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THE "FETAL ORIGINS" HYPOTHESIS: Challenges and Opportunities for Maternal and Child Nutrition

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■ **Abstract** The "fetal origins" hypothesis postulates that conditions, most likely nutritional, "program" the fetus for the development of chronic diseases in adulthood. Associations between the newborn's size at birth and various determinants or consequences of chronic diseases have been identified in many, but not all, of the available studies. It remains to be established whether these associations are causal. Remarkably little information is available on the specific role of maternal nutritional status. The role of birth weight remains difficult to interpret except as a proxy for events in intrauterine life. Unfortunately, birth weight does not make an important contribution to the population attributable risk of cardiovascular disease; lifestyle factors during adulthood make much greater contributions. Data from experimental species suggest possible mechanisms for the origin of chronic disease early in life. It is too soon to use this research as a basis for new interventions directed at pregnant women for the purpose of reducing chronic disease in their offspring.

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INTRODUCTION

In the late 1980s, Barker introduced what has come to be known as the "fetal origins" hypothesis. It states that ". . . poor nutrition, health, and development among girls and young women is the origin of high death rates from cardiovascular disease in the next generation. . . . The fetus responds to undernutrition with permanent changes in its physiology and metabolism, and these lead to coronary heart disease and stroke in adult life" (7). Size at birth is thought to be linked to chronic disease in adulthood via "programming." According to Lucas (67), "programming occurs when an early stimulus or insult, operating at a critical or sensitive period, results in a permanent or long-term change in the structure or function of the organism." This "occurs because different systems and organs of the body develop in fetal life and infancy during critical and sometimes brief periods" (5). Over time and with additional data, Barker has expanded this hypothesis to distinguish between effects that might occur if fetal growth were compromised at different periods of gestation. In particular, he has proposed that compromises to fetal growth in the first trimester of pregnancy might result in hemorrhagic stroke via raised blood pressure; in the second trimester, in coronary heart disease (CHD) via insulin resistance or deficiency, and in the third trimester, in both CHD and thrombotic stroke via growth hormone resistance or deficiency (8).

That there are "critical periods of development" has been known since the 1920s (105). That the events that occur during such periods have consequences far beyond infancy also has been known for many decades. What is novel here is the notion that events in early life might be linked to such chronic degenerative diseases as non–insulin dependent diabetes mellitus (NIDDM) and cardiovascular disease (CVD), which do not usually appear until mid-life or later.

This concept is important because, according to Barker, it represents "a new point of departure for cardiovascular disease research" (6). Such a new point of departure was needed because "the search for influences in the adult environment that lead to the disease has met with limited success" and "adult lifestyle is a poor predictor of individual risk for CVD" (6). If supported, Barker's ideas could aid scientists in identifying new ways of preventing chronic disease. Inasmuch as such chronic conditions now cause the majority of deaths in both developed and developing countries (121), and their contribution to total mortality can only be expected to rise in the coming years, careful attention to the fetal origins hypothesis is certainly warranted.

The fetal origins hypothesis has already been the subject of numerous reviews by Barker and his coworkers (e.g. 5, 6, 9, 10, 12, 13, 32–34, 38), several books (e.g. 7, 11), and many reviews, editorials, and critiques by others (e.g. 2, 24, 39 49, 50, 55, 64, 68–70, 78, 80, 83, 100). In addition, there is now a book on this topic for the lay public (85) that in 1999 was the impetus for a cover story in *Newsweek* (14). In the past year alone, several small scientific meetings that were focused on these ideas were held, and in 2001, the First World Congress on Fetal Origins of Adult Disease will take place in India. To avoid redundancy, this review focuses on the implications of the fetal origins hypothesis for maternal and child health because, if supported, these ideas could change current concepts about, for example, optimal weight at birth and recommendations for maternal weight gain during pregnancy. The fetal origins hypothesis is reviewed from this perspective with particular attention to the importance of maternal nutritional status (MNS) and birth weight (BW). The implications of these findings for public health policy are then explored.

THE MEANING OF BIRTH WEIGHT

The determinants and consequences of the infant's size at birth are well understood (e.g. 22, 53, 55). Most of the morbidity and mortality associated with small size at birth is related to the duration of gestation, not the rate of growth in utero. In other words, it is preterm birth—not low BW (LBW) per se—that is the primary cause of the excess morbidity and mortality in the perinatal period and shortly thereafter. Worldwide, however, small size at birth is much more common than is premature delivery.

