$P = 0.05$) was observed when SDs of seven-point glycemic profiles were substituted for MAGE values.

Even though the MAGE determination requires continuous glucose monitoring, we believe that this parameter should be the "gold standard" for assessing glucose fluctuations in all prospective interventional studies designed to estimate glucose variability. We therefore believe that additional studies are required to definitively determine the role of glycemic variability in the pathogenesis of the micro- and macrovascular complications of diabetes. Even though the technology of continuous measurements of glucose in interstitial fluid remains a subject of debate, the use of continuous glucose sensors might be useful for conducting such trials.

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The Effect of Glucose Variability on the Risk of Microvascular Complications in Type 1 Diabetes

Response to Kilpatrick et al.

We have read with interest the article by Kilpatrick et al. (1), which reports the lack of effect of glucose variability on the risk for microvascular complications in type 1 diabetes using the Diabetes Control and Complications Trial database. We are pleased that the authors came to the same conclusions as we did in our examination (2) of this question using the same database. Since Diabetes Control and Complications Trial subjects were studied for differing durations and not all subjects provided complete seven-point glucose samples, how were these factors dealt with in the analysis? Furthermore, what were the reasons to limit the assessment of glucose variability to SD and omit measurements of M value and mean amplitude of glycemic excursion, two established indexes of glucose variability? The authors may wish to reexamine their literature research technique; it appears to be less than rigorous.

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The Effect of Glucose Variability on the Risk of Microvascular Complications in Type 1 Diabetes

Response to Kilpatrick et al. and Bolli

We read with interest the article by Kilpatrick et al. (1) and the accompanying editorial by Bolli (2). While the analysis of seven-point glucose profiles reported in this study (1) suggested that glucose variability is not an independent risk factor for microvascular complications, the seven-point profile may not be an accurate representation of true glycemic variability as measured by continuous blood glucose monitoring (3). Although there are not enough data at present to justify new treatment guidelines based on glycemic variability, there certainly are important published data (3) showing that glycemic variability leads to greater oxidative stress. Since increased intracellular superoxide production has been shown to initiate a large number of hyperglycemia-induced mechanisms related to the pathogenesis of diabetic complications (4), we believe that further investigation of the hypothesis that increased glycemic variability is a risk factor for diabetic complications is warranted.

Indeed, it was not that long ago that there was widespread doubt in the medical community that increased levels of hyperglycemia were a risk factor for diabetic complications (5). However, this doubt was addressed by further clinical research (6).

A little-noticed but very important observation published (6) by the Diabetes Control and Complications Trial Research Group >10 years ago was that sub-

groups of patients receiving more physiologic insulin replacement had a significantly less risk of retinopathy than subgroups having the identical A1C levels for the entire study but were treated with insulin less frequently. In light of these observations, we feel that it is scientifically unwarranted to conclude that "increasing the number of daily injections of insulin or moving to continuous subcutaneous insulin infusion in place of multiple daily injections might not be necessary if the current treatment results in A1C consistently <7.0% over time" (2).

Rather, given the potential harm that would result if in fact glycemic variability turns out to be a significant risk factor for diabetes complications, we advocate resolving this important issue by conducting randomized clinical trials. Given their well-deserved place in the pantheon of diabetes physician and scientists, we are certain that the Kilpatrick et al. and Bolli would all agree.

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The Effect of Glucose Variability on the Risk of Microvascular Complications in Type 1 Diabetes

Response to the Diabetes Research in Children Network (DirecNet) Study Group, Service and O'Brien, and Monnier et al.

Our analysis (1) of the Diabetes Control and Complications Trial (DCCT) dataset showed no relationship between pre- and postprandial glucose variability (SD) and the risk of microvascular complications. Wilson, on behalf of the Diabetes Research in Children Network (DirecNet) Study Group (2), makes the point that continuous glucose monitoring can detect larger postprandial glucose excursions than the single-point measurements taken in the DCCT. We agree that it would seem appropriate that future studies should employ this technique.

As part of their analysis of glucose measurement in the DCCT, the article by Service and O'Brien (3) did indeed contain an analysis that found glucose variability to have the same lack of influence on retinopathy risk as ourselves, and for that they deserve credit. By specifically investigating the question of glucose variability, our article (1) was also able to assess the effect of variability both within and between each glucose profile, to apply this to nephropathy as well as retinopathy, and to adjust the data for possible confounders such as treatment group, age, sex, and duration of disease.

Our approach to missing data was different from that of Service and O'Brien (3). In their analyses, they excluded those with missing blood glucose values, accepting a bias that this might create. In contrast, we tried to take account of some of this data. We included all profiles with five or more observations during the 24-h period, assuming that a missing value lay on a straight line between the two surrounding data points. The compliance with glucose profiling using these criteria was extremely good, with a median of 91% of patients (range 84–97%) having such a profile during each quarter of our study period and a minimum of three-quarters of these being full seven point. We are aware that many methods can be used to extrapolate missing values for longitudinal data (4), with each method having its advantages and disadvantages depending on the setting (5).

Both Monnier et al. (6) and Service and O'Brien (7) are curious as to whether our findings would have been the same had we used the mean amplitude of glycemic excursions (MAGEs) assessment of variability rather than SD. We chose SD after undertaking preliminary work (not shown in our article) using a variety of methods for assessing variability. They all pointed to one thing: that variability in blood glucose was not related to microvascular risk after adjusting for mean blood glucose. We therefore only presented our SD data, citing a reference to a study in type 1 diabetes, which showed that SD was highly correlated with other measures of glucose variability (8).

From a statisticians viewpoint, we must admit to having reservations about the use of MAGE. The 1 SD difference used in the calculation seems somewhat arbitrary (9), and, crucially, a review of the archive JSTOR failed (unlike SD) to find one statistical critique of the method. However, for the record, with regard to retinopathy progression, the adjusted hazard ratio for MAGE was 1.06 (95% CI 0.94–1.19), $P = 0.33$.

We entirely agree with Monnier et al. (6) that to definitively establish any possible role of glucose variability in microvascular complications requires a prospective interventional study. We never thought that our article would, or should, be the last word on the subject. However, one of the attractions of analyzing the DCCT dataset is that the study was conducted before possible confounders, such as antihypertensive and lipid-lowering agents, came into common use. Consequently, it seems likely that the feasibility of any new study powered to take into account any of these and other factors could prove to be challenging to any future investigators.

As things stand, the world's most complete dataset relating glycemia to microvascular complications has found glycemic instability to play no additional role in complication risk. As such, it means that the burden of proof for any future study is no longer to confirm an association but to disprove the lack of one.