Malnutrition and Brain Development

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1. My interest as a pediatrician, with a master's degree in embryology, is growth and development.

2. During a Journal Club meeting while I was a postdoctoral fellow at Stanford University I was asked to discuss a paper by Enesco and Le Blond. This was in 1964, the early days of the DNA revolution. And these authors noted that the amount of DNA in every cell of a particular species was the same. This number was already known in many species—6.2 picagrams of DNA in every rat cell; 6.0 picagrams in every human cell. Thus the total amount of DNA in any organ indicated the number of cells in that organ, and by dividing by the amount of DNA per cell one could calculate the number of cells in that organ. Since the rest of most body cells is some form of protein, the average amount of protein per cell could be calculated. So just as the total DNA content was an indication of cell number, the protein-DNA ratio indicated cell size.

Enesco and Le Blond measured these parameters in the rat and reported the number and size of cells in all of the organs of the adult animal. For me, this paper defined what I spent the next twenty years studying. As I thought about this work, certain questions immediately rose. The first and most important was: When an animal (or human) grows, does this mean the addition of new cells or the enlargement of already existing cells or some combination of the two?

3. We studied the growth of the rat from birth to adult life and found that a distinct pattern emerged. In every organ studied early growth was entirely by an increase in the number of cells. Late growth was entirely by increase in cell size. The change occurred at different times for every organ and during the change both cell number and cell size increased. Thus in the brain and the lung the period of growth by cell number increase was 21 days, in the liver fifty days, and in the various muscle tissues later than that. But in every case cells stopped increasing in number before growth stopped. The rest of growth was by an increase in cell size.

4. Retarded Growth

Examination of the literature demonstrated that growth could be slowed or even entirely stopped by undernutrition during any part of the growing period. The late Elsie Widdowson showed this for a number of species including rats, mice, and very dramatically in growing pigs. She also found that the earlier in life the poor nutrition occurred the more likely the animal would remain permanently stunted regardless of how the animal was refed thereafter. For example, animals malnourished from birth to weaning would never recover in statute even if fed
normally for the rest of their lives. By contrast, animals malnourished later in the growing period, although stunted after the period of malnutrition, were able to "catch up" to reach normal size. Could the reason for these differences be explained by the cellular growth pattern that we have previously described? We repeated Dr. Widdowson's experimental model and showed that during the period when cells were rapidly increasing in number animals that were malnourished were stunted because their organs had fewer cells and this change was permanent. By contrast, animals malnourished during the period of cell enlargement had smaller cells at the end of the period of malnutrition, but if they were subsequently refed the cells refilled with protein and reached their normal size.

5. Brain Growth

Since cell division stopped earliest in a rat brain, and since the result of malnutrition during the nursing period was a brain with fewer cells no matter how the animal was fed later, we decided to put our major focus on malnutrition and brain development.

In humans, nothing was known about brain growth from a cellular standpoint. Our next series of studies were done using brains of infants and young children who died of accidents, poisoning, or crib deaths, but who had been well fed until one of these catastrophic events occurred. Thus we were looking at the pattern of cellular growth in the "normal" human infant’s brain. Cell number reached its maximum around twelve months of age. Thus by the time an infant was one year old he or she had all the brain cells they would ever have.

It did not take any knowledge of science to know that millions of children around the world in Africa, Asia, South America, and the Caribbean, and yes in many "developed" countries including the U.S., were severely malnourished during the first year of life. Did these children have brains that had fewer cells and would this change be permanent?

I was fortunate enough to be able to spend five months in Santiago, Chile, at the Hospital Roberto del Rio (the largest children's hospital in Chile) in 1967 with my wife and one-year-old son. While there we set up a laboratory where we studied children who were admitted to the hospital with such severe malnutrition that they did not survive. We were able to show that in infants below one year of life who died of malnutrition brain cell number was reduced. Presumably had they lived this change would have been permanent. We were able to do a similar study in Jamaica several years later, confirming our initial observations in Chile. To my knowledge these are the only such studies done on brains from malnourished infants.

These results were frightening. Were there millions of people who had been severely malnourished as infants who had brains with fewer cells than normal, and if so did this have any meaning as far as brain function went?
6. Malnutrition and Brain Function

At the same time as we were studying early malnutrition and brain growth, several groups of investigators were examining brain function in animals subjected to early malnutrition. A classical experiment by Levitsky and Barnes demonstrated that an interaction between early malnutrition and environmental isolation produced the most striking effects on animals later subjected to a battery of psychological tests. Malnourished animals did poorly; isolated animals did poorly even if well nourished; but the combined effect of isolation and early malnutrition produced the worst performance on the battery of tests.

In the world today, most children who are malnourished early in life receive very little environmental stimulation. Thus the question arose immediately whether the later functional effects seen in children who had suffered early malnutrition were due, at least in part, to their having been isolated from their environment as early infants.

We carried out a study designed to answer this question. A group of Korean orphans were studied. All had been severely malnourished in the first six months of life. Some were adopted by U.S. families before the age of one. At twelve years of age those infants adopted by U.S. families (presumably stimulated) had IQs at the U.S. norms (average 103). A similar group that had not been malnourished as infants also adopted by U.S. families had IQs averaging 116. The difference was statistically significant but environmental stimulation lessened the effect of early malnutrition. If the same groups were studied after being adopted at three years or older all of their IQs dropped and the previously malnourished children did significantly below the U.S. norms and also below the children who were not previously malnourished. Hence in children as in animals there seemed to be an interaction between environmental isolation and early malnutrition which gave the poorest functional results.

7. Back to Animals

The last group of experiments I would like to describe were carried out by Dr. Brian Morgan while he was working in our group. He showed that in rat pups who were malnourished in the first 21 days a particular chemical found in the normal brain, n-acetyl neurominic acid (NANA), was markedly reduced. In isolated animals it was also reduced and in isolated malnourished animals NANA was virtually absent. Finally, he showed that by injecting NANA into isolated or malnourished animals he could bring the NANA concentrations in the brain to normal and reverse the later functional effects. Is a lack of NANA in the brain responsible for the effects seen in humans? We don't know. But a more simple solution is to eliminate early malnutrition and provide stimulation during infancy.