SCIENCE

Published by the **American Association for the Advancement of Science (AAAS),** *Science* serves its readers as a forum for the presentation and discussion of important issues related to the advancement of science, including the presentation of minority or conflicting points of view, rather than by publishing only material on which a consensus has been reached. Accordingly, all articles published in *Science*—including editorials, news and comment, and book reviews—are signed and reflect the individual views of the authors and not official points of view adopted by the AAAS or the institutions with which the authors are affiliated.

**Membership/Circulation**

**Director:** Michael Spinella
**Fulfillment:** Marlene Zendell, *Manager*; Gwen Huddle, *Assistant Manager*; Mary Curry, *Member Service Supervisor*; Pat Butler, Helen Williams, Laurie Baker, *Member Service Representatives*
**Promotions:** Dee Valencia, *Manager*; Hilary Baar, Angela Mumeka, *Coordinators*
**Research:** Kathleen Markey, *Manager*; Robert Smariga, *Assistant*
**Financial Analyst:** Jacquelyn Roberts
**Administrative Assistant:** Nina Araujo de Kobes
***Science* Member Services**
Marion, Ohio: 800-347-6969;
Washington, DC: 202-326-6417

**Advertising and Finance**

**Associate Publisher:** Beth Rosner
**Advertising Sales Manager:** Susan A. Meredith
**Recruitment Advertising Manager:** Janis Crowley
**Advertising Business Manager:** Deborah Rivera-Wienhold
**Financial Manager:** Leslie Gelder
**Marketing Manager:** Laurie Hallowell
**Traffic Manager:** Tina Turano
**Recruitment:** Michele Pearl, *Operations Manager*; Dan Moran, *Traffic Manager*; Debbie Cummings, Millie Muñoz-Cumming, Angela Wheeler, *Sales*
**Marketing Associate:** Allison Pritchard
**Reprints Manager:** Corrine Harris
**Permissions Manager:** Arlene Ennis
**Sales Associate:** Carol Maddox

**ADVERTISING SALES: East Coast/E. Canada:** Richard Teeling, 201-904-9774, FAX 201-904-9701 • **Southeast:** Mark Anderson, 305-856-8567, FAX 305-856-1056 • **Midwest:** Donald Holbrook, 708-516-8882, FAX 708-516-8883 • **West Coast/W. Canada:** Neil Boylan, 415-673-9265, FAX 415-673-9267 • **UK, Scandinavia, France, Italy, Belgium, the Netherlands:** Andrew Davies, (44) 457-838-519, FAX (44) 457-838-898 • **Germany/Switzerland/Austria:** Tracey Peers, (44) 270-760-108, FAX (44) 270-759-597 • **Japan:** Mashy Yoshikawa, (3) 3235-5961, FAX (3) 3235-5852
**Recruitment:** 202-326-6555, FAX 202-682-0816
**European Recruitment:** AnneMarie Vis, (44) 0223-302067, FAX (44) 0223-302068
Send materials to *Science* Advertising, 1333 H Street, NW, Washington, DC 20005.

■

**Information for Contributors** appears on pages 40–42 of the 1 January 1993 issue. Editorial correspondence, including requests for permission to reprint and reprint orders, should be sent to 1333 H Street, NW, Washington, DC 20005. ***Science* Telephone:** 202-326-6500, TDD 202-408-7770. **Other AAAS Programs:** 202-326-6400.

# LETTERS

## DNA Fingerprinting: The NRC Report

Peter Aldous's News & Comment article about the National Research Council (NRC) committee's report on DNA fingerprinting (*1*) (News & Comment, 5 Feb., p. 755) misconstrues the committee's goal. For scientific evidence to be legally admissible in court, it must satisfy the test that the methodology be "generally accepted in the scientific community," that is, that there is no significant controversy about the validity of the method. Early on, the NRC committee recognized that there was significant controversy brewing over DNA fingerprinting—a judgment abundantly confirmed by regular eruptions in *Science*. [Indeed, several state appellate and supreme courts have excluded DNA evidence citing the news and peer-reviewed pages of *Science* to prove the lack of "general acceptance" (see, for example, *2*).]

