Letter to the Editor

Measurements of Renal Glucose Release

I am responding to Dr. Weir's query for more details concerning how we handled our raw data in our article "Role of the Human Kidney in Glucose Counterregulation" (1).

Due to high rates of renal blood flow, small arteriovenous differences, and analytical variation, physiologically impossible results such as negative or extremely high fractional extractions (FXs) are not uncommonly observed. These phenomena are not unique to renal experiments, but they can be observed also in splanchnic balance experiments (2).

Some investigators, when obtaining physiologically impossible negative renal glucose FXs, have chosen to consider them as zero; other investigators have accepted these data at face value, while others have repeated what they have considered to be erroneous measurements. The first approach seems reasonable, although it would introduce some bias favoring increased renal glucose uptake, which would lead to an increase in the calculation of renal glucose release (RGR). The second approach is very conservative but would have the greatest variance, thereby decreasing the power to detect small changes in RGR.

In our studies, we chose the third approach, i.e., to either rerun specific activity or eliminate an obvious statistical outlier among the triplicates of blood glucose concentrations if either a negative or a too high FX value (>6%) was observed. We used the results of the reruns regardless of outcome to minimize bias. Nevertheless, we realize that our approach is not founded on any statistical precedent and, being somewhat subjective, could lead to biased or even erroneous results. However, we believe that our use of this approach has not led to biased or erroneous results.

Our conclusion is based on the reanalysis of our data and the reproducibility of our results by other independent investigators (3) (Table 1). Analysis of the data of our study (1) indicated that 18 of ~200 samples initially yielded negative FXs; 13 yielded unrealistically high FXs. With our approach (i.e., reassaying samples or deleting obvious statistical outliers), all high FXs became lower. Fifteen of the negative FXs became less negative while three became more negative. There were still seven negative FXs (3.5% of all determinations). The initial average FX of all these samples changed from 1.4 to 1.8%. However, due to the robustness of equations used to calculate RGR (i.e., changes in glucose concentration produce changes in net balance that affect changes in FX), RGR did not significantly change (1.74 vs. 1.71 $\mu mol \cdot kg^{-1} \cdot min^{-1}$). Nevertheless, in retrospect it would have been preferable to determine glucose specific activity and concentration measurements with sufficient replicates to apply a statistically recognized approach, such as that of Winsoring (4), to minimize the effect of analytical imprecision. We plan to do this in the future.

TABLE 1
Comparison of results of Meyer et al. (1) and Cersosimo et al. (3)

	Meyer et al. rerun data	Meyer et al. raw data	Cersosimo et al.
RGR*			
Basal	2.24 (21)	2.31 (21)	2.10 (22)
Hypoglycemia	2.49 (30)	2.28 (27)	3.65 (36)
Euglycemia	0.82 (16)	0.10 (2)	1.20 (21)
Increment (hypoglycemia vs. euglycemia)	1.67	2.18	2.45
HGR*			
Basal	8.50 (79)	8.54 (79)	7.40 (78)
Hypoglycemia	5.86 (70)	6.14 (73)	6.60 (64)
Euglycemia	4.17 (84)	4.89 (98)	4.45 (79)
Increment (hypoglycemia vs. euglycemia)	1.69	1.25	2.15

Data are mean (%). *Measured as $\mu mol \cdot kg^{-1} \cdot min^{-1}$. HGR, hepatic glucose release.

Regardless of how one feels about the validity of our approach, one may wonder how this approach affected the results and conclusions of our experiments. To address this issue, we compared results using the original data with those arrived at using our approach (Table1). There were no major changes except that the increment in renal glucose release during hypoglycemia relative to euglycemia would have been greater than that of the liver with the original data, because the use of the rerun determinations yielded comparable increments for kidney and liver. Thus, our approach could have underestimated the role of the kidney relative to that of the liver. Irrespective of how the data were analyzed, they fully support an important role for the kidney in glucose counterregulation and are quite similar to those reported by Cersosimo et al. (3) (Table 1).

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