Editorial

The Fetal Origins of Coronary Heart Disease and Non-Insulin Dependent Diabetes in India

Coronary heart disease (CHD) is common in India and rates are rising(l). Death rates from the disease are expected to overtake those due to infectious disease by the year 2010(2). Already, cardiovascular deaths account for half the deaths occurring under 70 years. These high rates of CHD in India are not explained by known risk factors including obesity, raised blood pressure, smoking and raised cholesterol. CHD in Indian populations is, however, associated with a particular metabolic profile that is known to be unfavorable, which includes impaired glucose tolerance or non-insulin-dependent diabetes (NIDDM), insulin resistance, raised serum triglyceride and low HDL-cholesterol concentrations, abnormal plasma clotting factors and central obesity(3). This metabolic profile, which has been called the 'Insulin Resistance Syndrome', is common in India and is often associated with NIDDM requiring treatment. CHD in India has other particular characteristics. It is more common in urban areas and among lower socio-economic groups(4,5), and rates in women are similar to those in men, even though women in many parts of India do not smoke.

When people from India migrate to other countries they take their high rates of coronary heart disease with them. Indeed, the rates rise still further(6). A recent study comparing migrants from the Punjab living in London with their siblings who remained in India showed that the migrant men and women had higher serum cholesterol and blood glucose concentrations and lower HDL-cholesterol concentrations^). Serum Lp(a) concentrations, which are believed to be determined genetically, were similar in both groups. The observations raise the possibility that Indian people have a genetically determined susceptibility to CHD which is enhanced on exposure to a sedentary lifestyle, high energy intake and other aspects of westernization(7-9). The genes responsible for this have not been identified, but it is hypothesized that they conferred a survival advantage to Indian people in past times when food supplies were unreliable and physical work was demanding. The implications of this speculation are that Indian people will continue to have high rates of coronary heart disease unless they return to a more primitive way of life. This conflicts, however, with experience elsewhere in the world, where epidemics of coronary heart disease have been followed by declining rates(10) which, though perhaps assisted by health education are largely unexplained.

Is there an alternative to the genetic hypothesis? Recently, CHD has been shown to be associated with small size at birth. In a study of 16,000 men and women born in Hertfordshire, England during 1911-1930, death rates from coronary heart disease fell two-fold between the upper and lower ends of the birthweight distribution(11,12). A study in Sheffield showed that it was people who were small for dates, rather than born prematurely, who were at increased risk of the disease(13). The association between low birthweight and coronary heart disease has now been confirmed in the USA; among 88,000 women in the Nurses study there was a similar twofold

fall in the relative risk of non-fatal CHD across the range of birthweight(14). Recent findings from Hertfordshire and Sheffield show that death from stroke is also associated with low birth weight(15). These associations are independent of adult lifestyle including smoking, obesity and socio-economic status. They have led to the hypothesis that cardiovascular disease is 'programmed' *in utero*. Programming is the process, well documented in animals, whereby undernutrition and other adverse influences acting during early life permanently change the structure and function of the body. If pregnant animals are undernourished their offspring show permanent changes, which include raised blood pressure and altered lipid and glucose metabolism(16). The 'fetal origins hypothesis' proposes that undernutrition *in utero* leads to fetal adaptations that permanently alter the physiology and metabolism of the body in ways which lead to cardiovascular disease in adult life.

