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THE FETAL TIME BOMB*

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Fetal growth

During the 8 weeks after conception, the form of the human baby is laid down in miniature. The 5 week old embryo does not contain a description of the person to whom it will give rise, but in its genes is a programme for making a person that has been likened to a recipe.[1] As development proceeds the destiny of cells becomes determined by their surroundings; by the position they come to occupy in the body; by the signals they receive from neighbouring cells and hence the genes which become activated. Nine weeks after conception a phase of rapid growth begins. Growth does not simply expand the miniature human being but, through differences in growth rates of different parts of it the baby's form is moulded. Cell division is the main feature of fetal growth. There are periods of rapid cell division in the different tissues, so-called 'critical' periods,[2] and the timing of these differs; the kidney, for example, has one in the weeks immediately before birth. Growth depends on nutrients and oxygen and the fetus adapts to lack of these by slowing its rate of cell division, especially in those tissues which are undergoing critical periods of growth at the time. Cell division slows either as a direct effect of undernutrition on the cell or through altered concentrations of growth factors or hormones, of which insulin and growth hormone are particularly important.

Disproportionate growth can occur *in utero* because different tissues have critical periods of growth at different times. The diversity of size and form of babies born after normal pregnancies is remarkable. This variation in size at birth is determined by the intrauterine environment rather than by the fetal genome.[3,4] Widdowson and McCance were among the first to show that brief periods of undernutrition may permanently reduce the numbers of cells in particular organs.[2,5] This is one of the mechanisms by which undernutrition may permanently change or 'programme' the body. Other lasting 'memories' of undernutrition include changes in the distribution of cell types, in hormonal feedback, in metabolic activity and in organ structure.

It is not in question that the human body can be programmed by undernutrition. Rickets for long served as a demonstration that undernutrition at a critical stage of early life leads to persisting changes in structure. What is new is the realisation that some of the body's 'memories' of early undernutrition may become translated into pathology and thereby determine disease in later life.

Fetal growth and coronary heart disease

The main focus for research into coronary heart disease, the commonest cause of death in the Western world, has been the lifestyles of men and women. Inappropriate behaviours—a high fat diet, cigarette smoking, becoming obese—have been implicated. Adult lifestyles, however, fail to explain much about the geography of the disease, its trends over time, and why one person dies from coronary heart disease while another does not.

In the search for a new model for coronary heart disease an important clue came from studies of death rates among babies in Britain during the early years of this century.[6] Death during infancy was remarkably common in those days. In 1917 the Bishop of London remarked 'while nine soldiers died every hour in 1915, twelve babies died every hour, so that it was much more dangerous to be a baby than a soldier'. The usual certified cause of death in these newborn babies was low birthweight. Death rates in the newborn differed considerably, being highest in some of the northern industrial towns and the poorer rural areas in the north and west. We now know that this geographical pattern in death rates closely resembles today's large variations in death rates from coronary heart disease, one aspect of the continuing north-south divide in health. A conclusion suggested by this observation was that low rates of growth before birth were linked to the development of coronary heart disease in adult life. The suggestion that events in childhood influence the pathogenesis of coronary heart disease was not new. A focus on intrauterine life, however, offered a new point of departure for research.

Small size at birth and later disease

Early epidemiological studies were based on the strategy of examining individual men and women in middle and late life, whose size at birth had been recorded. The records for these studies came to light when the Medical Research Council's systematic search of the archives and records offices of Britain discovered three important collections of birth records, in Hertfordshire, Preston and Sheffield. In Hertfordshire the Lady Inspector of Midwives from 1905 onwards, Margaret Burnside, had recruited an army of trained nurses to attend women in childbirth and to advise mothers on how to keep their babies healthy. The babies had been weighed at birth by the attending midwife and again at one year. These weights were recorded in ledgers.