Low Birth Weight

LBW is usually defined as a weight at delivery of <2500 g for an infant born at term (≥ 37 completed weeks of gestation) (122). In developed countries, most LBW infants are preterm; the opposite is true in developing countries (112). Infants can also be characterized as small or large for their gestational age relative to an appropriate reference population (118). This approach provides a statistical definition of small size at birth and identifies those who are born at a relatively lower weight, but it does not provide information on the trajectory with which they reached this weight. In other words, it does not distinguish those who grew slowly throughout gestation from those whose growth faltered during gestation (3). It is important to recognize that some small babies have achieved their genetic potential, are not "growth retarded" and are properly in the lower tail of the distribution of BW for gestational age. Others, however, may have suffered from some time-limited insult or long-term condition that suppressed their growth, be properly classified as growth-retarded, and still be of appropriate weight for their gestational age. The classic example of this situation is the infant born to the tall, well-nourished

cigarette smoker (23). It also has recently been suggested that babies who are small relative to their mothers' BW are at increased risk of mortality (100a). Thus, it is difficult to identify accurately which infant is growth retarded, yet it is important to know why this condition occurred before choosing a treatment for it.

The postnatal growth of small-for-gestational-age infants is strongly influenced by their length and body mass index at birth as well as by their "target height" (74) and may be modified by the way they are fed (71). However, although there is catch-up growth in the early months of life, babies who are born small—even in developed countries—tend to stay small throughout childhood (44). They remain lighter and shorter and have smaller head circumferences (generally about −0.5 standard deviations) than do babies born at weights appropriate for their gestational ages. Nor do they accumulate fat at greater rates. In fact, at 6 years of age, they have a relative deficit of fat (45). According to Martorell et al (76), in the literature on intrauterine growth retardation, there is no support for a relationship between LBW and greater fatness at follow-up.

It has been postulated that, among term infants, absolute weight is less important than body proportionality for the development of chronic diseases in adulthood. Further, it has been postulated that the different fetal phenotypes are associated with different long-term outcomes: proportionally small and reduced BW with hemorrhagic stroke, thin and reduced BW with CHD, and short and normal BW with CHD and thrombotic stroke (7, 13). These different phenotypes are distinguished by their ponderal index (weight/height^3). Body proportionality was first advanced as a way to disentangle the heterogenous determinants of intrauterine growth retardation (97), and it was proposed that body proportionality reflected the timing of the intrauterine insult (111). However, critical analysis does not support this concept or the idea that MNS is an important determination of fetal proportionality—at least in well-nourished populations (58). Rather, it appears that body proportionality at birth reflects the severity of the intrauterine insult (57), and once this is accounted for, proportionality is of little additional use in predicting risk of adverse outcomes in the perinatal period (59). It is perhaps not surprising then that studies on the fetal origins hypothesis that have been based on the concepts of body proportionality have produced inconsistent findings (50).

High Birth Weight

At the other extreme of the distribution of BW, prematurity is infrequent; babies may be postmature instead. High BW (>4000 g, "macrosomia") is associated with a variety of negative outcomes for both the mother and the infant. Determinants of macrosomia include (*a*) high maternal age, parity, and height, (*b*) maternal obesity before conception, (*c*) high maternal weight gain during pregnancy, and (*d*) gestational diabetes mellitus (16, 120). Women who deliver macrosomic infants are more likely to have a cesarean section and complications of delivery (120). Macrosomia increases the risk for shoulder dystocia, birth injury, low Apgar scores, and perinatal death (101, 120). Nationally representative data in the United

States (1988–1994) show that 10% of infants are large for gestational age (for those born at term, 77% weighed more than 4000 g at birth) (44). As a group, these infants experienced catch-down growth in the first 6 months of life but thereafter remained heavier and longer and had larger head circumferences (generally about +0.5 standard deviations) than did babies born at weights appropriate for their gestational ages. In addition, unlike infants born at gestation age–appropriate weights, the large-for-gestational-age group consistently accumulated fat after 2 years of age (45).

Normal Birth Weight

It is noteworthy that most of the reports by Barker and his coworkers include few (if any) LBW infants. The "BW effect" in these papers refers to associations between BW values primarily within the normal range (i.e. 2500–4000 g) and outcomes in later life. In fact, according to Barker, "[i]t is clear from our data that growth retardation in early life is not limited to a rather small number of extremely underweight babies who are at risk of dying or of complications after birth. That is a hospital obstetric view of growth retardation. Rather, growth retardation occurs in humans across the whole spectrum of growth. There are many babies of average or even above average birth weight who are growth retarded" (5). In another review article, he states that "[i]f the criteria for successful fetal growth include good health in adult life and longevity, these findings reinforce the view that babies with significant intrauterine growth retardation need not necessarily be 'light for gestational age"' (6).

