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Synthetic Poliovirus: Bioterrorism and Science Policy Implications

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Summary

In July 2002, an online scientific journal published a report describing how to make the virus that causes polio from mail-ordered pieces of DNA. This sparked widespread concern that the same process could be used by terrorists to make this or other biological agents. Most bioterrorism experts agree that it would be much easier, cheaper, and quicker to obtain most such agents from naturally occurring sources. Smallpox and Ebola are frequently cited as exceptions; however, these agents would be significantly more difficult to synthesize than poliovirus. To limit the threat posed by this type of research, policymakers have discussed approaches that include: increasing oversight of the DNA suppliers, limiting access to the genetic information of select pathogens, and regulating the publishing of information deemed possibly helpful to terrorists. This report will be updated as events warrant.

In July 2002, a group of scientists from the State University of New York at Stony Brook led by Dr. Eckard Wimmer published a report in the online journal *Science Express* describing that they had constructed infectious poliovirus from mail-ordered pieces of DNA.[1] This research was funded by the Department of Defense through the Defense Advanced Research Projects Agency (DARPA). The publication of this report has intensified the debate on how best to balance the need for openness in science with the need to protect national security.

Technical Background

The disease poliomyelitis (or polio) is caused by poliovirus. Like many viruses, the genetic material of poliovirus is made of RNA (ribonucleic acid) instead of DNA (deoxyribonucleic acid) which comprises human genes. Poliovirus is essentially a small

[1] *Science Express* 10.1126/science.1072266. This report was subsequently published as J. Cello, A. V. Paul, and E. Wimmer. "Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template." *Science*. Vol. 297. August 9, 2002. pp. 1016 - 1018.

piece of RNA encapsulated in a protein shell. As with all viruses, poliovirus cannot reproduce on its own; it must hijack its host's protein-making enzymes to reproduce. After infecting the host cell, poliovirus forces the host cell to produce so many viral copies that eventually the cell bursts. This releases the viral copies, freeing them to infect other cells.[2]

To make poliovirus in the laboratory, the scientists first assembled a DNA version of the viral RNA genome. This was done because DNA is much easier to manipulate in the laboratory than RNA, and short, prefabricated, custom-made DNA pieces are readily available by mail order from laboratory supply companies. The complete genetic sequence of poliovirus has been known since 1981 and can be downloaded from the Internet from sites that cater to researchers.[3] Polio is one of the smallest of all viruses with a genome of only about 7,500 bases. For comparison, smallpox has about 185,000 bases and humans have over 3 billion bases. Because only short pieces of custom-made DNA are available for mail order, the scientists ordered over one hundred DNA snippets at a cost of about $100,000.[4] These snippets were painstakingly strung together in the correct order. Although theoretically simple, this process is technically demanding and requires a great deal of thorough double checking done by skilled molecular biologists. When the scientists finished the DNA version of the complete viral genome, they used an enzyme to make an RNA version of their DNA template.

When placed in a test tube with appropriate chemicals and protein-making enzymes, the pieces of RNA did what they do in nature: made duplicates of themselves. This included the required protein shells which spontaneously enclosed the viral RNA. The researchers proved that the new viral particles were functional by showing that mice infected with this virus developed polio and became paralyzed.

Reaction to the Publication

The publication of this research produced an instant debate among the public, other scientists, and the federal government about the merits of this type of research, the ethics of doing or publishing this type of research, and the ramifications it may have on public health and bioterrorism defense.

Public reaction to this research was largely negative. The public was taken by surprise; there had been no previous indication in the popular press that such a thing could be remotely possible. These experiments seemed to arm terrorists with yet another tool to use against the American people.[5] Some commentators, perhaps underestimating the technical barriers imposed by the underlying biology, suggested that this experiment could

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[2] S. J. Flint, L. W. Enquist, R. M. Krug, V. R. Racaniello, and A. M. Skalka. *Principles of Virology: Molecular Biology, Pathogenesis, and Control*. ASM Press. Washington DC. 2000. pp. 750-753.

[3] For example, GenBank which is maintained by the National Institutes of Health.

[4] G. Cook. "Researchers Build a Polio Virus, Project Highlights a New Terror Risk." *Boston Globe*. July 12, 2002. p. A1.

[5] For example, see "Surfing for a Satan Bug: Why are We Making Life So Easy for Would Be Terrorists?" *New Scientist*. July 20, 2002. p. 5.

easily be repeated with more dreaded diseases such as smallpox or Ebola.[6] One newspaper went so far as to mail-order some Ebola DNA claiming it to be an "Ebola kit."[7]

Some scientists attacked this research on scientific and ethical grounds. Some experts said that there was no scientific need to have done this "inflammatory"[8] research, since nearly all scientists believed that this approach would work.[9] Dr. Wimmer, the study's director, disagreed, reportedly stating, "This approach has been talked about, but people didn't take it seriously. Now people have to take it seriously."[10] Dr. Donald Kennedy, the editor of *Science*, argued that the public debate following the publication justified his decision to publish this work.[11] However, some may feel that the wide dissemination of this knowledge was too high a cost for sparking a debate that could have been started through more benign means.

