This Week's Citation Classic

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Winick M & Noble A. Cellular response in rats during malnutrition at various ages. *J. Nutrit.* **89**:300-6,1966.

By measuring DNA content and RNA/DNA and protein/DNA ratios of various rat organs, neonatal malnutrition was shown to retard the rate of cell division, permanently reducing cell number. By contrast, later malnutrition prevented the increase in cell size, a change that was reversible on refeeding. [The *SCI*® indicates that this paper has been cited 306 times since 1966.]

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"While working as a postdoctoral fellow, I read a paper by Enesco and Leblond that was to influence my research for the next fifteen years. They proposed using total organ DNA to measure total cell number and using the weight/DNA or protein/DNA ratio to measure average cell size. Using these measurements, they concluded that early growth was characterized by an increase in the number of cells (hyperplasia) whereas later growth was characterized by an enlargement of already existing cells (hypertrophy).[1]

"I have always wondered why they never followed up on these observations. Perhaps this is another example of basic science awaiting clinical application. To me, as a pediatrician interested in growth, these results suggested the solution to the problem of why certain children recover from early growth retardation whereas others remain stunted for the rest of their lives.

"Employing malnutrition to retard growth in rats, McCance and Widdowson had suggested some years earlier that the key to this problem was time.[2] The earlier the malnutrition, the less likely was recovery. Although they suggested a fundamental difference between early growth and later growth, their work did not resolve this difference.

"Could recovery depend on whether the organ was in the hyperplastic or hypertrophic phase of growth when the malnutrition occurred? Did a stimulus that retarded growth early in life result in an organ with fewer cells, whereas the same stimulus applied later resulted in smaller cells? Was the early retardation permanent and the later reversible?

"To a beginning investigator ready to launch an independent career, this problem seemed both important and solvable. It required simply using an experimental design, similar to that of McCance and Widdowson, combined with the measurements of Enesco and Leblond. This paper, written with Adele Noble, who helped carry out the measurements, reported the results of a study combining these two ideas. As previously postulated, malnutrition during hyperplastic growth retarded the rate of cell division and resulted in a stunted animal whose organs had fewer cells. This reduction in cell number was permanent. By contrast, malnutrition during hypertrophic growth curtailed cell enlargement, also resulting in a stunted animal. However, subsequent refeeding induced a return to normal cell size.

"I am delighted to learn that this paper is among those most cited by other investigators. To me, it represents my most creative single study. It launched all of my subsequent investigations in the area of cellular growth of the brain both in animals and in children. It stimulated my interest in the general problem of early malnutrition in young children and pregnant women, which has ultimately led to broadening my own horizons in the science of human nutrition."

REFERENCES

1. **Enesco M & Leblond C P.** Increase in cell number as a factor in the growth of the young male rat. *J. Embryol. Exp. Morphol.* **10**:530-4, 1962.
2. **McCance R A & Widdowson E M.** Nutrition and growth. *Proc. Roy. Soc. Lon. Ser B.* **156**:326-37, 1962.