determined whether S100B can be detected in urine of preterm and term infants.

Eighty-three women with normal physiological pregnancies (23 preterm, 60 term) whose deliveries occurred between 26–42 weeks of gestation were enrolled in the study. Gestational age was defined by the presence of ultrasonographic signs according to Campbell and Thoms (5) and by postnatal confirmation. Exclusion criteria were multiple pregnancies, intrauterine growth retardation, and third trimester maternal diseases. The study protocol was approved by the local Ethics Committee after consent was given by parents.

After birth, the first urination was collected, and S100B concentrations were measured in duplicate in all samples using a Lia-mat Sangtec 100 (AB Sangtec Medical, Bromma, Sweden) according to the manufacturer’s recommendations. Cord blood samples were collected at the same time and measured in 42 patients selected without conscious bias. The detection limit of the assay was 0.02 μg/L. The S100B concentrations in the groups are expressed as the mean ± SE. Statistical analysis was performed by Kolmogorov–Smirnov one-way ANOVA and Mann–Whitney U-test when data were not normally distributed. The relationship between the urine concentration of S100B and weeks of gestation was analyzed by linear regression analysis. P <0.05 was considered significant.

Normal clinical conditions and an absence of overt neurological injury were observed on discharge of all infants from the hospital. In the preterm group, gestational age at birth and birth weight were significantly lower than in the term group (P <0.01), whereas no differences were observed regarding delivery mode and Apgar score at the 1st and 5th min (P >0.05, not significant). Tests of renal function were within reference intervals and did not differ between the two groups (P >0.05, not significant). Urine concentrations of S100B were significantly higher in the preterm group, peaking in the earliest weeks of gestation and progressively decreasing near term, being undetectable or at the detection limit of the assay in the term group (3.17 ± 1.02 vs 0.70 ± 0.23 μg/L; P <0.001). The same pattern was found when S100B cord blood concentrations were measured in the same selected patients (data not shown). When urine S100B concentrations in preterm newborns were subgrouped according to gestational age and weight at birth (6), they were significantly higher in the very low birth weight group compared with both the low birth weight and term groups (P <0.001) and significantly higher in the low birth weight group than in the term group (P <0.001). A significant correlation between S100B urine concentrations and gestational age was observed when all newborns were considered (r = −0.79; P <0.001).

The data presented constitute the first observation of S100B in urine and offer a urinary S100B concentration reference curve (available from the authors) at different gestational ages. These findings also fit previous observations on cord blood S100B concentrations (4). Because renal function tests were normal in all examined infants, it did not appear to influence the results. The higher concentrations of S100B in preterm newborns may be related to the neurotrophic role possibly exerted by S100B (1). This possibility seems to be consistent with high concentrations of the trophic factor at earlier gestational ages, when brain maturation processes are more active, and lower concentrations at later stage of brain maturation.

In conclusion, the present S100B urinary pattern could provide the basis for a new and easier means of studying brain pathophysiological conditions, which have hitherto been investigated by measuring the protein in cerebrospinal fluid or blood.

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Is It Necessary to Order Aspartate Aminotransferase with Alanine Aminotransferase in Clinical Practice?

To the Editor:

We read with great interest the articles by Dufour et al., “Diagnosis and monitoring of hepatic injury. I. Performance characteristics of laboratory tests” (1) and “Diagnosis and monitoring of hepatic injury. II. Recommendations for use of laboratory
tests in screening, diagnosis, and monitoring" (2). These articles address an important but somewhat controversial subject. Broughton and Worthington (3) reported that an order for liver function tests produced 17 different test combinations in 19 different laboratories. This shows that there is no real consensus on the use of liver function tests. We thus want to add some remarks to the articles regarding aspartate aminotransferase (AST) and alanine aminotransferase (ALT). In our opinion, the use of AST can be reduced, and we think that it is not necessary to order AST with ALT in routine practice.

The information presented by Dufour et al. (1) on factors affecting the transaminases is important, but drug effects must be added. Several hundred drugs have been reported to affect AST or ALT (4).

Many laboratories still offer "standardized liver test panels". In our opinion, laboratory investigations should always be ordered selectively, depending on the clinical situation. Several reports have shown that a high AST value in relation to the ALT value is associated with alcohol-dependent liver damage. It is known that alcohols often suffer from minor trauma and that alcohol affects other organs in addition to the liver. Part of the AST activity may thus be from other organs. Such an increase in AST is probably not attributable to muscle injury because creatin kinase typically is only slightly increased in these patients (5). Patients with suspected liver damage also have damage to other organs (e.g., trauma patients and patients with autoimmune diseases) and thus have high AST/ALT ratios that may be interpreted as alcohol dependent.

Several of the studies showing a high AST/ALT ratio were performed many years ago. In the older studies, ALT may have been analyzed without addition of pyridoxal-5′-phosphate. Alcoholics have low pyridoxal-5′-phosphate, which in animal models is associated with decreased ALT activities (6). The high AST/ALT ratio seen in alcoholics was at least partly attributable to low pyridoxal-5′-phosphate (7). At present, all AST and ALT tests in Sweden are preincubated with pyridoxal-5′-phosphate. This should cause a reduction in the AST/ALT ratio. Were the ratios presented in Table 1 of Ref. (2) analyzed in the presence of pyridoxal-5′-phosphate? What are the specificity and sensitivity of the AST/ALT ratio in an emergency ward setting with modern AST and ALT assays?

Serum AST decreases more rapidly than ALT because of a shorter half-life. This means that the AST/ALT ratio changes over time, which further reduces the usefulness. To be able to evaluate the ratio, we thus need to know when the damage occurred. If the time of damage is known, it is likely that the cause is also known. Patients with viral hepatitis have a low AST/ALT ratio in comparison with alcoholics (2). Could this be at least partly attributable to differences in disease duration in previous studies?

