their safety should be established before they are made available to the public. We doubt, however, that any of the health products discussed by Zeisel represents a major public health threat. Zeisel states that more than $44 billion worth of nutraceuticals have been purchased since 1990, yet he cites only four products linked to adverse events, all affecting a limited number of people. Prescription drugs, on the other hand, pose a measurable health risk. In 1994, more than 2 million people had adverse reactions to prescription drugs, and an estimated 100,000 died after receiving medications that were properly prescribed and administered, a distinction that ranks the consumption of pharmaceuticals among the top five causes of death in the United States (*1*). The fact that drugs approved by the U.S. Food and Drug Administration (FDA) cause significant morbidity and mortality suggests that increased legislation of nutraceuticals would have limited benefits, but substantial costs.

Matthew Curry
Center for Health Services Research and Development, Division of Health Sciences, East Carolina University, Greenville, NC 27858–4354, USA. E-mail: mcurry@brody.med.ecu.edu

Amy Hazard-Daniel
Blue Banks Farm, Greenville, NC 27858, USA

Hal J. Daniel
Departments of Biology and Anthropology, East Carolina University, Greenville, NC 27858–4354, USA

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Response

Curry, Hazard-Daniel, and Daniel note that despite careful oversight by the FDA, pharmaceuticals still result in adverse reactions and death. But consider how many more adverse events might occur if there were no governmental oversight. That the current drug-monitoring system is not perfect does not mean that we should allow manufacturers to market dietary supplements without some premarketing oversight as to the safety of their preparation. I continue to advocate a sensible modification in the Dietary Supplement Health and Education Act legislation. Dietary supplements that are to be administered at doses that exceed reasonable normal dietary exposure to the active agent should be shown to be safe before they are marketed, and the FDA should review these safety data. Under current rules, this is not the case.

Steven H. Zeisel
School of Public Health and Department of Nutrition, School of Medicine, University of North Carolina, Chapel Hill, NC 27599–7400, USA. E-mail: steven_zeisel@unc.edu

Transplants from Pigs

In their research article "Search for cross-species transmission of porcine endogenous retrovirus in patients treated with living pig tissue" (20 Aug., p. 1236), Khazal Paradis *et al.* describe the results from their study of 160 patients exposed to pig tissue, most of whom were exposed for less than 60 minutes. They conclude that "[w]e have not detected any conclusive evidence for cross-species or human-to-human transmission of PERV [porcine endogenous retrovirus]," and they suggest that we should proceed with further experiments on transplanting pig cells, tissues, and organs into people.

I question their conclusion, however. The genome of PERV is permanently integrated into the pig genome. Therefore, PERV was probably transmitted to all 160 patients. Paradis *et al.* detected PERV by polymerase chain reaction (PCR) techniques in the blood of 30 of these patients. Not only was the genome transmitted, but pig cells persisted in 23 recipients for up to 8.5 years.

The authors stress that no active infection was found; however, the possibility of infection remains in the four patients with positive antibodies to PERV and in another four patients with unexplained symptoms (skin rashes). In addition, a lack of antibodies to PERV may not exclude the existence of infection. Prion diseases [for example, bovine spongiform encephalopathy (mad cow) disease] cannot be detected by antibody or cellular immune responses.

Who would have predicted that so many patients only transiently exposed to pig tissue would have persistent pig cells (and PERV) in their blood? We also can't confidently predict what infection problems may occur in the future. However, if 20,000 transplants occurred annually, even a 1% infection rate means 200 infections annually. This would be a large reservoir of people who could then transfer a "novel" infection to other people.

There are major theoretical risks from infection to the graft recipient and to the wider community from xenografts (*1*). We need much more data and testing and longer follow-up on those patients who have already received xenografts before we recommence these experiments.

Peter Collignon
Infectious Diseases Unit and Microbiology Department, Canberra Hospital, Garran, Australian Capital Territory 2605, Australia

