HbA_{1c} 6% or more [7]. We therefore tried to lower the HbA_{1c} level of the patient with intensive insulin therapy, and after 3 months of treatment, good glycaemic control was obtained without lowering the glucose level below 2.8 mmol/l and the HbA_{1c} level was decreased from 10.9% to 7.4%. Previous studies have shown that the counter-regulatory hormone response to hypoglycaemia could be improved after meticulous prevention of hypoglycaemia [8–10], but in these patients, HbA_{1c} levels increased in order to avoid hypoglycaemia with intensive insulin therapy [8, 9]. Our results show that intensive therapy with regular insulin improved not only the glycaemic control but also the counter-regulatory hormone response to hypoglycaemia in a young patient with Type I diabetes. We agree with previous reports [8, 9] that meticulous prevention of hypoglycaemia is important for maintaining and improving the counter-regulatory hormone response.

In conclusion, at least when the HbA_{1c} level is high even after treatment with intermediate-acting insulin, intensive therapy with regular insulin is likely to be very useful for improvement of the counter-regulatory hormone response to hypoglycaemia as well as of the glycaemic control. Although strict glycaemic control is often accompanied by hypoglycaemia, intensive insulin therapy enables us to avoid hypoglycaemia and improve control in poorly controlled Type I diabetes patients, both of which seem to improve the counter-regulatory hormone response to hypoglycaemia and awareness of it.

Yours sincerely,
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Hereditary haemochromatosis mutations (HFE) in patients with Type II diabetes mellitus

Dear Sir,

Recently the gene and its mutations responsible for hereditary haemochromatosis, a well-established, albeit rare, cause of diabetes mellitus, were identified on the short arm of chromosome 6 [1, 2]. Hereditary haemochromatosis is one of the most common genetic disorders and predominantly affects Caucasians, with a prevalence of between 1 in 200 and 1 in 400 for homozygotes [3, 4]. More than 83% of patients studied who had hereditary haemochromatosis were found to be homozygous for a mutation of the *HFE* gene resulting in a Cys282Tyr amino acid exchange, 5% were heterozygous [1]. A second mutation (His63Asp) that is not linked to the Cys282Tyr polymorphism occurred on the remaining allele in 8 of 9 heterozygotes. Recent studies showed that this variant is also associated with the development of hereditary haemochromatosis but with lower penetrance [1, 5]. In total, 87% of patients with haemochromatosis were reported to be homozygous for *C282Y* or compound heterozygotes *C282Y/H63D* [1]. Iron overload such as in idiopathic haemochromatosis can cause diabetes and therapy with an iron-chelating agent improved glycaemic control in a group of patients with Type 2 diabetes [6]. Type 2 diabetes is typically, however, not associated with subclinical iron overload [2]. Since heterozygosity for clinical haemochromatosis was associated not only with an increased risk for colorectal neoplasia but also for diabetes mellitus [7], we hypothesised whether heterozygosity for hereditary haemochromatosis causing mutations could be a risk factor for diabetes mellitus. Accordingly we screened patients with Type 2 diabetes for the two identified *HFE* mutations. The Cys282Tyr mutation was analysed in 206 patients and 175 control subjects, the His63Asp mutation in 195 patients and 180 control subjects. Patients with Type 2 diabetes had been treated for at least 3 years from diagnosis by diet or oral antihyperglycaemic agents. Healthy control subjects had no family history of diabetes. Oligonucleotides for poly-

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Table 1. HFE Cys282Tyr polymorphism in patients with Type II diabetes and control subjects

nucl. 845 (amino acid)	a/a (tyr/tyr)	a/g (tyr/cys)	g/g (cys/cys)	Σ
Type II	1 (0.5 %)	17 (8.5 %)	177 (91 %)	195[a]
control subjects	0	26 (14 %)	154 (86 %)	180

[a] p = NS

Table 2. HFE His63Asp polymorphism in patients with Type II diabetes and control subjects

nucl. 187 (amino acid)	c/c (his/his)	c/g (his/asp)	g/g (asp/asp)	Σ
Type II	147 (71 %)	55 (27 %)	4 (2 %)	206[a]
control subjects	121 (69 %)	49 (28 %)	5 (3 %)	175

[a] p = NS

merase chain reaction (PCR) were constructed according to the published DNA sequence [1] (GenBank U630319): 5'-GGAGTTCGAACCTAAAGACGT and 5'AGGGCTCC-CAGATCACAATG for the Cys282Tyr mutation; 5'-TCA-GAGCAGGACCTTGGTCTT and 5'-ACTCTGACT-CAGCTGCAGCCA for the His63Asp mutation. Amplified fragments were purified and subsequently digested with RsaI (Cys282Tyr) respectively with DpnII (His63Asp).

The distribution of *HFE* genotypes did not differ significantly between patients and control subjects: Cys282Tyr heterozygosity occurred in 17 patients (8.5 %) and in 26 control subjects (14 %, Table 1). The His63Asp mutation was found in 55 patients (27 %) and 49 control subjects (28 %) in its heterozygous form (Table 2). These figures are in accordance with those published previously except for a slightly higher frequency of Cys282Tyr heterozygotes in control subjects. Other studies have found heterozygotes in frequencies varying from 5 to 10 per cent in control subjects derived from European populations [8, 9].

Our screening led to the identification of one diabetic patient who presented with high iron/ferritin levels at diabetes manifestation. He is homozygous for the Cys282Tyr mutation and liver biopsy confirmed the diagnosis of genetic haemochromatosis.

In conclusion, the *HFE* mutations Cys282Tyr and His63Asp do occur in similar frequencies as heterozygotes in patients with Type 2 diabetes mellitus and in control subjects. Heterozygosity for hereditary haemochromatosis mutations does not represent a genetic risk marker for Type 2 diabetes mellitus in our study group. However, when suspecting iron overload as a cause of secondary diabetes, the *HFE* mutation analysis can confirm the diagnosis of genetic haemochromatosis.

Yours sincerely,
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Serum levels of vascular endothelial growth factor in diabetic subjects: the relationship with blood pressure

Dear Sir,
Vascular endothelial growth factor is a cytokine whose main actions are to increase vascular permeability, and to induce angiogenesis [1]. Since these functions have parallels with the major manifestations of endothelial dysfunction in diabetes, this growth factor has provoked interest, particularly in respect of diabetic microvascular disease [2–4].

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It is now possible to measure vascular endothelial growth factor in blood. We therefore embarked upon pilot work to assess the value of such measurements in respect of clinical markers in diabetic subjects using a commercially available kit (R&D Systems Ltd. Abingdon UK). This is directed against the 165 amino acid isoform of vascular endothelial growth factor which is the most abundant circulating isoform in humans. During this work, we discovered an intriguing association with arterial blood pressure which we report here.

Sixty three diabetic subjects were recruited to the study [39 male, 24 female, 33 on insulin, age 51.3 ± 13.2 years (standard deviation), 32 with no retinopathy]. Subjects were selected with a minimum duration of diabetes of 5 years, to allow for the development of diabetic retinopathy. Those with a raised creatinine or any other significant medical condition were excluded. Non-diabetic subjects were recruited from amongst the staff at the Hospital (26 male, 22 female, age 38.8 ± 13.9 years). Serum vascular endothelial growth factor was