More on Drug Assay Interferences

To the Editor:

The Letter to the Editor by Kelner (*Clin Chem* **30**: 1430, 1984) reinforces the fact that information concerning substances that interfere with laboratory tests should be made available to all professionals working in the field. This is especially important when testing for drugs of abuse because, in many cases, the patient's future may be adversely affected.

In 1980, we conducted a project to determine the "specificity" of the EMIT-d.a.u.® (Syva Co., Palo Alto, CA) assays. We studied the incidence of "false positives" with more than 160 different drugs added individually to drug-free urine. We were disappointed that some journals did not feel this information was sufficiently important for publication. However, it was published in easy-to-read tabular form the following year (*1*). It is unfortunate that all this information has not been incorporated into the manufacturer's literature. This first study supports the false-positive results alluded to by Kelner.

This study has since been expanded to include the EMIT tests for tetrahydrocannabinol (THC) and phencyclidine (PCP), although these results have yet to be published. Reprints of the first study are available upon request to the address below.

Reference

1. Allen LV Jr, Stiles ML. Specificity of the EMIT drug abuse urine assay methods. *Clin Toxicol* 18, 1043–1065 (1981).

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Negative Interference with the Ektachem (Kodak) Enzymic Assay for Creatinine by High Serum Glucose

To the Editor:

The enzymic assay for creatinine on the Ektachem-400 (Cr-E) offers improved specificity over conventional alkaline picrate methods (Cr-P) (*1–5*). However, high serum glucose reportedly causes a slight inhibition of Cr-E (*1, 3, 4*).

Recently, we reported that concentrations of glucose approaching 15 g/L can markedly inhibit Cr-E (*5*). We have since evaluated patients' sera over a wide range of creatinine concentrations. As shown in Figure 1, creatinine inhibition by glucose concentrations of 10 to 20 g/L ranged from 15 to 40%. We also found that the measurement of ammonia by the Ektachem was inhibited to the same degree as that of creatinine. Because Cr-E depends on the measurement of ammonia, we conclude that high glucose inhibits creatinine by inhibiting ammonia. However, we have not further characterized the mechanism of inhibition.

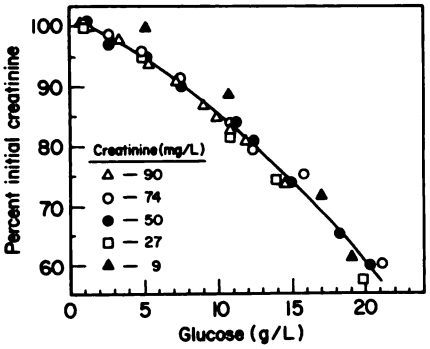

Fig. 1. Creatinine inhibition on the Ektachem by high serum glucose

Patients' serum specimens that initially contained approximately 1 g/L glucose were stored at −20 °C, thawed, and adjusted to glucose concentrations between 1 and 20 g/L. Glucose was measured in the Ektachem. Values plotted were calculated from the means of duplicate (for initial Cr-E = 50 and 9 mg/L) or triplicate (for initial Cr-E = 90, 74, and 27 mg/L) creatinine determinations by Cr-E

The inhibition of creatinine that we observed at glucose concentrations >10 g/L is greater than that suggested by previous reports (*1, 3, 4*). Although glucose values >10 g/L may seem unlikely, not infrequently we see up to 15 g of glucose per liter in samples from markedly decompensated diabetic patients. Therefore, the inhibition by high serum glucose on Cr-E may or may not be clinically significant, and merits further evaluation.

References

1. Sundberg MW, Becker RW, Esders TW, et al. An enzymic creatinine assay and a direct ammonia assay in coated thin films. *Clin Chem* 29, 645–649 (1983).

2. Smith CH, Landt M, Steelman M, Ladenson JH. The Kodak Ektachem 400 Analyzer evaluated for automated enzymic determination of plasma creatinine. *Ibid.*, pp 1422–1425.

3. Toffaletti J, Blosser N, Hall T, et al. An automated dry-slide enzymatic method evaluated for measurement of creatinine in serum. *Ibid.*, pp 684–687.

4. Powers D, Kringle R, Fame N, et al. Specificity of the Ektachem Analyzer enzyme-based creatinine assay compared with Jaffé and HPLC methods. *Ibid.* 28, 1570 (1982). Abstract.

5. Gerard S, Khayam-Bashi H. Comparison of Ektachem-400 with alkaline picrate methods for the measurement of creatinine in ketotic patients. *Ibid.* 30, 968 (1984). Abstract.

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In Acetaminophen Assay, Only Unconjugated Drug Should Be Measured

To the Editor:

Novotny and Elser (*1*) recently reported optimized conditions for measurement of acetaminophen by the indophenol colorimetric method of Frings and Saloom (*2*), a method based on the acid-catalyzed hydrolysis of acetaminophen to *p*-aminophenol, which then reacts with phenol under alkaline conditions to form a blue indophenol product. This method, as indeed all methods based on acid hydrolysis to form *p*-aminophenol, measures inactive glucuronide and sulfate conjugates of acetaminophen as well as the potentially hepatotoxic unconjugated drug (*3, 4*). In a study of 18 patients, White (*5*) demonstrated that conjugated forms of acetaminophen represented 1 to 65% of the total drug concentration. Thus, the concentration of the clinically important unconjugated drug may be considerably overestimated when acetaminophen is measured by such. For instance, Stewart et al. (*4*) observed a positive error of between 40 and 700% when acetaminophen was measured in sera from overdosed patients by methods based on acid hydrolysis, as compared with liquid chromatography. They and others (*3, 6*) have recommended that methods based on acid hydrolysis to *p*-aminophenol without prior separation of acetaminophen from its conjugates no longer be used in clinical chemistry laboratories.

It was therefore disconcerting to see the article by Novotny and Elser, but even more so to witness the promulgation of such serious misconceptions. These authors state that a method which measures total acetaminophen (conjugated plus unconjugated) is preferred because nomograms used to relate serum acetaminophen concentrations to probable hepatotoxicity are based on the measurement of total drug by a method such as that of Glynn and Kendal (*7*). This is incorrect on two counts. First, the nomograms are based on measurement of the poten-