0031-3998/03/5402-0151
PEDIATRIC RESEARCH
Vol. 54, No. 2, 2003
Printed in U.S.A.

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

CARLO AGOSTONI AND
ELVIRA VERDUCI

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.

1. Barker DJ, Eriksson JG, Forsen T, Osmond C 2002 Fetal origins of adult disease: strength of effects and biological basis. Int J Epidemiol 31:1235–1239
2. Vehaskari VM, Aviles DH, Manning J 2001 Prenatal programming of adult hypertension in the rat. Kidney Int 59:238–245
3. Singhal A, Fewtrell M, Cole TJ, Lucas A 2003 Low nutrient intake and early growth for later insulin resistance in adolescent born preterm. Lancet 361: 1089–1097
4. Earle S 2002 Factors affecting the initiation of breastfeeding: implications for breastfeeding promotion. Health Promot Internation 17:205–214
5. Lucas A, Boyes S, Bloom SR, Aynsley-Green A 1981 Metabolic and endocrine responses to a milk feed in six-day-old term infants: differences between breast and cow's milk formula feeding. Acta Paediatr Scand 70:195–200
6. Gillman MW, Rifas-Shiman SL, Camargo CA, Berkey CS, Frazier AL, Rockett HR, Field AE, Colditz GA 2001 Risk of overweight among adolescents who were breastfed as infants. JAMA 285:2461–2467

Department of Pediatrics, San Paolo Hospital
8 Via A di Rudinì, 20142 Milan, Italy
e-mail: agostoc@tin.it

DOI: 10.1203/01.PDR.0000082991.69946.B9