D.J.P. Barker (1998)
Mothers, Babies and Health in Later Life.
Edinburgh: Churchill Livingstone

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From birth to death

MARGARET BURNSIDE'S LEDGERS

To examine the hypothesis that coronary heart disease and stroke are programmed in utero has required novel epidemiological studies, since evidence from geography and time trends can only be suggestive. To advance the hypothesis by epidemiological methods it is necessary to use size at birth as a marker of fetal nutrition and relate it, in groups of men and women, to the occurrence of cardiovascular disease in later life.

Staff from the Medical Research Council (MRC) searched archives and hospital record departments throughout Britain, looking for maternity and infant welfare records from the early years of the century. Many were found. Some were in large collections preserved over many years; in some there were no more than a few hundred records kept by one clinic or even one midwife. Some were detailed and some perfunctory. Some were in archives; others were in lofts, sheds, garages, boiler rooms, or flooded basements. The largest set of records were those made by health visitors in the county of Hertfordshire.

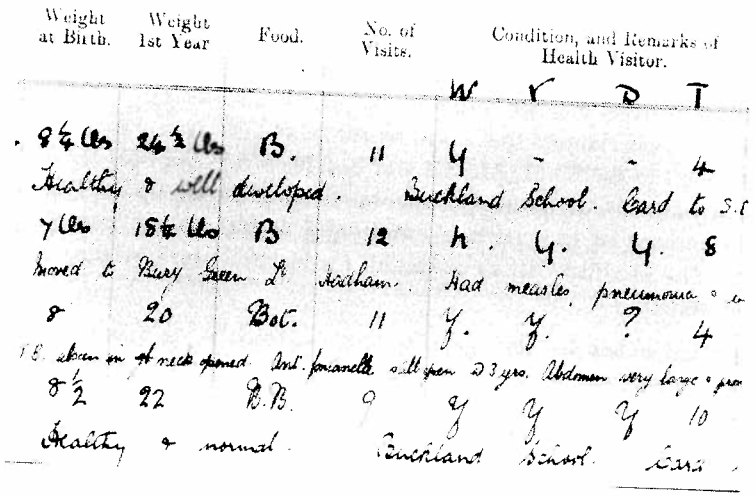
In Britain, in the early years of the century, there was widespread concern about the apparent physical deterioration of the British people. The birth rate was declining. One in 10 babies died before they were a year old and many of those who survived reached adult life in poor health. During 1902, reports in the national press claimed that up to two-thirds of the young men who volunteered to fight in the South African war had been rejected because of unsatisfactory physique.[1] An interdepartmental committee set up in 1903 drew a shocking picture of the nation's children – malnourished, poorly housed, deprived. The Medical Officer of Health for Hertfordshire, writing at around this time, stated:

> Hertfordshire does less than forty out of the fifty-five counties to perpetuate the national stock; for England and Wales the birth-rate has for thirty-three years been steadily declining, only two Continental countries (Belgium and France) having lower birth-rates in 1909, while that for Japan is increasing and is now ahead of every white race but Russia and three of the Balkan States. The new census figures show a lower rate of

Fig. 3.1 Mothers in Hitchin, Hertfordshire at the turn of the century.

physical factor arise to defeat it. [He added] it is of national importance that the life of every infant be vigorously conserved.

Miss Ethel Margaret Burnside, the county's first ever 'Chief Health Visitor and Lady Inspector of Midwives' set up an 'army' of trained nurses to attend women in childbirth and to advise mothers on how to keep their babies healthy. From 1911 onwards when women in Hertfordshire, like those shown in Figure 3.1, had their babies, they were attended by a midwife. She recorded the birthweight and notified the birth to the county medical officer of health. The local health visitor was informed. She went to the baby's home at intervals throughout infancy and recorded its illnesses and development on a card. When the baby was 1 year old the visits ceased; the card was handed in to the county health visitor and the details carefully transferred into ledgers. Figure 3.2 shows details from one of the ledgers, with birthweight, weight at 1 year,



Weight at Birth.	Weight 1st Year	Food.	No. of Visits.	Condition, and Remarks of Health Visitor. W	R	D	T
8¼ lbs	24½ lbs	B.	11	4	-	-	4
Healthy & well developed.				Buckland School. Card to S.C			
7 lbs	18¼ lbs	B	12	h.	4.	4.	8
Moved to Bury Green & Standon. Had measles, pneumonia & o							
8	20	Bot.	11	4.	4.	?	4
V.E. shown in at neck opened 2nd fontanelle still open 23 yrs. Abdomen very large & pen							
8½	22	B.B.	9	4	4	4	10
Healthy & normal.				Buckland School. Card			

whether the baby was weaned at 1 year, number of teeth, and other details. From 1923 onwards the health visitors continued their visits until the child was 5 years old. Records of these visits were also entered in the ledgers. The ledgers were maintained until 1945, many years after Miss Burnside had retired. In 1986, the MRC found that those which covered the eastern part of the county had been sent to the County Record Office. Over the next 2 years those for other areas of the county came to light, preserved in local hospitals.

Surprisingly little is known about Margaret Burnside (1877–1953), whose foresight and dedication have given us the Hertfordshire records. The only known photograph of her (Figure 3.3) was taken when she was 17 years old. She was born in 1877, one of six children. Her father was rector of Hertingfordbury, a village near Hertford. After training as a nurse at St George's Hospital, London, she became Lady Inspector of Midwives for Hertfordshire in 1905. We know that she worked energetically; 'The cyclometer of my bicycle registered 2,921 miles for the year [1907]', she reported. In 1910 she was made a Queen's Nurse and the county nursing association recorded its 'high appreciation' of her 'unremitting labours'. The following year she was appointed as County Health Visitor, following the Notification of Births Act in 1907 which required such an appointment. In 1913 she persuaded the County Council to buy her a car. It was 9.5 horsepower and she called it 'little hero'.

She is remembered as a reserved but formidable woman. The Clerk to the County Council would make himself immediately available if he knew Miss Burnside was in the building and wished to see him. In 1919 she moved to London, to the newly formed Ministry of Health. Systematic observations of the growth and health of each baby born in Hertfordshire continued for another 25 years.

LOW BIRTHWEIGHT AND INFANT WEIGHT AND CARDIOVASCULAR DISEASE

The Hertfordshire records made it possible, for the first time, to relate people's early growth, feeding, and illness to their health in later life. The National Health Service Central Register at Southport was used to trace 16 000 men and women born in the county from 1911 to 1930. Tracing required both the forename and surname, and where forenames of the Hertfordshire babies were not recorded they were found through the national index of births or local baptismal registers. In Britain women are more difficult to trace than men because of their change of name at marriage, and it proved impossible to trace most women born before 1923, many of whom married before the Central Register became fully operational. The study was therefore based on 10 141 men born during 1911–30 and a younger cohort of 5585 women born during 1923–30.[2,3] Of these people 2990 men and 875 of the women had died at ages from 20 to 74 years.

Hertfordshire is in the south of England and the death rates from coronary heart disease were below the national average, the standardised mortality ratios being 79 in men and 64 in women. In men 35% of all deaths were due to coronary heart disease and Table 3.1 shows that standardised mortality ratios for both coronary heart disease and stroke fell with increasing birthweight. There were stronger and highly statistically significant trends with weight at 1 year. These did not depend on the way the infants were fed. The trends in cardiovascular disease with birthweight and weight at 1 year were reflected in falls in all-causes mortality (Table 3.1). They were specific: there were no corresponding trends in deaths from non-cardiovascular causes.

Only 14% of the deaths among women were due to coronary heart disease and, because of the smaller numbers of women, there were too few deaths from stroke for useful analysis. Table 3.2 shows that as in men deaths from coronary heart disease fell with increasing birthweight and this was reflected in a similar trend in all-causes mortality. There were however, no trends with weight at 1 year.

Table 3.1 Standardised mortality ratios (SMR) among 10 141 men born in Hertfordshire according to birthweight and weight at 1 year

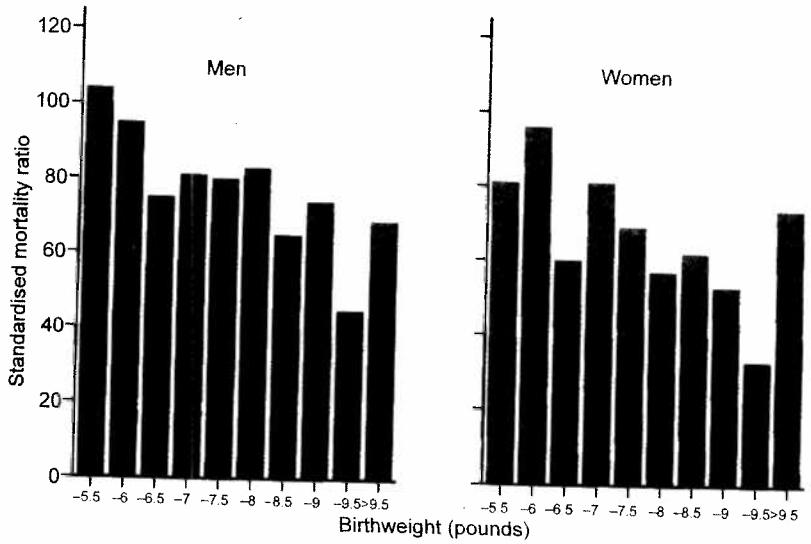
Weight pounds (kg)	Cause of death, SMR		
	Coronary heart disease	Stroke	All causes
At birth			
≤5.5 (2.5)	110 (63)	67 (6)	99 (163)
–6.5 (2.9)	88 (147)	97 (25)	81 (390)
–7.5 (3.4)	82 (311)	85 (50)	82 (895)
–8.5 (3.9)	78 (321)	64 (41)	78 (920)
–9.5 (4.3)	62 (124)	68 (22)	71 (413)
>9.5 (4.3)	70 (67)	52 (8)	76 (209)
1 year old			
≤18 (8.2)	108 (80)	100 (12)	92 (196)
–20 (9.1)	87 (190)	89 (31)	91 (573)
–22 (10.0)	88 (369)	87 (57)	84 (1012)
–24 (10.9)	70 (251)	53 (30)	70 (724)
–26 (11.8)	64 (113)	61 (17)	74 (371)
>26 (11.8)	47 (30)	49 (5)	62 (114)
All	79 (1033)	74 (152)	79 (2990)

