The thrifty phenotype hypothesis

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The thrifty phenotype hypothesis proposes that the epidemiological associations between poor fetal and infant growth and the subsequent development of type 2 diabetes and the metabolic syndrome result from the effects of poor nutrition in early life, which produces permanent changes in glucose-insulin metabolism. These changes include reduced capacity for insulin secretion and insulin resistance which, combined with effects of obesity, ageing and physical inactivity, are the most important factors in determining type 2 diabetes. Since the hypothesis was proposed, many studies world-wide have confirmed the initial epidemiological evidence, although the strength of the relationships has varied from one study to another. The relationship with insulin resistance is clear at all ages studied. Less clear is the relationship with insulin secretion. The relative contribution of genes and environment to these relationships remains a matter of debate. The contributions of maternal hyperglycaemia and the trajectory of postnatal growth need to be clarified.

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The thrifty phenotype hypothesis[1] was put forward 10 years ago in an attempt to explain the associations between poor fetal and infant growth and increased risk of developing impaired glucose tolerance[2] and the metabolic syndrome[3] in adult life. Figures 1 and 2 show the original findings of these associations among men in Hertfordshire[2,3]. In the intervening years, many data have emerged showing the reproducibility of these epidemiological findings in different populations and ethnic groups. The validity of the findings is now generally accepted. A key matter for debate is to what extent the underlying mechanisms explaining the links are genetic or environmental. It is clear that genetic causes of poor insulin secretion can be associated with poor fetal growth, though they are rare (*see* Frayling & Hattersley, this issue). This is not in principle surprising, since insulin is a major fetal growth hormone. There is some indication that other genetic polymorphisms may be linked to birth weight and subsequent changes in glucose metabolism[4], but these effects are considerably less strong than the effect of birth weight itself[5]. It is facile to state that the pathogenesis of type 2 diabetes resides in a mixture of genetic and environmental factors, since this is true of every

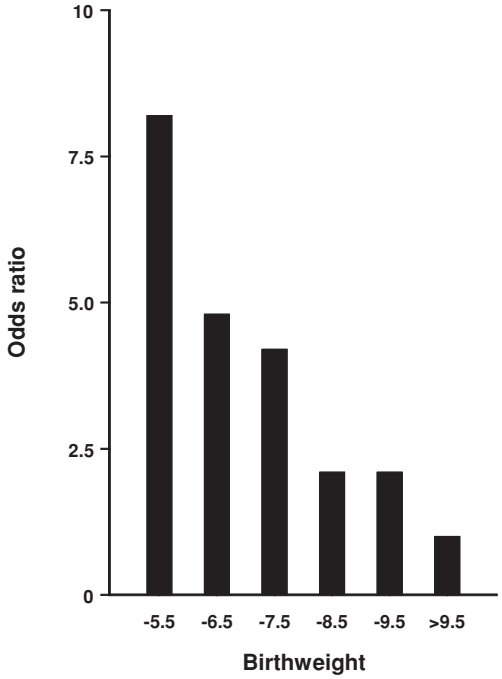

Fig. 1 Odds ratio for impaired glucose tolerance or type 2 diabetes according to birth weight among 370 men aged 64 years born in Hertfordshire (adjusted for adult body mass index).

