Maternal and fetal origins of coronary heart disease

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Recent research has shown that babies who were small at birth and during infancy will be at increased risk of developing coronary heart disease, stroke, diabetes or hypertension during adult life. That a person's destiny and lifespan may be determined before birth is well known. Genetically determined diseases such as Huntington's chorea illustrate how a long period of normal development and adult life can be prematurely brought to an end by the action of inherited defects. What is new is the realisation that it is not only the presence or absence of genes that controls our destiny but the way in which gene expression may be permanently changed by the nutrient environment in early life.

There are three reasons why this new field of research has developed. First, the current explanation of coronary heart disease, a 'destructive' model in which inappropriate adult lifestyles hasten the normal ageing process, fails to account for the time trends of the disease, or its geography, or why one person gets the disease and another does not. Second, the search for alternative explanations led to a strong geographical clue that the role of fetal life in the genesis of coronary heart disease was much greater than had been expected [1]. Third, animal experiments show that changes in nutrition in early life can permanently change the growth and form of the body and a whole range of its structures and functions [2].

The substantial body of evidence on the plasticity of the fetus, its ability to adapt to undernutrition by reduction in growth rate, and the permanent effects of these adaptations, derives from the work of Widdowson and McCance, and more recently Lucas [3] in Cambridge, and from a series of workers in the USA, including Winick [4], Hahn [5], Dubos [6] and Mott [7]. Studies of animals enable us to say two things about the human fetus. One, if it is undernourished it will have persisting defects which include reduced cell numbers in tissues and organs, modified organ structure, selection of particular clones of cells and altered 'settings' of key hormonal axes. This last is a theme to which I will return. Two, the long-term effects of undernutrition depend on the stage at which it occurs. Tissues and systems are vulnerable to programming during phases of rapid cell replication, and different tissues undergo these 'critical' or 'sensitive' phases of development at different times. The kidney, for example, develops in the last third of gestation. Undernutrition before that time will not programme it, because it has not yet developed; undernutrition after birth will not affect it because the complement of renal cells and nephrons which is present at birth is the total final complement [8]. The 'sensitive' period for renal development is the last three months of gestation.

Fetal growth and adult disease

We have been able to make progress in exploring programming because, in the past, nurses and health visitors in Britain kept detailed records on newborn babies. Figure 1 shows records from a maternity hospital in Preston in 1935. The record shows not only the weight of the baby but its length, its head circumference, six diameters of its head and the weight of the placenta. Similar records, going back to 1907, were kept in a hospital in Sheffield. In the county of Hertfordshire, the weight of every baby born from 1911 onwards was recorded together with its weight at 1 year of age. The Hertfordshire records were established by Ethel Margaret Burnside, chief health visitor in the county. It was she who ensured that the babies born in the county were weighed at birth and followed up, initially to 1 year and later up to 5 years. We have now studied 15,700 people—5,600 women and 10,100 men—born there before 1930. Figure 2 shows the death rate from cardiovascular disease in these men and women in relation to their birthweights [9]. In both sexes death rates fall between those who had low and those who had high birthweights; rates rise again at the highest extremes of birthweight, which may be due to associated gestational diabetes though there is no direct evidence for this. From other studies we know that the small babies who as adults had high cardiovascular disease rates were small in relation to the duration of gestation rather than small because they were prematurely born [10]. Figure 3 shows that, for men, weight at 1 year, ie growth in infancy, is a stronger predictor of coronary heart disease than birthweight [9]. Death rates from coronary heart disease fall steeply between those who were small and those who were large at 1 year. There is no similar trend with weight at 1 year among women.

These findings pose the question of what processes link reduced early growth with adult disease. From

LABOUR WARD REPORT.