As described above, it is indeed possible for babies to be born with a normal BW and be growth retarded (particularly with BW values <3000 g). In the relatively affluent areas studied by Barker and his coworkers in the early 1900s (8), as well as in developed countries currently, the frequency of this condition is likely to have been low and be low. However, the prevalence of true growth retardation within the normal range of BW is unknown (19). This is because determining the prevalence would require either serial measurements of intrauterine size from which growth retardation can be ascertained or the use of a customized BW reference (79, 117), resources that are, respectively, unavailable or not in wide use.

It can be argued that infants who experience "catch-up" growth (i.e. who cross weight-for-age percentiles upward) are those who experienced some restraint of growth prenatally. Therefore, the proportion of such children provides an estimate of prenatal growth retardation. Such an estimate is available from the Avon longitudinal study of pregnancy and childhood, a geographically defined cohort of children born in Avon, United Kingdom, in 1991–1992 (87). Size at birth was similar to national data, but 30.7% of the children showed catch-up growth in weight (defined as an increase of 0.67 standard deviation score from birth to age 2). Those who experienced catch-up growth had mothers with lower BW values themselves and were more likely to be the first child of a smoker—all known predictors of small size at birth. They also had taller fathers, which suggests a genetic component

to the rate of postnatal growth. It is noteworthy that they were significantly less likely to have been breastfed at 3 mo than those who did not change growth percentiles or experienced catch-down growth, leaving open the possibility of mode of infant feeding as an important cause of the difference in growth trajectory. This is because appropriate-for-gestational-age infants who are fed infant formula grow more rapidly than those fed human milk. In addition, 24.5% of the cohort showed catch-down growth in weight (defined as a decrease of 0.67 standard deviation score from birth to age 2). They were larger at birth, but their growth pattern was not explained by characteristics of their parents. In this sample it was the pattern of postnatal growth, not BW per se, that explained differences in body weight and fatness at 5 years of age. Furthermore, although the proportion of children who might be regarded as having experienced prenatal growth restraint was higher than might have been expected, the proportion who experienced growth excess was also high—an additional cause for concern. It is likely that both of these proportions are too high because the authors did not account for the statistical phenomenon of regression to the mean.

THE EVIDENCE FROM EPIDEMIOLOGIC STUDIES

There is a paucity of information on maternal nutrition in the context of the fetal origins hypothesis. MNS is one of the few determinants of BW that is modifiable immediately before and during pregnancy (53), and observations about the conditions of women have had a central role in the presentation of the fetal origins hypothesis (7). The available evidence is considered as three groups of studies: those of well-nourished women living under good circumstances, those of previously well-nourished women subjected to famine, and women living under poor circumstances.

Maternal Nutritional Status

Data From Well-Nourished Women in Developed Countries Historical data on the domestic conditions and probable diets of young women at the time of Barker's initial work have been collected from interviews of women aged 80 and over (27). Godfrey and Barker have presented data from three samples of well-nourished women that identify associations between some measure of MNS (e.g. anemia) (37) and the BW of their infants or between dietary intake and BW (31, 35). They also have presented studies that link measures of MNS to blood pressure at age 10–12 in Jamaica (36) and that link diet during pregnancy to blood pressure at age 40 in Aberdeen, Scotland (17). The relationships between MNS and childhood blood pressure were complex and not readily explainable. Maternal triceps skin-fold thickness apparently explained the observed association between maternal anemia and raised blood pressure in the children. Both low triceps skin-fold thickness and weight gain during pregnancy were associated with raised blood pressure in the children (36). The data on dietary intake during pregnancy in the study of adults

come from a classic investigation conducted by Thomson in the 1950s (107a). In this study there was also a complex relationship between the dietary characteristics and later blood pressure that is not easily interpreted within the framework of the fetal origins hypothesis. As expected for well-nourished women, others (76a) who have studied them have been unable to find an association between maternal dietary intake and BW.

To explore the relationship between MNS and blood pressure in late adolescence, data on MNS that were obtained as part of the Jerusalem Perinatal Study were linked to data from physical examinations of men being inducted into military service. Mothers' body weight and body mass index before pregnancy—but not weight gain during pregnancy or the BW of the baby—were positively associated with both systolic and diastolic blood pressures at age 17 (62). The finding on BW is opposite that predicted by the fetal origins hypothesis and the findings on MNS are opposite those of Godfrey et al (36). These results cannot easily be explained by confounding by socioeconomic status or length of gestation, as both were included in the analysis. It is noteworthy that, even with these opposite findings, in both cases there was an association between measures of MNS and blood pressure in the offspring without a significant relationship between BW and blood pressure.

The longest-term follow-up of MNS, by Forsén et al (28) using the national registry, linked birth data (1924–1933) from a hospital in Helsinki, Finland, to deaths (1971–1995). The authors identified a positive association between mothers' body mass index (among those below the median height) and mortality of their sons from CHD; they also found a negative association of the infant's ponderal index with this outcome. In this study on mortality, as for the two discussed above on blood pressure in children and draftees, there was no association between BW and the later outcome—even with an association between the measure of MNS and that outcome. These findings do not support a biological pathway between MNS and these outcomes via BW, as suggested by the fetal origins hypothesis.

