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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Comments to: Tarnow L, Kjeld T, Knudsen E et al. (2000) Lack of synergism between long-term poor glycaemic control and three gene polymorphisms of the renin angiotensin system on risk of developing diabetic nephropathy in Type I diabetic patients. Diabetologia 43: 794–799

To the Editor: Chronic hyperglycaemia is the most important risk factor in the development of diabetic complications including diabetic nephropathy. Since not all patients with long-term, poor metabolic control develop nephropathy, interaction between poor metabolic control and putative genetic risk factors for nephropathy is clearly a major contributor to its aetiopathogenesis. Many of the studies on this interaction could be criticised for using short-term observation of glycated haemoglobin, which might not reflect glycaemic control over several years, let alone over decades.

The recent study of Tarnow et al. [1] showed a significant correlation ($r = 0.74$, $p < 0.001$) between a random and long-term (13.5 years) measurement of glycated haemoglobin within the usual therapeutic range (7–11 %) in a large number of adult diabetic patients. This observation, in accordance with an earlier study of Barnas et al. [2] suggests that a single random measurement of glycated haemoglobin offers a valid estimate of glycaemic control during the preceding decade.

No such studies have been carried out in children. We compared a random glycated haemoglobin value with the average of 15 (range 5 to 23) previous measurements (HPLC, Bio-Rad Diamat) made over a period of 5 years in 190 diabetic children and adolescents with a mean duration of diabetes of 9.2 ± 5.6 (SD) years. In this cohort, a significant correlation ($r = 0.75$, $p < 0.001$) was found (Fig. 1). Our observation shows that despite the possibly larger fluctuation in glycaemic control in children compared with adults [3], a significant correlation exists between a recent random measurement and a long-term measurement of HbA_{1c}. Single random glycated haemoglobin values could therefore be used as surrogate markers for long-term metabolic control in the paediatric age group in retrospective studies similar to that of Tarnow et al.

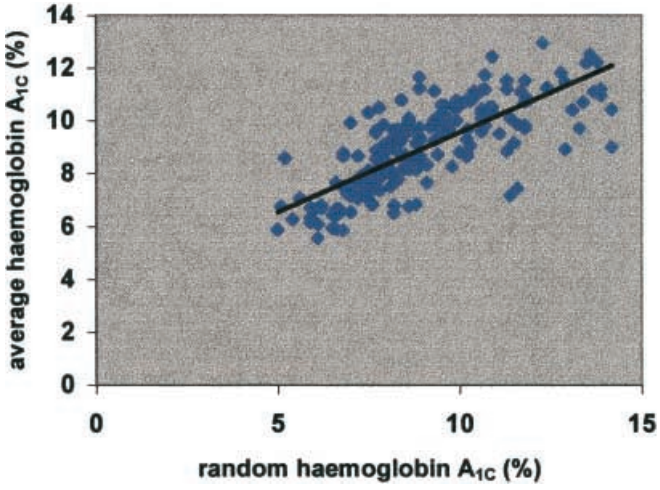

Abb. 1. See text

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