Fig 1. *A birth record from Sharoe Green Hospital in Preston in 1935.*

Admitted 20 of February 1919 at 10.15 p/o'clock. Warded of 19 at o'clock.
Delivered 25 of 1919 at 12 p.m o'clock. Discharged undelivered of 19 at o'clock.
by cause

	I. H. M.	II. H. M.	III. H. M.	TOTAL. H. M.
Duration of labour	4 - 30	25	15	5 - 10

Measurement of Pelvis—
Interspinous   Intercristal   Conj. ext.   Conj. diag.   Conj. vera (estimated)   Conj. vera (actual)

Abnormal conditions on admission—Discharges Lo Ulcers Lo Œdema Lo   Catheter   Urine clear

Presentation of Child Vertex   Position of Child R o a.

Pains began   date 20-2-19. hour 4 p.m.   Rupture of membranes   date 20-2-19 hour 11-35 p.m
Delivery   date 20-2-19. hour 12 p.m   (1) Spontaneous   (2) Artificial

Operation or important complication   Hæmorrhage, amount   Time of occurrence (a) Before (b) With (c) After Placenta
                                             Source { Uterus / Lacerations   How arrested
Placenta and membranes expelled Complete Weight 1 lb   Laceration { Cervix / Vagina / Perinæum { Through Sphincter / To Sphincter / Slight Union { Complete / Partial / None Labia
(a) Spontaneously. (b) By expression. (c) By hand introduced.
CHORION. (1) Intact. (2) Imperfect. (3) Retained.

PULSE. 80 On Admission.   During second.   After third.

INFANT. Male, female, weight, lb. 6–10 oz. 20 ½ length, inches   Male, female, weight, lb.   oz.   length, inches
3rd day   " 6.10 "   3rd day
5th "   " 6.12 "   5th "
8th "   " 6.16 "   8th "
14th "   " 7 - "   14th "
Born, alive, dead. Died before labour. Peeling. Macerated. Died during labour. Cause
Apparent age, Full Term · Malformations,

CHILD'S HEAD.   NAMES OF ALL WHO EXAMINED PATIENT.   CORD.
                                                          Length 19 inches
Circumference. 14 ½   Convolutions round child
bi P. 3.2   Physicians   Insertion
bi.T. 2.4   Date of separation
O.M. 5.2   R.M.O.   Condition of navel on leaving 9
O.F. 4.8   Labour Ward Sister L. Eastburn   Method of feeding   Condition of child on leaving Hospital
S.O.F. 4.4   Pupil Midwives N. Hunt   Breast   Good
F.M. 1.6   Students   Vaccination.—Date   Result.

examining samples of men and women who still live in Preston, Sheffield and Hertford, we now know that babies who were small have, as adults, raised blood pressure [11], raised serum cholesterol [12], raised plasma fibrinogen and factor VII concentrations [13] and impaired glucose tolerance [14]—the main risk factors for coronary heart disease. Table 1 shows the mean systolic pressures of men and women aged 64–71 years. Systolic pressure falls away progressively between those who were small at birth and those who were large [11]. The relation between birthweight and blood pressure has now been demonstrated in a range of studies of children and adults [15–18], and there is a secure base for saying that impaired fetal growth is strongly linked to blood pressure at all ages except adolescence, when the tracking of blood pressure

levels which begins in early childhood is perturbed by the adolescent growth spurt. Law has shown that the differences in blood pressure associated with birth-weight are small in childhood but are magnified throughout life [11]. This suggests that there may be an amplification process as well as an initiation process, as was suggested by Folkow [19]. We do not know what initiates high blood pressure in intra-uterine life, but there are interesting clues including the work of Edwards and Seckl who have pointed to the possible importance of cortisol [20,21]. Nor do we know what amplifies blood pressure, but again there are clues which suggest a modification of vascular structure *in utero*, with a reduction of elastic tissue in larger vessels [22].

