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This Week's Citation Classic

Singer M. The influence of the nerve in regeneration of the amphibian extremity. *Quart. Rev. Biol.* **27**:169-200, 1952.
[Harvard Medical School, Boston, MA]

This paper is a review of works on the relation of the nerve supply to regenerative capacity. It includes the oft-cited stages in regrowth of an amputated limb. It also presents theories on the nature of the nerve action, the relative importance of different nerve components, the importance of quantity of axons for initiating the regeneration process, the problems of induction of regeneration in nonregenerating vertebrates, and the nature of the trophic neuronal quality. [The SCI® indicates that this paper has been cited in over 260 publications since 1961.]

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"The ability to regenerate external body parts is widespread among animals, particularly in invertebrates and lower vertebrates, although higher ones including man can regenerate liver, bladder, and some other internal parts. Illingworth[1] has recently observed that children can regenerate amputated fingertips, leading one to support the prediction made 200 years ago by the eminent zoologist, Spallanzani, that innate within higher forms is the power to regrow external body parts requiring only useful circumstances (manipulations) to express the capacity.

"The most popular animals for the study of replacement of limbs, tails, and other parts are amphibians, especially the newt and salamander. These studies have taken various forms: cytological and histological analyses, and experimental manipulations of the various tissues at the wound surface. In recent years, an interesting and productive group in H.J. Anton's laboratory[2,3] at the University of Cologne, Federal Republic of Germany, have subjected the cytological analyses to quantitative computerized methods which detect the earliest cell changes at the wound surface preparatory to formation of the new part. The work on the newt also influenced the direction of the work by Jacqueline Geraudie of the University of Paris, who demonstrated a similar dependence of fish fin regeneration on the nerve.[4]

"In regeneration of the limb, what apparently occurs is first a wound-healing process with the liberation of cells which appear embryonic-like. These collect to form a bud of rapidly dividing cells which later differentiate into the various tissues of the limb. The bud is invaded by numerous new nerve fibers which eventually make connections to give a completely functional (sensitive and motile) limb.

"The study of two tissues (nerve, epithelium) has been especially intense for they play a leading part in the regrowth. The epithelium (epidermis) grows over the wound surface from the old skin bordering the amputation wound. The laboratory of the late C.S. Thornton,[5] University of Michigan, defined the epithelial role without which regeneration cannot occur. Indeed, regeneration of the fingertips in children does not ensue if the wound is surgically closed showing that bare epithelium in contact with the wound is a precondition of the regrowth. As for the nerve, it is known from many works that denervated amputation stumps in the newt will not regrow. Partially denervated ones will, but the speed of regeneration depends on the number of fibers available at the wound surface, also as shown well in the fish fin.[4] It is widely held now that the nerve fibers emit a trophic substance, the nature of which is being pursued in a number of laboratories, needed to stimulate and maintain the growth. At the moment, it appears to be a protein or peptide of low molecular weight.

"A major regeneration problem is the limited growth capacity of central nervous structures in higher vertebrates including man. Studies show that individual nerve fibers of the central, as in the peripheral, nervous systems are capable of growth but for some reason are blocked or suppressed in their growth. This is not the case in the lower animals. The newt and fish can regenerate the spinal cord and parts of the brain and recover complete function. They can do it because certain cells can recall their embryonic history and reproduce the part. It is a major challenge to find out how they manage to do this for the information may someday be applied to reconstructing the damaged nervous system of man. Many subsequent works, a sampling of which are cited here, have been built upon this classic review paper.[6-8]

"The reasons why this work has been highly cited are: 1) it is one of the first to give a historical perspective on the trophic nerve quality; 2) it provides a theory on the quantitative and qualitative action of the nervous action on regeneration; and 3) it opened the field to numerous subsequent studies testing these various hypotheses."

1. **Illingworth C M.** Trapped fingers and amputated finger tips in children. *Clin. Phys. Physiol. Meas.* **1**:87-9, 1974.
2. **Anton H J & Eben W.** Cell activation and nuclear volume. *Microsc. Acta* (Suppl. 3):205-11, 1979.
3. **Anton H J & Bouraael M.** Volumen und Proteinsynthese der Kerne des Stratum Basale in der Stumpfepidermis während des Wundverschlusses nach Amputation der Vorderextremität bei *Triturus vulgaris*. *Develop. Growth Differ.* **24**:173-82, 1982.
4. **Geraudie J & Singer M.** Relation between nerve fiber number and pectoral fin regeneration in the teleost. *J. Exp. Zool.* **199**:1-8, 1977.
5. **Thornton C S.** Amphibian limb regeneration. *Advan. Morphogenesis* **7**:205-49, 1968.
6. **Singer M.** The trophic quality of the neuron: some theoretical considerations. *Prog. Brain Res.* **13**:228-32, 1964.
7. ------------. Neurotrophic control of limb regeneration in the newt. *Ann. NY Acad. Sci.* **228**:308-22, 1974. (Cited 95 times.)
8. **Kriegler J S, Krishman N & Singer M.** Trophic interactions of neurons and glia. (Waxman S G & Ritchie J M, eds.) *Demyelinating diseases: basic and clinical electrophysiology.* New York: Raven Press, 1981. p. 479-504.