Data From Famine-Stricken Women in Developed Countries Links between maternal malnutrition during pregnancy and long-term outcomes for the fetus are available from follow-up studies of three famines. Two of these are ecologic studies because they lack data on the specific exposure of individuals. However, each was so severe and prolonged that it is reasonable to assume that everyone was affected. Three sequential crop failures caused a famine and then epidemics in Finland in 1866–1868 that resulted in the death of 8% of the population; infant mortality was 40% in 1868 (52). Survival from birth to age 17 was significantly lower in the cohorts born before and during the famine than in those born afterwards. However, there was no difference in adult survival among cohorts born before, during, or after the famine (52). The 872-day siege of Leningrad during World War II created a famine during which at least 30% of the city's inhabitants died, most of starvation (102); BW dropped by >500 g during the siege (4). Stanner et al (102) found no differences between those exposed and those not exposed to the famine in glucose intolerance, dyslipidemia, hypertension, or CVD in adulthood.

Although both these investigations provide evidence counter to the fetal origins hypothesis, the conditions were so severe that it is possible only the healthier individuals survived. This could account for the lack of difference between the exposed and unexposed groups.

Data from the famine during the "Dutch hunger winter" of 1944–1945 have been used to evaluate the association between MNS during pregnancy and determinants of chronic disease at about age 50: glucose tolerance, blood pressure, and obesity. It has previously been shown that exposure to this famine was associated with reduced BW, increased perinatal and infant mortality, and obesity in men at the time of induction into military service (only with famine exposure in the first trimester; later exposure was associated with a reduction in obesity) (107). In these three investigations, subjects born in one hospital in Amsterdam and exposed to the famine were compared with a random sample of infants from the same hospital born before or after the famine. In women, but not in men, exposure to famine was associated with obesity, but only when the exposure to famine occurred early in gestation (94). Exposure to famine during gestation was associated with some but not all measures of decreased glucose tolerance. The effects were greatest in those who became obese as adults, but the association was not mediated by obesity (93). In contrast, exposure to famine during gestation was not associated with blood pressure, even though those who were small at birth had higher blood pressures (96). Thus, the findings from these three "natural experiments" provide only occasional support for the fetal origins hypothesis.

Data From Developing Countries Studies from developing countries, where maternal malnutrition remains common, are recent additions to epidemiological studies on the fetal origins hypothesis. Data from Mysore, India, show the predicted negative association between BW and CHD for those older than 45 years (103). The mean BW in this population was low (about 2750 g) and mothers' weights also were low, but no data on maternal height were presented so body mass index cannot be calculated and, thus, MNS is unknown. Maternal weight was not related to the prevalence of CHD, but it was only available in a subset of the cases, so adequate statistical power may have been a problem in this analysis. In contrast to data from developed countries, there was no association between BW and NIDDM (26), and there were positive associations between BW and blood pressure (61) and measures of lung function (men only) (104) in this population.

Distinct differences in seasonal food availability and agricultural work load create differences in MNS in Gambia. In the harvest season, MNS is normal, but in the hungry season, women lose weight and BW declines by 200–300 g; this is reversed by maternal supplementation (18). In three rural villages, those born in the rainy (hungry) season had the highest blood pressures at 8–9 years of age; a proxy for MNS (mother's weight at 6 months of pregnancy) was not related to the child's blood pressure. The opposite was true for younger children: Those born in the dry season had the highest blood pressures, and MNS was positively associated with their blood pressure (75). Using demographic data collected since 1949, Moore

et al (82) observed that those born in the hungry season had a significantly higher mortality rate after age 15 and, especially, between 35 and 50 years of age. However, mortality in this population was dominated by infections and pregnancy-related deaths, and no deaths were attributed to chronic degenerative diseases. In a further case-control analysis of these data, the authors found no differences between cases and controls in measures of nutritional status at 18 months of age, but they observed a close correlation between temporal pattern of BW and that of death (81). They speculated that their findings might have resulted from nutritional programming of immune function, which could have occurred prenatally, postnatally, or both. Thus, the findings from these two developing countries provide no support for an association between MNS and the predictors or consequences of chronic diseases. The mortality data from Gambia suggest that something about season of birth is related to mortality at 15–48 years, but what this might be is unknown.

