Programming by Early Nutrition: An Experimental Approach

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ABSTRACT That events during critical or sensitive periods of development may “program” long-term or lifetime structure or function of the organism is well recognized. Evidence for programming by nutrition is established in animals, in whom brief pre- or postnatal nutritional manipulations may program adult size, metabolism, blood lipids, diabetes, blood pressure, obesity, atherosclerosis, learning, behavior and life span. Human epidemiological data link potential markers of early nutrition (size at birth or in infancy) to cardiovascular disease and its risk factors in adulthood. However, these retrospective data cannot prove nutritional cause or underpin health policies. After 16 y, however, of ethical, randomized intervention studies of early nutrition in humans with long-term follow-up to test experimentally the nutritional programming hypothesis, we find that humans, like other species, have sensitive windows for nutrition in terms of later outcomes; for instance, perinatal diet influences neurodevelopment and bone mineralization into mid-childhood. Possible biological mechanisms for storing throughout life the “memory” of early nutritional experience and its expression in adulthood include adaptive changes in gene expression, preferential clonal selection of adapted cells in programmed tissues and programmed differential proliferation of tissue cell types. Animal and human evidence supporting nutritional programming has major potential biological and medical significance.

KEY WORDS: • nutritional programming • sensitive period • adult health • cognitive development

CLINICAL AND HISTORICAL CONTEXT
Over the past three centuries there has probably been more research on infant nutrition than on any other area of pediatrics. By 1953, Macy et al. were able to collate over 1,500 publications on the biochemistry of breast milk—just one small area of infant nutrition research. Yet, despite the massive scientific effort, fundamental issues in infant nutrition practice remain unresolved, resulting in confusion among health professionals and in inconsistent, inadequately supported public health recommendations and standards of practice. When such uncertainty exists in the presence of such a large body of research and knowledge, it is reasonable to challenge whether the right questions have been addressed.

To throw more light on this uncertainty, it is instructive to examine how other fields of health intervention have generally evolved. Usually this has been a three-stage process (Lucas 1987). In stage I, anecdotal observations raise the question, “is this worth pursing?” In stage II, epidemiological and physiological research provide descriptive and mechanistic data that raise testable hypotheses concerning the potential effect of intervention. Finally, in stage III, formal intervention experiments test the efficacy and safety of clinical or public health practice. Thus, taking the analogy of research into high blood pressure, stage III research shows whether intervention with antihypertensive drugs matters in terms of improving long-term health (e.g., reduced risk of stroke, improved survival). The ability of antihypertensive drugs simply to lower blood pressure (stage II research) has real value only if it improves outcome (stage III research).

Twenty years ago, the field of early nutrition had largely become arrested in stage II. Research generally focused on collection of physiological and epidemiological data on growth, nutritional status, metabolic response to feeding, energetics, nutrient absorption and retention, composition of foods, prevalence of nutritional disorders, and so on. It is true that considerable earlier efforts had been made to define intakes that would prevent overt nutritional deficiency, and that was, of course, of obvious clinical importance. However, formal experimental stage III research on whether early nutrition mattered in terms of critical health and developmental outcomes was seldom undertaken and usually poorly conceived.

In recent decades there has been a significant shift in thinking about nutrition from a preoccupation with meeting nutrient needs to a concern about its effect on health, including adult degenerative diseases, cancer and cognitive function (Barker 1993, IARC 1990, Lucas 1994). More recently, an important new dimension to the nutrition and health theme has been the appreciation that there may be critical windows in early development, both pre- and postnatal, during which nutrition could have lifetime consequences for development and major disease in adult life. The idea that early nutrition could influence or “program” such outcomes has obvious biological and public health implications.

In this article I examine here the concept of nutritional
programming and the new “stage III” experimental approach to it in humans and consider in general terms the fundamental biological mechanism that may be involved. Before consideration of nutritional programming, however, the following section describes the much broader concept of programming as a key biological phenomenon.

