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RESEARCH NEWS

Early Nutrition and Programming: Too Little, Too Much, Or–?

A review of: Singhal A, Fewtrell M, Cole TJ, Lucas A 2003 Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. Lancet 361:1089–1097

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According to the *programming* theory, the future development of chronic diseases is written in genes, but, even more, in intrauterine growth (*fetal origin hypothesis*) (1). Any stress in terms of postnatal accelerated growth (compared with the expected rates "proportional" to body size) would result in earlier signs (at first) and symptoms (later on) of chronic-degenerative disorders.

This hypothesis lacks complete scientific evidence in humans. Currently, we have the retrospective data from the Barker group (1) and elegant animal studies (2) but no clear evidence in humans followed from the first stages of development through the life span.

The study on preterms by Lucas' group gives us for the first time human evidence that lower nutrient intakes, and the consequent slower growth rates in postnatal life, might favorably program healthy outcomes in later life (3). One hundred and ten preterm infants were randomized to receive a lower nutrient diet (expressed banked/fresh human milk or a standard formula) and 106 preterm infants were fed a nutrient enriched diet (higher in energy, protein and micronutrients). The diets were continued until the infants weighed 2000 grams or were discharged from hospital. At adolescence (13–16 years), those subjects who had received a lower nutrient diet had 20% lower fasting 32–33 split proinsulin concentrations (a marker of insulin resistance) than did subjects who had received a nutrient enriched diet. Even more intriguing, fasting 32–33 split proinsulin concentrations were associated with greater weight gain *in the first two weeks of life,* independent of any clinical and/or demographic confounder and irrespective of whether the growth of the fetus was impaired.

Thus, we now have a randomized trial showing that relative undernutrition in early life could have positive effects, in contrast to the less favorable outcome observed in the case of diets associated with early rapid growth. The crucial window appears to be the first two weeks of life, a slightly longer period than standard antibiotic therapy. Should we refer to dietary components as "drug-like" compounds, able to act upon hormones, growth factors and intermediate metabolites so as to influence health outcomes years and years later? And should we be prepared to accept the idea of *nutritional predestination* leaving us such a narrow time frame to interpret and understand the most advantageous dietary supply for each infant according to his/her condition at birth? The present results suggest a "reinterpretation" of the Barker fetal origin hypothesis of adult disease as primarily an immediate postnatal event.

The randomized trial was limited to preterms. Indeed, what happens to term infants? The paper includes a third reference group of adolescents who were born at term and who were found to have fasting 32–33 split proinsulin concentrations similar to the nutrient enriched group. We do not know how the group born at term had been nourished, but it is possible that most of them were formula fed, since breastfeeding rates in United Kingdom are the lowest in Europe (4). The protein and energy supply of breastfed infants is lower than in formula-fed counterparts in the first days of life, as shown by a more limited insulin secretion (5). Accordingly, it is tempting to speculate that early postnatal *programming* could have long-term favorable effects. Indeed, breastfeeding is negatively associated with overweight and obesity in adolescence; the longer breastfeeding occurs, the greater the prevention of obesity in later years (6).

So, between too little (mildly undernourished) and too much (enriched formula), the gold standard may still be the metabolic model of the term, breastfed baby.

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Big Problems from Little Kidneys

A review of: Keller G, Zimmer G, Mall G, Ritz E, Amann K 2003 Nephron number in patients with hypertension N Engl J Med 348:102–108

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DEVELOPMENT OF THE human kidney begins at about 5 weeks fetal age when the ureteric bud, an outpouching of the nephric duct, grows into the metanephric mesenchyme and begins to branch. Iterative interactions between each new branch tip and the adjacent mesenchyme generate the nephrons of each kidney. At birth, this crop of nephrons hangs like fruit on branches of the arborized collecting system and constitutes the individual's nephron endowment for life. Occasionally, when the process goes awry, neonates may be born with obvious hypoplasia (1:400) or aplasia (1:3600) of at least one kidney (1, 2). Very rarely, children are born with hereditary syndromes (e.g., renal-coloboma syndrome) in which congenital bilateral nephron deficit is associated with progressive renal insufficiency (1, 3).

While our medical paradigms easily accommodate these developmental "errors", we tend to accept as "normal" the wide variance in nephron number (0.3 to 2.0 million nephrons per kidney) reported from autopsies of adults who die from non-renal causes (4, 5). Yet, since 1988, Brenner and colleagues have challenged this notion, proposing that "normal" humans born at the lower end of the nephron endowment scale are predisposed to "essential" hypertension (6). They hypothesized that signals driving compensatory hypertrophy of the few overworked nephrons cause glomerulosclerosis and a cycle of subtle, slowly progressive renal dysfunction (7). Their hypothesis is supported by studies showing lower nephron number in inbred hypertensive rats compared to normotensive control strains (8) and showing that longevity of transplanted rat kidneys was influenced by allograft nephron number (9). However, it has been understandably difficult to gather evidence that suboptimal nephron endowment has any clinical consequence for the "normal" human population.

In this context, the recent article by Keller *et al.* (10) is important. The authors used a careful, well-validated method for measuring whole-kidney nephron number in autopsies on 10 German subjects with clear evidence of primary hypertension vs 10 control subjects, closely matched for gender, age, height and weight. The subjects were less than 60 years old, after which glomerular obsolescence might confound the issue. On average, the hypertensive subjects had 46.6% fewer nephrons per kidney than controls. The kidneys of hypertensive subjects also had larger glomeruli (glomerular volume = 233% of controls) – enough compensatory hypertrophy to restore total glomerular volume per kidney to baseline. As predicted by Brenner's hypothesis linking suboptimal nephron number, compensatory glomerular hypertrophy and progressive glomerular damage, there was also more glomerulosclerosis in the affected kidneys (5.5% vs. 0%).

Although their patient sample was small, the observations by Keller *et al.* provide clear support for Brenner's hypothesis and demand our attention. Children born with fewer nephrons may not only be at greater risk for essential hypertension but presumably have less renal reserve to contend with diabetes, glomerulonephritis and other acquired nephropathies later in life. Recently it was shown that low birth weight (<2.5 kg) is associated with a 13% reduction in nephron number (11). Perhaps even more significant is the observation in rodents that nephron number is reduced (20%) by moderate maternal vitamin A deficiency (12). If this observation is translatable to humans in developing countries such as India (population = 1 billion), where up to 20% of pregnant women are vitamin A deficient, the public health implications of a nutritional cause for suboptimal nephron endowment are staggering.

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