Disclosures:
Dr. Lustig has never accepted money from the food industry, and has no disclosures with respect to this article. However, Dr. Lustig has authored three popular books as a public health service: Fat Chance: the hidden truth about sugar; Sugar Has 56 Names: a shopper’s guide; and The Fat Chance Cookbook. He is also President of the non-profit Institute for Responsible Nutrition (USA), and an advisor to Action on Sugar (UK).

Q. Can you name an energy source that is not nutrition, for which there is no biochemical reaction in the human body that requires it, that causes disease when consumed chronically and at high dose, yet we love it anyway — and it’s abused?

A. Alcohol. It’s calories (7 kcal/gm), but it’s not nutrition. There’s no biochemical reaction that requires it. When consumed chronically and in high dose, alcohol is toxic, unrelated to its calories or effects on weight. Not everyone who is exposed gets addicted, but enough do to warrant public health interventions. Clearly, alcohol is NOT a food — it’s a dangerous drug, because it’s both toxic and abused — and we regulate it by taxation and restriction of access.

Dietary sugar is composed of two molecules: glucose and fructose. Glucose is the energy of life. Glucose is so important that if you don’t consume it, your liver makes it (gluconeogenesis). Conversely fructose, while an energy source, is otherwise vestigial; there is no biochemical reaction that requires it. Yet when consumed chronically and at high dose, fructose is similarly toxic and abused. Not everyone who is exposed gets addicted, but enough do, to warrant a similar discussion.

Toxic
In order to demonstrate toxicity, I must show that fructose (and therefore sugar) is an independent contributor to metabolic disease, unrelated to caloric equivalence or effects on weight, and I must show causation.

Prospective cohort studies. Three recent studies, controlled for calories, adiposity, and time, support added sugar as a cause of type 2 diabetes. First, a prospective cohort analysis found that sugar-sweetened beverage (SSB) consumption increased risk for development of diabetes over a 10-year period. Each SSB consumed increased the hazard risk (HR) ratio by 1.29. A second group performed a meta-analysis of studies isolating consumption of soda (n = 17) and fruit juice (n = 13) separately, controlling for calories and adjusting for adiposity, and showed that both increased the relative risk (RR) ratio for diabetes (1.27, 1.10 respectively) over time. Lastly, our group analyzed NHANES adolescent data between 2005-2012, and showed that added sugar increased prevalence of metabolic syndrome; the 4th and 5th quintiles of sugar consumption exhibited a 9.9-fold increase in prevalence over the 1st quintile.

Econometric analysis. Our group joined three databases: 1) the Food and Agriculture Organization statistics database, which lists by food availability per person by country (2000-2010) and by line item (total calories, fruits excluding wine, meats, oils, cereals, fiber-containing foods, and sugar/sweeteners); 2) the International Diabetes Federation database listing diabetes prevalence by country; and 3) the World Bank World Development Indicators Database which controlled for the confounders poverty, urbanization, aging, physical activity, and obesity.

Only sugar generated a signal. For every 150 calories per day in excess, diabetes prevalence increased 0.1%, but if those 150 calories happened to be a can of soda, diabetes prevalence increased 11-fold, by 1.1%. This study meets the Bradford Hill criteria for “causal medical inference” — the same level of proof we have today for tobacco and lung cancer.

Interventional starch-for-sugar exchange. Our group examined the effects of isocaloric substitution of sugar with starch in 43 children with metabolic syndrome over a 10-day period. We reduced percent calories as dietary sugar from 28% to 10%, keeping calories and weight constant. Every aspect of metabolic

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health improved: diastolic BP reduced by 5 mmHg, triglycerides by 46%, LDL by 0.3 mmol/L, and glucose and insulin area under the curve dropped by 8% and 57%, respectively.

Abused
Fructose directly increases consumption independent of energy need. It appears to be, along with caffeine, the food additive that makes “fast food” addictive. Animal studies. Sucrose infusion directly into the nucleus accumbens reduces dopamine and m-opioid receptors similar to morphine, and establishes hard-wired pathways for craving in these areas that can be identified by fMRI. Indeed, sweetness surpasses cocaine as reward. Animal models of intermittent sugar administration induces behavioral alterations consistent with dependence; i.e. binging, withdrawal, craving, and cross-sensitization to other drugs of abuse. Human studies. Fructose and glucose, despite being equally calorically (4.1 kcal/gm), and despite the fact that both molecules have effects on the brain, have two completely different sites of action, and generate two completely separate effects. Jonathan Purnell first explored this dichotomy by infusing each sugar intravenously, and measuring the blood oxygenation level-dependent (BOLD) functional MRI signal in the brain. Glucose lit up the cortical executive control areas, but fructose suppressed the signal coming from those control areas. Katherine Page took this a step further by giving an oral glucose or fructose drink. She saw regional cerebral blood flow (CBF) within the hypothalamus, thalamus, insula, anterior cingulate, and striatum (appetite and reward regions) was reduced after glucose ingestion, where it’s the sugar that drives the reward. Finally, while sugar does not exhibit classic withdrawal, it does demonstrate what the DSM-V qualifies as “dependence,” that is: Craving or a strong desire to use; Recurrent use resulting in a failure to fulfill major role obligations (work, school, home); Recurrent use in physically hazardous situations (e.g. driving); Use despite social or interpersonal problems caused or exacerbated by use; Taking the substance or engaging in the behavior in larger amounts or over a longer period than intended; Attempts to quit or cut down; Time spent seeking or recovering from use; Interference with life activities; Use despite negative consequences. Sugar recapitulates all the chronic detrimental effects on health as does alcohol, and is a cause of metabolic syndrome. Sugar is both toxic and abused, similar to alcohol, and should be also treated as a dangerous drug. Indeed, sugar meets all public health criteria for regulation. And indeed, with the passage of municipal soda taxes in Berkeley, San Francisco, Oakland, Albany, Boulder, Chicago, and Philadelphia, the public is now engaged. Robert H. Lustig, M.D. is a neuroendocrinologist, with basic and clinical training relative to hypothalamic development, anatomy, and function. He is Professor of Pediatrics in the Division of Endocrinology at University of California, San Francisco, and Director of the Weight Assessment for Teen and Child Health (WATCH) Program at UCSF. Prior to coming to San Francisco in 2001, he worked at St. Jude Children’s Research Hospital in Memphis, TN. Dr. Lustig can be reached at: rlustig@peds.ucsf.edu, or: (415) 502-8672.

References