in our work to adopt accuracy requirements more stringent than those resulting from simulations.

Simulations are always based on assumptions, and unfortunately, a model is only a model. An extended version of the error model will remain another approach of reality. What is probably more important to reduce errors when defining clinically realistic accuracy thresholds is that our study, to the best of our knowledge, is the first that is based on glucose dynamics originating from real-life critically ill patients (i.e., independent of any mathematical glucoregulatory model and avoiding the associated errors). Further, clinical studies to validate a (new) glucose sensor should be appropriately designed (sufficient number of target patients, adequate reference sensor, etc.) to compare its accuracy performance to such thresholds. Next, glucose sensor accuracy thresholds do depend on the robustness of the control algorithm and should be specified (using simulations) for each individual glucose controller (1, 5). Generalization of these thresholds will underestimate errors for less robust glucose controllers and potentially harm patients; it should be avoided, accordingly. Finally, we wish to underline the need for clinical trials investigating the combination glucose sensor/glucose controller (each with its specific characteristics) in a real-life critically ill setting to overcome the shortcomings typical of simulation studies.

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Is Ferrotoxicity a New Great Public Health Challenge?

To the Editor:

The recent report of ferrotoxicity as a marker of increased risk of mortality by Ellervik et al. (1) needs to be viewed against the background of the study design, its weaknesses and strengths. Likewise, the metaanalysis in that study, which the authors found supportive of their own findings, needs to be judged against the fact that, of 72 relevant studies identified by the search strings they used, they threw out 70; thus, only 2 other studies besides their own entered into the metaanalysis. Their main finding, that high serum ferritin is associated with increased mortality in this cohort, may simply be because ferritin is an acute-phase reactant, and individuals affected by various chronic diseases often have a chronic inflammatory state that includes raised ferritin as part of the inflammatory biomarker signature. Although the authors adjusted for well-recognized major risk factors (modifiable and unmodifiable), no adjustments for inflammatory status appear to have been made (1), although it is known from previous publications that at least C-reactive protein is available for this cohort. It would be interesting to learn why the authors chose not to adjust for this, because it seems to be a flaw in the
study design. Also, in their metaanalysis they threw out studies that used the more recent study design of Mendelian randomization, which is currently regarded as a principal tool to avoid bias in epidemiological research (2).

Therefore, we bring attention to the results of Swedish prospective studies of risk for first myocardial infarction and first stroke, which assessed iron status as a possible risk factor for events by a combination of biomarkers of iron status and HFE (hemochromatosis) polymorphisms affecting iron status in nested case-control studies (3, 4). The studies addressed specifically first-ever cases (most relevant from a public health perspective), by meticulous exclusion of individuals with prior diseases at recruitment, as well as controls who developed disease during the full follow-up period. These studies found no risk association between high iron stores (total iron binding capacity and ferritin) and first-ever myocardial infarction or stroke. There was also no risk association between HFE C282Y and myocardial infarction or stroke, confirming the findings from the serum biomarker studies using a Mendelian randomization design. In addition, they also found no evidence for a role of ferritin in colorectal cancer (5).

Other types of evidence contradicting ferrotoxicity are also omitted, such as the cardioprotective effects of iron substitution therapy.

Thus, the Copenhagen study may be overestimating the dangers of iron owing to built-in sources of bias, not sufficiently accounted for in their study design, and to omissions in their metaanalysis. Ellervik et al. have not provided firm evidence of ferrotoxicity as a new major threat to public health. Interestingly, their own concluding statement seems to take this into account: “In conclusion, moderately and markedly increased ferritin concentrations represent a biological biomarker predictive of early death in a dose-dependent manner in the general population.” Thus, in the final analysis, they do not actually claim that iron is a risk factor in itself. We endorse this interpretation.

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**In Reply**

We thank L.H. Breimer and T.K. Nilsson for their response to our article.

First, we are puzzled by their statement that our results are about ferrotoxicity. Rather, we concluded that moderately to markedly increased ferritin concentrations represent a biological biomarker predictive of early death (1), and we did not use the concept of ferrotoxicity. Ferrotoxicity was mentioned only in the accompanying editorial (2). That said, we naturally cannot exclude that our results may partly be explained by toxic effects of iron, but we also address and propose other disease mechanisms.

Second, the results presented in our paper are from the 1981–1983 examination of the Copenhagen City Heart Study, and C-reactive protein (CRP) could not be measured in the samples frozen for 28 years at −20 °C. In fact, in pilot experiments on a few hundred of the frozen samples, we attempted to measure high-sensitivity CRP, but the quality of the measurements was very poor, in contrast to the ferritin measurements. Thus, as we were not able to adjust for CRP (or any other marker of acute phase/inflammation), we agree that this is a limitation of our study (1). However, we find it unlikely that the associations in our paper are mediated only by inflammation, as the P-values are extremely significant, and both moderately and markedly increased ferritin concentrations were associated with early death. Ferritin is an acute-