Commentary: The thrifty phenotype and the hierarchical preservation of tissues under stress

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In Naples, they say ‘O napulitane se fa sicco, ma nun more’ [The Neapolitan may get thin (when times are tough), but will not die]. In 1992, this folk representation of plasticity was given a scientific basis in the context of physiological development by Nick Hales and David Barker.1 Their classic Diabetologia article on the ‘thrifty phenotype hypothesis’ has since been cited over 1600 times.

The thrifty phenotype paper made a number of novel contributions to the field of chronic disease risk. For clinicians, the most powerful message was the assertion that type 2 diabetes, and by extension other chronic diseases, might be under substantially less genetic control than the orthodox view assumed, and highly sensitive to environmental exposures during the early life-course. Subsequent data from animal experiments and diverse human cohorts has provided compelling support for this hypothesis.2,3

But there was another seminal contribution, more conceptual in nature. If type 2 diabetes were essentially a genetic condition, then population variability in diabetic risk would derive from differential ancestral experience. This was the basis of Neel’s thrifty genotype hypothesis,4 proposing that some populations had undergone severe exposure to cycles of feast and famine, and had been selected to become more efficient at storing fat. Such genetic thriftiness was hypothesized to have been beneficial in environments with high famine risk, but to be detrimental in the modern industrialized niche. The thrifty genotype hypothesis, itself cited 2100 times, rapidly became influential but has received very modest support from genetic analyses. Although genetic variability relevant to metabolism and adiposity exists both within and between populations,5,7 environmental factors are now considered to play a key role in diabetes aetiology, and to be especially important in accounting for group differences in risk.8 Importantly, population genetic variability in metabolism appears to derive from subtle variability in gene frequencies rather than more overt local adaptation.9

The thrifty phenotype hypothesis was, like its genetic cousin, consistent with evolutionary theory. The hypothesis specifically posed that under nutritional stress during early development, some tissues such as the brain would be preserved, at the expense of other tissues such as the pancreas.1 This hierarchical growth strategy would be adaptive in the short term, maintaining a viable organism during a tough period. It would however predispose to poorer tolerance of the full spectrum of ecological conditions in later life. For human populations undergoing rapid industrialization, generating secular increases in dietary fat and sugar intake and secular declines in physical activity level, a key penalty was reduced tolerance of such ‘energy-overload’, manifesting first as inadequate glycaemic control and finally as diabetes. Extensive subsequent research has supported the notion that the ‘diabetes penalty’ of excess weight gain from childhood onwards is greater in those of low birthweight.10,11

The thrifty phenotype is an inherently useful concept: ‘good for thinking’. It fits closely with an evolutionary approach that was consolidating around the same period, known as ‘life history theory’.12 Two of the key principles of life history theory are as follows: first, that energy is a scarce resource, such that investment in one trait inevitably comes at the expense of investment in other traits; second; that the nature of the environment shapes these energy trade-offs, giving rise to a wide variety of developmental strategies across and within species.12 Early work on life-history trade-offs had focused on functions—growth, maintenance, immune function and reproduction.12 The notion of brain-sparing broke new ground by extending the notion of such trade-offs to physiological organs and tissues.

Trade-offs between tissues

In their 1992 paper, Hales and Barker had focused on a brain-pancreas trade-off.1 Subsequent work in rodents found further organs sacrificed to protect the brain,13 and similar research in humans has found that the liver and kidney are likewise more sensitive to nutritional supply in foetal life than the brain.14 Over the past decade, a wider variety of trade-offs
between physiological components has been observed across different species, as summarized in Table 1. These trade-offs may occur within the life-course, as described by the thrifty phenotype hypothesis, or they may occur through genetic adaptation in response to more consistent ecological stresses, and hence pertain to populations or species.

In another classic article, for example, Aiello and Wheeler posited an evolutionary trade-off in our species between brain and gut masses, known as the expensive tissue hypothesis. Although this hypothesis remains controversial in humans, due to a paucity of appropriate evidence, a recent study found that artificially selecting for larger brains in fish improved learning capacity, but reduced gut mass. Other studies have shown that brain mass is traded off against flight muscle mass in birds, whereas in mammals, a negative association between brains and adipose tissue was recently reported. In the latter study, the authors suggested that to address stochastic environments, some species invested in cognitive abilities for finding food, others in the capacity to store energy. Since each trait is costly, species tend to select one or other strategy, although humans are notable high outliers for each trait, which suggests that we evolved under conditions of regular energy stress.