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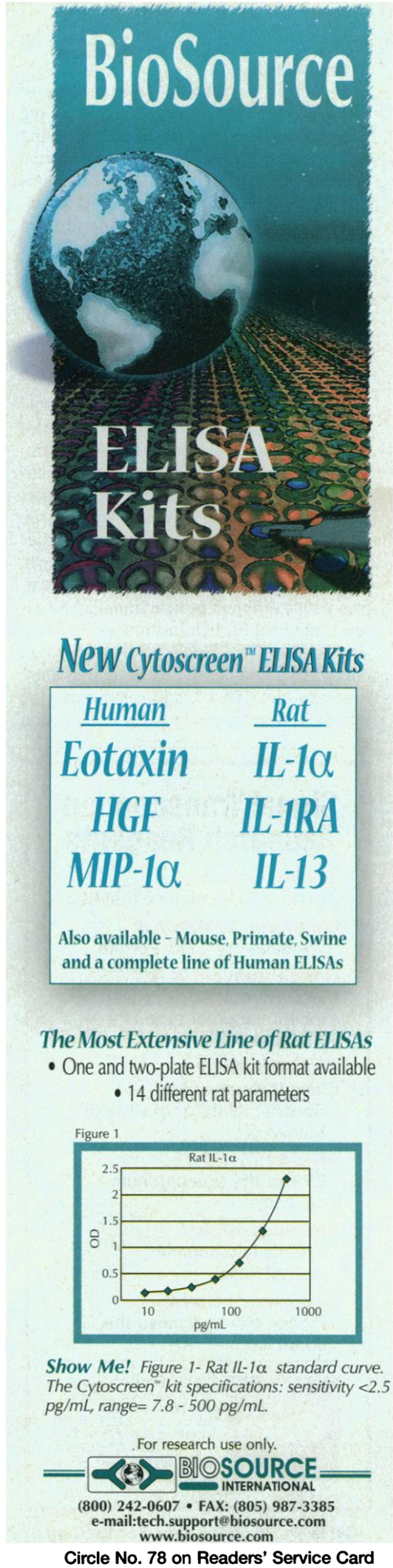

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Response

Collignon is correct that "[t]he genome of PERV is permanently integrated into the pig genome," as stated in the introduction to our research article. However, we do not believe that this can be extended to support the idea that the presence of pig cells in patients indicates cross-species transmission of viral infection. The objective of this and previous studies was to detect cross-species *infection*, which would have meant detecting either PERV DNA integrated into the genome of the patients' peripheral blood mononuclear cells, or infectious viral particles in serum or saliva, neither of which we found.

We did find that four patients had a positive response to an antibody test at one of the two testing laboratories. Testing of samples collected earlier indicated that the antibodies in at least two of these four patients were unrelated to the treatment with pig tissue. Unfortunately, there were no earlier samples available for the other two patients. Subsequent investigation of these four samples with a different protein immunoblot assay at the Paul Ehrlich Institute in Germany showed that there was a positive response only to Gag and not to Env protein in these four samples. This finding supports the statement that the most likely explanation for the positive antibody response was cross-reactivity to an unrelated antigen, because one would usually expect a response to both Gag and Env proteins (*1*).

As for the possibility of infection due to prions, the transmissible agent of transmissible spongiform encephalopathies (TSEs) has not been definitively identified. Given the uncertainty about the identity of the etiologic agent for TSEs, as well as the unconventional nature of prion diseases, it seems questionable to use prions as an analogy for PERV. A more appropriate model of infections would be the feline leukemia virus (FeLV), which is closely related to PERV. Antibodies to FeLV are present in FeLV-infected cats, and thus one could reasonably expect to find antibodies to PERV in PERV-infected humans.

Transplants from pigs—proceeding with caution.

Collignon also suggests that "[i]n addition, a lack of antibodies to pig PERV may not exclude the existence of infection." However, aware of the limitations of using a single diagnostic technique, we also looked for an active infection in patient sera by reverse transcription–PCR and latent infection in peripheral blood mononuclear cells by DNA PCR and found no indication of infection.

The theoretical risks raised by Collignon could be addressed with closely monitored prospective studies. We suggest that these trials should initially include small numbers of compliant patients who would be tested for cross-species infection, with appropriate contingency plans in place if infection was detected. Only when safety is convincingly demonstrated in small prospective trials would it be justified to proceed to larger numbers of patients. Tests such as the ones used in our study could be used to monitor patients receiving a xenotransplant in a regulated environment, along with other microbiological tests and control procedures as suggested by Collignon (*2*). Monitoring would be maintained throughout the clini-

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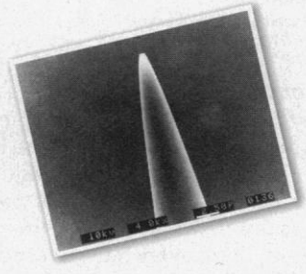

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cal program. Well-validated tests would need to be used to avoid the pitfalls of attributing a result to infection rather than to cross-reactivity, as was done by Collignon in his review (*2*) of the work performed by A. Tibell and C. G. Groth (*3*).

We stand by our conclusion that "[t]hese results support the use of closely monitored clinical trials as an approach to assessing the safety and efficacy of using porcine cells, tissues, or organs therapeutically in humans," as has been proposed by others (*4*, *5*).

Khazal Paradis
Gillian Langford
Imutran Ltd. (a Novartis Pharma AG company), Post Office Box 399, Cambridge CB2 2YP, UK

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CORRECTIONS AND CLARIFICATIONS

John Marchalonis's name was misspelled in the News Focus article "The misconduct case that won't go away" by Eliot Marshall (5 Nov., p. 1076).

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