Regional Focus on GM Crop Regulation

THE RECENT MEDIA COVERAGE OF THE DEVELopments in Brazil, China, and Mexico (*1*–*3*) demonstrates their emergence as the future developing country forerunners for commercial genetically modified (GM) crops in both the scientific and regulatory arena.

The release of GM crops in these countries might result in the unintentional entry of GM seeds into neighboring countries that have not yet harnessed the technology and implemented sufficient regulatory systems. Unregulated "genetic contamination" of areas intended for growing GM-free or organic products, perhaps for export, could be potentially devastating for some neighboring economies and could set a negative example in the international efforts for the safe use of GM crops."

Should Brazil, China, or Mexico decide to allow the commercial release of GM crops,

GM Bt cotton crop in China.

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countries in the region must ensure that a border control system is included in their biosafety framework. Sharing information on the risk assessment and risk management strategies could also help. A regional perspective in national decision-making is necessary to maintain the benefits for small-scale farmers while pursuing export-oriented agricultural priorities. Current efforts such as the United Nations Environmental Programme–Global Environment Facility biosafety projects (*4*) might provide a forum for such discussions, although it must be owned and driven by the countries themselves for its success in the long run.

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4. See www.unep.ch/biosafety.

Accommodation or Prediction?

IN HIS COMPARISON BETWEEN ACCOMMOdating (a posteriori) and predictive (a priori) hypotheses, P. Lipton asks which is better suited for scientific investigation ("Testing hypotheses: prediction and prejudice," 14 Jan., p. 219). This question is misleading because it ignores the process of scientific inquiry, which starts with observations about the natural world. These observations are interpreted using the tools, worldviews, and values of the scientific community [Kuhn's (*1*) paradigms] that are available to the observer, and an accommodating hypothesis is formed. This hypothesis is the prerequisite for the continuation of the scientific process.

The real focus of Lipton's article is whether this next step should be additional observations leading to more accommodation, or whether a prediction should precede additional observations. He concludes that predictive hypotheses should be preferred. He acknowledges that well-supported hypotheses often have both accommodations and successful predictions to their credit, but he ignores the historical component. Lipton assumes that both options are equally available to the observer. In reality, the availability of this choice will depend on the field of science, and its state in history. An astronomer in 1531, upon seeing the comet that would be later known as Halley's Comet, would have been unable to predict its return in 1607, because most of the hypotheses on the motion of comets were not published until the early 1600s (*2*). By the time of Halley's prediction (1705), many observations of comet movements and accommodating hypotheses of their pathways were available. W. D. Hamilton accommodated the influence of Darwin (focus on the individual), R. D. Fisher (genetic theory of natural selection), and his personal knowledge of insects in the concept of inclusive fitness (Hamilton's rule). This concept is very powerful in generating predictive hypotheses in the field of evolutionary biology and has paved the way to an entirely new field, sociobiology (*3*). Before Fisher or Darwin, or without sufficient background knowledge in natural history, this would not have been possible. If predictions are formulated without sufficient background knowledge, they are unlikely to be successful. If accommodation is the only method employed, it is likely not very convincing. It is only when sufficient information is available that successful predictive hypotheses can be formulated, and this is where Lipton's discussion is relevant. The incorporation of predictive hypotheses at this point does more than just reduce "fudging"—it adds a new framework to an otherwise accommodation-based process of inquiry, which should strengthen our confidence in the outcome. Together, accommodation and prediction will lead to scientific progress where either one in isolation would be incapable of doing so.

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3. See entry on W. D. Hamilton at http://en.wikipedia.org/wiki/The_Genetical_Theory_of_Natural_Selection.

IN HIS REVIEW "TESTING HYPOTHESES: PREDICtion and prejudice" (14 Jan., p. 219), P. Lipton echoes widespread impressions that predictions, because they cannot be "fudged," are epistemically superior to ad hoc accommodations. His analysis lacks appropriate controls and reference classes. Predictors can fudge too, through excess predictions. They may also hedge by using alternative versions of a hypothesis. Many other predictions are loosely consistent with, but not rigorously determined by, their hypotheses. Failed efforts in such cases are typically disregarded. Thus, Mendeleev's predictions of eka-aluminum (gallium) and eka-boron (scandium) are widely celebrated, whereas his failed predictions of eka-niobium and eka-caesium are largely forgotten (*1*). Meselson and Stahl's dramatic results on DNA replication kindly hide the predictive uncertainty that preceded their study (*2*). By discounting error, predictors indirectly "accommodate" available evidence. Like astrologers' or psychics' missed guesses, failures belong in a complete epistemic analysis of predictions. Conversely, accommodations are not so easily fudged—if they are to meet the standards of systematicity and coherence ("simplicity"). Accommodators thus encounter risk and may discard hypotheses well before any announcement. Their failures matter too. Darwin's evolutionary synthesis and Einstein's special relativity were extraordinary accommodations (*3*). They justly earned merit by the conventional

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standards of evidence and theoretical virtues of scope and accuracy. By not controlling for relevant error, Lipton gives predictors the appearance of risk and rigor and accommodators only the ability to fudge.

