or innocence, and we support further efforts to resolve the issue. More important, before "unblinding," we removed from the ESPS 2 study all observations submitted by this institution. The data that were analyzed and on which conclusions were based are unaffected by the questionable data.

This example illustrates that we must always be vigilant in our efforts to safeguard the integrety of science. In this instance, the value of intensive field monitoring has been confirmed: the credibility of the scientific record was preserved, and the consequences of any attempt to deliberately undermine the veracity of scientific experimentation will rest with the individuals who are found to be responsible.

With regard to the ethics of using placebos, it is self-evident that placebos should not be given instead of effective treatments. The question in this case is whether or not aspirin had been established as an effective stroke preventive at the time the trial was conducted. At the beginning of the trial, 60 independent ethical review committees (one at each study site) all agreed that the use of the placebo was appropriate. During the trial, additional studies emerged, but the results were conflicting (*1*); at no time during the trial was any suggestion made to discontinue the placebo. The meta-analyses cited in Enserink's article as having " 'convincingly proved' that aspirin worked" did not describe the effect of aspirin on stroke (*2*). Instead, a combined outcome grouped stroke with myocardial infarction and death. The authors' conclusion that "aspirin offers worthwhile protection against myocardial infarction, stroke, and death" (*2*) is misleading, because their analyses did not and cannot answer the question of whether aspirin prevents stroke. Even today, 2 years after the study's completion, the role of aspirin in stroke prevention is disputed. A U.S. Food and Drug Administration Advisory Committee hearing in January 1997 debated whether aspirin is clearly effective in preventing secondary stroke in a patient population comprised largely of those who had suffered a completed stroke.

The ESPS 2 trial was conducted according to the highest ethical and scientific standards. The important issues raised by Enserink's article should not overshadow the fact that this study found that a new therapy combining aspirin with dipyridamole was twice as effective as aspirin alone in preventing stroke.

Andreas Barner
Corporate Medical Director,
Corporate Medical Division,
Boehringer Ingelheim GmbH,
D66216 Ingelhelm am Rhein, Germany

References

1. SALT (Swedish Aspirin Low-Dose Trial) Collaborative Group, *Lancet* **338**, 1345 (1991); U.K.-TIA Study Group, *J. Neurol. Neurosurg. Psychiatry* **54**, 1044 (1991).
2. Antiplatelet Trialists' Collaboration, *Br. Med. J.* **308**, 81 (1994).

■

Biospherian Viewpoints

Biosphere 2 was designed as an experimental facility to be brought into equilibrium over several years, to yield fundamental data on ecosystem function in the process but specifically to learn how to operate closed, large-scale integrated ecosystems. Joel E. Cohen and David Tilman (Perspectives, 15 Nov., p. 1150) state, "it proved impossible to create a materially closed system that could support eight human beings with adequate food, water, and air for 2 years," but experimentation had barely begun in those 2 years. Biosphere 2 was planned for 100 years of investigative experiments. The "large daily and seasonal oscillations" of carbon dioxide (CO_2) were well anticipated, both theoretically and from experiments in the smaller test module. Carbon dioxide variation carries basic ecosystem metabolism information.

Had Biosphere 2 been sealed merely 10

times tighter than NASA's plant growth chamber at the Kennedy Space Center (often called a "closed system," which leaks 11% per day), then oxygen would have stabilized at 19.6%, losses being almost entirely masked by replenishment from leakage. We made the "mistake" of building a nearly true seal to see what really happens. Imbalance between oxygen and CO_2 and human physiological response (and other gases) were measured for 30 months as never before possible.

Species were deliberately overpacked to encourage rapid selection. Losses were allowed in the design, but Cohen and Tilman attribute such losses to the original management. Pollinators and more than 40 vertebrates remained up until the "takeover" of 1 April 1994 (*1*). The juxtaposition of electrical and thermal energy with Biospherian labor as if one were traded for the other is baseless. Biospherian work logs (*2*) reflect no "enormous . . . personal efforts."

Cohen and Tilman cite my paper (*3*), but ignore its main thrust, which explains the experimental nature of Biosphere 2. That "ecologists doubted that a viable closed habitat to support human life could have been assured, even had the best ecological knowledge of the time been brought to bear" is why Biosphere 2 was built: to begin necessary experimentation. The "failure" viewpoint discredits those who conceived and built an ecological laboratory of appropriate scale.

William F. Dempster*
26 Synergia Road,
Santa Fe, NM 87505, USA

References

1. A. Alling, personal communication (1996).
2. M. Nelson and W. Dempster, in: *Strategies for Mars*, C. R. Stoker and C. Emmart, Eds. (Science and Technology Series, American Astronautical Society, Springfield, VA, 1996), vol. 86.
3. W. F. Dempster, *Tech. Pap. Ser. 932290* (Society of Automotive Engineers, Warrendale, PA, 1993).

*Director of Systems Engineering for Biosphere 2 from its inception to 1994.

Cohen and Tilman present a viewpoint of Biosphere 2 that I believe is misleading. Biosphere 2 was built as a long-term experiment, and the fact that so much went as anticipated during the first 2 years, despite the boldness of the experiment, was perhaps the greatest surprise. It was fully understood that Biosphere 2 would differ significantly from Earth's biosphere, in part because of the unique properties of a 1.2-hectare enclosed facility where cycles occur in shorter time periods and buffering reservoirs are smaller.