Table 3.2 Standardised mortality ratios among 5585 women born in Hertfordshire according to birthweight and weight at 1 year

Weight pounds (kg)	Cause of death, SMR	
	Coronary heart disease	All causes
At birthweight		
≤5.5 (2.5)	72 (7)	102 (58)
–6.5 (2.9)	84 (30)	81 (167)
–7.5 (3.4)	62 (40)	83 (311)
–8.5 (3.9)	61 (32)	76 (228)
–9.5 (4.3)	47 (9)	80 (87)
>9.5 (4.3)	36 (2)	75 (24)
1 year old		
≤18 (8.2)	91 (19)	101 (120)
–20 (9.1)	54 (27)	79 (227)
–22 (10.0)	69 (44)	73 (270)
–24 (10.9)	54 (20)	82 (175)
–26 (11.8)	64 (8)	91 (64)
>26 (11.8)	57 (2)	96 (19)
All	64 (120)	81 (875)

Figures in parentheses are numbers of deaths.

Figures 3.4 and 3.5 illustrate these trends. They show premature deaths, that is deaths below the age of 65 years, from coronary heart disease in men and women. Standardised mortality ratios fell between people who had low birthweight and those who weighed 9.5 pounds (4.3 kg). Above this birthweight there was a small increase in both men and women. The trends with weight at



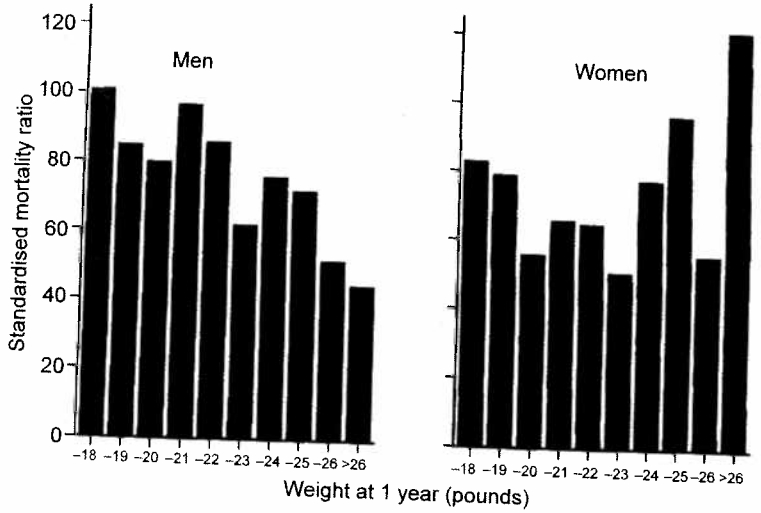


Fig. 3.5 Standardised mortality ratios for coronary heart disease below the age of 65 according to weight at 1 year.

1 year were different in the two sexes, the large fall in disease rates between men with low and high weights at 1 year contrasting with the absence of any trend in women. Among men the highest rates of coronary heart disease were in those who had below average birthweight and remained small in infancy – that is, their growth failed to catch up. Among women the highest rates were in those who had below average birthweight. Studies of men who still live in Hertfordshire have shown that failure of infant weight gain, with a low weight at 1 year, is followed by persisting short stature. While weight at 1 year is closely correlated to adult height, it is only weakly linked to adult body mass (weight/height^2), which is an index of obesity.

Birthweight and weight at 1 year are related, although not as strongly as is sometimes suggested (the correlation coefficient was 0.36 in Hertfordshire). Their combined effect on death rates from coronary heart disease in men is shown in Figure 3.6, which was derived using Cox's proportional hazards method.[4] The lines join points that have an equal risk of coronary heart disease, and the values are the risks relative to the value of 100 for those with average birthweight and weight at 1 year of age. Clearly the combination of poor prenatal and postnatal growth leads to the highest death rates from coronary heart disease. Few men with low birthweight attained the heavier weights at 1 year of age, and hence the lowest risks of coronary heart disease.

A study of deaths from coronary heart disease and stroke among 3108 men born in the Jessop Hospital, Sheffield, England, which is described on page 50, confirmed that mortality from coronary heart disease and stroke fell between those with the lowest and highest birthweights.[5] Confirmation that low birthweight is associated with coronary heart disease and stroke in women has come from the large study of 121 000 American female nurses who were recruited into a postal questionnaire study of health and lifestyle in 1976.[6,7] In 1992 they were asked to ascertain their birthweights and 70 000 were able to do so. Figure

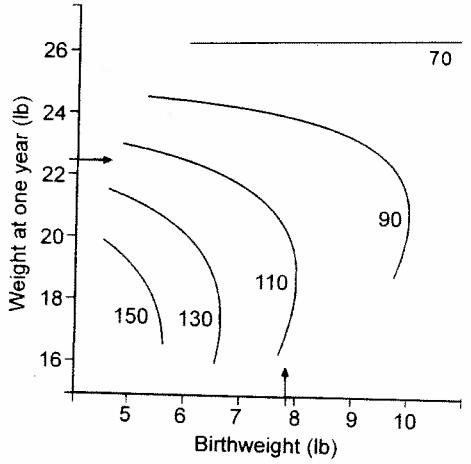
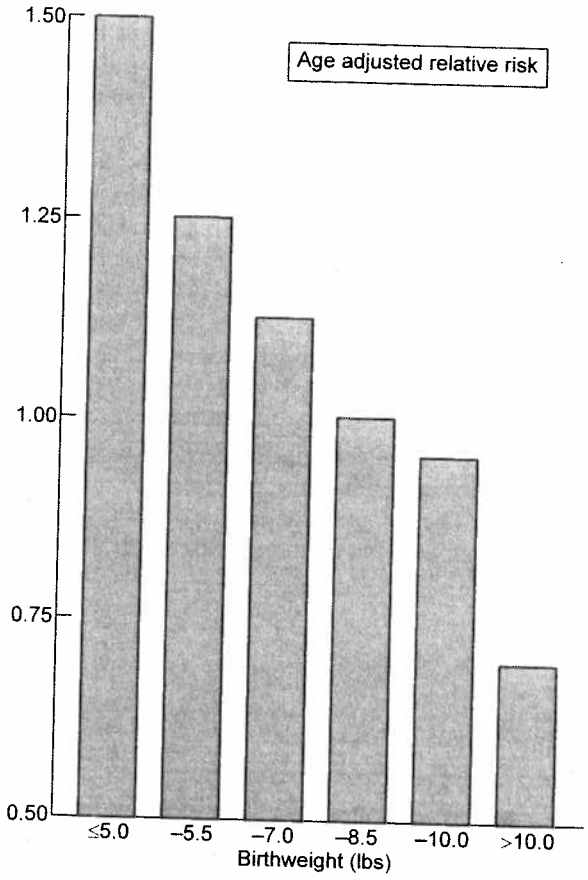


Fig. 3.6 Relative risks for coronary heart disease in men according to birthweight and weight at 1 year. Lines join points with equal risk. Arrows indicate mean weights.



fell across the range of birthweight. Hypertension, non-insulin-dependent diabetes and raised serum cholesterol concentrations, which were self-reported, showed similar trends but the trends in cardiovascular disease were largely independent of these. A study among 1200 men in Caerphilly, Wales, also showed that those who had had high birthweight had lower rates of fatal and non-fatal coronary heart disease.[8] Again this association was independent of conventional coronary risk factors. Among 1300 men in Uppsala, Sweden, low birthweight was related to death from both coronary heart disease and stroke.[9]

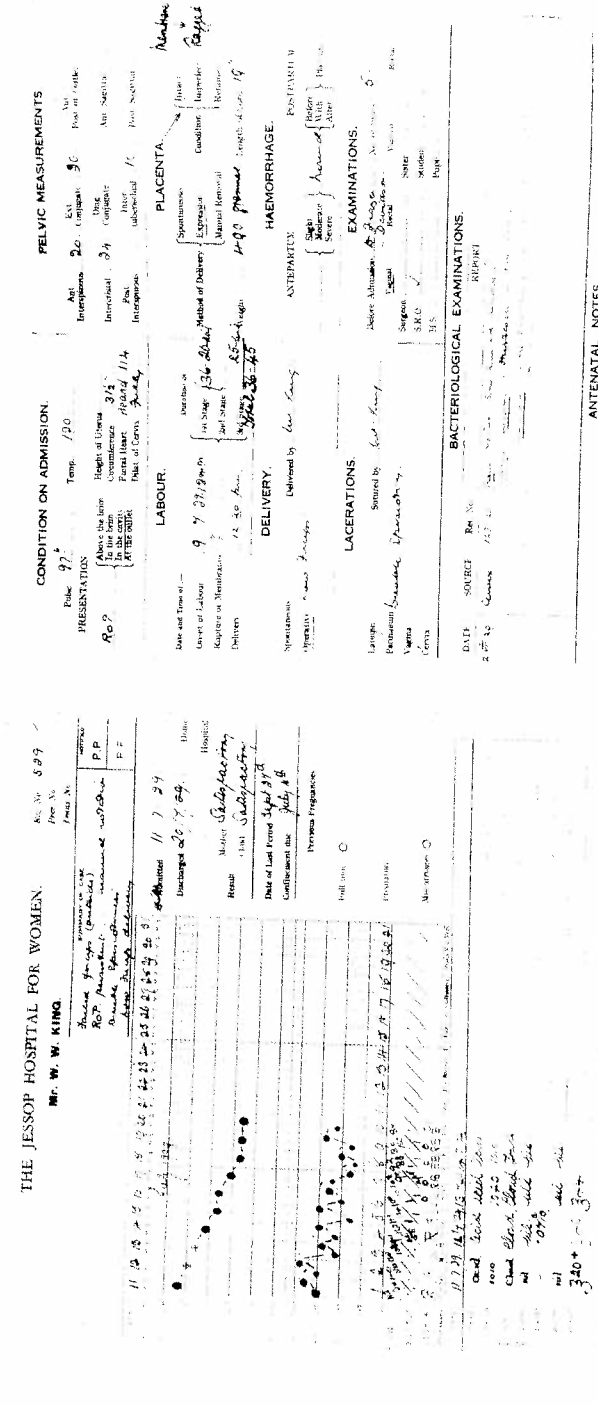
BODY PROPORTIONS AT BIRTH AND CARDIOVASCULAR DISEASE