Other tissue trade-offs reflect the competing costs of maintenance vs immune function. In mice, dietary restriction reduces the ability to mount an immune response, but the nature of tissues affected varies according to whether the mice are adapted to a colder environment by having higher metabolic rate. In humans, the impact of cold adaptation varies between the sexes, most likely because males and females differ in the relative importance of fat and lean masses for reproduction. Muscle mass is important for attracting mates in males, whereas fat is critical for meeting the costs of reproduction in females. It has long been known that human populations are heavier in colder environments, in keeping with classic ‘ecological laws’. An ecogeographical analysis suggested, however, that males invest preferentially in lean mass, and females in fat mass, at colder temperatures.

Given its widespread availability in many cohorts, birthweight represents one convenient marker of nutritional conditions in utero that may drive tissue-organ trade-offs. However, birthweight is also problematic in this context, because it is a cumulative index of many individual organs and tissues, because it cannot differentiate genetic from non-genetic influences and because it is a marker of postnatal growth as well as foetal weight gain. An opportunity to confirm the importance of ecological stresses driving trade-offs is therefore to consider the same scenario in postnatal life. Hales, Barker and colleagues themselves observed that thinness at 1 year of age also predicted later diabetes. This suggests that the pancreas remains sensitive to nutritional stress throughout the 1st year of life, whereas brain growth is relatively protected from infant malnutrition.

### Thrift in post-natal life

Infant weight gain therefore represents an independent marker of variable nutrition in early life, but historically, such data were less widely available than birthweight. An alternative approach has considered relative leg length as a retrospective marker of

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**Abbreviations**: GS, genetic selection; ES, ecological across species; EP, ecological across populations; LC, life-course (within individuals).

*This trade-off may also be favoured in the opposite direction, ie reversing the tissues sacrificed versus protected.*
environmental conditions that acted specifically in childhood. Ideally, this marker would (unlike infant weight gain) be relatively independent of foetal nutrition, as demonstrated in several cohorts. In industrialized populations, shorter leg length predicts poorer function in adulthood, for example lower levels of liver enzymes, increased insulin resistance, and greater intima media thickness. These developmental associations may arise because organ growth tracks linear growth during childhood. Recent work in Peru showed that the reduced stature of high-altitude versus low-altitude populations is disproportionately a consequence of reduced lower leg growth, whereas head girth, trunk height and foot length are protected. Thus, the thrifty phenotype hypothesis can be extended to body proportions, with the tibia sacrificed to protect limb components more essential for organ growth and locomotion.

What exactly is a functional trait meriting prioritization in the face of energy stress may vary according to context. Vital organs such as the brain are clearly protected, and lean tissue, comprising a variety of specific organs and tissues, might appear generally more important than fat. In ground squirrels preparing for hibernation, however, experimental exposure to energy stress results in the oxidation of lean tissue and the preservation of fat. This makes sense because fat has a much higher energy content per gram than does lean mass, hence preserving fat at the expense of lean mass will increase energy reserves while simultaneously scaling down energy requirements for the period of minimal energy income.

A similar scenario can be seen in low birthweight Indian neonates, who have substantial deficits in lean tissue relative to UK neonates, but maintain similar levels of subcutaneous fat. Similarly, women with eating disorders demonstrate much greater loss of adipose tissue in peripheral depots than in the visceral depot. Peripheral adipose tissue is associated with reproductive function, whereas other fat depots may be more important for immune function, and hence survival.

Critical periods for thrift

The fundamental importance of the Hales-Barker thrifty phenotype for human health is that early-life trade-offs are not reversible, but rather occur within critical periods of physiological sensitivity to environmental stresses. This sensitivity does not last, and consequently, developmental trade-offs become incorporated into physiological phenotype and track on into adult life. This irreversibility explains why traits that are ecologically sensitive in early life become so important for chronic disease risk in later life, should ecological conditions change through the life-course. Whatever the magnitude of body weight in adult life, the number of nephrons in the kidney, important for blood pressure regulation, is fixed at birth.

