of a definitive method (we call for a reference method). As justification, they cite difficulties encountered by joint National Institute of Standards and Technology (NIST)-CAP efforts to use a thermal ionization mass spectrometry method for serum iron measurements. Also mentioned are negative experiences with plasmaemission spectrometry and atomic absorption spectrophotometry (we assume without prior extraction). All of these methods measure total iron and are thus unsuited for serum iron measurements, as is NIST Standard Reference Material 1598. Accordingly, these efforts were doomed from the start. More innovative approaches are required to reach the goal of a satisfactory reference or definitive iron method.

Eckfeldt and Witte indicate that in most clinical situations serum iron measurements must be combined with determinations of serum TIBC to be useful for clinical interpretation. There is no argument that TIBC (or transferrin) measurements enhance the diagnostic utility of serum iron measurements. (This, however, was not the topic of our communication, which dealt with the analytical accuracy of serum iron measurements.) The authors then discourage this approach because "almost all clinical TIBC methods are at least as laborious as serum ferritin assays." Aside from the fact that our assays should be selected on the basis of accuracy and clinical utility and not on the basis of efforts required, transferrin assays can be substituted for TIBC determinations. Transferrin tests are easily done, and they are analytically sound, of good clinical utility, and relatively inexpensive.

The authors' statement that "... the comparable proportional errors in iron and TIBC would still tend to cancel each other" is also puzzling. (Do they now suggest that we should perform serum iron and TIBC determinations after all?) Our data very clearly show that the error in the low analytical range is random (not proportional). The error in the high range is more difficult to characterize but it is, in part, also random; for some methods, a constant error is apparent.

In their editorial, Eckfeldt and Witte state that we have shown that iron measurements are more accurate and precise at higher concentrations. We stated, instead, that method performance in the low-concentration range was significantly worse than in the normal and high range of values. The National Committee for Clinical Laboratory Standards method, for example, shows an average negative bias of 17.5%; i.e., the average error at the upper decision limit of 1600 μg/L is nearly 300 μg/L. Such differences are clearly of clinical significance and might result in a missed diagnosis of iron overload. In our recent study (2) 24% of values that were near 1600 μg/L and above by the method of the International Committee for Standardization in Haematology were 9-18% lower by routine methods.

One additional concern should be raised. In certain clinical conditions, perhaps ferritin assays may ultimately be shown to be superior to serum iron measurements. However, how can we be certain of that as long as we use for some of the studies iron methods that give errors of >600%?

We support the call by Eckfeldt and Witte to the readership of Clinical Chemistry to make their views known to the leadership of their professional societies on whether they think it is worthwhile to spend resources on improving iron methodology. (Efforts by industry toward such improvements are clearly not out of place either.) But then, it was the implicit purpose of our article to motivate readers and leaders in clinical chemistry to work towards better iron methods. Let us not be divisive. Let us combine our analytical skills and develop a reliable iron method and then apply these skills to the resolution of the clinical issues. We can make more progress if we put the horse before the cart!

References

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Specificity of Digoxin Immunoassays Toward Digoxin Metabolites

To the Editor:

Fuji et al. (1) recently described their development of a new antiserum highly specific for digoxin. The antiserum, as evaluated in an equilibrium RIA format, showed very low cross-reactivity toward all the major metabolites of digoxin: digoxigenin monodigitoxoside (0.92%), digoxigenin bisdigitoxoside (0.58%), digoxigenin (0.14%), and dihydrodigoxin (2.1%). Additionally, the cross-reactivities of cholesterol, progesterone, testosterone, spironolactone, and digitoxose were reported as <0.05%. The authors claimed the antiserum to be more "ad-

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The authors of the editorial reply:

To the Editor:

We agree with Tietz and Rinker that serum iron analysis still plays a role in clinical medicine; however, we believe that its role is mostly limited to overload situations, where current clinical methods show better (albeit not perfect) analytical accuracy and precision. We basically have relatively little quarrel with most of the points Tietz and Rinker list.

We agree with Tietz and Rinker that new approaches are needed to resolve the discrepancies (both systematic and specimen-specific biases) among the current clinical and "reference" serum iron methods. Furthermore, different reference methods for serum iron methods yield different results, and as Tietz and Rinker suggest, the "total" serum iron concentration (i.e., the amount of total iron/volume of serum, including that bound to hemoglobin, dextran, etc.) appears not to be what one wants to measure clinically.

We wanted to stimulate public discussion with our editorial. We join with Tietz and Rinker in encouraging those with "innovative approaches" (which are not at all obvious to us right now) and with the resources to develop and test them (unfortunately also seriously lacking) to come forward, so that a coordinated approach for diagnosis and management of iron disorders can be offered to our physicians and their patients.

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