Fetal Growth and Adult Diseases

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Evidence that the quality of fetal growth and development has strong and, in widely varying populations, reproducible effects on susceptibility to many common adult human diseases has only been acquired relatively recently. The importance of this largely environmentally determined process in relation to genetic factors remains a topic of great debate. Diseases that have been implicated include cardiovascular disease, hypertension, osteoporosis, schizophrenia, depression, breast cancer, and the polycystic ovary syndrome. This short review focuses on fetal programming of appetite and obesity, coronary artery disease and hypertension, type-2 diabetes, and cancer. The enormous importance of establishing the precise role of environmentally determined poor fetal growth in causing susceptibility to adult disease, usually in combination with adult obesity, (which may itself be a consequence of the same process) is emphasized. Once this is clear, there will be a major opportunity for disease prevention.

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The idea that the quality of fetal growth and development could have major consequences for susceptibility to disease in adult life may seem obvious. Indeed, it seems to be so among many lay people. However, it has only become a focus of major research effort relatively recently and even today many specialists in the disease areas potentially implicated are very reluctant to accept the proposal. Of course we live in the age of genetics and it is probable that the phenomenal advances, culminating in the sequencing of the human genome, have pushed aside consideration of other potentially important pathogenic mechanisms. Advances in the technology of genetic research and the ready commercial availability of kits with which to pursue the genetic basis of disease have greatly added to the attraction and ease of pursuing this line of research. Nevertheless, as was pointed out several years ago, common diseases are largely environmental in origin.1 Teasing out such pathogenic processes is difficult and very challenging but potentially enormously rewarding in terms of disease prevention.

The number of adult diseases that may have their major origin in the course of fetal growth and development grows steadily. It includes cardiovascular disease, hypertension, stroke, type-2 diabetes, chronic renal failure, chronic obstructive lung disease, osteoporosis, schizophrenia, depression, breast cancer, and polycystic ovary syndrome.2 We do not intend in this short review to explore all these areas. We consider appetite and obesity, coronary artery disease and hypertension, type-2 diabetes and cancer since these diseases themselves are known from epidemiological studies to be themselves strongly interlinked. Therefore, it is entirely possible that altered patterns of fetal growth explain at least in part these links.

A further general point to be made in relation to studies in this area as they relate to human disease is the extremely crude nature and limited scope of the observations available reflecting the quality of human fetal growth and development at the present time. Human epidemiological studies largely rely on birth measurements such as weight, length, and abdominal and head circumference. With placental weight and indices derived from expressing these measurements one relative to another, this represents the major part of the historical data that can be related to disease outcomes in adult life. Studies using these indices have nevertheless been amazingly informative and have in a number of examples revealed very strong relationships. Still it must be recognized that the data
relating to fetal growth and development are very crude and nonspecific in terms of individual organ structure and function. Another important point to recognize is that there is no such thing as a “normal” birth weight. At present, we have no way of knowing what the optimal fetal growth potential is of any particular child. It is sometimes assumed that when we refer to poor fetal growth we are only considering new-borns with weight below some arbitrary cut-off weight described as “low birth weight.” Because the proportion of infants that fall into this category is small in the Western World, it is considered that the burden of adult disease that can be attributed to this factor must itself be small. However, the relationship of the prevalence of a disease to birth weight is often continuous throughout the range of birth weights. It is clear that a child in the middle of the range of birth weight may still have experienced growth restriction by virtue of being thin but of greater than average length. Studies in experimental animals have indeed shown that it is possible to expose pregnant women to particular insults, which do not change the birth weight of the offspring but yet do change their phenotype in other respects. It is to be hoped that more recently available techniques to monitor fetal growth and development will greatly enhance our ability to link more subtle changes of fetal growth both to their causation and outcome in terms of adult disease.

**Appetite and Adult Obesity**

It is well established that obesity is a major risk factor for type-2 diabetes, cardiovascular disease, and more recently certain forms of cancer. It is also clear that not all obese people develop these diseases. Therefore, different individuals must have different susceptibilities to the detrimental effects of obesity. Individuals who were born small for their gestational age are one group of people who appear to be at increased risk of the detrimental consequences of obesity.

