The pertinent clinical question arising from our work is whether therapeutic interventions that improve peripheral or central insulin resistance modify sympathetic responsiveness. To this end, we have shown in a follow-on study that moderate weight loss (8.6% of body weight) markedly reversed blunted sympathetic neural responsiveness to glucose, but only in insulin-resistant subjects (11). The ratio of the norepinephrine spillover AUC\(_{0-120}\) to the insulin AUC\(_{0-120}\) which gives an index of sympathetic responsiveness for a given increase in insulin concentration, increased from 3.6 ± 0.4 to 5.0 ± 1.0 (P = 0.05) in the insulin-resistant subjects but did not change in the insulin-sensitive group. Further intervention trials using insulin-sensitizing agents are needed to confirm the role of insulin resistance in mediating blunted sympathetic responsiveness in metabolic syndrome obesity. Intranasal insulin delivery may offer another therapeutic avenue to test whether manipulating brain insulin concentrations affects sympathetic nervous system function in this clinical setting.

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Safety of iron-fortified foods in malaria-endemic areas

Dear Sir:

On the basis of the finding that supplementation with iron and folic acid in malaria-endemic areas may cause an increased risk of hospitalization and death (1), an expert group convened by the World Health Organization (WHO) recommended that iron supplementation should be restricted in areas in which malaria transmission is intense and infectious disease highly prevalent (2). The group exempted industrial fortification from these restrictions, under the assumption that the iron would be consumed in smaller amounts throughout the day and therefore absorbed more slowly. It also recommended that iron preparations added to food after cooking ("home fortification") should not be used in malaria-endemic areas because, when administered in a single meal, the dose of iron is still relatively high (2).

To circumvent this problem, Troesch et al (3) studied the effects of consuming food that was home-fortified with micronutrient powders containing low amounts of highly bioavailable iron. We disagree with their conclusion that this approach may allow for effective, untargeted in-home fortification of complementary foods: it can be valid only if the adverse effects of iron observed by Sazawal et al (1) were due to an increased proliferation and invasion of enteric pathogens. It is indeed conceivable that iron leads to

| TABLE 1 | Amounts of iron absorbed through various iron interventions |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Native iron in food | Dose of iron ingested | Fractional iron absorption | Amount of iron absorbed |
| Native iron in food | Dose of iron ingested | Fractional iron absorption | Amount of iron absorbed |
| Complementary food (60 g whole maize flour) fortified with 3 mg iron as NaFeEDTA | 0.75 | 3 | 7.39 | 0.28 |
| Complementary food (60 g whole maize flour) fortified with 3 mg iron as ferrous sulfate | 0.75 | 3 | 1.55 | 0.06 |
| Complementary food (60 g whole maize flour) fortified with 12.5 mg iron as ferrous fumarate | 0.75 | 12.5 | <1.55 | <0.21 |

1. Dose and formulation of iron as investigated by Troesch et al (3).
3. The fractional iron absorption is <1.55% because it is known to be negatively associated with the dose of iron ingested (5).
invasive nontyphoid *Salmonella* bacteremia, a complicating factor associated with death in African children with severe malarial anemia (4).

The WHO expert group considered an alternative explanation, however, that a large bolus of iron taken in a single dose leads to the transient formation in plasma of non-transferrin-bound iron (2), which may act as a nutritional source and favor the proliferation of pathogens such as malaria. If this were indeed the underlying mechanism, then the increased risk of adverse events can be avoided only by reducing the amount of iron absorbed.

The micronutrient powder containing 3 mg iron as NaFeEDTA investigated by Troesch et al (3) would in fact supply more absorbed iron than the original formulation of Sprinkles (Sprinkles Global Health Initiative, Toronto, Canada), which contains 12.5 g iron as ferrous fumarate (0.28 mg as compared with <0.21 mg; Table 1). Moreover, in African populations, this difference would probably be more than indicated in Table 1, because iron absorption is exponentially increased in individuals with iron deficiency (5), as opposed to the volunteers investigated by Troesch et al (3), who were mostly healthy and iron replete.

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