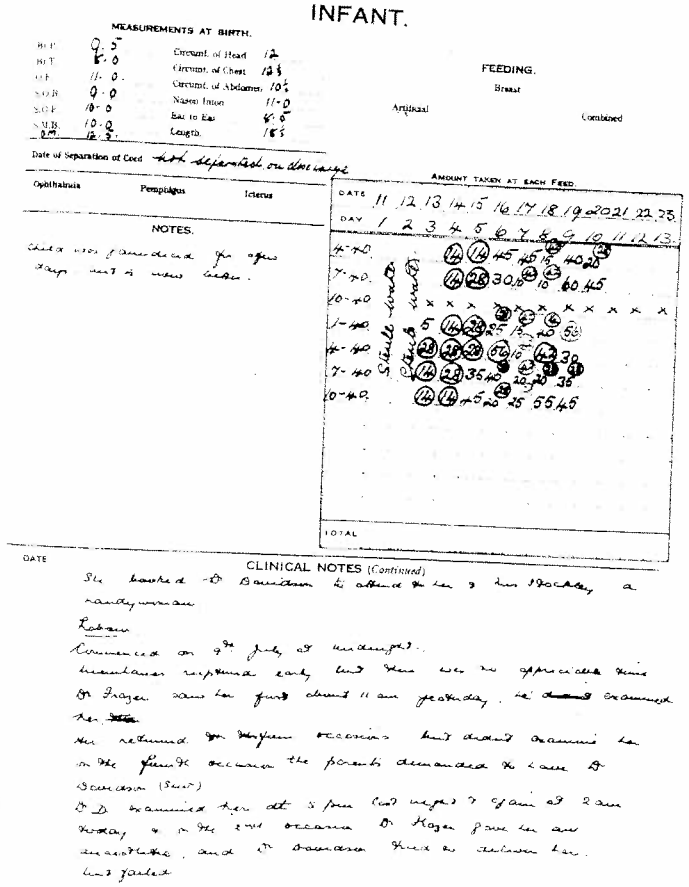
The Hertfordshire records and the American nurses and Caerphilly studies did not include measurements of body size at birth other than weight. The weight of a newborn baby without a measure of its length is as crude a summary of its physique as is the weight of a child or adult without a measure of height.[10] The addition of birth length allows the long thin baby to be distinguished from the short fat baby. With the addition of head circumference the baby whose body is small or stunted in relation to its head, as a result of 'sparing' of brain growth, can also be distinguished. Thinness, stunting and a small trunk reflect differing fetal adaptations to undernutrition and other influences and they have different long term consequences.

The first study linking body proportions at birth and later death rates from coronary heart disease, was carried out on a group of men and women born in the Jessop Hospital, Sheffield.[11] Since 1907 this hospital has kept unusually detailed records on each newborn baby. The baby was not only weighed but its length from crown to heel, head circumference, biparietal and other head diameters, and placental weight were recorded. Chest and abdominal circumference were later added to this list of measurements. Figure 3.8 shows one of the records from the hospital. Not only was the baby measured in detail, but external measurements of the mother's pelvis were recorded, including the conjugate diameter, that is, the distance between the symphysis pubis and the fifth lumbar vertebra, and the intercristal diameter, that is, the distance between the iliac crests. The reason why such astonishingly detailed observations were made on each baby in this and other hospitals in Europe is not known.

Stunting and thinness at birth

In Sheffield death rates for coronary heart disease were higher in men who were stunted or thin at birth.[5] The mortality ratio for coronary heart disease in men who were 18.5 inches (47 cm) or less in length was 138 compared with 98 in the remainder.[5] A study of men and women in South India (p. 58) showed a similar association with short body length at birth. In Sheffield thinness at birth, as measured by a low ponderal index (birthweight/length^3), was also associated with coronary heart disease. Table 3.3 shows that among 3300 men born in




INFANT.

MEASUREMENTS AT BIRTH.

FEEDING.

Breast

Artificial

Combined

AMOUNT TAKEN AT EACH FEED.

NOTES.

CLINICAL NOTES (Continued)

Fig. 3.8 Detailed birth records kept at the Jessop Hospital, Sheffield, from 1907 onwards.

only weakly related to low birthweight,[12] but were strongly associated with thinness at birth, measured by a low ponderal index, especially in men born at term. Men who were thin at birth had death rates that were twice those of men who had a high ponderal index at birth.

A thesis of this book, which is developed in later chapters, is that babies who are thin at birth were undernourished.[13, 14] Among the consequences of this are persisting elevation of blood pressure (Chapter 4), disturbance of glucose/insulin metabolism (Chapter 6) and death from coronary heart disease. Figure 3.9 shows such a baby. Babies who are stunted at birth, and have a reduced abdominal circumference, were also undernourished.[14] Among the consequences of stunting are persisting elevation of blood pressure (Chapter 4) and disturbances of liver function with altered cholesterol metabolism and blood clotting (Chapter 5). Figure 3.10 shows such a baby. It is disproportionately short in relation to the size of its head. It also has a low birthweight in relation to its head size. These body proportions suggest that there was interruption of growth of the trunk in late gestation with relative 'sparing' of brain

Table 3.3 Standardised mortality ratios for coronary heart disease in 3302 Finnish men

	SMR	*p* value for trend
Birthweight, kg (lb)		
≤2.5 (5.5)	84 (11)	
–3.0 (6.6)	83 (44)	
–3.5 (7.7)	99 (124)	
–4.0 (8.8)	76 (80)	
>4.0 (8.8)	66 (27)	
All	85 (286)	0.09
Term babies only: ponderal index at birth, kg/m³		
≤25	116 (59)	
–27	105 (88)	
–29	72 (64)	
>29	56 (33)	
All	86 (244)	<0.0001

Figures in parentheses are numbers of deaths

to head circumference are associated with undernutrition comes from the Dutch study of people exposed to war-time famine when they were in utero.[15] Those exposed in mid or late gestation tended to be either thin at birth or had low birthweight in relation to head circumference (Table 8.1)

The pattern of infant growth which follows reduced intrauterine growth differs according to the body proportions at birth.[16–19] Thin babies tend to catch up in weight during infancy whereas short and proportionately small babies do

Fig. 3.10 The newborn baby on the right has a similar head circumference to the other baby but is shorter and has a smaller abdominal circumference.

not. Among men in Hertfordshire the stronger relationship of coronary heart disease to weight at 1 year than to birthweight is thought to reflect an association with shortness at birth and consequent failure of infant growth. Catch-up growth of growth-retarded babies seems to depend on two phenomena: first, the rate of catch-up during the first months of postnatal life, which is higher in industralised than developing countries, and second, the occurrence of growth-faltering between 6 and 18 months of age, which is widespread in developing countries.[20]

Head circumference at birth

Head circumference at birth is strongly related to birthweight, and in Sheffield coronary heart disease showed similar trends with head circumference as with birthweight (Table 3.4). Standardised mortality ratios fell progressively between the men with the smallest and largest head circumferences. In Helsinki the trends were similar, though weaker. The trends in stroke, which have only been reported in Sheffield were different. There were no trends with head circumference (Table 3.4). When, however, head circumference and birthweight were analysed together, stroke was found to occur in men who had a low ratio of birthweight to head circumference.

Length of gestation

The data from Sheffield, Uppsala and Helsinki include the length of gestation in weeks, estimated from the date of the mother's last menstrual period.[5,9,12]

Table 3.4 Standardised mortality ratios (SMR) among men born in Sheffield, according to head circumference at birth

Head circumference inches (cm)	Cause of death, SMR		
	Coronary heart disease	Stroke	Non-cardiovascular causes
≤13 (33.0)	116 (98)	104 (15)	84 (107)
–14 (35.6)	104 (126)	89 (21)	102 (190)
14 (35.6)	90 (119)	143 (34)	106 (212)
>14 (35.6)	88 (83)	90 (16)	107 (152)
All	99 (426)	108 (86)	101 (661)

Figures in parenthesis are numbers of deaths

size at birth reflect slow intrauterine growth or premature birth can therefore be resolved. The associations of coronary heart disease with low birthweight, thinness and stunting were independent of the length of gestation and strongest in term babies. This shows that the disease is associated with low rates of fetal growth. In Sheffield, however, the disease showed a U-shaped variation with length of gestation, the highest SMRs being in men born at 37 weeks of gestation or less and in men born after 41 weeks. In Helsinki there was similarly a raised death rate in men born after term. Stroke seems unrelated to the length of gestation, though the smaller numbers of deaths makes this conclusion less secure.[5]

Placental size

In Finland raised death rates for coronary heart disease were associated with low placental weight, which in turn was strongly associated with thinness at birth. In Sheffield, however, coronary heart disease did not vary with placental weight but showed a U-shaped relation with the ratio of placental weight to birthweight, the highest mortality ratios being at either end of the distribution. The pattern of body proportions at birth which predicts death from coronary heart disease may be therefore summarised as a small head circumference, stunting or thinness, which reflect retarded fetal growth, and either low placental weight or an altered ratio of placental weight to birthweight.

