

## Letters to the Editor

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## Retraction

### WE WISH TO RETRACT OUR RESEARCH ARTICLE

“The bacterial condensin MukBEF compacts DNA into a repetitive, stable structure” (*I*). The conclusions of our paper, which used a single-molecule assay with an optical-trap microscope, were based on the interpretation of a flat sawtooth pattern in the force-extension curves as a progressive unraveling of compact MukBEF/DNA filaments. However, subsequent experiments done after the paper appeared suggested that the sawtooth pattern corresponds to the unzipping of the two strands of DNA (*2*). We now believe that nicks that arose indiscriminately along the DNA molecules from normal pipetting allowed interior biotin and Digoxigenin derivitization of the DNA tether. The combination of interior and terminal labels most likely generated a pulling geometry between the beads that led to the denaturation of the DNA. To test these ideas, we have now performed an extensive set of experiments.

First, the double-strand DNA was cross-linked with one psoralen cross-link per 100 base pairs to prevent the opposite strands from separating. The cross-linked DNA alone produced the expected force-extension curves for naked DNA (102 out of 103 cases). When the cross-linked DNA was incubated with purified MukBEF protein under our published conditions, in no case ( $n = 180$ ) did we observe the previously observed sawtooth pattern.

Second, we designed a DNA tether that had both a nick and an adjacent biotin label 2-kb interior from its Digoxigenin-labeled end. The labels and nick were placed so that if the streptavidin bead attaches to both the interior and end-labeled biotin and the anti-Digoxigenin bead attaches to the Digoxigenin labeled DNA end, then pulling the beads apart would unzip the DNA between the interior- and the end-biotin label. With this DNA alone, the flat sawtooth pattern in the force-extension curves was readily observed, displaying little or no hysteresis between the pulling and relaxation paths. When these tethers were incubated with MukBEF protein, hysteresis then appeared between the pulling and relaxing pathways and the pattern was indistinguishable from the published sawtooth pattern.

Thus, we now believe that two DNA attachments were made to one of the beads in our published experiments. MukBEF interacted with the unzipped tether to slow reannealing, giving rise to the observed hysteresis. We deeply regret the misinterpretation and the confusion the original publication has caused.

RYAN B. CASE,<sup>1,2</sup> YUN-PEI CHANG,<sup>3</sup>

STEVEN B. SMITH,<sup>2,4</sup> JEFF GORE,<sup>2</sup> NICHOLAS R.

COZZARELLI,<sup>1,3</sup> CARLOS BUSTAMANTE<sup>1,2,3,4</sup>

<sup>1</sup>Department of Molecular and Cell Biology,

<sup>2</sup>Department of Physics, <sup>3</sup>Biophysics Graduate Group, <sup>4</sup>Howard Hughes Medical Institute, University of California, Berkeley, Berkeley, CA 94720, USA.

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## An Open Letter to Elias Zerhouni

THE NIH PEER-REVIEW PROCESS AND NIH investments in research on microbial physiology, genetics, and pathogenesis have made possible remarkable advances in science and public health and have underpinned the development of recombinant DNA technology and the biotechnology industry.

“ The diversion of research funds from projects of high public-health importance to projects of high biodefense but low public-health importance represents... a crisis for NIH-supported microbiological research.”

—ALTMAN ET AL.

However, the NIH peer-review process, and the research sector responsible for these achievements, are threatened by unintended consequences of the 2001–02 decision by the NIH National Institute for Allergy and Infectious Diseases (NIAID) to prioritize research of high biodefense, but low public-health significance (see Appendix 1) (*I*).

This prioritization, which was implemented by creation of funding set-asides, special funding review panels, and special funding review procedures, has transformed NIH-supported research in microbial physiology, genetics, and pathogenesis.

The result has been a massive influx of funding, institutions, and investigators into work on prioritized bioweapons agents: i.e.,

the agents that cause tularemia, anthrax, plague, glanders, melioidosis, and brucellosis. The number of grants awarded by NIAID that reference these agents has increased by 1500% (from 33 in 1996–2000 to 497 in 2001 to January 2005; see Appendix 2) (*I*).

Over the same period, there has been a massive efflux of funding, institutions, and investigators from work on non-biodefense-related microbial physiology, genetics, and pathogenesis. The number of grants awarded to study non-biodefense-related model microorganisms has decreased by 41% (from 490 in 1996–2000 to 289 in 2001 to January 2005; NIH Microbial Physiology and Genetics Initial Review Group; see Appendix 3) (*I*), and the number of grants to study non-biodefense-related pathogenic microorganisms has decreased by 27% (from 627 in 1996–2000 to 457 in 2001 to January 2005; NIH Bacteriology and Mycology Initial Review Group; Appendix 3) (*I*).