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P. LIPTON SHOULD BE COMMENDED FOR HIS lucid and persuasive argument in support of testing hypotheses by predictions rather than by accommodations ("Testing hypotheses: prediction and prejudice," Reviews, 14 Jan., p. 219). I wish Lipton had addressed another central theme in the search for truth in biomedical science, namely, testing hypotheses through experimentation (intervention) versus observations.

For ethical and other reasons, clinical research leaves little room for hypothesis testing through human experiments. As such, it often yields data that demonstrate association rather than causality. The so-called "descriptive" nature of many clinical investigations is frequently contrasted with the precise, cause-and-effect methodology of bench research. The not-so-subtle message here is that while basic biological research is real science, most clinical research is not.

Snap judgments that employ the "descriptive/mechanistic" yardstick tell us little about quality or relevance. Far too much effort and expense have been wasted on exploring "mechanistic" trivialities. The true standard that gauges the merit of any biomedical enterprise is the dividend of biological insight into how we came to be and who we are.

Darwin's *The Origin of Species* and *The Descent of Man* are quintessentially "descriptive," and for that matter accommodative, yet the ramifications of these works have transformed biology. The original investigations that found associations of cardiovascular disease with hypertension and elevated LDL cholesterol have ushered in large-scale preventive and therapeutic interventions, changing forever the way we practice medicine and saving millions of lives in industrialized societies. Very few "mechanistic" studies in yeast, worms, mice, and, for that matter, humans can claim the same impact on humanity as these originally "descriptive" achievements.

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P. LIPTON ("TESTING HYPOTHESES: PREDIC-tion and prejudice," Reviews, 14 Jan., p. 219) argues that a prediction published before it is verified by observation provides more support than an "accommodation" published afterward (the "advantage thesis"). Lipton gives no evidence that scientists, past or present, actually accept this thesis. He asserts that the successful prediction of the 1758 appearance of Halley's Comet was "far more impressive" evidence for the hypothesis that it was the same comet as those seen in 1531, 1607, and 1682 than the fact that those previous appearances could be accommodated by postulating a comet that returns every 75 or 76 years. But the only evidence he cites to support this assertion (*1*) does not mention Halley's Comet at all.

Lipton cites five authors who found it irrelevant whether observations supporting a hypothesis were made before or after the prediction was published: They still furnish the same amount of support for the hypothesis. As one of those authors, I would like to clarify my position. In the specific case of Einstein's general theory of relativity, theoretical physicists in the 1920s did not give greater weight to the observed bending of starlight by the sun just because it was a prediction published before the observation was reported; they gave equal (or sometimes greater) weight to the fact that the theory explained the advance of Mercury's perihelion, an observation made decades earlier but not satisfactorily explained (*2*).

Although Lipton's "advantage thesis" was refuted in this case, it could be true in others. I looked at the reception of several well-known theories and found that in most cases, confirmation after publication of a prediction did not count more than supporting evidence known earlier (*3*–*9*). In only two cases, Mendeleev's periodic law (*10*) and Morgan's chromosome theory (*11*), did scientists explicitly mention predictiveness as a reason for acceptance, but even in those cases it was not the most important reason. So there is little reason so far to accept the advantage thesis as a general statement about science.

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12. I thank D. Allchin for calling my attention to Lipton's article.

IN HIS REVIEW "TESTING HYPOTHESES: PRE-diction and prejudice" (14 Jan., p. 219), P. Lipton argues that we sometimes have more reason to accept a confirmed prediction than a corresponding accommodation of a hypothesis because accommodations have more opportunity to be affected by fudging than predictions. This emphasis on fudging overlooks the powerful ability of statistics to evaluate the degree of validity of confirmed predictions and accommodations. We illustrate this with the example of Halley's prediction of the comet of 1758 mentioned by Lipton. Halley found a sequence of 3 of 24 comet appearances observed over 362 years that were separated by ~76-year intervals and had similar orbital characteristics, and on this basis predicted an appearance in 1758 that was subsequently confirmed (*1*). Using randomly simulated comet appearances, we estimate a P value of ~0.03 for confirmed prediction (P_{pred}) of a fourth appearance beyond a 362-year period that continues a sequence of three found within it, and P values for corresponding accommodations (P_{acc}) for finding four appearances in sequence anywhere within a period of $362 + x$ years, finding P_{acc} ranging between ~0.09 ($x = 10$) and ~0.11 ($x = 60$) (*2*). As here $P_{pred} < P_{acc}$, there is indeed more reason for confidence in prediction than accommodation, but this may not always obtain. For example, if instead of predicting a fourth appearance from three observations, we consider prediction of a fifth based on four, P_{pred} should stay nearly the same because it depends mainly on the random success of a single prediction with unchanged probability, while P_{acc} should drop because it depends on finding random sequences of five versus four; here $P_{pred} = \sim 0.02$ and $P_{acc} = \sim 0.08$ ($x = 60$). With increasingly well-fit data and no change in free parameters, accommodation should eventually impart greater confidence than prediction.

