LETTERS

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.

Democratization Is More Than Lower Prices

IN HIS POLICY FORUM, "GENOMICS, GENETIC engineering, and domestication of crops" (4 April, p. 61), Steven H. Strauss makes a plea for less onerous field trial regulations for less radical genetic modifications, such as genomics-guided transgenes (GGT), thereby helping smaller companies and public-sector investigators to be able to afford to try out crop variants. Unfortunately, his plea ignores the politics of the genetically modified (GM) food debate.

In a perfect world, no critic of biotechnology would object to so modest and reasonable a proposal as looser regulations for GGT. But, likewise, in a perfect world, no biotechnology advocate would object to (for example) the modest and reasonable proposal to label GM food. In the imperfect real world, though, biotechnology critics see their main concerns kept off the table (such as food labeling), blocked by the biotechnology industry and its advocates. They retaliate by taking a hard line on the only issue left on the table: biosafety. Consequently, the GM debate has the political dynamic of a feud, not a negotiation.

The labeling of GM foods is just one of the debates surrounding GM organisms.

Strauss's proposal, reasonable as it may be, asks critics to surrender a major bargaining chip—strict regulation of field trials—but offers them nothing in return. Only in the very last sentence does Strauss even acknowledge the critics' main concerns—"the widespread suspicion of the power and ethics of many large corporations"—and correctly recognize that "'democratization' of biotechnology might be as important as biological advances in promoting public approval of [genetic engineering] in agriculture." But the step toward democratization he offers—lower- cost field trials through looser regulations—is insignificant and certainly will not tempt critics.

It is the patenting of crops that biotechnology critics find so antidemocratic. To these critics, the patenting of the world's food supply by corporations is an assault on democracy more enormous than any military assault. Until the patenting of plants and animals is back on the table and negotiated in good faith, I doubt that crumbs like the one Strauss is offering will get critics to ease their hard line on biosafety.

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Response

CAYFORD SUGGESTS THAT FOR MANY opponents of agricultural biotechnology, scientific uncertainties over biosafety are more bargaining tools than critical issues in global wars over patents and regulation of biotechnology. He acknowledges that my proposal to regulate genomics-guided transgenes (GGTs) less onerously is "modest and reasonable," yet sees this as too few "crumbs" to get anti–genetically modified organism (GMO) hardliners to support the changes proposed.

My hope is that this "hostage-taking" approach does not represent the new morality of most of the Green movement, which appears to be the main anti-GMO force around the globe. The costs to people and environment of effectively losing genetic engineering from most agricultural sectors as a result of excess regulation are too great for so simple-minded a political approach.

Labeling and the required bureaucracy for food tracking and segregation it demands, when carried out to the high levels of fidelity required in places such as the EU, are very costly. It is the poor who will suffer most from this seemingly "reasonable proposal to label GM food," both in the form of higher food costs and effective trade barriers to products from developing countries (who will often not be able to afford the expensive bureaucracy needed to adequately comply with strict regulations).

Although there are many evolutions to the intellectual property rules surrounding biotechnology that are needed to cope with its complexity and rapid rate of growth, few would call for a complete cessation of patents. They stimulate innovation, publication, and development of new products. Earlier forms of patent and germplasm protection have been widely incorporated into agriculture with little acrimony. And there are few practices more "democratizing" than protecting and promoting the ideas and work of society's innovators when applied to improve food quality, dependability, and affordability.

If anti-GMO groups continue to seek stringent regulations for all GMO crops, regardless of benefit, safety, and familiarity, then their credibility with the public will diminish over time. Of most import, however, may be that public confidence in important environmental issues brought forward by Green groups may be tarnished by association with scientifically reckless anti-GMO campaigns. Unfortunately, with the high level of regulation and stigma successfully implanted in places such as Europe, policies and attitudes may take a generation or more to change course. The opportunity costs in dollars, and costs to human health and environment, will be incalculable.

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The Reliability of *P* Values

JON COHEN'S ARTICLES ON THE VAXGEN HIV vaccine ("AIDS vaccine trial produces disappointment and confusion," News of the Week, 28 Feb., p. 1290; "Vaccine results lose significance under scrutiny," News of the Week, 7 March, p. 1495) raise concerns about the reliability (or lack of reliability) of the subgroup analyses used to analyze parts of the vaccine data set. The problem, however, is more complicated than whether or not to perform a Bonferroni adjustment. Rather, the central issue is the prior probability of the research hypothesis that was tested, in this case whether the vaccine is effective (*1*–*3*). In subgroup analyses, the prior probability of the particular subgroup hypothesis being tested is usually quite low. So even if a *P* value is "significant" for a subgroup analysis, it does not usually carry the same

weight as a significant *P* value for the original hypothesis. In this vaccine trial, for example, the investigators almost certainly did not originally hypothesize that the HIV vaccine would be ineffective in whites, but effective in blacks, Asians, and people of mixed race. If they had, they would have stated that specific hypothesis in advance of the study, and they would likely not have enrolled any white subjects.

A Bayesian approach that accounts for the prior probability of a particular hypothesis can be quite useful when attempting to understand *P* values, especially surprising ones. Suppose an investigator did a randomized, double-blind, placebo-controlled study that "showed" that sugar water could cure advanced breast cancer, at $P < 0.05$ (or even at $P < 0.0001$). Would anyone be 95%, or 99.99%, "confident" in the truth of the results? Certainly not; thus, it is a good idea to avoid the word "confident" entirely in discussions of results. A *P* value simply reflects the probability of a set of findings (or ones more extreme) under the null hypothesis that there was no difference in the groups being compared. *P* values (and confidence intervals, for that matter) do not account for the likelihood of the hypothesis being tested and cannot distinguish "true" from "false" results. They are purely data-based.