Table 2 shows the prevalence of non-insulin depen-
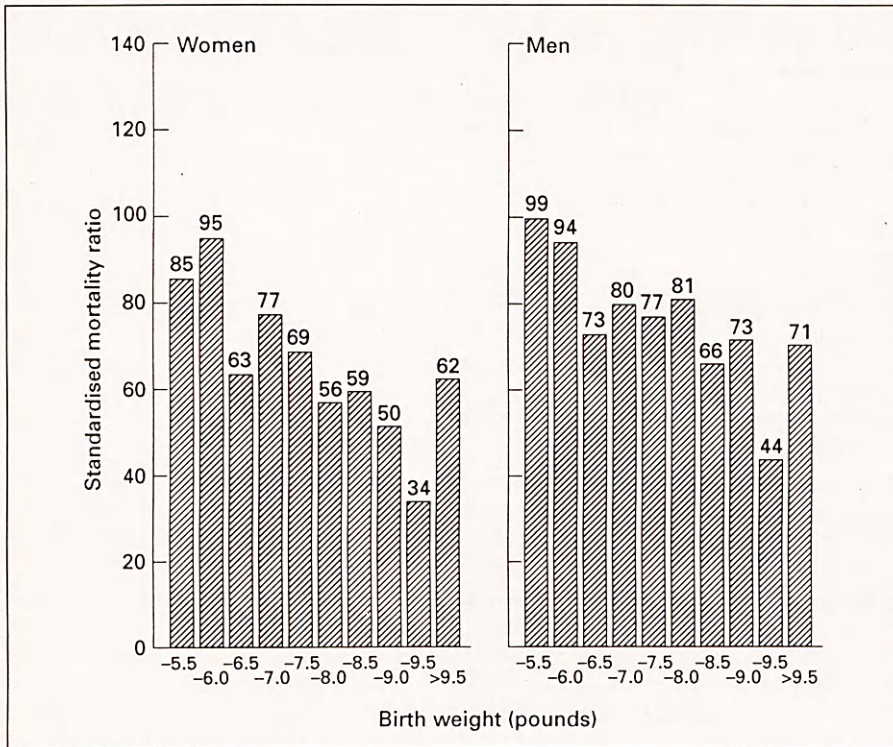
**Fig 2.** *Standardised mortality ratios for cardiovascular disease below age 65 according to birthweight.*

dent diabetes and impaired glucose tolerance according to birthweight in a group of men. The prevalence falls sharply between men who were small at birth and men who were large [14]. There are similar findings in women. The association between birthweight and diabetes first shown in collaboration with Hales has been replicated in two other studies in Britain [23,24] and in two studies in the United States [25,26]. In summary, people who were small as babies are more resistant to insulin and may also be less able to produce insulin.

The occurrence of insulin resistance in adults is characterised in syndrome X, in which diabetes, hypertension and raised plasma triglyceride concentrations coincide in the same patient, together with insulin resistance and hyperinsulinaemia. Table 3 shows the prevalence of this condition in a group of men. It falls from 30% to 6% between those who were small and those who were large at birth [27]. Allowing for current body size, the relative risk of having syndrome X among people who weighed six and a half pounds or less at birth is around 10 times higher than among people who weighed more than nine and a half pounds. This is a large risk. For comparison, the risk of coronary heart disease among smokers compared with non-smokers is around 2. Syndrome X is associated not only with low birthweight but with thinness at birth, as measured by a low ponderal index (birthweight/length^3). Babies who are thin at birth lack muscle as well as fat, and muscle in adult life is the peripheral site of insulin action. Phillips carried out insulin tolerance tests on men and women aged 50

and confirmed that those who were thin at birth are less sensitive to insulin [28].

