EDITORIAL

Biological theories, evidence, and epidemiology

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Earlier this year a distinguished group of biologists and biomedical researchers wrote a hypothesis paper that appeared in the prestigious science journal Nature. Its title was Developmental plasticity and human health. Elaborating ideas published in this journal in 2001, the Nature paper set out to establish the basic biological principles underlying the early-life origins of coronary heart disease and type II diabetes. A similar paper in the US journal Science has appeared more recently.

The concept of developmental plasticity overlaps with the notion of early-life programming as initially defined by Lucas, although it is more general and its origins are elaborated in terms of evolutionary biology. It is based on the notion that ‘a given genotype can give rise to different phenotypes depending on environmental conditions. … The varied developmental pathways triggered by environmental events may be induced during sensitive, often brief periods in development. Outside these sensitive periods an environmental influence that sets the characteristics of an individual may have little or no effect.’

The Nature paper includes a series of intriguing examples of animals whose early development can result in different adult phenotypes depending upon a particular environmental stimulus in early life. The crustacean Daphnia develops a helmet to protect it against predators in response to maternal exposure to chemical traces of a predator. This illustrates what is regarded as the key evolutionary rationale for the existence of developmental plasticity in early life in higher animals. It has evolved as a mechanism whereby maternal information concerning the external environment can influence the phenotypic development of offspring, so that in turn they are best adapted to the circumstances they will be born into. Put simply, developmental plasticity is a means whereby the developing fetus or neonate can adapt in response to a ‘weather forecast’ transmitted by the mother about the external environment.

A generalized thrifty phenotype

There is one further crucial step in the arguments advanced in the Nature and Science papers that completes the link with the early origins of adult disease. It is that the particular developmental pathway taken in response to the maternal forecast can have adverse consequences if the external environment of the offspring is not what was predicted. This is the generalized version of the thrifty phenotype hypothesis put forward by Hales and Barker to explain the link between small size at birth and increased risk of later type II diabetes. This proposes that impaired nutrition in utero is interpreted by the fetus as a signal of nutritional adversity in the external environment. As a result it develops a thrifty (insulin mediated) metabolism so it is better adapted to survive in a nutritionally stressed post-natal environment. However, if instead of nutritional scarcity the offspring is delivered into a world of energy-dense food and plenty, this metabolic adaptation will instead predispose to adult onset diabetes. It is the discordance, or mismatch, between the weather forecast and reality that causes the problem.

The developmental plasticity hypothesis in relation to later health is expressed in its most general form in terms of the interaction of ‘phenotypic size’ with nutritional level of the external environment. It predicts that in environments that provide a very low plain of nutrition ‘small phenotypes’ have better adult health/survival than ‘large phenotypes’. However, in environments that have a high nutritional level the reverse is true. Unfortunately the Nature paper does not elaborate on whether ‘phenotypic size’ refers to anything beyond anthropometric dimensions. Does it for example extend to include the size of specific organs or body composition? It is unclear how one could put phenotypes such as insulin sensitivity (central to the thrifty phenotype) on a scale from ‘small’ to ‘large’.

Evidence for fetal adaptation in humans

How does the developmental plasticity hypothesis fit with current epidemiological knowledge about early growth and development? This question is distinct from considering the evidence for an association between growth in early life and risk of adult disease. Instead, it is important to consider how far there is human evidence of changes in early life phenotypes in response to maternal signals about the nature of the external environment that are potentially adaptive. Restricting ourselves to considering maternal signalling to her offspring in utero, the developmental plasticity hypothesis may be represented schematically as follows:

External environment > Mother > Fetal adaptation > ‘Adaptive’ post-natal phenotype

As this makes clear, the ultimate association of interest is therefore between the external environment and the post-natal phenotype, which must in some way be adaptive, i.e. lead to...
increased fitness if the weather forecast provided by the mother is accurate. Birthweight is an obvious post-natal phenotype to look at, not least because data on it is widely available, although as discussed later it may not be the most biologically pertinent outcome. Nevertheless, what is the evidence that it is responsive to either long-term or short-term variations in the external environment experienced by the mother?

Since 1950, infant mortality rates have fallen consistently in most countries of the world. This decline started over 100 years ago in countries such as Sweden and Britain. Over this period there has also been a substantial increase in linear growth and adult height. However, surprisingly, there is very little evidence that the improvements in the standard of living, nutrition, and perinatal health have been accompanied by a secular increase in birthweight of any magnitude. In a study comparing differences in birth outcome over a 60 year period in Sweden, the mean birthweight of liveborn infants in Uppsala, Sweden 1920–24 was 3437 g. For Sweden as a whole in 1985, the mean birthweight was 3494 g—a difference of 57 g. A similar comparison of birthweights in Iceland, between 1901–10 and 1972–81 found there was a mean increase in birthweight among singleton livebirths of 85 g. Other data from different settings also suggest rates of secular increase of this order. Thus the substantial improvements in the external environment (nutrition, sanitation, and hygiene and other aspects of standard of living) that have occurred in high income countries during the 20th century and have led to reductions in infant mortality and increases in adult height do not appear to have been paralleled by equally striking increases in birthweight.

