THE GENESIS OF 'FETAL ORIGINS OF ADULT DISEASE'

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ABSTRACT

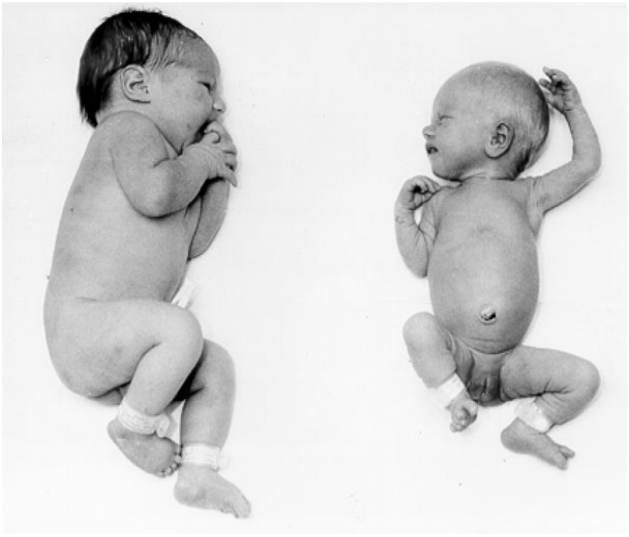
Research into the causes of coronary heart disease (CHD) and the associated diseases, hypertension and type 2 diabetes has largely focused on the degenerative effects of factors related to adult lifestyle. The idea that CHD originates during development in early life is not a new one, but has been neglected until recently. Interest was re-awakened by two epidemiological features of the disease: its decline in western countries since 1970 (predating changes in adult risk factors) and a correlation between current CHD death rates and infant mortality rates 100 years ago. Old birth records, found in Hertfordshire, UK, and thereafter in many locations around the world, have now led to the discovery that low birthweight and poor growth in infancy are followed in later life by an increased risk of CHD, hypertension, type 2 diabetes, insulin resistance and dyslipidaemia. These findings have led to the 'fetal origins hypothesis' that CHD has its roots in fetal and infant undernutrition. Occurring at critical periods of development, the effects on organ growth, body composition and metabolism persist throughout life, a phenomenon known as 'programming'. They are exacerbated by, and may increase susceptibility to, adult risk factors such as obesity. This hypothesis has generated a new field of science, aimed at defining the mechanisms of programming and ways of improving the early-life development and adult health of future generations.

KEYWORDS : Coronary heart disease, type2 diabetes, birthweight, infant weight, programming

INTRODUCTION

These two full-term babies, born on the same day in Southampton, UK, illustrate the wide range in size of human neonates (Figure 1). Both were of 'normal' birthweight, 2.5 kg, and 4 kg, and clinically, represent successful reproductive outcomes. However, recent research has shown that the smaller thinner baby carries a lifelong health disadvantage. In adult life, she is two to three times more likely than the larger baby to develop coronary heart disease, hypertension, type 2 diabetes and the insulin resistance syndrome. This discovery has led to the'fetal origins hypothesis', that sub-optimal nutrition in utero has permanent adverse effects on human structure and metabolism. The hypothesis has its greatest relevance for developing countries like India which have high rates of intra-uterine growth retardation.

Figure 1: Clues from a 20th century epidemic – coronary heart disease



Of 50 million deaths worldwide in 1990, coronary heart disease (CHD) was the leading killer, responsible for 6 million deaths (1). This stark statistic, emphasises the importance of the disease, but reveals nothing about its complex epidemiology over the past 100 years (2). Although atherosclerosis has been found in Egyptian mummies, and contemporary descriptions of CHD date from the 1500's (3), CHD was uncommon until the early 20th century. The incidence then rose steeply in Western countries, CHD becoming the commonest single cause of death. Between 1920 and 1970 mortality rose 5-fold in Britain (4,5). CHD appeared to be a disease of prosperity, affecting the most affluent sections Western society, and remaining rare in of developing countries (6,7). Since 1970, however, the epidemic has receded in most Western countries. As its rise was associated with prosperity, so is its decline; rates have fallen faster in the USA than elsewhere, and faster in high than in low income groups (6,7.) Meanwhile, the epidemic has started to repeat itself in developing

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countries, where deaths from coronary heart disease are predicted to overtake those from infectious disease in the next 10-15 years (8).