The association between diabetes in adult life and low rates of fetal growth is perhaps unsurprising, given that insulin is central to the control of fetal growth, linking maternal glucose supply to rates of cell replica-

Fig 3. *Standardised mortality ratios for cardiovascular disease below age 65 according to infant weight.*
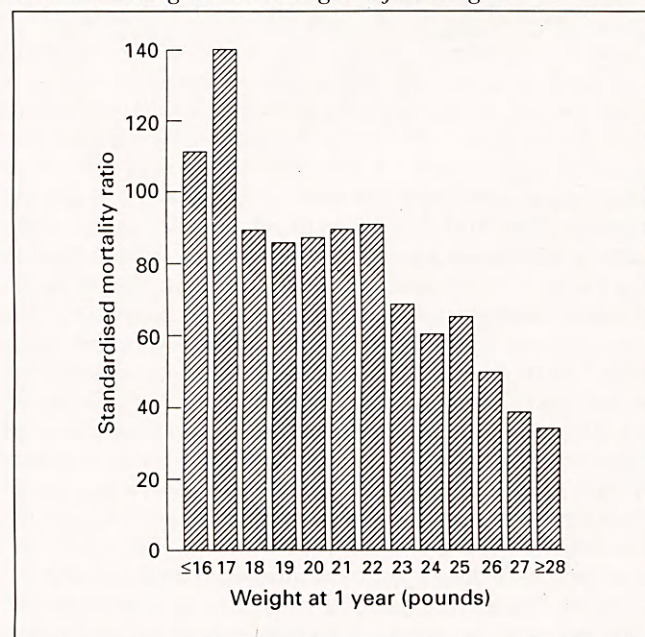
Table 1. Mean systolic pressure (mm Hg) in men and women aged 64–71 years according to birthweight.

Birthweight in pounds (kg)	Men	Women
≤ 5.5 (2.50)	171 (18)	169 (9)
– 6.5 (2.95)	168 (53)	165 (33)
– 7.5 (3.41)	168 (144)	160 (68)
– 8.5 (3.86)	165 (111)	163 (48)
> 8.5 (3.86)	163 (92)	155 (26)
Total	*166 (418)*	*161 (184)*
Standard deviation	24	26

Number of subjects in parentheses

tion [29]. We are hoping to make progress with an understanding of the thin baby through a programme of studies in India supported by the Wellcome Trust. The Indian baby is characteristically thin and Indian people tend to be insulin-resistant. At the turn of the century Mary Calvert Holdsworth was a missionary in Mysore, India. She died leaving behind her husband and four children. Her husband raised money by public subscription to build a hospital for women and children in Mysore, and from 1930 onwards they kept the same kind of records as were being kept in parts of Britain. Fall and Stein have traced a sample of the babies and it is proving possible to replicate in India what has been done in Britain, relating size and body proportions at birth to physiology and metabolism in later life, in particular to glucose metabolism.

Raised blood pressure in adult life is associated not only with thinness at birth but also with short body length in relation to head size. Short babies are thought to have encountered undernutrition in late gestation and to have sustained brain growth at the expense of the trunk, including the abdominal viscera. Table 4 shows mean serum cholesterol concentrations in a group of men and women aged 50 according to abdominal circumference at birth. The concentrations of total LDL cholesterol fall between people who had small and large abdominal circumferences [30]. Abdominal circumference reflects liver size, the liver being disproportionately large in the fetus. An inference from Table 4 is that babies who have impaired liver development reset their cholesterol metabolism, whether by increased synthesis or reduced excretion we do not know, and this persists into adult life. In other studies Fall has shown that cholesterol metabolism in adult life is also importantly related to the method and duration of infant feeding [31]. Martyn has shown that reduced abdominal circumference at birth is associated with raised plasma concentrations of fibrinogen, another strong predictor of coronary heart disease. Babies who are short at birth may have low growth rates in infancy, and low weight at 1 year is also strongly associated with raised plasma fibrinogen concentrations [13]. The dif-

Table 2. Prevalence of non-insulin dependent diabetes and impaired glucose tolerance (2 h plasma glucose concentration >7.8 mmol/l) in men aged 59–70 years.