In order to ensure the admissibility of this important technology, the NRC committee sought to define common ground, namely, a standard of practice so conservative as to ensure that there would be no serious scientific argument that the evidence could be said to *overstate* the case against a defendant. We anticipated that some scientists would argue that the standard *understates* the evidence, but decided that (i) their arguments had merit but were not absolutely definitive (and the current round of articles adds little to the submissions these same authors made to the committee) and (ii) any loss of statistical power could be offset by testing one or two additional genetic loci.

Accordingly, it comes as no surprise to learn that the original proponents of a more liberal approach to population genetics now decry the committee's decision as "illogical" or "arbitrary." The committee prescribed an upper bound of 50:1 for the contribution of each genetic locus to the overall odds on the basis of quantitative estimates (of the effects of sample error and genetic drift) that indicated this would make adequate allowance for fluctuations among population subgroups. To be sure, all margins of safety involve some element of judgment, but this does not render them "illogical" or "arbitrary." In this case, the NRC committee simply concluded that the chosen upper bound sufficed to eliminate serious scientific objections to the population genetic statistics (whether based on theoretical or empirical grounds) while still allowing odds of up to 6,250,000:1 for a match at four genetic loci.

The NRC committee has clearly achieved its goal. DNA fingerprinting evidence prepared and presented in accordance with the NRC report is and should be legally admissible in all U.S. courts because it meets the test of "general acceptance" (notwithstanding that some would accept a looser standard). Even courts that cited previous controversies when they excluded DNA fingerprinting evidence have acknowledged that the NRC report now provides the basis for admissibility.

Critics are welcome to try to achieve "general acceptance" of a looser standard for DNA fingerprinting. However, this may be slow in coming, not least because, according to Aldous's article, the critics each prescribe a different solution. More important, a looser standard will not significantly increase the power of forensic DNA typing in courts (which is already sufficient to obtain convictions against guilty defendents), but it will likely provoke continued litigation that will hamper the use of this important and powerful criminalistic tool.

*Eric S. Lander*
*Center for Genome Research, Whitehead Institute for Biomedical Research, and Department of Biology, Massachusetts Institute of Technology, Nine Cambridge Center, Cambridge, MA 02142–1479*

### References

1. Committee on DNA Technology in Forensic Science, *DNA Technology in Forensic Science* (National Academy Press, Washington, DC, 1992).
2. *California* v. *Barney*, 8 Cal. App. 4th 798 (1992).

■

## Directed Mutation

Any challenge to the conventional wisdoms of science must expect to face some opposition; most beliefs have been hard-won and they should not be discarded lightly. But the defense of orthodoxy by Richard E. Lenski and John E. Mittler (Articles, 8 Jan., p. 188) is surely too selective and partisan to be useful.

In 1988, my co-workers and I found that populations of bacteria undergoing selection for a particular phenotype seemed to accumulate the appropriate mutations without at the same time accumulating unselected mutations (*1*). Our paper provoked an outcry because, although there had been no test to see if cells have any special way of producing

adaptive mutations (*2*), the discoveries of molecular biology were thought by most biologists to be the final proof that mutations must be random (*3*). People came up with all kinds of alternative explanations for our results. To answer these critics, we needed to find better evidence and to have better control of possibly confounding factors.

Two years ago, we described adaptive mutations (reversion of a frameshift mutation in a *lacI-Z* fusion in *Escherichia coli*) that continuously accumulated in the stationary phase, although only when the mutation allowed the cell to resume growth (that is, only when the change was adaptive). We found no measurable growth or death in the population undergoing selection; we found no mutants accumulated in the absence of lactose or in its presence when the cells lacked some other requirement for growth; we showed that the process producing these frameshifts required expression of the *recA* gene when the mutants arose under conditions of selection, but this did not appear to hold for the process producing them during normal growth (which suggests that adaptive and nonadaptive mutations arise from different mechanisms) (*4*).