Because, as Lipton notes, fudging may be "neither fully conscious nor readily visible," it is difficult to evaluate its impact. Science has thus developed objective data collection and analysis procedures to supress it, allowing the validity of confirmations to be assessed statistically. When these procedures are employed and statistics are comparable, there is no reason to stress predictions over accommodations.

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2. See supplementary information at http://arep.med.harvard.edu/Halley.

Response

I AM GRATEFUL FOR THE MANY THOUGHTFUL responses to my discussion of prediction and accommodation. Two recurring and well-taken points are that predictions are sometimes unavailable (Stanger-Hall) and that a theory may be strongly supported without them (Allchin, Aviv). The aim of my discussion was to suggest that predictions sometimes have an edge over accommodations because they do not encourage theory-fudging, not to deny that accommodations ever provide powerful support.

Other Letters suggest liabilities of prediction that may remove any net advantage over accommodation (Aach and Church, Allchin). Even if prediction is not susceptible to theory-fudging, because the investigator does not know the right answer in advance, it is susceptible to "data-fudging," where the empirical results are either massaged or selectively ignored. Data-fudging occurs, but it does not cancel out the asymmetry between accommodation and prediction. For one thing, it applies to accommodation as well as to prediction; for another, data fudging may often be easier to detect and control than theory-fudging. I also accept Allchin's more specific point that predictions may in practice serve to select from different versions of a hypothesis, but I do not see that this necessarily introduces additional fudging. Of course, if the investigator reacts to a failed prediction by mangling the hypothesis to get a fit, that is indeed fudging, but I would also count it as an accommodation, not a prediction.

Another recurrent reaction to my argument is that the difference between prediction and accommodation may be simply irrelevant. Thus, Brush, a distinguished historian of science, suggests that scientists have in fact typically not given greater weight to predictions. On the historical question, there is a variety of views and cases to be distinguished. Brush has studied a number of instances where he has found no contrast, although he has also found two cases where scientists did claim to put particular weight on predictiveness. And in the case of Halley that I cited in my essay, the entry in the *Dictionary of Scientific Biography* states that "although [Halley's cometary views] aroused the interest of astronomers, it was not until the 1682 comet reappeared as predicted in 1758 that the whole intellectual world of western Europe took notice… This successful prediction acted as a strong independent confirmation of Newtonian gravitation…" (*1*). Moreover, the claim Brush makes of the similar weight given to perihelion shift (known beforehand) and starlight bending (predicted) in the confirmation of the general relativity may not bear directly on my argument, for I do not claim that each of a theory's predictions is worth more than any of its accommodations. Moreover, it is not clear that the data concerning the shift in the perihelion of Mercury count as an accommodation in the sense relevant to my argument, since Einstein claimed not to have used those data to form his theory. Thus, he and Infeld wrote, "The deviation of the motion of the planet Mercury from the ellipse was known before the general relativity theory was formulated, and no explanation could be found. On the other hand, general relativity developed without any attention to this special problem" (*2*). It is interesting both that the theory was developed independently and that Einstein and Infeld thought this a point worth emphasizing.

Of course, it is possible that even if scientists in fact place weight on the distinction between accommodation and prediction that they ought not do so, or vice versa, and my Review focused on the normative question. Aach and Church suggest that the case for taking account of whether data were accom-

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modated or predicted will evaporate where sophisticated statistical techniques are available to evaluate the data. Those techniques are important, but I doubt that, even when they are applicable, they obviate any appeal to the contrast between accommodation and prediction. One reason for this is that fudging, as many of my commentators have observed, may take so many different forms.