In summary, evidence is lacking for a link between MNS and the determinants or consequences of chronic disease in offspring as children or adults. This same conclusion was reached by Leon & Koupilová, who called this "a priority area for future work" (65). The following question then arises: Is any association of BW with later outcomes really driven by MNS? Lucas (69) has labeled this a "key area for debate," noting that "[p]oor intrauterine growth might be associated with other, non-nutritional derangements that could be responsible for long-term programming."

The Role of Catch-Up Growth

The role of postnatal catch-up growth in modifying the association between BW and CVD has begun to receive some attention. Cianfarani et al (21) have proposed that the metabolic adaptations that permit survival for growth-retarded infants are a liability postnatally and result in a higher-than-expected risk of NIDDM in adulthood. An evaluation of a variation of this proposition is provided by Eriksson et al (25). They used data on growth from school records combined with information on MNS during pregnancy and mortality from CHD that was already available (28). Body mass index at age 11 was associated with CHD; adjustment for ponderal index at birth strengthened this association. As described previously, there was no association between BW and mortality in this population. The authors interpreted these findings as evidence of a detrimental effect of catch-up growth. It is not clear from these data whether the children experienced catch-up growth (that is, crossed percentile lines upward shortly after birth as a reflection of prenatal growth restriction) or became fat at some time later during childhood. Osmond et al (88) had previously reported an association between weight at age 1 and premature death from CVD that was even stronger than that for BW. It is not possible to tell from the analyses they presented whether catch-up growth was responsible for this association. Thus, at this point there is no persuasive data from human subjects to establish a relationship between true catch-up growth and determinants or consequences of chronic disease. This lack of evidence, however, does not rule

out the possibility of effect modification by postnatal events, such as method of infant feeding. This is an important area for additional research, as the feeding and growth of infants and children are changing rapidly worldwide (99).

Assessment of the Associations Between Maternal Nutritional Status or Birth Weight and Outcomes

Barker and his coworkers have published a very large number of papers in which associations between some characteristics of the newborn, particularly BW, and various later outcomes are documented. These later outcomes include hypertension, diabetes mellitus, CHD, stroke, chronic obstructive lung disease, renal failure, ovarian cancer and other disorders. This work is summarized in Barker's most recent book (11). Other groups of investigators also have contributed similar findings from different population groups. However, there also have been important contrary findings. When examined in more detail, the relationships between specific characteristics of the newborn and specific conditions in later life are much less consistent. They appear in some studies but not others, or in some population subgroups (e.g. males or the obese) but not others (47, 50, 89).

The general problems with these epidemiological studies on BW also apply to those described above on MNS. These difficulties have been enumerated and discussed in detail (24, 48, 50, 55, 56). They include (*a*) substantial losses to follow-up because members of the cohort have died, moved, or refused to participate, (*b*) absent or inadequate control for obvious potential confounding factors (often because such information was not available in the data set)—an important concern in evaluating an association with such a long latency period, and (*c*) inconsistencies in findings between one study and another, compounded by the use of multiple combinations of dependent and independent variables. In addition, the hypothesis itself does not explain temporal and international trends in BW and CVD (56). It is especially difficult to control for confounding by behavioral, lifestyle, and socioeconomic factors and, even when this is attempted, to provide assurance that all residual confounding has been eliminated. Joseph (49) has made this point clearly in his examination of the BW/blood pressure relationship.

Arguably the strongest epidemiological study published to date is that of Leon and his coworkers (66), in which birth records from a large cohort of Swedish men and women born between 1915 and 1929 were linked to census data (to provide information on socioeconomic status at multiple times during follow-up) and to death registers. A high proportion of the subjects were traced. These features of the study design addressed two of the major critiques of prior investigations. For men only, they found an inverse association between BW and all-cause mortality after 65 years of age; this resulted from a reduction in ischemic heart disease and circulatory disease in general. The investigators were able to adjust for the duration of gestation and, thereby, to distinguish between BW (attained size) and growth rate (weight for gestational age). They used this information to conclude that it is

the rate of fetal growth, not attained size at birth, that is important for long-term mortality from ischemic heart disease.

