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.

Hooked on Hooke

RICHARD STONE'S COGENT REVIEW OF Robert Hooke's incredible achievements ("Championing a 17th century underdog," News of the Week, 11 July, p. 152) evokes fascinating facets of his incomparably productive life. He produced weekly Royal Society demonstrations without compensation, promised lecture honoraria were never paid despite polite reminders, and the Council of the society even voted to deduct the amount from his promised salary.

Isaac Newton's aloofness toward and disparaging belittling of "this miserable philosopher" was not without benefit for him: He awaited Hooke's death before publishing his dormant "Optics" without fully acknowledging Hooke's prior work. Newton was not his only enemy; Henry Oldenberg, Secretary of the Royal Society, often omitted Hooke's name from recorded comments and rightful priority credits.

An original composite rendering of Hooke, at about age 25 to 30, using databases on a compu-sketch instrument coordinated by Henry Lee, Nick Skebeta, and Martin E. Gordon.

Their intensifying disputes caused Hooke to call Oldenberg a "trafficer in intelligence." Little wonder that Hooke's digestive tract required "tailoring" of his "stomach and gutt" by his "one dish/meal," supplemented by potable metals such as licking powdered silver, syrup of poppy seed, and liberal use of the famous ancillary treatments of clysters and bleedings with cuppings. Despite these problems, Hooke was able to perceive and correlate projected applications of his nearly 1000 inventions.

While always dressed in his personally chosen long fabrics, sewn by himself, he gregariously interacted in coffee shops with many notables, including Samuel Pepys, but was never able to sustain wide recognition of his work. Hooke died a feeble, depressed, reclusive man, despite his wealth of legacies to science and his personal wealth, found dormant in an iron chest filled with several thousand pounds of earned silver and gold coins.

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Hooke and Generation of Molds

IN HIS ARTICLE "CHAMPIONING A 17TH century underdog" (News of the Week, 11 July, p. 152), Richard Stone reports on the current interest in the scientific achievements of Robert Hooke (1635–1703), including his remarkable insights in several areas of biology. One aspect of his many contributions that has gone largely unnoticed by historians of science is his proposal of a spontaneous generation of microbes based on purely mechanical forces, which was prompted by his observations of various molds. As summarized by Lechevalier and Solotorovsky (*1*), both the drawings and descriptions that Hooke included in his 1665 *Micrographia* suggest that he observed the teleutospores of a rust, which, together with a blue mold "and several kinds of hairy mouldy spots" (*2*), could be found in decaying organic matter and which reproduced without seeds, requiring only a convenient substratum and the proper amount of warmth (*1*). However, a detailed reading of the *Micrographia* demonstrates Hooke's adherence to a more sophisticated scheme largely based on Cartesian mechanistic concepts. As he wrote, "I must conclude, that as far as I have been able to look into the nature of this Primary kind of life and vegetation, I cannot find the least probable argument to perswade me there is any other concurrent cause then such as purely Mechanical, and that the effects or productions are as necessary upon the concurrence of those causes as that a Ship, when the Sails are hoist up, and the Rudder is set to such a position, should, when the Wind blows, be mov'd in such a way or course to that or t other place; Or, as that the brused Watch, which I mention in the description of Moss, should, when those parts which hindred is motion were fallen away, begin to move, but after quite another manner then it did before" (*2*).

Not surprisingly, his explanation of the appearance of molds and other microorganisms lacks an evolutionary perspective. Nonetheless, the delightful analogy used by Hooke demonstrates that he accepted a continuity between the nonliving and the living without invoking any vital force of supernatural character. To substantiate his claims, he compared the emergence of molds with that of the "silver tree," a dendritic structure with plantlike morphologies formed from an amalgam of silver and mercury dissolved in nitric acid, which had been studied, among others, by his major foe Isaac Newton (*3*).

The temptation to compare biological structures with artifacts of purely inorganic nature may have begun with Newton and Hooke, but it did not end with them. In an attempt to understand the origin and nature of life, 19th century scientists like Leduc and Herrera devoted themselves for several decades to the production of lifelike structures from various combinations of crystals and inorganic fluids, as part of the now largely forgotten fields of "synthetic biology" and "plasmogeny" (*4*). Advocates of complexity theory, which likens the emergence of complex patterns in dynamical systems with biological phenomena (*5*), do not shy away from such comparisons, which also have a bearing on the ongoing discussions of the significance of complex morphologies as biological signatures in early Archean sediments and Martian meteorites (*6*). Sometimes our current debates have a long genealogy.

