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# This Week's Citation Classic

**Russell D & Snyder S H.** Amine synthesis in rapidly growing tissues: ornithine decarboxylase activity in regenerating rat liver, chick embryo, and various tumors. *Proc. Nat. Acad. Sci. US* 60:1420-7, 1968.
[Depts. Pharmacol. and Exp. Therapeutics, and Psychiat. and Behavioral Sci., Johns Hopkins Univ. Sch. Med., Baltimore, MD]

A decarboxylase, specific for ornithine decarboxylation, was shown to be rapidly and dramatically elevated in regenerating rat liver and in developing chick embryos. Ornithine decarboxylase activity was elevated threefold within one hour and 25-fold within 16 hours in rat liver after partial hepatectomy. In chick embryo, activity correlated with embryonic growth rate. It was suggested that ornithine decarboxylase was involved in the initiation of the growth process. This report implicated ornithine decarboxylase and polyamine biosynthesis as important parameters of mammalian cell growth regulation. [The *SCI*® indicates that this paper has been cited in over 630 publications since 1968.]

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"In 1967, I finished my PhD degree under the tutelage of Donald S. Farner, a renowned avian physiologist, and embarked on a postdoctoral fellowship with Solomon H. Snyder at Johns Hopkins University School of Medicine. Evidence was accumulating that polyamines, organic cations implicated in the regulation of protein and RNA synthesis in bacteria and other microorganisms, also might be of importance in similar physiological regulation processes in mammals. The stigma to the study of these compounds in higher animals can be attributed, in retrospect, to the common names assigned to these important nitrogen-rich, ubiquitously occurring, short-chain hydrocarbons. Spermine, a polyamine containing four amine groups, was described first in human semen by van Leeuwenhoek,[1] the inventor of the microscope. Spermidine, a triamine-containing polyamine, was found later to be present also in high concentrations in seminal fluid. Putrescine, the diamine precursor of spermidine and spermine, was isolated by Brieger in 1887 from the cholera-producing bacterium, *Vibrio cholerae*.[2] The possibility that these misnamed compounds might be important in mammalian metabolism was suggested by Dykstra and Herbst[3] who demonstrated in regenerating rat liver the rapid and extensive uptake of [$^3$H]putrescine and its conversion to spermidine in parallel with ribosomal RNA synthesis. These data coupled with the ubiquitous presence of putrescine, spermidine, and spermine in plant and animal tissues led us to determine whether ornithine decarboxylase, the enzyme which catalyzes putrescine formation, might be important in the initiation of rapid growth processes. We chose to measure ornithine decarboxylase activity as a function of time after partial hepatectomy in the rat, after fertilization in chick embryos, and in rat hepatomas and sarcomas. In regenerating rat liver, the activity of ornithine decarboxylase was threefold of control within one hour and was 25-fold elevated within 16 hours. The peak activity in chick embryos occurred at five days of age, the time of limb-bud formation and the most rapid growth rate. The very early and striking increase in ornithine decarboxylase activity in regenerating rat liver and in chick embryo, which preceded increased nucleic acid synthesis, suggested a physiological function for the enzyme in the initiation of the growth process.

"At this time, ornithine decarboxylase is an established biochemical marker of growth initiation and has been shown to increase in a dose-dependent manner in target tissues after exposure to trophic hormones, growth factors, and steroid hormones. Its extent of increase (up to 1,000-fold) and rapid half-life have indicated further its unique position as an internal marker of cell surface receptor-mediated activity.

"The large number of citations may be due to: 1) the establishment of elevated ornithine decarboxylase activity as an early pronounced event in a variety of rapidly growing animal tissues; 2) the presence in the paper of a useful, simple method for the measurement of ornithine decarboxylase activity in avian and mammalian tissues; 3) the demonstration in regenerating rat liver that the enzyme was specific for ornithine as a substrate; and 4) widespread interest generated by the paper for the measurement of ornithine decarboxylase as a biochemical marker of hormone action.

"A recent monograph of the field was published in 1978[4] and sketches from my point of view some important physiological aspects of polyamines and of polyamine biosynthesis as biochemical markers of normal and malignant growth."

1. **van Leeuwenhoek A.** Observationes D. Anthonii Lewenhoeck de natis e semine genitali animalculus. *Phil. Trans. Roy. Soc. London* 12:1040-3, 1678.
2. **Cohen S S.** *Introduction to the polyamines.* Englewood Cliffs, NJ: Prentice-Hall, 1971. p. 4.
3. **Dykstra W G, Jr. & Herbst E J.** Spermidine in regenerating liver: relation to rapid synthesis of ribonucleic acid. *Science* 149:428-9, 1965.
4. **Russell D H & Durie B G M.** *Polyamines as biochemical markers of normal and malignant growth.* New York: Raven Press, 1978. 178 p.