Introduction
Type 2 diabetes is a complex disorder likely to have multiple genetic and environmental causes. Enormous efforts are being made to discover the genetic determinants of the disease. Recently important additions have been made to our knowledge of the physiology of glucose and energy homeostasis at the molecular level – including our understanding of the mechanics of insulin action, insulin secretion, and control of appetite and energy balance. In addition, the genetic causes of a number of relatively rare causes of diabetes and obesity (one of the major risk factors for the development of type 2 diabetes) have been discovered, such as the multiple forms of maturity onset diabetes of the young (MODY) and mutations in leptin and the leptin receptor.

It seems likely that these advances along with efforts to positionally clone candidate genes for type 2 diabetes in a number of populations, will eventually identify genes that predispose to developing type 2 diabetes.

Dramatically high rates of type 2 diabetes have been observed in historically undernourished and recently urbanised populations. A comparative model is the high risk of diabetes in individuals who were growth-restrained in utero and subsequently showed ‘catch up’ in size. While it is proposed that undernutrition may somehow adversely programme metabolism, both models could be explained by genotypes that promoted survival during early nutritional adversity but later add to the risk of diabetes.

The ‘thrifty genotype’ hypothesis
Type 2 diabetes is common in Europe and the USA, with the lifetime risk reaching almost 10%. There is also compelling evidence for a genetic predisposition. In 1962, James Neel, a population geneticist at the University of Michigan at Ann Arbor in the USA, noted a high frequency of diabetes in previously undernourished communities. He suggested that the predisposition to type 2 diabetes may have carried some selective advantage in evolutionary history.

This ‘thrifty genotype’ hypothesis has since taken many twists and turns. However, it is supported by observations made regarding historically disadvantaged ethnic populations, such as Pima Indians who, after centuries of poor nutrition and low survival rates, have experienced nutritional plenty in recent years. The Pima Indians now demonstrate a prevalence of diabetes up to 50%, and there is also a strong familial association in disease risk.

Similarly, a ‘thrifty genotype’ may have contributed to the survival of Polynesian populations during their settlement of the Pacific islands 1500–3000 years ago. Following more recent urbanisation, their nutritional deficits have decreased, and they now have very high rates of obesity and type 2 diabetes.

Proponents of the ‘thrifty genotype’ hypothesis have argued that rapid deposition of fat during periods of feasting improves survival rates during fasting, when mobilisation of fat stores occurs with resulting peripheral insulin resistance. This may preserve glucose and essential fuel for brain development and metabolism. Although much of Neel’s proposed mechanism has been abandoned, the main concept that the risk of type 2 diabetes may be related to a genetic survival advantage remains attractive.

The ‘thrifty phenotype’ hypothesis
Like all good theories the ‘thrifty genotype’ hypothesis has generated an equally convincing but opposing theory: the ‘thrifty phenotype’ hypothesis. In 1992, Hales and Barker proposed the concept that environmental factors acting in early life (in particular undernutrition) might influence later risk of type 2 diabetes. This hypothesis arose, in large part, from the pioneering work of the MRC Environmental Epidemiology Unit in Southampton which, under the directorship of David Barker, explored the geographical and socioeconomic distribution of chronic diseases.

In particular they were interested in the temporal relationships of socio-economic conditions and vascular disease. Historically, cardiovascular disease has been prevalent among the socially affluent, but over time this association appeared to become inverted, such that cardiovascular disease became more prevalent in poorer parts of society, at least in countries such as the UK. This was linked with the paradox that whilst on a worldwide basis cardiovascular disease might be considered a disease of ‘affluence’ (being concentrated in more prosperous nations), within some of these societies rates of cardiovascular disease was generally highest in the least affluent. This led to the investigation of relationships of early life experiences, measured by factors such as infant mortality and birthweight, to later cardiovascular disease.
An association of low birthweight to later disease was first observed in relation to cardiovascular disease, and later extended to cardiovascular risk factors. Relationships of low birthweight and type 2 diabetes was demonstrated by Barker, in collaboration with Hales, and termed the ‘thrifty phenotype hypothesis’. They described the novel association of low birthweight with later type 2 diabetes in a cohort of men from Lancashire, and later Hertfordshire in England. The original observations have now been replicated in several populations and have been extended to examine important antecedents of type 2 diabetes, including markers of insulin resistance and insulin secretion.