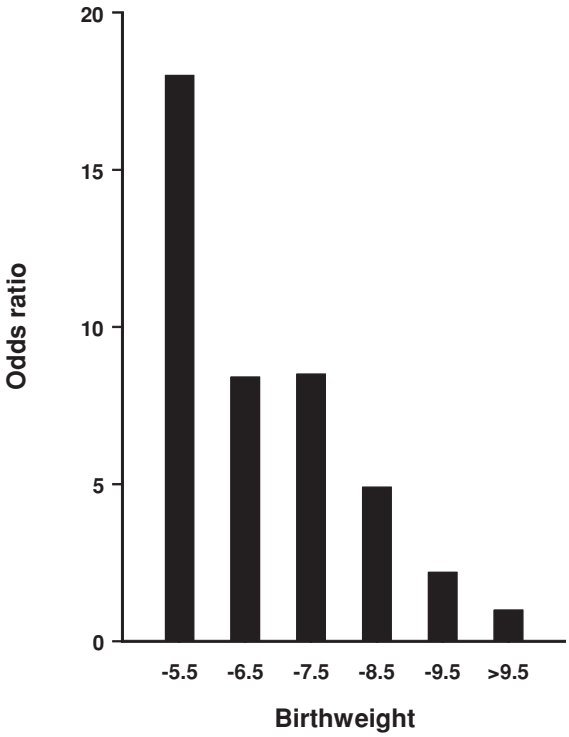

Fig. 2 Odds ratio for the metabolic syndrome according to birth weight among 407 men born in Hertfordshire (adjusted for adult body mass index).

human characteristic. Genetic factors are known to be involved in diseases such as tuberculosis and malaria, but the only credible approach to their prevention and treatment is to attack their major environmental cause – infection. It is, therefore, important to establish whether environmental factors acting in early life play a major role in the pathogenesis of type 2 diabetes.

The thrifty phenotype hypothesis proposes that environmental factors are the dominant cause of type 2 diabetes. In this chapter, we shall summarise the hypothesis as originally proposed; review the human and animal data which have emerged subsequently; consider, in the light of this how the hypothesis should be refined; and finally present what we believe are the key issues to be tackled by future research.

The thrifty phenotype hypothesis

Figure 3 shows the original diagrammatic representation of the thrifty phenotype hypothesis. The central element is that poor fetal and infant nutrition are the insult that drives the process. World-wide, the most important cause of malnutrition in early life is maternal malnutrition (*see* Barker, this issue). However, other influences, maternal and placental, may also be involved. A contribution of malnutrition in infancy was included because of our finding that the link between low weight at 1 year and the subsequent risk of glucose intolerance among men could not be explained simply by the strong association between weight at 1 year and birth weight. In considering the downstream effects of poor fetal nutrition, we proposed that poor development of pancreatic β-cell mass and function (including islet of Langerhans vasculature and possibly innervation) were key elements linking poor early nutrition to later type 2 diabetes. We also suggested that fetal malnutrition led to insulin resistance. Fetal nutrition thereby set in train mechanisms of fetal nutritional thrift, which had a differential impact on the growth of different organs, with selective protection of brain growth. Altered growth permanently changes the structure and function of the body.

A poor functional capacity for insulin secretion would not be detrimental to individuals who continued to be poorly nourished and remained thin and, therefore, insulin-sensitive. Glucose intolerance would be triggered by a positive calorie balance as a result of increased food intake and decreased energy expenditure leading to obesity. The combination of malnutrition during fetal life and infancy followed by overnutrition in childhood and adult life characterises populations undergoing the transition from chronic malnutrition to adequate nutrition (*see* Fall, this issue). The thrifty phenotype hypothesis postulated a key role for protein supply because of the extensive

