## 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.

# Smallpox Bioterror Response

IN THEIR REPORT "CONTAINING BIOTERRORIST smallpox" (15 Nov., p. 1428), M. E. Halloran *et al.* state that their "structured simulator" does not produce the "two orders of magnitude difference" between the number of deaths under targeted vaccination and the number of deaths under mass vaccination that we obtained in modeling an emergency response to a smallpox attack (*1*). Although Halloran *et al.* attribute this finding to our use of homogeneous (or free) mixing versus their structured pattern of population interactions, the real explanation lies in the different scales of the scenarios considered: Halloran *et al.*'s scenario is one to five initial infections in a community of 2000, whereas our scenario is 1000 initial infections in a city of 10 million (*1*). The table (at right) compares the number of deaths per thousand that result from Halloran *et al.*'s model (as reported in the first column of Table 2 in their Report) with the number of deaths per thousand that result from our model when we supply the same model inputs used by Halloran *et al.* in their Report: a population of 2000, a single initial infection, an average of 3.2 secondary infections per initially infected person (i.e., $R_0$ = 3.2), 80% vaccination coverage, and response delays of 7, 27, and 37 days to match the detection of smallpox after the first, 15th, and 25th case, as in Halloran *et al.*

Once the models are compared on the same scale, the results are very similar. Because newly identified cases are required to trigger contact tracing, targeted vaccination proceeds with the pace of the epidemic, and the number of deaths scales with the population size, independently of the number of initial infections. By contrast, mass vaccination operates on its own timetable—10 days in the examples above—and thus the number of deaths, although dependent on how many are infected initially, is largely independent of the population size. Consequently, the ratio of deaths from targeted vaccination to mass vaccination increases with the size of the population.

The most important factor in the control of smallpox or any other contagious disease is the level of population immunity against the infectious agent. Postattack mass vaccination provides the most efficient method for rapidly increasing such immunity in the unlikely event of a smallpox bioterror attack.

EDWARD H. KAPLAN[1] AND LAWRENCE M. WEIN[2]
[1]School of Management and School of Medicine, Yale University, New Haven CT, 06520–8200, USA. [2]Graduate School of Business, Stanford University, Stanford, CA 94306, USA.

Reference
1. E. H. Kaplan, D. L. Craft, L. M. Wein, *Proc. Natl. Acad. Sci. U.S.A.* **99**, 10935 (2002) (published online 12 July 2002; 10.1073/pnas.162282799).

### Comparison of results of Halloran *et al.* and Kaplan *et al.*

| | Deaths per 1000 | |
|---|---|---|
| **80% MV after:** | **Halloran *et al.*** | **Kaplan *et al.* (*1*)** |
| 1st case | 0.9 | 0.4 |
| 15th case | 9.4 | 6.4 |
| 25th case | 13.7 | 17.8 |
| **80% TV after:** | **Halloran *et al.*** | **Kaplan *et al.* (*1*)** |
| 1st case | 10.9 | 8.8 |
| 15th case | 19.6 | 12.0 |
| 25th case | 28.2 | 33.9 |

MV, mass vacination; TV, targeted vaccination.

## Response

WE APPRECIATE THE OPPORTUNITY TO emphasize that dynamic models are useful tools to guide and to structure our thinking, but their results should not be accepted uncritically. Kaplan and Wein demonstrate that, on a small scale under a particular scenario, the two models produce similar results. Thus, they confirm our conclusion that mass vaccination is not that much better than targeted vaccination under some circumstances. However, this does not mean that their second claim is correct. That is, in a heterogeneous population, it may not be true that with targeted vaccination, the number of deaths scales with population size, whereas with mass vaccination, it is independent of population size. When we scale up the heterogeneous model, mass vaccination will not necessarily be 200 times better than targeted vaccination, as in their results. The complexity of the heterogeneous stochastic model precludes being certain of what will happen when it is scaled up to 10 million or more. This requires further research.

Many choices are available in scaling up the heterogeneous model, such as how to structure the interconnectivity among smaller communities and how people move among them, as well as the various attack scenarios. For example, a large, focal introduction would need to disperse among smaller communities to cause extensive geographic spread, whereas several smaller, dispersed introductions might tend to die out. The ratio of transmission attributed to close contacts versus casual contact is crucial. None of these choices are available in Kaplan *et al.*'s homogeneous mixing model (*1*).