Birthweight in pounds (kg)	Number of men	Number (%) with impaired glucose tolerance or diabetes	Odds ratio adjusted for body mass index (95%CI)
≤ 5.5 (2.50)	20	8 (40)	6.6 (1.5 to 28)
– 6.5 (2.95)	47	16 (34)	4.8 (1.3 to 17)
– 7.5 (3.41)	104	32 (31)	4.6 (1.4 to 16)
– 8.5 (3.86)	117	26 (22)	2.6 (0.8 to 8.9)
– 9.5 (4.31)	54	7 (13)	1.4 (0.3 to 5.6)
> 9.5 (4.31)	28	4 (14)	1.0
Total	*370*	*93 (25)*	χ^2 *for trend = 15.4 (p < 0.001)*

Table 3. Prevalence of syndrome X (type 2 diabetes, hypertension and hyperlipidaemia) in men according to birthweight.

Birthweight in pounds (kg)	Number of men	% with syndrome X	Odds ratio adjusted for body mass index (95% CI)
≤ 5.5 (2.50)	20	30	18 (2.6 to 118)
– 6.5 (2.95)	54	19	8.4 (1.5 to 49)
– 7.5 (3.41)	114	17	8.5 (1.5 to 46)
– 8.5 (3.86)	123	12	4.9 (0.9 to 27)
– 9.5 (4.31)	64	6	2.2 (0.3 to 14)
> 9.5 (4.31)	32	6	1.0
Total	*407*	*14*	χ^2 *for trend = 16.0 (p < 0.001)*

Table 4. Mean serum lipid concentrations according to abdominal circumference at birth in men and women aged 50–53 years.

Abdominal circumference (inches)	Number of people		Total cholesterol (mmol/l)			LDL cholesterol (mmol/l)		
	Men	Women	Men	Women	All	Men	Women	All
≤ 11.5	28	25	6.5	6.8	6.7	4.5	4.6	4.5
– 12.0	22	21	6.8	6.9	6.9	4.8	4.4	4.6
– 12.5	13	18	6.7	6.8	6.8	4.6	4.2	4.4
– 13.0	21	24	6.0	6.5	6.2	3.8	4.2	4.0
> 13.0	26	19	6.0	6.4	6.1	3.9	4.1	4.0
Total	*110*	*107*	*6.4*	*6.7*	*6.5*	*4.3*	*4.3*	*4.3*
p-value adjusted for gestational age by regression			0.009	0.16	0.003	0.003	0.12	0.0007

ferences in serum cholesterol and plasma fibrinogen concentrations associated with the range of abdominal circumference at birth and infant growth are large, equivalent to at least 30% differences in risk of coronary heart disease.

It has been suggested that the associations between early growth and adult disorders which have been discovered over the past 10 years merely indicate that small babies are born into poorer families and live lives at continuing disadvantage so that their adult lifestyles impair their health. There are five reasons for rejecting this. First, the associations have been found in different adult populations around the world and in children. Second, there are now twelve published studies of cardiovascular risk factors in adults in which the influences of social class now or at birth, cigarette smoking and other aspects of lifestyle have been explored and do not explain the relationships between early growth and adult risk factors. Third, the associations are specific, in that reduced early growth is not associated with death from all non-cardiovascular causes. Fourth, the associations are statistically strong and the relative risks are large. Finally, what has been found in humans is being replicated in animals.

The physiology of programming

Undernutrition and other adverse influences leave permanent marks on the physiology and structure of the body [3]. For example, in four groups of pregnant rats given varying amounts of dietary protein, from 18% down to 6% by weight, the offspring of mothers who had lower protein diets had raised blood pressure 9 weeks after birth [32] (Table 5); subsequent observations showed that this higher blood pressure persisted through adult life. Experiments on animals also show that undernutrition at different times in early life has different effects. Undernutrition in early gestation leads to proportionate 'symmetrically small' babies. In mid or late gestation it leads to disproportionate babies who are thin or short. Disproportionate growth

Table 5. Effects on systolic blood pressure in adult rats of fetal exposure to maternal low protein diets.