One of the best possibilities for eliminating confounding in an epidemiological design is to study twins because for those raised together, there is no difference in socioeconomic conditions during infancy and childhood, and for monozygotic twins, there is no difference in genetic characteristics. Twins are also of interest for testing the fetal origins hypothesis because their BW is substantially lower than that of singletons, and there is reason to suppose they experienced a "suboptimal intra-uterine environment" in the third trimester of pregnancy (108). Compared with nontwins in the general Swedish (108) or Danish populations (20), twins had no excess mortality. However, these kinds of studies have been criticized for (*a*) failing to control as well as desired for socioeconomic status because dizygotic twinning does not occur randomly in the population (98) and (*b*) using an inappropriate model because twins, although small, do not have the hypoinsulinemia characteristic of growth-retarded infants (109). In another study, twins had lower blood pressures than singletons at ages 9 and 18 years (119), contrary to expectations from the fetal origins hypothesis. These authors used path analysis to explore the relationships between available variables and concluded that the effect of BW may have been overestimated by previous authors because they did not account for current height or body mass index. Differences within twin pairs have now been examined in several studies. In one study (90), 55–74-year-old subjects were drawn from the Danish twin registry. Oral glucose tolerance tests were used to identify pairs who were discordant for NIDDM. Among both mono- and dizygotic twins, the twin with NIDDM had a lower BW than the twin without NIDDM. A within-pair design has been used in two studies to examine the association between BW and blood pressure at age 8 (23a) in adulthood (90a). In both studies, large decreases in blood pressure were associated with increases in BW, but these associations were not statistically significant. These three studies make the best use of the twin design and support the idea of in utero programming of later effects. However, they do not support the postulate that programming results from variation in MNS as both twins were exposed to the same maternal conditions. In summary, the studies of twins provide some improvement in methodology, but the two strongest of the studies come to conflicting conclusions about the fetal origins hypothesis.

Future Directions

Particularly problematic in this literature is the lack of well-articulated, testable causal sequences that include both biological and nonbiological factors (89) and also allow for effect modification by factors acting after birth. Barker has provided various biological models for the fetal origins hypothesis (7) and has acknowledged the possible importance of lifestyle factors (10). Including such factors will require richer data sources than those used to date and appropriate modeling (91). Several researchers (47, 60) have recently called for using a "life course" approach. This

approach suggests that "throughout the life course exposures or insults gradually accumulate through episodes of illness, adverse environmental conditions and behaviours increasing the risk of chronic disease and mortality. Accumulation of risk is different from programming in that it does not require (nor does it preclude) the notion of a critical period" (60). Such an approach would not only allow for effect modification in the postnatal and other subsequent periods, but would also include consideration of other modifying or confounding factors. Using this approach may be a more appropriate way to proceed, rather than continuing with efforts to eliminate all confounding while ignoring the important contributions of adult circumstances and characteristics (64).

Summary

The studies described above are all observational and, thus, are unsuitable for establishing a causal relationship. Although their results suggest various causal sequences depending on the outcome of interest, such sequences cannot be taken as causal "until the result repeatedly and consistently survives rigorous tests that might disprove the hypothesis" (89). To date, such a refutation has only been attempted in one study (119), and the fetal origins hypothesis did not turn out to be robust (106). Unfortunately, as a result of the lack of specificity in the independent variable as well as the multiplicity of dependent variables, these many associations remain difficult to interpret except via the more specific biologic information now being accumulated. Furthermore, it is not appropriate to describe these relationships between BW and later outcomes as associations between intrauterine growth retardation and some later outcome, as evidence is lacking that the infants studied were actually growth retarded.

There is no persuasive evidence of a causal pathway that leads from MNS through BW to determinants or consequences of chronic disease among either well-nourished or presumably undernourished women. This may be because the investigations that included individual-level data on MNS were obtained from well-nourished women, and no relationship between MNS and BW would be expected among these women. Unfortunately, there was also no association between BW and later outcome in these studies, so interpreting any association found between MNS and the later outcome is problematic. It is well known that MNS is important for fetal growth (53, 55). However, MNS is not the only determinant of fetal condition in utero, so attention could more profitably be directed to these other determinants in the search for an early origin for CVD.

THE EVIDENCE FROM INTERVENTION STUDIES

Intervention studies provide stronger evidence with which to evaluate the fetal origins hypothesis, but these are few in number and limited to outcomes observed in childhood or young adulthood. Individuals in Guatemala whose mothers were supplemented during pregnancy and lactation and who themselves were

supplemented up to 3 years of age between 1969 and 1977 have been studied as young adults. These results show, for example, that later physical work capacity is improved for the males, with a positive dose response to the amount of supplemental energy consumed (40). In this trial, pre- and postnatal contributions to the observed outcome cannot be distinguished.

Two trials with still stronger designs provide data on blood pressure following supplementation of pregnant women with calcium (15) or preterm infants with various formulas (72). In neither case was there a significant overall effect on blood pressure when children were 5–9 years old or 7.5–8 years old, respectively. However, the subgroup of children whose mothers received the calcium supplement and were currently above the median body mass index had lower systolic blood pressures than those whose mothers did not receive the supplement.