We traced 15,726 men and women born in Hertfordshire during 1911–1930 from birth to the present day.[7,8] Death rates from coronary heart disease fell progressively between those who weighed less than 5·5 pounds at birth and those who weighed 9·5 pounds. By examining men and women who still live in Hertfordshire it was shown that these trends in coronary heart disease with birthweight are paralleled by similar trends in two disorders, hypertension and diabetes, that are associated with the disease. There was a steep fall in prevalence of adult onset diabetes and its preclinical state impaired glucose tolerance, between men who were small and those who are large at birth.[9]

One response to such findings is to argue that people who were exposed to an adverse environment *in utero* and failed to grow continue to be exposed to an adverse environment in childhood and adult life, and it is this later adverse environment that produces the effects attributed to programming in utero. There is little evidence to support this argument. Rather, associations between birthweight and later disease are found in each social group, and are independent of adult behaviours such as smoking and becoming obese.[8] Variations in disease rates associated with birthweight are large and strongly statistically significant. They are being replicated in different populations around the world, and are supported

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by animal experiments. It is reasonable to conclude that influences that lead to low growth rates in utero also determine later coronary heart disease.

Adult lifestyle does, however, add to the intra-uterine effects. The highest prevalences of non-insulin dependent diabetes and impaired glucose tolerance, for example, are seen in people who were small at birth but obese as adults.[9] Around the world the communities with a high prevalence of diabetes generally conform to this pattern. We know something of why people who had low growth rates *in utero* are unable to withstand the stress of becoming obese as adults. There is evidence that their poor fetal growth reduces the number of pancreatic β cells and hence the capacity to make insulin.[10] There is stronger evidence that they became resistant to the effects of insulin.

Disproportionate size at birth

In the early years of the century a new record form, known as the Queen Charlotte form, came into use in maternity hospitals in Britain; this required measurements of the newborn's head circumference and length as well as its weight; these measurements allow thin and short babies to be distinguished. The Hertfordshire study showed that low birthweight was associated with the so-called insulin-resistance syndrome, a common disorder in adult life in which impaired glucose tolerance, raised blood pressure and disturbed lipid metabolism coincide in the same patient. Biochemically the syndrome is characterised by raised serum insulin concentrations and it leads to coronary heart disease. Studies in Preston, where the Queen Charlotte form was used, showed that it is specifically thinness at birth, measured by a low ponderal index (birthweight/length^3), that is associated with resistance to insulin and its associated disorders in later life.[11]

Muscle growth in utero

In fetal life insulin has a key role in stimulating cell division.[12] The thin newborn baby lacks skeletal muscle, as well as fat. It is thought that at some point in mid–late gestation the thin neonate becomes undernourished, and in response its muscles become resistant to insulin. Growth of its muscle is therefore slowed but not that of the brain, which does not require insulin to utilise glucose. Persisting resistance to insulin through childhood into adult life impairs the response to a glucose challenge, because muscle is the main peripheral site of insulin action. Adults who were thin at birth have reduced rates of glycolysis in their muscles.[13] It is unclear how this is linked to insulin resistance, but studies of muscle metabolism of people who were thin at birth may lead to a new understanding of insulin resistance.

Liver growth in utero. In Sheffield, where the Queen Charlotte form was also used, neonates who had a short body in relation to the size of the head, although within the normal range of birthweight, had persisting disturbances of cholesterol metabolism and blood coagulation. Disproportion in body length relative to head size is thought to result from undernutrition in late gestation. The fetus uses an adaptive response present in mammals and diverts oxygenated blood away from the trunk to sustain the brain. One of the organs whose growth is prejudiced by this is the liver. Two of its functions, regulation of cholesterol and of blood clotting, seem to be permanently disturbed. A small abdominal circumference at birth, reflecting small liver size, predicts raised serum low density lipoprotein

cholesterol concentrations, a major coronary risk factor.[14] The difference in serum cholesterol concentrations between people who had a small abdominal circumference at birth and those who had a large one is equivalent to around 30 per cent difference in risk of coronary heart disease. The findings for plasma fibrinogen concentrations, a measure of blood coagulability, are of similar size.[15]

In keeping with these associations a small abdominal circumference at birth is also associated with raised death rates from coronary heart disease.[14] This, however, is only seen in babies of below average weight. In large babies the trend is reversed, so that it is the large baby with the large abdominal circumference who is at increased risk. This kind of baby is known to result from a pregnancy in which the mother develops diabetes. The fetus is exposed to abnormally high concentrations of glucose and is therefore, in a sense, overnourished. In these babies the abdomen enlarges rapidly in late gestation. It seems that accelerated as well as reduced liver growth in late gestation are linked to later coronary heart disease.