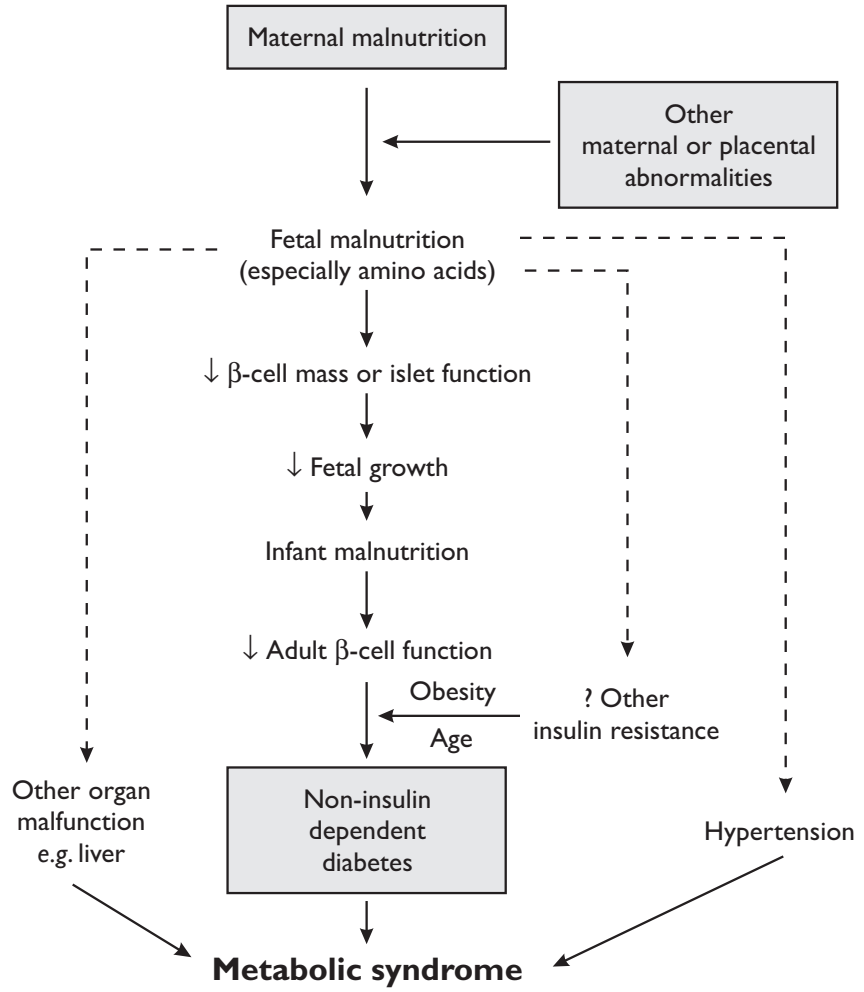

Fig. 3 The original diagrammatic representation of the thrifty phenotype hypothesis.

literature on this aspect of nutrition, but other nutritional deficits were not excluded. Indeed the variety of combinations of metabolic changes seen in patients with the metabolic syndrome might be accounted for by a variety of combinations and timings of nutritional deficiencies in fetal life and infancy. The hypothesis also proposed that the emergence of pathological changes following undernutrition in early life was critically dependent upon the superimposition of other factors, notably obesity, ageing and physical inactivity.

We suggested that those interested in candidate genes for type 2 diabetes should widen their horizons and consider genes involved in fetal growth and development. Since then mutations in transcription factors relevant to β-cell development have been shown to be a cause of maturity onset diabetes of the young, albeit a rare cause. Gene defects

which reduce fetal insulin production and polymorphisms of the insulin gene itself, are associated with type 2 diabetes and exemplify the crucial role of early development in determining the disease.

Recent studies

Body size at birth and the metabolic syndrome

Since the original descriptions of the relationships between birth weight or thinness at birth, indicated by a low ponderal index (birth weight/length^3) and the later development of type 2 diabetes and the metabolic syndrome,

Table 1 Populations in which relationships between birth weight, shortness or thinness at birth and altered glucose and insulin metabolism or the metabolic syndrome have been described

	Age (years)
Indian children	4[6]
Pima Indians (USA)	5–29[7]
Black South African children	7[8]
Jamaican school children	6–10[9]
Salisbury children (UK)	7[10]
Prepubertal children (New Zealand)	8.5[11]
British children	10–11[12]
Italian children	8–14[13]
Southampton men (UK)	18–25[14]
French adults	21[15]
Australian men	21[16]
Danish men and women	18–32[17]
British pregnant women	27[18]
Pima Indians (USA)	20–38[19]
Mexican Americans and non-Hispanic whites	32[20]
Indian men and women	39–60[21]
Health professional men (USA)	40–75[22]
Oxford men and women (UK)	43[23]
Chinese men and women	45[24]
Danish men and women	48[25]
Preston men and women (UK)	46–54[26]
Preston men and women	47–55[27]
Swedish men	40–60[28]
Swedish men	50–76[29]
Dutch men and women	50[30]
Postmenopausal women (USA)	50–84[31]
Sheffield men and women (UK)	52[32]
Danish twins	55–74[33]
Hertfordshire men (UK)	55–74[2]
Nurses' health study (women USA)	59[34]
British women	65[35]
Swedish men	70[36]

