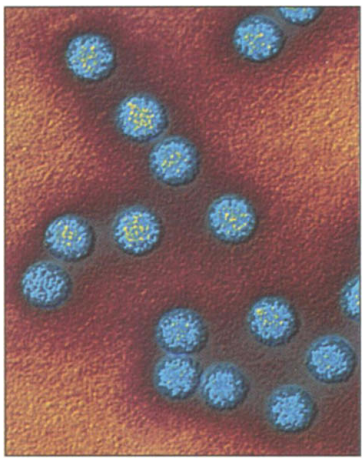
A Not-So-Cheap Stunt

THE RECENT DEMONSTRATION BY ECKARD Wimmer and co-workers ("Chemical synthesis of poliovirus cDNA: Generation of infectious virus in the absence of natural template," J. Cello *et al.*, Reports, published online 11 July, www.sciencemag.org/cgi/content/abstract/1072266) that active poliovirus could be synthesized "from scratch," i.e., by assembling oligonucleotides into a full-length cDNA coding for the RNA of the published sequence of the poliovirus genome and then introducing this cDNA into a cell-free system derived from HeLa cells, amounts to little more than a stunt—and not a particularly cheap stunt at that, given that the effort was reportedly bankrolled by hundreds of thousands of dollars from the Defense Advanced Research Projects Agency.

This work was published with considerable fanfare by *Science* as a *Science* Express paper. The criteria for *Science* Express papers "include timeliness and importance of the research" (*1*). The timeliness of this finding seems beyond question, given post–September 11 events, renewed concerns about biological weapons, and new threats posed by genetic engineering (*2*). Indeed, the report was immediately picked up by the news media and generated a firestorm of commentary—much of it sensational. However, I question the scientific importance of the research and, therefore, *Science*'s decision to publish it. A classic experiment by V. Racaniello and D. Baltimore, published more than 20 years ago, showed that cDNA derived from the poliovirus genome was sufficient to produce active virus in a transfected mammalian cell line (*3*), i.e., that the DNA alone is "infectious." Wimmer's own group demonstrated in 1991 that de novo synthesis of poliovirus from a genomic clone could be achieved in a cell-free translation system (*4*). The recent work merely substitutes a chemically synthesized DNA for one biosynthesized from the genomic clone. But DNA is DNA is DNA, and few molecular biologists would have seriously doubted the inevitability of the results, which scarcely advance our state of knowledge. After all, DNA coding for desired gene sequences is today routinely produced by chemical synthesis and then recombined with DNA produced by biosynthetic means. Even the length of the poliovirus cDNA, at ~7500 nucleotides, did not apparently represent that much of a technical challenge: More than half of the construction work was simply farmed out to a commercial outfit.

In light of the extraordinary press coverage, there are several misconceptions worth dispelling. Entirely synthetic viruses are unlikely to present a biological weapons threat in the near term, for several reasons. Poliovirus itself causes human disease with low mortality and morbidity, weak infectivity, and limited transmissibility. For this reason, it's never been a pathogen of choice for a biological weapon, and it doesn't appear on the CDC List of Select Agents (indeed, polio is available for legitimate scientific work from the ATCC). Despite representations to the contrary by Cello *et al.*, it seems unlikely that the strategy of the World Health Organization's poliovirus eradication campaign now needs to be reassessed. But what about using the synthetic approach on some other virus? In most cases, it would be far easier to obtain a sample of the virus or a genomic clone of the virus than it would be to synthesize something from scratch. The single exception here would seem to be smallpox, stocks of which are held closely by the United States and Russia. However, unlike polio, the DNA of smallpox (and a good many other viruses) is not itself infectious, requiring the activity of proteins conveyed by the virion, such as polymerases. These factors might be supplied, in principle, by helper viruses or some other means, but this complicates the fabrication process considerably (*5*). Moreover, the genome of smallpox is among the largest of viral sequences, around 200,000 nucleotides. Anyone bent on creating smallpox would have an easier task starting from a closely related orthopox virus and introducing the necessary mutations. Also of future concern are chimeric viral constructs incorporating genes from more than one natural—or synthetic—source.



