Fetal undernutrition and disease in adult disease

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ABBREVIATIONS

CHD coronary heart disease
PEPCK phosphoenol pyruvate carboxykinase

INTRODUCTION

During embryonic life, that is during the 8 weeks after conception, the basic 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. Rather it contains in its genes a generative programme for making a person, a programme 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 by the genes which become activated.

FETAL GROWTH

The body does not increase greatly in size during embryonic life but in the fetal period, from 9 weeks after conception onwards, there is a phase of rapid growth which continues until after birth. Growth does not simply expand the miniature human being but, through differences in growth rates of different parts of the body, it moulds the baby’s form. The main feature of fetal growth is cell division. Different tissues of the body grow during periods of rapid cell division, so called ‘critical’ periods (2). The timing of these critical periods differs for different tissues: the kidney, for example, goes through a critical period in the weeks immediately before birth. Growth depends on nutrients and oxygen, and the main adaptation of the fetus to lack of these is a slowing of the rate of cell division, particularly in those tissues which are undergoing ‘critical periods’ at the time. Cell division slows either as a direct effect of undernutrition on the cell or as a result of 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. Studies of the birth weights of relatives have led to the conclusion that variation in size at birth is essentially determined by the intrauterine environment rather than the fetal genome (3,4). Widdowson and McCance (2,5) were among the first to show that brief periods of undernutrition may permanently

reduce the numbers of cells in particular organs. This is one of the mechanisms by which undernutrition may permanently change or ‘programme’ the body (6). Other lasting ‘memories’ of undernutrition include change in the distribution of cell types, in hormonal feedback, in metabolic activity and in organ structure, each of which will be discussed further.

It is not in question that the human body can be programmed by undernutrition. Rickets has for a long while served as a demonstration that undernutrition at a critical stage of early life leads to persisting changes in structure. What is new is the realization that some of the body’s ‘memories’ of early undernutrition become translated into pathology and thereby determine disease in later life. This is perhaps unsurprising, given the numerous experiments on animals which have shown that undernutrition in utero leads to persisting changes in blood pressure, cholesterol metabolism, insulin response to glucose, and in a range of other metabolic, endocrine and immune functions known to be important in human disease (6–8).

**FETAL GROWTH AND CORONARY HEART DISEASE**

The main focus for research into coronary heart disease (CHD), the most common cause of death in the Western world, has been the lifestyles of men and women. Inappropriate behaviours, such as a high fat diet, cigarette smoking and obesity, 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 the disease while another does not.

In the search for a new model for coronary heart disease an important clue, suggesting that it might originate in utero, came from studies of death rates among babies in Britain during the early years of the century (9), when death during infancy was remarkably common. 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 newborn babies was low birth weight. Death rates in the newborn differed considerably between one part of the country and another, 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 CHD, variations which form one aspect of the continuing north–south divide in health. A conclusion suggested by this observation was that low rates of growth before birth are linked to the development of CHD in adult life. The suggestion that events in childhood influence the pathogenesis of CHD 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 simple strategy of examining in middle and late life individual men and women whose size at birth was recorded. The records on which these studies were based came to light as a result of the Medical Research Council’s systematic search of the archives and records offices of Britain –