these findings have been replicated in a variety of populations around the world (Table 1). We are not aware of any study which contradicts them. In considering the impact of poor fetal growth on later type 2 diabetes, a number of factors have to be taken into account. Birth weight or thinness at birth are but poor surrogates for the estimate of the success of a pregnancy. Weight alone does not reveal the relative contributions of fat mass and lean body mass. It was clear from the early studies of men in Hertfordshire that in this population there was a continuous relationship between birth weight and glucose tolerance. There was no threshold. Thus it is incorrect to argue that since in the Western world low birth weight is rare the impact of poor fetal growth on the risk of diabetes must, therefore, be small. Whatever the factors may be which low birth weight is signalling as being important in determining the risk of type 2 diabetes, they operate across the range of birth weights. Whilst they may operate most intensely in low birth weight babies, they also operate in the much greater number of babies who fall within what we consider to be the 'normal' birth weight range. It is, therefore, important that we try to define the phenotypes of growth-retarded babies at risk of later type 2 diabetes as precisely as possible. The hope is that animal experiments will reveal in detail, at the level of gene and protein expression, just what aspects of metabolism are programmed in association with reduced early growth.

Glucose tolerance itself is determined by both insulin secretion and insulin sensitivity. In epidemiological studies, the relationship of poor early growth to subsequent insulin resistance is much clearer and stronger than it is to poor insulin secretion. The latter has been observed in young men but not in older populations. In the elderly, the effects of life-long insulin resistance may have caused adaptive changes to insulin secretion, which obscure its relationship with early growth restriction. The relative roles of insulin secretion and sensitivity appear to differ between individuals. There are indications that men tend to be more insulin-resistant than women and the converse in relation to insulin secretion. This could represent sexual dimorphism in response to a similar insult. In experimental animals, there are large differences in the impact of poor maternal nutrition on the relative growth of different organs in males and females.

Childhood growth and the metabolic syndrome

A question arising from the association between type 2 diabetes and small body size at birth is whether, or to what extent, the increased risk of the disease associated with reduced prenatal growth is modified by particular patterns of growth throughout childhood. Suggestive evidence that childhood growth may be important comes from a study showing that obesity in childhood has a greater effect on the development of the

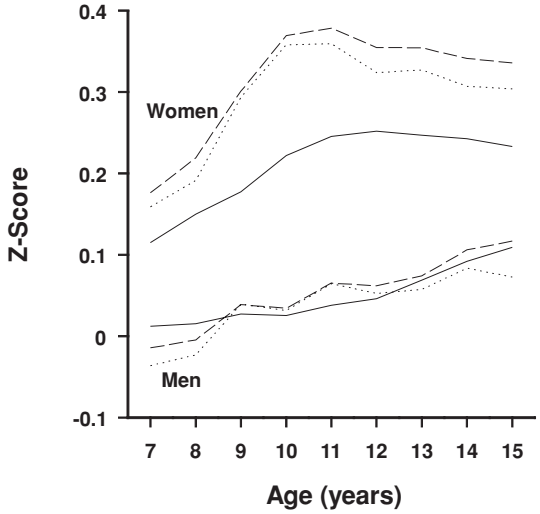

Fig. 4 Height, weight and body mass index (BMI) during childhood of 286 men and 185 women who later developed type 2 diabetes. The solid line indicates height; dashed line indicates weight; dotted line indicates body mass index.

