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Marked Hypouricemia in Purine Nucleoside Phosphorylase Deficiency—Serendipitous Finding on Screening

To the Editor:

The finding by Ducorps and Helie [1] of hypouricemia in a patient subsequently shown to have xanthine oxidase (dehydrogenase) deficiency is further emphasized by our observation, during a biochemical screen, of a very low serum urate (20 $\mu\text{mol/L}$) and undetectable urine urate in a 4-year-old girl. The child, whose parents were first cousins, had severe developmental delay, spastic tetraparesis, and hemolytic anemia associated with a positive Coombs test [2]. The patient was diagnosed as having purine nucleoside phosphorylase deficiency (PNP; EC 2.4.2.1) on the basis of a urine purine profile that demonstrated increased concentrations of deoxyguanosine; neurological, immunological, and clinical observations; and family studies. An elder sister who was severely developmentally retarded died at age 4 years of chickenpox complicated by pneumonia and carditis.

The observation of hypouricemia is an important and often misinterpreted finding in children. It can suggest the "Dalmatian dog syndrome" [3], in which there is a high renal urate clearance (hereditary renal hypouricemia), or xanthine dehydrogenase deficiency. The latter is rarely associated with the clinically much more severe combined xanthine dehydrogenase/sulfite oxidase deficiency (also known as the molybdenum cofactor defect). Considerable genetic heterogeneity in enzyme expression is now documented in both xanthine dehydrogenase/sulfite oxidase and PNP deficiency, such that milder disease is seen with late presentation. The plasma urate may be in the low to normal range and the defect can only be recognized from the presence of abnormal purine metabolites [3, 4].

Errors in the diagnosis of these and other defects of purine metabolism can occur if the patient has a urinary tract infection or if urine is collected without the correct preservative. The deoxynucleosides that accumulate in PNP deficiency are acid labile [3]. Urines collected into acid may have their deoxynucleosides break down into the corresponding bases, causing confusion between PNP and xanthine dehydrogenase deficiency. Furthermore, because bacterial contamination can cause degradation of nucleosides and deoxynucleosides to their bases and subsequently to uric acid, the presence of live bacteria in urine may result in a missed diagnosis of xanthine dehydrogenase deficiency as well if only uric acid is measured in urine [3].

The serendipitous finding of hypouricemia can suggest a defect in purine metabolism, which can best be resolved by assaying red cells, plasma, and a 24-h urine specimen (preserved with 1 g of thymol and analyzed by HPLC). Close clinical liaison is essential, as is referral of samples to a specialized laboratory.

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Salivary Reagent Stick Measures Serum Ethanol Concentrations

To the Editor:

Patients presented to an accident and emergency department often are affected by alcohol; a rapid diagnosis of intoxication and an estimation of blood alcohol content are sometimes essential. Furthermore, in comatose patients it is important to assess whether the unconsciousness is caused by an intracranial hematoma, an epileptic insult, or a diabetic coma, or is an effect of excessive ethanol consumption. Therefore, fast, easy-to-perform determinations of the concentration of blood alcohol are needed. Reagent kits for determinations of blood or serum ethanol concentrations are based on enzymatic reactions with either alcohol dehydrogenase [1] or alcohol oxidase [2] and require the use of manual spectrophotometers or automated analyzers. These methods, however, are cumbersome and time-consuming. Easier and faster methods include breath-alcohol devices [3] and devices for measuring ethanol in saliva [4]. We applied the latter for determination of ethanol in serum because patients who present to an accident and emergency department always undergo routine phlebotomy; therefore, blood instead of saliva is the material of choice.

The Q.E.D.TM Saliva Alcohol Test (STC Diagnostics, Bethlehem, PA) looks like a small thermometer. Instead of saliva, we use 200 μL of serum as the

sample. The ethanol in the sample is oxidized to acetaldehyde with alcohol dehydrogenase as a catalyst, and with the simultaneous reduction of NAD^+ to NADH. Alkaline pH and an acetaldehyde-trapping agent force this reaction to the generation of NADH. In the presence of an oxidizing agent, diaphorase, and a tetrazolium salt (all incorporated into the solid phase of the measuring device), the NADH is oxidized, and a colored end product is formed. The length of a colored bar is proportional to the concentration of ethanol in the specimen, such that this concentration can be read from a scale on the device. The whole procedure can be performed within 5 min.