Differences between the two current models could also become more manifest when scaled up. In our structured model, people know with whom they live and with whom they have close contact, such as in the schools, corresponding to reality. Thus, our simulated targeted vaccination differs essentially from Kaplan *et al.*'s simulated tracing in their homogeneous model. Even apparent similarities in the models harbor subtle differences. We set minimums followed by uniform distributions on critical epidemiologic parameters such as the latent period and the prodromal period, i.e., the period of influenza-like symptoms, whereas Kaplan *et al.* use exponential distributions. Thus, although both models have a mean latent period of 11 to 12 days, the median in ours is also 12 days, whereas in theirs it is much shorter. Thus, epidemics move more quickly in their model than in ours. Also, epidemics in homogeneous models generally move more quickly than in heterogeneous models.

Assumptions common to both models that deserve revisiting include the following: (i) that the prodromal period is the highly infectious period and (ii) that the period of postinfection sensitivity to vaccination is just 3 days. Many researchers now believe that most of the infectious period falls after the onset of recognizable rash and that postinfection sensitivity to vaccination is longer than 3 days in many people. Under these changed assumptions, both models could possibly show an improved performance of the targeted (tracing) strategy compared with mass vaccination.

Further research will reveal which aspects of the models produce particular results, laying the assumptions open to critical examination. We hope that smallpox is never reintroduced, so that we never have

an opportunity to find out which assumptions are correct.

M. ELIZABETH HALLORAN AND IRA M. LONGINI JR.
Department of Biostatistics, Rollins School of Public Health, Emory University, 1518 Clifton Road NE, Atlanta, GA 30322, USA.

Reference
1. E. H. Kaplan, D. L. Craft, L. M. Wein, *Proc. Natl. Acad. Sci. U.S.A.* **99**, 10935 (2002) (published online 12 July 2002; 10.1073/pnas.162282799).

## MDMA ("Ecstasy") and Neurotoxicity

**G. A. RICAURTE AND COLLEAGUES REPORT** dopamine neurotoxicity in primates injected repeatedly with MDMA ("ecstasy") ["Severe dopaminergic neurotoxicity in primates after a common recreational dose regimen of MDMA ("ecstasy"), Reports, 27 Sept., p. 2260]. Because humans rarely die from MDMA use (*1*, *2*), the high mortality in Ricaurte *et al.*'s primates suggests that they failed to administer a "common recreational dose regimen," calling into question their interspecies scaling model (*3*–*5*). Ricaurte *et al.* previously reported that subcutaneous injection of MDMA in squirrel monkeys was twice as neurotoxic as oral administration (*6*), yet they now claim that oral administration offers "little or no" neuroprotection. They nonetheless suggest that even one night's recreational use of MDMA may result in dopamine toxicity and increased risk of Parkinson's disease. Curiously, they fail to cite studies finding normal dopamine (but reduced serotonin) levels in heavy MDMA users. Two reports used in vivo imaging to estimate brain dopamine transporter levels (*7*, *8*); another conducted postmortem analysis of an individual (*9*). Furthermore, previous studies in heavy MDMA users conducted by Ricaurte and McCann failed to find reduced dopamine metabolites in cerebrospinal fluid (*10*–*12*). The dopamine changes produced by MDMA in this study have long been known as potential effects of d-amphetamine and d-methamphetamine, two prescription drugs that have been available for over 80 years (*13*). There is no credible evidence linking these drugs or the monoaminergic changes they can produce in animals (and, perhaps, humans) to Parkinson's disease, nor is there any evidence of increased incidence of early-onset Parkinson's (*14*). We hope the theoretical risks suggested by this study are not inappropriately generalized to clinical MDMA research, which has been conducted without evidence of toxicity (including no detectable changes in serotonin transporter or memory) (*3*, *15*, *16*).

