Letters and Comments

Human Insulin and Hypoglycemia Unawareness

The clinical observation that patients with insulin-dependent diabetes mellitus (IDDM) treated with human insulin are less aware of hypoglycemia, and thus at higher risk of iatrogenic hypoglycemia, has been reported (1–4) and debated (5–7). Reports of 17 unexplained deaths of individuals with diabetes, at least 6 of whom had changed from animal to human insulin within the previous year, from the United Kingdom have raised concern in the United States as well (8).

Based on this controversy, Heine et al. (9) studied the neuroendocrine and symptomatic responses of eight healthy subjects to comparable hypoglycemia (2.0 mM) produced on separate occasions by the intravenous infusion of porcine insulin and semisynthetic human insulin. The study was double blind with respect to insulin type, and the sequence of insulin administration was randomized. Nadir plasma glucose concentrations and recovery from hypoglycemia were identical. Plasma glucagon, cortisol, and growth hormone responses to hypoglycemia and symptoms attributed to neuroglycopenia by Heine et al. (9) were similar in both studies. However, the following differences in response to hypoglycemia were found with human compared with porcine insulin: *1*) the mean (95% confidence intervals) number of sympathoadrenergic (neurogenic; 10) symptoms was reduced (2.9 [1.7–4.1] vs. 3.6 [2.4–4.8], $P < 0.05$); 2) mean peak plasma norepinephrine concentration was reduced (1.30 [0.99–1.61] vs. 1.78 [1.46–2.12] nM, $P < 0.02$); 3) mean peak plasma epinephrine concentration tended to be reduced (3.59 [2.23–4.95] vs. 4.78 [3.37–6.19] nM), but this was not statistically significant; and 4) mean peak heart rate was reduced (71 [64–78] vs. 77 [70–84] beats/min, $P < 0.05$).

These data lend scientific credence to the clinical impression that patients with IDDM treated with human insulin are less aware of hypoglycemia than those treated with animal insulins. The observed differences in neurogenic symptoms, plasma norepinephrine responses, and heart-rate responses to hypoglycemia were small, with significant overlap of the 95% confidence intervals in the two studies. However, they were significant by null hypothesis testing and were derived from a well-designed study. Note that the clinical impression came first. Therefore, even small differences demonstrated experimentally may be markers for clinically important differences in the sympathochromaffin responses and the presumably resultant neurogenic symptoms of hypoglycemia (10).

On the other hand, the data of Heine et al. (9) do not establish that nondiabetic humans, much less patients with IDDM, are less aware of hypoglycemia produced by human insulin than that produced by porcine insulin. Awareness of hypoglycemia was not addressed in the published study. Nonspecific symptoms that might serve as clues to hypoglycemia were apparently not sought, and the subjects were not asked whether they were aware that their plasma glucose levels had been lowered. Given the marked degree of hypoglycemia studied (2.0 mM), the subjects were probably aware of hypoglycemia on both occasions, at least in the absence of data to the contrary. It is conceivable that despite small differences in the limited number of neurogenic symptoms sought, one dominant symptom or other symptoms, perhaps idiosyncratic, might allow recognition (awareness) of hypoglycemia with the two insulins at a given plasma glucose concentration. The addition of euglycemic control limbs of the same duration as the

hypoglycemia studies with the two insulins, the inclusion of the question of whether subjects could distinguish between the euglycemic and hypoglycemic studies with both insulins, and the addition of higher hypoglycemic steps in addition to the low one studied would have strengthened the experimental design and made it more relevant to the clinical hypothesis. Finally, the authors' classification of symptoms is open to question. Is anxiety a neuroglycopenic symptom as the authors suggest?

Despite these reservations, this issue is potentially relevant to insulin-treated patients and warrants further study. First, the data of Heine et al. (9) need to be replicated independently, preferably with the design modifications mentioned earlier. Although there is a case report of an association between therapy with human insulin and reduced plasma epinephrine responses to hypoglycemia in a patient with IDDM (11), earlier studies showed no convincing differences in symptomatic, norepinephrine, epinephrine, glucagon, growth hormone, or cortisol responses to hypoglycemia induced with human compared with porcine insulin (5,12–18). Second, such studies need to be extended to patients with IDDM. The rationale for starting with nondiabetic subjects is sound. Nonetheless, it is patients with IDDM who have experience with the recognition of hypoglycemia who are relevant clinically. Issues such as autonomic neuropathy and the effects of antecedent levels of glycemia are relevant but can be controlled with an appropriate experimental design (9,10). Third, given further scientific support for the hypothesis that patients treated with human insulin are less aware of hypoglycemia than those treated with animal insulins, prospective randomized clinical trials in many patients with IDDM, including sensitive ascertainment of the frequency of hypoglycemia, will be required to establish the concept and define its clinical relevance. After all, the pragmatic issue is clinical hypoglycemia. Decreased symptoms or awareness of hypoglycemia during treatment with human insulin would be interesting scientifically but irrelevant clinically if they did not result in an increased frequency, severity, or both of clinical hypoglycemia. Several previous clinical trials failed to demonstrate an increased frequency of clinical hypoglycemia in patients treated with human insulin compared with those treated with animal insulins (5,19–23). Because these trials did not test the hypothesis specifically, they cannot be considered definitive. However, they do not support the hypothesis. The importance of an appropriately controlled experimental design in any future clinical trials cannot be overemphasized. In clinical practice it is difficult, perhaps impossible, to separate specific differential effects of a new insulin preparation from the impetus to achieve better glycemic control along with the change in insulin in many patients and the distrust of a new drug by some individuals.

