



Science's Policy on Data Deposition

SCIENCE HAS A LONG-STANDING POLICY THAT molecular sequence data supporting research papers must be made available through a public repository at or before the time of publication. The International Society for Computational Biology (ISCB) (1), on behalf of its 1300 members, is concerned about the repeated acceptance of manuscripts for publication in *Science* that violate this policy (2, 3).

Deposition of sequence data with public repositories guarantees uniform free access to the data, facilitates the development and use of sequence analysis and sequence comparison software, and assures the archival preservation of the data. Free access to the data supporting a publication is fundamental to the scientific process. The consensus in the scientific community supporting deposition of molecular sequence data in public repositories is undermined by the practice of making exceptions to this policy for some groups.

PHILIP E. BOURNE*

International Society for Computational Biology,
University of California, San Diego, 9500 Gilman
Drive, La Jolla, CA 92093-0505, USA.

*President, ISCB.

References and Notes

1. See www.iscb.org.
2. J. C. Venter *et al.*, *Science* **291**, 1304 (2001).
3. S. A. Goff *et al.*, *Science* **296**, 92 (2002).

Response

BOURNE'S FIRST SENTENCE IS INCORRECT; *Science*'s long-standing policy, rather, has been that such data be deposited in a publicly accessible repository. That policy was adhered to in the case of both of the papers he

cites; indeed, over 12,000 downloads have been made from the Celera sequence so far, from nearly 500 institutions.

What many computational biologists and others have recommended is something more: that such data should be deposited in a particular repository, namely, GenBank. As we pointed out editorially with regard to the Goff *et al.* paper, we are insisting on that, but we argued that in the case of the rice genome, the public benefit resulting from publication outweighed the cost associated with the exception (1). Thus, we agree with the arguments made in Bourne's second paragraph.

Would we ever make another exception? Not likely, but circumstances (not to mention "accepted community standards") may change over time—and "never" is a long word.

DONALD KENNEDY

Reference

1. D. Kennedy, *Science* **296**, 13 (2002).

Drug Approval and Testing on Children

ELIOT MARSHALL'S DESCRIPTION OF THE Food and Drug Administration's (FDA's) vacillation about retaining the requirement for drugmakers to test drugs on children ("Challenge to FDA's authority may end up giving it more," *News of the Week*, 3 May, p. 820) is unbalanced. He gives short shrift to the shortcomings of the policy, which makes drug development more costly, might actually be detrimental to children, and could delay the availability of new drugs, if the FDA were to withhold approval for adult uses while data from pediatric studies are being collected (as the agency has threatened to do). Moreover, the regulation is a rigid, governmental solution to a nonproblem, according to many pediatricians. Even the FDA concedes that physicians routinely and safely prescribe pain relievers, asthma drugs, antihistamines, antibiotics, and other therapeutics for children, despite the fact

that clinical trials for those products have been performed only in adults.

The requirement for pediatric testing ignores the nuances of drug development. Creating a dosage form appropriate for children is often especially challenging, for a number of reasons. Can the active ingredient be incorporated into a chewable or syrup form? Will it have special storage requirements and adequate shelf-life? Does it taste good enough so that kids will actually take it?

A pediatric form of GlaxoSmithKline's antibiotic, Cefdin, required more than double the cost and man-hours to develop than did its adult formulation. The same company also experienced serious problems in finding effective preservatives for its pediatric syrup form of Epivir, an anti-HIV drug, even after the adult formulation had been fully developed.

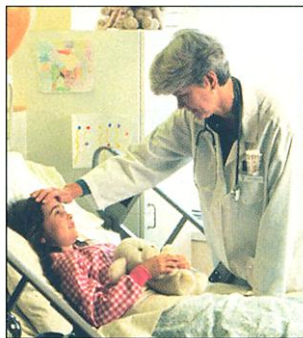
Clinical trials are difficult to perform with children. For ethical reasons, testing is done in subjects who are ill, not in healthy volunteers. Study participants may be scarce because a disease is rare in children, because the population is geographically diverse, or because parents are reluctant to enroll their sick children in an "experiment."

Finally, for the purposes of drug testing, the term "children" implies several groups that are physiologically and metabolically

distinct: newborns, infants, preschoolers, primary-schoolers, and teens. Moreover, children may pass through two or more age groups during the course of a multiyear clinical study, complicating statistical analysis.

Even if additional testing of drugs in children were needed, there are more imaginative and effective ways to accomplish it. For

example, the FDA could simply require a prominent label or logo on drugs whose safety and efficacy have not yet been determined in children, or the agency could publish a list of such drugs annually. This would make parents and physicians aware that such information is not available, and they, in turn, could exert pressure on drug companies to obtain it. (Consider, too, that it is in drug companies' own interest to expand the population that



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will purchase and benefit from their products, and to avoid harming patients.)

The pediatric rule further increases the already high costs of drugs to consumers and puts them at greater risk.

HENRY I. MILLER*

The Hoover Institution, Stanford, CA 94305-6010, USA. E-mail: miller@hoover.stanford.edu

*Miller was an official at the FDA from 1979 to 1994.

Medial Prefrontal Cortex and Error Potentials

WILLIAM J. GEHRING AND ADRIAN R.

Willoughby ("The medial frontal cortex and the rapid processing of monetary gains and losses," Reports, 22 March, p. 2279) report that a "medial-frontal negativity" (MFN), a negative-going deflection in the human event-related brain potential (ERP), was elicited by feedback stimuli indicating monetary gains or losses. The MFN was greater in amplitude following losses than following gains and was attributed to activity in medial frontal cortex. Previous studies have identified a similar negative deflection in the ERP that occurs following incorrect responses in speeded reaction time tasks (1, 2) and following feedback stimuli that indicate

incorrect performance (3). Both of these response and feedback "error-related negativities" (ERNs) were thought to be produced in medial frontal cortex by a mechanism for error detection (1-3). As Gehring and Willoughby note, the MFN and the feedback-related ERN share identical scalp distributions and latencies, suggesting that they are the same phenomenon. Importantly, however, Gehring and Willoughby emphasize that the MFN/feedback ERN is sensitive to the "utilitarian" (gain or loss) value of feedback, rather than to the "performance" (correct or incorrect) value of feedback. In so doing, they dissociate that component from the response-related ERN and its associated function, error detection.

We have proposed a unifying theory that explains the response- and feedback-related ERNs in terms of a single neural mechanism for reward prediction (4-7). This theory renders the distinction between utilitarian and performance feedback artificial by highlighting a shared functional property: the reinforcement of adaptive behavior. Our argument holds that both types of ERN are elicited by the impact of phasic activity of mesencephalic dopamine neurons—a system associated with the computation of utility—on medial frontal cortex. This phasic signal, representing

changes in expected reward, is used by medial frontal cortex to select behaviors that elicit reward. Application of a reinforcement learning algorithm previously used to describe phasic dopamine activity (8) predicts an inverse relationship between the amplitudes of the response and feedback ERNs (4-7). This result is what we find empirically (6, 7).

CLAY B. HOLROYD,¹ MICHAEL G. H. COLES,²
SANDER NIEUWENHUIS¹

¹Princeton University, Department of Psychology, Princeton, NJ 08544-1010, USA. E-mail: cholroyd@princeton.edu, snieuwen@princeton.edu. ²F. C. Donders Centre for Cognitive Neuroimaging, 6500 HB Nijmegen, Netherlands, and Department of Psychology, University of Illinois, Champaign, IL 61820, USA. E-mail: mcoles@s.psych.uiuc.edu

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