than is stated in the study. The figures given in Table 2 relating to the frequency of severe hypoglycemia in the preceding year are also incorrect for our center and are likely to be incorrect for other centers as well. The table states that there were three episodes of severe hypoglycemia during the last year on human insulin compared with 25 on animal insulin. Among the 25 events attributed to animal insulin, however, 14 actually occurred during treatment with human insulin. Patients were transferred back to porcine insulin precisely because they had suffered severe hypoglycemia with human insulin! The first discrepancy illustrates that patients are an unreliable source of information for the assessment even of current insulin species. The latter discrepancy is explained by the design of the questionnaire. Patients were asked for the species (human, porcine, or bovine) of the insulin they were currently using and for the number of severe hypoglycemia episodes over the last year. The questionnaire, however, did not assess the insulin species used at the time of the hypoglycemic events. The data were then analyzed assuming that insulin species had not changed over the past year. As demonstrated by our patients, this assumption clearly is invalid.

These critical comments were related to the authors at the end of August 1990, but they were not taken into account. Instead, the authors stated that ". . . it will be the reviewers' task to evaluate the data and decide if, and in which form, they should be published and thus made public." But how could the reviewers possibly decide without the information we report here?

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TYPE I DIABETES, INSULIN-DEPENDENT DIABETES MELLITUS.

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Response From Authors

The comments raised by Dr. Kriegstein are repetitive of those put forward by Dr. Teuscher in a letter to the *Lancet* (1) and another letter by Dr. Teuscher to *Diabetes Care* (2), the latter one being an almost verbatim repetition of the first one. We have answered Dr. Teuscher's comments (3). We do not think Dr. Kriegstein raises any issues that have not been addressed already in our paper (4) and in the subsequent correspondence.

Like all other heads of the participating centers, Dr. Kriegstein agreed to the study protocol (including the questionnaire as the principal assessment method) before initiation of the study in September 1989; but he raised his concerns about the protocol only in August 1990, 3 mo after preliminary results had been communicated at the Annual German Diabetes Meeting. During the course of the study it turned out to be impossible to recruit 1000 type I diabetic patients as planned in the protocol, mainly because the vast majority of patients in Germany had already been switched to human insulin at that time. In this context, matching of both patient groups, i.e., those on human insulin and those on animal insulins, with respect to the duration of diabetes, had become indispensable in order to avoid a selection bias in favor of human insulin. The fact that the patient groups were matched has been stated in our paper (METHODS)—in contrast to Dr. Kriegstein's allegation—and the procedure used for matching has been reported in further detail in our response to Dr. Teuscher's letter.

The discrepancies between the data assessed by the structured patient interview technique according to the study protocol and the data given by Dr. Kriegstein concerning 5 of 29 patients have been mentioned already in the acknowledgement section of our original publication and again in the letter by Dr. Teuscher and our response. The patient interviews conducted by the two students on 19 September 1989 at the diabetes center of Dr. Kriegstein were supervised by Dr. Kriegstein. In fact, some missing data were supplemented by Dr. Kriegstein himself, and the protocols were later sent to us by him. We are astonished by Dr. Kriegstein's statement in his most recent letter that this "discrepancy illustrates that patients are an unreliable source of information for the assessment even of current insulin species." In fact, based on our experience and those from other diabetes centers, we believe that patients do know what type of insulin they use, including the insulin species. If Dr. Kriegstein were right in that his patients do not know the

insulin species they use, further serious doubt on the validity of data reported on the alleged hypoglycemia unawareness associated with human insulin in his center is warranted.

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Questionable Accuracy of a Filter Paper Method for Measuring GHb

Gay et al. (1) report that a fingerstick capillary blood GHb method was highly correlated ($r = 0.89$, $P = 0.0001$) with venous plasma HbA_1 by an ion-exchange chromatography method (HbA_1). They conclude that the GHb method is accurate and should be considered a credible alternative research and clinical tool to HbA_1. However, a high correlation coefficient, r, a measure of association between variables, does not necessarily imply good agreement in terms of their clinical significance (2). Similarly, as the methods both measured glycated hemoglobin, it would be most surprising if the P value did not indicate a highly significant relationship.

Linear regression is not the best approach for comparing two methods because it assumes that all the error is associated with the dependent (y) variable. In practice both methods have imprecision. The quoted coefficients of variation at equivalent concentrations, and therefore the variances, indicated slightly more variability in HbA_1 than in GHb. A more representative comparison would be achieved with a regression technique, which takes this into account using a ratio of the method variances (3). Alternatively, the difference between methods can be plotted against the mean for each pair of results (4). This difference plot is simple to perform and lends itself to straightforward clinical interpretation.

The classification as multiples of the method SD is a valid indicator of clinical significance, but the data presented showed that 24 of 58 samples (41%) were classified differently. In the range between the upper limit of the reference range and +10 SD, which should be sensitive to changes in glycemic control in average to well-controlled patients, the two methods would give the clinician different messages on 57% of occasions. Treatment decisions in patients whose samples were classified differently may be similar, as suggested, but the acceptability of such a high discordance rate is questionable. If glycated hemoglobin is to be employed as an accurate and objective measure of glycemia, then different methods for its measurement should agree. The authors suggest that much of the error may be attributable to the known problems of the ion exchange assay. However, they eluted their filter paper samples at 7 days after collection rather than 14 as originally reported (5). This could have contributed to the discrepancy, because at 7 days continuing and unpredictable in vitro glycosylation was demonstrated, which introduced variability and persisted until 14 days. It is not stated whether the change in the GHb protocol has been validated. Changes to the affinity chromatography method, if introduced in other laboratories, could lead to further variability (6).

Important differences in clinical classification have recently been reported between paired filter paper GHb by affinity chromatography and plasma HbA_1 by microcolumn ion-exchange chromatography (7). In view of the different analytical principles and the difficulties in calibrating glycated hemoglobin assays (8,9), method differences should be assessed carefully, with appropriate use of statistical tests. On the evidence of Gay et al. (1), the accuracy of the filter paper method remains open to question.

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