Dietary protein (% by weight)	Number	Systolic pressure (mm Hg) 9 weeks after birth
18	15	137 ± 4
12	13	152 ± 3
9	13	153 ± 3
6	11	159 ± 4

seems to hold a key to the origins of coronary heart disease. Small size at birth does not of itself seem as important. This conclusion echoes Widdowson's conclusions 30 years ago, when she showed that undernutrition could effect profound changes in the size of particular organs without any major change in overall body size [1]. Body proportions as a surrogate for the size of particular organs are now a focus of attention in work on programming.

A rapidly growing baby is more vulnerable to undernutrition than one that grows slowly. When rickets was common 70 years ago it was not the small babies who got the disease but the larger, more rapidly growing ones. Widdowson showed that if rats were undernourished for a brief period after weaning, those that were growing fast were profoundly influenced, with reduced growth of the liver and the spleen, while those that were growing slowly were unaffected [1]. Harding has shown a similar phenomenon in sheep [33]. When rapidly growing fetuses experience undernutrition their growth slows abruptly whereas the more slowly growing fetuses continue to grow through the period of undernutrition to become larger than the more rapidly growing ones. If downregulation of growth early in gestation protects against undernutrition later, it may explain why fetal undernutrition is not always associated with coronary heart disease; for instance, in some countries such as China, where intrauterine

growth retardation is widespread, coronary heart disease is rare. Growth retardation in China, however, leads to babies that are proportionately small at birth. Downregulation of growth in early gestation may protect them from the effects of undernutrition later in gestation, and from the development of the dispro-portion that is associated with coronary heart disease. In contrast, babies in India do not downregulate their growth in early gestation; undernourished in later ges-tation, they are born thin and susceptible to syndrome X.

A recent study showed that twins do not, as a group, have raised death rates from coronary heart disease, though the shorter of two twins does have a higher risk than the taller [34]. The fetal growth of twins is varied. The growth trajectories of some depart from that of singletons early in pregnancy while the growth of oth-ers departs from the singleton growth track late or even not at all. These heterogeneous growth trajecto-ries give no *a priori* basis for predicting whether twins as a group will be protected from coronary heart disease or be more susceptible to it. This inability to make some kind of *a priori* prediction is compounded by the fact that twins tend to be born prematurely. There is a sense in some of the data collected in the past 5 years that babies who are small for dates may be protected from adverse programming by early expul-sion from the uterus.

Fetal undernutrition, which programmes the body, itself results from inadequate maternal intake of food, or inadequate transport or transfer of nutrients. There was a time when people thought that the problems of fetal nutrition might be resolved by giving mothers who were pregnant an adequate nutrient supply. We now know that this is incorrect. We know that nutri-tion before conception is important. In 1944, for a period of 7 months, there was an embargo on food supplies to the population of western Holland. People starved. A generation of babies was conceived or born during famine and we now know something about what happened to them as adults. Girls who were con-ceived in the famine but born after liberation by the allies had normal birthweight and grew up to be nor-

mal women, but their babies were small at birth [35]. The ability of these women to deliver nutrients to their babies had, it seems, been impaired by their own fetal experience. Osmond, in collaboration with Van der Meulen at the Amsterdam Medical Centre, is now studying a sample of 700 survivors of the Dutch famine. Measurements of their physiology and metabolism will be important to our understanding of the long-term effects of undernutrition.

We know little about the cellular and molecular mechanisms that underlie programming. Animal experiments suggest that they include reduced cell numbers, altered organ structure, including vasculari-sation, and the setting of the hormonal axis [3]. Our own framework of ideas focuses on the effects of undernutrition at different times on the synthesis of hormones and the sensitivity of the body to them [36]. We suggest that disturbance of nutrition in the second trimester produces insulin resistance. At birth the babies are thin. During infancy their growth tends to catch up. As adults they have syndrome X [27] and are at increased risk of coronary heart disease. With undernutrition in the third trimester the baby arrests its trunk growth to sustain brain growth. We think, on limited evidence, that these babies have long-term growth hormone deficiency and resistance [36]. At birth these babies are short, though they may have normal birthweight. In infancy they have low growth rates. As adults they have raised blood pressure and raised serum cholesterol and plasma fibrinogen con-centrations. This is a framework of ideas only. No doubt it will need to be revised.

