ever, in neither trial was the APACHE II score used to stratify randomization. Therefore, subpopulations defined according to APACHE II scores cannot be assumed to be comparable. On the basis of PROWESS, DrotAA was approved for use in patients at high risk for death, but only after extensive analyses of important characteristics of the subgroups. In the ADDRESS trial, the subgroups defined by an APACHE II score of 25 or more differed statistically, in that more patients receiving DrotAA had multiple-organ dysfunction (46.7 percent vs. 31.4 percent, P=0.02) and respiratory dysfunction (64.2 percent vs. 50.3 percent, P=0.01) and more were 65 years of age or older (62.4 percent vs. 56.6 percent, P=0.02). Such imbalances in baseline characteristics limit the assessment of outcomes in this subpopulation.

Dr. Friedrich has similar concerns but also notes that combining the subgroups of patients with multiple-organ dysfunction in the ADDRESS and PROWESS trials does not indicate a major benefit of DrotAA (relative risk of death, 0.84; 95 percent confidence interval, 0.70 to 1.01). However, there seems to be an error in his estimate of the number of patients with multiple-organ dysfunction in the ADDRESS study. The number of patients with multiple-organ dysfunction included 455 who received DrotAA and 407 who received placebo, reflecting the higher number of patients with multiple-organ dysfunction who were randomly assigned to the active-treatment group. With the use of the correct data and a chi-square test, a combined analysis of all 2133 patients with multiple-organ dysfunction from both the PROWESS and ADDRESS trials yields a relative risk of 0.82 (P=0.007; 95 percent confidence interval, 0.71 to 0.95). Furthermore, sensitivity analysis with the use of logistic models to investigate a potential study effect reveals no significant interaction between the study and the assigned treatment, and the treatment-effect estimate (P=0.01) was unaltered.

Dr. LaRosa is correct to inquire about the baseline characteristics of the subgroups of patients in the ADDRESS trial with an APACHE II score of 25 or more. Imbalances in baseline characteristics coupled with the small sample size limit the interpretation of outcomes in this subgroup of patients.

The ADDRESS trial was designed to enroll patients who had severe sepsis and a low risk of death and for whom DrotAA was not indicated under the approved label applicable to the investigative site. The study was discontinued for reasons of futility, limiting any comparison between subpopulations in the ADDRESS trial and the high-risk populations in the PROWESS trial.

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γ-Hydroxybutyric Acid in Hair

TO THE EDITOR: The review (June 30 issue)[1] on γ-hydroxybutyric acid (GHB) generated correspondence (Oct. 13 issue),[2] which revealed that biochemical genetics laboratories can detect GHB.[2] There is an additional detection method worth noting.

When a medicolegal issue is present (e.g., a drug-facilitated crime), finding a hard-to-detect drug can be important.[3] GHB has amnesic properties[3] and is fully and rapidly metabolized to carbon dioxide and water. Even succinic acid, a product of GHB metabolism, becomes undetectable in urine within hours of ingestion.

However, the GHB in the body of a crime victim is still present, even after it has been totally removed from the circulation: GHB, like other substances, accumulates in hair, after a single exposure.[4] If the hair shaft is negative for GHB, the drug may still be detected in the root bulb, at hair concentrations measured in nanograms per milligram.[5]

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Ketoacidosis during a Low-Carbohydrate Diet

TO THE EDITOR: It is believed that low-carbohydrate diets work best in reducing weight when producing ketosis.[1] We report on a 51-year-old white woman who does not have diabetes but had ketoacidosis while consuming a "no-carbohydrate" diet. There was no family history of diabetes, and she was not currently taking any medications. While adhering to a regimen of carbohydrate restriction, she reached a stable weight of 59.1 kg, a decrease from 72.7 kg. After several months of stable weight, she was admitted to the hospital four times with vomiting but without abdominal pain. On each occasion, she reported no alcohol use. Her body-mass index (the weight in kilograms divided by the square of the height in meters) was 26.7 before the weight loss and 21.7 afterward. Laboratory evaluation showed anion-gap acidosis, ketonuria, and elevated plasma glucose concentrations on three of the four occasions (Table 1). She had normal concentrations of plasma lactate and glycosylated hemoglobin. Screening for drugs, including ethyl alcohol and ethylene glycol, was negative. Abdominal ultrasonography showed hepatic steatosis.

On each occasion, the patient recovered after administration of intravenous fluids and insulin, was prescribed insulin injections on discharge, and gradually reduced the use of insulin and then discontinued it while remaining euglycemic for six months or more between episodes. Testing for antibodies against glutamic acid decarboxylase and antinuclear antibodies was negative. Values on lipid studies were as follows: serum triglycerides, 102 mg per deciliter; high-density lipoprotein (HDL) cholesterol, 50 mg per deciliter; and calculated low-density lipoprotein (LDL) cholesterol, 189 mg per deciliter.

The patient strictly adhered to a low-carbohydrate diet for four years, with an estimated carbohydrate intake that was often less than 20 g per day. When she was put on a diet containing normal amounts of carbohydrates, her fasting plasma glucose concentration and the results of oral glucose-tolerance tests were normal. With a normal carbohydrate intake, she had no more episodes of ketoacidosis.

Citrate generated by glycolysis inhibits carnitine palmitoyltransferase complex I, limiting the beta-oxidation of fatty acids and thereby reducing ketogenesis. Lactate, which increases during starvation, can induce hepatic ketogenesis.[2] Low-carbohydrate, fat-rich meals can enhance alpha-cell secretion of glucagon and lower insulin concentrations.[3,4] Plasma fatty acid concentrations can be twice as high during low-carbohydrate diets as compared with the usual carbohydrate intake in the postabsorptive period.[5] Increased concentrations of free fatty acids in the absence of carbohydrate-induced inhibition of beta-oxidation of fatty acids and in the presence of an abnormally high ratio of glucagon to insulin and elevated concentrations of lactate may have caused ketoacidosis in our patient, who was trying to avoid all dietary carbohydrates. Low-carbohydrate, high-fat diets are generally associated with higher

Table 1. Laboratory Values during Four Episodes of Ketoacidosis.

Variable	Date			
	June 1999	May 2000	June 2002	Dec. 2002
Anion gap	33	26	35	31
pH	7.2	7.1	6.9	7.1
Urine ketones	Large	Large	Large	Large
Plasma glucose (mg/dl)	265	103	219	275
Glycosylated hemoglobin (%)	5.4	5.4	5.4	5.4
Lactate (mmol/liter)	—	0.8	0.8	1.2