The influence of extreme and acute maternal nutritional privation on birthweight has been intensively studied in records from the Dutch Hunger Winter. Under conditions of semi-starvation that lasted for 6 months over the winter of 1944 in northern Holland the maximum decline in mean birthweight was around 300 g for those babies delivered following exposure to famine in the third trimester of pregnancy. This is a much larger change than seen in the secular trends discussed above. Nevertheless, it is striking that this most extreme and acute circumstance of semi-starvation did not produce even greater declines in mean birthweight. To put this decline in perspective, it is only slightly greater than the mean difference in birthweight within mothers between their second and first livebirths, which are typically of the order of 150–200 g at term. Moreover, cross-sectional differences in mean birthweight between different social classes in Britain are of a similar magnitude.

The large literature on nutritional and dietary interventions during pregnancy suggests that it is difficult to bring about appreciable changes in birthweight through nutritional interventions. The most recent Cochrane review of trials of balanced protein energy supplementation in pregnancy found a mean increase of 50 g in undernourished women and 28 g among adequately nourished women. In contrast these interventions did result in a reduction in the prevalence of small-for-gestational age babies. Overall, however, the size of the effects of supplementation on mean birthweight are small.

In summary, therefore, the available human evidence suggests that changes in the environment of the mother (especially those that affect her nutritional intake) have minimal impact upon fetal growth as measured by birthweight. Of course there are good evolutionary arguments for expecting fetal growth to be relatively robust to long-term and short-term perturbations in the external environment. These are generally framed in terms of the need to protect the nutritional supply to the developing brain. This fits within a much more general literature on the buffering of biological development much of which takes its inspiration from the work by Waddington in the 1940s on canalization.

From the perspective of developmental plasticity the evidence on birthweight suggests that either the ‘weather forecast’ is not being adequately communicated to the fetus or it does not make adaptive responses to it. Of course, there is one further possibility: that the adaptive responses that are made are not reflected in birthweight. The problem with testing this last possibility is that there are few measures of growth and development, apart from weight and other anthropometric measures at birth, for which data are widely available. Nevertheless, as discussed below, it is possible that variations in neonatal adiposity may be a much more plausible adaptive response that birthweight per se.

Unequivocal evidence of impact of fetal nutrition

In contrast to the modest effects of the maternal external (nutritional) environment, there can be no doubt that fetal growth in humans is very sensitive to the nature of the in utero environment. One aspect of this contrast is between maternal and fetal nutrition, a distinction that is often overlooked in literature pertaining to fetal origins. Problems with placental function, for example, can have a profoundly negative effect on fetal growth. A further example is provided by gestational diabetes. This is associated with macrosomia, or fetal overgrowth, in part through raised levels of maternal serum glucose that then leads to raised levels of glucose in the fetal circulation as originally proposed by Pedersen. In passing it is interesting to note that the model of gestational diabetes was the starting point for Freinkel’s concept of fuel mediated teratogenesis elaborated in the 1980 Banting lecture.

Buffering and maternal–offspring conflict

The capacity of the mother to buffer the fetus from the nutritional stresses of the environment that she lives in will have limits. At a certain point a pregnant mothers’ own survival (and capacity to care for existing offspring) will take precedence over the growth of the fetus she is carrying. This is consistent with what was observed in a supplementation trial among pregnant women in Guatemala. Women recruited in early pregnancy were followed up through the pregnancy and a subsequent pregnancy. Among those who weighed <50 kg on study entry and were not given the high energy/high protein supplement the later offspring weighed less at birth than the offspring from the earlier index pregnancy. However, among this same group of women there appeared to be a tendency for the mothers themselves to gain weight between the two pregnancies. The authors state that this ‘suggests a preferential partitioning of nutrients to the mother … which protects the mother at the expense of the fetus’.
The concept of buffering implies that the provision of fuels to the fetus in normal pregnancy will be managed to ensure an appropriate level of nutrition at each step of gestation. However, as illustrated by the Guatemalan example above, the level of nutrition available to the fetus represents a balance between the interests of the mother and of the fetus. This tension is central to the parent–offspring conflict theory. This starts from the observation that mother and fetus only share 50% of their genes. Thus the successful transmission of a mother’s genes to future generations lies not soley with the success of her current pregnancy but with the survival and reproduction of her other existing and future offspring.

This theory provides an elegant explanation for the existence of imprinted genes, i.e. genes that are expressed depending upon whether they are derived from the father or mother. It has been found that most imprinted genes that are expressed on the placenta appear to have a direct role in the regulation of fetal growth, such as IGF2. Most importantly, paternally imprinted genes (i.e. those where it is only the gene from the father that is expressed) generally up-regulate fetal growth, while maternally imprinted genes serve to down-regulate fetal growth.