THE CONCEPT OF PROGRAMMING

Generally, events in early life might influence long-term outcome in the following three ways: 1) direct damage (e.g., loss of a limb due to vascular accident); 2) induction, deletion, or impaired development of a somatic structure resulting from a stimulus or insult during a critical period; or 3) physiological “setting” by an early stimulus or insult at a critical period, with long-term consequences for function. Lucas (1991) suggested the term programming be applied to the latter two processes in which the programming stimulus exerts long-term effects only when applied at a critical or sensitive period.

Evidence for programming, other than by nutrition, is considerable (Lucas 1991). Illustrative examples are cited here. Early imprinting of behavior in birds has been recognized for centuries (Spalding 1873). Hormonal signals operating during critical windows have numerous programming effects. Thus, in rats, testosterone secreted by the testis at a critical period programs the brain for male sexual behavior; a single dose of testosterone given during at this time to a female fetus will permanently reorientate sexual behaviour to the male form (Angelbeck and Du Brul 1983). Teratogenic drugs, recognized since the 1920s, have powerful programming effects on somatic development. But postnatal programming by drugs may also occur: a single dose of phenobarbitone given to a neonatal rat may induce lifelong change in the activity of a key enzyme, cytochrome P450-dependent mono-oxygenase (Bagley and Hayes 1983). Normal visual inputs are essential for development of the visual pathway, hence squint amblyopia. The programming window is usually early fetal life or infancy, but, arguably, in the case of antigen-induced programming of the immune system, sensitivity may be lifelong. These examples indicate that programming in fetal or postnatal life may result in initiation of normal development processes, resulting from endogenous or exogenous signaling during critical periods of development, or may result in a lasting response to an environmental stimulus. Arguing teleologically, the ability to respond to early environment to produce a lifetime change in structure or function could have evolved as a mechanism that allowed the organism to fine-tune its machinery in an adaptive way according to its early milieu. It could also be envisaged, however, that some environmental insults could trigger programming mechanisms in a non-adaptive, adverse way.

NUTRITIONAL PROGRAMMING: ANIMAL STUDIES

The question, then, is whether early nutrition could operate in this programming manner. The pioneering work of McCance (1962) provided key evidence for this. He manipulated litter size in rats, so that rats from large litters received less breast milk than those from small litters during the 21-d suckling period, by which time rats from large litters were substantially smaller than those from smaller litters. At this point both groups were fed normally, but the smaller animals (from large litters) continued to diverge in body size from the larger animals; 3 wk of dietary intervention had resulted in a lifetime programming of growth trajectory. However, McCance then showed that it was only the early weeks that constituted a critical period for such effects. Equivalent dietary manipulation for a 3-wk period a few weeks later had no lasting effect: the underfed animals showed catch-up growth when they were re-fed; the critical window for growth programming by early nutrition had passed.

Following these studies in the 1960s, increasing numbers of animal experiments on nutritional programming have demonstrated the wide variety of lifetime programming effects on metabolism, blood pressure, diabetes, obesity, atherosclerosis, behavior and learning (see below) that would be of considerable public health importance were they to apply to humans.

NUTRITIONAL PROGRAMMING IN ANIMALS

Extensive animal data, largely on rats, show that nutrition at a vulnerable period of brain development may have permanent effects on brain size, brain cell number, behavior, learning and memory (Dobbing and Sands 1971, Smart 1986). In Smart’s review of 165 animal studies (1986) on early undernutrition and later learning, the number of studies in which undernourished animals fared worse than controls greatly outweighed those that favored the controls. The extent to which these animal data have relevance to human cognitive development, however, is uncertain.

With regard to “health” outcomes, experimental studies on fetal nutrition have shown, for instance, that protein-undernourished fetuses had long-term reduction in pancreatic cells and insulin secretion (Snoek et al. 1990). Hahn (1984) manipulated litter size in neonatal rats so that rats from small litters were temporarily overfed during the brief suckling period and found that in adulthood these animals had permanent elevation in plasma insulin and cholesterol. Weaning these animals on to a high carbohydrate diet further induced life-long elevation in the activities of HMG-CoA reductase and fatty acid synthetase (key enzymes for cholesterol and fat synthesis).