**Thrifty phenotype or genotype?**

In the ‘thrifty phenotype’ model, undernutrition acts not as a selection pressure acting over many generations to alter the genetic makeup of the population, but rather as an early environmental influence acting in an individual to increase the risk of type 2 diabetes.

In Neel’s hypotheses, however, entire populations may have an increased predisposition to type 2 diabetes because of genetic selection, adapting them to different nutritional circumstances than those they currently experience. In the ‘thrifty phenotype’ hypothesis, maladaptive responses occur as a result of environmentally induced alteration of physiology in the early life of the individual. Both hypotheses offer explanations of why the frequency of diabetes and obesity may vary in different populations, and why predisposition to diabetes is common, albeit by very different mechanisms.

In an attempt to reconcile the ‘thrifty phenotype and genotype’ hypotheses, Hattersley and Tooke suggested (based on data from families of glucokinase gene mutations) that genetic defects in insulin secretion and insulin responsiveness in both mother and foetus could link size at birth and type 2 diabetes in the offspring. However, such genetic abnormalities are rare. Furthermore, many recent epidemiological studies suggest that the risk of disease is highest in those small infants who show catch-up growth, perhaps suggesting again that intrauterine growth restraint, rather than genetic defects in the foetus, links small birth size and adult disease.

There are therefore attractive arguments for both the ‘thrifty genotype’ and ‘thrifty phenotype’ hypotheses in the pathogenesis of type 2 diabetes. Animal studies may give interesting insights into the mechanisms, but doubt will remain as to whether mechanisms operative in species with multiple litters and an overwhelming need for foetal growth restraint are valid in humans. Contemporary birth cohort studies can demonstrate the relative importance of the intrauterine environment and foetal genes on size at birth, childhood growth rates, and early risk markers for type 2 diabetes.

**The ALSPAC birth cohort**

Ong and Dunger have based their studies on a contemporary birth cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC), which comprises nearly 140000 consecutive births in the Avon district of the UK. A subcohort representing 10% of ALSPAC (‘Children in Focus’) has been particularly informative. In addition to providing detailed information collected during pregnancy and measurements of size at birth, children continue to be measured regularly by the research study team, and DNA and other biological samples are readily available. Furthermore, the mean and distribution of their birthweights are identical to the current UK reference. As in previous studies, size at birth was related to a number of maternal variables during pregnancy, such as parity, smoking, infant size, and interestingly also the mother’s birthweight (supporting the suggested maternal inheritance of birthweight). In contrast, paternal height and mid-parental height were related less strongly to birthweight.

Considerable variation in growth rates was observed during the first 2 years of life. Over 50% of babies showed clinically significant ‘catch-up’ or ‘catch-down’ growth, and, by 2 years of age correlations between mid-parental height and offspring size had improved. Subsequent growth then continued along the genetic growth trajectory without substantial movement between percentile bands until puberty.

**Foetal genes**

In children who do not show postnatal catch-up or catch-down growth (approximately 50%) the correlation between size at birth and mid-parental height is similar to that observed at 2 years of age. In these ‘non-changers’, the genetic influence on size at birth is more pronounced whereas maternal uterine influences are diminished.

Thus, the association of the insulin gene (INS) VNTR III/III with larger birth size was stronger in non-changers than in the entire cohort.

This class III/III genotype was associated with an increased risk of type 2 diabetes in the original Hertfordshire cohort, and paternally transmitted class III alleles have recently also been linked to type 2 diabetes. Tissue expression studies suggest that class III alleles may inhibit the expression of INS and IGF2, the gene encoding insulin-like growth factor II (IGF-II). However, in the ALSPAC study the III/III genotype was associated with higher levels of IGF-II and insulin in cord blood at birth. It is suggested that this finding may represent the development of insulin resistance and thus explain the long-term predisposition of patients with this genotype to type 2 diabetes. Therefore the INS VNTR III/III genotype could represent a ‘thrifty genotype’, which historically could enhance survival during early infancy by promoting foetal growth, but may also confer a greater risk of diabetes during adulthood.