Two other outcomes have been measured at 7.5–8 years in the study of preterm infants: growth and cognitive function. As was the case for blood pressure, there was no difference between the treatments (in this case standard compared with preterm formula among women who did or did not choose to provide their own milk for their infants) in growth at 9 or 18 months or 7.5–8 years of age (84). In contrast, boys (but not girls) fed the standard formula as their sole diet had a significantly lower intelligence quotient measured at 7.5–8 years of age than those fed the preterm formula (73). The authors interpreted these findings as evidence that for preterm babies, the period between birth and hospital discharge is one during which nutritional programming takes place for cognitive function, but not for growth or blood pressure. Losses to follow-up in these trials were minimal, and their designs permit causal inference. As a group, these studies provide mixed support for the fetal origins hypothesis. As is the case in the epidemiologic studies, "programming" seems to occur erratically in these studies as well—for some outcomes, at some times, for some subgroups of the population.

THE EVIDENCE FROM STUDIES USING EXPERIMENTAL SPECIES

Studies using experimental species have provided strong evidence for the concept of programming across a wide range of organ systems and for both short- and long-term outcomes (69, 100). It is clear that the critical period depends both on the species used and on the outcome studied and that both pre- and postnatal periods are important. Some of these studies have produced results that are concordant in direction and effect with the fetal origins hypothesis, and some have not (69, 114). Recent reviews of the metabolic and endocrine responses to undernutrition that may be relevant to the later development of chronic disease in human subjects are available from a variety of model systems (e.g. 29, 42, 46, 77, 95, 110).

Research to date has generated additional hypotheses, with a change in emphasis from environmental to genetic factors. Hattersley & Tooke (43) propose in the fetal insulin hypothesis that "the association between low birthweight and adult

insulin resistance is principally genetically mediated." This could result in poor growth in utero mediated by insufficient insulin as well as by insulin resistance in childhood and adulthood; thus, all these conditions would be manifestations of the same insulin-resistant genotype. This raises the interesting problem of genetic confounding; that is, the same factors that caused the fetus to be small at birth would also cause later chronic disease. They go on to state that "Central to this fetal insulin hypothesis is the concept that insulin-mediated fetal growth will be affected by fetal genetic factors that regulate either fetal insulin secretion or the sensitivity of fetal tissues to the effects of insulin" (43). These possibilities are now being investigated. However, others disagree with their assertion of a genetic basis for the association between BW and later insulin resistance (78).

More recently, Waterland & Garza (114) have taken the concept of programming further and used the term metabolic imprinting to describe "the basic biological phenomena that putatively underlie relations among nutritional experiences of early life and later diseases." The term is intended to encompass adaptive responses to specific nutritional conditions in early life and to assist in the development of a concise list of underlying mechanisms. Metabolic imprinting is characterized by "(a) a susceptibility limited to a critical ontogenic window early in development, (b) a persistent effect lasting through adulthood, (c) a specific and measurable outcome (that may differ quantitatively among individuals), and (d) a dose-response or threshold relation between a specific exposure and outcome" (114). This definition allowed them to identify five specific candidate mechanisms by which metabolic imprinting could occur: "(a) organ structure (morphological development, (b) alterations in cell number, hepatocyte polyploidization or myocyte multinucleation, (c) clonal selection, (d) apoptotic remodeling and (e) metabolic differentiation" (115). In reviewing this list, it is clear that these mechanisms of metabolic imprinting could—and do—occur after the fetal period as well as during it (115). In addition, experimental evidence for an effect of perinatal nutrition on epigenetic gene expression is now available (113).

POSSIBLE IMPLICATIONS FOR PUBLIC HEALTH ACTION

The many studies that link BW to the development of chronic disease challenge us to rethink our definition not only of growth retardation but also of optimal BW. Currently, the optimal BW is considered to be that with the minimal perinatal mortality. Perinatal mortality is lowest for infants of 3501–4000 g born at a gestational age of 38–42 weeks (122). This target BW is lower than the BW values with the lowest CVD mortality in the studies by Barker (9–9.5 lb, or 4091–4328 g) (7) and also the recent study by Leon et al (3750–4249 g) (66) and is much lower than the maximum reported BW values. From a public health perspective, the question to address is which of these possibilities should be used as the target—our current approach (the lower end of the range for minimal perinatal mortality) or

some higher number that could be based on minimizing chronic disease in offspring? It is important to recognize that setting any higher-target BW will require some intervention(s) to achieve it because it is even farther away from the mean BW than the current target for BW. Possible interventions include actions to reduce the rate of LBW (alleviation of poverty, more adequate provision of prenatal care, distribution of food supplements to needy women, smoking cessation programs for smokers who want to quit, etc) and/or to shift the entire BW distribution to the right (by using some of the same interventions as above, as well as by using campaigns to encourage women to weigh more when they conceive and eat more while pregnant, etc). Other possibilities also have been discussed (41).

