Early Growth Retardation and Syndrome X: Conceptual and Methodological Issues Surrounding the Programming Hypothesis

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In the last decade, we have seen a phenomenal growth in research on the fetal origins of chronic disease in later life. The basic premise underlying this research is that in response to undernutrition during critical periods of growth and development, the structure and function of organs and tissues are “programmed,” or permanently altered in ways that predispose individuals to chronic disease in later life, most notably diabetes and coronary heart disease. Although the programming hypothesis has been portrayed by some as a new paradigm for chronic disease, others are more skeptical about the precise role played by early development. Programming research is of particular interest in developing countries. There, historically high levels of intrauterine and early postnatal growth retardation, coupled with the current nutrition transition to increased energy and fat intakes and decreased physical activity (1,2), may play an important role in the rapid increase in chronic disease prevalence.

In this chapter, we explore the relation of fetal and early postnatal growth retardation to the cluster of risk factors and disease states among adults, described alternatively as “syndrome X,” the “insulin resistance syndrome,” or “the metabolic syndrome.” The risk factors include obesity, raised blood pressure, raised serum triglycerides and low-density lipoprotein (LDL) cholesterol, insulin resistance, and hyperinsulinemia (3). We ignore the debate (4,5) on whether this is a true syndrome with a common etiology tracing to insulin resistance and focus instead on the components that make an uncontroversial contribution to morbidity and mortality. We begin with a brief summary of the associations found in the epidemiologic literature, relating size at birth to later chronic disease. We then explore some of the main problems in the conceptualization and design of programming research. We focus on the limitations of birthweight as a marker for intrauterine insults, the failure to adequately consider postnatal factors, the possible role of genetics, and the absence of a clear conceptual framework linking early exposures with later outcomes. Finally, we consider health policy implications of the programming hypothesis and identify needs for future research.
OVERVIEW OF HUMAN STUDIES

The vast majority of studies purporting to test the programming hypothesis in human populations focus on blood pressure, insulin resistance/hyperinsulinemia, serum lipids, type 2 diabetes, and coronary heart disease. Numerous reviews have already been published (6–11), so we will not duplicate those efforts here. Instead, we summarize the associations reported as a background to a more extensive critique of programming research. Together, the studies show a heightened disease risk associated with small size at birth or in early infancy.

Coronary Heart Disease Mortality

Barker’s initial studies of coronary heart disease mortality among British men showed a strong inverse relation of birthweight to coronary heart disease mortality [see Barker (12) for a summary and historical perspective], providing an important catalyst for further research. These results have since been substantiated in other countries, including Sweden (13), Wales (14), the USA (15), and India (16), and are believed to reflect the effects of programming on a range of coronary heart disease precursors and risk factors.

Blood Pressure

Blood pressure is the most extensively studied outcome. Leon and Koupilova (7) recently published a comprehensive review of epidemiologic reports on the relation of birthweight to blood pressure. After assessing studies in 47 different populations meeting their inclusion criteria, they concluded that “there is substantial and consistent evidence for a negative association between birthweight and systolic blood pressure from childhood through the eighth decade of life,” with the relation strengthened when adjusted for concurrent size. This relation tends to be less apparent during adolescence, when effects of birthweight may be obscured by maturational events (9). Less evidence and less consistency are apparent from studies of diastolic blood pressure, but there is a similar inverse relation with birthweight. Relatively few of the studies controlled for confounding by socioeconomic status or behavioral risk factors. Several studies focus on more specific defects that might account for altered blood pressure, including decreased arteriolar compliance (17), alterations in left ventricular mass (18), or patterns of blood flow (19).

Atherosclerosis Risk: Triglycerides, Lipoproteins, and Fibrinogen

Fewer studies have examined the association between birth outcomes and lipid profiles in the context of the programming hypothesis. Results are inconsistent, alternatively showing raised serum total cholesterol with short birth length (20), raised cholesterol with low birthweight (21), or raised triglycerides but not LDL or total cholesterol with low birthweight (22). Plasma fibrinogen results are also mixed: Martyn et al. (23) and Barker et al. (24) found an inverse relation of birthweight and plasma fibrinogen in adult men, whereas Cook et al. (25) found no relation between birthweight or ponderal index and fibrinogen in children from the United Kingdom.
Diabetes and Its Precursors

Small size at birth, in particular, low weight for length, is more consistently associated with impaired glucose tolerance, insulin resistance, and type 2 diabetes (for reviews, see refs. 6, 10, and 11). Barker (11) emphasizes the importance of thinness as a proxy for third-trimester undernutrition resulting in a low muscle mass. However, most research tests the association with birthweight alone. For example, in the Nurses Health Study, Rich-Edwards and colleagues (26) found that women with lower birthweight (<2.25 kg) had a relative risk of roughly 1.8 for developing non-insulin-dependent diabetes mellitus (NIDDM) compared with those in the median birthweight category (3.16–3.82 kg). This estimate was not substantially modified when a wide range of potentially confounding variables was included. Some studies have documented a U-shaped relation between birthweight and later diabetes, with individuals born at both the low and the high ends of the birthweight distribution having higher NIDDM rates (27). This U-shaped relation is not apparent in the large Nurses Health Study cited above. There is evidence that fetal exposure to raised glucose in pregnancies complicated by gestational diabetes, or the resultant macrosomia, may program heightened risk for problems of glucose control in the offspring, through a pathway distinct from that of prenatally undernourished individuals (28).