metabolic syndrome than does obesity that occurs in adulthood[37]. The detailed information on body size at birth and during childhood that is available in a cohort of 7086 men and women born in Helsinki, Finland, allows the issue to be addressed directly[38]. Figure 4 shows the childhood growth of the 471 men and women who developed type 2 diabetes. Height, weight and body mass index (weight/height^2) are expressed as standard deviation or so-called Z-scores. These represent the differences, expressed in standard deviations, from the mean value for the whole cohort, which is set at zero. Children maintaining a steady position as large or small in relation to other children would follow a horizontal path on the figure. Children who later developed type 2 diabetes, however, having been short or thin at birth continued to have low rates of growth in infancy, as was found in Hertfordshire[2], but from 7 years onwards had accelerated growth in weight and height. By the age of 15 years, boys and girls who later developed type 2 diabetes were above the average for the cohort in weight and body mass index. Data from a second Helsinki Cohort, which includes growth measurements between birth and 7 years, show that the accelerated weight gain began at 2 years of age (manuscript in preparation). Accelerated weight gain had a greater effect on increased risk of type 2 diabetes among men and women who weighed 3000 g or less at birth. It occurred among children born to heavier mothers with higher body mass indices, suggesting that it resulted from high energy intakes in childhood. In families where the mother was well-nourished it seems likely that there would have been more food available to the children.

The processes through which accelerated childhood weight gain increases the risk of type 2 diabetes are not known. It does not seem to be through worsening of insulin resistance. Examination of 500 men

and women from an older cohort, born in Helsinki during 1924–1933[39], showed that the development of insulin resistance was associated with thinness at birth and continued thinness in childhood, followed by the development of overweight in adult life. One possible explanation for the adverse effect of accelerated weight gain is that fetal growth restriction leads to reduced cell numbers in the endocrine pancreas and subsequent accelerated growth in childhood leads to excessive metabolic demand on this limited cell mass.

Famine and the metabolic syndrome

The role of accelerated child growth in the genesis of type 2 diabetes may explain the differing results of the effects of wartime famine in Holland[30] and Leningrad[40]. The famine in western Holland began abruptly in November 1944 and ended abruptly with the liberation of Holland in May 1945. Men and women exposed to the famine while they were *in utero* had higher plasma glucose concentrations 2 h after a standard glucose load. They also had higher fasting pro-insulin and 2 h plasma insulin concentrations, which suggests that their poor glucose tolerance was partly determined by insulin resistance. The 'Dutch famine' is unique in that it was a brief period of intense deprivation in a well-nourished population whose level of nutrition was promptly restored after the famine. Children exposed to famine *in utero* were, therefore, well-nourished in childhood and could have had accelerated weight gain.

In contrast, the siege of Leningrad occurred over a prolonged period, 1941–1944, in a previously malnourished population who remained badly nourished after the siege was lifted. Children probably did not have accelerated weight gain. This (together with the small size of the Leningrad study) offers one explanation of why the associations between famine exposure and altered glucose-insulin metabolism, although in the expected direction, were small and not statistically significant.

Consistent with other studies, the people in the Dutch study who had low birth weight had raised 2 h plasma glucose concentrations, but the effects of famine were largely independent of this. One explanation is that the initial adaptation of the fetus to undernutrition is to alter its metabolism, including its glucose-insulin metabolism, and continue to grow. Only if these adaptations fail does it reduce its rate of growth. Whatever the explanation, the findings from the Dutch famine are important because they provide direct evidence that undernutrition *in utero* leads to impaired glucose tolerance and type 2 diabetes, and they show that the mother's dietary intake during pregnancy can programme metabolism without altering size at birth. Because of its brief duration,

the Dutch famine provides information about the effects of fetal undernutrition at different stages of gestation. The findings require confirmation in further studies, but it seems that famine exposure in early gestation led to disturbance of lipid metabolism while in mid and late gestation it led to disturbance of glucose-insulin metabolism.

Genes versus the environment

Whilst there is now little dispute that indices of poor early growth are linked to increased risk of impaired glucose tolerance and the metabolic syndrome, the extent to which genes or the early environment underlie the relationship remains controversial. We have argued elsewhere that the evidence linking a genetic cause to the aetiology of type 2 diabetes is poorly founded[41]. Studies of identical twins (which spuriously initiated the current preoccupation with the genetic causes of type 2 diabetes) have shown that poor fetal growth operates to increase the risk of the condition independently of the genetic constitution[42]. On the other hand, recent studies of paternal effects on birth weight and subsequent diabetes have been interpreted as evidence of genetic causation[43].

