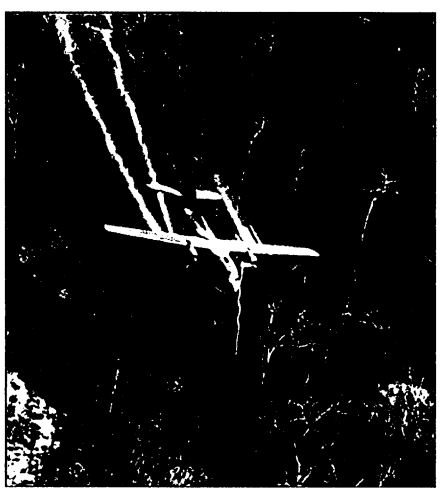
Continuing Research into Gulf War Illness

EVIDENCE SUPPORTS A LINK BETWEEN lasting health problems in some Vietnam veterans and wartime exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) in the defoliant Agent Orange. Martin Enserink, in his News Focus article "Gulf War Illness: The Battle Continues" (2 Feb., p. 812), omits this point in his review of postwar syndromes of the past.



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A U.S. Air Force C-123 flies over South Vietnam in 1966, spraying defoliants containing dioxins.

The Agent Orange example suggests that sustained research might yield important information on the cause of health effects observed in Gulf War veterans. A major research effort was initiated in response to health effects observed in people who had contact with Agent Orange in Vietnam. The Environmental Protection Agency and others built on this work and found that 2,3,7,8-TCDD and related compounds ("dioxins") may affect the health of people in the general population (*1*). It is now feasible to avoid future health problems by preventing this pollution (*2*), and a global treaty seeking this goal is in the works (*3*). However, while Enserink reports scepticism regarding identification of a cause of Gulf War Illness after 10 years and $155 million spent on research, the research on dioxins spanned decades and cost more than $2 billion (*4*).

Lacking mention of these findings following the Vietnam War, Enserink's report appears overly pessimistic about the prospects for health research following the Gulf War. The concern is that we might lose opportunities to identify a new environmental exposure factor in order to to prevent recurrent problems, if we fail to continue use of present scientific tools.

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References and Notes
1. J. Kaiser, *Science* **290**, 1071 (2000).
2. G. Karras, in *Persistent, Bioaccumulative, and Toxic Chemicals II, Assessment and New Chemicals*, R.L. Lipnick *et al.*, Eds. (American Chemical Society, Washington, DC, 2001).
3. J. Kaiser, M. Enserink, *Science* **290**, 2053 (2000).
4. D.R. Zook, C. Rappe, in *Dioxins and Health*, A. Schecter, ed. (Plenum, New York, 1994).

I WISH TO TAKE ISSUE WITH THE DESCRIPTION IN Martin Enserink's New Focus article on Gulf War Illness (GWI) of our discovery (*1, 2*) of *Mycoplasma fermentans* in ~40% of GWI patients that "it is not clear whether *M. fermentans* really causes disease." In fact, there are numerous peer-reviewed papers on this issue (reviewed in *3*), and a patent supported by the U.S. Army has been issued entitled "Pathogenic Mycoplasma" (*4*). Studies of its pathogenic properties have been published by the Armed Forces Institute of Pathology showing that healthy monkeys injected with *M. fermentans* developed a chronic illness that progresses to become fatal (*5*). Also, civilian patients with similar symptoms also show high rates of infection (*2, 6, 7*). *M. fermentans* fulfills almost all of the criteria of pathogenicity (*8*), including recovery on specific antibiotics (*7*). On the basis of this information the Department of Veterans Affairs established Cooperative Clinical Study Program #475, a blinded, placebo-controlled study on the effects of antibiotic treatment on GWI patients with *M. fermentans* infections. Although the clinical results of this study are not yet available, the laboratory entry criteria to the study indicate that a high percentage of GWI patients have systemic *M. fermentans* infections.

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References and Notes
1. G. L. Nicolson, N. L. Nicolson. *Intern. J. Occup. Med. Immunol. Tox.* **5**, 69 (1996); G. L. Nicolson, N. L. Nicolson, M. Nasralla. *Intern. J. Med.* **1**, 80 (1998).
2. A. Vojdani, A. R. Franco, *J. Chronic Fatigue Syndr.* **5**,187 (1999).
3. G. L. Nicolson *et al.*, *J. Chronic Fatigue Syndr.* **6** (3/4), 23 (2000).
4. S.C. Lo. Pathogenic Mycoplasma. U.S. Patent 5,242,820. September 7, 1993.
5. S. C. Lo, *et al. Clin. Infect. Diseases* **17** (S1), 283 (1993).
6. M. Nasralla, J. Haier, G. L. Nicolson. *Eur. J. Clin. Microbiol. Infect. Dis.* **18**, 859 (1999).
7. M. Nasralla, J. Haier, G. L. Nicolson. *Intern. J. Med. Biol. Environ.* **28**, 15 (2000).
8. D. Taylor-Robinson. *Clin. Infect. Diseases* **23**, 671 (1996).

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 6 months or issues of general interest. They can be submitted by e-mail (science_letters@aaas.org), the Web (www.letter2science.org), or regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

Statistics: What Seems Natural?