In primates (baboons), overfeeding during infancy in the female resulted in obesity that did not manifest until early adult life (Lewis et al. 1986), raising the question of where the “memory” of the early event had been stored in the intervening period. In further studies, baboons were randomly assigned to breast feeding or formula (Mott et al. 1991), and then both groups were placed on a “Western-style” high saturated-fat diet. The previously breast-fed group had, in adult life, higher plasma LDL and VLDL cholesterol, lower “protective” HDL cholesterol and increased cholesterol absorption, perhaps relating to the permanent change in bile acid secretion. These data imply that breast-feeding may program these primates to be conservative with cholesterol but that this might be disadvantageous to lipid metabolism if they were subsequently placed, unphysiologically, on a high saturated fat diet. Indeed, at postmortem the previously breast-fed baboons had significantly more atherosclerosis than those fed formula.

Our own studies using rats demonstrate that both pre- and postnatal nutrition may influence adult outcomes but that the critical period for programming depends on the outcome studied. Thus, experiments were designed in which adult rats were studied whose mothers were fed either a normal diet (providing 20% protein) or a low protein diet (8% protein) given during pregnancy or lactation or both (a model chosen because of the previous demonstration that it produced life-time programming effects) (Snoek et al. 1990). Life-time effects on body size were seen only in relation to postnatal nutritional manipulation; thus animals fed by mothers fed a low protein diet during lactation were permanently smaller, whereas prenatal low protein diet fed to the mother had no long-term effect on
the size of the offspring (Desai et al. 1996). In contrast, lifetime changes in hepatic glucose metabolism [glucokinase and phosphoenol pyruvate carboxykinase (PEPCK) activities] were induced only by prenatal dietary manipulation in the mother (Desai et al. 1995). For some outcomes, however, the critical window for programming was longer. Thus either prenatal or postnatal low protein diet (or both) given to the mother resulted in a programmed reduction in plasma triglycerides, HDL and total cholesterol in the offspring when they reached adult life (Lucas et al. 1996). Our unpublished data also show that a low protein diet fed to maternal rats during either pregnancy or lactation and followed by a nutrient-enriched diet resulted in a significantly lower systolic blood pressure in the offspring by adulthood. For some outcomes, the direction of response may depend on timing of the programming stimulus; our data (Hales et al. 1996) indicate (at least in males) that life span was significantly decreased in animals born to mothers that had a low protein diet in pregnancy but were then suckled by mothers on a normal protein diet, whereas the converse (offspring of mothers fed normally during pregnancy but suckled by mothers fed a low protein diet) resulted in a significant increase in life span. The programmed effect may be complicated further by post-weaning diet. For instance, whether prenatal low protein diet in the mother produces high, normal or low blood pressure in the offspring may depend on complex interaction between pre- and postweaning nutrition (unpublished data).

Data from such animal models have importance in suggesting human interventions and in defining underlying programming mechanisms (see below). However, public health policy for early nutrition in humans must ultimately depend on human studies.

**NUTRITIONAL PROGRAMMING IN HUMANS**

Given the evidence for programming in general and the evidence for nutritional programming in animals, nutritional programming in humans might be predicted. This has not been easy to prove, largely because most studies have not had an experimental design but have documented retrospective epidemiological associations often subject to alternative explanations. Collectively, the human epidemiological data are extensive, and illustrative studies are discussed here.

**EARLY NUTRITION AND LATER COGNITIVE FUNCTION: EPIDEMIOLOGICAL STUDIES**

Considerable effort has been invested in testing the hypothesis, supported by animal data (see above), that suboptimal nutrition at a vulnerable stage in brain development has permanent effects on cognitive function. Epidemiological associations found between malnutrition and reduced cognitive performance, however, might not be causal (Grantham-McGregor 1987). Malnutrition, principally studied in developing countries, is inextricably associated with poverty, poor social circumstances and lack of stimulation, which might explain the adverse outcomes. Prospective, randomized or satisfactorily controlled studies are rare, and most do not provide unequivocal data.