Obesity and Fat Patterning

Most reports relating birth outcomes to later adiposity are concerned with the effects of high birthweight, often in the context of gestational diabetes. The question most often posed is whether fat babies become fat adults. There is more evidence for such “tracking” of weight and adiposity over time than for an inverse effect of birthweight on later adiposity (for review of the roles of prenatal undernutrition and overnutrition on later obesity, see ref. 29). Although low birthweight typically predicts lower body mass index (BMI) in adult life, a few studies have shown that individuals with low birthweight tend to have a more central pattern of fat deposition, as reflected in such markers as the ratio of subscapular to triceps skinfolds (for review, see ref. 30). Others have examined the relation of stunting during early childhood to later BMI, with an increased risk of overweight in older children who were stunted by 2 years of age (31), and increased abdominal fat, as reflected in the waist/hip ratio, among Guatemalan adults stunted during infancy (32).

CRITIQUES OF PROGRAMMING RESEARCH: METHODOLOGICAL AND CONCEPTUAL PROBLEMS

Design of Epidemiologic Studies

Epidemiologic studies tend to adopt similar analytic strategies. To date, nearly all published human studies of the relation of early growth and later disease outcomes are observational and therefore cannot form the basis of causal inferences. To our knowledge, the only experimental human studies have examined long-term
developmental outcomes, including blood pressure, in premature infants fed on different dietary regimens (33). The relative newness of the programming hypothesis means that, to date, investigators have tended to take advantage of existing data rather than beginning new prospective, longitudinal studies designed specifically to test the programming hypothesis. Thus, information about fetal or early infant characteristics is typically retrospective and limited to what is available in birth or research records. This raises concerns about the validity and reliability of birth outcome measures and limits the ways in which fetal growth can be characterized. For example, when using birth records, we are often missing accurate data on gestational age, length, or head circumference. Two large ongoing studies in the USA (the Nurses Health Study and the Male Health Professionals Study) rely on self-reported birthweight. The problems related to the over-reliance on birthweight are discussed in greater detail below.

Similarly, many researchers use risk factor or health outcome data collected for other purposes. It is often difficult to compare results of studies conducted in dramatically different settings and at different points in time, because of differences in measurement technique (e.g., circumstances of measurement and instrumentation when measuring blood pressure or methods of assessing glucose tolerance). Studies vary substantially in the research setting (e.g., in developing versus industrialized countries), sample size, age of subjects, and the degree to which concurrent risk factors are taken into account. Joseph and Kramer (8) criticized the epidemiologic programming literature as fraught with inconsistencies and conflicting results as well as failing to deal adequately with confounding and potential selectivity bias. They further argue that the programming hypothesis cannot explain international trends in coronary heart disease prevalence.

More basic is a set of problems related to the conceptualization of the programming hypothesis in general. In the next sections, we highlight several issues that we feel have received inadequate attention in published reports to date. These include the misplaced emphasis on birthweight, the need for an understanding of the pathways through which programming may affect chronic disease risk in humans, and the role of the postnatal environment.

**Misplaced Emphasis on Birthweight**

Birthweight is the most common and easily obtained birth outcome measure. It is therefore not surprising that most epidemiologic studies rely on birthweight to assess the relation of fetal growth to later disease states. Whereas some studies acknowledge the limitations of this approach, few (34) systematically address the difficulties of interpreting birthweight variation or, more generally, give adequate consideration to the heterogeneous factors that birthweight reflects. At best, birthweight is a sensitive but nonspecific indicator of fetal growth and development. When gestational age information is available, small size for gestational age—rather than low birthweight because of prematurity—is more consistently and more powerfully associated with later disease outcomes. This has led to the assumption that intrauterine growth retardation (IUGR) is centrally important to the programming process. However, even the
designation of IUGR does not differentiate potentially relevant patterns of fetal
growth or timing of growth-retarding influences, nor can it tell us which specific fac-
tors resulted in limited growth. In this section, we emphasize the multiple paths lead-
ing to common birthweight endpoints and the resultant challenge of interpreting the
significance of birthweight variation in programming research.