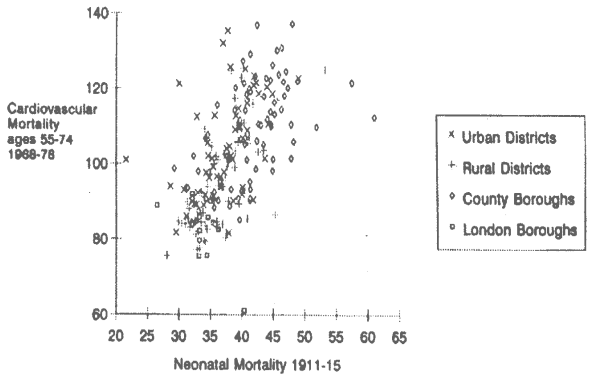
Such rapid changes in disease incidence must have environmental causes. Research has focused on the 20th century Western lifestyle, and identified high dietary fat intakes, obesity, lack of exercise, cigarette smoking and stress as factors which increased the risk of disease (9-11). Metabolic risk factors have been identified, including hypertension, insulin resistance, type 2 diabetes, raised serum LDL-cholesterol and triglyceride concentrations, low serum HDL-cholesterol concentrations and raised plasma clotting factors, which can in turn be linked to lifestyle. A tendency for CHD and its metabolic risk markers to run in families suggested underlying susceptibility genes. CHD is now thought of as a multifactorial degenerative disease, which people develop or avoid depending on the damage done by the sum of risk factors they inherit and accumulate through life. The known risk factors do not, however, explain all the epidemiology of the disease (12). At an individual level, they are poor predictors of who will and will not develop CHD. For men in the UK in the lowest risk factor groups, the commonest cause of death is still CHD (13). This may be because risk factor measurements are too crude. Alternatively, there may be other factors in the aetiology of the disease which have not yet been identified or measured.

EARLY-LIFE ORIGINS OF CORONARY HEART DISEASE:

The idea that CHD may be a developmental disease, influenced by factors acting in early life is not new, but was until recently ignored. In the 1920's and 30's, Derrick and Kermack showed that death rates (from all causes) in Britain and Europe over the preceding two centuries, fell with each successive year-of-birth cohort (14,15). In 1964, Rose showed that the siblings of CHD patients had stillbirth and infant mortality rates twice those of the siblings of controls (16). In 1977, Forsdahl showed a geographical correlation within Norway between CHD mortality in 1964-67 and the infant mortality rate (IMR) 70 years earlier (1896-1925) (17,18). He suggested that since a high IMR indicated a poor childhood environment, growing up in poverty caused 'some form of permanent damage' (perhaps due to a 'nutritional deficit'), which left people with a 'life-long vulnerability' to aspects of an affluent adult lifestyle such as high fat intakes.

In 1984, Barker and his colleagues in Southampton, UK showed three-fold differences in CHD mortality across England and Wales, lowest in south-east England and highest in northern industrial towns and in poor rural areas of northern England, Wales and south-west England (19,20). As in Norway, this geographical pattern was similar to that for infant mortality rates at the turn of the 20th century. Across 212 districts, the correlation (r) between infant mortality rates in 1921-25 and current death rates from CHD and stroke was 0.73. Mortality from cardiovascular disease was correlated with both neonatal (Figure 2) and post-neonatal mortality. While the latter reflects the infant environment, such as household crowding and undernutrition, the former reflects intra-uterine factors, including maternal ill-health and low birth weight. Barker suggested that the roots of CHD lay not in a poor childhood environment, but in the effects of poverty on the mother resulting in fetal and early infant undernutrition. He proposed a 'two-hit' pathogenesis of CHD, early deprivation increasing an individual's susceptibility to later affluence. This provided a possible explanation for the rise and fall of CHD. The affluent would be exposed first to adult risk factors for the disease, but also the first to experience improvements in maternal nutrition and fetal growth. People of poorer socio-economic status would lag behind in both phases.