Several studies suggest that breast-feeding promotes long-term neurodevelopment, in some cases even after attempts to adjust for confounding factors (Lucas et al. 1992, Rodgers 1978, Taylor 1977), though whether these effects reflect residual confounding by educational and parenting differences between groups is uncertain. The evidence that human milk may promote neurodevelopment and higher IQ in infants born preterm is stronger (Lucas et al. 1992 and 1994), with implications for clinical management. Such effects would be biologically plausible, because human milk contains factors, including hormones and long-chain polyenoic fatty acids (LCP), that could theoretically influence neurodevelopment.

**NUTRITION AND LATER DISEASE: EPIDEMIOLOGICAL STUDIES**

Most studies on early nutrition and later health have been epidemiological and inconclusive. Unlike the studies in baboons (above), breast- and bottle-fed infants have not been shown to differ in later total plasma cholesterol at 8 y (Fomon et al. 1984) or in total cholesterol, LDL or HDL at up to 16 y (unpublished data). Early salt intake has been associated with later high blood pressure in some studies, but others have failed to show a causal link in either normal or preterm individuals (Lucas et al. 1988).

Breast- and formula-fed babies may have potentially important differences in later health outcomes, although these might be confounded by the major demographic differences between groups. Breast-feeding has been associated with a protective effect against insulin-dependent diabetes (Gerstein 1994, Viren et al. 1993) (not observed by all) and a reduced incidence of lymphoma (Davis et al. 1988), and, in one epidemiological study, prolonged breast-feeding in males was associated with a greater incidence of atherosclerosis in late adult life (Fall et al. 1992). Whether these associations are causal needs further exploration.

In the past decade, a series of studies, notably those by Barker, Hales and co-workers, has shown relationships of anthropometric indices at birth and at 1 y (possible markers of early nutrition) with cardiovascular disease and its risk factors (Barker 1993, Fall et al. 1992). Low body weight, head circumference and ponderal index at birth and low weight at 1 y have been associated with increased risk of later cardiovascular disease. Small size at birth and up to 1 y has also been associated with higher blood pressure and adverse changes in plasma concentrations of glucose, insulin, fibrinogen, factor VII and apolipoprotein B; abdominal circumference at birth is inversely associated with higher serum concentration of total cholesterol, LDL cholesterol and apolipoprotein B. These provocative and important observations have been interpreted by the investigators as supporting the hypothesis that poor fetal nutrition, perhaps resulting from poor maternal nutrition, adversely programs the individual for later cardiovascular disease, hypertension and diabetes. Their suggestion is that improvement of fetal nutrition might be an important public health measure (Barker 1993). In favour of this thesis is the evidence that early nutrition in animals has been shown to program corresponding outcomes. There are inconsistencies, however: in rats, overnutrition rather than undernutrition may be associated with later elevation of blood cholesterol (Hahn 1984), and chronic undernutrition has been associated with longevity (McCay et al. 1939). A key area for debate is the proposed nutritional interpretation. Poor intrauterine growth might be associated with other, non-nutritional derangements that could be responsible for long-term programming.

**AN EXPERIMENTAL APPROACH TO NUTRITIONAL PROGRAMMING IN HUMANS**

Two key points emerge from the brief discussion above of epidemiological evidence for nutritional programming: firstly, that although such studies generate hypotheses, they do not prove nutritional cause, and, secondly, it is speculative to use
these findings to underpin public health or clinical interventions in human nutrition.

Clearly, public health and clinical policy would be most soundly based on experimental rather than epidemiological studies. In the light of this, 15 y ago I elected to devote major attention of my research group to developing the use of the infant nutrition intervention experiments in a formal way to explore the concept of nutritional programming in humans and to underpin nutritional practice. The elements of this programme, which collectively were novel at that time, included the following in each clinical trial: 1) formal randomized nutritional intervention in infancy with planned long-term follow-up; 2) carefully calculated size to detect differences between groups for a key targeted health or developmental outcome ("efficacy") with adequate power; and trials large enough to detect differences in adverse outcome ("safety") between groups; 3) trials conducted in a manner similar to a pharmaceutical intervention trial employing what are now termed "good clinical practice" guidelines; and 4) cohort details documented to facilitate long-term (or lifetime) follow-up.