We are beginning to understand the mechanisms by which cardiovascular disease is programmed. The trends in cardiovascular disease with birthweight have been found to parallel similar trends in the major risk factors, including non-insulin-dependent diabetes, hypertension, and disordered lipid metabolism and blood coagulation(16). These are strong trends. For example, the prevalence of non-insulin dependent diabetes and IGT fall threefold between people who weighed 2.5 kg or less at birth and those who weighed more than 4.3 kg(17,18). Obesity in adult life adds to the effect of low birthweight, so that the highest prevalence of NIDDM is seen in people who were small at birth and obese as adults. There is evidence that people who have low growth rates *in utero* have a reduced number of pancreatic beta cells, and thus have an impaired capacity to secrete insulin. There is stronger evidence that they became resistant to the action of insulin. Insulin resistance is associated with a particular pattern of fetal growth which leads to a reduced ponderal index (birthweight/birth length^3) at birth. Men and women who had a low ponderal index have been shown to be insulin resistant as children and adults, and they have a markedly increased susceptibility to the Insulin Resistance Syndrome(19-21). The thin neonate lacks muscle as well as fat, and muscle is the main peripheral site of insulin action, which has a key role in stimulating cell division in fetal life. It is thought that at some point in mid-late gestation the thin neonate became undernoursihed, and that in response its muscles became resistant to insulin. Muscle growth was therefore sacrificed, perhaps to spare brain growth. Other components of the Insulin Resistance Syndrome may similarly be persisting effects of adaptations which enabled the fetus to continue fetal growth in the face of a limited nutrient supply, and to protect key organs and tissues, amongst which the brain is paramount. Thirty two studies worldwide have shown that low birthweight is associated with raised blood pressure in childhood and adult life(22). This association may reflect persisting loss of elasticity in arteries, or permanent resetting of hormonal axis including the growth hormone/IGF axis and the renin-angiotensin system(23). A reduced abdominal circumference at birth, rather than low birthweight, has been shown to predict persisting abnormalities in systems which are regulated by the liver such as cholesterol and blood coagulation. One interpretation of these findings is that reduced abdominal circumference at birth reflects impaired liver growth and consequent programming of liver metabolism. Animal studies demonstrate that both blood pressure and liver metabolism are readily programmed by undernutrition in intrauterine life(24,25).

The possibility that these new explanations for the origins of adult disease may have important implications for the epidemic of CHD and NIDDM in India has not gone unremarked(7,26), but until recently there has been no firm evidence. A recent study in South India, however, has shown that, as in other countries, low birth weight and CHD are linked(27). Five hundred and seventeen men and women who were born during 1934-1953 in the Mary Calvert Holdsworth Hospital, Mysore, were traced. The occurrence of CHD and the related disorders was linked to birthweight and body proportions at birth which were recorded at the time. Among men and women aged 45 years and over the prevalence of CHD fell from 15% in those who weighed 2.5 kg or less at birth to 4% in those who weighed 3.2 kg or more. CHD was also related to low maternal weight in pregnancy so that the highest rates were found in people who had low birthweight and whose mothers were thin. Average birthweights and maternal weights were low by European standards though consistent with values from other parts of India (mean birthweight 2.8 kg, and mean maternal weight 47 kg). A study in Pune suggests that components of the insulin resistance syndrome that are established *in utero* may already be apparent in early childhood. Among 201 four-year old children those with lower birthweight had higher plasma glucose and insulin concentrations after an oral glucose load, independently of their current size(28).

Clearly these early findings in India need to be replicated and extended. In this context, in a recent meeting in Khandala a group of obstetricians, pediatricians, cardiologists, diabetologists and nutritionists met to discuss the recent advances and future possibilities. A strategy to develop the initial epidemiologic al observations is now in place, and studies have begun in a number of centers in India. Perhaps the health of future generations in India will depend on improvements in the nutrition and health of girls and young women.

C.H.D. Fall,
D.J.P. Barker,
MRC Environmental Epidemiology Unit,
University of Southampton,
Southampton General Hospital,
Southampton S016 6YD, U.K.

REFERENCES

1. Chadha SL, Radhakrishnan S, Ramachandran K, Kaul U, Gopinath N. Epidemiological study of coronary heart disease in urban population of Delhi. Indian J Med Res 1990; 92[B]: 424-430.
2. Bulatao RA, Stephens PW. Global estimates and projections of mortality by cause 1970-2015. Pre-working paper 1007. Population, Health and Nutrition Department, World Bank, Washington D C.
3. McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. Lancet 1991; 337: 382-386.
4. Gupta R, Gupta VP, Ahluwalia NS. Educational status, coronary heart disease, and coronary risk factor prevalence in a rural population of India. BMJ 1994; 309: 1332-1336.
5. Pais P, Poque J, Gerstein H, *et ah* Risk factors for acute myocardial infarction in Indians: A case-control study. Lancet 1996; 348: 358-363.
6. Singh RB, Niaz MA. Coronary risk factors in Indians. Lancet 1995; 346: 778-779.
7. Bhatnagar D, Anand IS, Durrington PN, *et al.* Coronary risk factors in people from the Indian subcontinent living in West London and their siblings in India. Lancet 1995; 345: 405-409.
8. Williams B. Westernized Asians and car-

diovascular disease: Nature or nurture? Lancet 1995; 345: 401-402.