The diversion of research funds from projects of high public-health importance to projects of high biodefense but low public-health importance represents a misdirection of NIH priorities and a crisis for NIH-supported microbiological research.

The diversion of research funds comes at a time when research on non-biodefense-related microbial physiology, genetics, and pathogenesis is poised for significant breakthroughs, made possible by the application of genomics, proteomics, and systems-biology methods (see Appendix 4) (*I*). These breakthroughs, and the accompanying dividends for public health and economic development, now either may not occur, or may occur only outside the United States, to the detriment of the U.S. national interest.

As researchers who have served on the NIH Microbial Physiology and Genetics and NIH Bacteriology and Mycology Initial Review Groups, or who have received grants reviewed by those Initial Review Groups, we urge you to take corrective action (see policy recommendations in Appendix 4) (*I*).

SIDNEY ALTMAN, BONNIE L. BASSLER, JON BECKWITH, MARLENE BELFORT, HOWARD C. BERG, BARRY BLOOM, JEAN E. BRENCHLEY, ALLAN CAMPBELL, R. JOHN COLLIER, NANCY CONNELL, NICHOLAS R. COZZARELLI, NANCY L. CRAIG, SETH DARST, RICHARD H. EBRIGHT, STEPHEN J. ELLEDGE, STANLEY FALKOW, JORGE E. GALAN, MAX GOTTESMAN, RICHARD GOURSE, NIGEL D. F. GRINDLEY, CAROL A. GROSS, ALAN GROSSMAN, ANN HOCHSCHILD, MARTHA HOWE, JERARD HURWITZ, RALPH R. ISBERG, SAMUEL KAPLAN, ARTHUR KORNBERG, SYDNEY G. KUSTU, ROBERT C. LANDICK, ARTHUR LANDY, STUART B. LEVY, RICHARD LOSICK, SHARON R. LONG, STANLEY R. MALOY, JOHN J. MEKALANOS, FREDERICK C. NEIDHARDT,

NORMAN R. PACE, MARK PTASHNE, JEFFREY W. ROBERTS,  
JOHN R. ROTH, LUCIA B. ROTHMAN-DENES,  
ABIGAIL SALYERS, MOSELO SCHAECHTER, LUCY SHAPIRO,  
THOMAS J. SILHAVY, MELVIN I. SIMON, GRAHAM WALKER,  
CHARLES YANOFSKY, NORTON ZINDER

Affiliations for these signatories and the names and affiliations of over 700 additional signatories are available in the Supporting Online Material (7).

## Reference

1. Appendices and a complete list of signatories are available in the Supporting Online Material at [www.sciencemag.org/cgi/content/full/307/5714/1409c/DC1](http://www.sciencemag.org/cgi/content/full/307/5714/1409c/DC1).

## A Small-Scale Foreign Aid Strategy

**DONOR NATIONS SEND BILLIONS OF DOLLARS** of aid to developing countries with little evidence for lasting positive effects (1). It is clear that more effective aid programs must be conceived that will have an enduring impact in spite of the difficult conditions prevailing in recipient nations (2, 3). Small-scale efforts can make contributions to the global aid effort. I wish to share my experiences with one small organization that has achieved remarkable success with limited financial resources and a structure that demands only a modest commitment from the individual participants. "Coopération Genève-Yaoundé" (CGY) is an alliance between the medical faculties of the Universities of Geneva, Switzerland, and Yaoundé, Cameroon, whose primary goal is to improve the training of Cameroonian medical doctors. Two guiding principles of the CGY are that raising the standards of medical practice will have an immediate impact on the health of a population and that aid provided in the form of educational training is relatively immune to misappropriation and corruption.

Volunteers from Swiss medical faculties actively collaborate in the teaching and evaluation of medical students at the University of Yaoundé. Although each Swiss participant devotes only a period of 2 to 3 weeks of teaching per year, the students and local staff members also benefit greatly from the opportunities to interact informally with the foreign medical professionals.

The CGY organizes residency training in Swiss hospitals for young Cameroonian doctors committed to returning into active practice in their native regions. A major challenge facing programs that train health-care workers in developing countries is the drain of graduates to countries offering higher salaries and a vastly superior work environment (4). The CGY has been fortunate in that all but one of the over 60 Cameroonian doctors selected for residency training in Geneva subsequently returned to work in their native country. This success rate reflects the requirement that candidates must have already com-

pleted an internship in Cameroon, as doctors trained entirely in our medical system will find it extremely difficult to adapt to working in African hospitals.

The medical faculty in Cameroon hosts 10 medical students from Geneva every year for a 2-month rotation in tropical medicine and community health. Apart from providing a unique opportunity to experience a different culture and its distinctive attitudes to health and disease, firsthand exposure to the daily frustrations encountered in African hospitals sensitizes these future Western doctors to our humanitarian obligations in the developing world.