Growth in infancy

In late gestation rates of cell division fall and growth slows. After birth growth mainly consists of the development and enlargement of existing cells rather than addition of new ones.[2,5] Babies who are short at birth, with reduced abdominal circumferences, tend to grow slowly after birth. Low rates of infant weight gain are highly predictive of coronary heart disease among men.[8,16] In Hertfordshire, men who were small at one year are three times more likely to develop or die from coronary heart disease than those who were large, an association which does not depend on the way in which the infants were fed.

Low weight gain during infancy is also followed by hypertrophy of the left ventricle in adult life, which predicts coronary heart disease independently of the systemic blood pressure.[17] One possible explanation, for which there is only limited evidence, is that short babies are resistant to growth hormone, which takes over control of growth from insulin in late fetal life. Resistance to growth hormone is associated with high circulating concentrations of the hormone. In patients with pituitary tumours producing growth hormone, the high concentrations lead to cardiac enlargement, atheroma in the vessels and death from coronary heart disease. Long term consequences of programmed patterns of hormone release, or of tissue sensitivity to them, may be important disease mechanisms underlying not only coronary heart disease and diabetes but also hormonally related cancers.

The thin and short babies are two forms of disproportionate baby, whose growth was restricted at different stages of gestation and in different tissues, notably muscle and liver, and this may have helped to sustain the brain. Perhaps the origins of coronary heart disease partly lie in the large size of the human brain, in comparison with that of other mammals. Adaptive responses that protect the brain do so at exaggerated costs to other tissues.

Proportionate small size at birth

Some babies are proportionately small: their length, head size and weight are reduced in proportion to each other. Such babies are thought to have established a slow growth rate in early gestation which they were able to sustain throughout late gestation and thereby avoided becoming disproportionate. Early slowing of

the growth trajectory is a major adaptation to undernutrition because it reduces the subsequent demand for nutrients.[5] We know little about what sets the early growth trajectory in humans or when in embryonic or early fetal life it is set and whether it may be hormonally controlled. We also know little about proportionately small babies. There is no evidence that they develop coronary heart disease, but they do develop raised blood pressure. Persisting elevation of blood pressure seems to follow interference with growth at any stage of gestation, since it is seen in people who were small, thin or short babies. A progressive fall in blood pressure with increasing birthweight has been shown in 20 studies of men, women and children.[18] The mechanisms underlying this association may depend on the stage of gestation when they are initiated. One possible mechanism is changes in vascular structure, with persisting loss of elasticity. People who were small at birth have reduced compliance in their large arteries as adults.[19] This will increase pulse pressure. Another mechanism may be the effects of glucocorticoid hormones.[20,21] In animals modest glucocorticoid excess retards intrauterine growth and programmes raised blood pressure. Such an excess may occur either from feto-placental stress or from deficiency in the normal placental enzyme barrier which protects the fetus from its mother's glucocorticoids.

The placenta

At an early stage of development an embryo comprises two groups of cells, the inner and outer cell masses. The one on the outside does not give rise to any structures in the embryo but develops into the placenta. It is from the inner cell mass that we have our origins. Experiments in animals suggest that the distribution of cells between the two groups is influenced by nutrition and hormones. In the ewe undernutrition in early pregnancy leads to placental enlargement, thought to be an adaptation to extract more nutrients.[22] This only occurs if the ewe was well nourished before mating. There is evidence that placental enlargement may also be an adaptive response in man. Ultrasound studies in humans show that at around 18 weeks fetuses of a given size already have a range of placental volumes;[23] and we know that mothers who are anaemic, who exercise heavily in pregnancy, or who live at altitude have babies with large placentas.

Our observations suggest that expansion of the placenta is another fetal adaptation that exacts a long term price. We measured the blood pressures of a group of men and women in Preston whose birthweight and placental weight had been recorded.[24] As expected pressures fell with increasing birthweight. At any birthweight, however, pressures rose as placental weight increased; so that the highest pressures were in those in whom, in fetal life, a greater proportion of their resources had been allocated to placental development rather than to their own growth. Other studies have shown that placental enlargement is followed in adult life not only by elevated blood pressure, but by impaired glucose tolerance, disordered blood coagulation and death from coronary heart disease. Placental enlargement therefore seems a general marker of fetal undernutrition and its consequences rather than a specific marker of later hypertension. In a group of men born in Sheffield, raised death rates from coronary heart disease were found to be associated with a high placental/birthweight ratio. The distribution of death rates was U-shaped, however, both a high and a low placental birthweight ratio being associated with raised rates.