There are several windows of opportunity for infant nutritional intervention experiments that are feasible and ethical. 1) Preterm infants can be randomized to diet to test the importance of the perinatal period as a window for nutritional programming. Some years ago milk banking was commonly practiced in neonatal care, so that for babies whose mothers did not provide their own milk it was possible, among other interventions, to randomly assign infants to human milk (from unrelated donors) or formula—a key "experiment" that would be difficult to achieve in full-term infants. 2) Formula-fed full-term infants could be randomly assigned to formulas of different nutrient content to test ways in which early infancy might be critical for nutrition. These interventions can also be targeted to full-term infants growth-retarded at birth, who have been shown epidemiologically to be at long-term risk for growth and neurodevelopmental deficits and for ischaemic heart disease and its antecedents. A key question is whether early nutritional intervention could "re-programme" these infants following poor intrauterine growth and ameliorate risk. 3) Infants can be randomly assigned to different weaning foods to test whether nutritional sensitivity extends into infancy or beyond.

In 15 major outcome studies now, testing a range of key hypotheses, we have around 5000 infants and children in all 4 studies for the following reasons: 1) Because it was unknown (15 y ago) which were the optimal diets for this population, it was ethical to randomly assign available diets during hospital study to address the question: which diet was associated with better long-term outcomes? 2) Because since preterm infants are a "captive" population, intensive nutritional, physiological, biochemical and clinical monitoring was feasible during the intervention period. 3) It might be predicted that preterm infants, born during a stage of rapid development, might be particularly sensitive to programming stimuli.

Illustrative results from this work, comprising two parallel nutritional intervention studies, are presented in this article. The study design has been presented elsewhere (Lucas et al. 1990 and 1994), and only brief details are given here. The 926 infants weighing less than 1850 g at birth represented an unselected cohort from the five centers recruited between 1982 and 1985. No parent refused consent. In study 1 (Lucas et al. 1994), conducted in three centers that had a human milk bank, subjects were randomly allocated to banked donated breast milk (from unrelated donors) or a special nutrient-enriched preterm infant formula, designed by us to meet the nutrient needs of fast-growing immature preterm infants. Donor human milk was ununsupplemented, as frequently given in the early 1980s. When mothers failed to provide their own breast milk, the infants received donor milk or preterm formulas as sole diets (n = 159). When mothers did provide their expressed milk, donor milk and preterm formula were randomly assigned as a supplement to mother's milk (n = 343) in volumes according to the mother's success in providing their own milk (mean, close to 50% of intake). In study 2 (Lucas et al. 1990), the random allocation was to standard term formula (suitable for full-term infants used frequently in the 1980s) or preterm formula, with 160 in the sole diet group and 264 in the supplement to mother's milk group. The protein (g/100 mL), energy (kcal/100 mL) and calcium (mg/100 mL) contents of the four diets were, respectively, as follows: preterm formula: 2.0, 80 and 70; standard formula: 1.5, 68 and 35; and mother's expressed milk: 1.5, 62 and 30 (values for the latter are mean values for 6000 pooled

PRETERM INFANT TRIALS

Of our trials, the most long-standing (now running for 15 y) has been a five-center study on 926 infants born preterm (mean gestation 31 wk) (Lucas et al. 1990 and 1994). Such infants were considered to be valuable for nutritional programming studies for the following reasons: 1) Because it was unknown (15 y ago) which were the optimal diets for this population, it was ethical to randomly assign available diets during hospital study to address the question: which diet was associated with better long-term outcomes? 2) Because since preterm infants are a "captive" population, intensive nutritional, physiological, biochemical and clinical monitoring was feasible during the intervention period. 3) It might be predicted that preterm infants, born during a stage of rapid development, might be particularly sensitive to programming stimuli.

