inducing the metabolic syndrome via ATP depletion and uric acid generation is weakened by an over-reliance on unphysiologic protocols that do not reflect real-world human diets.

Much of the experimental evidence cited in support of a significant role for fructose was generated in experimental systems using elevated levels of pure fructose to induce metabolic upsets. The commonly used nutritive (caloric) sweeteners are sucrose, high fructose corn syrup (HFCS), honey and fruit juice concentrates. All are composed of fructose and glucose and deliver approximately equal amounts of each to the bloodstream after absorption. The incidence of individuals consuming only fructose or only glucose in the diet is surely so rare as to be insignificant.

Studies using very high fructose levels may be useful for probing metabolic pathways, but they have very little predictive value for most human diets. Contemporary fructose protocols often compare the effects of pure fructose versus pure glucose in human subjects at levels between 15 and 30% of total energy (see e.g. [2]) and in animals at levels exceeding 60% of calories (see e.g. Cirillo et al. [1], references 23 and 27). Using NHANES 1999–2004 data, Marriott recently estimated mean total fructose intake (added + naturally occurring) at 9.1% of energy for all ages and genders; total fructose intake for even the heaviest consumers—95th percentile 19- to 22-year males and females—was <18% of energy [3].

The practical implications of pure sugar comparisons are seldom discussed, because the dietary consequences are so absurd. Humans get some fructose from natural sources (fruits, vegetables, nuts), but most comes from added nutritive sweeteners, which are half fructose and half glucose. To take in 30% of calories as fructose, 60% of calories in the form of a nutritive sweetener must be consumed. This is clearly a gross distortion of the diet, violates all nutritional guidelines and would occur in only the rarest of circumstances. And since glucose fares so well in comparative metabolic tests, it has been proposed as a replacement for current fructose-containing sweeteners. But glucose lacks the functionality and sweetness of fructose-containing sweeteners; more would be required, at nearly twice the calories of current food choices.

Absence confirmation in real-world diets characterized by moderate fructose use and mixtures of sugars, the conclusion of Cirillo et al. that fructose has a meaningful role in inducing the metabolic syndrome must be considered speculation.

Conflict of interest statement. The author is a consultant to the food and beverage industry in nutritive sweeteners, including HFCS and sucrose. His professional associations, past and present, include individual food industry companies as well as such organizations as the American Chemical Society, American Council on Science and Health, Calorie Control Council, Corn Refiners Association, Institute of Food Technologists and International Life Sciences Institute.

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Reply

Sir,

Dr White raises the clinical relevance of the experimental and human studies showing that fructose can induce inflammation and features of metabolic syndrome. Fructose (0.25 mM) induces intercellular adhesion molecule-1 (ICAM-1) expression and ATP depletion in endothelial cells [1]; similar serum concentrations are routinely achieved following a sugary meal in humans [2]. A diet in 20% fructose raises sICAM-1 levels in rats [1], and a diet of 25% fructose raises sICAM-1 in humans [3]; this is not distinct from diets of 15–20% fructose seen in the upper quintile of society [2]. A diet of 25% fructose was able to induce insulin resistance, dyslipidaemia and increased intra-abdominal fat in overweight adults [4]. Recent reports suggest that at least 16% of the studied American populations, especially adolescents and children, are consuming over 25% of daily energy requirements from sugar-sweetened beverages. While most experimental studies use higher doses of fructose, this is done so that we can see effects in days to weeks, not months to years. Rats fed 15% fructose do develop insulin resistance, but it takes months [5]. The reason why we give pure fructose is that by doing so we can separate its effects from glucose; however, the combination is actually worse since glucose stimulates fructose absorption. Some studies show that fructose can induce features of metabolic syndrome more effectively when combined with glucose [6].

Throughout the world, there has been a marked increased intake of fructose, with the primary sources being from table sugar (sucrose) or high fructose corn syrup (HFCS). Intake correlates with the epidemic of obesity and metabolic syndrome; experimental studies show that fructose can induce features of the metabolic syndrome, and the cellular mechanisms are now being elucidated. We recommend a tax on sugar and HFCS with the aim of reducing the intake by 60%; the millions of dollars from the tax could support medical research, and the billions saved in health care costs would boost our ailing economies.

Conflict of interest statement. R.J.J. and Y.S. are listed as inventors on patent applications by the University of Florida related to the role of fructose in hypertension and metabolic syndrome. Dr Johnson has also written a book on fructose for the lay public (Rodale Press, 2008).
A male patient, born in 1984, was diagnosed at the age of 12 years with PR3-ANCA-associated glomerulonephritis due to Wegener’s Granulomatosis. He was treated with cyclophosphamide, methyprednisone and azathio-prine. During follow-up, from 1999 to 2004, he suffered several relapses that were treated with cyclophosphamide or methotrexate in combination with corticosteroids.

In 2004, the patient developed a biopsy-proven renal relapse. Deoxyspergualin, an anti-proliferative drug with effects on lymphocyte and macrophage function and neutrophil production, was started in combination with high-dose steroids [2]. During the first three cycles, a partial remission was induced. Because haematuria and proteinuria persisted, the kidney was re-biopsied and showed persistently active glomerulonephritis with new necrotizing and crescentic lesions. The fourth and fifth cycle went uncomplicated. In the sixth cycle, our patient received an influenza vaccination. Shortly after this vaccination, a severe relapse occurred with purpura, arthralgias, new nodular lung lesions and active glomerulonephritis. Deoxyspergualin was stopped, and mycophenolate mofetil (2 g/day) in combination with high-dose corticosteroids and plasma exchange was given [3]. Despite this therapy, he developed severe ulceration of the legs, abdominal pain with bloody diarrhoea and intracerebral haemorrhage due to cerebral vasculitis resulting in death.

Our patient experienced a fatal relapse occurring shortly after influenza vaccination. Vaccination was done while our patient had active glomerulonephritis suggesting that (further) activation of the vasculitic process after influenza vaccination was caused by so-called bystander activation [4] in which vaccination resulted in activation of antigen presenting cells expressing the autoantigen proteinase 3.

Stassen et al. [1] demonstrated that influenza vaccination is probably safe in patients with quiescent AAV. However, in AAV patients with active disease, we think that clinicians should be very careful with preventive vaccinations.

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