

This Week's Citation Classic®

Winick M & Noble A. Quantitative changes in DNA, RNA, and protein during prenatal and postnatal growth in the rat. *Develop. Biol.* 12:451-66, 1965.

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By using total DNA content to reflect cell number, protein/DNA ratio to reflect average cell size, and RNA/DNA ratio to reflect the RNA content per cell, cellular growth of various organs of the rat from before birth to adulthood was measured. Growth can be divided chronologically into three distinct periods: increase in cell number (hyperplasia), increase in cell number and size (hyperplasia and hypertrophy), and increase in cell size alone (hypertrophy). The timing of each phase differed with each organ. [The *SCI*® indicates that this paper has been cited in over 455 publications, making it the most-cited paper for this journal.]

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There is a certain excitement in developing a hypothesis that can perhaps be exceeded only by proving it. The hypothesis of the 1965 paper discussed in this *Citation Classic* commentary was later tested in a 1966 paper written by Adele Noble and myself (and chosen as a *Citation Classic*® in 1979). Thus, the two papers together demonstrate the movement from an idea to a scientifically tested reality. These papers launched my scientific career and provided the underpinning for my subsequent studies in children. The honors I received, such as the Mead Johnson Award in Pediatric Research (1970), the Osborne Mendel Award in Nutrition Research (1976), and the Agnes Higgins Award for research on nutrition and pregnancy (1983), are all for work that could not have been carried out without these initial studies.

In this paper, we confirmed and extended experiments of M. Enesco and C.P. Leblond in which they used DNA content of an organ to represent total cell number and the weight to DNA ratio to represent average cell size. They had concluded that normal postnatal growth of certain organs could be divided into at least two phases: early increase in DNA content with no change in the weight to DNA ratio (pure hyperplasia) and later increase in the weight to DNA ratio with no change in total DNA content (pure

hypertrophy).² We were able to confirm their findings, extend them to prenatal growth, and include organs not previously studied. In addition, by more frequent measurements we were able to define a third period in which DNA content was still increasing and the weight to DNA ratio was also increasing (combined hyperplasia and hypertrophy). We suggested that normal organ growth involved all three phases merging into each other and that the timing for these events differed in different organs. Thus, the findings of Enesco and Leblond were carried a small step forward.

However, I wondered whether these three phases of growth could explain why some children could be permanently stunted following an illness or a growth-retarding stimulus, such as malnutrition, whereas others were able to recover. Review of the literature suggested that the earlier the growth failure, the more apt it was to be permanent. A hypothesis was put forth that suggested that if growth retardation occurred during the hyperplastic phase, the organ would contain fewer cells, a change that would be permanent. By contrast, if the growth retardation occurred during the hypertrophic phase, recovery would occur since the cells were capable of resuming their normal size once the cause of the growth retardation was removed. I believe it is this hypothesis that is the most important contribution of this paper.

The stimulus we subsequently used to test this hypothesis was undernutrition. And the impact of our work was understandably greatest on the field of nutrition. Therefore, it is not surprising that the next paper that tested our hypothesis in growing rats initially received more attention than this one. I believe, however, that the continued citation of the present paper reflects the application of this work to fields outside nutrition: in, for example, studies of the effects of hypoxia,³ alcohol ingestion,⁴ and smoking during pregnancy.⁵

For me, the choice of this paper as a *Citation Classic* is very gratifying because it recognizes what I consider to be my most important conceptual contribution to science. The experiments described in this paper were straightforward and not particularly imaginative. The interpretation of the results, however, enabled us to use our imaginations and to suggest a hypothesis that could be tested. The hypothesis turned out to be correct, and it has explained, at least partially, why some tissues recover and some tissues do not when exposed to an initial stimulus.

1. Winick M & Noble A. Cellular response in rats during malnutrition at various ages. *J. Nutrition* 89:300-6, 1966. (Cited 655 times.) [See also: Winick M. Citation Classic. (Barrett J T, ed.) *Contemporary classics in the plant, animal, and environmental sciences*. Philadelphia: ISI Press, 1986. p. 279.]
2. Enesco M & Leblond C P. Increase in cell number as a factor in the growth of the organs of the young male rat. *J. Embryol. Exp. Morphol.* 10:530-62, 1962. (Cited 470 times.)
3. Winick M. Cellular growth in intrauterine malnutrition. *Pediatr. Clin. N. Amer.* 17:69-78, 1970. (Cited 95 times.)
4. Gordon B H J, Street M L, Rosso P & Winick M. Prenatal alcohol exposure: abnormalities in placental growth and fetal amino acid uptake in the rat. *Biol. Neonate* 47:113-9, 1985.
5. Winick M, Rosso P & Brasel J A. Malnutrition and cellular growth in the brain. (Somogyi J C & Fidanza F, eds.) *Nutrition and nervous system*. Basel: Karger, 1972. p. 60-8.