Thus, although it is prudent to inform patients with IDDM about this issue, it is premature to present the hypothesis that patients treated with human insulin are less aware of hypoglycemia, and therefore at increased risk of iatrogenic hypoglycemia as established, and to switch patients managed successfully with human insulin to an animal insulin on the basis of available data. If this hypothesis is ultimately proved, it will represent the value of careful clinical observations, in the context of patient care, in the recognition of unanticipated untoward effects of new drugs. This will not be diminished if the hypothesis is disproved. In either event, the principle that clinical impressions must be confirmed or denied by rigorous scientific testing will be reaffirmed.

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Employment for People With Diabetes in the United Kingdom

I found the article by Songer et al. (1) on the employment spectrum of insulin-dependent diabetic people of interest. There have been few studies in the United Kingdom that have investigated the employment of people with diabetes (2–4). Much of the published work in this field originated in the United States and was carried out >20 yr ago (5–9).

We have completed a large survey in the U.K. of employment and its problems for people with diabetes (10,11). Questionnaires were sent to a random sample of 4000 insulin- and non-insulin-treated diabetic patients aged 17–65 yr attending clinics in eight different geographic areas of the U.K. Matched control data were also collected from people without the disease. Of the people with diabetes, 22% of men and 12% of women were currently unemployed, i.e., looking for work, compared to 8 and 5% of nondiabetic control subjects ($P < 0.001$). A greater proportion of people with diabetes were economically inactive, i.e., retired, unable to work, ill, or housewives compared with the control group (29 vs. 14%, $P < 0.001$). Young people with diabetes (17–25 yr old) had the highest rates of unemployment. A matched-pairs analysis confirmed that diabetic men had higher unemployment rates than their control counterparts (14 vs. 7%, $P < 0.001$). When comparisons were made between unemployment rates for the eight geographic areas and published unemployment statistics, unemployment was significantly higher for men with diabetes except for one center. A stepwise multiple logistic regression analysis indicated that variables predictive of unemployment were similar to those expected for people without diabetes. Over one-third of diabetic respondents from all areas reported having been unemployed at some point for >3 mo. We therefore concluded that unemployment was apparently a problem for the person with diabetes and particularly acute for the young. In terms of health and social outcome, this may have serious consequences.

Data on employment were linked to information collected from patients' diabetic clinic notes; this included the presence and treatment of any diabetic complications and the quality of diabetic control. Difficulties in obtaining employment because of diabetes were reported by 13% of the diabetic patients and because of illness by 2% of control subjects ($P < 0.001$). Nine percent of diabetic patients and 2% of control subjects reported having to change their job because of their illness ($P < 0.001$), and 7% of people with diabetes and 2% of people without diabetes reported losing a job because of their illness ($P < 0.001$). Diabetic shift workers were twice as likely as control subjects working shifts to experience problems with their job (18 vs. 8%, $P = 0.045$). Reports of any absence due to sickness in the last 12 mo were not significantly different for people with and without diabetes (49 vs. 45%). This finding is similar to that reported by Songer et al. for insulin-treated diabetic patients. However, absence due to sickness in >20 days in the last 12 mo was more common among diabetic patients than control subjects (29 vs. 16%, $P < 0.001$). Differences in employment problems between insulin- and non-insulin-treated diabetic patients are being analyzed (N.R., N.A. Yateman, L.E. Protopapa, unpublished observations). Eight percent of diabetic workers had not told their employers that they were diabetic compared to 35% in Songer et al.'s study. The people in our study who had not told their employers were more likely to be non–insulin treated, to be older, to have a shorter duration of diabetes, and to belong to an ethnic minority group. Songer et al. reported that dia-