MICHAEL MITHOEFER,[1] LISA JEROME,[2] RICHARD DOBLIN[3]*
[1]208 Scott Street, Mount Pleasant, SC 29464, USA. [2]Multidisciplinary Association for Psychedelic Studies, 2105 Robinson Avenue, Sarasota, FL 34232, USA. [3]Multidisciplinary Association for Psychedelic Studies, 3 Francis Street, Belmont, MA 02478, USA. *To whom correspondence should be addressed. E-mail: Rick@maps.org

References
1. S. M. Gore, *Lancet* **354**, 1265 (1999).
2. J. A. Henry, J. G. Rella, in *Ecstasy: The Complete Guide*, J. Holland, Ed. (Inner Traditions, Rochester, VT, 2001), pp. 71–86.
3. F. X. Vollenweider, R. T. Jones, M. J. Baggott, *Neuropsychopharmacology* **24**, 461 (2001).
4. I. Mahmood, J. D. Balian, *Life Sci.* **59**, 579 (1996).
5. C. S. Grob, *Addiction Res.* **8**, 549 (2000).
6. G. A. Ricaurte, L. E. DeLanney, I. Irwin, J. W. Langston, *Brain Res.* **446**, 165 (1988).
7. L. Reneman *et al.*, *Psychopharmacology* **159**, 335 (2002).
8. D. M. Semple, K. P. Ebmeier, M. F. Glabus, R. E. O'Carroll, E. C. Johnstone, *Br. J. Psychiatry* **175**, 63 (1999).
9. S. J. Kish, Y. Furukawa, L. Ang, S. P. Vorce, K. S. Kalasinsky, *Neurology* **55**, 294 (2000).
10. U. D. McCann, M. Mertl, V. Eligulashvili, G. A. Ricaurte, *Psychopharmacology* **143**, 417 (1999).
11. U. D. McCann, A. Ridenour, Y. Shaham, G. A. Ricaurte, *Neuropsychopharmacology* **10**, 129 (1994).
12. G. A. Ricaurte, K. T. Finnegan, I. Irwin, J. W. Langston, *Ann. N.Y. Acad. Sci.* **600**, 699, 708 (1990).
13. T. Ernst, L. Chang, M. Leonido-Yee, O. Speck, *Neurology* **54**, 1344 (2000).
14. D. Concar, New Scientist News Service on-line, 28 September 2002, www.newscientist.com/news/news.jsp?id=ns99992849.
15. C. S. Grob, R. E. Poland, L. Chang, T. Ernst, *Behav. Brain Res.* **73**, 103 (1996).
16. F. X. Vollenweider *et al.*, paper presented at the 2000 Conference of the German Society for Psychiatry, Psychotherapy and Neuromedicine (Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde) (2000).

### Response

**MITHOEFER AND COLLEAGUES RAISE A NUMBER** of points. For example, they suggest that the death of a monkey calls into question the method of interspecies dose scaling (*1*). However, as specifically stated in our paper, this method was not used in our recent studies. Although one of ten monkeys treated with the sequential dosing regimen of MDMA that we used died of complications related to hyperthermia, we believe it is premature to draw firm conclusions regarding mortality rates, given the sample size. Further, isolated human deaths after MDMA ingestion in which hyperthermia was a prominent factor have been described in the literature (*2*–*5*). MDMA-induced hyperthermia is not purely related to dose, because single dosages of MDMA have led to malignant hyperthermia and death (*5*). Notably, with the increasing popularity of raves (dance parties where MDMA use is common) over the past 10 to 15 years, the number of MDMA-related emergency room visits has increased from 500 visits in 1994 to about 4500 visits in 2000, and a significant portion of these visits involved complications related to increased body temperature. Therefore, although the causes and mechanisms of MDMA-induced hyperthermia are not fully understood, it should not be entirely unexpected that nonhuman primates, like humans, can sometimes develop marked, life-threatening hyperthermia when exposed to recreational dosage regimens of MDMA.

Mithoefer also questions our "claim" that the oral route of administration offers little or no protection from MDMA-induced neurotoxicity. However, we cite all of the studies that have addressed this issue (*6*–*9*). Three studies found no protective effect (*6*–*8*). A fourth found varying levels of protection, dependent on brain region (*9*).

Mithoefer and colleagues challenge our finding that MDMA has potential dopamine (DA) neurotoxicity, because previous studies failed to note evidence of dopamine changes in MDMA users. However, they ignore previous findings in mice demonstrating MDMA-induced DA neurotoxicity (*10*), as well as the fundamental observation of our study [i.e., that three sequential doses of MDMA administered over several hours lead to dual DA/serotonin (5-HT) neurotoxicity, whereas more widely spaced, higher dosages of MDMA produce selective 5-HT neurotoxicity]. Thus, by merely changing the dosage pattern of MDMA, the neurotoxic profile of MDMA in the primate is significantly altered. Because none of the clinical studies cited by Mithoefer *et al.* took into account dosage patterns, subject groups were likely heterogeneous and, therefore, DA markers were likely to be highly variable. Indeed, if "binge" MDMA users were not included or were insufficiently represented, DA markers [including the dopamine transporter (DAT)] would not be expected to differ significantly from those in controls. Notably, Mithoefer and colleagues point out that concentrations of the DA metabolite homovanillic acid (HVA) were not reduced in MDMA users previously studied. However, because cerebrospinal fluid (CSF) HVA is neither a sensitive nor specific marker of DA neurotoxicity (*11*, *12*), it is unlikely that CSF HVA would be reduced, even in a homogeneous group of MDMA users that used a sequential dose regimen.