A central assumption in programming research is that birthweight is a reflection of
fetal nutritional sufficiency. At a basic level, cellular growth is contingent upon the
availability of substrate, and in this sense, nutrient flow across the placenta is a phys-
ical requirement of fetal growth, as emphasized in classic models of IUGR. Fetal nu-
trition also regulates growth indirectly, through effects on the production of hor-
mones such as insulin and insulin-like growth factor-1 (35). Given the importance of
substrate supply for growth regulation, growth may be impaired by any process that
interferes with delivery of energy, oxygen, and nutrients to the fetus, including inad-
equate maternal nutrition, compromised placentation, maternal infections, or inter-
ference with other regulatory mechanisms (36). Alternately, premature exposure to
hormones that trigger tissue and organ maturation in preparation for parturition (e.g.,
cortisol) may reduce fetal growth and birthweight. Also, deficiencies of hormones
with growth-promoting effects targeted to specific organs and tissues (e.g., thyroid
hormone) can modify body proportions, the size of specific organs or tissues relative
to body weight, or overall body composition (37).

Timing of growth impairment may have long-term consequences, as tissues and
organs growing most rapidly at the time of insult are believed to be most susceptible
to growth impairment or, in the case of programming, to permanent alterations in
structure or function. When experienced early in gestation, poor fetal nutrition may
have an effect on placental size and uteroplacental blood flow (38), resulting in a pro-
portionately growth-retarded newborn. In contrast, nutritional insufficiency late in
gestation may have disproportionate effects on skeletal muscle and adipose tissue,
which grow rapidly approaching term. Infants who differ in body proportions at birth
may also differ in their postnatal growth capacities. Studies of Filipino infants show
that those who are compromised in weight but not in length at birth grow more
rapidly in weight during the first 2–4 months of life (39), whereas those who are
small and well proportioned tend to remain short into adolescence (40).

Pathways Linking Fetal Growth and Adult Disease

Given the heterogeneous factors reflected in birth outcomes, focusing on birthweight
as a generic marker of prenatal insult hinders efforts to untangle the causal chain link-
ing fetal growth with postnatal disease risk (see Table 1 for a summary of program-
mapping mechanisms proposed in published reports). This limitation is important, as
careful consideration of the different possible pathways linking prenatal growth with
specific outcomes is essential if we are to develop testable hypotheses and (eventu-
ally) targeted interventions. In some cases, poor growth per se may be a cause of later
disease. For instance, growth retardation of skeletal muscle near term could reduce
the mass of insulin-sensitive tissue, which has been proposed to contribute to insulin
TABLE 1. Summary of proposed fetal responses to undernutrition and stress

<table>
<thead>
<tr>
<th>Organ/tissue</th>
<th>Defect</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>Reduced β-cell size, no., and function, ↓insulin production</td>
<td>Heightened susceptibility to insulin insufficiency (IGT and NIDDM)</td>
</tr>
<tr>
<td>Liver</td>
<td>Smaller size</td>
<td>↑Cholesterol, ↑Fibrinogen, ↑Glucoreogenesis (IGT and NIDDM)</td>
</tr>
<tr>
<td>Vascular tissue</td>
<td>Decreased elastin Atherosclerosis</td>
<td>Poor vascular compliance ↑CVD risk</td>
</tr>
<tr>
<td>Kidney</td>
<td>Reduced nephron number</td>
<td>↑BP</td>
</tr>
<tr>
<td>Hypothalamic-pituitary-adrenal axis</td>
<td>Altered sensitivity</td>
<td>Altered stress response, ↑BP, central fat pattern, poor glucose control,</td>
</tr>
<tr>
<td>Tissue action of insulin</td>
<td>Insulin resistance, hyperinsulinism</td>
<td>Could affect BP, progression to IGT/NIDDM</td>
</tr>
</tbody>
</table>

BP, blood pressure; CVD, coronary vascular disease; IGT, impaired glucose tolerance; NIDDM, non-insulin-dependent diabetes mellitus.

resistance (11). In other cases, growth may merely serve as a proxy for unmeasured factors that cause the outcome in question. Gluckman and Harding (36) hypothesize that programmed tissue resistance to insulin in response to fetal undernutrition could reduce growth in utero while later predisposing to hyperinsulinism and related disease risk factors postnatally. In this example, poor growth is not in the causal pathway of disease development but serves as a marker for altered insulin metabolism, which is a common factor contributing to both growth retardation and later health outcomes. Yet another possibility is that genetic factors with effects on both fetal and postnatal growth and disease outcomes could contribute to birthweight–disease associations (8). If so, birthweight would effectively function as a marker for the presence of certain disease susceptibility genes. Although this possibility warrants careful scrutiny, cross-breeding experiments (e.g., between ponies and horses) have classically illustrated the overriding influence of maternal body size on offspring size at birth, suggesting that genes alone are unlikely to explain the results of programming studies.

