

More on Mice and Men: Fructose Could put Brakes on a Vicious Cycle Leading to Obesity in Humans

To the Editor:

The role played by dietary fructose in the 'epidemic' of obesity has recently been debated in the *Journal of the American Dietetic Association* (1,2) following the earlier review by Lustig (3) in which fructose is argued to have a prominent role in the causation and perpetuation of obesity. These warrant comment because the arguments do not represent the literature in humans on this topic and literature is cited inaccurately, particularly in regard to my own work.

In addition to these problems, there is a question of whether the review article (3) meets acceptable evidence-based standards sufficient to affect nutrition policy and practice. Moreover, evidence synthesis needs to focus on practice needs recognizing one policy may not fit all circumstances. Correspondents Sievenpiper and colleagues (1) appear concerned primarily with the acceptability and potential benefits of moderate intake of pure or crystalline fructose in diabetics. By contrast, correspondents Lustig and Schwarz (2) appear concerned primarily with the risks of excessive sucrose or high-fructose corn syrup consumption in infants, children, and adolescents. Both camps work on respectable hypotheses, and one ought not to be seen as to exclude the other.

The idea that moderate intakes of pure fructose is acceptable and potentially beneficial for the control of dysglycemia and diabetes is not new. However, the idea has been given a boost by recent systematic and meta-analytical evidence of human intervention studies showing moderate doses of pure fructose (up to at least 90 g daily) lower glycated hemoglobin (HbA1c) in a dose-dependent manner (4) when provided by carbohydrate exchange, with possible implications for diabetes and coronary heart disease (5). This is contrary to expectations about HbA1c offered in the re-

view article by Lustig (3). The idea received a further boost when it was shown that moderate and high doses of pure fructose (up to 150 g/d) in human intervention studies leads to improvement in insulin sensitivity (5). Again this is contrary to the expectations raised in the review article by Lustig (3).

Consistent with Lustig's expectations, nevertheless, a reduction in insulin sensitivity does arise with excessive pure fructose intake in humans, as in mice. However, in humans, this has not been demonstrated unless fructose intake is higher than the published threshold of ~150 g/d (5), a value from meta-analysis that holds true after recently doubling the number of intervention studies available for analysis (6). According to the most recent published information on fructose intakes in a representative sample of the US population, the 150 g/d threshold is much higher than the 95% percentile fructose intake for the highest consumer group (19- to 22-year-olds) and adolescents. It is also three times higher than the published population average intake of 49 g/d (7), an intake value falling since the turn of the millennium (8).

According to the review article (3), insulin resistance and hyperinsulinemia are central to the vicious-cycle hypothesis that describes possible events thought to contribute to obesity. The hypothesis is well articulated in earlier reviews (9,10), but elsewhere is promoted by Lustig with a focus on fructose (3,11-14). All those reviews focusing on fructose are narrative—none has followed the principles of systematic review and meta-analysis that are essential to the establishment of evidence-based practice and, later, practice-based evidence. Now we have some insight from such information (4-6) the vicious cycle hypothesis might be elaborated further.

Abbreviating the hypothesized vicious cycle to its most basic (Figure), excessive carbohydrate food intake promotes an insulin response that can facilitate the retention or storage of energy in adipose tissue as fat. Excess fat accumulation leads to insulin resistance and hyperinsulinemia. Subse-

quent leptin resistance and ghrelin hyposecretion promote greater food intake, so advancing the obese state. Excessive glucose intake from high-glycemic sugars or starchy foods helps to turn the cycle by promoting an insulin response and increasing fat storage. By contrast, firstly, pure fructose could put a brake on the vicious cycle owing to its poor ability to stimulate an insulin response and storage of fat in adipose tissue. This of course might be somewhat balanced by a lower ghrelin response to fructose than glucose in some (15), but not all, studies (16,17). Second, fructose would put a further brake on the cycle by promoting insulin sensitivity at doses <150 g/d (5,6). Doses of fructose >150 g/d do the opposite and override the first brake on the cycle posed by the low insulin response to fructose. According to this perspective, fructose at doses <150 g/d or approaching would not promote obesity via this cycle. This perspective is consistent with systematic and meta-analytical evidence from interventional studies in normal, overweight, obese, and diabetic persons (4,18,19, and J. L. Sievenpiper, MD, PhD, unpublished data, December 2010) and consistent with an approach to >95% caloric compensation to fructose (and other sugars) in sweetened beverages as the duration of chronic studies approaches 1 year (20).

