

This Week's Citation Classic

La Vail J H & La Vail M M. Retrograde axonal transport in the central nervous system. *Science* 176:1416-17, 1972. [Dept. Neuropathology, Harvard Medical School, Boston, MA]

When the enzyme horseradish peroxidase is injected into the optic tectum of young chicks, the peroxidase is taken up and transported in a retrograde direction by the axons of retinal ganglion cells to the cell bodies in the retina. Likewise, when the enzyme is injected into the vitreal space of the eye, it is taken up and transported centripetally along efferent axons and is found histochemically in cell bodies within the isthmo-optic nucleus. This retrograde movement of protein from axon terminal to cell body suggests a possible mechanism by which neurons respond to their target areas. [The *SCI*[®] indicates that this paper has been cited in over 495 publications since 1972.]

Jennifer H. LaVail
Department of Anatomy
School of Medicine
University of California
San Francisco, CA 94143

May 11, 1983

"In 1971, Matthew LaVail and I were postdoctoral fellows in the Laboratory of Neuropathology at Harvard Medical School where we worked under the sponsorship of Richard Sidman. Sidman had assigned me a lecture on axonal transport during development, and in the course of preparing the lecture, I noticed a gap in the literature. Although there was growing evidence of the importance of transport of macromolecules from neuron cell body to axon, there was no information about what happened to macromolecules once they reached the axon terminal. Obviously, homeostasis in the cell required that material move back as well. In fact, that suggestion had been made in 1948 by Weiss and Hiscoe.¹ Other evidence, for example, that viruses might gain access to the central nervous system (CNS) by incorporation by the axon and transport to the cell body, had appeared in 1941 when Bodian and Howe described the dissemination of poliomyelitis virus in the nervous system.²

"One morning after I had given the lecture, Sidman left a copy of a brief report on my desk on the uptake and transport of horseradish peroxidase by peripheral nerve to motor neurons in the spinal

cord by Kristensson, Olsson, and Sjöstrand.³ Matt and I discussed the importance of the paper and decided it should be repeated in a site where no direct impalement of the axon was possible, and in the CNS where, we erroneously reasoned, the phenomenon of retrograde axonal transport might not exist, thus possibly explaining the absence of axonal regeneration in the CNS.

"From our graduate studies we were familiar with the structure of the retina and chick brain. Therefore, we chose to inject horseradish peroxidase intravitreally in the chick and look for evidence of its retrograde transport and accumulation in neuron cell bodies in the midbrain. In another series of experiments we injected the enzyme into the tectum and looked for its accumulation in retinal ganglion cell bodies. In both experiments, after retrograde transport the horseradish peroxidase was obvious in the tissue sections using a light microscope.

"The publication has been highly cited probably for two reasons. First, it demonstrated that the phenomenon of retrograde axonal transport occurred in the CNS in the absence of direct mechanical injury to the axons. Second, the fact that axon terminals in an injection site would pick up peroxidase and transport it to the cell somas meant that neurobiologists could determine whether or not a neuron cell body projected an axon to a particular site by simple light microscopic histochemistry. Such an experiment usually took only a day or two to complete as compared to the weeks or months necessary to obtain the same kind of information using other techniques. Previously we were handicapped by the fact that origins of long axonal projections could be determined only if the cell bodies died after axon transection, and often the neuron cell body would not respond in such a dramatic way. Moreover, visual detection of cell loss with the traditional methods often required that large populations of neurons die in response to axonal transection, whereas the retrograde transport method made use of a physiological property of the cell and individual neurons that transported a marker could be detected. Since then, advances in chromagens for horseradish peroxidase and additional probes have become available,^{4,5} and we now have further information about the retrograde transport of endogenous macromolecules."⁶

1. Weiss P & Hiscoe H B. Experiments of the mechanism of nerve growth. *J. Exp. Zool.* 107:315-95. 1948.
2. Bodian D & Howe H A. The rate of progression of poliomyelitis virus in nerves. *Bull. Johns Hopkins Hosp.* 69:79-85. 1941.
3. Kristensson K, Olsson Y & Sjöstrand J. Axonal uptake and retrograde transport of exogenous proteins in the hypoglossal nerve. *Brain Res.* 32:399-406, 1971.
4. Mesulam M-M & Rosene D L. Sensitivity in horseradish peroxidase neurohistochemistry: a comparative and quantitative study of nine methods. *J. Histochem. Cytochem.* 27:763-73, 1979.
5. Kuypen H G J M, Bentivoglio M, Catsman-Berrevoets C E & Bharos A T. Double retrograde neuronal labeling through divergent axon collaterals, using two fluorescent tracers with the same excitation wavelength which label different features of the cell. *Exp. Brain Res.* 40:383-92, 1980.
6. Graisteln B & Forman D S. Intracellular transport in neurons. *Physiol. Rev.* 60:1167-283. 1980.