Animal models of maternal protein restriction provide us with our best evidence of programming mechanisms and suggest that various direct and indirect pathways are likely to be involved in any given outcome. In the well studied model of programmed hypertension in the rat, maternal protein restriction facilitates the passage of maternal glucocorticoids into fetal circulation, which has the dual effect of slowing growth and resetting the hypothalamic–pituitary–adrenal axis (41). Offspring are born lighter and have higher blood pressure as a result of heightened cortisol production and an exaggerated response of the renin–angiotensin system to cortisol (42,43). In addition to these functional changes, protein-restricted rats have growth-related
changes in kidney size and in the numbers of nephrons and glomeruli, which may further increase the blood pressure (44). Thus, in this rat model, impaired fetal growth is linked to postnatal outcomes through a complex set of direct and indirect pathways. Researchers hoping to understand programming in human populations must find innovative ways to chart this complexity through the use of appropriate markers reflecting specific exposures.

There are numerous examples of anthropometric, behavioral, and biochemical measures that allow greater resolution of the timing and nature of prenatal insults and that could provide feasible alternatives to birthweight in future programming research. When more birth information is available, retrospective studies have used such birth indicators as body proportions, abdominal circumference (interpreted as a marker of liver size), head circumference, and placental size relative to birthweight. Some relations have been found using these measures when there is no relation with birthweight. For instance, disproportionately small or disproportionately large placental size relative to birthweight is associated with increased coronary heart disease mortality rates, whereas small abdominal circumference at birth has been linked to later cholesterol metabolism (12). Thinness at birth, represented by the ponderal index, is typically a marker of late gestation growth impairment and has been shown to be a stronger predictor than low birthweight of developing insulin resistance and type 2 diabetes in adult life (45). These and other easily measured indexes may hold promise as markers of growth impairment or nutritional insufficiency during specific stages of gestation (12), but future research is clearly needed to establish such linkages with greater certainty. One less investigated marker is fingerprints, which are believed to reflect conditions of early fetal growth. The number of fingerprint whorls has been shown to correlate positively with indexes of prenatal growth impairment such as reduced abdominal circumference and a high ratio of head to abdominal circumference (46). Studies are needed to clarify the significance of these associations and the potential value of fingerprint patterns as markers of growth retardation specific to early gestation.

Another strategy is to include measures of maternal factors known to directly contribute to fetal growth variation and IUGR. To date, few studies have included such measures, and the results are generally inconsistent. Several have assessed factors reflecting maternal nutritional status during pregnancy, including BMI, weight gain, and skinfold thickness. In a study of Jewish military conscripts, Laor et al. (47) found no evidence for an association between blood pressure and previous birthweight, maternal BMI before pregnancy, or weight gain during pregnancy. Stanner et al. (48) similarly found no evidence of increased coronary heart disease or diabetes rates in adults who had been subjected to nutritional deprivation in utero during the siege of Leningrad. In contrast, Clark et al. (49) found that maternal weight gain between 18 and 28 weeks of gestation was inversely related to offspring blood pressure among women with low energy stores early in pregnancy, as indexed by below-median triceps skinfold thickness at 18 weeks’ gestation, whereas Godfrey et al. (50) found an inverse relation between maternal skinfold thickness during pregnancy and blood pressure in Jamaican children.
These studies move one step back from the black box of birthweight to consider maternal characteristics during pregnancy. However, few programming studies have assessed the direct effect of maternal dietary intake during pregnancy (51,52), and, to our knowledge, none has included measures of psychosocial stress or other proximate factors known to influence fetal growth. Techniques could also be borrowed from studies of fetal growth in pathologic conditions, such as gestational diabetes, which routinely assess levels of hormones or substrate concentrations in cord plasma at parturition (53). Similar methods could be incorporated into programming studies to provide information on the hormonal and metabolic milieu before birth or even during pregnancy.

ROLE OF POSTNATAL FACTORS

The role of postnatal factors has been ignored in most programming research. In some cases, the study of postnatal factors is constrained by lack of data. This is often true because, as mentioned above, most human studies published so far were not originally designed to test the programming hypothesis. In the classic retrospective study design used in much of the human research, little information is available from the time between birth and when the outcome of interest was measured—a period covering decades of exposures that may influence the development of disease.

