sence of hyperglycaemia during pregnancy in M + women and the presence of gestational diabetes in M– women. This suggestion is against all the available evidence. After correction for fetal mutation status the birth weight was more than 500 g higher when the mother had the mutation than when she did not. We feel this can only be explained by a difference in the degree of maternal glycaemia. We have not obtained measurements of glycaemia during pregnancy for all cases but to suggest the M + women were hyperglycaemic is a logical and easily supported extrapolation. Hyperglycaemia of MODY2 starts in infancy; all but 2 out of 50 pre-puberal M + children of our cohort have diabetes, impaired glucose tolerance (IGT) or a fasting plasma glucose (FPG) of 6.1 mmol/l or more, i.e. greater than 3 S.D. above the normal average for their class of age. Moreover, all M + mothers included in our study had documented diabetes before or after pregnancy or both, IGT or a FPG of 6.1 mmol/l or more. Finally, hyperglycaemia is seen in all pregnant M + women that have been measured [7], and these results are confirmed in studies of glucokinase knockout mice showing severe hyperglycaemia during pregnancy (FPG > 10 mmol/l) in heterozygous animals [3]. The suggestion that the M– mothers had gestational diabetes (which affects less than 3 % of the French Caucasian population) is not supported. This diagnosis was not found in their medical records obtained from their personal physicians and before inclusion in the study these women had a strictly normal OGTT. A significant amount of undetected gestational diabetes does not seem very likely.

In summary, there is clear evidence to contradict the suggestions of Harder and Plagemann that our failure to show a long-term effect of altered levels of fetal insulinaemia is due to methodological errors or incorrect assumptions. Whether our findings in our monogenic human model can be extrapolated to the more common polygenic forms of Type II (non-insulin-dependent) diabetes mellitus is an interesting question to which we think there is no clear answer. The predisposition of offspring of diabetic pregnancy to Type II diabetes seen in some populations [8] might be related to the effects of the diabetic environment in utero, to the sharing between mother and offspring of a polygenic diabetic or obesity background or to an interaction between both. Our results in a highly selected and lean cohort with little or no peripheral insulin resistance and a clearly monogenic cause of hyperglycaemia do not support the hypothesis of a direct effect of a maternal hyperglycaemic environment in itself. The late effects of an interaction between the diabetic maternal environment and a polygenic diabetic or obesity background in the offspring cannot be dealt with in our study. Thus, our results are not necessarily at odds with those observed, for instance, in Pima Indians [8], another highly selected population, which is believed to have the strongest polygenic background to both affections.

We completely agree with Harder and Plagemann that large studies on long term effects of maternal hyperglycaemia on the offspring are needed. It should, however, be recognised that the aetiology of the maternal glycaemia and the fetal genetic predisposition are likely to play a critical part in the outcome of such studies. The possibility to study defined discrete genetic subgroups such as our glucokinase patients adds a new dimension to these investigations.

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Comments to: Yudkin J, Panahloo A, Stenhouwer C et al. (2000) The influence of improved glycaemic control with insulin and sulphonylureas on acute phase and endothelial markets in Type II diabetic subjects. Diabetologia 43: 1099–1106

To the Editor: We read with interest the recent article by Yudkin et al. on the effects of improved glycaemic control with insulin and sulphonylureas (glibenclamide) on acute phase and endothelial markers in Type II (non-insulin-dependent) diabetes mellitus [1]. The lack of significant changes in these markers despite improved insulin sensitivity was intriguing for the authors and for ourselves. Perhaps the use of metformin or thiazolidinediones to test whether these drugs might affect insulin action and acute phase markers concomitantly would have been more informative. Interestingly, the use of another sulphonylurea (gliclazide) has been associated both with increased insulin sensitivity [2], decreased cytokine production [3] and with improved endothelial function [4]. In the study by Yudkin et al. fasting insulin was significantly higher after sulphonylurea or after insulin treatment, indicating, at first glance, a worsening of endogenous insulin action. The authors found, however, that the metabolic clearance of glucose, evaluated using exogenous insulin at pharmacological doses, improved after both treatments. It would be interesting to ob-

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serve the effects of both lowered glucose and insulin concentrations on those same markers.