The framework of maternal–offspring conflict may also provide an alternative evolutionary basis for explaining the emergence of a thrifty phenotype. Wells has put forward a strong argument that adaptations made in utero by the fetus in response to variations in available fuels may in fact benefit maternal fitness more than the fitness of individual offspring. The mother may indeed manipulate the growth trajectory of the fetus to suit her interests both in utero and post-natally during breast feeding. In a nutritionally stressed environment, the mother may benefit from having a thrifty baby whose demands for nutrition are limited. Further debate around the issues raised by Wells are likely to be productive.

Advantages of being small or being fat?
A central tenet of the developmental plasticity hypothesis when applied to the thrifty phenotype is that adaptations are made to maximize post-natal survival of the offspring given the resources available to the fetus in utero. It is not stated, however, precisely what these adaptations may be beyond the assertion that a ‘small phenotype’ confers a survival advantage in an environment with poor nutrition. While it can be argued that the minimal nutritional requirements of a small individual are going to be lower than for a large individual, whether this means that they will be more able to survive in a nutritionally marginal environment is another matter. There is in fact little quantitative human evidence to demonstrate that small size does confer such an advantage in these circumstances, although anecdotes have been employed to support the case. Observations by survivors of Nazi concentration camps and from the siege of Leningrad have been cited in support of the notion that in these extreme contexts being born small and remaining small as an adult conferred a survival advantage.

Whether it is absolute size alone that matters is of course a moot point. Historical evidence has suggested that a more adipose body composition is associated with a survival advantage at times of famine. Ancel Keys, in his monumental two volume work The Biology of Human Starvation published in 1950, discusses the relatively good evidence from the Second World War and other periods that indicates that women survive starvation better than men. His interpretation of this is that the survival advantage may be a consequence of women having larger stores of body fat: ‘since fat per unit weight provides more energy than protein, muscular men are at a disadvantage as compared to women during period of starvation.’

From this one could speculate that if there are in utero adaptations to improve post-natal survival changes, body composition rather than overall size may be more important. The importance of adiposity for humans is underlined by the fact that we have one of the most adipose body compositions at birth than any mammalian species. It has been suggested that this has evolved to provide protection against post-natal nutritional stresses.

There is indeed a growing body of literature that indicates the importance of distinguishing between different body compartments, their relative size and distribution rather than looking at global measures such as birthweight or weight or body mass index (BMI). Gestational diabetes has again provided fruitful insights in this regard. It has been known for many years that the macrosomic offspring of women with gestational diabetes, as well as being large, are also considerably more adipose than the offspring of non-diabetic mothers. Recent research has extended this to show that even babies within the normal birthweight range whose mothers have impaired glucose tolerance in pregnancy are more adipose than similar birthweight infants born to normoglycaemic mothers. This is due to greater accretion of fat mass, there being minimal differences in fat-free mass. This study also found that the strongest predictor of fat mass in infants of women with gestational diabetes was maternal fasting glucose.

These findings may well fit into a larger picture that has already been sketched out to explain the increased risk of metabolic disturbances in adult life among people from the Indian subcontinent. The Indian phenotypic baby has been described by Yajnik as being small and thin relative to European neonates, but nevertheless appears to have a more adipose body composition. This is regarded as being of significance, as it is adiposity (particularly central adiposity) in adult Indians that is believed to be implicated in their increased risk of type II diabetes and coronary heart disease. The need for a more sophisticated approach to thinking about neonatal size and body composition also comes from recent work that suggests that birthweight is positively correlated with BMI in later life in part because it is positively associated with the amount of lean body mass. Thus the elements of a coherent story linking the nature of the in utero environment and available fetal fuels, fetal growth and neonatal body composition and survival, and later life body composition and disease may now be emerging.

What does this mean for epidemiology?
Epidemiologists like to keep close to their data. Of course we may also be conversant with specific biological mechanisms particularly when we are searching for biologically plausible explanations for our data. However, the area of the fetal origins of adult disease, or the developmental origins of adult disease as it is now been renamed, is unusual in that it has entailed the articulation of a number of more general biological theories. These have all involved arguments to explain why early life...
individual differences in placental function are urgently needed. Which has to be a very poor proxy for its functional capacity. Generally only appears in epidemiology in terms of its weight, the placenta itself needs to receive more attention. This crucial organ risk factors if we are to really understand the determinants of a need for us to move beyond the conventional sets of peri-natal ultrasound also need to be given more priority, as has recently made above. This requires special techniques that are only now becoming possible to use with confidence in field studies. Longitudinal studies of specific aspects of growth in utero using ultrasound also need to be given more priority, as has recently been suggested in relation to the effects of zinc. There is also a need for us to move beyond the conventional sets of peri-natal risk factors if we are to really understand the determinants of fetal growth and body composition, including more detailed longitudinal studies of physiology in pregnancy. Finally, the placenta itself needs to receive more attention. This crucial organ generally only appears in epidemiology in terms of its weight, which has to be a very poor proxy for its functional capacity. Other more biologically grounded ways of characterising inter-individual differences in placental function are urgently needed.

Time to raise our game?

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References