A more basic problem is the lack of a clear conceptual framework to articulate the likely ways in which postnatal factors affect the risk of chronic disease. The potential for programming is not restricted to the prenatal period in humans. There is evidence that mode of feeding (independent of birthweight) has long-term effects that could be interpreted in the context of programming. Several studies in Finland have shown significantly lower systolic blood pressure in children or adolescents who were previously breast-fed compared with those who were bottle-fed (54,55). Others have shown a relation of breast-feeding to lipid profiles in childhood or adolescence (56) or in adult life (57,58) and an increase in type 2 diabetes in adult Pima Indians who were bottle-fed compared with those who were breast-fed (59). Growth patterns during infancy may also affect later disease (although it is difficult to determine their independence from prenatal growth patterns). For example, Fall et al. (60) interpreted their findings of an inverse relation of weight at 1 year with coronary heart disease prevalence in adult British men as evidence of a postnatal growth effect, as coronary heart disease was not related to birthweight in this sample. Others have noted that linear growth retardation, manifested as stunting by age 2, is related to overweight in later childhood in diverse samples from Brazil, China, Russia, and South Africa (31). This is an important point because although the incidence of low birthweight has been reduced substantially in developing countries in the last several decades, there remains a high level of stunting related to poor growth in the first 2 years of life in these countries. For example, in China, the current prevalence of low birthweight is about 9%, but stunting occurs in about 19% of children by age 2. More striking, in our Cebu, Philippines, study cohort, nearly 65% of children were stunted by age 2, but only about 11% had low birthweight (40).
More generally, postnatal exposures may independently affect later risk of chronic disease, confound the relation of birth outcomes with later disease, or interact with birth outcomes to affect later disease. The analytic models used in the vast majority of programming studies have not included explicit tests of these alternatives. Most involve simple regression or hazard models, where the outcome (e.g., systolic blood pressure) is seen as a function of some measure of size at birth (usually birthweight alone) and—depending on the nature of the sample—variables such as age and sex. Some studies include body size or composition (usually indicated solely by height or BMI) measured concurrently with the outcome, and some include suspected confounders such as socioeconomic status or smoking. These models are fraught with problems and must be carefully interpreted. We first address problems related to inclusion of concurrent body size measures.

Consider a simple model testing the association of systolic blood pressure at age 40 with birthweight and BMI at age 40. The inclusion of adult BMI is usually justified on the grounds that it is a strong predictor of blood pressure. Lucas and colleagues (61) recently discussed the statistical interpretation of this type of model and cautioned readers that when a subsequent size measure is included, birthweight can be interpreted only in the context of that size measure. Following our example above, when birthweight and adult BMI are included, the correct statistical interpretation is that change from birth to age 40 is what matters. Lucas et al. argue persuasively that failing to consider this interpretation will lead to an underestimation of the effects of postnatal factors. However, most investigators interpret the results from such models as evidence of the relative importance of birthweight and later body size, reporting the following alternatives:

- Birthweight becomes significant or its association with later disease strengthens when later size is taken into account. For example, Leon et al. (34) concluded that the effect of birthweight on blood pressure in adult Swedish men is potentiated by BMI in later life, and Stanner et al. (48) suggested that early nutritional deprivation and later obesity acted synergistically to affect blood pressure in women.
- There is no effect, or an attenuation of the effect, of birthweight when later size is taken into account. For example, Vanhala et al. (62) found no effect of birthweight on risk of metabolic syndrome in adulthood but found an increased risk associated with being in the highest BMI quartile at age 7 and with an increase in weight or BMI quartile from birth to age 7; similarly, Whincup et al. (63) found that size in childhood was more strongly related to glucose and insulin levels than was size at birth.
- There is no change in the effect of birthweight when size is taken into account. In the Nurses Health Diabetes Study, Rich-Edwards et al. (15) found similar associations between birthweight and type 2 diabetes at all levels of adult BMI.

From a conceptual perspective, we might ask several other important questions. Is adult body composition, represented by BMI at age 40, itself programmed by the same factors that affect systolic blood pressure and therefore in the causal pathway? Is adult BMI independently a risk factor for raised blood pressure? Does adult BMI
modify the relation of birthweight to adult blood pressure? More complex models are needed to fully answer these questions. At a minimum, statistical tests for confounding versus effect modification and testing of interactions of size at birth with later size should be included in analysis plans.

An important interaction of birthweight and later obesity is suggested by studies that show the highest levels of disease risk in groups of individuals characterized by low birthweight and high BMI or adiposity in later life. According to the "thrifty phenotype" notion, fetal programming represents an adaptive strategy to cope with undernutrition. Later, pathology develops only in the presence of adequate or excess nutrient availability. For example, glucose intolerance is greatest among those who move from low birthweight to high BMI as adults (45,60). It is also possible that pathology develops at lower levels of risk factors among individuals who had growth restriction in early life, as illustrated by the findings in previously malnourished Indian children that insulin resistance is seen at lower levels of body fat than in Western populations (64).

