Editorial

The thrifty genotype hypothesis: concepts and evidence after 30 years

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There is no doubt that the thrifty genotype hypothesis is alive and well more than 30 years after Neel gave birth to the concept in 1962.[1] Indeed, it seems to be flourishing. It is used by diabetologists, epidemiologists, anthropologists, metabolic and obesity researchers, human biologists and geneticists to explain variations in diabetes prevalence, adiposity, body shape and muscularity among populations.

The mechanisms originally proposed to account for the genetic influence on the metabolic origins of obesity and diabetes have since been largely unsubstantiated, but this is hardly surprising because they were postulated at time when very little was known about the variety of metabolic effects of insulin and the pathogenesis of obesity and type II diabetes. Even with our increased knowledge, we are still a long way from an agreed description of the thrifty genotype hypothesis at the mechanistic level and even further away from clearly demonstrated metabolic differences between populations with high and low rates of diabetes and obesity.

The essence of the hypothesis remains intuitively valid and little disputed. This is that type II diabetes is:

a) common,
b) detrimental to health (and survival), and
c) is significantly genetically determined.

Thus, Neel argued, the diabetes genotype which is now detrimental to survival must have originally been advantageous for survival to have such a high frequency within a population.[1] Beyond these broad concepts, the opinions begin to differ. What is the genotype in question: one which predisposes to insulin resistance, reduced or increased insulin secretion, low metabolic rate, large appetite, greater fat storage capacity? What are the mechanisms? How much of type II diabetes does it explain? It was to address these questions that the Thrifty Genotype Symposium was organised by the New Zealand division of the Australasian Clinical Nutrition Society in December 1994. The symposium covered a wide range of specialty interests and it was this diversity of view points that was one of the main strengths of the papers presented and the debate of the issues.

An overview of the topic by O'Dea examines the original hypotheses proposed by Neel in light of the emerging knowledge and speculation about the dietary patterns in prehistorical times and the aspects of the western lifestyle which may be responsible for turning the genotype from an benefit to a detriment. She also explored potential metabolic mechanisms and introduced the "thrifty phenotype" concept of Barker and Hales.[2] McGarvey drew on his and others' research among Samoans as they become increasingly modernised and presented data on the increasing prevalence of obesity in the populations of Western and American Samoa.

An overview of the unique and remarkable prehistory of Polynesia is presented by Brewis *et al* as they examine the evolutionary and selective forces during their colonisation of the Pacific. They argue that the selective forces were subdued and that the origins of the genotype predisposing to diabetes and obesity were more ancient than the Polynesian migration period. A fascinating aspect of Polynesian phenotype which may be linked to diabetes is examined by Houghton. He notes that the heavily muscular physique of the Polynesians is unusual for a population living in the tropics where slighter, more linear physiques are generally the rule. His argument is that the maritime environment of Polynesia is a cold one and that this would select for a physique of high muscle mass (to maximise heat generation) in a round, stocky body habitus (to minimise heat loss). He supports this hypothesis with detailed computer models of simulated canoe voyages under a variety of weather conditions. Pollock adds a social dimension with the concept that obesity in Polynesian cultures was a positive attribute which was actively encouraged by the community. Two examples of this "cultural elaboration" are provided.

The more metabolic aspects of the thrifty genotype hypothesis are described by the final three papers. Swinburn provides strong evidence against insulin resistance (and hyperinsulinaemia) being the metabolic expression of a genotype predisposed to obesity. Insulin

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resistance, in fact, appears to attenuate weight gain. Evidence is also lacking, implicating an important role for a low metabolic rate as a cause of obesity. Swinburn also points out that, as with the predisposition to obesity, the predisposition to insulin resistance would have held significant survival advantages in the past but these would now be overshadowed by the detrimental effects in promoting the development of diabetes. Simmons provides an overview of the epidemiology of diabetes in different ethnic groups and some of the metabolic differences in insulinaemia from early life. He also explores in more depth the three current hypotheses for producing a predisposition to diabetes: the thrifty genotype, the thrifty phenotype, and the fuel-mediated teratogenesis hypotheses. He concludes that all three mechanisms could be operating in a population, although the increasing numbers of pregnant women with obesity and/or diabetes means that the fuel-mediated teratogenesis mechanism has the potential to add a significant multiplier effect. Maling *et al* examine in considerable detail some of the metabolic differences between Maori and Caucasians to help explain the higher rates of diabetes, hypertension and gout among the Maori. They have found that Maori have greater central obesity, higher fasting and stimulated insulin levels, higher erythrocyte sodium and serum urate concentrations, and lower urate clearance.

Finally, one important point about the whole discussion of the thrifty genotype hypotheses was emphasised by many of the participants. This was that the concept was very "Eurocentric" and that the true nature of the population differences could probably be defined as the "non-thrifty genotype of Europeans". Of all the ethnic groups in the world living under western conditions of an ample food supply and a sedentary lifestyle, the Europeans are clearly the "odd" population with unusually low rates of type II diabetes. Perhaps the research should focus more on trying to explain the environmental conditions which selected against the diabetes genotype among Europeans and what is about their metabolism that makes the Europeans such an unusual ethnic group.

References

1. Neel JV. Diabetes mellitus: A "thrifty" genotype rendered detrimental by "progress"? Am J Human Genetics 1962; 14:353-362

2. Hales CN, Barker DJP. Type 2 (non-insulin dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia 1992; 35:595-601.