Q.E.D. Saliva Alcohol Tests are available in two detection ranges: 0–1.5 and 0–3.5 g/L. According to the manufacturer, compounds such as ethylene glycol, acetone, methanol, and butanol do not interfere. We tested L-lactate (30 mmol/L), β -hydroxybutyrate (30 mmol/L), triglycerides (25 mmol/L), and hemoglobin (0.6 mmol/L) and also found no interferences. The functionality and stability of the test can be checked by examination of a control spot located at the closed end of the device. For a valid test, this spot must turn purple within seconds after the device has been filled.

We compared the Q.E.D. test with an enzymatic method based on alcohol dehydrogenase, using a Cobas FARA analyzer (Hoffmann-LaRoche, Basel, Switzerland). We added to distilled water as well as to pooled serum various amounts of ethanol and measured the concentrations of ethanol by both methods (Fig. 1A). Both experiments showed statistically significant correlations. Next, we obtained blood samples from 24 emergency department patients with altered mental status or suspected alcohol intoxication for serum ethanol determinations by Q.E.D. and Cobas FARA. Samples with a serum alcohol concentration >2.5 g/L were reanalyzed after dilution with saline; the results are given in Fig. 1B. Linear regression analysis with the non-parametric method of Passing and Bablok [5] revealed a line with the equation $y = 1.00x + 0.10$ ($r = 0.98$).

We conclude that the Q.E.D. Saliva Alcohol Test can be used for determining the ethanol concentration in serum samples. The test is very easy to perform, reliable, and rapid and is a useful device for bedside analysis of alcohol at hospital emergency units.

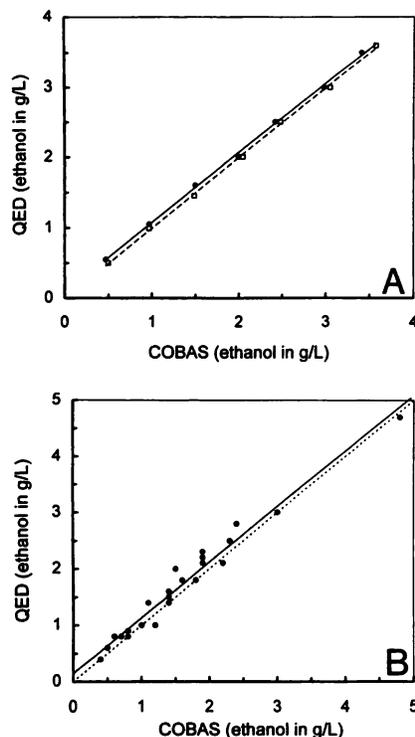


Fig. 1. Ethanol concentrations determined by the Q.E.D. method compared with values obtained by an enzymatic Cobas method: (A) aqueous solutions ($\square \cdot \cdot \square$) and serum ($\bullet \cdot \bullet$) supplemented with ethanol; (B) patients' samples ($n = 24$).

The dotted line in panel B represents complete identity ($y = x$).

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Presentation of Receiver-Operating Characteristic (ROC) Plots

To the Editor:

We were happy to read the Letter by Henderson and Bhayana [1] and support their recommendations for the presentation of ROC plots. However, we would like to make some additional suggestions.

With regards to their second recommendation, "Indicate decision thresholds, particularly diagnostic rule-in and rule-out thresholds," we suggest indicating on the graph the threshold value that corresponds to a sensitivity of 95% and the threshold value that corresponds to a specificity of 95%. The reader can then read from the ROC plot the specificity corresponding to a sensitivity of 95%, and the sensitivity corresponding to a specificity of 95%. Authors can select other levels of sensitivity and specificity (e.g., 90%, 99%, 100%), depending on the clinical sense of the test and the possible cost of a decision made on the basis of a false-positive or false-negative classification.

If authors prefer not to publish the ROC plot—although this is recommended [2]—the same information should be given in the text or in a table. Also, we stress the importance of reporting the number of cases in the two groups studied, namely, the positive "diseased" group and the negative "control" group.

When making a comparison between two ROC curves, investigators should keep in mind that almost any laboratory test can be made highly specific or highly sensitive just by choosing a very low or a very high threshold value. It is more interesting, therefore, to compare the sensitivity of the two tests corresponding to a given specificity (e.g., 95%) and the specificity of the tests corresponding to a given sensitivity (e.g., 95%), as in the example in Fig. 1. Even when the areas under the two curves are not different, this information may result in a quite different appreciation of the usefulness of the two diagnostic tests. For example,