**Maternal genes**

The maternal inheritance of birthweight suggests an effect of maternally expressed genes or maternally transmitted genes such as mitochondrial DNA. The prevalence of
the 16189 variant in mitochondrial DNA is about 7% in Caucasians, but it is greater in some Polynesian populations at high risk of developing type 2 diabetes. It has recently been demonstrated that there was a link with this variant and the risk of type 2 diabetes in men from the original Hertfordshire cohort of Hales and Barker, and also thinness at birth in the ALSPAC cohort. These findings recall the hypotheses that paternally expressed genes (e.g. IGF-II) could promote foetal growth and, therefore, survival of the paternal line, whereas maternally inherited genes restrict foetal growth and thereby improve the mother’s chance of survival.

It has been suggested that maternally expressed IGF2R, the gene encoding the IGF2 receptor, might restrain foetal growth. Recent data from the ALSPAC cohort indicate that the IGF2 receptor, by clearing circulating IGF2, does inhibit size at birth. However, in contrast to rodents, in humans this gene may not be exclusively maternally expressed. Nevertheless these findings raise the possibility that ‘selfish’ maternal genes restrict foetal growth and thus promote survival of the maternal genetic line, whereas paternally expressed genes such as the INS VNTR III/III genotype may increase foetal size.

**Early environmental influence before and after the thrifty phenotype**

The basic concept advanced by the ‘thrifty phenotype’ hypothesis is that human disease may arise due to early environmental influences and cause disease much later in life. A question frequently asked is whether the metabolic changes resulting from the foetal genotype or in utero programming continue or can be modified in early postnatal life. Cord-blood leptin levels at birth are strongly associated with weight gain during infancy. In babies whose growth was restrained in utero low leptin levels are highly predictive of catch-up growth. More pertinent to the risk of type 2 diabetes, these infants were also the most obese at 5 years of age. Thus intrauterine growth restraint leads to a biological drive to catch-up growth during infancy.

A consequence of this growth pattern, at least in contemporary affluent societies, may be the early development of obesity and other related markers of adult diabetes risk.

Thus, the influences of environmental exposure are not confined to the time frame in which they are experienced, but may continue to act through the life of the organism and long after an adverse exposure has ended. As a further refinement of this hypotheses, it is proposed that certain key developmental windows exist during which exposures ‘set’ physiological systems and thus lead to long-term consequences. This concept has been termed ‘environmental programming’.

When the ‘thrifty phenotype’ hypothesis was proposed this concept was not new to the field of metabolic disease in humans. The importance of the early environment had already been invoked as an explanation for the increased propensity to diabetes in offspring of diabetic mothers – a very different early nutritional model to that proposed in the ‘thrifty phenotype’ hypothesis.

As early as 1960, White9 made fundamental observations regarding the high prevalence of abnormal glucose tolerance in offspring of diabetic mothers. Around the same time, Pederson10 developed the hypothesis that early overexposure to glucose in utero resulted in organomegaly and excessive growth that may later lead to the development of diabetes. Freinkel11 then extended this hypothesis to propose that over-exposure to a range of intermediary metabolites, most importantly glucose and amino acids, might in the long term lead to alteration in metabolism and later disease – a concept he termed ‘fuel-mediated teratogenesis’.

In the field of obesity it has already been proposed that influences in early life might be important to later predisposition to obesity. In 1972, Brook12 proposed that obesity might be influenced by events in utero, following the concept of the time that adipocyte differentiation occurred primarily in the intrauterine period.

Ravelli and colleagues16 explored the effect of early undernutrition due to exposure to wartime famine on later predisposition to obesity finding that exposure to famine early in intrauterine life was associated with an increase in later obesity. The presence or absence of breast feeding in early life has been proposed to influence later development and predisposition to diabetes. Breast feeding in the first 2 months of life was associated with a lower risk of development of type 2 diabetes in the Pima Indian population.13 Such a protective effect of breast feeding has also been observed for obesity14.

**Future challenges**

We do not know yet how great a role nutrition plays in development of later diabetes. One cannot doubt that there is an important role for the ‘thrifty genotype’ and ‘thrifty phenotype’ hypotheses in stimulating research and a high prevalence of type 2 diabetes in many populations adds weight to this concept. On a clinical level, any hypothesis attempting to understand the aetiology of such a common disease is important if new understanding helps to treat or prevent the disease in the future.

The thrifty phenotype has stimulated researchers to readdress concepts on the plasticity of human responses, hormonal and physiological, in the face of environmental insults and the way that such insults may exert permanent effects on the organism. Early environmental influences on later disease may carry implications for all clinicians, but may be most important for those who develop health policy, addressing the nutrition and health of mothers and their children.

References