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Plutonium-238 and Cassini

***SCIENCE* IS TO BE COMMENDED FOR THE** Cassini series of articles (25 Feb., pp. 1222–1276). Plutonium-238–powered isotopic generators supplied the electricity that allowed Cassini's data gathering and transmission. Without Pu-238 sources, there would have been no Cassini. Yet, Cassini was almost scrubbed because activists tried hard to block the Pu-238 generators. Worst-case scenarios of Cassini disasters were ubiquitous in Washington, DC. The Office of Management and Budget became a last-resort safety review board that had to be convinced before the White House would allow the Department of Energy to proceed with Cassini. The plutonium-powered sources worked, and now we have marvelous data from Saturn via Cassini.

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A Historical Note on Superconductors

I ENJOYED READING M. RICE'S PERSPECTIVE "Superfluid helium-3 has a metallic partner" (12 Nov. 2004, p. 1142) about the elegant work of K. D. Nelson *et al.* ("Odd-parity superconductivity in Sr_2RuO_4," Reports, 12 Nov. 2004, p. 1151), in which they confirmed the nature of superconductivity in strontium ruthenate to be odd parity $l = 1$, as had been supposed but not proven for a number of years. In Rice's second paragraph, I found a historical remark that does not describe the actual course of events. Rice writes, "Not long after this [the BCS] theory was developed, Kohn and Luttinger speculated that superconductors in which the pairs have finite angular momentum… could also occur." It is true that it was "not long after BCS" that such ideas appeared, but it was some 5 to 6 years before the Kohn-Luttinger paper (*1*) in 1965.

The first papers on higher angular momentum states appeared within a few months of each other in 1960, by Pitaevskii (*2*), Brueckner *et al.* (*3*), and Emery and Sessler (*4*), all independently and approximately in that order. These focused on ^{3}He to some extent, but a more comprehensive and general study of this kind of state was made shortly after by Anderson and Morel (*5*, *6*). The classic papers of Balian and Werthamer (*7*) and of Leggett (*8*) had also appeared by 1965.

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CORRECTIONS AND CLARIFICATIONS

ScienceScope: "Pig flu scare—case closed?" (15 Apr., p. 339). Henry Niman, who has backed claims that Korean pigs harbor the WSN/33 virus, is not based in Philadelphia, but in Pittsburgh.

Special Section: Cassini at Saturn: Reports: "Ultraviolet imaging spectroscopy shows an active saturnian system" by L. W. Esposito *et al.* (25 Feb., p. 1251). On page 1252, in the third column, in the paragraph after reactions 4 and 5, line 10, the citation of reference 8 is incorrect. The citation should be to the following paper, which is not in the reference list: M. T. Leu, M. A. Biondi, R. Johnsen, *Phys. Rev. A* **7**, 292 (1973).

Reports: "Control of excitatory and inhibitory synapse formation by neuroligins" by B. Chih *et al.* (25 Feb., p. 1324). While this manuscript was under review, a related paper was published in *Cell* reporting a role for neuroligins and neurexins in GABA synapse assembly: E. R. Graf, X. Z. Zhang, S. X. Jin, M. W. Linhoff, A. M. Craig, "Neurexins induce differentiation of GABA and glutamate postsynaptic specializations via neuroligins," *Cell* **119**, 1013 (2004).

Reviews: "Editing at the crossroad of innate and adaptive immunity" by P. Turelli and D. Trono (18 Feb., p. 1061). Didier Trono's e-mail address was listed incorrectly; it is Didier.Trono@epfl.ch.

Reports: "Two abundant bioaccumulated halogenated compounds are natural products" by E. L. Teuten *et al.* (11 Feb., p. 917). There was a small error in reference 32. Line 12 should read "(with funding provided by The Camille and Henry Dreyfus Foundation, Inc..."

TECHNICAL COMMENT ABSTRACTS

COMMENT ON "Abrupt and Gradual Extinction Among Late Permian Land Vertebrates in the Karoo Basin, South Africa"

Charles R. Marshall

Reanalysis of the high-precision field data of Ward *et al.* (Reports, 4 February 2005, p. 709) fails to significantly support a gradual extinction prior to the Permian-Triassic boundary and more strongly suggests that the Triassic taxa originated in the Triassic than in the Permian. Thus, the data are consistent with a simple catastrophic extinction and concomitant recovery.

Full text at
www.sciencemag.org/cgi/content/full/308/5727/1413b

RESPONSE TO COMMENT ON "Abrupt and Gradual Extinction Among Late Permian Land Vertebrates in the Karoo Basin, South Africa"

Peter D. Ward, Roger Buick, Douglas H. Erwin

Our data from the land vertebrate record of the Permian-Triassic transition of the Karoo Basin of South Africa support both gradual and sudden extinction mechanisms. In our response, we show why Marshall's support of a single catastrophic event is untenable.

Full text at
www.sciencemag.org/cgi/content/full/308/5727/1413c

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