Some scientists also questioned the ethics of publicizing a recipe for recreating a disease that the World Health Organization and the United Nations Children's Fund have almost eliminated from nature. As the human-genome-sequencing pioneer Dr. J. Craig Venter reportedly stated, "To make a synthetic human pathogen is irresponsible."[12]

The publication of this research also drew the attention of Congress. H.Res. 514, introduced by Rep. D. Weldon on July 26, 2002, "express[es] serious concern regarding the publication of instructions on how to create a synthetic human polio virus." It called on the scientific and publishing community to adopt guidelines to avoid similar publications in the future. It also requested that the executive branch examine all policies including national security directives, to ensure that information that may be useful in the development of chemical, biological, or nuclear weapons is not made accessible to terrorists or countries of proliferation concern. This resolution, referred to the House Science, Energy and Commerce, and Armed Services Committees, received no further action.

Implications for Bioterrorism

Some people worry that poliovirus could be made easily by a terrorist group and used against the United States. Most bioterrorism experts agree that this is unlikely, however,

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[6] For examples see G. Dyer. "Polio Lab Stunt Looks a Lot like an Ego Trip." *Newsday.* August 1, 2002. p. A37; "Infectious Skepticism." *The Times-Picayune*. July 15, 2002. p.4; and N. Boyce. "A Recipe For Trouble?" *U.S. News and World Report*. July 22, 2002.

[7] G. Walsh. "Deadly Ebola Virus 'Kit' for Sale over Internet." *Sunday Times (London)*. August 4, 2002. p. 4.

[8] J. Craig Venter quoted in "New Life for Polio? Scientists Synthesize a Once-feared Virus." *Pittsburgh Post-Gazette*. July 19, 2002. p. A12.

[9] "Synthetic Bioterror" *New York Times*. July 18, 2002. p. A20; and S. Block. "A Not-so-cheap Stunt." *Science*. Vol. 297. August 2, 2002. p. 769.

[10] "DNA Firm Had Warned Government Genetic Material Used to Create Polio Virus." *Boston Globe*. July 20, 2002. p A3.

[11] D. Kennedy. "Response." *Science.* Vol. 297. p. 770. August 2, 2002.

[12] "New Life for Polio? Scientists Synthesize a Once-feared Virus." op. cit.

because poliovirus would make a poor and ineffective weapon.[13] Because childhood polio vaccination is still required in the United States, the population is well protected against any outbreak. Also, even without a vaccination program, poliovirus would be an unlikely choice for terrorists, since it is weakly infective, has low mortality and morbidity, and causes symptoms only in a low percentage of infected people.

A related concern is the use of this technique to make other more dangerous viruses. Dr. Wimmer suggested that this same technique could be used to make other viruses with small genomes such as HIV, hepatitis B and C, and yellow fever.[14] However, it would be easier, cheaper, and quicker to obtain these viruses from naturally occurring sources.[15]

One obvious exception is that it would be difficult to obtain the smallpox virus *Variola major* from nature. The only two acknowledged sources are under guard, one in Russia and the other in the United States. Therefore, making *Variola major* from scratch may be easier than obtaining it from these sources. Based on the costs and length of time required to produce poliovirus, making *Variola major* the exact same way would take more than $2 million for mail-ordered DNA and about 50 years to string it together based on current technology.[16] Bioterrorists could shorten the time considerably by increasing the number of well-trained team members, but it would still likely take many years. Also, because the infectious mechanisms of *Variola major* are more complicated than those of poliovirus, this exact technique would not work. Molecular biological methods that would probably work for *Variola major* are known to some experts in the field, but these methods are considered much more technically demanding than those used for poliovirus. Because of these issues, most experts believe it would be much easier to make *Variola major* by modifying an easily obtained and closely related virus such as camelpox.[17]

Although Ebola virus is theoretically available in nature, some experts believe that it is difficult to obtain.[18] Ebola's genome is only twice the length of polio's, but its infectious mechanisms are as complex as those of smallpox. It may be possible to make in the lab, but as one expert reportedly put it, "few people in the world have that skill."[19]

Policy Issues

The publication of the poliovirus study has intensified the debate on how best to

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[13] S. Block. "A Not-so-cheap Stunt." op. cit.

[14] "Boffins Build Deadly Virus." *Belfast Telegraph*. July 12, 2002.

[15] "Surfing for a Satan Bug." op. cit. and "Synthetic Bioterror." op. cit.

[16] CRS estimate based on simple extrapolation of the time and cost required to synthesize poliovirus by Dr. Wimmer's group. Improvements to current technology may greatly decrease the time and cost required to manufacture a virus in this manner.

[17] "Scientists Build Polio Virus– Could Terrorists Do It, Too?" *Dallas Morning News*. July 12, 2002. p. A1 and "Synthetic Bioterror" op. cit.

[18] This is largely based on the inability of the Japanese doomsday cult Aum Shinrikyo to acquire it from nature despite their attempts. See David Kaplan. "Aum Shinrikyo" in *Toxic Terror*. Ed. Jonathan Tucker. MIT Press. Cambridge MA. 2000. p. 213.

