Diagrammatic representation of a regenerating ear-punch hole. Quantitative image analysis has shown that the density of innervation is higher in the proximal ear base of the pinna compared to the distal tip [37]. Epithelial downgrowth into the regenerating tissue is an interesting feature of the blastema. (b) Association of haematopoetic stem cells (HSCs) and Schwann cells in bone marrow. The endothelial cells and non-myelinating Schwann cells lie in close proximity along the sinusoid. The majority of the HSCs are in contact with Schwann cells. Denervation of the postganglionic fibres results in a reduction in HSCs [41]. (c) Innervation of the telogen hair follicle. The upper bulge of the hair follicle is extensively innervated by cutaneous fibres. This domain of the perineural microenvironment is populated by Gli1-positive multipotent stem cells, which receive Shh from the nerves. During regeneration, these cells behave as epidermal stem cells. Denervation of the cutaneous nerves results in loss of Gli1 epidermal stem cells in the regenerated epidermis because of a lack of nerve-induced signalling [42]. (d) The cornea is densely innervated and limbal corpuscular nerve endings are located immediately beneath the epithelium. Innervation is essential for maintenance of corneal limbal stem cells in mice [43].