The apparent interaction between early nutritional experiences and adult obesity has been shown by a number of human epidemiological studies. A study of 64-year-old men in Hertfordshire UK, showed that the individuals with the worst glucose tolerance were those who were born small and who were currently obese. Individuals with a high birth weight were relatively protected from the detrimental effects of obesity. Individuals who were born small but remained thin were also protected from diabetes. This would explain why in countries where there is chronic malnourishment, the prevalence of diabetes is very low. Studies of individuals who were in utero during the famine known as the Dutch Hunger Winter have also shown that for any current body mass index, glucose tolerance was worse in those individuals exposed to the famine in utero compared to those born the year before the famine. This meant that frank diabetes was generally only present at age 50 in those individuals who were malnourished in utero and were currently obese. The detrimental effects of poor early nutrition and adult obesity have also been shown in animal models. For example, early protein restriction and adult obesity (induced by the feeding of a cafeteria diet) have been shown to independently and additively cause an increase in systolic blood pressure in rats (reviewed in reference 5).

**Programming of Appetite**

In addition to being key to the full detrimental effects of early growth restriction to become apparent, it is also possible that obesity itself is a manifestation of altered nutrition in early life. The earliest evidence that suggested that early nutrition had long-term consequences on appetite came from animal studies; however, more recent evidence suggests that similar events may occur in humans.

**Studies in animals.** Studies in rodents have provided direct evidence that early nutrition can have long-term consequences for appetite. Early studies with rats where nutrition during lactation was manipulated by altering litter size revealed that reduced nutrition during lactation resulted in a permanent reduction in appetite. A similar outcome has been found in studies on the effects of maternal protein restriction in the rat. The offspring of rats fed a low (8%) protein diet during pregnancy undergoes in utero growth restriction. However, if these animals are nursed by control (20% protein) fed dams they undergo postnatal catch up growth and have a similar weight to control offspring by the time of weaning. In contrast, control offspring that are nursed by low protein fed dams undergo post-
natal growth restriction. Such offspring remain smaller and permanently eat less, even following weaning onto a control diet fed ad libitum (reviewed in reference 5). Our recent studies with mice have extended these findings to show that the down regulation of appetite that occurs as a result of poor nutrition during lactation is powerful enough to prevent excess weight gain from a highly palatable diet. In contrast, animals that were growth restricted in utero but then underwent postnatal catch up growth gained excess weight compared to controls when fed a highly palatable diet ad libitum. Similar observations have been observed in rats after severe calorie restriction during pregnancy.7

Studies in humans. Several studies have linked low birth weight to changes in body composition in adulthood including increased central fat and reduced lean mass (reviewed in reference 8). There is some evidence that the timing of the nutritional insult may also have an impact on the future susceptibility to obesity. Studies of men who were exposed to the Dutch Hunger Winter in early life have revealed that those who were exposed to the famine during the first half of pregnancy were more obese at age 19. In contrast, those who were exposed to the famine during the last trimester of pregnancy and in early postnatal life had reduced obesity.8

The detrimental effects of poor antenatal growth are exaggerated by rapid postnatal weight gain.8 Rapid weight gain in infancy has been shown to be a risk factor for future obesity. Infants who were growth restricted in utero and underwent postnatal catch up growth between birth and 2 years of age have been shown to be fatter and to have more central fat than other children. The mechanisms underlying postnatal catch up growth are not well defined. However, such rapid growth may be the consequence of programmed changes in gene expression that were established in utero. It has been shown in a rodent model that maternal protein restriction is associated with increased expression of insulin receptors that could drive postnatal weight gain.5 It may also be a consequence of programmed changes in appetite.

Increased rates of postnatal weight gain have been associated with reduced satiety in small for gestational age (SGA) infants (as assessed by volume of milk consumed by bottle-fed infants).9 Leptin is one of many potential candidates that could mediate these changes in appetite. It has been shown that cord blood leptin is inversely related to rates of growth during infancy and that SGA infants have lower leptin concentrations. One possibility, therefore, is that low leptin levels in SGA infants lead to reduced satiety and rapid postnatal weight gain. Recent studies have also suggested that breastfeeding is protective against the risk of obesity in later childhood.8 Bottle-fed infants are known to have higher total energy and protein intakes than breast-fed infants so one possible explanation is that early breast feeding may program appetite regulation.