Another shortcoming of many human studies is their failure to consider the effects of a broader range of postnatal exposures. In some cases, analyses have controlled for potentially confounding variables such as socioeconomic status indicators or behaviors such as smoking. More proximate risk factors such as diet and physical activity have not been tested, most probably because they are more rarely measured (exceptions are studies such as the longitudinal Nurses Health and Male Health Professionals studies in the USA). Decades of epidemiologic literature show strong relations of fat patterning, diet, and physical activity to type 2 diabetes, lipid profiles, and coronary heart disease. Moreover, the effects of birthweight on blood pressure or diabetes may be mitigated or exacerbated by later diet and activity patterns; conversely, the effects of diet and activity may be different in previously well nourished compared with poorly nourished children. It is important to include factors such as diet and activity in models relating early developmental factors to chronic disease outcomes because we need to be able to quantify the relative contribution of risks associated with the pre- and early postnatal environment versus those associated with later (and possibly more modifiable) lifestyle factors.

We also need to consider the importance of timing of postnatal exposures. We may acknowledge that diet and activity should be considered, but at what ages? Whereas many epidemiologic studies of programming are longitudinal, in that they typically relate an early exposure to a later outcome, none has incorporated a longitudinal conceptual model or analysis method. If models do not include repeated measures of exposure over time, they cannot consider the dynamic effects of factors over the life course of the individual. Susser et al. (65) suggest that we should broaden the traditional epidemiologic concept of multiple risk factors to encompass consideration of development over time. They encourage us to think in terms of dynamic processes, including consideration of critical periods at particular phases and interaction of early and later factors. An important implication of a dynamic model is that we cannot simply control for an exposure at one phase of the life cycle; rather, we need to consider (and properly model) multiple exposures over the life course, with special attention
to changing exposures. Given the lifetime of developmental processes that contribute to the risk states or disease endpoints measured in epidemiologic studies, the personal historical factors most relevant to the development of disease are less likely to be measured. Moreover, salient aspects of environment may change over time. In infants and children, environmental factors that influence growth and development may be more important, whereas in later life, factors that affect physiology rather than growth may be of greater concern. Similarly, the effect of the same environmental factor may vary over the life course, affecting growth at one stage but other aspects of physiological functioning at another.

POLICY IMPLICATIONS

Programming research has tended to focus our attention on birthweight. Although advocates of improving maternal nutrition and health during pregnancy have welcomed this focus, it raises numerous concerns. If low birthweight is viewed as "the problem," it is tempting to think that solutions should take the form of interventions aimed at increasing birthweight. Such a simplistic and narrowly focused approach is premature and, indeed, dangerous, given that we do not yet know why and how birthweight is linked to later disease. Further, this approach may lead us to ignore—as has been done in many reports on programming to date—the possibility that programming continues into the early postnatal period. This is of particular importance for developing countries, where postnatal growth retardation continues to occur at higher prevalence than IUGR.

The programming model, as has been stated, is too deterministic and simplistic. Any relation between prenatal factors and later childhood or adult outcomes is likely to involve a complex cascade of factors and their interaction. At present, there is insufficient consideration of the importance of potentially modifiable risk factors in later life. Thus, we cannot properly weigh the risk of early growth restriction against later risk factors, nor can we estimate the degree to which early risk factors can be mitigated by prudent health behaviors from birth onward. Those most concerned with adult chronic disease fear that the importance of prudent health behaviors in adult life may be underplayed if the programming hypothesis is not put into proper perspective. It is important to keep in mind that early exposures and responses are likely to be but some of many factors affecting the lifelong process of chronic disease development. The challenge is to determine the magnitude of the risk and the degree to which it can be altered in both the prenatal and the postnatal environments.

To the extent that we can develop a better understanding of why and how programming affects later disease risk, two possible categories of intervention emerge (each of which is still far in the future). First, markers of fetal insults may serve to identify individuals with a heightened risk of later disease. If we then understand more about the potential mitigating or interactive effects of postnatal factors such as diet and exercise, more intensive interventions could be targeted at those individuals identified as at risk. Second, it may be possible to manipulate maternal factors during pregnancy to program the developing fetus proactively so as to minimize the
long-term chronic disease risk. Given the large number of questions left unanswered by programming research, such interventions are not yet warranted. How are we likely to make progress in the future?