9. Shaukat N, de Bono DP, Jones DR. Like father like son? Sons of patients of European or Indian origin with coronary artery disease reflect their parents risk factor patterns. Br Heart J 1995; 74: 318-323.
10. Barker DJP Rise and fall of western diseases. Nature 1989; 338: 371-372.
11. Barker DJP, Winter PD, Osmond C, *et al.* Weight in infancy and death from ischemic heart disease. Lancet 1989; ii: 577-580.
12. Osmond C, Barker DJP, Winter PD, *et al.* Early growth and death from cardiovascular disease in women. BMJ 1993; 307: 1519-1524.
13. Barker DJP, Osmond C, Simmonds SJ, Wield GA. The relation of small head circumference and thinness at birth to death from cardiovascular disease in adult file. BMJ 1993; 306: 422-426.
14. Rich-Edwards J, Stampfer M, Manson J, *et al.* Birthweight, breastfeeding and risk of coronary heart disease in the nurses' health study. Am J Epidemiol 1995; 141: S78.
15. Martyn CN, Barker DJP, Osmond C. Mother's pelvic size, fetal growth, and death from stroke and coronary heart disease in men in the UK. Lancet 1996; 348: 1264-1269.
16. Barker DJP. Fetal origins of coronary heart disease. BMJ 1995; 311:171-174.
17. Hales CN, Barker DJP, Clark PMS, *et al.* Fetal and infant growth and impaired glucose tolerance at age 64. BMJ 1991; 303: 1019-1022.
18. Lithell HO, McKeigue PM, Berglund L, Mohsen R, Lithell U-B, Leon D. Relation of size at birth to non-insulin dependent diabetes and insulin concentrations in men aged 50-60 years. BMJ 1996; 312: 406-410.
19. Phillips DIW, Barker DJP, Hales CN, Hirst S, Osmond C. Thinness at birth and insulin resistance in adult life. Diabetologia 1994; 37:150-154.
20. Law CM, Gordon GS, Shiell AW, Barker DJP, Hales CN. Thinness at birth and glucose tolerance in seven-year-old children. Diabetic Med 1995; 12: 24-29.
21. Barker DJP, Hales CN, Fall CHD, *et al.* Type 2 (non-insulin dependent) diabetes mellitus, hypertension and hyperlipidemia (Syndrome X): Relation to reduced fetal growth. Diabetologia 1993; 36: 62-67.
22. Law CM, Shiell AW. Is blood pressure inversely related to birth weight?. The strength of evidence from a systematic review of the literature. J Hyperten 1996; 14: 935-941.
23. Edwards CRW, Benediktsson R, Lindsay RS, Seckl JR. Dysfunction of placental glucocorticoid barrier: Link between fetal environment and adult hypertension? Lancet 1993, 341: 355-357.
24. Langley SC, Jackson AA. Increased systolic blood pressure in adult rats induced by fetal exposure to maternal low protein diets. Clin Sci 1994; 86: 217-222.
25. Hales CN, Desai M, Ozanne SE, Crowther NJ. Fishing in the stream of diabetes: From measuring insulin to the control of organogenesis. Biochem Soc Trans 1996, 24: 341-350.
26. Indian Consensus for Prevention of Hypertension and Coronary Artery Disease: A Joint Scientific Statement of Indian Society of Hypertension and International College of Nutrition. Indian Consensus Group. J Nutr Environ Med 1996; 6: 309-318.
27. Stein CE, Fall CHD, Kumaran K, Osmond C, Cox V, Barker DJP. Fetal growth and coronary heart disease in South India. Lancet 1996; 348:1269-1273.
28. Yajnik CS, Fall CHD, Vaidya U, *et al.* Fetal growth and glucose and insulin metabolism in four-year old Indian children. Diab Med 1995; 12: 330-336.