The pattern for stroke is different. In Sheffield death rates for stroke were highest in men who had low placental weight at birth, particularly if the placenta was light in relation to the size of the head.[5] The standardised mortality ratio for stroke in men whose placental weight was 1.25 pounds (560 g) or less and whose head circumference was 14 inches (35.6 cm) or more was twice that in men whose placental weight was more than 1.25 pounds (560 g) and head circumference less than 14 inches (35.6 cm). The pattern of body proportions at birth which predicts death from stroke is therefore low birthweight and low placental weight in relation to normal head size at birth. One interpretation is that normal head growth, which occurs relatively early in gestation, has been

CONFOUNDING VARIABLES

These findings suggest that influences linked to early growth have an important effect on the risk of coronary heart disease and stroke. It has been argued, however, that people whose growth was impaired in utero and during infancy may continue to be exposed to an adverse environment in childhood and adult life, and it is this later environment that produces the effects attributed to programming.[21–24] The findings in this chapter, and in later chapters, which describe the links between early growth and cardiovascular risk factors such as blood pressure, provide strong evidence that this argument cannot be sustained.

In three of the studies which have replicated the association between birthweight and coronary heart disease data on lifestyle factors, including smoking, employment, alcohol consumption and exercise were collected. In the nurses health study allowance for these factors had little effect on the association between birthweight and coronary heart disease.[6] Similar results came from the Caerphilly and Uppsala studies.[8,9] Lifestyle factors also did not explain the association between low weight at 1 year and the prevalence of coronary heart disease in a sample of Hertfordshire men who were examined clinically.[25] The association was found within each social class and in both smokers and non-smokers. In the British Regional Heart Study of middle-aged men, low socioeconomic status during childhood increased the risk of coronary heart disease independently of socioeconomic status during adult life, though such data cannot distinguish prenatal and postnatal influences.[26] Finally in a study in South India, described on p. 58, associations between short body length at birth and prevalent coronary heart disease were independent of socioeconomic status and smoking habits.[27]

In studies of blood pressure (see Ch. 4), plasma fibrinogen and serum cholesterol concentrations (see Ch. 5), and non-insulin-dependent diabetes (see Ch. 6) the associations with size at birth are again independent of social class as an adult, cigarette smoking and alcohol consumption. Adult lifestyle, however, adds to the effects of early life. For example, the prevalence of impaired glucose tolerance is highest in people who had low birthweight but become obese as adults (Table 6.3).

The associations between small size at birth and cardiovascular disease are specific, strong and graded. They are specific in that non-cardiovascular disease is mostly unrelated to small size at birth, though chronic airways obstruction is one important exception to this. The associations are strong despite body weight being only a proxy for the changes in the body's structure, physiology, and metabolism which have been programmed in utero. Yet the relative risks associated with low birthweight are large: for example, the risk of the insulin resistance syndrome (non-insulin-dependent diabetes, hypertension, and hyperlipidaemia) is 10 times higher among men whose birthweight was 6.5 lb or less (≤ 2.9 kg) than among men whose birthweight was more than 9.5 lb (> 4.3 kg).

It is reasonable to conclude that reduced growth in utero and cardiovascular disease are causally linked. This conclusion is greatly strengthened by recent animal and clinical studies which are beginning to reveal the cellular and

EFFECTS OF THE LIFE-COURSE

The associations between low birthweight and cardiovascular disease raise two questions about the possible effects of the biological and social environment in childhood. First, does birthweight serve as a 'highly sensitive marker of family socioeconomic circumstances' and is it therefore a predictor of influences acting in early childhood rather than in utero which determine later susceptibility to coronary heart disease?[24–28] Second, do growth, nutrition and development in childhood modify risks established in utero?

The answer to the first question seems reasonably clear. Birthweight is not a sensitive marker of the conditions in which the mother is living and into which the baby will be born. Chapter 8 describes how the nutrition of the fetus reflects the nutrition of the mother throughout her life, including her own fetal life, and not simply what happens to her during pregnancy. Even famine during pregnancy has little effect on birthweight. Although in industrial Britain in the past poorer families had smaller babies, this did not apply in rural counties like Hertfordshire. Chapter 10 describes how the low neonatal mortality of babies born in London at the beginning of this century was consistent with the good nutritional state of the mothers, many of whom grew up in the home counties, but quite at variance with the wretched conditions under which many of them lived during pregnancy. Furthermore studies of today's children show that associations between size at birth and blood pressure and glucose tolerance (Chs 4 and 6) are not determined by the child's socio-economic circumstances after birth. Animal experiments (Ch. 2) strongly support the conclusion that undernutrition before birth has persisting effects irrespective of the living conditions of the animals after birth.

Given that events in utero have persisting effects on the structure and function of the body, are these effects modified by experiences in childhood? The evidence from animals is that they can be, though not in ways that are readily predictable. Rats undernourished in utero but fed normally after birth have much shorter lives than those undernourished throughout life (p. 21). Findings in the Helsinki study, described in Chapter 11, are similar in that men who were thin at birth but became overweight in childhood were at greatly increased risk of coronary heart disease. It is clear from the Hertfordshire study that failure of growth in infancy strongly predicts later coronary heart disease in men (Fig. 3.5). This does not result from the way the men were fed during infancy nor from their exposure to infections.[3] Rather it is thought to reflect prenatal 'settings' of hormones, including growth hormone, which control fetal growth.[14] A similar issue arises in interpreting the association between reduced leg length in childhood and later coronary heart disease, a finding based on follow-up of children who took part in the Carnegie survey of family diet and health in Britain before the Second World War.[29] Does this reflect the consequences of poor living conditions in childhood or is it the result of prenatal settings of growth hormone and the other hormones that regulate the childhood phase of growth?

Preliminary studies of adults, in which information on childhood socioeconomic conditions was obtained retrospectively, have given varying results. Among 2636 men in Finland childhood socioeconomic conditions were not

cardiovascular disease, their relative risk being 1.13 compared with women from 'white collar' backgrounds.[31] At present we do not know whether and how a child's health, housing, family life and schooling influence its risk of later cardiovascular disease but studies now in progress in several countries should help to resolve this.

Meanwhile it is important that the debate remains open. It is ominous that Susser, in the preface to a new book on life course epidemiology writes:

> But it [intrauterine programming] cannot by itself account for much of many adult disorders and, even less, for cardiovascular disease. Too much can already be attributed to other factors that accumulate over the life course . . .[32]

Is the old orthodoxy being replaced by a new one, even before the necessary research has been carried out?

INTERACTION BETWEEN FETAL GROWTH AND OBESITY IN ADULT LIFE?

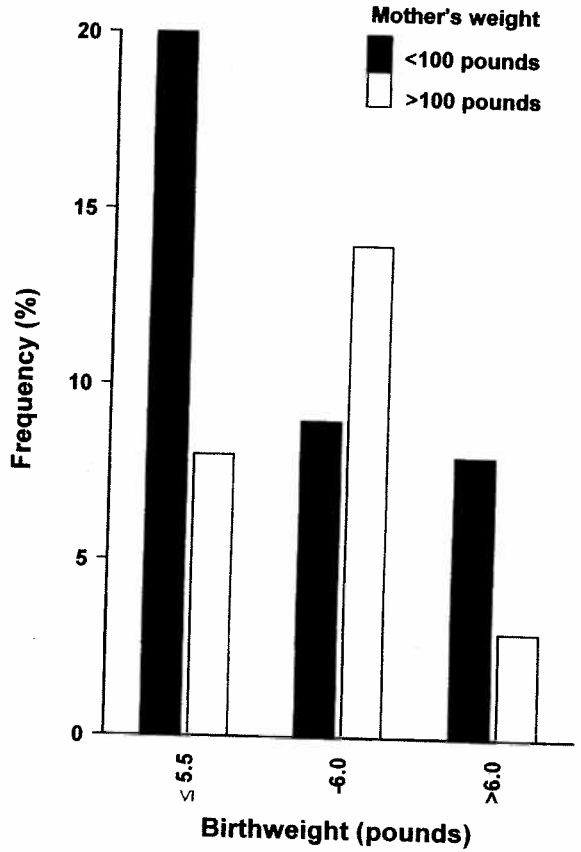
In the Caerphilly study the increased risk of coronary heart disease was restricted to men who had a high body mass index.[8] The authors suggested that disease risk was therefore defined by the combination of poor growth in utero and an affluent environment in later life. An obvious objection to this is that birthweight, unaccompanied by other measures of body size at birth, or placental size, or length of gestation or infant growth is an inadequate index of fetal growth from which to draw such a conclusion. Furthermore the findings in Wales do not match those from other studies, in which small size at birth was related to coronary heart disease at all levels of body mass index.[25,27] Chapter 6 demonstrates how the effects of low birthweight on adult onset diabetes are compounded by adult obesity; but also points out that the extent to which adult obesity is entrained by events in early life is unknown.

