

Obesity is very widespread and detrimental to health. Obesity brings with it many changes including heightened immune function, and a higher prevalence of major cardiovascular disorders, cancer, diabetes, and Alzheimer disease. Obesity is also associated with shortened lifespan. The detrimental effects of obesity are linked to the "metabolic syndrome", a broad range of changes in metabolic processes and immune function.

As a first approximation, we agree with this formulation but we will then proceed to document some of its weaknesses. (i) Crude mortality rates increase with increasing body mass index (BMI) but as the BMI approaches the normal range, mortality rates reverse (the now classic "J-shaped curve") so that individuals with reduced BMI have elevated mortality. (ii) A multiplicity of medical and surgical conditions have been reported where short term and medium term outcomes are better for overweight patients. These conditions are placed under the heading of "obesity paradox". (iii) The medical community has introduced a binary system for the metabolic syndrome ---- yes, patient has it or *no*, the patient does not have it, despite the fact that all of the changes that are considered components of the metabolic syndrome are continuous variables.

Our work is focused on sharpening focus and improving understanding of these three weaknesses in the conceptualization of obesity as a medical problem. Using historical perspective, we have hypothesized that the metabolic syndrome is evolutionarily ancient. In addition to the wellaccepted harm associated with late-in-life disorders, we propose that throughout human history, the so-called syndrome has benefited younger individuals by enhancing host defenses against infectious diseases. We posit that the major benefits of the metabolic syndrome accrue in controlling the widespread potentially ravaging infections that the body cannot self-cure, including tuberculosis and (the subject of the thesis) *Trypanosomiasis cruzi* also known as Chagas disease or American trypanosomiasis. Infection with *Trypanosoma cruzi*, the protozoan parasite that causes Chagas disease, results in chronic infection that leads to cardiomyopathy with increased mortality and morbidity in endemic regions.

iv

In support of our hypothesis that the consequences of the metabolic syndrome may be positive or negative, depending on age and on life events such as infectious diseases, we induced the metabolic syndrome in CD-1 mice by high fat feeding prior to infection with *T. cruzi*. The lethality of *Trypanosoma cruzi* infection was reduced from 55% to 20%.

In a companion study, our group found that a high-fat diet (HFD) protected mice from *Trypanosoma cruzi*-induced myocardial damage and significantly reduced post-infection mortality during acute *Trypanosoma cruzi* infection.