Image not available for online use.

Mithoefer *et al.* also note that methamphetamine and d-amphetamine are known DA neurotoxins that are abused by some humans, yet there is no evidence that these drugs lead to Parkinsonism. However, we (*13*) and others (*14*, *15*) have found that past methamphetamine use is associated with reductions in DATs in living, abstinent methamphetamine users. Of note, reductions of the DAT in methampheta-

CREDITS: ANDREW BROOKES/CORBIS

mine users have been associated with motor slowing (*15*), and DAT deficits and motor slowing are seen in Parkinsonism.

Finally, Mithoefer and colleagues contend that clinical MDMA use has taken place without evidence of toxicity and cite three references to support this view. The first is a conference presentation and, to our knowledge, has not yet been published. The second reference refers to an exchange of letters that was primarily focused on the merits and drawbacks of interspecies dose scaling for the estimation of neurotoxic dosages of MDMA in humans. The third citation refers to a Phase I study in which previous MDMA users were administered two different dosages of MDMA (and placebo). No measures of neurotoxicity were obtained during that study. Although we understand that Mithoefer and colleagues feel strongly about the potential therapeutic effects of MDMA, we remain of the opinion that there are not sufficient data to conclude that clinical MDMA research can be conducted without running the risk of monoaminergic brain neural injury.

GEORGE A. RICAURTE,[1]* JIE YUAN,[1] GEORGE HATZIDIMITRIOU,[1] BRANDEN J. CORD,[2] UNA D. MCCANN[3]

[1]Department of Neurology, [2]Department of Neurosciences, [3]Department of Psychiatry, Johns Hopkins Bayview Medical Center, Johns Hopkins University School of Medicine, Baltimore, MD 21224, USA.

*To whom correspondence should be addressed. E-mail: Ricaurte@jhmi.edu

References

1. J. Mordenti, W. Chappell, in *Toxicokinetics in New Drug Development*, A. Yacobi, J. Kelly, V. Batra, Eds. (Pergamon, New York, 1989), pp. 42–96.
2. J. A. Henry, K. J. Jeffreys, S. Dawling, *Lancet* **15**, 340, 384 (1992).
3. G. R. Screaton *et al.*, *Lancet* **339**, 677 (1992).
4. I. S. Chadwick *et al.*, *J. R. Soc. Med.* **84**, 371 (1991).
5. P. D. Mueller, W. S. Korey, *Ann. Emerg. Med.* **32**, 377 (1998).
6. K. T. Finnegan *et al.*, *Brain Res.* **447**, 141 (1988).
7. M. S. Kleven, W. L. Woolverton, L. S. Seiden, *Brain Res.* **488**, 121 (1989).
8. W. Slikker Jr. *et al.*, *Toxicol. Appl. Pharmacol.* **94**, 448 (1988).
9. G. A. Ricaurte, L. E. Delanney, I. Irwin, J. W. Langston, *Brain Res.* **446**, 165 (1988).
10. E. O'Shea, B. Esteban, J. Camarero, A. R. Green, M. I. Colado, *Neuropharmacology* **40**, 65 (2001).
11. D. A. Loeffler *et al.*, *J. Neural Transm. Park. Dis. Dement. Sect.* **9**, 45 (1995).
12. Parkinson Study Group, *Arch. Neurol.* **52**, 237 (1995).
13. U. D. McCann *et al.*, *J. Neurosci.* **18**, 8417 (1998).
14. N. D. Volkow *et al.*, *Am. J. Psychiatry* **158**, 377 (2001).
15. Y. Sekine *et al.*, *Am. J. Psychiatry* **158**, 1206 (2001).