In several intervention studies in Sweden, we have tried to optimize the use of clinical chemistry investigations in primary care. In a primary care setting we have recommended that ALT is sufficient to screen for liver damage. The recommendations produced a reduction in AST ordering. Initially, AST and ALT tests were ordered with equal frequency, and this decreased to 0.23 AST tests per ALT ordered (8). In the rheumatology outpatient unit in Uppsala, the ordering ratio decreased to 0.2 (9), and in the University Hospital in Odense to 0.006. We believe that the use of AST should be questioned in a dialog with our clinical colleagues (10). Our experience is that discussion of the value and use of AST is important but somewhat controversial subject. Broughton and Worthington (3) reported that an order for liver function tests produced 17 different test combinations in 19 different laboratories. This shows that there is no real consensus on the use of liver function tests. We thus want to add some remarks to the articles regarding aspartate aminotransferase (AST) and alanine aminotransferase (ALT). In our opinion, the use of AST can be reduced, and we think that it is not necessary to order AST with ALT in routine practice.

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not increase plasma activities of these enzymes except by causing hepatic injury. We did, however, include drug-induced injury in the differential diagnosis of both acute and chronic liver injury and emphasized the importance of taking a drug history. We agree with the authors that this is an important consideration.

The issue of whether to include both AST and ALT in “standardized liver tests panels” was of considerable interest to our group. Our position, as stated in the guidelines, is that both enzymes, along with several other tests, should be included in a “hepatic panel” (1, 2). We agree, however, that there are cases where a complete hepatic panel is not needed. For example, we did not recommend use of AST or ALT for monitoring patients with acute hepatitis once they have begun to decrease. We also stated that ALT is the most important test in screening for chronic hepatic injury.

There is considerable evidence, however, that AST and ALT together are of use in the differential diagnosis of acute hepatic injury and in monitoring patients with chronic hepatic injury. In acute hepatic injury, AST typically is increased to a greater degree than ALT in the very acute stages of injury, as with acetaminophen or ischemic liver injury. Recognition of this ratio often provides a clue to the presence of one of these two etiologies. As pointed out by Larsson and Tryding and in our guidelines, a high ratio is typical of alcoholic hepatitis. Although they suggest that modern assays with pyridoxal-5'-phosphate may not show such a ratio, the article by Matloff et al. (3) showed that correction of plasma pyridoxine deficiency did not abolish the high AST/ALT ratio in alcoholic hepatitis. In unpublished studies of patients with hepatitis C, we have consistently seen a much higher AST/ALT ratio in persons with both alcohol abuse and hepatitis C than in those with hepatitis C alone, and in 7% of samples, only AST is increased. Furthermore, as indicated in our guidelines, an increasing AST/ALT ratio is relatively specific for development of cirrhosis in patients with chronic hepatitis C infection, and may be present long before clinical symptoms of decompensation develop. Thus, we believe that use of both AST and ALT is indicated in monitoring persons with chronic hepatic injury.

We do agree with the authors that “routine” use of both AST and ALT in screening tests is excessive. We applaud their intervention efforts in reducing AST ordering after consultation with clinical colleagues. For screening purposes, as our guidelines indicate, ALT is a superior test and can usually be used alone. In patients with known liver disease, we believe that use of both tests provides additional clinical information that is worth the small additional cost.

References

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Significance of Autoantibodies to Oxidatively Modified LDL in Plasma of Children with Down Syndrome

To the Editor:
Oxidative modification of blood lipoproteins is an important risk factor in the development of some pathological states such as atherosclerosis (1, 2). One of the sources of oxidatively modified lipoproteins in blood is the interaction of native lipoproteins with active oxygen species generated by activated neutrophils and monocyte-macrophages. In vitro studies have suggested that modification of LDL by lipid peroxide products is one potential mechanism (3–5). Modification of LDL by malondialdehyde (MDA) or other lipid peroxides in vivo is a prerequisite to the formation of arterial foam cells (6), and the presence of antibodies to lipid oxidation products suggests that oxidatively modified LDL (ox-LDL) is expressed in the artery wall (7). In vitro treatment with MDA can induce the expression of specific epitopes on oxLDL (8).

In the general population, antibodies to oxLDL and lipoperoxidations in plasma are correlated with a high risk of premature atherosclerosis. Individuals with Down syndrome (DS) show signs of premature aging, and several authors have proposed the DS population as an “atheroma-free model” (9, 10). Opinions differ as to which lipid or lipoprotein is the most important in predicting the development of atherosclerosis. Most studies compared subjects with DS with matched individuals admitted to the same institution for other disabling disorders or with unselected healthy controls. Simon et al. (11) found high serum cholesterol in young DS patients, but subsequent studies have not confirmed this in groups of affected individuals ranging in age from 6 to 60 years (12). Triglyceride concentrations have been reported to be decreased (10), increased (13), or unchanged (9) in patients with trisomy 21 compared with matched controls.

We studied two groups of children: 15 apparently healthy controls (8 males, 7 females; mean age, 4 years; range, 3–5 years) and 40 children with trisomy 21 (20 males, 20 females; mean age, 4.5 years; range, 2–7 years). We determined MDA by the LPO-586 assay (Oxis International), which is based on the reaction of a chromogenic reagent (10.3 mmol/L N-methyl-2-phendimidole in acetonitrile) with MDA at 45°C (14). One molecule of MDA reacts with two molecules of the reagent to yield a stable chromophore with maximal absorbance at 586 nm. For the measurement of oxLDL antibodies in plasma, we used an ELISA (GULL; Design International, Kennebunk, ME) with purified oxLDL bound to