SUGGESTED DIRECTIONS FOR FUTURE RESEARCH

- We need more specific markers of birth outcomes that allow greater resolution of the timing and cause of growth restriction. We could begin immediately with more widespread use of easily obtainable indexes that validly represent body composition (such as the ponderal index), but prospective studies designed to test programming hypotheses should include measures that are targeted as much as possible to the timing and nature of the insult, given the hypothesis in question.
- Research should test alternative pathways through which early exposures and responses may affect later health outcomes. In developing models, the programming concept should be integrated with other theoretical frameworks, particularly those pertaining to the separate and interactive effects of other proximate factors known to affect chronic disease risk, and in consideration of the role of genetics. Future models should generate more rigorous, testable hypotheses.
- True longitudinal studies are needed, in which multiple measures of exposure over time are collected and considered in proper sequence. At a minimum, researchers should use models that correctly assess the importance of prenatal and postnatal factors by looking specifically at markers of growth at several different ages, as suggested by Lucas et al. (61).
- Relations should be explored in diverse populations with different factors affecting maternal, fetal, and infant nutrition. It would be a mistake to uncritically extrapolate findings from one context to another.
- Better bridges must be built between experimental animal model research and epidemiologic or clinical studies in human populations. Animal model research should aspire to better reflect the determinants of human birthweight variation (i.e., assessing factors other than protein restriction). Conversely, programming mechanisms suggested by animal studies should be explicitly tested in human epidemiologic studies rather than merely cited as evidence for the plausibility of documented associations.

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DISCUSSION

Dr. Uljaszek: I'm in strong agreement with your approach. With existing designs, we need large samples to detect small effects. What you are suggesting in prospective studies implies that we could reduce the sample size needed if we can move to longitudinal study designs with greater power. Have you any idea of what sort of sample sizes you might expect in order to create those cohorts?

Dr. Adair: I'm not sure what we are going to need in terms of sample size. With our Cebu studies of cardiovascular disease risk factors, we are looking at a sample of around 600 and finding results that are biologically important, for example, a 6- to 8-mm Hg difference in blood pressure between the lowest and the highest BMI groups. But there is a tremendous amount of variability within the population, so the statistical significance of these results is at the 0.03–0.05 level, in other words not highly significant. Thus, a sample size of 600 is barely adequate to look at these differences. In a population with less variability, it's hard to say what one would need.

Dr. Molinari: Are you aware of any significant publication bias in this context?

Dr. Adair: Yes, I think there is a publication bias. People don't rush to publish a result that says there is no relation between birthweight and some later outcome. However, as the literature is growing, there are increasing numbers of publications showing no relation or showing a relation in one particular age group but not in another. The problem is that not all of the studies are conducted under the same circumstances. The populations are very different, the sample sizes are very different, and the outcomes may be measured differently, so it is hard to compare negative results and positive results. Several meta-analyses include studies reporting no relation whatsoever of birthweight to subsequent outcomes (1,2), but yes, I do think there is publication bias.

Dr. Walker: Last year, Alan Lucas published a paper in which he said that the important factor may not be birthweight (3); because you often have to adjust for current size before you see the relations, the important factor may actually be crossing centiles from birthweight to childhood or adult size. Could you comment on that?

Dr. Adair: I think that is exactly what Cebu results show, as well. We don't see any crude relation between birthweight and blood pressure, cholesterol, or LDL. I have also looked at age of menarche in girls, and there is not a crude relation with birthweight. What is apparent is the effects of rapid postnatal growth. It may be this rapid growth that represents the risk factor. There is some intriguing evidence from the adoption studies of Romanian orphans who undergo very rapid growth after adoption. The girls mature earlier and they are relatively fatter, so it may be that the rate of postnatal growth is particularly important, and studies that focus on birthweight obscure that pattern. That is why I think it is so important to look at other postnatal factors and postnatal growth rates. Of course, postnatal growth rates are related to birthweight, so we see different patterns of postnatal growth in infants who are of different weights and proportions at birth. It is really difficult to tease out some of those effects. Lucas et al. (3) have also recently published a paper in which they suggest that we need to look at different ages to see whether it is the change in growth between the different ages that matters most. If we are looking at an adult outcome, and if we control for, say, BMI in adulthood, adolescence, childhood, and at birth, what is the most important time to look at? So, they have challenged researchers to take different approaches and not limit their focus to birthweight. Of course, to do that you need longitudinal studies.
Dr. Ramakrishnan: I was intrigued that in the Cebu results, the group that had the lowest value for cholesterol as well as for blood pressure were those who were in the middle band of birthweight and had the lowest BMI. What is your interpretation of that?

Dr. Adair: One of the things that was very surprising to us was that the lipid levels were relatively high in the Cebu girls. The mean total cholesterol levels were around 180 mg/dl, which strikes me as relatively high for a population that has such a low BMI and low dietary fat intake. There were substantial differences between the boys and girls in cholesterol levels, which we have yet to explain. We need to explore the effect of diet, in particular the reliance on oils—palm oil or coconut oil—which are used in the Philippines. We also don’t fully understand the relation between the cholesterol levels that we observe in adolescents and later disease risk. That is going to require more longitudinal data. The Cebu data suggest that having a normal birthweight and moderate fatness later on represents the lowest risk profile. But we really need to look more carefully at the data and follow these children over a longer period to see what kinds of disease risks emerge.

Dr. Martorell: One theme that comes across from your review and other reviews is that what seems to matter is change—that is, being born thin or small or being small at a certain age and then rapidly moving up across centiles. Can you comment on this?