## Research Fraud, Public Policy, and Gun Control

DONALD KENNEDY'S EDITORIAL "RESEARCH fraud and public policy" (18 April, p. 393) alleges that I made up a computer hard disk crash when challenged about the loss of data on a 1997 survey. Unfortunately, *Science* did not contact me about these allegations. I have provided editors with statements from nine different academics, verifying the hard disk crash. Four of them were coauthors who also lost data with me.

When the disk crashed on 3 July 1997, I lost all my data for virtually all the research projects that I had conducted up to that point in time, including the text and data files for my book *More Guns, Less Crime*. With the help of other academics, primarily David Mustard (University of Georgia), I replaced all the massive crime data sets so that academics at dozens of universities could replicate and reexamine every single regression reported in my book. All the additional data have also been supplied for the book's second edition. The survey data Kennedy mentions involve merely one number in one sentence in my book, and he fails to note that I later redid the survey on a smaller scale and obtained similar results. Those data have also been released (www.johnlott.org).

Kennedy discusses criticisms that I made of Ian Ayres and John Donohue's work (only Donohue is mentioned in the Editorial), but fails to note that I have provided them with my different city, county, and state level crime data sets both before and after they refused to provide me with data for their own work. I feel that the comments that I posted about their paper were entirely accurate.

I used a pseudonym in Internet chat rooms because earlier postings under my own name elicited threatening and obnoxious telephone calls.

JOHN R. LOTT JR.

American Enterprise Institute, 1150 17th Street, NW, Washington, DC 20036, USA.

IT IS VERY DISAPPOINTING TO SEE THE FOCUS of the Editorials in Science shifting from science to politics and gun control. Although Donald Kennedy assails the work of John Lott ("Research fraud and public policy," 18 April, p. 393), he fails to mention the publications of Gary Kleck (Florida State University) on the same issue (*1*). By his own declaration, Kleck is a card-carrying member of the American Civil Liberties Union (ACLU) and a registered Democrat who does not own a gun. I am confident that he expected, when he undertook his investigations, to reach the same conclusions as the gun-banning advocates. To the contrary, he came to the same conclusions as Lott, and his work preceded Lott's. An incontrovertible fact is that violent crime in general as well as gun-related shootings have decreased substantially in all states that have liberalized their gun-permit laws (*2*). It is unfortunate that Kennedy did not consider this information worth including in his Editorial. With more than 20,000 gun laws on the books, enacting more will have the same effect on the gun-violence problem as enacting one more drug law will have on our illegal drug problem.

CHARLES G. SMITH

Post Office Box 9814, Rancho Santa Fe, CA 92067–4814, USA.

References

1. J. R. Lott Jr., "Gun control misfires in Europe," *Wall Street Journal*, 30 April 2002.
2. G. Kleck, *Point Blank* (De Gruyter, New York, 1991).

### Response

LOTT'S EXPLANATION OF THE LOSS OF HIS DATA should certainly be accepted, although, of course, it does not restore life to the data—which, far from being "one number in one sentence," were at the center of the controversy between Lott and his critics. And Lott cannot dismiss his use of a fictitious ally as a "pseudonym." What he did was to construct a false identity for a scholar, whom he then deployed in repeated support of his positions and in repeated attacks on his opponents. In most circles, this goes down as fraud.

Smith takes me to task for ignoring Kleck's work. My Editorial focused on two cases of questionable research conduct; it wasn't a review. Interested readers may assess whether Kleck's current position supports Lott's; I believe it does not.

DONALD KENNEDY

### TECHNICAL COMMENT ABSTRACTS

#### COMMENT ON "Climate and Management Contributions to Recent Trends in U.S. Agricultural Yields"

Lianhong Gu

According to Lobell and Asner (Brevia, 14 February 2003, p. 1032), the atypical summer cooling trend from 1982 to 1998 increased U.S. yields of corn and soybeans during the same period. However, three potential problems with their analysis bring their results and conclusion into question.

Full text at www.sciencemag.org/cgi/content/full/300/5625/1505b

#### RESPONSE TO COMMENT ON "Climate and Management Contributions to Recent Trends in U.S. Agricultural Yields"

David Lobell and Gregory Asner

The comment by Gu reflects a misunderstanding of our study and does not invalidate our conclusions. Instead, it highlights the importance of quantification in assessing climate impacts on yield trends and the need to better understand the relative roles of causal mechanisms.

Full text at www.sciencemag.org/cgi/content/full/300/5625/1505c