I believe that this conceptually straightforward program can serve as a useful model for universities with an interest in contributing to education in poorer nations.

URS GERBER

Brain Research Institute, University of Zurich, Winterthurerstrasse 190, Zurich CH-8057, Switzerland.

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## What Kind of Farming Works Best?

**IN HIS REVIEW OF MENDEL IN THE KITCHEN: A Scientist's View of Genetically Modified Foods** by N. Fedoroff and N. M. Brown ("Changing genes to feed the world," *Books et al.*, 29 Oct. 2004, p. 815), D. Pimentel misrepresents the impacts of genetically modified herbicide-tolerant (HT) crops and the consequences of organic farming, which he offers as a more sustainable way to meet the food challenges of the 21st century.

Pimentel derides HT crops because they result in increased herbicide use and potential pollution, yet are not significantly more effective against weeds than herbicides and tillage combined. This completely overlooks the drastically reduced soil erosion, increased soil organic matter, and reduced fossil fuel consumption made possible by herbicides and HT biotech crops. The Soil and Water Conservation Society says that herbicide-based, low- and no-tillage cropping systems are the most sustainable ever (1), points made in the book.

Pimentel further denies the benefits of HT crops when he claims that "the soil has to be tilled" with current annual grain crops, causing "serious soil erosion." Perversely, Pimentel uses this misrepresentation to promote organic farming, which relies heavily on erosion-causing tillage for its weed control.

Pimentel selectively cites Rodale Institute research to claim that organic crop yields are equivalent to nonorganic. Yet,

many long-term studies have shown a 10 to 40% organic yield deficit (2–4).

Pimentel may be correct in claiming "organic approaches would reduce the use of fossil energy in corn production by about 30 percent" due to not using synthetic fertilizer, but as Fedoroff and Brown note, only by using far more land per ton of food produced. Replacing synthetic nitrogen fertilizer would require at least a fourfold increase in manure applications or equivalent green manure crops (5).

Humanity already farms more than one-third of Earth's total land area, and additional land cleared for organic fertility and yield deficits would be of lower productivity, greater erosion potential, and higher ecological sensitivity. As Fedoroff and Brown make clear, genetic engineering offers us powerful and important tools to sustainably feed the larger and more affluent global population without using more land and wasting resources.

ALEX A. AVERY,<sup>1\*</sup> C. S. PRAKASH,<sup>2</sup> ALAN MCHUGHEN,<sup>3</sup> ANTHONY R. TREWAVAS,<sup>4</sup> THOMAS R. DEGREGORI<sup>5</sup>

<sup>1</sup>Hudson Institute, Center for Global Food Issues, Post Office Box 202, Churchville, VA 24421, USA. <sup>2</sup>Center for Plant Biotechnology Research, Tuskegee University, Tuskegee, AL 36088, USA. <sup>3</sup>Botany and Plant Sciences, University of California, Riverside, Riverside, CA 92521, USA. <sup>4</sup>Institute of Cell and Molecular Biology, University of Edinburgh, Darwin Building, Edinburgh EH9 3JR, Scotland, UK. <sup>5</sup>Department of Economics, University of Houston, Houston, TX 77204–5019, USA.

\*To whom correspondence should be addressed.

E-mail: [aavery@cgfi.org](mailto:aavery@cgfi.org)

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## Response

**AVERY ET AL. INCORRECTLY EQUATE HERBICIDE tolerance (HT) in crops with the no-till cultivation system.** No-till may or may not be used with HT. For example, 75% of U.S. soybean plantings include HT, but only 30% of them are planted with no-till (1). No-till conserves soil and water resources, but HT itself does not conserve soil or increase soil organic matter. In fact, HT with clean culture (using an herbicide or other treatments to eliminate all weeds and leave only the crop growing cleanly without competition from weeds) significantly increases soil erosion. HT in crops increases the application of herbicides, and herbicides are the most serious pesticide pollutants in streams and groundwater in the United States (2). Ninety-five percent of corn production

acreage in Iowa receives herbicides, and 70% of this land is also cultivated for weed control (3). Soil erosion is a serious problem in the United States. Agricultural soil is being lost about 10 times faster than soil reformation and sustainability (4).

In reviewing the book, I was surprised that Federoff and Brown devoted such a large portion of it to attacking organic agriculture, when organic agriculture has little or nothing to do with plant breeding and genetic engineering. Because of this intense and misleading attack, I felt that I should present the results of the 22-year corn-soybean example of the Rodale Institute in which corn and soybean yields equaled those of conventional corn and soybean production. I agree that not all organic culture of crops produces yields the same as those of conventional crop cultivation (5).