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Risks of Genetically Engineered Crops

STEVEN H. STRAUSS'S GENERAL CONCEPT that the inherent riskiness of a genetically engineered (GE) crop should determine the

extent of regulation ("Genomics, genetic engineering, and domestication of crops," Policy Forum, 4 Apr., p. 61) makes sense in principle. The bigger issue is that the Department of Agriculture (USDA) and the Environmental Protection Agency (EPA) have not adequately identified which transgenic crops should receive limited or heightened review based on relative risk to health or the environment. The issue applies to GE crops that have received inadequate scrutiny, as well as those that may receive more scrutiny than necessary.

Several cases of inadequate USDA oversight have been identified in recent National Academy of Sciences (NAS) reports. For example, NAS criticized USDA's assessment of cross-breeding between transgenic virus-resistant squash and wild sexually compatible relatives (*1*, *2*). NAS also criticized insufficient USDA oversight of transgenic avidin-containing maize (*2*). In these and other cases, more stringent oversight is needed, not less.

Additionally, contamination of soybeans and possibly corn, due in part to inadequate USDA monitoring policies for transgenic "pharma" crops, resulted in fines for the company ProdiGene and erosion of food industry confidence in the regulation of transgenic technology (*3*). More stringent confinement policies by the USDA, such as requiring redundant physical and biological isolation techniques, could minimize similar incidents. In response to public concern, USDA is revising its oversight of "pharma" and "industrial" crops, but concern remains that food contamination will not be prevented. The utilization of nonfood "pharma" crops would better prevent food contamination.

Although it may be difficult to delineate GE traits that could allow reduced regulation at the field trial level, Strauss suggests domesticating phenotypes coded by genes similar to genes from the crop genus as a starting point. However, predicting invasiveness of plants based on particular traits has not been reliable (*4*). In retrospect, traits from the crop sorghum transferred to a wild relative in the same genus have been implicated in the notorious weediness of johnsongrass (*5*). Therefore, it is premature to exempt "agronomic" GE traits from regulation.

The problems outlined here and by Strauss are symptomatic of inadequate effort by USDA and EPA to determine how to assess and rank environmental risks of GE crops. USDA's GE risk assessment grant program amounts to only about $3 million per year. EPA's Office of Research and Development eliminated GE risk-assessment research in the mid 1990s and now has only a shoestring program. The public confidence in GE crops that Strauss desires—especially in the era of Enron—will only occur when sufficient resources are devoted to developing testing requirements for GE crops based on input from independent scientists and the public. Confidence would be further enhanced if Congress gave the FDA the authority to conduct safety approvals of new GE foods.

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Response

GURIAN-SHERMAN SUGGESTS THAT IT IS premature to reduce regulations for genetically engineered organisms (GEOs). However, my Policy Forum and another recent essay (*1*) did not suggest a general reduction of regulations, but instead called for greater discrimination in how regulations are implemented, based on the trait and the degree of evolutionary novelty of the genes employed. Others have made similar suggestions (*2*).

I agree that more stringent and tailored rules for pharma-crops, as the USDA Animal and Plant Health Inspection Service has already put into place, are warranted. What I am suggesting is that regulatory agencies could also be doing the same customizing of regulatory scrutiny at the other end of the novelty spectrum—by relaxing regulatory oversight for traits where there is a strong a priori case to be made that they will be neutral or domesticating (i.e., will not improve invasiveness or weediness). The intention is to make GEO regulation more congruent with that of conventional crop improvement. Breeding, as a result of its large benefits for agricultural productivity and human health, continues to have overwhelming social support in the absence of any government regulation, despite tangible levels of ecological and toxicological risk.

It is unclear to me why the ability to predict invasiveness of exotic organisms placed into novel ecosystems, usually without their native assembly of parasites and predators, is viewed by Gurian-Sherman as relevant to assignment of homologous genes to risk classes. In terms of information novelty, the product of new genomes × new biotas × new abiotic environments is astronomically more complex than that of individual, carefully selected homologous genes and putative domestication traits in familiar

species. In neither case is the risk absolute zero, but the ecological and evolutionary uncertainties are many orders of magnitude apart. In addition, nowhere did I propose that all "agronomic" traits be exempt from regulation, as Gurian-Sherman implies.

