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For debates

Hypothesis: muscle insulin resistance is the ("not-so") thrifty genotype

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Approximately 45 years ago [1] James Neel addressed the question of how diabetes mellitus, an apparently genetic disease with such an adverse effect on survival and reproduction, could have become so common. In that process he raised a question that has become increasingly important as the prevalence of non-insulin-dependent diabetes (NIDDM) has reached epidemic proportions [2]. Specifically Neel asked "If the considerable frequency of the disease is of relatively long duration in the history of our species, how can this be accounted for in the face of the obvious and strong genetic condition against it?" Neel went on to consider possible explanations and suggested "that the diabetic genotype is, to employ a somewhat colloquial but expressive term, a "thrifty" genotype, in the sense of being exceptionally efficient in the intake or utilization of food" [1]. Although Neel's view as to how this "thrifty" gene led to diabetes was modified over the next several years [1, 2], a constant part of his argument was "that the basic difference between those who developed diabetes and those who did not was a 'quick insulin trigger' in response to hyperglycaemia". The survival benefit of this phenotype was to minimize urinary glucose loss when fasting was replaced by feasting, leading to the more efficient utilization of food and storage of energy. The frequent association of obesity and NIDDM has been considered by many to serve as evidence for the validity of the "thrifty" gene as outlined by Neel; a "quick insulin trigger" that helped primitive man survive famine by storing energy more efficiently, now leads to obesity, and eventually NIDDM.

During the same period of time that Neel was speculating upon the survival benefits of a "quick insulin trigger", Cahill and associates published a series of fundamental experiments that led to a quite different view of how primitive man survived famine [4–7]. The results of these elegant clinical studies led Cahill and associates to postulate that the crucial element necessary to withstand famine was the ability to conserve as much muscle protein as possible. By so doing, the individual was able to hunt successfully at the first opportunity, as well as protect himself when preyed upon. The dilemma primitive man faced in accomplishing this task was how to maintain muscle mass during periods when muscle protein was the major source of glucose for the central nervous system. Obviously, the less muscle protein broken down during food deprivation, the greater the likelihood of survival. In this context, adipose tissue plays a crucial role. It contains by far the greatest amount of stored energy [5]; the non-esterfied fatty acids that are released serve as an ideal energy source for cardiac and skeletal muscle, and their conversion to ketone bodies provides an alternative source of fuel for the nervous system [6].

The difference between these two hypotheses as to how primitive man survived famine is substantial. Neel believed the essential attribute to be a "quick insulin trigger" leading to more efficient accumulation of energy, thus permitting primitive man to survive a fast longer. The alternative view, based upon the work of Cahill and colleagues, states that the more efficient one is in conserving muscle protein, the better the chances of survival. One theory focuses on energy storage, the other on maintaining muscle mass. In the remainder of this presentation an argument will be made that the phenotype Neel was searching for was muscle insulin resistance, not "a quick insulin trigger".

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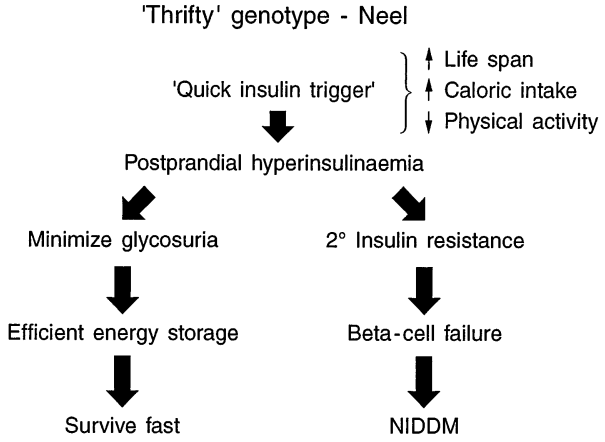

Fig. 1. The advantages of a "quick insulin trigger" to primitive man as suggested by Neel is seen on the left. The disadvantages of this phenotypes to modern man, and how it leads to NIDDM, is depicted on the right

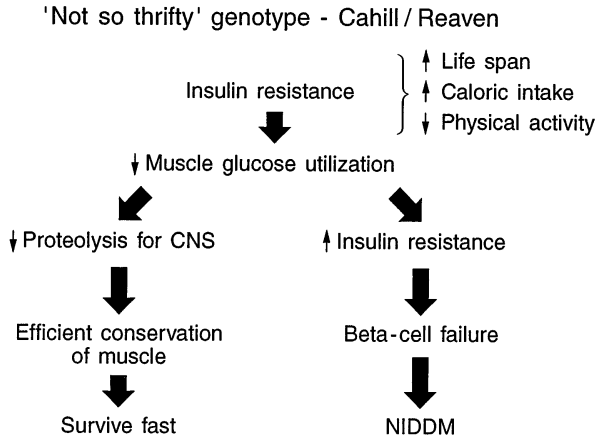

Fig. 2. An alternative view, based on the experimental studies by Cahill and colleagues. The survival advantages of muscle insulin resistance to primitive man is illustrated on the left. The sequence on the right outlines how such an "advantage" can lead to NIDDM in modern man

The "thrifty" versus the "not-so-thrifty" genotype

The left side of Figure 1 displays the "thrifty gene" helping primitive man survive famine as described by Neel. When feasting, the "quick insulin trigger", and ensuing hyperinsulinaemia, decreases urinary loss of glucose, and leads to enhanced energy storage. The consequences of a "quick insulin trigger" for modern man, faced with a longer life-span, obesity, and decreased physical activity, are outlined in the right portion of Figure 1. As formulated by Neel, the hyperinsulinaemia associated with the "quick insulin trigger" in modern man leads to a state of *acquired* insulin resistance, followed by beta-cell failure, and NIDDM.