So what about the role of de novo lipogenesis (DNL) debated by the correspondents—might this add fat to obesity? Excessive dietary fats add directly to fat accumulation in adipose tissue, so an excess would favor insulin resistance and obesity. A contribution to fat accumulation is made by dietary carbohydrate via hepatic DNL, but does this add a significant amount? It is argued by one group of correspondents that fructose adds little to DNL as assessed by appearance of plasma lipids using stable isotope techniques (1). Meanwhile the other correspondents (2) argue it is important to be aware of the time course of DNL rather than assume fasting rates are representative. This is well illustrated by the work of Stanhope and colleagues (21) in overweight/

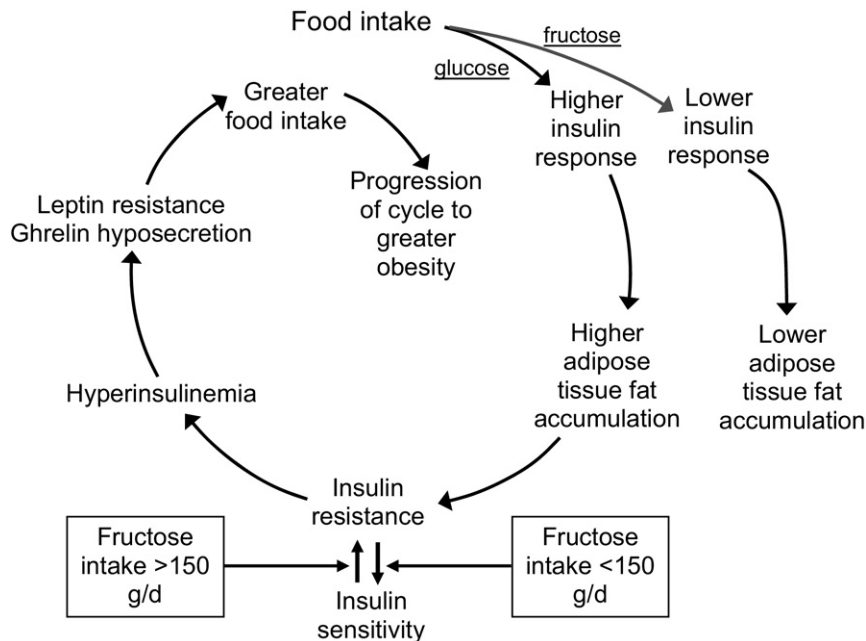


Figure. Hypothesized cycle of obesity in relation to fructose consumption. Fructose has the potential to put a brake on the vicious cycle in adults that otherwise is hypothesized to promote obesity.

obese patients (mean body mass index 29), who estimated the time-course of fractional DNL over a 24-hour period, and which peaked highest after the third meal of the day.

However, from their data (21) estimates of 24-hour average rates expressed as the fraction of triglyceride exported by liver due to DNL (μ DNL) are still low, and only ~3% more for their diet—excessive with 25% of energy requirement as fructose—compared with a similar glucose loaded diet. This corresponds to <1.5% of the energy in the daily fructose dose being converted to lipid. Others have provided lower estimates (22). On a proportional basis, the average consumer (49 g fructose daily) would increase μ DNL by only 1% corresponding to approximately 1 g fat daily—not much to fuss about. An even lower increment would be expected in normal weight persons. Further, even 1 g daily in an overweight or obese person is likely to be an overestimate since an increment in postprandial plasma triglyceride fails to materialize unless fructose intake is higher than the average daily intake of fructose, while fasting triglycerides may not rise at all unless >100 g fructose

is consumed daily (ie, approximately >33 g/meal), among studies of longest duration (Table 3 and Figure 7 in reference [4]). DNL in adipose tissue can be expected to be less still (23).