Figure 2: Cardiovascular disease mortality in England and Wales 1968-78 and neonatal mortality 1911-1915



The discovery of birth records, dating from 1911-1948, and covering all births in the UK county of Hertfordshire, first made it possible to test this hypothesis. From 1911, Hertfordshire midwives and doctors were required by law to notify births and record birthweights. Health visitors recorded how the babies were fed during infancy and their weight at the age of one year. By matching these

early records to death certificates, we were able to study causes of death in relation to birthweight for over 15,000 men and women born in Hertfordshire(21,22) (Figure 3). Death rates from CHD fell two-fold between those at the lower and upper ends of the birthweight distribution. The trend was continuous across the range of birthweight, not confined to people of abnormally low birthweight, and present in both sexes. There were similar trends for stroke and obstructive lung disease, but no association between birthweight and the other common cause of death, lung cancer. In men, CHD mortality was also strongly related to low weight at the age of one year.

Figure 3: Death Rate from Coronary Heart Desease (22) Men and women born in Hertfordshire 1911-1930

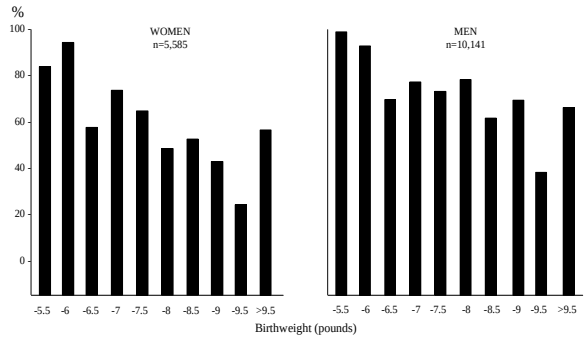
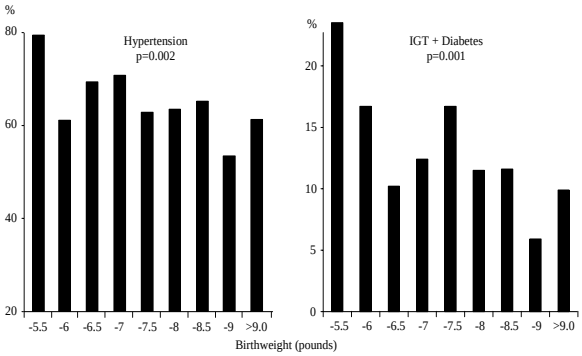


Figure 4: Prevelance of hypertension, and impaired glucose tolerance (IGI) or diabetes according to birthweight; men born in Hertfordshire 1920-30, n=370



We subsequently measured risk factors for CHD: blood pressure, glucose tolerance, serum lipids, plasma insulin and clotting factors in men and women born in Hertfordshire between 1920 and 1930, and still living there. The trends in CHD mortality with birthweight were paralleled by similar trends in some of its major known risk factors, notably hypertension, type 2 diabetes (Figure 4) and insulin resistance (23-25). Low weight at one year, in men, was associated with higher adult fibrinogen and LDL-cholesterol concentrations (26,27). These trends remained after adjustment for confounding factors such as adult social class, obesity, smoking and alcohol consumption. Indeed, these factors appeared to add to the birthweight or infant weight effects; for example the prevalence of impaired glucose tolerance was highest in people of low birthweight who were also obese as adults (23) (Table 1).

