formation about base rates (e.g., of cancer), whereas conditional probabilities are normalized with respect to these base rates. As a consequence, the probabilities in Eq. 2 (0.5 and 0.03) need to be multiplied by the base rates (0.003 and 0.997) in order to reintroduce base rate information. In other words, natural frequencies facilitate Bayesian reasoning because part of the calculation is already "done" within the representation itself.

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The Bioenergetics of the Immune System

NUTRIENT CONSERVATION AT TIMES OF starvation is an important survival trait for any organism. This principle is elegantly demonstrated in the Report entitled "Survival for immunity: The price of immune system activation for bumblebee workers" by Yannick Moret and Paul Schmid-Hempel (10 Nov., p. 1166), in which the survival of bumblebees was significantly impaired by their inability to perform this function. Activation of the innate immune system of these insects caused increased mortality only when their nutrient intake was limited. The most likely cause of this increased mortality was the energy demands imposed by the immune response in the context of a paucity of energy substrate.

In mammals, it has been shown that the adipocyte-derived hormone leptin is a regulator of metabolism and bodyweight (*1*). An important physiological role of leptin is as a signal of starvation, in that a falling serum leptin concentration leads to neurohumoral and behavioral changes that seek to preserve limited energy reserves for immediately vital functions (*2*). It has been proposed that reduced leptin levels during conditions of starvation lead to impaired reproductive, thermogenic (*2*), and immune capabilities (*3*). One of the key features of the innate immune response is that its response is the same on each subsequent exposure to a certain stimulus, whereas the cognate immune system shows markedly different responses upon subsequent reexposure to a particular antigen. Indeed, the cognate immune response is far more energy-expensive than the innate response, because of the necessity for the large-scale antigen-specific clonal expansion of lymphocytes.

Bumblebees pay a hidden survival cost when their immune system is activated.

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The data presented by Moret and Schid-Hemple suggest that down-regulation of the immune response observed during starvation is an adaptive process, preserving vital energy supplies for cardiac and cerebral metabolism and hence the survival of the organism. We would propose that a falling leptin concentration during starvation causes a much-reduced cognate immune response. To date, leptin expression has been detected as far back in the evolutionary tree as ectotherms (*4*). It is interesting to note that it is at this stage of evolution that a cognate immune system emerged, with its intrinsic energy-expensive requirements.

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Response

SEVERAL OF THE THEORETICAL AND EMPIRICAL points that Lord and colleagues touch on deserve further elucidation. For example, they refer to down-regulation of the immune defense under stressful conditions. This has not only been suggested for humans, performing excessive physical exercise (*1*), but has been experimentally demonstrated, for example, with birds forced to increase parental effort (*2*), or

with bumblebee workers that forage and have to stay in flight (*3*). However, our experimental paradigm is the inverse: We activated the immune system and observed the consequences (survival). Therefore, this paradigm does not necessarily require that the immune response is lower under starvation, only that the consequence of the activated immune response is to shorten life-span when the organism is starved. Our data do not allow a direct check of whether starvation leads to a down-regulated immune response.

Lord *et al.* raise the interesting perspective that the evolution of an expensive immune defense, such as cognate immunity in mammals, might be coupled with the evolution of physiological mechanisms that ensure appropriate down-regulation in case of resource shortage, as is achieved through the actions of leptin in mammals (*4*). In insects, there is no comparable cognate response. Antibacterial peptides (as induced by lipopolysaccharides) are primarily expressed in cells of the fat body that also serves as a major energy storage organ for the organism (*5*). Whether this innate response is regulated in a similar way to mammals is not known, but the answer would be of major interest for understanding the evolution of immunity.

Finally, Lord *et al.* appear to assume that energy, rather than anything else, is the limiting resource for the expression of the immune defense. We think this is an open question, but the fact that the only difference between our starved and control groups was indeed the availability of sugars is at least supportive for this view in insects. More generally, it still remains to be empirically tested whether the cognate immune response in mammals is costly in the sense as shown by us, and whether the cognate response is indeed much more costly in fitness terms than the innate response.

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A Metaphor for the Map

VARIOUS METAPHORS HAVE BEEN USED TO describe the importance of sequencing the human genome (*1*): finding the Rosetta Stone, walking on the moon, and discovering nuclear fission are among them.

Rather tame stuff. A better comparison is the discovery of the use of fire. This set us humans on the path toward control of energy and, subsequently, control of the environment outside our bodies. Sequencing the human genome sets us on the path toward control of the environment inside our bodies. It should be an interesting journey.

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CORRECTIONS AND CLARIFICATIONS

PERSPECTIVES: "The risk of extinction—what you don't know will hurt you" by J. L. Gittleman and M. E. Gompper (9 Feb., p. 997). In the first paragraph, "Falkland Island wolf" was in error. It should have read "Chiloe Island wolf."