On the other hand, endothelial function is highly variable between subjects and in the same subject over time. As reported by the authors in their references, acute hyperglycaemia attenuates endothelium-dependent vasodilation [5]. It is not known whether the usual oscillations of glucose concentration, as observed with premixed human soluble and isophane 30:70 once or twice daily, provoke changes in endothelial function or endothelial markers that might have masked the authors' findings. The use of continuous insulin infusion with stable glucose concentrations would have contributed to overcoming these difficulties.

The authors have uncovered interesting aspects about the pathophysiology of inflammatory markers in Type II diabetes. Some field conditions with an acknowledged impact on vascular function (smoking [6] or recent infections [7]) are difficult to control. Finally, it cannot be excluded that genetic susceptibility to inflammation and insulin resistance contributes to a vicious cycle of events that cannot be prevented once Type II diabetes has become manifest [8].

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Comments to: Yudkin J, Panahloo A, Stenhouwer C et al. (2000) The influence of improved glycaemic control with insulin and sulphonylureas on acute phase and endothelial markers in Type II diabetic subjects. Diabetologia 43: 1099–1106

To the Editor: Increased concentrations of acute phase serum proteins including haptoglobin, α-1-acid glycoprotein, C-reactive protein (CRP), serum amyloid A and of the cytokine interleukin-6 have been reported in patients with Type II (non-insulin-dependent) diabetes mellitus or with impaired glucose tolerance [1]. Atherosclerosis, which is often associated with Type II diabetes, is clearly an inflammatory disease and does not result simply from the accumulation of lipids [2]. Therefore, the recent study by Yudkin et al. [3] on the influence of improved glycaemic control with insulin and sulphonylureas on acute phase proteins and endothelial markers in Type II diabetes is very interesting.

The main finding of the study was that markers of endothelial dysfunction and concentrations of proinflammatory cytokines in Type II diabetes are not influenced by improved glycaemic control over 16 weeks. Improved metabolic control with insulin, however, was associated with reduced CRP concentration. In a previous study by another group, improved glycaemia with intensive insulin treatment in patients with Type II diabetes was associated with normalisation of initially increased E-selectin [4].

Theoretically both insulin and glibenclamide have the potential to reduce the concentrations of acute phase proteins. Insulin inhibits the production of acute phase proteins from the liver [5] and glibenclamide inhibits dose-dependency secretion of interleukin-1β from macrophages [6]. Because hyperglycaemia causes oxidative stress [7], the reduction of glycaemia in itself could also have an effect on some markers. Therefore, the results by Yudkin and co-workers, if conclusive, are very crucial. The patients had not had prior drug therapy for diabetes before insulin or glibenclamide treatment.

The effects of both treatments on glycaemic control were impressive, with a reduction in HbA_{1c} from 11.8 % to 8.6 %.

According to our opinion, however, and before drawing final conclusions, the possibility of confounding factors should also be considered. The study was initially designed to investigate the effects of different modes of glycaemic control on fibrinolytic activity [3]. It is not stated how the existence of possible preceding or current mild infections or inflammations was excluded. According to our experience, in patients with Type II diabetes and who are treated with insulin, the concentrations of acute phase proteins are very stable if no other treatment is added [8]. The CRP values in the study by Yudkin et al. varied according to their Figure 1 greatly in some patients suggesting a possible effect of underlying inflammations. If true, this could also have had some impact on the concentrations of other markers of inflammation. For most of the measured variables this probably has little significance but more studies are needed to confirm if the effects of improved glycaemia, glibenclamide and insulin on acute phase proteins, proinflammatory cytokines and endothelial markers are as insignificant as reported in this important study.

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