WHICH STATISTICAL DATA SEEM EASIER TO understand, 10 cases in 100, or 10%? In their Policy Forum "Communicating statistical information" (*Science*'s Compass, 22 Dec., p. 2261), U. Hoffrage and colleagues offer persuasive evidence that both experts and novices find it to be the former. When prevalence, sensitivity, and false positive rates are given as probabilities (e.g., 10%), most physicians misinterpret the information in a way that could be potentially disastrous for the patient, but when they are presented as "natural frequencies" (e.g., 10 cases in 100), the physicians' performance is dramatically better. The authors suggest ways to improve both communication of statistical information and medical education by using frequencies rather than probabilities.

The discussion by Hoffrage *et al.* leaves open the question as to why this is the case. Elsewhere, Gigerenzer and Hoffrage

suggest that "humans seem to be developmentally and evolutionarily prepared to handle natural frequencies" (*1*, p. 430) by accumulating examples of the category in question. However, this would not, in itself, explain why this accumulation is preferentially represented as frequencies rather than being transformed into some other representation, such as rate or probability.

Frequencies (e.g., 10 cases in 100) can be thought of as a subcollection (with a numerosity of 10) in a collection (with a numerosity of 100). I have suggested that we are born with a specialized capacity for representing collections and their numerosities (*2*). The evidence for this comes from a range of studies showing that infants, even in the first week of life, are sensitive to changes in the numerosity of a collection of visual objects (*3*) and that, at 6 months, they are able to form arithmetical expectations on the basis of adding an object to a collection or taking it away (*4*). The almost universal use of fingers as the representative collection in counting and arithmetic suggests that collections and numerosities form the basis of later representations also (*2*). This suggestion has been supported by recent brain-imaging evidence showing that key number areas are closely connected to the finger circuit in the intraparietal sulci (*5*).

Of course, the big developmental gap between the capacities of young children and the performance of adult decision-makers is typically filled by an education system that teaches children about collections and numerosities far more than about probability. It is thus plausible that educational practices are, in part, responsible for the biases Hoffrage *et al.* report. However, there is indirect evidence that probability concepts are intrinsically difficult for humans. Although the computational techniques required by probabilities of the type described by the authors would have been available to the ancient Greeks, an understanding of the concepts began only with Girolamo Cardano's *Liber de ludo aleae* (1525, published in 1663) and in the correspondence between Pascal and Fermat about games of chance in 1654.

"[W]e are born with a specialized capacity for representing collections and their numerosities."

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References and Notes

1. G. Gigerenzer, U. Hoffrage, *Psychol. Rev.* **106**, 425 (1999).
2. B. Butterworth, *What Counts: How Every Brain Is Hardwired for Math* (Free Press, New York, 1999) [in the UK, *The Mathematical Brain* (Macmillan, London, 1999)].
3. S. E. Antell, D. P. Keating, *Child Devel.* **54**, 695 (1983); P. Starkey, R. G. Cooper Jr., *Science* **210**, 1033 (1980); E. Van Loosbroek, A. W. Smitsman, *Devel. Psychol.* **26**, 916 (1990).
4. K. Wynn, *Nature* **358**, 749 (1992).
5. S. Dehaene, E. Spelke, P. Pinel, R. Stanescu, S. Tsivkin, *Science* **284**, 970 (1999); B. Butterworth, *Science* **284**, 928 (1999).

Response

BUTTERWORTH SUGGESTS THAT NATURAL frequencies facilitate reasoning because people are born with a specialized capacity for processing collections of discrete objects, rather than probabilities and fractions. There is certainly evolutionary and developmental evidence supporting this explanation, but there is also a second, more specific reason: Bayesian computations are simpler when information is represented in natural frequencies than in probabilities, percentages, or relative frequencies (*1*, *2*).

With natural frequencies, people can calculate the conditional probability of a hypothesis H (e.g., the occurrence of cancer) given data D (e.g., a positive test) simply:

$$p(H|D) = a/(a + b) \quad (1)$$

where a is the natural frequency of people with cancer who tested positive and b is that of people without cancer who tested positive. In the colorectoral cancer example used in our Policy Forum, a equals 15 and b equals 300 people, respectively. Communicated this way, it is easy to see that 15 out of the 315 people who tested positive actually have cancer. In contrast, when the same information is communicated in terms of conditional probabilities, as is common practice, the calculation is complicated:

$$p(H|D) = p(H)p(D|H)/p(H)p(D|H) + p(\neg H)p(D|\neg H) \quad (2)$$

Equation 2 is known as Bayes' rule. In our example, applying this rule would require the nontrivial computation $(0.003)(0.5)/[(0.03)(0.5) + (0.997)(0.03)]$. The reason why natural frequencies facilitate Bayesian inference is because they retain in-

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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References and Notes

1. G. Gigerenzer, U. Hoffrage, *Psychol. Rev.* **102**, 684 (1995).
2. G. Gigerenzer, U. Hoffrage, *Psychol. Rev.* **106**, 425 (1999).

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.

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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References and Notes

1. J. L. Halaas *et al.*, *Science* **269**, 543 (1995).
2. R. S. Ahima *et al.*, *Nature* **382**, 250 (1996).
3. G. M. Lord *et al.*, *Nature* **394**, 897 (1998); J. K. Howard *et al.*, *J. Clin. Invest.* **104**, 1051 (1999).
4. R. M. Johnson, T. M. Johnson, R. L. Londraville, *J. Exp. Zool.* **286**, 718 (2000).

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

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