cells. A role for NO produced by macrophages in the pathogenesis of Type 1 diabetes would be supported if significant induction of iNOS and NO synthesis is caused by relevant stimuli. The role of FOR is far from settled and further studies are needed. NO and FOR can react to form peroxynitrite anion, which rapidly decomposes to hydroxyl anions and nitrogen dioxide [21], of which the former is a highly reactive and toxic compound. Thus, a complex interplay between NO and FOR may exist.

In conclusion, we would suggest that IL-1 secreted from macrophages in the earliest as well as later phase of the insulinitis process induces expression of iNOS and production of NO selectively in beta cells and not in other islet cells, leading to destruction of mitochondrial iron-sulphur containing enzymes, resulting in reduced glucose oxidation, energy production and ultimately beta-cell death.

Yours sincerely,

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Can twin studies assess the genetic component in Type 2 (non-insulin-dependent) diabetes mellitus?

Dear Sir,

In interpreting the data from their twin study, Kaprio et al. [1] overlook recent observations that impaired glucose tolerance and Type 2 (non-insulin-dependent) diabetes mellitus in adult life are strongly linked with impaired prenatal growth [2, 3].

Monozygotic (MZ) twins have a more adverse prenatal environment than dizygotic (DZ) twins. They have lower mean birthweight, higher perinatal mortality rates and a higher prevalence of congenital malformations [4]. These effects are more marked in MZ twins who have a monochochial type of placentation suggesting that they are a result of placental competition for a limited supply of nutrients [5]. A subset of MZ twins characterised by an unusually adverse prenatal environment would be expected to have a high diabetes prevalence. This would lead to higher concordance rates in MZ than DZ twins. It would be interesting to know the true prevalence of diabetes in MZ and DZ twins.

We have previously argued that the influence of maternal nutrition on fetal growth explains the familial clustering of diabetes [2]. It is likely that similarities in fetal nutrition explain a large part of the increased concordance rates of diabetes in MZ twins. Consequently, twin studies may be an unreliable method of assessing the genetic contribution to Type 2 diabetes.

Yours sincerely,

DIW Phillips, CN Hales and DJP Barker

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Response from the authors

Dear Sir,

We thank Drs. Phillips, Hales and Barker for their comments on our paper [1]. They suggest that fetal nutrition may play a role in the aetiology of Type 2 (non-insulin-dependent) diabetes mellitus. They suggest that as monozygotic (MZ) twins have lower mean birthweight than dizygotic (DZ) twins, an increased concordance for Type 2 diabetes in MZ twins could be due to fetal and not genetic factors. In our study the rate of Type 2 diabetes in MZ twins was not significantly increased compared to DZ twins, and we are not aware of other population-based twin studies finding such differences. Because our data was derived from multiple medical registers, we cannot know at present the true prevalence of Type 2 diabetes in the twin population without testing all twins in the population.

Phillips, Hales and Barker imply that a higher rate of low birthweight among MZ twins would result in greater concordance of Type 2 diabetes. At birth, the pairwise correlation of weight ($r = 0.62$, 95% CI 0.51–0.71) of MZ twins is no greater than that of like-sexed DZ pairs ($r = 0.66$, 95% CI 0.53–0.76) or even opposite sex DZ pairs ($r = 0.68$, 95% CI 0.53–0.79) according to the longitudinal data from the Louisville Twin Study [2]. Only after the age of 6 months is there higher concordance for weight in MZ pairs compared to DZ pairs [2]. In Aberdeen, Fraser and Nylander [3] found little evidence to substantiate the claim that the heavier twins will go on to grow taller than their lighter co-twins. They suggest that the birthweight of a twin is not on its own an indication of the quality of the prenatal environment, but has to be viewed in relation to that of its co-twin [3]. Thus, the special prenatal environment of twins would suggest that birthweights of twins cannot be compared directly to birthweights of singletons.

Should an increased prevalence of Type 2 diabetes in MZ twins compared to DZ twins be observed, this may be due to many other factors than prenatal nutritional factors. MZ twins tend to have more contact with each other than DZ twins in adulthood [4], which may result in greater similarity for behaviour relevant to the aetiology of Type 2 diabetes, for example dietary habits or physical activity patterns. Also, as we have speculated elsewhere [5, 6] a higher prevalence of disease in MZ pairs could be due to infectious mechanisms.

While we acknowledge the importance of the fetal period (maybe not only nutrition) for the development of various diseases, including diabetes, later in life, we would like to stress the strong influence of genetic factors in the aetiology of Type 2 diabetes. Without clustering of susceptibility genes there will be no familial clustering of diabetes. Before having a better understanding about the genetic susceptibility, it may be of little value to argue about the usefulness of different study designs in genetics of diabetes which all have their limitations. We believe that twin studies offer a good

potential to sort out the unsolved questions related to genetic-environmental interaction in the development of Type 2 diabetes although the actual birth weights may be more difficult to interpret among twins than singletons.

Sincerely yours,

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In addition to von Willebrand factor and urinary albumin excretion, plasma endothelin is an indicator of endothelial dysfunction in diabetes mellitus

Dear Sir,

Stehouwer et al. [1] demonstrated the increased concentrations of von Willebrand factor (vWF) in patients with Type 1 (insulin-dependent) diabetes mellitus independent of the presence or absence of retinopathy. Recently Stehouwer et al. [2] described in Type 2 (non-insulin-dependent) diabetes that an increase in urinary albumin excretion in patients with an increased baseline level of von

Table 1. Immunoreactive endothelin (ETi) and von Willebrand factor antigen (vWFi) blood concentrations in normal control subjects and in diabetic patients with microvascular complications

Group	n	HbA _{1c} (%)	vWFi (%)	ETi (pg/ml)
Control	10	5.5 ± 0.7	125 ± 35	5.3 ± 1.4
Microalbuminuria	10	8.7 ± 1.0	175 ± 83	5.7 ± 1.3
Macroalbuminuria	8	8.1 ± 1.0	160 ± 70	9.2 ± 1.9 ^a
Retinopathy	14	8.1 ± 1.8	147 ± 51	5.3 ± 3.9

^a $p < 0.05$ vs control group
Results are mean ± SD