Time-trends of coronary heart disease

Coronary heart disease was rare in Britain at the turn of the century; having risen rapidly to become the commonest cause of death it is now declining. Such rapid changes cannot be genetically determined; neither it seems can they be explained by coincident alterations in the lifestyles of adults. Could they result from changes during development? An important difference between fetal growth in the third world and in the western world is that proportionate growth retardation is common in the former while disproportionate growth retardation prevails in the latter. Perhaps coronary heart disease occurs in populations at a stage of nutrition between chronic maternal malnutrition, with early down regulation of fetal growth, and nutrition at a plane that allows adequate fetal nutrition throughout gestation. This intermediate phase of nutrition is characterised by disproportionate growth retardation. Studies currently in progress in India and China should illuminate this.

CONCLUSION

The search for the environmental causes of coronary heart disease has hitherto focused on a 'destructive' model in which influences acting in adult life, such as smoking and obesity, hasten ageing processes—the formation of atheroma, rise in blood pressure and reduced ability to metabolise glucose. The observations described in this paper suggest that origins of coronary heart disease may arise during fetal development. This points to a new focus for research. We know surprisingly little about how the nutrition of human mothers influences that of their fetuses—much less than is known in domestic animals. We need to discover how maternal nutrition, body composition and hormonal profile, interact to establish the fetus' growth trajectory in early gestation, and to sustain its growth thereafter.

It seems that many, if not all, human fetuses have to adapt to a limited availability of nutrients and oxygen. These adaptations programme the body's physiology, metabolism and structure. We now need to know more about them: what they are; what induces them; how they leave a lasting mark upon the body; and how they give rise to the diseases of later life.

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TUBERCULOSIS AND TANZANIA

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The International Union against Tuberculosis and Lung Disease (IUATLD) helps to implement and supervise national tuberculosis programmes in countries with a high incidence of tuberculosis and limited resources, such as Tanzania, Senegal, Malawi, Mozambique, Benin and Nicaragua. The increasing incidence of tuberculosis, especially in those with a high prevalence of HIV infection, led to an invitation to accompany, as visiting consultant, Dr Hans Rieder, chief of the tuberculosis section, IUATLD, during one of his twice-yearly trips to 'inspect' the national tuberculosis programme of Tanzania.

TANZANIAN NATIONAL TUBERCULOSIS PROGRAMME

The tuberculosis programme, brainchild of Dr Karel Styblo of the IUATLD, developed in the late 1970s in association with the Tanzanian government. Overseas donors funded the provision of drugs and diagnostic services, training and transport; the Tanzanian government provided and paid the staff. The present overseas financial aid amounts to one million Swiss francs annually, supplemented from 1995 by the addition of over one million US dollars per year from the Dutch Government and 250,000 US dollars from the Royal Netherlands Tuberculosis Association for the supply of drugs, diagnostic materials and training. The German Leprosy Relief Association provides Toyota Land Cruisers for all regional tuberculosis and leprosy control officers and Honda motorcycles for all district officers every three years. The Tanzanian government provides the petrol.

The service is centrally controlled from Dar es Salaam with drugs supplied through regions to districts. All districts maintain a tuberculosis register from which national case diagnostic and treatment data and outcomes can be determined.

Size of problem

By the early 1980s case registration in Tanzania was considered to be sufficiently reliable to reflect national trends in disease notification which at that time were reasonably stable at about 12,000 cases/year. In the last 10 years however there has been a continuing increase in notifications (Fig 1 for comparison with Scottish figures). This is in spite of the introduction of extremely effective short-course chemotherapy with an initial two months of directly observed rifampicin based daily quadruple chemotherapy for all smear positive pulmonary or infectious cases. These cases have increase from 12,092 per annum in 1984 to an estimated 40,000 per annum in 1994—an increase of over 300%. There was a greater increase in smear positive pulmonary (13%) and extrapulmonary (15%) cases from 1992 to 1993 than smear negative pulmonary cases (6%). The number of relapsed cases submitted to retreatment fell by 9%. Treatment outcomes have been remarkably good with 72% of new smear positive pulmonary cases demonstrated cured (smear negative at completion of chemotherapy) and a further 5% completing treatment without final bacteriological confirmation. Eight per cent