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24-h samples). The donor breast milk was donated by breastfeeding mothers in the community who collected milk which dripped from the contralateral breast when feeding their own infant. Many of the infants required initial parenteral nutrition, and the median number of days to attain full enteral feeds was 7 d in study 1 and 9 d in study 2. The assigned diet was given (for a median of 4 wk) until the baby attained a weight of 2000 g or was discharged from the neonatal unit, whichever was the sooner. After babies were discharged from the neonatal unit, mothers fed their babies as they and their advisors chose. Follow-up staff were blind to the original dietary assignment.

**Neurodevelopment.** At long-term follow-up of this cohort, the principal targeted outcome was neurodevelopment. Within each study, the sample size was calculated so as to be sufficient to detect a difference of one third of a standard deviation (5 quotient points) for trials with randomized diet used as sole diet (trial A) or breast milk supplement (trial B) combined, and half a standard deviation (8 quotient points) for the sole diet trial (trial A) alone. The subjects were seen at 18 mo corrected age and at 7.5 y. Data from the 18-mo follow-up only are published so far. In study 2, babies in trial A fed standard formula had a 6-point lower mental development index and a 15-point lower psychomotor score ($P < 0.001$); in trials A + B ($n = 310$; a balanced addition, preserving randomization) there was a 6-point lower psychomotor score ($P < 0.01$), despite the blunting effect of mother’s milk usage for the sole diet trial (trial B) in both randomized groups. The effect size was substantially greater in males (Lucas et al. 1990). We recently confirmed that the significant developmental disadvantage seen principally in male preterm babies fed a standard term formula (which we now recognize does not meet the nutrient needs of this group) was also seen at 7.5 y, when IQ, notably verbal IQ, was significantly depressed (unpublished data).

Thus, we showed that a brief period of dietary manipulation in the neonatal period (4 wk on average), using a nutrient-enriched rather than a standard formula, significantly influenced neurodevelopment at 18 mo. Our further follow-up at 7.5 y (unpublished data), when IQ is more predictive of that in adults, indicates that the disadvantage for the standard formula-fed group could now therefore represent a permanent effect. These data provide some of the only evidence from a large long-term randomized trial that early diet, during a critical or vulnerable period, could program neurodevelopment.

Surprisingly, in study 1, despite the poor nutrient content of donor breast milk, outcome of those individuals fed on it in the neonatal period was no worse than that seen with preterm formula. We have published data (Lucas et al. 1994) suggesting this may be due to ameliorating, beneficial factors in donor milk. Indeed infants fed solely on donor milk (in study 1) had a substantial psychomotor advantage over those fed solely on standard formula (study 2); in this (nonrandomized) comparison, both diets were similarly low in nutrient content, yet the donor milk-fed group had a 9-point advantage in psychomotor scores.

**Health outcomes: bone mineralization.** These preterm studies have provided an important opportunity to test whether a period of nutritional intervention during early life could affect propensity to disease in later life. This is currently being investigated, particularly with respect to two key endpoints: cardiovascular disease (and its markers) and bone health. Data on the latter are discussed briefly here.

Adult degenerative bone disease (osteoporosis), a major public health problem in the West, has been linked to peak bone mass attained in young adult life (Bonjour et al. 1994). Following attainment of peak bone mass, bone mineral content falls and may descend below the safety level for clinical disease. Most interventions to reduce the incidence of clinical disease have been in middle life. Little attention has been given until recently to the possibility that early factors could influence bone mineralization in childhood and hence peak bone mass.

We have tested the hypothesis that diet in the neonatal period in preterm infants could have a long-term effect on bone mineral content and bone metabolism, of potential relevance to propensity to bone disease in adulthood. At a 5-y follow-up we found that bone mineral content (adjusted appropriately for body size) was higher in children previously assigned randomly to human milk vs. formula (Bishop et al. 1996). These data raised the possibility that the duration of breastfeeding or, alternatively, a diet suboptimal for preterm infants (for instance, in calcium content), as human milk is, could program greater bone mineralization later in life. Our unpublished data at 9–12-y follow-up now indicate that children fed suboptimally in the neonatal period for just 1 mo on average, have an increase in plasma osteocalcin (a marker for bone formation) by early adolescence. Clearly this example of nutritional programming, determined in a strictly experimental context in humans, now needs further investigation in view of its potential implications for long-term bone health.