Table 1: Impaired glucose tolerance and type 2 diabetes. Men born in Hertfordshire 1920-30 (n-370) (23)

Birthweight (kg/m^2) (pounds)	Adult body mass index			
	<25	-28	>28	All
< 6.5	18 (6)	35 (8)	50 (21)	36(12)
-8.5	15 (5)	30 (4)	31 (10)	26 (6)
>8.5	5 (5)	18 (6)	14 (7)	13 (6)
All	13 (5)	28 (5)	31 (11)	25 (7)

Figures in brackets are percentages with type 2 diabetes

THE 'FETAL ORIGINS' HYPOTHESIS:

Low birthweight for gestational age is a sign of fetal under-nutrition, occurring through a failure of placental supply or because the mother is malnourished. The undernourished fetus is forced to prioritise its limited supply of nutrients, for example favouring brain growth at the expense of abdominal organs and musculo-skeletal growth. This may be achieved by adaptations in blood flow (the 'brain-sparing reflex') (28) or in the hormonal axes controlling fetal growth (insulin, the insulin-like-growth factors, and corticosteroids) (29). If it coincides with critical periods of development for specific tissues, their growth may be permanently impaired. Growth retarded fetuses have reduced numbers of nephrons and pancreatic islet cells, the capacity for production of which ceases in early life (30,31). In addition to structural effects, research mainly in animals shows that undernutrition at critical periods in early life can also lead to permanent alteration ('programming') of dynamic physiological processes such as enzyme systems and endocrine axes (32). The 'fetal origins hypothesis' proposes that CHD, and some of its metabolic risk factors, such as hypertension, type 2 diabetes and the insulin

resistance syndrome, result from these changes, made in fetal life in response to under-nutrition and then 'hard-wired' into the individual's structure and physiology (Figure 5) (33).

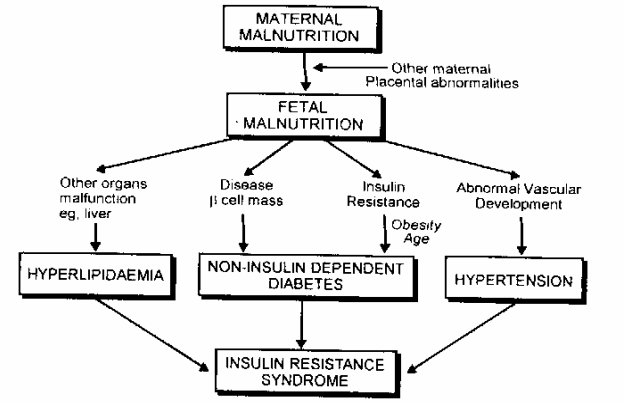


Figure 5 : Fetal Origins Hypothesis (33)

Since the original Hertfordshire studies, similar results have been replicated in other populations, including (for the metabolic risk factors) children, in the UK, Europe, and the USA (33-45). With some important differences, similar findings have also been reported from developing countries notably India (46-48) and China (49). Some studies are based on birth records containing more detailed data, such as gestational age at birth, measurements of birth dimensions as well as weight, maternal diet and body composition, and follow-up data on childhood growth. It is people who were small at birth because they failed to grow, not because they were born prematurely, who are at increased risk of CHD (33,34). Dysproportion at birth, for example a low ponderal index (weight for length), is often more closely related to CHD and its risk factors than low birthweight, perhaps reflecting the timing of the intr
a-uterine insult (33-35,38,40). Effects of low birthweight differ according to the mother's body composition and nutritional status, and the baby's growth in infancy and childhood (40,47,49,50). Evidence from large studies in the USA and from the Pima Indians suggest that babies born with a weight at the very top end of the scale due to maternal gestational diabetes, as well as growth-restricted babies, are at risk of developing adult type 2 diabetes (41,51).

The future challenges for FOAD research are to identify the mechanisms by which disease is programmed, to determine whether effects are reversible or amenable to treatment, and to find interventions to prevent disease by improving fetal growth. The latter will require greater knowledge of the effects of a mother's health and nutritional status, not just during pregnancy but throughout her lifecycle, on her ability to support healthy fetal growth.

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