Time trends

Experience on the Pacific Island of Nauru gives an insight into how improving nutrition may be associated with a rise in type 2 diabetes followed by a fall[44]. The island population was chronically malnourished until the end of the Second World War. The flourishing phosphate mines built up after the war drastically changed the economic and nutritional welfare of the population. The immediate consequence of this was a great increase in obesity and the emergence of an 'epidemic' of type 2 diabetes. However, subsequent studies of individuals born after the war in better nutritional circumstances (but for whom unfortunately we do not have birth weights or infant weights) have shown a substantial reduction in glucose intolerance[44]. This population is particularly informative because over the years of study the amount of obesity, although great, has not increased. In contrast, in the Western world obesity is increasing and, until this trend ceases or is reversed, the benefits of improved fetal and infant growth may not be evident in declining rates of type 2 diabetes.

Animal models

Investigations in animals to examine the mechanisms and results of altered fetal and early postnatal nutrition are described elsewhere in this issue (experiments specifically designed to test and elaborate on the

thrifty phenotype hypothesis in rats are described by Ozanne). Poor fetal growth may result from a variety of causes. It is not clear whether the long-term phenotypic consequences of the different causes of reduced fetal growth are the same, varied or totally discrepant. Intuitively it seems likely, but is by no means clearly established, that the consequences of fetal growth restriction will vary according to the stage of pregnancy at which they operate, and findings in the Dutch famine studies encourage this view. Equally it seems likely that different nutritional influences will lead to different phenotypic results. Studies of the latter question are still at an early stage. At the present time, however, what is most apparent is the relative consistency of results irrespective of the type of insult provided. Perhaps it would not be altogether surprising if the fetus had a limited range of responses. While the use of reduced maternal protein intake as an experimental model in animals may not reflect the commonest problem facing human populations, it may evoke common fetal responses to undernutrition. This may explain why this specific and limited nutritional deficiency induces a phenotype with such remarkable parallels to the human metabolic syndrome and type 2 diabetes. In continuing animal studies, we need more specific molecular markers of changes in gene expression to examine this question. Whole body markers of change such as glucose tolerance and blood pressure have an inherent wide variability demanding the use of large numbers of animals to define end points.

In parallel with the human studies already described, studies of the effects of postnatal growth in animals have revealed relevant and potentially interesting changes. The longevity of male rats is linked to their pattern of early growth: female rats show the same pattern, but much smaller differences. Male rats which had been growth restricted during fetal life, having been produced by a dam fed a reduced protein diet, but who had accelerated growth postnatally, by being cross fostered to normally fed lactating dams and weaned onto a normal diet fed *ad libitum*, died young (13.1 months of age compared with controls 15.1 months). The converse pattern was observed in male pups born to a normally fed mother but who were then cross-fostered onto low protein fed dams (mean age at death 17.0 months). They suffered considerable growth restriction whilst suckling, but surprisingly when weaned onto a normal diet fed *ad libitum* they did not 'catch up' in growth, remaining permanently growth restricted[45]. We were able to show that this growth restriction was accompanied by a reduced food intake. One explanation of this is that nutrition during suckling 'sets' appetite. If the nutrition of rat litters is manipulated, by changing litter sizes, this permanently changes food intake even after weaning. Good nutrition, produced by culling litters to small numbers, leads to animals with an increased appetite. Poor nutrition, produced by expanding the

litter with additional pups from other newly delivered animals, leads to animals with a decreased appetite.

The hypothesis updated

Whilst we are not aware of data from epidemiological studies or animal research which contradict any of the key features of the thrifty phenotype hypothesis, as originally proposed, it is clear that with increased insight into the biological processes, the content and precision of the hypothesis can be improved. Our current understanding of the links between maternal malnutrition and fetal malnutrition is described elsewhere (*see* Barker, this issue), which also describes the inter-generational effects of poor maternal nutrition.

