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Metabolic syndrome: An ill wind that blows some good?

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Throughout human history, people have struggled to understand the causes of human suffering and human illness. For example, in the Book of Job, Satan afflicted Job with painful skin sores. Job, his family, and his friends all inquired why Job became ill despite the fact that he is described as a man who was upright, feared God, and avoided evil. In recent years, the search for explanations has been extended from the realm of religion to include scientific inquiry. In the case of genetic diseases, scientists have inquired why Evolution did not eliminate disease-causing mutations through natural selection. For example, 60 years ago, Allison suggested that heterozygosity for HbS ("sickle trait") provides partial protection from malaria [1]. This protection from endemic malaria provided a positive selection to maintain the HbS mutation in the gene pool – despite the fact that homyzygosity for the same mutation causes a severe illness (i.e., sickle cell disease). More recently, a genetic variant form of apolipoprotein L1 has been demonstrated to lyse *Trypanosoma brucei rhodesiense* [2,3], and the same variant has been reported to increase the risk of developing chronic renal disease – including focal segmental glomerulosclerosis [24] . In a parallel vein, over 50 years ago, Neel [56] proposed a "thrifty gene" hypothesis – that evolution selected for the ability to store energy efficiently to prepare for famine which was a constant threat during most of human history. In recent years, such a thrifty gene may have become maladaptive by promoting obesity in modern times when food has become quite abundant for many (albeit not all) people.

In the present issue of *Diabetes and Metabolism Reviews*, Brima *et al*. [7] have provided another example whereby a predisposition to develop a chronic disease may be associated with resistance to an infectious disease. Specifically, they report that high fat diet induced metabolic syndrome but also protected CD-1 mice from the lethality associated with *Trypanosoma cruzi* infection. As emphasized by the authors, there is a complex relationship between nutrition and the state of host defenses to fight infection. At one extreme, starvation and under-nutrition compromise host defenses, and render the individual highly susceptible to infectious disease. At the other extreme, a surfeit of calories produces metabolic syndrome, which is associated with multiple abnormalities including obesity, dyslipidemia, insulin resistance, and a pro-inflammatory state. In the study by Brima et al. [7], a high fat diet dramatically decreased mortality due to T. cruzi infection by ~65% (i.e., from 55% to 20% mortality). Based upon this seminal observation, the investigators initiated an inquiry into the mechanisms whereby high fat feeding protected CD-1 mice from lethality due to T. cruzi infection. Unexpectedly, metformin therapy provided added protection from lethality even though the drug partially mitigated the metabolic abnormalities induced by high fat feeding. It is likely that future studies with additional anti-diabetic drugs (e.g., PPAR-gamma

agonists) may shed additional light on the mechanisms whereby high fat feeding protects T. cruzi infected mice from lethality.

In the Discussion section of the paper, the authors refer to one specific molecular mechanism that could potentially contribute to the protective effect of a high fat diet. Trypanomastigotes hijack the LDL receptor, which mediates entry into adipocytes [8]. Thus, alterations in lipoprotein metabolism have potential to alter expression or function of LDL receptors, and indirectly inhibit the entry of the infectious agent into cells. A growing literature has suggested complex interactions between hepatitis C virus (HCV) and lipoprotein metabolism [9]. Thus, this type of mechanism may be broadly relevant to multiple infectious diseases.

In conclusion, the paper of Brima *et al.* [7] is a thought-provoking study that highlights the complex interactions between nutrition and host defenses against infectious disease. According to a modern understanding of systems biology, there are complex regulatory networks that mediate multiple physiological changes in response to simple perturbation. In the case of high fat feeding, it is most common to emphasize the adverse effects such as obesity, dyslipidemia, insulin resistance, diabetes, and cardiovascular disease. Brima *et al.* [7] remind us that high fat feeding represents an ill wind that may blow some good – in this case, protection from lethality due to *T. cruzi* infection.

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