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## CORONARY HEART DISEASE AND DIABETES ORIGINATE IN THE WOMB

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*"Man brings all that he has or can have into the world with him. Man is born like a garden ready planted and sown". William Blake.*

### **Why westernisation brings epidemics of coronary heart disease and diabetes.**

We have become accustomed to the idea that coronary heart disease, the commonest cause of death in the western world, may be the price we pay for our 'unhealthy' affluent lifestyle. Obesity and cigarette smoking are indeed clearly implicated, and evidence on dietary fat is sufficient to make reduced consumption prudent, if unproven. Psychosocial stress also seems to play a role. Unfortunately formulation of public health policies to try and prevent coronary heart disease has simultaneously created a scientific orthodoxy. This states categorically that the disease results from the affluent lifestyle of westernised adults together with a contribution from genetic inheritance. Such a view of coronary heart disease offers little insight into why one person develops the disease while another does not, and does little to illuminate why the westernisation of less affluent countries is so regularly followed by epidemics of the disease, which rises steeply to become the commonest cause of death, but thereafter declines. The orthodox view also contributes little to the resolution of one of the over-arching questions in public health in western countries. Why do the highest rates of coronary heart disease occur among the poor? The idea that it is because the poor have especially unhealthy western lifestyles is unproven and sustained only by exaggerated claims for the effects of cigarette smoking and obesity. The commonest cause of death among non-

smokers is coronary heart disease: and rates of the disease are falling dramatically in the USA while people are becoming more obese.

### **Coronary heart disease originates in the womb**

Recent research suggests that some answers to these questions may come from an understanding of how the structure of the heart and blood vessels, and processes such as blood pressure regulation and the way the body handles sugar and fat, are established in the womb. Until recently we have overlooked a large body of evidence that systems of the body which are closely related to adult disease, such as the regulation of blood pressure, can be 're-set' during early development. In animals it is surprisingly easy to produce lifelong changes in the blood pressure and metabolism of a fetus by minor modifications to the diet of the mother before and during pregnancy. **The 'fetal origins' hypothesis states that coronary heart disease, and the disorders related to it – hypertension, diabetes and stroke – originate through adaptations that the fetus makes when it is under-nourished. These adaptations permanently change the body's structure and function. They allow the fetus to survive and continue to grow but at the price of a shortened life.**

The platform for this hypothesis is that, like other living creatures in their early life, human beings are 'plastic' and able to adapt to their environment. The development of the sweat glands provides a simple example of this. People's ability to adapt to hot climates depends on the number of functioning sweat glands they have. Those with more glands cool down faster. At birth everyone has similar numbers of sweat glands, but none of them function. In the first three years after birth, a proportion of the glands become functional depending on the climate to which a child is exposed. At three years of age the number of functioning sweat glands is fixed for life. This exemplifies a developmental path shared by many systems of the body. A critical period when the system is plastic and sensitive to the

environment followed by loss of plasticity and fixed functional capacity. Much of human development is completed before birth. Thereafter our capacity to grow new cells is limited, our hormonal systems are largely set and the way we handle nutrients has been 'primed' by our experiences in utero. There are many possible evolutionary advantages in the body remaining plastic during development, rather than having its growth driven only by genetic instructions at conception. Why adaptations in early life tend to be permanent, while those in adult life are generally reversible, is a fundamental question to which we have only speculative answers.

#### **Low birthweight babies are at increased risk of coronary heart disease**

Ten years ago studies in Britain showed for the first time that people who had low birthweight are at increased risk of coronary heart disease and its related disorders. In a study of 16,000 men and women born in Hertfordshire, UK, for example, death rates from coronary heart disease fell two-fold between those at the upper and lower ends of the birthweight distribution. The prevalence of non-insulin dependent diabetes fell threefold. Associations between low birthweight and later disease have been widely replicated in studies in Europe and the USA. 38 studies, on populations totalling 250,000 people confirm that low birthweight is associated with raised blood pressure through childhood and into adult life. The risk of disease falls across the range of birthweights, so that the 7 pound baby is at lower risk than the 6 pound and the 8 pound baby is at lower risk than the 7 pound. Furthermore, we now know that these associations do not occur through people who experienced worse growth in the womb, having a worse environment in childhood and adult life. Rather it is events in the womb which initiate later disease. Influences that act after birth do, however, add to the effects of low birthweight. The highest prevalence of non-insulin dependent diabetes, for example is found in people who had low birthweight but were obese as adults.

