by isosorbide dinitrate and hydralazine therapy. The improved responses of black subjects to isosorbide dinitrate and hydralazine therapy may suggest severely disrupted vascular homeostasis in these subjects, which may be particularly responsive to nitrate therapy.

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1. Ferdinand KC, Elkayam U, Mancini D, Otii E, Pina I, Anand I, Feldman A, McNamara D, Leggett C. Use of isosorbide dinitrate and hydralazine in African-Americans with heart failure and reduced ejection fraction. The investigators have correctly pointed out that more genetic information is necessary to assess the impact of many other polymorphisms that may affect drug response. We would like to add important information that is relevant to nitric oxide (NO) biology and may help to explain mechanisms possibly involved in racial differences observed when patients receive isosorbide dinitrate and hydralazine, which are drugs that directly or indirectly affect NO activity. There is now evidence that combinations of genetic polymorphisms (haplotypes) in the gene encoding endothelial NO synthase (eNOS) may be more informative than single eNOS polymorphisms with respect to endogenous NO formation and bioavailability. Importantly, a specific eNOS gene haplotype combining partic-

erular in African-Americans. In addition, the fructose component of added sugars. Dietary sodium intake may happen to be predominant sources of processed foods, sodium will be increased proportionately. In other words, sugar consumption drives fluid intake, and sugar may just, coincidentally, come along for the ride. We would argue something more akin to the opposite. Sugar consumption leads to insulin spikes, low blood sugar, and hunger. Sugar is a major drive to hunger; an increase in sugar will increase the amount of fluid consumed, and if part of this fluid is in the form of soft drinks, [sugar] will be increased proportionately. In other words, salt consumption drives fluid intake, and sugar may just, coincidentally, come along for the ride.

Processed foods are the principal source of dietary sodium; they also happen to be predominant sources of added sugars. Dietary sodium intake tracks with the consumption of added sugars, but it is that sugar, not the salt, that may be the actual causative factor for increased blood pressure. This notion is supported by meta-analyses of randomized controlled trials suggesting that sugar is more strongly related to blood pressure in humans than sodium. Moreover, the fructose component of commonest sugars has been shown to dispose to hypertension in obese children and adolescents, although different eNOS haplotypes have been associated with hypertension in adults. In line with the suggestion by Ferdinand et al, it remains to be determined which eNOS haplotypes may predict the responses to isosorbide dinitrate and hydralazine therapy, particularly in African-Americans. In addition, there is evidence that black subjects have higher circulating concentrations of an endogenous NO inhibitor, the asymmetric dimethylarginine, and therefore, black subjects may be exposed to additional factors impairing endogenous NO formation that are counteracted by isosorbide dinitrate and hydralazine therapy.
increase blood pressure in a manner independent of sodium intake\(^5\) and salt sensitivity.\(^6\) Encouraging consumers to hold the sugar, not the salt, may be the better dietary strategy to achieve blood pressure control.

The authors go on to state that "sugar in soft drinks stimulates insulin secretion which could lead to sodium and water retention and, thereby, possibly increasing blood pressure." Although this might be true, clinical trial data do not support the notion that retention of sodium is clinically significant in regards to increased blood pressure with sugar-sweetened beverages. In a trial of 20 healthy normotensive men, consumption of a sucrose-sweetened beverage led to a significant increase in blood pressure, whereas consumption of a fructose-sweetened beverage did not, although the fructose-sweetened beverage had the greater antinatriuretic effect.\(^7\) What this result suggests is that retention of sodium is not the main mechanism for sugar’s ability to elevate blood pressure. Another, more likely, mechanism is activation of the sympathetic nervous system—both directly through sugar’s effect on the ventromedial hypothalamus and indirectly through hyperinsulinemia—with resultant changes to heart rate and vascular tone.\(^8\)–\(^12\) Hyperleptinemia,\(^13\)–\(^15\) increased production of methylglyoxal,\(^16\)–\(^20\) and reductions in adenosine triphosphate—leading to reductions in nitric oxide—may also play a role\(^21\) (Figure 1). Activation of the sympathetic nervous system by fructose is supported by its ability to increase blood pressure and heart rate in humans on acute ingestion.\(^22\)

He et al conclude that, "A reduction in population salt intake, which can easily be made by slowly reducing the amounts of salt added to foods by the food industry, will lead to a reduction in population blood pressure and cardiovascular mortality, as demonstrated in the prepared and processed foods became less salty, it is entirely possible that people would eat more of them to obtain the sodium their physiology demands (Figure 2). Would the concomitant increase in added sugars and other refined carbohydrates, trans-fats and other processed oils, and chemical colorings, flavorings, and preservatives from the increased consumption of processed foods result in overall benefit for population health?

The investigators state that "a reduction in salt intake will cause a reduction in sugar sweetened soft drink consumption and, thereby, a decrease in obesity and type II diabetes.” We argue the opposite (Figure 2); a reduction in salt intake may lead to an increased intake in processed foods (and added sugars) and, thereby, increase the risk of diabetes, obesity, and cardiovascular disease. We do, however, agree with the authors that, “efforts to reduce soft

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**Figure 1.** Hypertensive mechanisms of fructose. Arrows represent direct effects or indirect effects through intermediates, which are not shown for simplicity. ATP = adenosine triphosphate; NO = nitric oxide; RAS = renin-angiotensin system; RNS = reactive nitrogen species; ROS = reactive oxygen species.

**Figure 2.** Unintended consequences of population-wide sodium restriction.
drink consumption combined with a gradual reduction in the amounts of sugar added to soft drinks will provide additional beneficial effects on health.”

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17. Lana A, Rodriguez-Artalejo F, Lopez-Garcia E. Consumption of sugar-sweetened beverages...