There is clear evidence in rodents that appetite can be programmed upwards or downwards depending on the timing of the insult. Thus, the early postnatal period may be a time window for targeted intervention. The evidence from human studies, although more indirect, suggests that a similar phenomenon occurs in humans. There is therefore an urgent need for detailed studies of early programming of human appetite. The identification of the lactation period as a critical window for programming of appetite would provide enormous potential for reduction in the prevalence of obesity and therefore disease prevention.

Coronary Artery Disease and Hypertension

It is now nearly 70 years since it was observed that, once an individual had survived the neonatal period, the year of death was related to the year of birth. It was speculated that this link might be related to the early life environment and particularly the maternal role in this. Several years later a relationship between death rates from cardiovascular disease and the rates of infant mortality at the time of an individual’s birth was discovered in Norway. A little later, similar studies in England and Wales confirmed this relationship. Although the basis of the link was initially attributed to poverty in adolescence, Barker and Osmond10 were the first to suggest that it was poor nutrition in fetal life. Barker and Osmond then went on to discover old records of birth weights and weights at 1 year in a number of populations in the UK, which they exploited to investigate the relationships between these
measurements and deaths from ischemic heart disease. Low birth weight was related in a graded fashion to increased risk of death from this cause. Subsequently, blood pressure, as a major risk factor for ischemic heart disease, was shown to be strongly and inversely related to birth weight.11

These findings have now, for the most part, been replicated in many different studies and populations worldwide. There has been some discussion as to exactly how strong the relationship between birth weight and blood pressure really is. Some very large studies have tended to show a less strong relationship possibly because of the much greater imprecision of information when very large populations are involved. A consequence of this is that when the results of many studies are combined, the numerical weight of large studies reduces the overall size of the relationship. Nevertheless, the existence of the relationships is not a matter of dispute. An additional factor to be taken into account is the age of the population under study. Several studies have shown the relationship before puberty but of course the size of the differences observed are smaller than in adult life. The relationship appears to be obscured during puberty possibly because of the other dramatic developmental processes going on at that time and the wide age range over which they occur in different individuals. The relationship is again clearly established in young adult life. With age, the relationship strengthens as does the size of the pressure differences observed going from the lowest to the highest birth weight.

As we have indicated above, animal studies have revealed important interactions between fetal and early postnatal growth. Catch up growth in the immediate postnatal period has detrimental effects on the longevity of male rats. More recent human studies are beginning to suggest that similar interactions may play an important role in relation to risk of coronary artery disease. Boys who were thin at birth but after the age of 1 showed a rapid gain in weight and body mass index exhibited an increased risk of coronary artery disease.12

Type 2 Diabetes

Poor fetal nutrition evokes a number of adaptive responses in the fetus. Many of these are poorly understood but one that is clear from many animal studies is that the flow of nutrients, including oxygen, to the developing organs, is altered. In this way, there is prioritization of organ growth and development. Examples of this are the relative sparing of brain and lung growth at the expense of other organs—for example the viscera—and, in a gender specific way, tissues like muscle. The insulin-secreting β cells of the islets of Langerhans grow and multiply very rapidly in the later stage of pregnancy. Realizing that this process could be vulnerable to a selective undernutrition of the pancreas led us to contemplate a totally novel process by which susceptibility to type 2 diabetes might be conferred, ie, by poor nutrient supply to the pancreas with consequent reduced growth and production of β cells. Accordingly, we decided to undertake a study to determine whether loss of glucose tolerance in adult life was linked to indices of poor fetal and early postnatal growth utilizing the data available from Hertfordshire, UK. The outcome of this study was quite remarkable in the clarity and strength of the associations discovered. Men of average age 64 years with the lowest birth weight were over 6 times more likely to have poor glucose tolerance (impaired glucose tolerance or frank diabetes) than those in the highest birth weight group. The relative risk was graded across birth weight groups with no obvious threshold. A similar relationship was found with their weight at 1 year. However, recognizing that birth weight and weight at 1 year are themselves related, it was possible to show an effect of weight at one independent of birth weight. Thus, it appears that both poor fetal and early postnatal growth are separately linked to the risk of poor glucose tolerance as an adult.3

