Why getting healthy can seem worse than getting sick

March 20 2012

A new article in The *Quarterly Review of Biology* helps explain why the immune system often makes us worse while trying to make us well.

The research offers a new perspective on a component of the immune system known as the acute-phase response, a series of systemic changes in blood protein levels, metabolic function, and physiology that sometimes occurs when bacteria, viruses, or other pathogens invade the body. This response puts healthy cells and tissue under serious stress, and is actually the cause of many of the symptoms we associate with being sick.

"The question is why would these harmful components evolve," asks Edmund LeGrand (University of Tennessee, Knoxville), who wrote the paper titled with Joe Alcock (University of New Mexico). The researchers contend that answer becomes clear when we view the acute-phase response in terms of what they call "immune brinksmanship."

The immune brinksmanship model "is the gamble that systemic stressors will harm the pathogens relatively more than the host," LeGrand said. The concept, he explains, is akin to what happens in international trade disputes. When one country places trade sanctions on another, both countries' economies take a hit, but the sanctioning country is betting that its opponent will be hurt more.

"One of our contributions here is to pull together the reasons why pathogens suffer more from systemic stress," LeGrand said.

The acute-phase response creates stress in several ways. It raises body temperature and causes loss of appetite and mild anemia. At the same time, certain vital nutrients like iron, zinc, and manganese are partially sequestered away from the bloodstream.

Some of these components are quite puzzling. Why reduce food intake just when one would expect more energy would be needed to mount a strong immune response? Zinc is essential for healthy immune function. Why pull it out of the bloodstream when the immune system is active? The benefits of a stressor like fever are fairly well known; heat has been shown to inhibit bacterial growth and cause infected cells to self-destruct. But what hasn't been clear is why pathogens should be more susceptible to this stress than the host.

LeGrand and Alcock offer some answers. For an infection to spread, pathogens need to multiply, whereas host cells can defer replication. Replication makes DNA and newly forming proteins much more susceptible to damage. It also requires energy and nutrients—which helps explain the benefits of restricting food and sequestering nutrients.

The act of invading a body also requires bacteria to alter their metabolism, which can make them more vulnerable to all kinds of stress, including heat.

Another reason pathogens are more vulnerable to stress is that the immune system is already pummeling them with white blood cells and related stressors at the site of the infection. That means that pathogens are already under local stress when systemic stressors are piled on. "In many ways, the acute-phase response reinforces the stress inflicted on pathogens locally at the infection site," LeGrand said.

As the term "brinksmanship" implies, there's an inherent risk in a strategy that involves harming oneself to hurt the enemy within. This self-

harm leaves the body more vulnerable to other dangers, including other infections. Additionally, it is possible for the immune stressors to do more damage than required to control the pathogens.

"But in general, systemic stressors when properly regulated do preferential harm to invaders," LeGrand said. Viewed this way, it's not surprising that natural selection has utilized the stressful parts of the acute-phase response in mammals, reptiles, fish, and even invertebrates.

More information: Edmund LeGrand and Joe Alcock, "Turning Up The Heat: Immune Brinksmanship In The Acute-phase Response." *The Quarterly Review of Biology* 87:1 (March 2012).

Provided by University of Chicago