Control of fetal growth

Penrose [37] and Morton [38] studied the birth-weights of families and showed a strong correlation between the birthweights of people related through their mothers but not of those related only through their fathers. The conclusion from these and later studies was that fetal growth is not predominantly controlled by the fetal genome but by the supply of nutrients and oxygen from the mother. An interesting

Table 6. Mean systolic blood pressure (mm Hg) of men and women aged 46–54 according to placental weight and birth-weight.

| Birthweight in pounds (kg) | Placental weight (pounds) | | | | |
	≤1.0	– 1.25	– 1.5	> 1.5	All
≤ 5.5 (2.50)	152 (26)	154 (13)	153 (5)	206 (1)	154 (45)
– 6.5 (2.95)	147 (16)	151 (54)	150 (28)	166 (8)	151 (106)
– 7.5 (3.41)	144 (20)	148 (77)	145 (45)	160 (27)	149 (169)
> 7.5 (3.41)	133 (6)	148 (27)	147 (42)	154 (54)	149 (129)
All	147 (68)	149 (171)	147 (120)	157 (90)	150 (449)

Number of subjects in parentheses.

clue linking control of fetal growth and blood pressure in the offspring came from Sharoe Green Hospital in Preston where they kept the detailed records shown in Fig 1 [39]. We measured the blood pressures of a group of men and women born in this hospital who are now aged 50. In Table 6 the men and women are arranged in four groups of birthweight and four groups of placental weight. As expected from previous findings, those who were of heavier birthweight have lower blood pressure. However, unexpectedly, at any birthweight men and women who had had larger placentae had higher blood pressure. From studies on humans and animals we know that placental enlargement is an adaptation to lack of nutrients, including oxygen. A high ratio of placental weight to birthweight is linked to cardiovascular disease, impaired glucose tolerance and raised plasma fibrinogen concentrations in later life, as well as to hypertension [10,13,23].

In humans three kinds of baby have disproportionately large placentae. They are the offspring of mothers who were anaemic in pregnancy, or exercised during pregnancy or live at high altitude [40–42]. The fetus, it seems, attempts to overcome the deficiency in supply of nutrients to it by increasing the area of its attachment to the mother [43]. This, as with so much of the story of programming, is already known in animals. A number of workers have shown that if a ewe is put on to poor pasture after mating, the placenta will enlarge. This could not, however, be replicated every time [44–46]. Two years ago Robinson took up the idea that it might be the level of nutrition before conception that determined the response to undernutrition in early pregnancy [47]. He showed that if a sheep is well nourished before mating and is then undernourished in early gestation, the placenta will enlarge. If the ewe is badly nourished before conception, placental hypertrophy does not occur. These observations have brought into focus the importance of pre-pregnant physiology and nutrient storage.

Acknowledgements

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1994–1995 Teach-In Programme

Teach-In sessions are designed for junior clinicians and those wishing to be updated with new advances in medicine

The sessions take place at the College at 8 pm.

6 December 1994
Acute renal failure
Dr C G Winearls FRCP
Churchill Hospital, Oxford

10 January 1995
How to examine the nervous system
Dr P K P Harvey FRCP
Royal Free Hospital, London

7 February
Practical problems in adult intensive care units
Dr D F Treacher FRCP
St Thomas' Hospital, London

7 March
Acute and chronic hepatitis
Professor H C Thomas FRCP
St Mary's Hospital Medical School

4 April
Assessing the brain — from local pathology to brain death
Professor C Kennard FRCP
Charing Cross and Westminster Medical School

2 May
Neonatal and paediatric intensive care
Professor A D Edwards FRCP
Royal Postgraduate Medical School

13 June
Cardiology update — arrhythmia, cardiomyopathy
Professor W J McKenna FRCP
St George's Hospital Medical School

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