**UNDERSTANDING PROGRAMMING MECHANISMS**

Nutritional programming has been convincingly demonstrated in animals including primates, and there is now compelling evidence from experimental studies that this process operates in humans. More recently, attention has turned to mechanisms (Lucas 1991). Some programming events might have immediate effects on structural development, for example, on dendritic arborization or glial cell growth in the brain, with long-term consequences. However, nutritional programming here might not simply reflect failure to fuel a growth process. Nutrients might be critical signals acting directly or via coupling mechanisms on “receptors” in sensitive tissues. With regard to the programming or “setting” of later function, for instance of a key metabolic pathway, the question is how the “memory” of an early event is “stored” throughout life despite continuous cellular replication and replacement. Proposed mechanisms include adaptive effects on gene expression via coupling mechanisms on “receptors” in sensitive tissues. With regard to the programming or “setting” of later function, for instance of a key metabolic pathway, the question is how the “memory” of an early event is “stored” throughout life despite continuous cellular replication and replacement. Proposed mechanisms include adaptive effects on gene expression transmitted to the progeny of the originally programmed cells. Alternatively, the early nutritional milieu may stimulate adaptive clonal selection or differential cellular proliferation so that the quantity or proportion of cell populations in a tissue is permanently affected.

In collaboration with Hales, we have obtained indirect evidence of the latter mechanisms (Desai et al. 1995) using the low maternal protein intake model in the rat described above. In this model we showed that the offspring of mothers exposed to a low protein diet in pregnancy had approximate doubling of liver PEPCK activity (key enzyme for gluconeogenesis) and a halving of glucokinase activity (key enzyme for glycolysis). The result reflected a permanent fourfold shift in hepatic carbohydrate metabolism in the opposite direction to that which would be induced by insulin. Paradoxically, these enzyme activities were affected by diet at a period in life (fetal life) when the relevant genes are not transcriptionally active. A clue to the underlying mechanisms here comes from the appreciation that PEPCK comes from the population of hepatocytes known as perportal cells and glucokinase predominantly from perivenous cells. Liver enzymes tend to be “zoned” differentially in these two groups of cells. We now find that activities of other enzymes in these zones are reduced or increased pari passu.
with those of glucokinase and PEPCK, respectively, implying, perhaps, that the programmed event is differential proliferation of periporal and perivenous cells with widespread implications for metabolism. The exploration of such fundamental processes is critical to an understanding of the biology of early nutrition.

PUBLIC HEALTH IMPLICATIONS

Medical and public health practice is ideally underpinned by research that establishes outcome benefit. The perceived benefits from infant nutritional practices have traditionally included the promotion of short-term growth to accepted reference rates and of nutrient retention sufficient to fuel estimated requirements and prevent insufficiencies. The possibility that nutrition in early life may have major biological effects on later health and development totally changes the targets for infant nutritional research. Indeed, with the exception of the early nutritional care of preterm infants that can now be considered in relation to long-term outcome data (see above), for normal infants, if not alone fetuses, there is hardly a nutritional management policy or recommended dietary allowance that could be adequately scientifically defended in terms of its beneficial effects in later life.

Can we then readjust our early nutritional policies on the basis of new observations relating to nutritional programming? Unfortunately, most published data are not based on outcome studies and cannot readily be translated into management policy. For instance, should we feed small infants intensively to make them large by 1 y, or is intensive feeding of a baby set up prenatally to be small: the worst programming stimulus? Perhaps, that the programmed event is differential proliferation of periporal and perivenous cells with widespread implications for metabolism. The exploration of such fundamental processes is critical to an understanding of the biology of early nutrition.

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