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Commentary: Thrifty phenotype: 20 years later

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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

association could be inverse, direct or U shaped,[3] and this suggested something more was involved. This was explained in the concept of 'programming' which refers to persistent alterations in the structure and function of a developing organism, in response to environmental influences.[4] This could influence disease susceptibility independently of birthweight.

Body composition and metabolic-endocrine phenotype

Indian research gave an interesting twist to the 'thrifty' story. Unlike in the Europeans, a study in Mysore showed that diabetes was related to 'larger' ponderal index.[5] A comparison of Indian babies born in the Pune Maternal Nutrition Study with English babies showed that Pune babies were 800 g lighter and considerably thinner, but had very similar skinfold thicknesses. Body composition studies showed that the Indian babies have smaller lean mass and higher abdominal adiposity,[6] thus qualifying for the description 'thin-fat babies'.[7] Indian babies also have higher insulin and leptin but lower adiponectin concentrations in their cord blood,[8] suggesting higher risk for T2D. This is reminiscent of babies born to obese and diabetic mothers who have an adipose body composition and similar endocrine profile.[9] Thus, the concept of 'thrifty phenotype' extended to unfavourable body composition and metabolic-endocrine profile. A foetus challenged *in utero* preserves its brain growth at the cost of less important 'caudal' structures. Increased risk of T2D in people with short legs[10] and in those with a larger ridge count difference between the first and fifth fingers (dermatoglyphic) are other examples of importance of disturbances in foetal growth.[11]

B-cell dysfunction and thrifty phenotype: genes or environment?

Insulin is essential for foetal growth, and reduced insulin action causes T2D. Hales and Barker argued for a defective foetal pancreatic B-cell development due to maternal amino acid deficiency. They suggested to the geneticists living the 'nightmare of diabetes' that they should concentrate on genes involved in foetal growth and development! The 'foetal insulin hypothesis' proposed that genetic rather than environmental factors explained the birthweight-diabetes association. Although a few genes influencing B-cell function, insulin action, birthweight and risk of T2D have been described, concentration on birthweight has limited this research. Increased risk of T2D in the smaller of monozygotic twins suggests that foetal nutrition is more important than genetic makeup.

Insulin deficiency vs insulin resistance

Estimating B-cell mass is in its infancy in humans; therefore, circulating insulin levels are used as a surrogate. The majority of human studies have shown 'hyperinsulinaemia' rather than insulinopenia in those born small.[12] This is interpreted as indicating 'insulin resistance', and the updated thrifty hypothesis[13] acknowledged that this appears to be a more consistent association of small size at birth. It is interesting that the controversy about disturbances in insulin physiology preceding the diabetic state is still debated.[14] Animal models, however, consistently show abnormalities in the pancreatic B-cells in the offspring of food-deprived mothers.[15]

Mechanisms of programming

The mechanisms of programming are only now being understood. Substrate availability will influence the structure, composition and number of the cells. It is not clear how the memory of intrauterine experiences is carried through life. The currently favoured mechanism is 'epigenetics'. The commonest mechanism appears to be methylation of DNA. A number of animal models and some human studies are suggestive.[16] Components of maternal diet and metabolism which influence the risk of diabetes in the baby are not exactly known. Norbert Freinkel suggested a role for macronutrients (glucose, fatty acids and amino acids), and Indian studies have suggested a possible role for imbalance in dietary micronutrients i.e. vitamin B_{12} and folate.[17] A trial of micronutrient-rich food supplements from before pregnancy has recently been completed in Mumbai, and a vitamin B_{12} trial has been recently started in Pune. The results are awaited.

Twenty years since its original publication, research has expanded the understanding of the 'thrifty phenotype' hypothesis towards understanding its mechanisms and implications for human health. It represents a paradigm shift in the strategies for diabetes prevention, offering primary (primordial) prevention when current practices concentrate on secondary and tertiary interventions without any benefit for the future generations.

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Commentary: The meaning of thrift

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According to the Oxford dictionary, 'thrifty' means many things: 'wisely economical, industrious, thriving, prosperous'. The term 'thrifty phenotype'[1] was used as a contrast to the 'thrifty genotype'.[2] The thrifty genotype hypothesis for type 2 diabetes proposed that diabetogenic genes persist at high levels in populations because they somehow confer a survival advantage in times of nutritional deprivation. There is little evidence to support such a speculation and the genes have not been found. The speculation rested on the stereotypic model of type 2 diabetes as a disease of high intakes of energy-dense food, physical inactivity and obesity. Across India, however, recently described as 'the world capital of diabetes', the disease occurs in vegetarians who are physically active and not obese.[3] A deeper scientific inquiry is now needed to stem the rising epidemic of a disorder which affects 366 million people around the world and will soon affect 552 million people.[4]

The thrifty phenotype hypothesis built on the work of the late Nick Hales who advocated that type 2 diabetes originates in deficient insulin secretion.[1] He pioneered the study of insulin precursors, importantly 32–33 split proinsulin. He pointed out that people with type 2 diabetes have a reduced early insulin response to oral glucose, indicating insulin deficiency.