Consequences of fetal malnutrition

It has become apparent that the consequences of fetal malnutrition on organ growth differ in males and females. Animal studies have indicated that as well as changes in organ size there may be substantial changes in organ structure. Offspring of low protein fed dams have livers with larger but fewer lobules. Even within these lobules, the gradient of cell types observed going from the periportal to the perivenous zones seems to have been altered. Such changes must have profound implications for the varied functions of the liver, which include the production of acute phase proteins, now well recognised as being changed in type 2 diabetes.

It has become increasingly apparent that the response to fetal malnutrition entrains not only (presumably advantageous) selective preservation of key organs but also metabolic adaptations of advantage for postnatal survival. Thus the thrifty phenotype is not only thrifty with respect to antenatal life, but also in relation to the use of poor nutritional resources postnatally. The poorly nourished mother essentially gives the fetus a forecast of the nutritional environment into which it will be born. Processes are set in motion which lead to a postnatal metabolism adapted to survival under conditions of poor nutrition. The adaptations only become detrimental when the postnatal environment differs from the mother's forecast, with an over abundance of nutrients and consequent obesity. Similar observations have been made in relation to cold exposure. Offspring of sheep exposed to cold during pregnancy are, on delivery, better adapted to respond to cold conditions after birth.

The altered metabolic features of the offspring of rat dams fed a low protein diet are reviewed elsewhere in this issue (*see* Van Assche *et al*). These include increased hepatic gluconeogenesis, enhanced release of

fatty acids from intra-abdominal adipose tissue, resistance to ketosis and increased expression of insulin receptors with enhanced uptake of glucose by adipose tissue. These are all features which could be expected to be advantageous to an animal exposed to poor nutrition in postnatal life.

An updated version of the diagrammatic representation of the thrifty phenotype hypothesis is shown in Figure 5. Also included in the diagram are more speculative suggestions that changes in the structure and function of blood vessels may play a key role in changing organ growth and function, and that maternal hyperglycaemia may contribute to the type and consequences of fetal malnutrition.

Future research

Continuing observational epidemiological studies are required to address two questions. First, what are the influences which, acting

