and these subjects also reported a progressive reduction in quality of life. These authors therefore concluded that initiation of insulin therapy in Type 2 diabetes should be associated with sustained education, monitoring and support for which the UKPDS intensive policy could be used as a model [5, 8].

More knowledge about the associations between insulin therapy and quality of life in people with Type 2 diabetes is of crucial importance. Therefore, we fully agree with Koopmanschap's initiative to study this topic in a large European sample using a validated measure of HRQoL. However, we regret that the author used only one overall score for HRQoL. This overall-score for HRQoL is calculated from five health status dimensions. These five dimensions are related, but for example, an extreme limitation in mobility does not necessarily mean that one also experiences extreme limitations in pain and discomfort. In our opinion, it would be most interesting to publish the associations between insulin therapy and all five dimensions. In the large sample of the CODE-2 study, this should preferably be done separately for each of the five countries, in order to study whether the associations are consistent across countries.

We believe that there is evidence from prospective studies to suggest that a substantial number of patients with Type 2 diabetes could use insulin therapy to achieve good or acceptable glycaemic control, without influencing their HRQoL. This should be accompanied by continuous support from the diabetes team. The recent results of the CODE-2 study regarding the impact of Type 2 diabetes on HRQoL are limited, due to the cross-sectional design of the study and the use of only one overall measure of health-related quality of life. We therefore consider the advice to avoid insulin therapy, in order to improve the patients' HRQoL, as premature and not based on convincing evidence.

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

To the Editor: One of the key concepts underlying discussions of the pathogenesis of Type 2 diabetes is that of the 'thrifty' organism, whether speaking of its genes [1] or its phenotypes [2]. But what's the evidence for thrift?

To block one diversion, we are considering 'usual' Type 2 diabetes in which patients are obese or over-weight at diagnosis or at least, if diagnosed very late, have been so previously. No one knows whether any group of 100 diabetic patients consists of ten groups of ten patients, with a different pathogenesis for each group; or whether 90 patients have the same pathogenesis, while the other ten each have a different pathogenesis from one another. The Type 2 diabetic patients with normal weight could be particularly well represented among these latter ten, who perhaps have ten different genetic modifications. Subjective impression favours the latter type of distribution, but it could be the result of many different abnormalities in a single biochemical or physiological pathways.

Neel's postulate [1] was an attempt to describe the nature of a constitution beneficial in 'lean' years but disadvantageous in 'fat' ones, and to explain its evolutionary origin and possible current disadvantage. However, there is no sustained evidence of alterations in metabolic rate certain enough to fulfil a 'thrifty' hypothesis [3], among either of those with Type 2 diabetes, those at very high risk of developing it in the future or even among obese non-diabetic subjects. But perhaps the search hasn't been made under the necessary circumstances to evoke the necessary difference.

A different explanation of the basic postulated ability to maintain weight in the face of famine would be success in obtaining resources when they're scarce. Many characteristics could underlie this but, given the importance of 'motivation' or 'drive', increased hunger could be an important component. Increasing knowledge of the multiple and complex pathways involved in hunger, satiety and reward offers ample sites for important alterations in levels of hunger. Such factors, or the

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capacity for some other mode of success in grasping scarce food, would seem as likely to be subject to both or either of genetic variation and of retuning by early deprivation as blood glucose concentrations or blood pressure levels.

The adaptations postulated to be important in recent ideas on the fetal origins of adult disease [4] fit the organism for safer levels (e.g., less hypoglycaemia) of the regulated factors while the environment remains disadvantageous, but can have deleterious effects in the long-term if the environmental conditions 'improve'. However, a mechanism that makes the best out of a poor start could well be advantageous via sexual selection if conditions should brighten up. Increased hunger could be such, as plausibly as higher glucose concentrations or blood pressure levels.

However life is always multi-factorial, and fetal or neo-natal resetting of the controlled (or balanced) levels for any of these factors doesn't exclude the re-setting of others. Indeed, depending on the organism's exact state at each of perhaps several different critical periods, the contributions of altered insulin supply, insulin sensitivity and of hunger could vary between different patients, indeed as do the different contributions from reduced HOMA-B and increased HOMA-R associated with the onset of diabetes in different patients [5].

Increased hunger at a given level of net calorie exchange will increase food intake, assuming it is reasonably available. Such increased intake, or that from some other mode of more successful hunting and gathering, will increase insulin resistance not only through the consequent obesity, but also day to day, in that substrate intake is an inevitable, immediate cause of apparent (often non-fasting) insulin resistance. The overnight fasting state can also change rapidly, for instance, with reduced glycaemia and insulin resistance long before commensurate change in body fat [6, 7].

Do present or future 'main-stream' Type 2 diabetic patients have increased hunger? There are anecdotes of increased craving for glucose among diabetic patients in the run-up to diagnosis, but these perhaps refer only to a relatively late stage and could include relatively slow-onset Type 1 diabetic patients. It seems that a battery of tests of 'hypothalamic' function must be developed based on the principle of measuring activity in the face of an infinite supply, whether or not with the provocation of initial deprivation; otherwise one's left groping to standardise patient's subjective responses on scales from 1 to 10, for it is not difficult to imagine that if a sensation such as hunger is 'turned up', then the subjective experience of a given deprivation may be reported as similar (i.e., going from three to seven, and down to one on refeeding) to that in the 'usual' subject, it's just all happening at a more intense level, suggested here to be more effective in motivating substrate capture. Any quibbles that it is reduced activity that underlies the observed obesity, described by Meyer and more fully summarised later [8], prompt the comments that (i) such behaviour could also be both subject to genetic influence and/or 'programmable' in response to fetal experience, and (ii) if calorie expenditure drops, why doesn't calorie intake *pari passu*?

The term 'thrifty' should be dropped for both genotype and phenotype, for depending on just how one defines it, it is either tautologous or possibly wrong (and it's just as reasonable to consider 'greedy', 'hungry', or 'rapacious'). Considering only the 'output' side of the equation may force the creation of unwarranted hypotheses [9].

Not surprisingly for biology, what is under consideration is (i) an organism adapting to be 'effective' in a given environment, which it 'anticipates' living in because of certain early signals; and whether or not the 'effectiveness' is a consequence of an up-regulation of a metabolic pathway, hunger sensations, hunting skills or whatever, and (ii) what happens when that environment changes from what is 'anticipated', which is one time when the struggle accelerates.

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