Response to Maser et al.

Factor V Leiden mutation, coronary heart disease, and diabetes

We appreciate the letter by Maser et al. (1), reporting an absence of association of factor V Leiden mutation with diabetes in subjects with coronary heart disease (CHD). Diabetic patients are at increased risk for developing coagulopathy as well as CHD, which is one of the most important causes of premature death in diabetic patients in many developed countries. Genetic abnormalities that are associated with CHD in nondiabetic subjects also tend to be risk factors for CHD in diabetic patients (2). However, marked ethnic differences are observed in the genetic predisposition (3–5). Maser et al. reported that the prevalence of the Leiden mutation is not increased in diabetic patients compared with nondiabetic subjects associated with CHD. The prevalence of this mutation in patients with CHD was similar to that in healthy white Americans. Their data are consistent with ours in that the mutation is not associated with NIDDM or CHD in Japanese subjects (3,6) but seems to be inconsistent with another report on its association with NIDDM in Italian subjects (7).

In genetic studies, several kinds of bias can be inadvertently included (8). If analyzed subjects are from different ethnic groups or from different regions, different conclusions may be drawn. Other bias can also be included if randomization of the subjects is incomplete. The presence or absence of the association of the Leiden mutation with diabetes may be partly because the analyzed populations were from different ethnic groups (3,7) or subgroups from different regions (1,7) or because the selection of the analyzed patients was not appropriate. The patients in the previous report (7) do not seem to be well randomized, because the researchers analyzed 147 patients consecutively admitted to a hospital. Hospitalized patients may have more severe clinical problems than those we see in outpatient clinics. They may have subclinical or overt cerebral infarctions or some other symptoms associated with minor thromboembolism. Direct or indirect reasons for hospitalization may be related to coagulative disorders associated with this mutation. There may be seasonal variance in the reasons for hospitalization. If the analyzed patients were admitted in winter, the proportion of patients with cardiovascular problems may be increased. Because little is known about the backgrounds of the patients who were included in the previous study (7), it is difficult to assess whether the selection of patients was appropriate. Proper selection of patients is crucial to conclusively determine the association of the Leiden mutation with NIDDM or CHD associated with NIDDM. Analysis of increased numbers of patients from many ethnic groups will contribute to the exclusion of such bias in genetic studies.

Although it is premature to conclude that the association of the Leiden mutation with NIDDM is absent in white patients, we think that the observations by Maser et al. add new important evidence to the study of one of the most important genetic mutations associated with coagulative disorders.

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Response to Rosenn et al.

We read with interest the article by Rosenn et al. (1) suggesting that impaired counterregulatory responses to hypoglycemia are associated with excess fetal growth in IDDM pregnancy. However, their results and interpretation may have been influenced by methodological aspects of the study. The level of 3.3 mmol/l at which the blood glucose was clamped may not have provided a hypoglycemic stimulus that was sufficient to trigger a counterregulatory response in all of their subjects. A recent study (2) in pregnant women with IDDM, in which the blood glucose was lowered to 2.2 mmol/l, demonstrated a tenfold rise from baseline in plasma epinephrine. A further study (3) has shown that the blood glucose threshold for release of catecholamines is modified in pregnancy, requiring a lower blood glucose to elicit a response. It is likely, therefore, that women in the study from Rosenn et al. had not been exposed to a sufficient degree of hypoglycemia to elicit a response and cannot therefore be proven to have deficient counterregulation. Several other factors may affect the glycemic threshold for counterregulatory hormonal responses, including the patients' state of symptomatic awareness of hypoglycemia and the frequency and severity of any antecedent hypoglycemia. Hypoglycemia unawareness in IDDM is associated with the sympathoadrenal (autonomic) response being triggered at a lower blood glucose level (4). In the present study, if those patients who did not exhibit an epinephrine response at a blood glucose of 3.3 mmol/l had coexisting impaired awareness of hypoglycemia, this blood glucose concentration would be unlikely to stimulate a response.

Repeated episodes of hypoglycemia are known to diminish the counterregula-

tory response to subsequent hypoglycemia (5), and if the patients not exhibiting a response had experienced recurrent episodes of biochemical or symptomatic hypoglycemia (as frequently occurs in diabetic pregnancy), this would diminish the epinephrine response to hypoglycemia. No information has been provided about the frequency or severity of previous hypoglycemia during pregnancy in these subjects. Finally, the insulin doses (units per kilogram) were not stated, and if these differed between the groups, this may indicate that some women were overinsulinized, thus provoking fluctuations in blood glucose, which may have been responsible for fetal hyperinsulinemia (6).

In our view, it is not possible to conclude from this study that any of the pregnant women with IDDM had impaired counterregulatory responses, and it is therefore inappropriate to suggest a causative role and speculate that "severely impaired counterregulatory epinephrine responses to hypoglycemia may be a factor contributing to excessive fetal growth" (1).

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Response to Gold et al.

We would like to thank Drs. Gold, Walker, and Frier (1) for their insightful comments on our study. We fully agree with their observation that the level of hypoglycemia attained in this study might not have been sufficiently low to evoke a counterregulatory response in all of our subjects. This is precisely one of the measures differentiating between subjects with and without impaired counterregulatory responses to hypoglycemia. The inability to secrete a normal amount of a hormone in response to a specific hypoglycemic stimulus may result from a reduced capacity to secrete the hormone or from an alteration in the blood glucose threshold for initiation of hormonal secretion (2). Indeed, in many IDDM patients with impaired counterregulatory hormonal responses, an adrenaline response can be evoked by continuously lowering the glucose concentration. In our study, we were not attempting to define the hypoglycemic threshold for counterregulatory responses or whether altered thresholds were a result of the underlying disease, pregnancy, intensive insulin therapy, repetitive episodes of hypoglycemia, or a combination of these factors. Rather, we demonstrated the association of impaired counterregulatory responses at a specific level of hypoglycemia with excessive fetal growth. It is quite possible that lowering the glucose concentrations further would have evoked a hormonal response in an additional number of subjects, but that would not change the fact that their counterregulatory responses were impaired compared with the responding subjects.

We have speculated that the impaired counterregulatory response (which may indeed reflect a lower threshold) is associated with an increased tendency for fluctuations in blood glucose concentrations and repetitive episodes of hypoglycemia and subsequent hyperglycemia, resulting in fetal hyperinsulinism and excessive growth.

In addition, we would like to emphasize that, in our study, plasma glucose was clamped at 3.3 mmol/l, equivalent to ~2.9 mmol/l whole-blood glucose concentration. Also, insulin dosages throughout pregnancy did not differ significantly between groups.

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