Figure 2 displays a similar analysis of the impact of primary muscle insulin resistance, the "not-so-thrifty gene", on glucose metabolism in primitive and modern man. As seen on the left, muscle insulin resistance conserves glucose for utilization by the central nervous system, decreasing the amount of muscle protein needed to be converted to glucose. As a result, muscle mass is preserved, thereby increasing the likelihood of a successful search for food. The muscle insulin resistance that permitted primitive man to survive is accentuated by the increased longevity, sedentary lifestyle, and obesity of modern man as depicted on the right. At some point the combined burden of muscle insulin resistance and lifestyle can no longer be overcome by compensatory hyperinsulinaemia, and NIDDM occurs.

Does the "thrifty" genotype predict the NIDDM phenotype?

In order for the "thrifty" genotype to be useful to primitive man, there had to be not only a "quick insulin trigger", but also insulin sensitive tissues to efficiently store ingested food. Given these two essential features of the "thrifty" phenotype, is there evidence that they account for the current epidemic of NIDDM? I believe the answer to this rhetorical question to be no.

If we begin with normal glucose tolerant individuals, there is evidence [8] that the more insulin *resistant* such individuals are, and the *lower* their early insulin response to glucose, the higher will be their plasma glucose response to oral glucose. Similarly, cross-sectional studies of non-diabetic, first degree relatives of patients with NIDDM indicate that they are insulin resistant, with no evidence of a "quick insulin trigger" [9]. Turning now to prospective studies of true pre-diabetic subjects, the evidence indicates that insulin resistance, not insulin sensitivity, significantly predicts conversion to NIDDM, accompanied by either a normal or reduced acute insulin response [10–13]. Finally, studies of the progression of patients with impaired glucose tolerance (IGT) to NIDDM have also identified insulin resistance and a low insulin response as the predictors of this conversion [10, 14]. Based upon the results of the above studies and the absence of contradictory data, the evidence in normal glucose tolerant individuals, non-diabetic first degree relatives of patients with NIDDM, pre-diabetic subjects, and patients with IGT demonstrates that neither a "quick insulin trigger" nor insulin sensitive tissues predict progression to NIDDM.

Genetic evidence of the "not-so-thrifty" genotype

Given evidence that muscle insulin resistance could have provided primitive man with a useful survival advantage, and that this phenotype predicts an inabil-

ity to maintain normal glucose homeostasis in modern man, it seems relevant to ask if there is any evidence that insulin-mediated glucose disposal is genetically related. Although this issue cannot be definitely settled at this time, the available data suggest that the answer is affirmative. At the simplest level, there is evidence [15] from cross-sectional studies in healthy volunteers of European ancestry and Pima Indians that only 50 % of the variance in insulin-mediated glucose disposal from person to person could be accounted for by known acquired variables like obesity, level of physical activity, age, etc. By inference it was suggested that genetic factors accounted for the remaining 50 % of the observed variability. More specifically, direct measures of insulin-mediated glucose disposal in family members demonstrated that in vivo insulin action was a familial characteristic in non-diabetic Pima Indians [16]. Essentially identical data have also been found in a somewhat similar study in family members of European ancestry [17]. Obviously, one cannot be sure that a familial characteristic is genetically determined, but available evidence strongly supports the view that muscle insulin resistance is, at least to some extent, a genetically determined characteristic.

Conclusion and hypothesis testing

Thirty years ago Cahill proposed [5] that survival of primitive man "required the capacity to withstand prolonged periods of deprivation and yet the sparing of as much body protein as possible in order to be able to hunt successfully at the first available opportunity, or, on the other hand, to escape if preyed upon. Another unique problem was the presence of a nervous system which was relatively hypertrophied compared to other animals and which required a constant supply of substrate throughout the period of deprivation." Results of a series of studies from the Cahill research group [4–7] showed that the ability to conserve muscle protein, and rely on adipose tissue fat depots for energy, was the way to solve both problems. In the same publication [5] he addressed the question as to whether "mild diabetes or a predisposition to diabetes does provide some survival advantage". His answer to this rhetorical question was the "if tissues are better able to exclude glucose, ... body protein should be spared. Preliminary studies have suggested that this may be true."

I believe it is muscle insulin resistance, not a "quick insulin trigger", that both favoured the survival of primitive man, as well as accounting for the current epidemic of NIDDM. This conclusion is consistent with available data, and the hypothesis is testable. Insulin-mediated glucose disposal varies approximately tenfold in normal volunteers [8], and this is true of obese and non-obese individuals. If insulin resistance permits human beings to conserve muscle mass when food is not available, the ability of individuals to limit their degree of proteolysis should vary directly with their degree of muscle insulin resistance. Thus, it is possible to measure insulin-mediated glucose disposal in obese individuals, separate them into insulin sensitive and insulin resistant groups, withdraw food, and quantify proteolytic rates. It is postulated that the more insulin resistant an individual, the more efficient will be their ability to decrease proteolysis when faced with caloric deprivation. We are currently planning such experiments, and hope to publish the definitive answer to the phenotypic characteristics of the genotype that once permitted survival and has become so dangerous to modern man.

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