An even stronger relationship was discovered when the men were categorized according to whether they had the main features of the metabolic syndrome—impaired glucose tolerance, hypertension, and hypertriglyceridaemia. Men in the lowest birth weight group were 18 times more likely to exhibit these features than were those in the highest group. Again there was a steady gradation of effect across the birth weight groups. Also of great interest in these findings relating to poor glucose tolerance and to the presence of features of the metabolic syndrome were the observations that the coexistence of low
birth weight and adult obesity was critical. Thinness in adult life protected against the effect of poor early growth. Conversely good early growth protected against the effect of obesity to increase the risk of poor glucose tolerance as an adult.

In an attempt to provide a conceptual framework for the basis of these findings and to put up testable hypotheses for further research the “thrifty phenotype” hypothesis was put forward. This suggested that poor fetal nutrition engendered at least 2 types of response geared to enhancing the chances of survival to conduct reproduction. The first thrifty process was to deploy limited nutritional resources during fetal life to the most critical organs at the expense of those less vital. Second, in this overall adaptive process metabolism would be permanently changed (“programmed”) to aid survival under postnatal conditions of continued poor nutrition.

Subsequently it has been possible, in our own and other laboratories, to test this hypothesis in a series of animal experiments. The progress of this research and further epidemiological studies has been reviewed in a recent monograph on the thrifty phenotype. Some features of the more recent progress are highlighted below.

The debate concerning the relative roles of environmental factors and genes in determining the emergence of type 2 diabetes continues. Although it is an easy option to ascribe the disease to a combination of these factors, this is simply to avoid an issue of great practical importance. The “explosion” of the “epidemic” of type 2 diabetes in developing countries suggests a few major aetiological factors that we surely need to define to counteract their effects. Twin studies have shown that nongenetic factors related to fetal growth are involved. Genetic studies, despite enormous investment, have yet to provide convincing evidence for major effects of gene mutation.

Experimental studies of animals have provided a number of means of inducing early growth restriction, which lead on to loss of glucose tolerance and hypertension. The growing list of parallels between these models and the human disease is striking. It remains to be determined how many different phenotypes may result from different types and timings of processes that interfere with optimal fetal growth.

The limited data available suggest that the fetal adaptive response is limited in its flexibility.

It is increasingly clear that in addition to poor fetal nutrition, maternal hyperglycaemia also has detrimental long-term effects on the fetus and its postnatal susceptibility to disease. The risk of an offspring developing type 2 diabetes is considerably increased if there was maternal gestational diabetes. This is clear both from animal and human epidemiological research. Thus, whereas poor nutrition over several generations maintains an intergenerational effect to enhance the risk of diabetes, the presence of diabetes during pregnancy also serves to perpetuate the condition in a nongenetic manner. It is not yet clear to what extent these processes have misled us into over-emphasising the role of genetics in the aetiology of type 2 diabetes.

Fetal Growth and Cancer

There is epidemiological evidence that both reduced and increased fetal growth may be linked to an increased risk of cancer. Furthermore, obesity and type 2 diabetes, which have been shown to be related to indices of reduced fetal growth, are themselves associated with an increased risk of certain cancers. Therefore, it is possible that a reduction in fetal growth may provide the explanation for these latter observations. The underlying mechanisms explaining these links are not clear but could well include permanent changes in growth factor expression and sensitivity.

Obesity, Postnatal Growth, and Cancer

Several studies have found a positive correlation between birth weight and adult body mass index. However, maternal undernutrition has also been linked to adult obesity, and recently, Leong et al. identified that both high and low birth weights were associated with a subsequent higher adult body mass index. The findings of Okasha et al. specifically identified body mass index in young adulthood to be associated with increased risk of prostate and breast cancer, while the IARC (International Agency for Research on Cancer) estimated that elevated body mass index accounts for a large proportion of some common cancers, in the general adult population, including 11% of all colon cancer
incidences, 10% of postmenopausal breast cancer cases and for endometrial, kidney and oesophageal cancer, the attributable risk for body mass index was calculated at 39%, 25%, and 37%, respectively.\textsuperscript{16} Taken together, these observations support the hypothesis that an individual’s fetal experience may influence adult obesity with potential consequences for the risk of several major cancers.