### **Low birthweight indicates fetal malnutrition**

Although the growth of the fetus is influenced by its genes, studies in humans and animals suggest that it is usually limited by the nutrients and oxygen it receives from the mother. The mother exerts a stronger affect on fetal growth than the father, and the mother's weight before conception is the strongest determinant of birthweight. The birthweights of babies born after ovum donation, where the egg from one woman is transferred to another, are strongly related to the weight of the recipient mother, but unrelated to the weight of the woman who donated the eggs. These and other observations, together with studies in domestic animals, suggest that birth size is essentially controlled by the mother rather than the genetic inheritance from both parents. Other than the mother's weight before conception the strongest determinant of birthweight is the mother's own birthweight, which strongly influences the birthweight of her own children, independently of her current body size. The performance of the fetal supply line, by which nutrients are transferred from the mother's blood stream to the fetal blood stream, seems to be strongly influenced by the mother's development as a fetus. The fetus becomes undernourished when its demand for nutrients exceeds its supply. Either the supply may be low, for example when the mother is thin or starving, or demand may be high because the fetus is growing rapidly.

### **Fetal responses to malnutrition**

When a fetus becomes malnourished it may re-distribute its blood flow to protect key organs, the brain in particular; or change the nutrients it consumes in order to obtain energy, for example by consuming protein rather than sugar, or it may 're-set' the hormones, importantly insulin, by which it regulates its growth. Slowing of growth is an important adaptation to undernutrition because it reduces the fetus' demand for nutrients. Nevertheless many undernourished fetuses are able to sustain their growth, but do so at a long-term cost.

The birthweights of babies who were in the womb during the war-time famine in Holland in 1944-5 were little changed; but as adult men and women their ability to respond to insulin is impaired and they are at increased risk of developing diabetes.

### **Thin and stunted babies**

Further insight into fetal responses to undernutrition and their long-term consequences has come from studies where detailed measurements of size at birth, including body length and head size are available. In the same way as is seen among malnourished children, new-born babies may be thin or short (stunted), or short and fat. These different body shapes reflect different responses to malnutrition in the womb. The long-term consequence of each of them is different, but all predispose to coronary heart disease and either raised blood pressure or diabetes.

There are many low birthweight, thin or stunted babies in the Third World. The average birthweight in India, for example, is only 2.7kg, and 30% of babies born there weigh 2.5kg or less. Furthermore, studies in India, China and Jamaica show that thin or short babies are at increased risk of later disease as they are in the west. Why, however, are epidemics of coronary heart disease and diabetes only now occurring in Third World countries. Answers may lie in the way in which the so-called 'nutritional transition' between chronic malnutrition and western nutrition brings imbalances in what has been called 'the escape from hunger'. There are either imbalances in the nutrient delivery to the fetus, or imbalances between pre- and post-natal growth.

### **The nutritional transition: mothers, babies and children**

The availability of nutrients to the fetus is determined by the mother's body composition, (that is her proportion of fat, lean tissue and bone) and her nutritional stores at the time of

conception and her diet in pregnancy. The low birthweights of babies in India reflects the thinness and short stature of their mothers, a result of chronic malnutrition, together with a poor diet in early pregnancy - low consumption of green vegetables, for example. Preliminary findings from studies in Europe and the Third World suggest that many babies today may be malnourished and at increased risk of coronary heart disease and diabetes either because their mothers are too thin, or too fat, or eat unbalanced diets. In China, for example, the adult offspring of women who were thin in early pregnancy are less responsive to insulin and are at increased risk of developing diabetes if they become overweight as adults. A study in Finland has shown that thin babies are at increased risk of coronary heart disease if their mothers were short and overweight, or if they themselves had accelerated weight gain in early childhood.

The nutritional transition brings imbalances in the nutrition of mothers, babies and children. Better availability of food immediately benefits the nutrition and growth of children, though if increases in height and muscularity are not achieved, because of persisting poor hygiene for example, children may remain stunted but fat. Better nutrition brings some immediate benefit to mothers, for example in greater availability of folate, iron and vitamins, but maternal malnutrition reflects a lifetime of deprivation and takes at least one generation to redress. The growth of the baby in the womb will be immediately improved if the mother's intake of micronutrients increases, but it remains constrained by the fetal supply line and, as we have discussed, this is partly dependent on the mother's own development in the womb. At least two generations may need to elapse before this constraint on fetal growth is released.

### **The future**

Hitherto in development projects, interest in the nutrition and health of young women before pregnancy has been subordinate to interest in young children. Recent findings from

epidemiological, clinical and basic science point clearly to the need to change the emphasis. In rural India and other Third World countries, girls are thin and undernourished, while in towns they are becoming overweight but remain short in stature. Children in many countries remain stunted but are now becoming obese. The likely benefits of improving the body composition and nutrition of girls and young women in developing countries include a reduction in the rising epidemic of coronary heart disease, diabetes and premature death.

### **Reference**

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