Less stress — more pressure?

A recent paper¹ and News & Views² considered the effects of stress upon penetration of a hydrophilic drug, pyridostigmine, across the blood-brain barrier of mice, concluding that stress may increase brain penetration of such drugs and suggesting that this may be relevant to understanding the "Gulf War syndrome." The stress model used was a modification of the forced swim model that places rats in cool (23 °C) water for some minutes³. The authors suggest that changes in the pituitary-adrenal axis underlie the increased permeability but did not address the role of acute hypertension. The induction of a leaky barrier by acute hypertension has been extensively studied and has been termed "hypertensive breakthrough" of the blood-brain barrier⁴ and is also seen in patients with hypertensive encephalopathy⁵. I am not aware of any convincing data in humans that stress per se increases cerebrovascular permeability to macromolecules or drugs. Although forced swimming raises blood pressure in rats, there are no data regarding its effects in mice. It is regrettable that the physiological consequences of forced swimming in mice on blood pressure and arterial pH, pCO₂, and pO₂ were not monitored before the authors invoked stress as the cause of increased drug entry. The suggestion that a leaky blood-brain barrier may have been induced by "stress" in Gulf War military personnel is an extravagant extrapolation of the limited data, and it is regrettable that the media have given credence to this dubious hypothesis.

ROBERT A. FISHMAN
Professor of Neurology
University of California
San Francisco, CA 94143-0114

Friedman *et al.* reply — We find Fishman's suggestion logical and we regret not having cited his work⁵. Our work² explored the possibility that pyridostigmine, previously considered to be excluded from the cerebrospinal fluid, reaches the brain when administered under stress conditions. We could not retroactively test for hypertension in soldiers who years later had come to our attention. However, psychological stress is associated with increased blood pressure and involvement of the adrenal-pituitary axis remains a plausible explanation for this intriguing phenomenon.

HERMONA SOREQ, DANIELA KAUFER & ALON FRIEDMAN
Department of Biological Chemistry, The
Institute of Life Sciences, The Hebrew University,
Jerusalem 91904, Israel

1. Friedman, A. *et al.* Pyridostigmine brain penetration under stress enhances neuronal excitability and induces early immediate transcriptional response. *Nature Med.* **2**, 1382–1385 (1996).
2. Hanin, I. The Gulf War, stress and a leaky blood-brain barrier. *Nature Med.* **2**, 1302–1308 (1996).
3. Sharma, H.S. *et al.* Increased blood-brain barrier permeability following acute short term swimming exercise in conscious normotensive young rats. *Neurosci. Res.* **10**, 211–221 (1991).
4. Johansson, B.B. Hypertension and the blood-brain barrier. in *Implications of the Blood-Brain Barrier and its Manipulation*, Vol. 2, *Clinical Aspects*. (ed. Neuwelt, E.A.), 389–410 (Plenum, New York, 1989).
5. Fishman, R.A. Cerebrospinal fluid. in *Diseases of the Nervous System*, 2nd ed., Vol. 83, 65–66 (Saunders, Philadelphia, 1992).

To test, or not to test?

To the editor — A recent article raised a number of questions about genetic susceptibility testing for breast cancer but failed to ask an important question: do women want to know if they are at a high risk of developing the disease? (Testing, testing... testing? *Nature Medicine*, February 1997). Many women with a family history of breast or ovarian cancer do want to know their risk, and genetic testing provides them with important information that will help them make better informed lifestyle and health-care decisions.

As members of a leading laboratory offering *BRCA1* and *BRCA2* genetic testing, we agree that genetic counseling is a vital component for those who are interested in taking the test. We provide a resource directory of genetic counseling services and require informed consent through a physician to ensure that women fully understand the benefits and limitations of genetic testing.

There is still much to be learned about breast and ovarian cancer. The discovery of the complete sequence of *BRCA1* and 2 by Myriad scientists was an important advance. Testing for *BRCA1* and 2 mutations will increase our knowledge by providing valuable scientific information about how the disease manifests in women at risk. We may not know everything about genetic susceptibility to breast and ovarian cancer, but we know too much to ignore the information.

TOM S. FRANK
Myriad Genetic Laboratories, Inc., 320 Wakara
Way, Salt Lake City, Utah, 84108, USA

HIV-1 antibody — debris or virion?

To the editor — Many hypotheses have been put forward to explain the inability of an antibody response to clear or control HIV-1 infection. These include viral variation, lack of efficacy against cell-to-cell spread and the inhibition of activity at certain privileged anatomical sites. We suggest an alternative: that the antibody response to HIV-1 envelope proteins is not directed to virus but instead is directed to viral debris (nonnative forms of the HIV-1 envelope released by lysis of infected cells or shedding from

the viral surface). We have been misled into describing this response as antiviral because the antibodies concerned react with envelope proteins in non-physiological forms such as isolated recombinant proteins. However, their reactivity with virions is weak. This is not to say that antibodies elicited to isolated envelope proteins cannot bind to native envelope. We suggest, however, that this binding is suboptimal, and this is in line with the observation that most human antibodies bind poorly to pri-

mary viruses, are weakly neutralizing and probably of limited efficacy *in vivo*.

We are drawn to this interpretation by consideration of the binding affinities of panels of human antibodies from HIV-1-infected individuals for various forms of HIV-1 envelope. These forms arise during envelope oligomerization and processing. The envelope is synthesized first as a monomeric precursor gp160 molecule, which oligomerizes before transport from the endoplasmic reticulum to the plasma membrane. During transport