Type 2 Diabetes and Cancer

The increased incidence of endometrial, colorectal, pancreatic and kidney cancers in type 2 diabetics provide indirect evidence for a relationship with chronic hyperinsulinemia. Chronically elevated insulin levels may enhance tumor development either directly by acting itself as a growth factor (ie, via the insulin receptor) or by increasing insulin-like growth factor -1 (IGF-1) bioactivity through the downregulation of IGF-1 binding proteins -1 (IGFBP-1) and/or IGFBP-2. Adult fasting hyperglycemia, which is often associated with peripheral insulin resistance, has been shown to predict breast and colorectal cancer, and since epidemiological studies have shown a relationship between low birth weight and insulin resistance, this suggests a potential link between fetal undernutrition, glucose metabolism, and cancer.\textsuperscript{17}

Indices of Fetal Growth and Cancer

A number of studies have found birth weight to positively correlate with breast cancer, and suggest that the increased risk is caused by intrauterine exposure to estrogens while a reduced risk is associated with an increase in levels of alpha-foetoprotein, which has antiestrogenic properties. However, the mechanism linking this prenatal exposure remains uncertain. It may influence the number of target (breast stem) cells at risk for malignant change or directly initiate a procarcinogenic event. Animal studies in which maternal exposures to an elevated estrogenic environment were induced either by oestradiol administration or synthetic oestrogen diethylstilbestrol have shown significantly increased breast cancer risk in female offspring, and have thus reinforced the role of in utero oestrogen exposure. Some studies have found a U-shaped association between birth weight and breast cancer risk. This leads us to the concept that postnatal compensatory growth or “catch-up growth” might influence subsequent risk by exploiting the increased rate of mitogenesis and cell division of (the same) target cells.

Therefore, while birth weight is widely used as a measure of nutrition in utero, it remains insensitive to a degree, as it does not take into account gestational age, birth length (linear growth in utero) or adiposity; nor does it account for maternal factors such as size, smoking and socio-economic position, which in themselves are related to cancer risk. As reviewed by Okasha et al,\textsuperscript{15} a few studies have used other markers such as childhood height and found that a one standard deviation greater height in boys was associated with a 42% higher risk of cancer mortality (Boyd Orr study); and a risk of breast cancer was increased for girls who were taller at age 7 in a British cohort. The present consensus is that childhood and adult tallness are related to a higher risk for cancers of the breast, prostate, colorectum, haemopoietic system, and endometrium, with leg length having the stronger association with cancer risk than trunk length. The findings of a recent Swedish cohort study suggest that fetal growth rate may also be aetiologically relevant.\textsuperscript{19}

IGF-1 Hypothalamo-Pituitary Axis and Cancer

One major class of mechanisms that may form a physiological and causal link between excess body weight and cancer risk is alterations in the metabolism of endogenous hormones, including insulin, bioavailable sex steroids, IGF-1, and IGF-binding proteins. Obesity causes insulin resistance and chronic hyperinsulinemia, which is in turn related to a decrease in IGFBP's-1 and -2, a decrease in sex-hormone binding globulin, and increases in plasma free IGF-1 and bioavailable sex steroids. Oestrogen is related to increased breast cancer and endometrial risk in postmenopausal women, while ovarian hyperandrogenism is associated with endometrial cancer development in premenopausal women. Prospective studies have shown positive associations between IGF-1 levels, either as absolute concentrations or relative to levels of IGFBP-3, and risk of breast, prostate and colorectal cancers.

The mechanism underlying the program-
ning of the fetal hypothalamo-pituitary axis is one of much debate. There is evidence that leptin resistance, which is one cause of obesity, may be established in utero. Over nutrition in early life may be associated with reduced satiety in SGA infants and this is thought to be caused by reduced leptin levels. Since hepatic IGF-1 is partially determined by nutritional intake, over nutrition in early life may elevate IGF-1 levels and this might therefore explain the association between obesity and high IGF-1 levels.

There is a clear need to understand how the intrauterine environment affects fetal development and how any adaptations to the postnatal environment may affect the organism’s growth rate, risk of obesity, and therefore cancer in later life. Animal studies may be able to address the importance of “catch-up growth” and identify the underlying mechanisms.

**References**

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