CORONARY HEART DISEASE AND FETAL GROWTH IN INDIA

It is a common objection to the fetal origins hypothesis that intrauterine growth retardation is common in many developing countries whereas coronary heart disease is rare.[21] An answer to this may lie in the different nature of fetal growth retardation in developing countries. This is discussed further in Chapter 11. Meanwhile studies in India have addressed the question of whether the hypothesis can contribute to an understanding of the rising epidemic of coronary heart disease in developing countries. Death rates from the disease are rising steeply in India and are expected to overtake those due to infectious disease by the year 2010.[33,34] Already, cardiovascular deaths account for half the deaths occurring under 70 years. These high rates of coronary heart disease in India are not explained by known risk factors including obesity, raised blood pressure, smoking and raised cholesterol. Coronary heart disease in Indian populations is, however, associated with a particular metabolic profile

or non-insulin-dependent diabetes, insulin resistance, raised serum triglyceride concentrations, low concentrations of high density lipoprotein cholesterol, abnormal plasma clotting factors and central obesity.[35] Coronary heart disease in India has other particular characteristics. It is more common in urban areas and among lower socioeconomic groups,[36,37] 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.[38] These observations raise the possibility that Indian people have a genetically determined susceptibility to coronary heart disease which is enhanced on exposure to a sedentary lifestyle, high energy intake and other aspects of westernisation.[39-41] The genes responsible for this have not been identified, but it is hypothesised 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.[42] This conflicts, however, with experience elsewhere in the world, where epidemics of coronary heart disease have been followed by declining rates[43] which, though perhaps assisted by health education, are largely unexplained.



The possibility that the associations between poor fetal growth and adult disease may have important implications for the epidemic of both coronary heart disease and non-insulin-dependent diabetes in India has not gone unremarked.[39] Fetal growth is known to be retarded throughout the country. The average birthweight is less than 6 pounds (2.7 kg). Until recently, however there has been no firm evidence. A recent study in South India has shown however, that, as in other countries, low birthweight and coronary heart disease are linked.[27] A total of 517 men and women who were born during 1934–53 in the Mary Calvert Holdsworth Hospital, Mysore, were traced. The occurrence of coronary heart disease and its biological risk factors was related 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 coronary heart disease fell from 15% in those who weighed 5.5 pounds (2.5 kg) or less at birth to 4% in those who weighed 7.0 pounds (3.2 kg) or more. Rates of the disease were also higher in men and women who were stunted at birth, and whose mothers had low weight in pregnancy. Figure 3.11 shows that the highest rates were in people who had low birthweight and whose mothers were thin. The average birthweight and maternal weight were both low by European standards though consistent with values from other parts of India (mean birthweight 6.2 pounds (2.8 kg), and mean maternal weight in pregnancy 103 pounds (47 kg)). Clearly these early findings in India need to be replicated and extended. Meanwhile the association between low maternal weight and coronary heart disease is further evidence that the fetal growth failure which leads to coronary heart disease is a consequence of fetal undernutrition.

CONSTRAINT OF GROWTH IN UTERO

The findings described in this chapter show that the relationship between fetal growth and cardiovascular disease is continuous. Rates of the disease fall across the range of birthweights and ponderal index and, in men, across the range of weight at 1 year. If the criteria for successful fetal growth are to include adult health and longevity, these findings reinforce the view that babies with significant intrauterine growth retardation need not necessarily be 'light for gestational age' as defined clinically.[44] Intrauterine growth retardation seems to be widespread, affecting many babies whose birthweights are within the normal range, not just those few who are recognised clinically by their unusually small size and high risk of perinatal complications and death.

The associations between cardiovascular disease and fetal growth are not adequately summarised by associations with birthweight, which is a crude summary of fetal experience. The associations with small head circumference, shortness and thinness described here suggests that coronary heart disease originates in particular patterns of altered fetal growth resulting from undernutrition at particular stages of gestation.

Summary

In men and women small size at birth is associated with raised death rates from cardiovascular disease in later life. These associations do not depend on length of gestation and therefore reflect low rates of fetal growth. Coronary heart disease is not only associated with low birthweight but with thinness and stunting at birth, and with a small head circumference, which result from reduced fetal growth at particular stages of gestation. Stroke is associated with low birthweight and placental weight in relation to head size and may originate in restriction of placental growth. In India, where there is a rising epidemic of coronary heart disease, the disease is similarly associated with low birthweight and short body length at birth. Cardiovascular disease in men, but not women, is strongly associated with failure of weight gain in infancy, which may be a consequence of reduced linear growth in late gestation. The associations between body size in early life and later cardiovascular disease cannot be explained by confounding variables. They are strong and statistically robust and support the conclusion that cardiovascular disease originates in utero.

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4

Blood pressure

The association of reduced growth rates in fetal life and infancy with increased death rates from cardiovascular disease poses the question of what processes link the two. Raised blood pressure increases the risk of coronary heart disease and stroke, and is one obvious possible link because there is already good evidence that it originates in childhood.[1–3] The persistence of rank order of blood pressure among subjects examined at intervals – so-called 'tracking' – has been repeatedly observed in longitudinal studies of children as well as of adults.[4–8]

FETAL GROWTH AND ADULT BLOOD PRESSURE

The first suggestion that adult blood pressure may be related to fetal growth came from the study by Wadsworth and colleagues[9] of a national sample of people who were born in Britain during 1946, and followed up and examined at 36 years of age. Those with lower birthweights had higher systolic blood pressure. This observation has been confirmed in a re-analysis of the data.[10] Another early indication that low birthweight is associated with raised blood pressure came from a study of recruits in the Swedish army.[11] These observations have now been confirmed in a series of studies of adults in Europe and the USA. Figure 4.1 shows mean systolic blood pressure in a group of men and women in Hertfordshire. The pressures fall progressively between those who weighed 5.5 lb or less (≤2.5 kg) at birth and those who weighed more than 8.5 lb (>3.9 kg).[12] Diastolic pressure shows similar trends. As would be expected blood pressure was higher in people who were currently obese, as measured by the body mass index (weight/height^2). However, men and women who had lower birthweight had higher systolic pressure at any level of current body mass.

Figure 4.2 shows the results of a systematic review of published papers describing the association between birthweight and blood pressure[13] – a review based on 34 studies of more than 66 000 people of all ages. Each point on the figure with its confidence interval represents a study population and the popu-

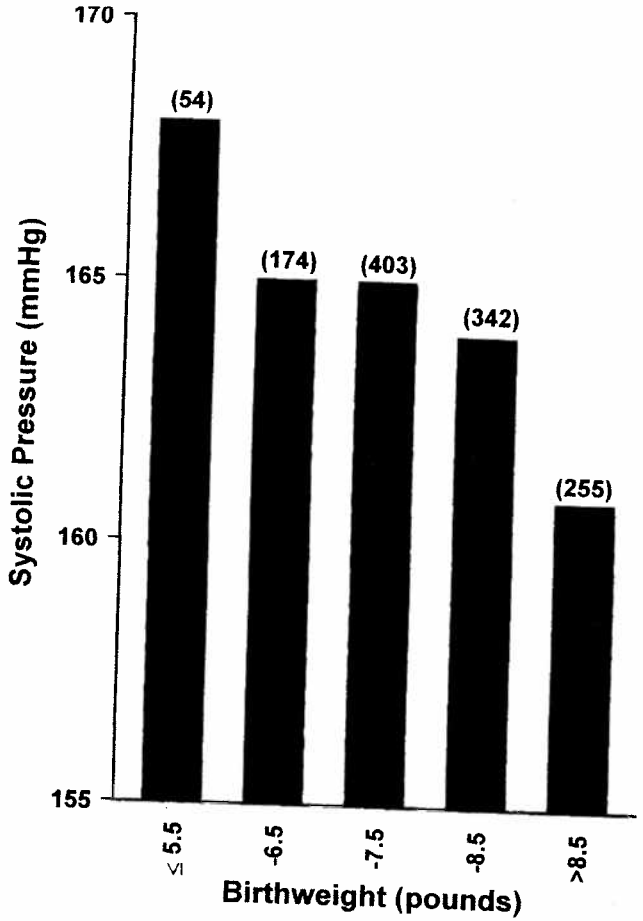

Fig. 4.1 Mean systolic pressure in 1228 men and women aged 60–71 years according to birthweight. (Figures in brackets are numbers of people).

increase in birthweight. In almost all the studies an increase in birthweight was associated with a fall in blood pressure; and there was no exception to this in the studies of adults which now total nearly 8000 men and women. These associations were not confounded by socioeconomic conditions at the time of birth or in adult life.[14] The difference in systolic pressure associated with a 1-kg difference in birthweight was around 3.5 mmHg. In clinical practice this would be a small difference but these are large differences between the mean values of populations. Available data suggest that lowering the mean systolic pressure in a population by 10 mmHg would correspond to a 30% reduction in total attributable mortality.[15]

The adult populations included in Figure 4.2 are European,[12, 16–19] but findings from 160 000 women taking part in the Nurses' Health Study in the USA were recently reported.[20] Blood pressure levels, which were self-reported, were lower than those in the European studies and the fall associated with an increase in birthweight was also smaller. Nevertheless low birthweight was associated with hypertension, the odds ratio in women with birthweights

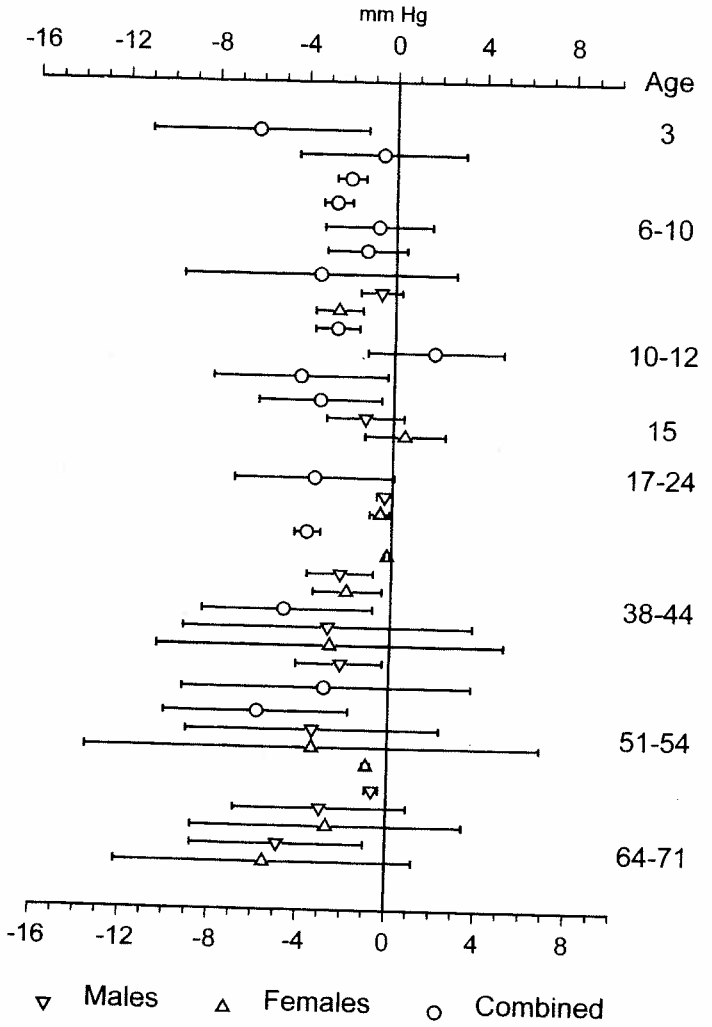

Fig. 4.2 Difference in systolic pressure (mmHg) per kg increase in birthweight (adjusted for weight in children and body mass index in adults).

average. Similarly to other studies, this association was little changed by allowing for a range of variables, including parental history of hypertension.