My Policy Forum focused on regulations that pertain to exploratory (small-scale) field testing. It did not discuss exemption from oversight at the point of commercialization, nor even suggest exemptions for large-scale (precommercial) field trials. It was a modest attempt to begin to identify a class of GEOs that are very safe and thus might not be encumbered by the stigmas, costs, and complexities of crops with ecologically novel genes. Without such a class, and thus a less encumbered breeding pathway, small companies and public-sector researchers will continue to find it difficult to use GEO methods to take full advantage of genomic knowledge in crop breeding. Indiscriminate regulation of GEOs also confuses the public about risk and novelty, inflaming rather than helping to resolve the GEO debate. The net result is likely to be large opportunity costs in the form of lower food quality, higher food prices, poorer health, and greater environmental impacts from agriculture.

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Good and Bad Amyloid Antibodies

ANTIBODIES THAT RECOGNIZE AN OLIGOMERIC state common to different amyloidogenic proteins described by R. Kayed *et al.* ("Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis," Reports, 18 Apr., p. 486) advance our understanding of Alzheimer's disease (AD) and other amyloid diseases, and provide a tool for probing such amyloid conformations in patients and in animal and cell culture models. Kayed *et al.* establish that the antibody they generated recognizes only oligomers of amyloid beta-peptides 1-40 and 1-42 (Aβ40 and Aβ42) that contain a minimum of eight peptide copies (octamers) and that it does not recognize amyloid fibrils. Previous studies had suggested that Aβ40 and Aβ42 are particularly toxic to cells when they are in an early stage of the peptide aggregation process (*1*, *2*). The findings of Kayed *et al.* confirm and extend this notion by showing that the state-specific amyloid antibody inhibits the cytotoxicities of a range of amyloidogenic peptides, including those

involved in prion disorders, Parkinson's and Huntington's diseases, and type II diabetes.

Efforts to develop a vaccine for AD based on immunization with Aβ42 or administration of Aβ antibodies (passive immunization) have encountered mixed results. Several laboratories have documented the clearance of Aβ aggregates from the brains of transgenic mice expressing mutant amyloid precursor protein, a mouse model of AD (*3*, *4*). However, the mouse studies did not establish whether the Aβ antibodies produced by or given to the mice modified the neurotoxicity of the Aβ in the brains of the mice. In an initial clinical trial in which AD patients were administered Aβ to elicit an immune response, some of the patients appeared to be benefiting from the vaccine (*5*), but several patients developed encephalitis (*6*). Although Kayed *et al.* found that their antibody against oligomeric Aβ was capable of protecting cultured cells against the toxicity of such forms of Aβ, we have found that several other Aβ antibodies potentiate the neurotoxicity of Aβ (*7*). Previous studies showed that Aβ generates reactive oxygen species, including hydrogen peroxide, only when the peptide is in an aggregating oligomeric form (*8*, *9*). When the latter process occurs when Aβ is in contact with cell membranes, lipid peroxidation occurs, resulting in perturbed membrane transporter and ion channel functions that can lead to cell death (*10*).

Aβ antibodies might facilitate the formation of a toxic peptide conformation (*7*). However, the possibility that the interaction of the antibodies with Aβ catalyzes or enhances the generation of reactive oxygen species should also be considered. Lerner and colleagues (*11*, *12*) have shown that many antibodies can convert molecular oxygen into hydrogen peroxide and short-lived hydroxylating radical species such as hydrotrioxy radical. When we tested several different Aβ42 antibodies to determine their ability to modify the amount of oxidative damage to cells induced by Aβ42, some of the antibodies increased the damage, whereas others decreased the damage. Because many different Aβ antibodies are produced in response to immunization with Aβ, our findings suggest that some of the antibodies may exacerbate the neurodegenerative process. Passive immunization with Aβ antibodies with predetermined effects on Aβ clearance and toxicity might reduce or eliminate potentially serious side effects resulting from vaccination with Aβ.

