Dear Sir,
We thank Smulders et al. for their comments. In our study the albumin excretion rate was more important than serum creatinine in determining plasma homocysteine concentrations [1]. However, this could vary in different diabetic groups depending on the proportion of patients with nephropathy and the distribution of its different stages. The actual existence of a link between albumin excretion rate and plasma homocysteine has been greatly reinforced, and extended, by the contemporaneous publication of three reports [2–4] with similar results to that of ours [1]. Especially relevant is one [3] reporting the study of a random sample (n =680) of Caucasians aged between 50 to 75 years in which a consistent link between microalbuminuria and plasma homocysteine concentrations was found in people with isolated microalbuminuria, in patients with hypertension and, especially, in patients with diabetes mellitus. Both Smulders et al., as well as the authors of the abovementioned study [3], favour the possibility that hyperhomocysteinaemia causes microalbuminurie rather than the other way around as suggested by us. In our study [1], introducing the albumin excretion rate as the dependent variable, and age, time of evolution of the diabetes, plasma glucose concentration, HBA_{1C} and homocysteine as independent variables in the multivariate analysis results in a significant ($p < 0.01$) β of 0.34 for homocysteine. Therefore, statistical relations exist in both directions and it is not possible, with this analysis, to establish a definitive cause-effect relation between them. Although our data cannot exclude hyperhomocysteinaemia causing microalbuminuria through dysfunction of the vascular endothelium, there is biological evidence inconsistent with this idea. We know of no report suggesting that severe hyperhomocysteinaemia (such as that of classical homocystinuria and folate or vitamin B12 deficiency), which is characterized by plasma homocysteine concentration two- to tenfold that of control subjects, causes microalbuminuria or any other kind of nephropathy [5]. A synergistic relation between diabetes mellitus (and, perhaps, other pathological conditions such hypertension, insulin resistance, etc.) and hyperhomocysteinaemia so as to cause vascular damage could, however, exist [2]. In our opinion, the increase of homocysteine caused by the diabetic nephropathy could promote, rather than provoke, the progression of the nephropathy similarly to what has been described for diabetic hyperlipidaemia. More studies – including prospective ones – are needed to confirm and extend the associations reported and to clearly establish cause vs effect, especially considering that hyperhomocysteinaemia in particular could increase the risk of cardiovascular disease in Type II diabetic patients [6].

Yours sincerely,
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Scant evidence of periodic starvation among hunter-gatherers

Dear Sir,
In the April issue of Diabetologia Reaven [1] proffered an alternative hypothesis to Neel's thrifty genotype hypothesis [2]. His proposal, called the 'not-so-thrifty' genotype hypothesis, argues that the gene was not one which conferred exceptionally efficient storage of food energy but instead conserved muscle protein during periods of starvation by reducing gluconeogenesis from amino acids. In our opinion the basis of both hypotheses – periods of food scarcity in pre-agricultural populations – is not supported by the scientific literature.

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Implicit in both Neel's and Reaven's hypotheses is the assumption that pre-agricultural people must have gone through regular, periodic episodes of starvation that had a negative impact on reproductive potential and hence resulted in the selection of a gene or genes which would have survival value during the fluctuations between 'feast and famine'. This concept is frequently invoked to explain the high incidence of diseases of insulin resistance [Type II (non-insulin-dependent) diabetes mellitus, hypertension, obesity and coronary artery disease] among recently acculturated populations.

Although Neel's hypothesis has become 'one of the orienting concepts of nutritional and biomedical anthropology', it is founded upon an assumption which cannot be corroborated by the available ethnographic data derived from living hunter gatherer populations nor by the fossil record. Indeed, periodic starvation became more frequent and nutritional status declined when hunter gatherer populations made the transition to agriculture less than 10 000 years ago [3, 4]. Starvation among early agriculturists was quite common because of the

dependence upon a few staple cereal crops. If one staple food crop failed, farmers ran a greater risk of starvation than did hunter gatherers who could use a much broader range of wild plant and animal foods. Modern studies of hunter gatherers show that there is a seasonal fluctuation in body weight, but these studies do not indicate evidence of periodic starvation or chronic malnutrition [5, 6]. In a review of 51 references examining human populations from around the earth and from differing chronologies, Cohen [7] concluded that there was an overall decline in both the quality and quantity of life during the transition from hunting and gathering to farming.

Generally, in most parts of the world, whenever cereal based diets were first adopted as a staple food, replacing the rich variety of wild animal and plant based foods of hunter gatherers, there was a characteristic reduction in stature [3], an increase in infant mortality [3, 4], a reduction in life span [3, 4, 7], an increased incidence of infectious diseases [3, 4, 7, 8], an increase in iron deficiency anaemia [3, 4, 7, 8], an increased incidence of osteomalacia, porotic hyperostosis and other bone mineral disorders [3, 4, 7, 8] and an increase in the number of dental caries and enamel defects [3, 4, 7]. Clearly, early farming brought on not a reduced mortality from starvation and nutritionally related diseases, but to the contrary, an increase [3, 7]. If either Neel's and Reaven's hypothesis is correct, then the advent of agriculture would not have reduced the selection for a thrifty genotype, but would have actually increased it. Obviously, population and epidemiological studies of Type II diabetes suggest that this is not the case. Europeans have had a relatively long exposure (5000–7500 years) to agriculture, including regular periods of severe famine right up to historical times, yet they have the lowest prevalence of Type II diabetes on a world wide basis [9]. Therefore, the assumption that starvation was the single and only factor selecting for a putative 'thrifty' or 'not-so-thrifty' genotype could not be correct.

Brand, Miller and Colagiuri [10] have suggested that the high protein intake and low carbohydrate intake of pre-agricultural diets would have represented a more likely environmental pressure responsible for selecting for multiple genes originally hypothesized by Neel to be 'thrifty genes'. Their hypothesis, 'the carnivore connection', proposes that an insulin-resistant genotype evolved to provide survival and reproductive advantages to populations adapted to a high meat, low plant food (low carbohydrate) nutritional environment. Unlike true carnivores, humans have a limited capacity for gluconeogenesis even on a high protein diet [11]. Insulin resistance would have conveyed a selective advantage for populations consuming high protein and low carbohydrate diets long-term because it would have maximized gluconeogenesis and thereby redirected glucose away from muscles, facilitating the preferential use of glucose by the brain, fetus and mammary gland [10]. It is likely that Neel's concept of 'thrifty' and Reaven's concept of 'no-so-thrifty' are a misinterpretation of the true function of the gene(s) which produce insulin resistance.

Yours sincerely,
L. Cordain, J. Miller, N. Mann

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Insulin resistance, the key to survival: a rose by any other name

Dear Sir,
My purpose in suggesting that muscle insulin resistance was once of evolutionary use to our species and is now responsible for the world-wide epidemic of Type II (non-insulin-dependent) diabetes mellitus [1], was quite simple. I believe the initial suggestion by Neel [2] that the basic abnormality that now increases risk of Type II diabetes must at one time have had survival value for primitive man. In his initial presentation, Neel suggested that a "quick insulin trigger" was the relevant physiological event. I believe this view to be physiologically incorrect and that muscle insulin resistance was the abnormality – not a primary increase in insulin secretion – and was at one time useful but now greatly increases the risk of Type II diabetes. It is obvious from the letter by Drs. Cordain, Brand-Miller and Mann that they are in fundamental agreement with the survival value of insulin resistance. Specifically, they state ". . . humans have a limited capacity for gluconeogenesis even on a high protein diet. Insulin resistance would have conveyed a selective advantage for populations consuming high

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