The original poliovirus (shown here) is almost indistinguishable from the one assembled by Cello *et al.*

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It's critically important to hold a national dialog among biologists, health care experts, politicians, and the general public about the future of biological work with biological weapons implications. But publishing research like this is a poor way indeed to open the conversation.

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References and Notes
1. See www.sciencemag.org/feature/express/introduction.shl.
2. S. D. Drell, A. D. Sofaer, G. D. Wilson, Eds., *The New Terror: Facing the Threat of Chemical and Biological Weapons* (Hoover Institution Press, Stanford, CA, 1999), chap. 2, pp. 39–75.
3. V. R. Racaniello, D. Baltimore, *Science* **214**, 916 (1981).
4. A. Molla, A. V. Paul, E. Wimmer, *Science* **254**, 1647 (1991).
5. S. J. Flint, L. W. Enquist, R. M. Krug, V. R. Racaniello, A. M. Skalka, *Principles of Virology* (American Society for Microbiology, Washington, DC, 2000), chap. 2, pp. 25–56.

Response

***SCIENCE* HAS RECEIVED A MIXTURE OF PRAISE** and criticism for publishing the paper on synthesizing poliovirus by Cello *et al.* The third paragraph of Block's thoughtful letter summarizes a number of reasons why the national security concerns are not worth serious consideration; we couldn't have put it better ourselves, and we are grateful for this clarification from a bona fide expert on biowarfare. This puts to rest sensationalist claims that the publication was somehow "irresponsible." It wasn't.

That leaves the claim that we have published a "stunt"—and with "fanfare" at that! Block cites previous work that would lead to a strong expectation of how the Cello *et al.* experiment would come out. But proof of principle sometimes involves doing all the steps, to demonstrate that the predicted

outcome can actually be achieved. Certainly, this result is hardly counterintuitive. Is it a stunt? We didn't think so, and our peer reviewers didn't think so either.

Sticking one's head in the sand and hoping that unpleasant realities will go away has never been a fruitful approach to science or to public policy. Nevertheless, it is surely true that there should continue to be serious conversations about the relationship between scientific research, publication, and security—in which we plan to participate in a responsible manner.

DONALD KENNEDY

Unfair Characterization of Industry Response

JOCELYN KAISER'S ARTICLE "SOFTWARE glitch threw off mortality estimates" (News of the Week, 14 June, p. 1945) unfairly characterizes industry groups' response to the recent discovery that a software issue had led researchers to overestimate the risks of fine particles—at least that of this industry representative. To portray industry as "crowing" or having "complaints" about this research is unfair.

Manufacturers of motor vehicles, diesel engines, and fuels are partners with the Environmental Protection Agency (EPA) and equal funders and supporters of Health Effects Institute research, including the research in question. In addition, these manufacturers spend billions of research dollars on reducing emissions and improving product efficiency—the results of which have been substantial. According to the EPA, particles from diesel engines make up only 5.56% of all fine particles in the air, and from 1990 to 1998, those levels dropped by 37%. Further improvements will come from the introduction of cleaner diesel engines later this year and in 2007.

Complex computer models and statistics are not widely understood or publicized, but they are the very foundation of virtually every important scientific and public policy decision. Thanks to the curiosity of researchers at Johns Hopkins University, the nuances and limitations of a popular statistical package were uncovered. The impacts of these findings and any restatement relative to particulate studies will ultimately strengthen scientific research.

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Academic Recruitment in Spain and Italy

ACCORDING TO XAVIER BOSCH'S ARTICLE "Reforms spark more jobs—and protests" (News of the Week, 1 Feb., p. 781), the Spanish government's reform of university hiring practices is an effort to circumvent cronyism by abolishing the system of five-member boards (two from the university that has advertised the new position) that select candidates for academic posts. Spanish universities had been criticized for hiring internal or local candidates over 90% of the time. The Italian system of university appointments (concorsi) is similar to the old Spanish one, and the results seem similar too. In fact, nearly 100% of concorsi select internal or local candidates.

Do Italian concorsi select the best applicants on the basis of the quality of their research? According to Italian law, each candidate is required to undergo a formal public examination in which a committee of five university professors, with one from the university advertising the position, choose the two best candidates (three candidates until the year 2000). We recently revisited 13 out of 14 concorsi from 2000 for the selection of full professors in the field of general surgery.