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Commentary: Reducing Substances in Urine: a Paradigm for Changes in a Standard Test

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Abstract. Detection of reducing substances in urine has been a standard laboratory procedure for about 50 yr. It is used as a screening test for inborn errors of carbohydrate metabolism. Although the test has poor specificity and most states perform mandatory newborn screening for the common genetic defects, most clinical laboratories still perform this as a reflex test on all pediatric urine samples. We suggest that laboratories should perform this test only at the specific order of a physician and that they should review their test menu frequently to delete tests that no longer have a clinical rationale.

Keywords: reducing substances, urinalysis, screening tests

Detecting non-specific reducing substances in urine is an old procedure that can be found in laboratory medicine text books [1-3]. This test, in combination with an enzymatic dipstick assay for urinary glucose, can detect inborn errors of sugar metabolism in pediatric patients. This test is usually run as a reflex test; only if the dipstick glucose is negative does the test 'reflex' to the reducing test. A negative dipstick glucose assay and a positive reducing test suggest that some substance other than glucose is present in the urine. However, the test, which involves the reduction of colorless cupric ion to colored cuprous ion, is not very specific for sugars [4]. A positive test for reducing sugars in urine requires clinical and laboratory follow-up tests, usually carbohydrate analysis by chromatographic analysis, to diagnose an actual inborn error of carbohydrate metabolism.

The clinical basis of this test goes back to the early-to-mid 1960s when investigations showed a relationship between the presence of reducing substances in the urine of newborns, and the presence of specific sugars [5,6]. The qualitative measurement of urinary reducing substances was accepted as a quick screening test of asymptomatic patients in the absence of any other screening procedure.

However, screening for a number of genetic-based diseases is now standard practice. Starting in about 1965, when phenylketonuria testing became widespread, additional tests have been added to state-mandated newborn screening profiles (Table 1). In all states, newborn screening for specific diseases is mandatory [7], and all include testing for deficiency of galactose-1-phosphate uridyl transferase [7], which is associated with classic galactosemia [8]. In addition, 18 states screen for a deficiency of galactokinase and galactose epimerase [7]. Other diseases of carbohydrate metabolism (except diabetes) have much lower prevalence (Table 2) or are clinically more benign than classic galactosemia and do not require screening of asymptomatic newborns.

Given the widespread screening for galactosemia, why haven't clinical laboratories dropped the urinary reducing substances test for newborns? When this question was posed at our institution, we performed a small survey of 17 hospital

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Table 1. Examples of diseases mandated by state-run newborn screening programs in the USA [7].

Condition/Disease	Number of States
Phenylketonuria	50
Galactosemia	50
Maple syrup urine disease	39
Homocystinuria	37
Homozygous sickle cell disease	50
Sickle-C disease (HbSC)	50
Primary hypothyroidism	50
Biotinidase deficiency	40
Cystic fibrosis	14
Multiple carboxylase deficiency	23
Congenital adrenal hyperplasia	43

laboratories, of which 16 were in the United States and 1 in Canada; 3 laboratories were in university hospitals and the remainder in private hospitals. We found that 13 of the 17 laboratories (76%) analyzed reducing substances as a reflex screening test for urine from pediatric patients. The age at which the reflex testing was performed varied from <6 months (2/17) to no age restrictions (2/17). Three of the 17 laboratories had discontinued the reflex testing of pediatric urine specimens for reducing substances as unnecessary and perform the test only upon a physician's order. One laboratory had discontinued the test altogether.

Almost all of the 13 laboratories that still performed reflex testing of reducing substances in pediatric urine specimens were considering changing the policy to one that would delete the reflex test. Based on this survey of current practice at other hospitals, our institution decided to make the test for urine reducing substances available only upon a physician's request; we recommend this change to other hospital laboratories.

Laboratories adopt new tests to benefit patient care but, as this example illustrates, they are less vigilant about removing tests or methods that have outlasted their clinical utility. We urge clinical laboratories to review their test menus and ask for each entry: "Why are we providing this test or this procedure at this time?"

Table 2. Genetic diseases of carbohydrate metabolism [8-10].

Disease	Prevalence	Defect
Essential fructosemia	1/130,000	Deficient enzyme activity
Hereditary fructose intolerance	1/20,000	Deficient enzyme activity
Hereditary fructose-1,6-deficiency	32 cases	Deficient/absent enzyme
Diabetes mellitus type I	1/130 C	Impaired insulin secretion
Pentosuria	1/2500 AJ	Deficient enzyme activity
Galactosemia	1/62,000	Absent enzyme
Galactokinase deficiency	1/100,000	Absent enzyme
Galactose epimerase deficiency	unknown	Absent enzyme
Alcaptonuria	1/250,000	Absent enzyme

AJ, Ashkenazi Jews; C, Caucasians

References

1. McNeely MDD. Urinalysis. In: Gradwhol Clinical Laboratory Methods & Diagnosis, 8th ed (Sonnenwirth AC, Jarett L, Eds), Mosby, St Louis, 1980; vol 1, p 486.
2. Caraway WT. Carbohydrates. In: Fundamentals of Clinical Chemistry, 2nd ed (Tietz N, Ed), Saunders, Philadelphia, 1976; p 257.
3. Bauer JD, Ackerman PG, Toro G. Clinical Laboratory Methods, 8th ed, Mosby, St Louis, 1974; pp 15-72.
4. Young DS, Pestaner LC, Gibberman D. Effect of drugs on clinical laboratory tests. Clin Chem 1975;21:1D-432.
5. Fiser-Herman M, Petrovacki M. Urinary reducing substances in alkaptonuria. Clin Chim Acta 1958;3:248-252.
6. Giovannini M, Consonni V, Calleri A. Research on urinary elimination of reducing substances in the first and second infancy: comparison of results obtained with paper and thin layer chromatography. Minerva Pediatr 1965;17:1702-1703.
7. National Newborn Screening and Genetics Resource Center. http://genes-r-us.uthscsa.edu/nbsdisorders.pdf (updated, 21 October 2005).
8. Segal S. Disorders of galactose metabolism. In: Metabolic Basis of Inherited Disease, 5th ed (Stanbury JB, Wyngaarden JB, et al, Eds), McGraw-Hill, New York, 1983; pp 167-191.
9. Gitzelmann R, Steinmann B, van den Berghe G. Essential fructosuria, hereditary fructose intolerance, and fructose-1,6-diphosphatase deficiency. In: Metabolic Basis of Inherited Disease, 5th ed (Stanbury JB, Wyngaarden JB, et al, Eds), McGraw-Hill, New York, 1983; pp 118-140.
10. Hiatt H. H. Pentosuria. In: Metabolic Basis of Inherited Disease, 4th ed (Stanbury JB, Wyngaarden JB, et al, Eds), McGraw-Hill, New York, 1978; pp 110-120.