Some have argued that developmental trade-offs anticipate future ecological conditions in which breeding will occur, but in a species such as humans, demonstrating plasticity only until late infancy yet requiring a further two decades to reach reproductive maturity, such a hypothesis appears implausible and has negligible supporting evidence. Hales and Barker did not propose any such anticipatory prediction, and their suggestion that early-life survival adaptations may have long-term costs is more in keeping with general ecological models. This approach may also be considered a life-course version of Williams’ gene-based model of antagonistic pleitrophy, which proposed that genes that promote early survival may accelerate ageing in later life.

This debate does however highlight one area where the thrifty phenotype hypothesis still requires further elaboration. The initial assumption that the thrifty phenotype was synonymous with low birthweight and foetal undernutrition has proven over-simplistic. Birthweight indexes a wide range of ecological stresses—indeed, one reason why it predicts future disease risk is that it integrates a variety of different stresses operating on different timescales (although there are also many relevant developmental stresses than are not indexed by birthweight, and birthweight may not always play a causal role in its association with mortality risk). I have recently built on the thrifty phenotype hypothesis by suggesting that chronic disease risk can be modelled as a function of two traits, defined as ‘metabolic capacity’ (traits conferring homeostatic capacity) and ‘metabolic load’ (ecological stresses challenging homeostasis). Such a model treats chronic disease risk as a function of the ratio of load to capacity, each of which can be expressed as a continuous trait. This approach helps understand the positive or negative dose-response increases in metabolic risk that characterize the majority of the ranges of birthweight and adult BMI. However, better markers of metabolic capacity than birthweight are required in order to improve understanding of the association between early environmental exposures and later disease risk.

Both the genetic and environmental factors may contribute to metabolic capacity and load. The concept of the thrifty phenotype has ultimately proven so valuable not because it displaces genetic models of phenotypic variability, but because it can combine with them to provide a more comprehensive model of disease risk. Both genotype and developmental experience reflect ecological exposures, they just vary in terms of the timescale over which those exposures accumulate.

Thrifty phenotypes are undoubtedly adaptive in promoting short-term survival. This becomes clear if we consider what happens to inflexible species, e.g. reptiles and precocial birds, which receive a ‘one-off’ parental investment when the egg is laid, and have minimal further opportunity to ‘manage their income’
until after hatching. Any compensatory physiological adjustments would need to be accommodated later in the life-course, which may reduce early survival as well as exacting more costly metabolic penalties. In this way, human developmental plasticity during foetal life and early infancy is simultaneously a fundamental adaptive process, yet also implicated in long-term chronic disease risk. This was the key insight of Nick Hales’ and David Barker’s paper.

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References
26 Bogin B, Baker J. Low birthweight does not predict the associations between height components (leg and trunk length) and adult levels of liver enzymes. J Epidemiol Community Health 2001;55:867–72.
When David Barker first visited Pune in 1991 and explained the 'low birthweight' story, I was incredulous. Didn’t they teach us that the macrosomic babies of diabetic mothers were at higher risk of diabetes? Foetal undernutrition and diabetes was an unintuitive idea. However, it took only a few minutes to appreciate the embarrassing fact that India, the undisputed capital of low birthweight babies, was marching fast towards becoming the world’s capital of diabetes!

Soon Hales and Barker published the ‘thrifty phenotype’ hypothesis: ‘type 2 diabetes (T2D) is the outcome of the foetus and early infant having to be nutritionally thrifty’.¹

Birth of the ‘thrifty’ hypothesis?
The idea developed out of Barker’s observation that coronary artery disease (CAD) was more common in those with lower birthweight, and the fact that T2D is a major risk factor for CAD. Hales and Barker reasoned that B-cell mass is established in foetal and infant life, and poor nutrition during this crucial period could affect B-cell development and its physiology, and predispose to T2D. The finding in Hertfordshire that lower birthweight and lower weight at 1 year were associated with higher risk of T2D clinched the issue.

Birth weight or something else?
The thrifty idea was based on foetal undernutrition. However, the ease of measurement and the availability in the old datasets of birthweight soon made it a low birthweight story. Weight is only a surrogate of nutrition, it is not specific to nutrition and is more influenced by growth in late pregnancy. Moreover, the macrosomic babies of diabetic mothers would be missing in these old cohorts. A study in Pima Indians soon showed that the birthweight-diabetes association was U shaped; the large weight arm was contributed by macrosomic babies of diabetic mothers.² A systematic review showed that the

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Commentary: Thrifty phenotype: 20 years later

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