Two of the early studies in Britain were carried out in Sheffield and Preston. The study in Sheffield was based on the detailed records kept at the Jessop Hospital for Women (Fig. 3.8). Similarly detailed records were kept at Sharoe Green Hospital, in Preston.[21] In both studies the association between low birthweight and raised blood pressure was shown to depend on babies who were small for dates, after reduced fetal growth, rather than on babies who were born preterm. This observation was confirmed by Leon and colleagues in a study of 50-year-old men born in Uppsala, Sweden.[19] Although in these studies alcohol consumption and higher body mass were also associated with raised blood pressure, the associations between birthweight and blood

highest pressures are found in people who were small at birth but become overweight as adults.[22]

As an alternative to a direct intrauterine influence on blood pressure, Ounsted and colleagues have postulated that the accelerated growth of healthy babies of low birthweight during the first 6 months after birth might, of itself, accelerate the rise in blood pressure, and the resultant above average values might persist.[23] Infant growth was recorded in the Hertfordshire data. Weight gain in infancy was not related to later blood pressure after making allowances for birthweight and current body size.[12] This suggests that high blood pressure is initiated pre- rather than postnatally. Table 4.1 shows findings from the Swedish study mentioned above.[19] The association between low birthweight and raised systolic and diastolic pressure was stronger in men who are above the median adult height. The authors conclude that low birthweight in tall men reflects a greater intrauterine impairment of growth potential than it does in short men. Again the suggestion is that it is the prenatal growth failure rather than the accelerated postnatal growth which initiates raised blood pressure.

As has already been discussed in Chapter 3, birthweight is a crude measure of fetal growth that does not distinguish stunting and thinness, differences in head size, or variations in the balance of fetal and placental size. In the Sheffield and Preston studies blood pressure in middle life could be related to body proportions at birth, as well as to birthweight. To examine the links between body proportions at birth and later blood pressure babies born preterm are excluded, because body proportions change during gestation. Analyses of the Preston data define two groups of babies who develop raised blood pressures.[24, 25] The first group are thin with a low ponderal index (birthweight/ length^3) and a below average head circumference (see Fig. 3.9). The second have a short crown–heel length in relation to their head circumference, and therefore a high head circumference to length ratio (Fig. 3.10). Short babies tend to be fat and may have above average birthweight.

The Preston analyses revealed a difficulty that occurs when there are both thin and short babies in a study sample. Thin babies tend to have a low head circumference to length ratio, and short babies tend to have a high ponderal index. The trends of raised blood pressure with low ponderal index and a high head circumference to length ratio therefore oppose each other. Table 4.2 shows that in Preston there was no trend in blood pressure with ponderal index. Thin babies, however, had below average placental weight, whereas short babies

Table 4.1 Mean systolic pressure (mmHg) among 50-year-old men in Uppsala, Sweden, according to birthweight and current height

Height (cms*) at age 50	Birthweight, kg (lb)				
	<3.25 (7.2 lb)	–3.75 (8.2 lb)	–4.25 (9.3 lb)	≥4.25 (9.3 lb)	All
≤176	133 (196)	135 (284)	130 (179)	137 (43)	133 (702)
>176	137 (110)	135 (233)	133 (212)	129 (76)	134 (631)

Figures in parentheses are numbers of men.

* 176 cm = 5 ft 9 in

Table 4.2 Mean systolic pressure (mmHg) of men and women aged 46–54, born after 38 completed weeks of gestation, according to ponderal index at birth and placental weight

Placental weight, g (lb)	Ponderal index, kg/m^3					
	≤20.8	–22.9	–25.5	>25.5	All	*p* value for trend
≤568 (1.25)	154 (53)	147 (54)	142 (42)	141 (25)	147 (174)	0.0001
>568 (1.25)	148 (27)	149 (27)	152 (48)	154 (50)	152 (152)	0.02
All	152 (80)	148 (81)	147 (90)	150 (75)	149 (326)	

Figures in parentheses are numbers of subjects.

had above average placental weight. Division of the data by placental weight revealed strong and opposing trends. At placental weights of 1.25 lb or less (≤591 g) a low ponderal index was associated with high adult blood pressure. At placental weights of more than 1.25 lb (>591 g), a high ponderal index was associated with high adult blood pressure.

The mean ponderal index of the babies in Sheffield was higher than that in Preston: fewer of the babies were thin.[18] Table 4.3 shows the strong association between birth length, abdominal circumference, and blood pressure in men and women born at term. Babies who were short and had a small abdominal circumference at birth had the highest blood pressures as adults.

In contrast to the associations between birth size and lipids (Chapter 5), glucose tolerance (Chapter 6) and coronary heart disease (Chapter 3) those between birthweight and blood pressure are generally as strong as those between thinness, stunting and blood pressure. Associations with thinness and stunting have been found in some studies[26] but not in others.[27] In a longitudinal study of young people in Adelaide associations between blood pressure and thinness and stunting were not apparent at age 8 years but emerged at age 20 (Moore, personal communication).

Table 4.3 Mean systolic blood pressure in men and women aged 50 years, born after 38 completed weeks of gestation, according to length and abdominal circumference at birth

Variable	Mean systolic pressure, mmHg*	*p* value for trend
Length, inches (cm)		
<20 (51)	154 (69)	
–20 (51)	153 (86)	
>20 (51)	143 (65)	0.0001
Abdominal circumference, inches (cm)		
<11.5 (29)	160 (45)	
–12.25 (31)	148 (52)	
–13 (33)	150 (74)	
>13 (33)	146 (47)	0.002

FETAL GROWTH AND BLOOD PRESSURE IN CHINA

The pattern of cardiovascular disease in China differs from that in Europe. Rates of stroke are higher, and more of the strokes are haemorrhagic rather than thrombotic.[28] Despite a high prevalence of hypertension and cigarette smoking among men, rates of coronary heart disease are low.[29, 30]

Figure 4.3 shows the Peking Union Medical College Hospital, a government hospital once owned by the Rockefeller Foundation, who purchased it from the London Missionary Society. The hospital kept exceptionally detailed obstetric records. Table 4.4 shows the blood pressures of a group of men and women aged 45 years who were born in the hospital during 1948–51, momentous years in Chinese history. Consistent with other studies systolic and diastolic pressures were higher in men than women and rose with increasing body mass index. They were inversely related to birthweight and ponderal index but were not related to length. It seems that in China it is the thin rather than the stunted baby who has raised blood pressure. Blood pressure was also raised in people who had low placental weight. We know an unusual amount about the placentas of these men and women because, remarkably, there are detailed ink drawings of each placenta in the birth records.

Fig. 4.3 The Peking Union Medical College Hospital.

Table 4.4 Blood pressure in Chinese men and women aged 45 years, according to ponderal index at birth

	Ponderal index at birth, kg/m³					
	≤24	–26	–28	>28	All	*p* value for trend
Systolic pressure*, mmHg	126	125	124	122	124	0.02
Diastolic pressure*, mmHg	76	76	75	73	75	0.001
Number of people	109	199	208	110	626	

FETAL GROWTH AND CHILDHOOD BLOOD PRESSURE

Figure 4.2 shows that the associations between birthweight and blood pressure which are consistently found in adults are also apparent in children before puberty. The children represented in Figure 4.2 come from Britain,[31] France,[32] Italy,[16] Japan,[33] India,[34] and Jamaica.[35] Current body size is the most powerful predictor of blood pressure in childhood, heavier children having higher blood pressure, and the data shown in Figure 4.2 are adjusted for this. Children's weight indicates biological maturity: at any age a heavier, taller child is likely to be more biologically mature than a lighter, shorter child. Although blood pressure variation in childhood is dominated by differences in the rate of development, it is not known whether these differences establish patterns of blood pressure in adult life.