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A Clarification on Data Availability

JOHN R. LOTT JR. RECENTLY RESPONDED ("Research fraud, public policy, and gun control," Letters, 6 June, p. 1505) to an earlier Editorial ("Research fraud and public policy," D. Kennedy, 18 Apr., p. 393) that stressed the need for integrity in research and alluded to serious allegations of academic misconduct by Lott in his efforts to advance the thesis that more guns will lead to less crime. In the course of his reply, Lott seems to deflect attention from the charges that have been leveled against him by making an untrue allegation that Ian Ayres and I have failed to give him the data related to our work showing that adoptions of concealed carry laws are not associated with drops in crime. As I assume Lott knows (since he responded to our paper), we state in footnote 33 of our paper "Shooting down the more guns, less crime hypothesis" (*1*) that the data set and computer programs we used are available on the Web, and indeed they are. In fact, I have always made my data available to any researcher for this work and every other research project I have worked on (and Lott has asked for and received from me data on other research projects of mine).

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Reference
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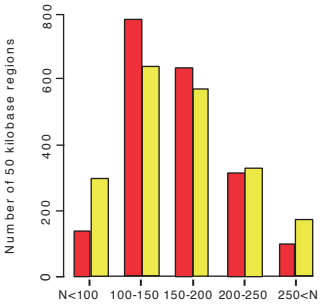
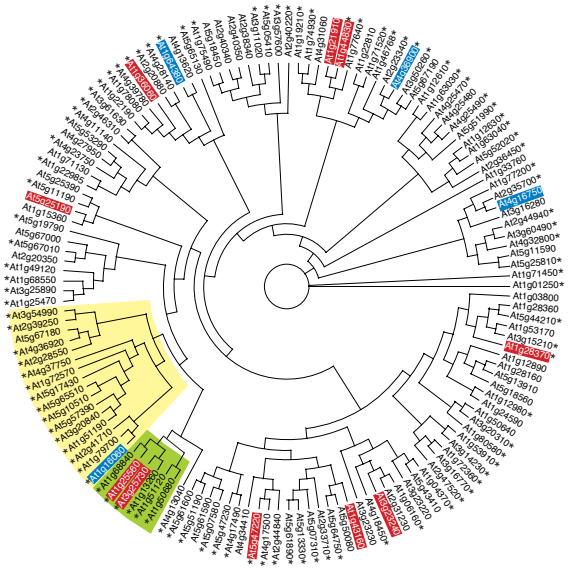
CORRECTIONS AND CLARIFICATIONS



REPORTS: "Genome-wide insertional mutagenesis of *Arabidopsis thaliana*" by J. M. Alonso *et al.* (1 Aug., p. 653). There were errors in two of the figures. In Fig. 1A (left), there was a bar missing from the graph. In Fig. 2 (below), genes in which insertions in promoters or transcribed regions were found should have been marked with asterisks. The corrected figures are shown here.



REPORTS: "Collection, mapping, and annotation of over 28,000 cDNA clones from *japonica* rice" by the Rice Full-Length cDNA Consortium (18 July, p. 376). Under the RIKEN part of the author list, three of the authors' names were spelled incorrectly: Wataru Hashizume, not Wataru Hashidume; Yoshiyuki Ishii, not Yoshiki Ishii; and Hideaki Konno, not Hedeaki Konno. Also, one author name was missing: Ayako Yasunishi. In the acknowledgments in reference 17, the following names should not have appeared: W. Hashizume, K. Imotani, A. Miyazaki, and A. Yasunishi.

REPORTS: "Reelin promotes peripheral synapse elimination and maturation" by C. C. Quattrocchi *et al.* (1 Aug., p. 649). The affiliation listed for the fifth author, David Benhayon, is incorrect. He is at St. Jude Children's Research Hospital, Memphis, TN 38105, USA, and Health Science Center, University of Tennessee, Memphis, TN 38163, USA. There was also information missing from the acknowledgments in the final reference. The work was supported by a grant from NIH/National Institute of Neurological Disorders and Stroke grant NS36558, and the work was also supported in part by NIH Cancer Center Support CORE grant P30 CA21765 and the American Lebanese Syrian Associated Charities.

VIEWPOINT: "Special section: Building signaling connections: Regulators of cerebellar granule cell development act through specific signaling pathways" by D. Vaudry *et al.* (6 June, p. 1532). The final sentence of the legend of Fig. 1 on p. 1533 should read: "Symbols: ⊥, inhibition; ↓, activation, or in the case of PARP and actin, degradation, which leads to cell death."