I agree completely with their conclusion: At present there is no demonstrated alternative to maintaining the viability of Earth. No one yet knows how to engineer systems that provide humans with the life-supporting services that natural ecosystems produce for free.

However, that was never the intention of Biosphere 2. Providing baseline data on creating life support systems that might eventually be needed for long-term survival in space, along with research on biospheric processes and the problems of living sustainably with ecologically sound agriculture and technology, were among the reasons that Biosphere 2 was built and designed to be operated as a "humans-in-biosphere" experiment. Certainly the capital and energetic costs of building and operating even a small system such as Biosphere 2 should underline the value of the "free" services that we receive from Earth's biosphere. Yet, it is premature to draw conclusions about the operation of Biosphere 2 and to dismiss the possibility of gaining fundamental knowledge about how ecosystems and biospheres operate.

I urge Columbia University, the current managers of Biosphere 2, to provide the scientific community with access to the enormous body of baseline research that was conducted during the facility's initial 3 years, when it was operated as a

materially closed biospheric system. Then the true "lessons" from Biosphere 2's operation can be more accurately drawn.

Mark Nelson*
Post Office Box 12718, Gainesville, FL 32604, USA

*Member, Biosphere 2 Crew, 1991–1993.

Cohen and Tilman repeatedly refer to "surprises" encountered by the Biosphere 2 management (which from 1991 through 1993 was me, Margret Augustine, William Dempster, and Abigail Alling). But they did not talk to those of us who designed and ran the experiment, nor do they cite our papers, with one exception. They omit the fact that the Biosphere 2 experiment immensely increased our predictive power in biospheric-scale phenomena, artificial and natural. My colleagues and I designed Biosphere 2 to be an experiment in biospherics with two things in mind: (i) to determine how much was known about biospheres (*1*) by seeing if what had been tested by us and the Russians on a smaller scale would work as predicted in Biosphere 2, and (ii) to see how much that was new could be discovered about designing sustainable, closed life systems (artificial biospheres) with humans living in them on a healthy, long-term basis. The goal was both to throw light on Earth's biosphere and to make settlements in space possible. Biosphere 2 has much to teach us, perhaps as much from the way its Mission Two has been destroyed and its achievements attacked as from its contributions to our knowledge (*2*).

John Allen
32038 Caminito Quieto, Bonsall, CA 92003, USA
E-mail: 100556.1127@compuserve.com

References

1. J. Allen, *Biosphere 2: Description, Purpose, and Conceptual Design* (Space Biospheres Ventures and Synergetic Press), Oracle, AZ, 1992).
2. http://www@biospherics.org

■

Correction: Raloxifene Response Needs More Than an Element

In our report "Identification of an estrogen response element activated by metabolites of 17β-estradiol and raloxifene" (30 Aug., p. 1222) (*1*), we examined regulation by raloxifene of the human transforming growth factor–β3 (TGF-β3) promoter and proposed a new pathway of gene transcription mediated by the estrogen receptor (ER) and a raloxifene response element (RRE).

In new experiments to characterize the RRE sequence further, we found that one of the reporter plasmids described in this study, pTGFβ+35Luc (figure 3A in the report), contained a deletion of the luciferase coding region introduced during DNA amplification in *Escherichia coli*. This alteration in the vector resulted in a lack of luciferase expression, which we had earlier interpreted incorrectly as the complete inability of this promoter region to respond to raloxifene. With the use of a newly constructed pTGFβ+35Luc with the correct vector sequence and $ER_{\Delta BCD}$, we have determined that the deletion of the +35 to +75 region, defined in our report as the RRE, causes only a partial loss of raloxifene-induced pTGFβ3-luciferase activation, as measured by fold induction. This result is consistent with our observation (*1*) that when this region was transferred to the SV40 promoter, only partial activity was detected (figure 3C in the report). Thus, we would like to change the statement in the report (p. 1223) that "the RRE may be essential, but not sufficient by itself, to mediate full hormonal regulation of the TGF-β3 gene" to read

although the originally defined RRE sequence appears to be a factor, it is not sufficient by itself to mediate full hormonal regulation of the TGF-β3 gene by this pathway.

Our new data indicate that regulation of the TGF-β3 gene by raloxifene may involve a complex mechanism and multiple regions of the promoter. To the best of our knowledge, all the other published data (*1*) are valid, and our conclusion that a new ER-mediated gene activation pathway of TGF-β3 regulation may be activated by raloxifene or metabolites of 17β-estradiol remains correct.

Na N. Yang
Murali Venugopalan
Sushant Hardikar
Andrew Glasebrook
Endocrine Research, Eli Lilly & Co., Lilly Corporate Center, Indianapolis, IN 46285, USA

References

1. N. N. Yang, M. Venugopalan, S. Hardikar, A. Glasebrook, *Science* **273**, 1222 (1996).

Letters to the Editor

Letters may be submitted by e-mail (at science_letters@aaas.org), fax (202-789-4669), or regular mail (*Science*, 1200 New York Avenue, NW, Washington, DC 20005, USA). Letters are not routinely acknowledged. Full addresses, signatures, and daytime phone numbers should be included. Letters should be brief (300 words or less) and may be edited for reasons of clarity or space. They may appear in print and/or on the World Wide Web. Letter writers are not consulted before publication.