In studies of adolescents the association between low birthweight and raised blood pressure is less consistently found.[13, 16, 36, 37] It was, however, apparent in a recent large study of 150,000 military conscripts in Sweden.[38] This inconsistency may be related to the spurt in growth during adolescence and the accompanying perturbation of tracking of both blood pressure and growth.[39] Studies of neonates have shown that blood pressure is positively related to birthweight during the first 4 days of life.[13, 40] A study in Holland has shown that among small babies there is a relatively large increase in blood pressure during early infancy.[40] This accelerated rise in blood pressure may reset blood pressure onto a higher track. The same study found a different pattern of blood pressure development in babies with high birthweight. Their blood pressure was high at birth and remained high so that at the age of 4 years the association between birthweight and blood pressure was U-shaped. We know little about the processes which underlie this. U-shaped associations with birth size have also been reported with coronary heart disease[41] and non-insulin-dependent diabetes.[42]

PLACENTAL WEIGHT AND BLOOD PRESSURE

Table 4.5 shows the systolic pressure of a group of men and women who were born, at term, in Sharoe Green Hospital in Preston, 50 years ago.[21, 24] The subjects are grouped according to their birthweight and placental weight. Consistent with findings in other studies systolic pressure falls between subjects with low and high birthweight. In addition, however, there is a hitherto unsuspected increase in blood pressure with increasing placental weight. Subjects with a mean systolic pressure of 150 mmHg or more, a level sometimes used to define hypertension in clinical practice, comprise a group who as babies were relatively small in relation to the size of their placentas. There are similar trends with diastolic pressure. The differences in

Table 4.5 Mean systolic blood pressure (mmHg) of men and women aged 50, born after 38 completed weeks of gestation, according to placental weight and birthweight

Birthweight, lb (kg)	Placental weight, lb (g)				
	≤1.0 (454)	–1.25 (568)	–1.5 (681)	>1.5 (681)	All
–6.5 (2.9)	149 (24)	152 (46)	151 (18)	167 (6)	152 (94)
–7.5 (3.4)	139 (16)	148 (63)	146 (35)	159 (23)	148 (137)
>7.5 (3.4)	131 (3)	143 (23)	148 (30)	153 (40)	149 (96)
All	144 (43)	148 (132)	148 (83)	156 (69)	149* (327)

Figures in parentheses are numbers of subjects.

difference in pressure associated with a 1-kg difference in birthweight found in other surveys of adults (see Fig. 4.2). The fall in systolic pressure of 10 mmHg, across the range of birthweight, is however statistically opposed by the rise of 12 mmHg associated with increasing placental weight. These two large and independent trends are concealed when all pressures at a given birthweight are combined as in the right-hand column.

A rise in blood pressure with increasing placental weight was also found in 4-year-old children in Salisbury, UK,[26] and among 8-year-old children in Adelaide, Australia.[43] Table 4.6 shows the findings in Adelaide. In studies of children and adults the association between placental enlargement and raised blood pressure has, however, been inconsistent.[44] Animal studies offer a possible explanation of this. In sheep the placenta enlarges in response to moderate undernutrition in mid-pregnancy.[45,46] This is thought to be an adaptive response to extract more nutrients from the mother. It is not, however, a consistent response but occurs only in ewes that were well nourished before pregnancy. In a study of men and women born in Aberdeen, Scotland, after the Second World War, at a time when food was still rationed, raised blood pressure was associated with small placental size.[17] In 3000 children in the UK blood pressure was inversely related to placental weight among the girls but was positively related to the placental weight to birthweight ratio in boys.[27]

Table 4.6 Mean systolic pressure (mmHg) among children aged 8 years, in Adelaide, Australia, according to birthweight and placental weight

Birthweight kg (lb)	Placental weight, g (lb)			
	≤500 (1.1)	–600 (1.3)	>600 (1.3)	All
≤3.2 (7.0)	101.4 (162)	102.3 (71)	103.0 (23)	102.2
–3.6 (7.9)	100.8 (75)	101.7 (107)	102.4 (63)	101.6
>3.6 (7.9)	99.7 (20)	100.5 (78)	101.3 (175)	100.5
All	100.6	101.5	102.2	

MATERNAL INFLUENCES ON BLOOD PRESSURE

In some studies the blood pressures of the mothers during and after pregnancy have been recorded.[18,26,47] They correlate with the offspring's blood pressure. Correspondingly, in Japan children's blood pressure was higher in mothers who had had pretibial oedema, a marker of raised blood pressure, during pregnancy.[33] However, the associations between body size and proportions at birth and later blood pressure are independent of the mothers' blood pressures. In the Salisbury study the blood pressures of the fathers were also measured and found to be related to those of the children.[26] The relationship was, however, weaker than that with the mothers' systolic pressures. This has been found before and has been ascribed to X-linked genes. Another possibility is that raised blood pressure in a mother reflects her own adverse fetal experience, which independently restricts the delivery of nutrients to the fetus (Chapter 8).

Recent observations show that if the mother's blood pressure is measured throughout a 24-hour period, rather than by isolated readings at antenatal clinics, there is a continuous inverse association between birthweight and maternal blood pressure.[48] It could be argued therefore that the association between low birthweight and raised blood pressure reflects an association, possibly genetic, between a mother's ambulatory blood pressure and the blood pressure of her offspring. The demonstration that undernutrition during gestation programs blood pressure in animals (p. 22) argues against this interpretation; an alternative explanation is that raised blood pressure during pregnancy reflects failure of maternal cardiovascular adaptations to pregnancy, which include peripheral vasodilation, with consequent fetal undernutrition, low birthweight and raised blood pressure in the offspring.

Several lines of evidence support the thesis that it is poor delivery of nutrients and oxygen which programs raised blood pressure in humans. Maternal height and parity, which influence fetal growth, have not been found to be related to the offspring's blood pressure other than in small preterm babies. In Jamaica, children whose mothers had thin triceps skinfolds in early pregnancy and low weight gain during pregnancy[49] had raised blood pressure. There were similar findings in a group of children in Birmingham.[50] In the Gambia low pregnancy weight gain was associated with higher blood pressure in childhood.[51] In Aberdeen, Scotland, the blood pressures of middle-aged men and women were found to be related to their mother's intakes of carbohydrate and protein during pregnancy.[17] In the Dutch study of men and women exposed to famine in utero (p. 100) those exposed in late gestation had raised blood pressure, though this was not statistically significant (Roseboom, unpublished). Among people exposed in utero to the famine in Leningrad the effect of obesity on blood pressure was enhanced.[52] A randomised controlled trial of calcium supplementation in pregnancy found that the children of mothers who received the supplement had lower blood pressures than the placebo group.[53] These findings are discussed further in Chapter 11.

Information on maternal smoking has been collected in studies of children.[26,54] Children's blood pressures were not related to whether their mothers smoked. Lucas & Morley have reported on the blood pressures of 8-year-old

and who were part of a trial of early feeding. Their blood pressures were not related to neonatal nutrient intakes,[55] but they were related to whether the mother smoked. Among babies who were born at or after 33 weeks of gestation those whose mothers smoked had raised blood pressure.[56] These findings may indicate that small, preterm babies are especially vulnerable to deleterious effects of maternal smoking. It is, however, difficult to generalise from these babies to the population as a whole. It is also difficult to interpret the lack of an association between their neonatal feeding and blood pressures. The programming effects of nutrition in the neonatal period may be quite different from the effects on babies still in utero. Findings described in this book suggest that the placenta plays a major role in programming, and brain-sparing cardiovascular adaptations that occur in utero are no longer possible after birth when the foramen ovale has closed.

AMPLIFICATION

Comparison of the results for adults and children in Figure 4.2 shows that the differences in blood pressure associated with birthweight in children are small compared with those between adults. Whereas in childhood a 1-kg increase in birthweight is equivalent to a fall in systolic pressure of 1–2 mmHg, in older adults the difference is around 5 mmHg. The regression coefficients in adults remain larger than those in children, even after dividing them by the standard deviation to take account of the increase in standard deviation with age.

An interpretation of these findings is that differences in blood pressure are established in utero but progressively amplified throughout life. Direct evidence of amplification comes from studies by Whincup and colleagues, who showed that blood pressure rose more rapidly with age in children who had low birthweight.[44] The existence of initiating and amplification mechanisms in the aetiology of essential hypertension was first postulated by Folkow.[57] In patients with secondary hypertension from phaeochromocytoma, Conn's syndrome, or renal artery stenosis, hypertension may persist even after the initiating cause, that is the tumour or stenosis, has been removed.[39, 58]

MECHANISMS

There are a number of possible mechanisms by which restricted intrauterine growth could either initiate or amplify raised blood pressure.

Childhood growth

Studies in the USA, the UK and Holland have shown that blood pressure in childhood predicts the likelihood of developing hypertension in adult life. These predictions are strongest after adolescence. In children the rise of blood pressure with age is closely related to growth and is accelerated by the adolescent growth spurt. These observations have led Lever & Harrap to propose that essential hypertension is a disorder of growth.[39] The hypothesis that hyperten-

association with low birthweight by postulating that postnatal catch-up growth plays an important role in amplifying changes established in utero.

Renin–angiotensin system

There is evidence that the fetal renin–angiotensin system is activated in intrauterine growth retardation.[59] However, in a follow-up study of men and women born in Sheffield, those who had been small at birth had lower plasma concentrations of inactive and active renin.[60] Causes of raised blood pressure that are not mediated by increased rates of renin release tend to result in low concentrations of renin and therefore, at first sight, these findings suggest that the association between impaired fetal growth and raised blood pressure must involve mechanisms other than the renin–angiotensin system. However, low concentrations of renin in adult life do not exclude the possibility that the renin–angiotensin system has exerted an earlier but lasting influence.