It might be argued that a high proportion of DNL triglyceride stays in the liver rather than being exported, but such accumulation is thought for the present to be no greater than the amount exported (24) and, of course, may reside in the liver only temporarily. Moreover, fat accumulation in the liver after excessive fructose intake has, so far, been observed to be no more than occurs after a similar glucose intake in sound and well-controlled studies of both men (25) and women (21). Another study in men also indicates similarity of glucose and fructose (26). Data for men in a further study (21) suggests a different outcome, but consideration has to be given to marked inequality between treatment groups at baseline.

Correspondents Lustig and Schwarz (2) suggest a visit to the Sick Children's Hospital in Toronto, Canada, to convince others about the relationship of sick children to fructose. More easily we might consult publication from that hospital (27) informing us

that lifestyle factors are important, and that a sample of obese children (average age 14 years) with fatty liver consume on average 33 g/d of fructose from sugars (7% of energy intake). The study had no case-control; however, the fructose intake was less than the US average for this age group at 48 g/d (10% of energy intake) (7). Other factors, but not fructose or sugars, were reported to associate with insulin resistance (27). Lifestyle including dietary factors also differ by much more than can be accounted for by simple caloric dilution with sugars (or 'fructose'), as noted elsewhere for adults (20) and likely so for sugar-sweetened beverages in adolescents, too (28).

In their correspondence, Sievenpiper and colleagues (1) incorrectly cite our revival work on fructose (4)—inadvertently, one trusts, citing another of our papers from the same journal published shortly afterwards but related to fiber and glycemia (29). This revival and subsequent work (5) indicated a need for researchers to take account of dose response and thresholds of effect in humans. There also is a need to take a balanced view of health markers, with the examples of HbA1c responding beneficially at regular fructose intakes and fasting triglycerides responding adversely at very high or excessive dose of fructose. It further used fasting triglycerides as an example of a potentially unwelcome response to excessive fructose for which studies of longest duration show least effect. These concerns are added to elsewhere (5), noting that fructose is not sucrose or high-fructose corn syrup, for which the same fructose dose would be accompanied by more energy, more carbohydrate, and greater glycemic load. These additional attributes confound interpretation of observational studies making appropriate intervention studies essential (20). Even interventional studies on fructose can inadvertently use confounding designs in which researchers seem to forget that fructose is also a source of carbohydrate and energy, thus appropriate systematic reviews including meta-analyses are essential as well (20). With exceptions from a limited number of research centers, knowledge of these problems seems to be gathering pace elsewhere, too, with more cir-

cumspect reviews about fructose (4,5,18,19,30-34).

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STATEMENT OF POTENTIAL CONFLICT OF INTEREST: The author holds shares in Independent Nutrition Logic Ltd. Independent Nutrition Logic Ltd is an independent consultancy with commissions from many organizations, a full list of which may be found at www.inlogic.co.uk. Among these now are The Calorie Control Council Fructose Committee, its members having a commercial interest in fructose and sugars containing fructose.

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Author's Response:

Livesey disputes several points in my original *Journal of the American Dietetic Association* article (1), in which I elaborate the parallels between fructose and ethanol. Livesey advances his argument that fructose when ingested alone is a safe, nontoxic foodstuff based on the following points: 1) measurement of *de novo* lipogenesis (DNL) in response to fructose ingestion alone is low; 2) the potential value of fructose for glucose exchange as a sweetener for type 2 diabetes because it does not raise blood glucose (and, therefore, hemoglobin A1c); 3) the assertion that studies of fructose do not show decompensation of insulin sensitivity until oral doses reach 150 g; 4) according to the proposed model, insulin resistance