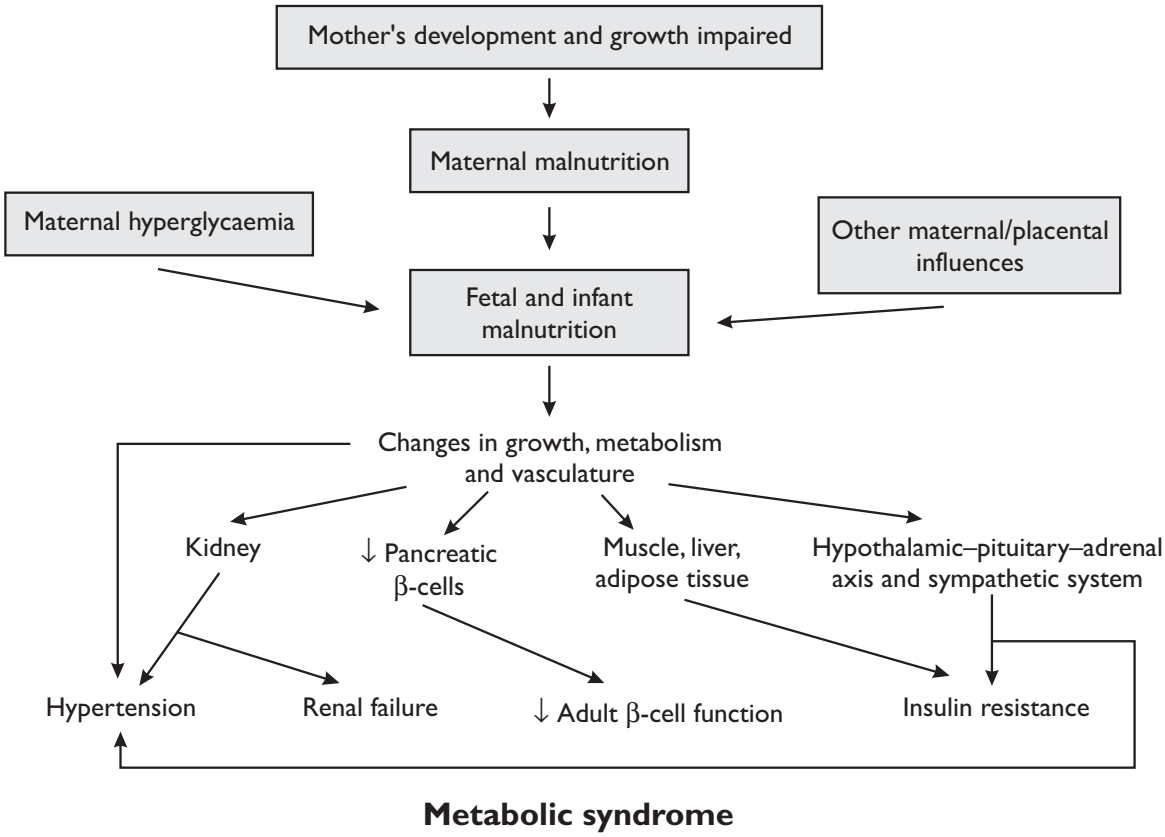

Fig. 5 An updated diagram of the thrifty phenotype hypothesis incorporating recent findings and concepts. Also included are new speculative features: maternal hyperglycaemia as predisposing factor and key roles of the vascular, hypothalamic-pituitary-adrenal axis and sympathetic systems.

through the mother or directly on the infant after birth, permanently change the body's structure and metabolism in ways which lead to type 2 diabetes? Second, how do these changes in structure and metabolism alter the body's responses to adverse influences in later life? The importance of the first question is self-evident; the second is proving a fruitful area of research. We now know that the effects of rapid weight gain in childhood, and obesity in adult life, on increased risk of type 2 diabetes is greater among men and women who had low birth weight. It is likely that many such interactions between body size in early life and influences acting in later life will be discovered.

As is argued in the preface, sufficient is now known to plan intervention studies and new public health policies. These will be refined as new information comes forward from clinical and animal studies.

More research needs to be done in animals to document the consequences of nutritional growth restriction. Few organs and systems have been studied in detail. It is also apparent that the effect of age is important, but few studies have been carried out on ageing animals – largely because of the facilities and time required. Provision needs to be made for such long-term studies. The range of animals studied remains narrow – rodents, guinea pigs and sheep. Little or no work has been carried out in primates and there is an obvious need for this. Experimental models of fetal growth restriction used have been limited. There is a need for the use of common end-points and their application to a range of relevant causes of growth restriction. It is far from clear how much phenotypic variability results from different types and timings of fetal and postnatal growth restriction. More needs to be known about the beneficial or detrimental effects of accelerated postnatal growth and how its impact varies with the stage in postnatal life at which it occurs.

Finally, and most crucially in relation to advancing human studies, we need molecular markers at the protein and RNA level which specifically define malnutrition at different stages of fetal life and infancy. These must first be uncovered in animal studies because of the limited nature of what can be done in humans. However, once these have been defined and tested in animals there will be great potential for them to refine and expedite human studies and, hopefully, reduce the number of subjects required. It should be possible to define end points in early postnatal life so that the success of intervention studies can be established more rapidly.

Conclusions

In the interval since the proposal of the thrifty phenotype hypothesis, the epidemiological data which led to its formulation have received

substantial and widespread international confirmation. There is a continuing debate as to the relative importance of genetic *versus* environmental factors in determining fetal growth and subsequent adult susceptibility to type 2 diabetes and the metabolic syndrome. Studies of identical twins show conclusively that the fetal environment is important. There is a major need for molecular markers of metabolic programming in fetal life. When these are available, it will be simpler to monitor at an early stage the success of intervention studies. We believe that the thrifty phenotype hypothesis continues to provide a useful conceptual framework within which to design and interpret human and animal studies in this field.

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