So what can be done to prevent a "significant" *P* value from attracting attention even when it is meaningless? First, we should realize that the main hypothesis of a study—in this case, that the VaxGen HIV vaccine was effective overall—usually has a reasonable chance of being correct; otherwise, the investigators (and company) would not have spent time and resources pursuing the study. (There are exceptions, of course; see the sugar water example above.) Second, all *P* values, especially those generated in subgroup analyses, need to be evaluated in their scientific context. Third, requiring that a hypothesis make biological sense is mandatory but may not be sufficient, because we are so clever at developing possible explanations for the data. For example, it seems reasonable that the vaccine might be effective only in those in whom antibodies against HIV were induced. But this appealing explanation also requires that the vaccine be harmful in the remaining subjects, because there was no overall effect. Finally, 0.05 is an arbitrary criterion, adjusted or not. We should not have dismissed the results of the study if the overall *P* value was 0.051 or even 0.09. An intelligent approach—rather than an inflexible one—is preferable.

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Toxicity and Protection in Prions

THE PERSPECTIVE "A VIEW FROM THE TOP— prion diseases from 10,000 feet" by S. A. Priola *et al.* (9 May, p. 917) about the recent Keystone Symposium on prion diseases concludes with certainty that evidence from S. Lindquist and D. Harris's laboratories shows that cytosolic prion protein is extremely toxic. However, at this meeting, we showed strong contrasting evidence that in human neurons in primary culture, cytosolic prion protein arising from the ERAD pathway is not only harmless, but can still protect these neurons against Bax-mediated cell death, as previously shown in our laboratory with normal cellular prion protein (*1*, *2*). Therefore, although cytosolic

prion protein is toxic in some cells, it is not toxic in all cell types. Unfortunately, our data may have gone unnoticed because our work was presented as a poster and there was not enough time after either Lindquist's or Harris's presentations for us to discuss our contrasting findings. However, our findings should not be ignored because, as highlighted by Kurt Würthrich at the symposium, it may be more important to find the function of normal cellular prion than to study the formation of the protease-resistant form of prion protein. Our data suggest that human neurons have less ability to convert the normal cellular or cytosolic prion protein into the scrapie isoform than some cell lines (*3*). Priola *et al.* conclude unequivocally that cytosolic prion protein toxicity is a general phenomenon, which is not supported by our data.

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3. J. Ma, R. Wollmann, S. Lindquist, *Science* **298**, 1781 (2002).

Response

The role of alternatively processed forms of normal cellular prion protein (PrP) in transmissible spongiform encephalopathy (TSE or prion disease) pathogenesis is currently a topic of intense debate. LeBlanc and Roucou are correct to point out that their work suggests that cytosolic PrP is not necessarily neurotoxic (*1*). Similarly to Ma *et al.*'s work in murine neuroblastoma cells (*2*), Roucou *et al.* demonstrated that inhibition of proteasome function in primary human cerebellar granular neurons led to accumulation of PrP in the cytosol (*1*). However, unlike in Ma *et al.*'s work, neither endogenous expression nor overexpression of cytosolic PrP in these cells was neurotoxic, but rather neuroprotective. This lack of cytotoxicity was consistent with observations by Drisaldi *et al.* in primary murine cerebellar granular neurons (*3*) as well as observations by Ma *et al.* in murine fibroblast cells (*2*). Thus, we would agree that cytosolic PrP may be toxic to some cells but not others.

However, it is important to note that truncated PrP molecules and certain PrP peptides, none of which accumulate in the cytosol, also have been associated with neurotoxicity in TSE diseases. Thus, it is quite possible that no single pathway of alternative PrP processing is responsible for the neurodegeneration associated with these diseases. The type of neuron, its metabolic state, and its surrounding environment may all contribute to its ability to cope with stresses on protein synthesis and degradation pathways. This in turn may influence how PrP is processed when such stress occurs and whether a neurotoxic, or neuroprotective, form of PrP is generated.

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TECHNICAL COMMENT ABSTRACTS

COMMENT ON "Ascent of Dinosaurs Linked to an Iridium Anomaly at the Triassic-Jurassic Boundary"

T. Thulborn

Olsen *et al*. (Reports, 17 May 2002, p. 1305) suggested that predatory dinosaurs of the suborder Theropoda did not attain large size until the Early Jurassic, in the wake of mass extinction at the Triassic-Jurassic boundary (~202 My). Fossil footprints, however, reveal that theropods bigger than *Allosaurus* inhabited East Gondwana some 20 million years before the close of the Triassic.

Full text at
www.sciencemag.org/cgi/content/full/301/5630/169b

RESPONSE TO COMMENT ON "Ascent of Dinosaurs Linked to an Iridium Anomaly at the Triassic-Jurassic Boundary"

P. E. Olsen, H.-D. Sues, E. C. Rainforth, D. V. Kent, C. Koeberl, H. Huber, A. Montanari, S. J. Fowell, M. J. Szajna, B. W. Hartline

Thulborn's only salient point is the extraordinary claim that very large theropod dinosaurs were present about 20 million years before the Triassic-Jurassic boundary. However, the only extant paleontological evidence is a plaster cast of a footprint that is not convincingly theropod in origin, and skeletal evidence is completely lacking.

Full text at
www.sciencemag.org/cgi/content/full/301/5630/169c

CORRECTIONS AND CLARIFICATIONS

Netwatch: "Bent Into Shape" (16 May, p. 1061). The Database of Simulated Molecular Motions has a new URL. Readers can now find it at http://projects.villa-bosch.de/mcm/database/dsmm.