Avery *et al.* imply that I reported that all U.S. and world agriculture could be grown organically without commercial nitrogen fertilizer. They are incorrect—I never said this in my review, nor have I ever said this in any of the more than 500 scientific papers that I have published.

Worldwide crops are cultivated on 11% of the world's land area, not 33% as Avery *et al.* report. Yes, the world has a severe food shortage problem; the World Health

Organization recently reported that 3.7 billion people are malnourished. This is the largest number of malnourished people in history. Certainly, we need sound genetic engineering, as well as soil and water conservation, to increase the yields of our food crops and make agriculture ecologically and economically sustainable.

DAVID PIMENTEL

College of Agriculture and Life Sciences, Cornell University, Ithaca, NY 14853-0901, USA.

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## An Explanation for the Placebo Effect?

THE ELEGANT COMPUTATIONAL MODEL OF addiction described by A. D. Redish in his Report "Addiction as a computational process

gone awry" (10 Dec. 2004, p. 1944) has the potential to provide an explanation for the placebo effect. In the temporal-difference reinforcement learning model (TDRL), actions by an individual are selected to maximize future reward. The greater the difference between expected and experienced rewards, the stronger the learning associating the sequence of states leading up to the reward.

A state in this context might describe the amount of satisfaction (or dissatisfaction) the individual derived from the outcome achieved by the most recent action. Dependencies between the states exist because the most recent action is, in part, shaped by the events of the previous state(s), through constant reevaluation of the initial expectation in each state and subsequent selection of action(s) for the next state. Consequently, by selectively minimizing the number of dissatisfying states in the association, an individual learns a specific behavioral path toward the reward.

Dopamine neurotransmission is involved in reward-mediated signaling, and dopaminergic neurons firing in response to behaviorally relevant stimuli exhibit a rapid burst of transmitter release (*1*). Because such phasing of dopamine has been hypothesized to signal the magnitude of the dis-

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crepancy between expected and observed reward in addiction (2), and release of dopamine has been postulated to underlie the response to placebo in Parkinson's disease (3), it seems worthwhile to explore the implications of Redish's model on the placebo effect.

The value function at the core of the model provides a measure of expected future reward based upon a specific state and the elapsed time until the reward is

obtained, such that the value function discounts rewards that take longer to achieve. Addiction is not the only condition where such a value function applies; the promise of improvement associated with a placebo justifies the use of Redish's model. Therefore, the value function for an individual suffering from an ailment for which a placebo has been given should demonstrate the discounting factor of delayed rewards. That is, the longer the placebo is supposed to take to

elicit efficacy, the less likely the individual is to experience the placebo effect. Furthermore, under this model, one might expect that the greater the expectation of efficacy, the greater will be the resulting phasing in endogenous dopamine released in expectation of reward, in a manner similar to the cuing effects in the addiction model. The release of dopamine may well mediate the analgesic effects of some placebos by decreasing activity in pain-sensitive regions, as described by Wager *et al.* (4).

The fact that Redish's model can be extended to the placebo effect suggests that the use of computational models may provide a means of integrating and unifying seemingly disparate brain phenomena that may share, at least in part, common underlying biological factors.

**KRISTOPHER J. L. IRIZARRY\* AND JULIO LICINIO**  
NPI, University of California, Los Angeles, 695 Charles Young Drive, Los Angeles, CA 90095, USA.  
\*To whom correspondence should be addressed.  
E-mail: kris@informatics.ucla.edu

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### TECHNICAL COMMENT ABSTRACTS

#### COMMENT ON "Avian Extinction and Mammalian Introductions on Oceanic Islands"

Raphael K. Didham, Robert M. Ewers, Neil J. Gemmill

Blackburn *et al.* (Reports, 24 Sept. 2004, p. 1955) showed a positive correlation between avian extinctions and numbers of predatory mammal introductions on oceanic islands. We show that habitat conversion rates also correlate with observed extinctions, demonstrating that single-factor approaches cannot address the synergies among multiple agents of extinction.

Full text at [www.sciencemag.org/cgi/content/full/307/5714/1412a](http://www.sciencemag.org/cgi/content/full/307/5714/1412a)

#### RESPONSE TO COMMENT ON "Avian Extinction and Mammalian Introductions on Oceanic Islands"

Tim M. Blackburn, Phillip Cassey, Richard P. Duncan, Karl L. Evans, Kevin J. Gaston

Didham *et al.* argue that the extent of habitat modification is confounded with the numbers of introduced mammal species on islands, such that the observed positive correlation between mammal introductions and avian extinctions may be spurious. We show that their analyses do not support this conclusion.

Full text at [www.sciencemag.org/cgi/content/full/307/5714/1412b](http://www.sciencemag.org/cgi/content/full/307/5714/1412b)