Nutritional interventions designed to increase BW (in populations in which the majority of small babies are born at term) have had only modest success. Such interventions may raise the lower tail of the BW distribution (i.e. lower the proportion of LBW births) and/or raise the mean BW. A meta-analysis of well-designed intervention trials revealed that the increase in mean BW with energy and protein supplementation during pregnancy was only 30 g (54). Larger effects (about 100 g) have been observed in less-well-controlled studies conducted among poorer populations (e.g. 54, 63) as well as in a primary health care setting in Gambia, where BW was increased by 136 g over the whole year and 201 g in the "hungry" season (18). There are still larger effects in the needier women, as high as 400–600 g among Guatemalan women with specific characteristics or combinations of characteristics (86). These findings provide an upper bound for the extent to which BW might be improved by nutritional interventions in poor populations (92). Thus, these studies provide causal evidence that maternal supplementation increases BW in populations with relatively low mean BW values, but even in these populations, the effect is small.

If one assumes that association shown by Barker and his coworkers between BW and mortality CVD is causal, would increasing BW improve cardiovascular outcomes? Joseph & Kramer (51) have done these calculations and the results are sobering. They estimated that a 100-g increase in BW (an achievable goal) would result in a 2.5% and 1.9% decrease in mortality from CHD in women and men, respectively. The change in mortality that has been documented with reductions in risk factors during adulthood is much larger (51). The results of these calculations suggest that although studying factors in early life has offered some new ways of thinking about the origins of CVD, increasing BW is likely to be much less effective in reducing mortality than modifying the traditional risk factors observed during adulthood.

Even if increasing BW within the normal range decreased mortality from CVD, is this an intervention worth doing? Answering this question requires consideration of possible negative consequences of this action (30, 51). The possible risks to the mother include an increase in the rate of cesarean section and the prevalence of obesity (via high maternal weight at conception or failure to lose the extra weight that was gained to increase BW). The possible risks to the infant include those

associated with being macrosomic at birth, as well as an increased risk of death from various kinds of cancer that is at least as large as the reduction in CVD mortality that could be achieved with a similar increase in BW.

These calculations all assume that the fetal origins act through BW and, therefore, that one would have to change the BW distribution to have an effect on later chronic disease. To the extent that BW is most likely only a proxy, and perhaps a poor one at that, for a process or processes that have affected the fetus, changing BW may not even be an appropriate target. As our understanding improves about how and when "programming" or "metabolic imprinting" occurs, different interventions may be suggested. Until that time, it seems inappropriate to intervene during pregnancy to reduce the development of chronic disease. However, there remain—in both developed and, especially, developing countries—ample other reasons to continue to intervene now in various ways to promote a good outcome of pregnancy for both mother and infant.

CONCLUSIONS

Barker's promotion of the idea that events during intrauterine life might have implications for the development of CVD has generated substantial interest as well as controversy. Both the importance of the idea and the controversy that has surrounded it have led to much additional research. Some of this research was similar to the investigations of Barker's group but in different populations; this has helped establish the robustness of the association between BW and various chronic conditions of later life and suggested specific avenues for future research. It still remains to be established, however, whether this association is causal.

Numerous studies in experimental species also have contributed to our understanding of the biological phenomena underlying the "fetal origins" hypothesis. These studies confirm the concept that different organs have different critical periods of development. These different critical periods, as well as the use of different experimental conditions, may help to explain the erratic associations that have been observed in the epidemiologic studies. Additional specific ways of investigating these phenomena have recently been proposed, with greater importance placed on genetic factors.

To date, remarkably little additional information has become available on the specific role of MNS before or during pregnancy, a central feature of the fetal origins hypothesis. What little information is available provides only minimal support for it.

The role of BW remains difficult to interpret except as a proxy for events in intrauterine life that are reflected in size at birth. Not all events that might be relevant for the later development of chronic disease would be expected to influence BW, and not all factors that influence BW would also be expected to affect the later development of chronic disease. In addition, compensatory changes occur after birth, some in response to BW and others in response to various environmental

conditions. These compensatory changes are likely to be important and, to date, have not been well studied.

Unfortunately, these investigations have not revealed any significant contribution of BW to the attributable risk of CVD; lifestyle factors during adulthood make a much greater contribution. BW also does not provide any appreciable improvement in the prediction of individual risk of chronic disease, which was Barker's hope when this research began.

Although it is tempting to use the excitement generated by this research to encourage policy makers to develop interventions aimed at pregnant women based on these findings, calculations of the reduction in CVD mortality as well as the increase in deleterious outcomes that might occur as a result suggest this would be inadvisable at this time.

Finally, it is difficult to justify continuing to refer to this body of knowledge as the fetal origins hypothesis because prior knowledge and more recent epidemiologic studies of humans and experimental studies using animals suggest that, in addition to effects that occur during adulthood, chronic disease may have it origins before, during, or after the fetal period.

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