N. Roglans, L. Vil, M. Farr, M. Alegret, R.M. Sanchez, M. Vazquez-Carrera, and J.C. Laguna. Impairment of hepatic Stat-3 activation and reduction of PPAR-alpha activity in fructose-fed rats. *Hepatology*, 45(3): 778 – 788, 2007.

Dr. Keith D. Lindor
Editor, *Hepatology*

Dear Editor,

I am a biochemist with over twenty-five years experience in the manufacture, applications and uses, consumption and metabolism of nutritive sweeteners, including sucrose, fructose and high fructose corn syrup (HFCS).

It is with this background that I read with interest the following article published in your journal:

N. Roglans, L. Vil, M. Farr, M. Alegret, R.M. Sanchez, M. Vazquez-Carrera, and J.C. Laguna. Impairment of hepatic Stat-3 activation and reduction of PPAR-alpha activity in fructose-fed rats. *Hepatology*, 45(3): 778 – 788, 2007.

The authors propose that the effects of fructose ingestion on [human] liver PPAR-alpha would "partially explain the observed association between increased consumption of fructose-containing beverages and the epidemics of obesity and metabolic syndromes in Western societies."

As the authors correctly point out, diets containing exaggerated amounts of fructose have been known for many years to "induce metabolic derangements" (their words). The literature is rife with such examples. What the literature lacks, however, is perspective. And without perspective we may have interesting observations, but with little relevance to the human condition.

I simply wish to make the following observations:

- Although it is impossible to calculate precisely from the data provided, it appears from Figure 1, graph D that the rats derived approximately 200 kcal/day from solid food and 50 kcal/day from fructose or glucose in drinking water. Added fructose thus represented around 20% of calories, an amount at least double that in the typical human diet. Attempting to predict an effect on humans using data obtained in such a fashion is obviously a perilous endeavor.

- The sweeteners in fructose-containing beverages referred to by the authors (i.e., sucrose and HFCS) contain nearly equal quantities of fructose and glucose. They are *not* 100% fructose. Therefore, to extrapolate the results of the authors' experiments – obtained with 100% fructose supplements — to caloric beverage sweeteners comprising 50% glucose/50% fructose represents an *over-exaggerated* effect, and quite possibly a gross one at that.

- The presence of dietary glucose has been shown by Riby et al to have a moderating effect on fructose; that is, glucose ingested at the same time at similar concentration tempers effects of fructose (*AJCN* 1993;58:748S). Thus, the effect with common sweeteners (containing *both* glucose and fructose) would more likely lie midway between the extreme effects of the two determined independently by the authors.

- The authors fail to show any weight gain differential between the fructose–glucose variables vs. water control. Surely to be relevant, the reported differences with fructose should be manifested in weight gain, the ultimate measure of obesity. Quite the opposite is actually observed: in an elegant display of caloric compensation, the test animals responded to added liquid calories by consuming less solid chow.

The most important question for the authors to have answered is whether fructose produces the effect at typically-consumed concentrations, in typically consumed forms (i.e., fructose *plus* glucose) and in mixed meals. The authors have succeeded in inducing yet another "metabolic derangement," but have certainly not demonstrated relevance to the human condition.