Much of the article by Lenski and Mittler is a reiteration of the criticisms of our earlier experiments, including their evidence that two DNA rearrangements (excision of *mu* and of an insertion sequence) occur in the stationary phase in the absence of selection [something that Hall (*5*) and I (*1*) did not observe]. Although Lenski and Mittler quote (and apparently accept) our recent conclusions about possible mechanisms for adaptive mutation (*1*, *6*), they make no mention of the most important part of our experiments, where we control for variables that they and others saw as confounding factors in our previous work. In effect, they seem to be saying that they are prepared to believe our conclusions about the cause of a phenomenon even though they do not believe the phenomenon exists, and for this reason they do not discuss the evidence that it does exist.

Anyone who wants a straightforward account of the issues will therefore have to read the original papers (*4*, *6*) or one of the recent reviews by nonpartisan outsiders (*7*).

**John Cairns**
*Clinical Trial Service Unit,*
*Radcliffe Infirmary,*
*Oxford OX2 6HE, United Kingdom*

**References**

1. J. Cairns, J. Overbaugh, S. Miller, *Nature* **335**, 142 (1988).
2. M. Delbrück, *Cold Spring Harbor Symp. Quant. Biol.* **11**, 154 (1946).
3. E. Mayr, *The Growth of Biological Thought* (Harvard Univ. Press, Cambridge, MA, 1982).
4. J. Cairns and P. L. Foster, *Genetics* **128**, 695 (1991).
5. B. G. Hall, *ibid.* **120**, 887 (1988).
6. P. L. Foster and J. Cairns, *ibid.*, **131**, 783 (1992).
7. J. W. Drake, *Annu. Rev. Genet.* **25**, 125 (1991); S. Brenner, *Curr. Biol.* **2**, 167 (1992); N. D. Symonds, *Mutat. Res.* **285**, 9 (1993).

*Response*: Cairns' charge that our article is a partisan defense of orthodoxy obscures the important point that this debate revolves around competing hypotheses that can be tested by careful experiments. In fact, we are one of the few groups that has sought to reexamine experimentally the evidence for directed mutation. When we have done so (*1*, *2*), we have confirmed many of the observations that led to the suggestions of directed mutation, but the purportedly huge effects of selective condition on mutation rate vanished when we performed additional controls and an accounting of population dynamics missing from the earlier studies.

Cairns says we ignored evidence consistent with directed mutation from one of his more recent papers (*3*). Cairns and others have repeatedly invoked new examples of directed mutation, even as old cases were called into question, raising the troubling impression that the advocates of directed mutation regard their hypothesis as unfalsifiable. We had neither the space nor the inclination to rebut each of more than a dozen alleged examples of directed mutation in bacteria and yeast (cited in our article). Instead, we illustrated the various classes of explanation for the phenomena with particular cases where the most information was available.

Cairns also states that his more recent paper on *lac* frameshift revertants (*3*) sought to address criticisms of his earlier work (*4*) on directed mutation. Yet, this recent paper did not cite any of the papers presenting these alternative hypotheses—even while it cited, without qualification, papers whose conclusions had been undermined by these alternatives. Even so, we would have spent more time discussing this paper had it clearly excluded relevant alternatives. Cairns and Foster's statement that the vast majority of reversions occur after plating on medium with lactose (3) relies on statistical deviations from the Luria-Delbrück distribution that are consistent with this interpretation. However, such deviations may also be caused by any of several other plausible departures from the assumptions of the fluctuation test (*5*), none of which were addressed in their paper. Even if it is correct that the majority of mutants have arisen after plating on lactose, the differential accumulation of revertants in the presence and absence of lactose might be explained by slight growth of the $Lac^-$ progenitor on lactose, death of starving cells (including $Lac^+$ mutants) in the absence of

