Although the study of Zakai et al., which shows increased mortality among subjects 65 and older with hemoglobin levels even in the “normal range,” is intriguing, in other studies2,3 confounding comorbid conditions accounted for most or all of the difference between anemic and nonanemic groups. Furthermore, even if 22% of the population were at risk for early demise because their hemoglobin levels were found to be low, it would remain to be shown that therapy directed at the hemoglobin level would have any effect on survival. In addition, given that high hemoglobin levels also have deleterious effects on function, it is likely that the normal distribution of hemoglobin represents a balance struck by evolutionary forces. Future studies, some of which we hope to be able to perform, may clarify some of these issues. In the meantime, we believe that physicians will have to content themselves with reference standards based on population norms, as we do with most other clinical laboratory measurements.

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To the editor:

Does liver biopsy overestimate liver iron concentration?

Cappellini and colleagues1 claim that the use of a superconducting quantum interference device (SQUID) biosusceptometer underestimates liver iron concentration (LIC) in their phase 3 study of deferasirox (DFX). LIC was measured either in deparaffinized liver samples excised by various biopsy techniques (Menghini with saline flushing, cutting needles) or in an anterior position above the right liver lobe by biomagnetic liver susceptometry (BLS) using low Tc–SQUID biosusceptometers. In vivo wet-weight LICs measured by BLS were converted by a factor of 3.33 into dry-weight values. This approximate conversion factor2 has been uncritically adopted throughout the literature, even by ourselves, although there were strong data available supporting a higher factor for the ratio of wet to dry weight3,4 and a significant difference between LIC from fresh tissue and from deparaffinized samples.5,6 Thus, the conversion factor between LIC as determined by BLS and from deparaffinized liver samples would have been at least 5.5 ± 1.0 (calculated factor ± uncertainty).7 Related to activities around this phase 3 study program of DFX, the authors have developed more direct knowledge of ratios of wet to dry weight by various biopsy processing techniques (eg, a conversion factor of 5.8 ± 0.6 for deparaffinized liver samples) and their “paramount importance” for comparison of LICs.8

Consequently, the authors should have corrected their LICs measured by SQUID-BLS in order to analyze their data more accurately in this important publication on a novel oral chelator. We think that it is allowed to correct an initially false study assumption in a scientific paper. Measurements by BLS would have the highest impact especially in the LIC group of 7 mg Fe/g dry weight or less, although the final outcome may not change significantly. Moreover, we would hope to avoid giving potential readers the wrong impression that BLS underestimates LIC per se. One could, in fact, claim the opposite, as in our title, particularly in the case of deparaffinized samples.

As part of this discussion, it should be emphasized that the different conversion factors also have a strong impact on the LIC safety thresholds in iron-overloaded patients with thalassemia. These recommended thresholds were based in part on LICs measured by BLS with an approximate conversion factor of 3.33. For example, the threshold for increased risk of cardiac failure of LICs equaling 80 μmol/L wet weight (about 15 mg/g dry weight) would convert to 26 ± 5 mg/g dry weight using the conversion factor of 5.8 for deparaffinized liver biopsies. Thus, dry-weight LICs could be very different depending on the selected biopsy techniques and processing methods.7

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