Dr. Adair: The programming hypothesis is particularly intriguing for those of us working in developing countries where there is rapid economic and social change. If we are talking about change that has occurred, for example, over the last decade, we are referring to cohorts in which there may have been a relatively high prevalence of low birthweight and IUGR 10 or 20 years ago. Those individuals are now moving into the years where exposure to risk factors is becoming more and more important. The rapidity of change associated with the nutrition transition ought to attract our attention, particularly as the child who was growth retarded in utero is most susceptible to the kinds of change we see in association with a nutrition transition. For example, a child who was underweight at birth may have a greater tendency to store excess energy as central fat and that child may be at greater risk as an adult. I think this is a very important area in the context of the nutrition transition.

Dr. Frongillo: I fully agree with your critique of the literature and your call for studies that address the issues raised by this research, but I want to think more about the policy implications. You are concerned about how these findings may lead to a reduction in interventions to prevent chronic disease in adults. My own experience in the policy arena is the opposite. I haven’t heard people arguing that we don’t need to worry about our adults because we can address the problems early on. In fact, I’m hearing this interpreted as an additional impetus for studies on prenatal nutrition. My own perspective is that this is an area that has been underfocused in policy. We tend to ignore pregnant women and infants in favor of the diseases we see directly in front of us in adults. I wonder whether this research may lead policy in the right direction but for the wrong reasons.

Dr. Adair: I have certainly heard some of the major proponents of this theory suggesting that because of programming, we need to pay less attention to other risk factors later on in life, though I don’t think that’s the mainstream argument. I think a more reasoned evaluation is that programming is an important factor, but not the
whole story. Obstetricians welcome it because it gives an additional impetus for studies on prenatal nutrition.

Dr. Frongillo: It would really be helpful if you could lay out what are different questions that need to be addressed. For example, does prenatal development lead to later functional outcomes? How does it do that? What is the relative importance of prenatal versus postnatal factors? Which factors are mostly likely to be modifiable? Are there synergistic or antagonistic relationships? The concern I have is that longitudinal designs are very expensive and complicated, and it seems to me that there is potential here for doing a lot of work at great cost without answering the questions that really need to be answered. Specific longitudinal designs may be optimal for answering certain questions but of no use for others. The issue of sample size was raised before, and actually very little is known about sample size calculations for longitudinal studies, but there are various ways to approach that. However, it will surely depend upon the exact design advocated for a particular situation.

Dr. Adair: I appreciate your comments. We probably need to proceed toward more case-control studies—for example, where we are identifying risk groups and following larger samples that we already know are at risk. One of the disadvantages of the Cebu data is that the cohort was not selected for birth characteristics; but by taking subsets, for example, in our immune study, and deliberately sampling low-birthweight full-term infants in a kind of case-control design we can use a smaller sample size to answer some of the questions. The problem is that if we feel that postnatal factors are really important, we need to have studies that can quantify those postnatal factors. That requires repeated measures of factors such as diet and activity. I don’t know how else we can get that sort of information unless we have well-designed longitudinal studies.

Dr. Frongillo: I agree with you, but I think that moving to longitudinal designs means that design and analytic issues and interpretation become much more complicated. I could give an alternative interpretation for one of your findings. You showed that the group that was the leanest at birth but got the fattest later was the one with the highest blood pressure. Another interpretation of that is simply that the group that had the opportunity to gain the most fat was also the group that had the greatest increase in blood pressure. That interpretation has nothing to do with programming at all, but it’s a consequence of using data that were not specifically designed to answer that question.

Dr. Adair: I am struck by the fact that these alternate explanations probably fit very nicely with what we have been talking about for the last couple of decades in the context of growth and development. Are we dealing with a programming effect, or are we dealing with the same kind of patterns of compensatory growth that Tanner was talking about? I’m personally skeptical about calling it programming when I see the effects of birth size and rapid postnatal growth on earlier maturation. There is nothing magic about it. I think, however, that we need to understand some of the hormonal mechanisms and other alterations that are occurring prenatally in order to determine whether there is a programming effect or whether it is something else. That’s where we need better measures of exposure during pregnancy to try to answer some of the mechanistic questions. I think research really needs to proceed along two lines: One is more epidemiologically oriented, and the other is clinically oriented to try to get better measures of exposures such as hormone levels and stress during pregnancy.
Dr. Gomez: Going back to the Cebu study, I would just like to comment that the basic Philippine diet is high in sodium, cholesterol, and fat. So, I guess it would be wise to look into dietary factors in the interpretation of results.

Dr. Adair: I agree that is very important. We will be looking at the contribution of different types of fats from different food sources. The percentage of dietary energy from fat, however, is pretty low in this population—only around 18%—which is why I was surprised to see the total cholesterol level as high as it was. It’s something we really do need to explore.

REFERENCES