lactose, delays in the growth of Lac$^+$ mutants upon exposure to lactose after they have been starving for many days (*1*), or some combination thereof. Cairns states that they observed "no measurable growth or death," but their data do not have the resolution to exclude small effects that could nonetheless account for the relevant differences. And no effort appears to have been made to determine the effect of starvation on the time course of colony formation after lactose was provided. Also, some of the Lac$^+$ revertants may have arisen by selection for two successive mutations, each of which partially restores the ability to grow on lactose. From data in their paper (*3*), it is obvious that many of the Lac$^+$ mutants are not true revertants (in the sense of having the ancestral *lac* sequence); some form visible colonies within 2 days on minimal lactose medium, whereas others take five or more days. This variation in growth rate on lactose indicates that some Lac$^+$ mutants have occurred by changes that do not precisely restore the original reading frame throughout the gene, but presumably do so over portions thereof. Some of these imperfect revertants may give rise to secondary mutants with faster growth on lactose. But without lactose, these imperfect revertants cannot grow to a sizable population and so secondary mutations do not occur, producing a discrepancy between the accumulation of Lac$^+$ mutants under selective and control conditions that is a result of selection, not mutation (*6*). Only one of these alternatives needs to be correct in order to undermine the inference that the *lac* frameshift revertants are directed. Moreover, these alternatives are typically multiplicative, so that several small effects could combine to produce much larger discrepancy.

Finally, Cairns wonders how we could accept his conclusion that certain molecular mechanisms were not responsible for directed mutation while not accepting his conclusion that directed mutation itself is real. Our article discussed two distinct classes of mechanistic explanations for the differential accumulation of mutants under selective and nonselective conditions. (i) Some molecular process increases the rate of certain mutations specifically when the resulting phenotype is advantageous. (ii) The differential accumulation of mutants results from nonspecific increases in mutation rate and differences in population dynamics (growth and death). The fact that tests of the molecular models performed by Foster and Cairns (*7*) and others have not explained any case of directed mutation, whereas the purported increases in mutation rate under selective conditions disappear when additional experiments to test (ii) are performed, supports our conclusions quite naturally.

We hope that Cairns and other propo-

nents of directed mutation will read our article with an open mind and not fall back on the unhelpful charge that those who disagree with their conclusions must be blindly committed to defending orthodoxy.

*Richard E. Lenski*
*Center for Microbial Ecology,*
*Michigan State University,*
*East Lansing, MI 48824*
*John E. Mittler*
*Department of Biology,*
*Emory University,*
*Atlanta, GA 30322*

**References**

1. J. E. Mittler and R. E. Lenski, *Nature* **344**, 173 (1990).
2. ———, *ibid.* **356**, 446 (1992).
3. J. Cairns and P. L. Foster, *Genetics* **128**, 695 (1991).
4. J. Cairns, J. Overbaugh, S. Miller, *Nature* **335**, 142 (1988).
5. F. M. Stewart, D. M. Gordon, B. R. Levin, *Genetics* **124**, 175 (1990).
6. R. E. Lenski, M. Slatkin, F. J. Ayala, *Proc. Natl. Acad. Sci. U.S.A.* **86**, 2775 (1989).
7. P. L. Foster and J. Cairns, *Genetics* **131**, 783 (1992).

*Editor's note*: Additional comments on the article by Lenski and Mittler will appear in a forthcoming issue.

## Liver Stem Cells

It is gratifying to discover that a concept that one has been espousing for a number of years (*1*) has finally received widespread acceptance (John Travis, Research News, 26 Mar., p. 1829). My collaborators and I began working on models of experimental chemical hepatocarcinogenesis in the early 1970s. Although I had learned the experimental systems at the University of Pittsburgh from Emmanuel Farber, our observations of the cellular changes in the liver preceding the appearance of cancers led us to a conclusion different from Farber's—that liver cancers arise from liver stem cells.

At first, this idea met with considerable skepticism, but by the mid-1980s others began to report similar results and gradually the concept of a liver stem cell gained respectability. It is fulfilling to find so many others who are taking the idea of a liver stem cell seriously.

*Stewart Sell*
*Department of Pathology and Laboratory Medicine,*
*University of Texas Health Science Center,*
*Houston, TX 77225*

**References**

1. S. Sell and H. L. Leffert, *Hepatology* **77**, 77 (1982).