Renal structure

An alternative explanation for the low plasma renin concentrations of people who were small at birth is that it reflects a relative deficit of nephrons. Brenner and colleagues have suggested that retarded fetal growth leads to reduced numbers of nephrons which in turn leads to increased pressure in the glomerular capillaries and the development of glomerular sclerosis.[61, 62] This sclerosis leads to further loss of nephrons and a self-perpetuating cycle of hypertension and progressive glomerular injury. The number of nephrons in the normal population varies widely, from 300 000 to 1 100 000 or more.[61] Animal and human studies have shown that low rates of intrauterine growth are associated with reduced numbers of nephrons (p. 25).[63] Studies using fetal ultrasound have shown that babies that are small for gestational age have restricted renal growth during the critical period at 26–34 weeks of gestation. This restricted the anteroposterior size of the kidney but does not diminish kidney length.[64] It has been suggested that during normal childhood development kidney growth lags behind the increases in body weight, and blood pressure rises in order to maintain renal homeostasis.[65]

Endocrine mechanisms

Chapter 2 described the animal studies which led to the hypothesis that fetal undernutrition leads to lifelong changes in the fetal hypothalamic–pituitary–adrenal axis, which in turn resets homeostatic mechanisms controlling blood pressure (p. 29). These findings could also explain the association between raised blood pressure and a high ratio of placental weight to birthweight. A recent study of 9-year-old children in Salisbury showed that those who had been small at birth had increased urinary adrenal androgen and glucocorticoid metabolite excretion.[66] Further evidence that the hypothalamic–pituitary–adrenal axis is programmed in humans comes from a study of 370 men in Hertfordshire.[67] Those who had had low birthweight had higher fasting

Table 4.7 Mean 9.00 a.m. fasting cortisol concentration according to birthweight in 370 men aged 65 years born in Hertfordshire

Birthweight, lb (kg)	No. of men	9.00 a.m. fasting plasma cortisol, nmol/l	'Free' cortisol index
≤5.5 (2.5)	20	408	11.5
–6.5 (2.9)	47	354	9.7
–7.5 (3.4)	104	347	9.6
–8.5 (3.9)	117	340	9.3
–9.5 (4.3)	54	337	9.4
>9.5 (4.3)	28	309	9.1
All	370	344	9.5
(Standard deviation)		(112)	(3.2)
p value for trend		0.007	0.02
p value for trend*		0.02	0.04

* Adjusted for age and body mass index.

The growth hormone insulin-like growth factor 1 (IGF-1) axis may also be programmed in utero. Children in Salisbury, England, and Pune, India, who had low birthweight were found to have raised plasma IGF-1 concentrations.[34] The highest concentrations were in children who had the lowest birthweights but attained the largest body size in childhood. Raised IGF-1 concentrations may therefore be linked to catch-up growth. IGF-1 is known to be important for the growth of blood vessels,[68] and raised concentrations could be one of the processes underlying the suggested association between catch-up growth and raised blood pressure in later life (p. 66).

Vascular structure

The elastic recoil of the aorta is important in maintaining blood flow in the peripheral circulation and in the coronary arteries during diastole. Reduced elasticity (compliance) in the aorta is a marker of cardiovascular disease.[69] It is associated with hypertension, and also with left ventricular hypertrophy because the work of the left ventricle is increased.[70, 71] In Sheffield 50-year-old men and women who were small at birth had reduced compliance in the large arteries of the trunk and legs.[18] Martyn & Greenwald have proposed that impaired synthesis of the scleroprotein elastin is one of the mechanisms underlying the association between low birthweight and raised blood pressure.[72] The elasticity of larger arteries largely depends on the scleroprotein elastin, which is laid down in utero and during infancy and thereafter turns over slowly.[73] Its half-life in humans is approximately 40 years.[74] Reduced elastin deposition leads to less compliant, that is 'stiffer', arteries which will lead to raised blood pressure.[72] The loss of elastin with ageing will amplify the increase in blood pressure. The elasticity of arteries is related to the blood flow in them during intrauterine life. In babies born with a single umbilical artery, the iliac artery which gave rise to it is elastic whereas the other iliac artery, in which blood flow was lower, is thin-walled and muscular.[75] In the growth-retarded fetus there are changes in blood flow in several

'brain-sparing' adaptations which lead to preferential perfusion of the brain at the expense of the trunk.[77] If sustained they may lead to reduced growth of the abdominal viscera and stunting at birth. Reduced blood flow in the large arteries of the trunk and legs may be associated with reduced elastin deposition, less compliant arteries, and consequent hypertension.

Diversion of oxygenated blood away from the trunk to sustain the growth of the brain also increases peripheral resistance and the load on the heart.[76, 78] Echocardiography has shown that growth-retarded fetuses have hypertrophy of both ventricles.[79, 80] Cardiac myocytes become terminally differentiated before birth and their rate of maturation is influenced by the load on the heart. Early pressure loading leads to fewer, but larger, myocytes. Left ventricular enlargement is known to be a strong predictor of morbidity and death from coronary heart disease independently of its association with raised systolic blood pressure and increased body mass.[81] Among 67-year-old men in Hertfordshire, those who had had low weight at 1 year had concentric enlargement of the left ventricle.[82] This may reflect the long-term effects of prenatal blood diversion to the brain in a baby that is short at birth (Fig. 3.10) and whose growth does not catch up in infancy. An association between low weight around the age of 1 year and later concentric left ventricular hypertrophy has been confirmed in a sample of children and adults in Lorraine, France.[32]

Recent studies suggest that low birthweight is associated with persisting alterations in vascular structure and function in addition to its associations with compliance. Among men in Hertfordshire those who had had low birthweight had narrow bifurcation angles in their retinal blood vessels.[83] People with hypertension have similar changes in retinal vascular geometry. In a study of children in the UK those who had low birthweight had reduced flow-mediated dilatation in the brachial artery after the artery had been occluded and released. Flow-mediated dilatation depends on the endothelium. These findings suggest, therefore, a link between low birthweight and endothelial dysfunction.[84] Since endothelial dysfunction is an early event in atherogenesis this may be a mechanism underlying the strong association between low birthweight and carotid atheroma in later life (Martyn, unpublished).

Nervous system

People with high blood pressure tend to have a high resting pulse rate.[85] This is associated with high cardiac output, hyperdynamic circulation and features of increased sympathetic nervous system activity.[86] Among men and women in Preston those who had low birthweight had a higher resting pulse rate.[87] This is consistent with the hypothesis that increased sympathetic nervous activity is established through retarded growth in utero and leads to raised blood pressure in later life.

BLOOD PRESSURE AND FINGERPRINTS

Fingerprint patterns and the shape of the palm provide additional evidence

tion and are established by the 19th week. Babies who are thin at birth (Fig. 3.9) tend to have 'whorls', patterns of ridges thought to result from swollen finger pads in early gestation. Studies in India and England have shown that people with a whorl on one or more fingers have raised blood pressure in adult life. Similarly, babies who are short at birth in relation to their head size tend to have narrow palms, and adults with hands that are narrow in relation to their length have raised blood pressure.

Interestingly the prognostic significance of fingerprint patterns differs in the right and left hands.[88] This may be explained by the different arterial supply to the two arms.[89] The right subclavian artery arises from the brachiocephalic artery, whose other branch is the right common carotid, whereas the left arises directly from the aorta. The right arm thus receives its blood supply from the same source as the brain, where there is increased blood flow in response to hypoxia, whereas the left arm vessels may constrict in response to hypoxia.

ADULT LIFESTYLE AND BLOOD PRESSURE

Although the customary explanation for the differences in people's blood pressure is that they depend on the environment during adult life, the findings described in this chapter raise the possibility that the intrauterine environment has a dominant effect. Birth measurements are associated with adult blood pressure, independently of current body weight or alcohol consumption. Research into the adult environment and hypertension has focused on salt.[90,91] A cross-cultural study in 52 centres concluded that 'lowering the daily intake of sodium from 170 mmol to 70 mmol corresponds to a 2 mmHg reduction in systolic pressure'.[91] This is a small effect compared with those associated with fetal growth (Table 4.5, for example). Adult body mass, however, is strongly correlated with blood pressure, and it remains to be seen whether this association reflects diet and other aspects of adult lifestyle which influence weight, or settings of hormonal output and metabolism which are programmed in utero.

Summary

Studies in many countries have shown that babies who are small for dates have raised systolic pressure in childhood and during adult life. These associations are independent of the subject's current body mass and alcohol consumption. Raised blood pressure is not only associated with low birthweight but with thinness and stunting at birth and with variations in the ratio of birthweight to placental weight. This suggests that it may be programmed at different stages of gestation, possibly through different mechanisms. The mechanisms may include persisting changes in vascular and renal structure, or in hormonal systems that control blood pressure. The hypothesis advanced is that blood pressure is programmed by lack of nutrition. This is supported by animal studies and by the associations between maternal thinness, diet in pregnancy and raised blood pressure in humans.

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5

Cholesterol and blood clotting

SERUM CHOLESTEROL

The reasons why serum cholesterol concentrations differ between populations and among people within populations are not understood. They are important because cholesterol may be directly involved in the pathogenesis of atheroma and is strongly associated with the risk of coronary heart disease.[1,2] Cholesterol and triglycerides are the lipids of central importance in the development of atheroma. They are transported in the blood as lipoprotein complexes, which are classified into low density lipoproteins (LDLs) and high density lipoproteins (HDLs). Around 65% of the serum total cholesterol is carried in the LDL fraction and 25% in the HDL fraction. Raised LDL concentrations are associated with an increased risk of coronary heart disease, whereas raised HDL concentrations seem to be protective.

Chapter 2 gave an account of animal experiments in which lipid metabolism was permanently changed by interference with diet, and other manipulations during gestation and shortly after birth. Speculation that the high cholesterol and saturated fat content of human milk influence lipid metabolism throughout life has not been supported by animal experiments or follow-up studies of children. The concentration of cholesterol in infant food seems to have only a transient effect on serum cholesterol concentrations. Animal studies unequivocally demonstrate, however, that interference with cholesterol metabolism during development affects lipid metabolism permanently, and that undernutrition in utero has persisting effects on the structure and function of the liver, which regulates cholesterol. This chapter describes early evidence that similar phenomena occur in humans. Follow-up studies have shown that children maintain their rank order by serum cholesterol concentrations from the age of 6 months.[3,4] Put another way cholesterol `tracks' from childhood into adult life.[5]

We do not yet know the relative contributions of pre- and early postnatal experience which establish an individual in his or her track