[19] C.J. Peters in "Study: Virus Can Be Made with Ease." *Chicago Tribune*. July 12, 2002. p. 10.

balance the need for openness in science with the need to protect national security. Several approaches to strike the appropriate balance have been proposed.

One such proposal is to increase oversight of custom DNA suppliers. Ironically, shortly before the publication of the synthetic polio report, Integrated DNA Technologies, the suppliers of mail-ordered DNA for the study, had reportedly written to the Department of Defense suggesting that some oversight of the industry was needed. One suggestion was that orders should be screened for specific sequences and that suspect orders should be investigated by some federal agency.[20] However, others argue that it would be hard to implement such a strategy. Because of the nature of DNA sequences, it may be difficult to identify that a short sequence belongs to an individual pathogen of concern rather than to a completely different unrelated and harmless organism.[21] Some also fear that a terrorist could easily circumvent any such regulations by splitting orders among several companies or by making the specific red-flag-raising sequences themselves. Additional steps, such as regulating and tracking the sale of DNA-synthesizing machinery, and encouraging a "know thy customer" expectation for DNA suppliers may help increase the effectiveness of increased industry oversight.[22]

A different approach would be to limit access to the genetic information of pathogens of concern. However, current federal policy is to not classify basic research information funded or held by the government, if it does not have national security implications. The genetic sequences of pathogens has been viewed, hitherto, as falling outside this category. Currently, the entire genomes of many potentially dangerous viruses are accessible on the Internet. Some have suggested removing this sequence information from these databases and not publishing future sequences of any potential biological weapons. However, some feel that legitimate and beneficial research will be hurt by this. For example, Dr. Paul Keim has reportedly stated that it would have been impossible for him to develop the method that is being used to distinguish between closely related strains of anthrax in the investigation of the anthrax mailings without open access to the genome information.[23] However, in an editorial, the journal *New Scientist* responded to this fear by arguing,

> "Removing the genomes of certain pathogens from public databases need not impede any *bona fide* research. Legitimate labs could apply for licenses to access the information. Even if complete control will never be possible, we could make the information harder to get a hold of."[24]

Some policymakers may feel that although removing this information now would not recall the copies already obtained online, it would stop any future terrorists from getting

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[20] "Regulatory Issues: Company That Provided DNA for Man-made Polio Virus Says Oversight Needed" *Genomics & Genetics Weekly*. August 9, 2002. p. 9.

[21] "Deadly Ebola Virus 'Kit' for Sale over Internet." op. cit.

[22] Sigma-Genosys has such an informal policy already in place in that they reportedly subject large orders sent to residential addresses to "some checks," ibid.

[23] D. Mackenzie. "Should the Genetic Sequences of Deadly Diseases Be Kept Secret?" *New Scientist*. July 20, 2002 p. 77.

[24] "Surfing for a Satan Bug." op. cit.

them as easily. This approach would be more effective for the pathogens of concern that have not yet had their sequences published.

Another approach that has drawn support of some policymakers is the development of guidelines to prevent the publication of information that could help terrorists. The House Committee on Science held a hearing to explore options of such policies.[25] The option generally preferred by some scientists and the publishing industry would be to have the scientific community develop and implement a set of guidelines. The American Society for Microbiology has adopted formal guidelines[26] for the prepublication review of papers in its journals that deal with agents deemed by the Centers for Disease Control and Prevention "to have the potential to pose a severe threat to public health and safety."[27] Under these guidelines, peer reviewers flag manuscripts that contain details of methods or materials that might be misused. These papers are subjected to greater scrutiny by the editors and the Publications Board. The manuscript can be rejected if it is felt that it may pose a threat to public safety. It should be noted however that these policies would likely still have allowed for the publication of the polio paper, since polio is not a select agent. Because science publishing is an international and competitive business, even if most publishers agree to adhere to standards, others might publish the papers if they deem that there is a market niche that they could capture by choosing not to adhere to any standards other than scientific merit. The National Academy of Sciences plan to hold a conference on this topic in 2003.

The Bush Administration is conferring with federal agencies and representatives from academia and scientific publishers to examine the possibility of withholding from the public some nonclassified but sensitive information held by federal agencies.[28] The Secretary of Health and Human Services and the Administrator of the Environmental Protection Agency have been given original classification authority.[29] Before receiving this power, these entities did not have a mechanism for limiting distribution of any information developed through intramural or extramural research. Some scientists say that this type of clearly defined mechanism is preferable to a new ambiguous category like "sensitive but unclassified." While many scientists share the desire to limit potential terrorists' access to some information, some fear that implementation of new policies might result in a tendency to not publish many important findings if there is any question of sensitivity.[30]

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[25] House Science Committee. "Conducting Research During the War on Terrorism: Balancing Openness and Security." October 10, 2002. Hearing Charter and witness testimony available at: [http://www.house.gov/science/hearings/full02/oct10/charter.htm]

[26] [http://www.journals.asm.org/misc/Pathogens_and_Toxins.shtml]

[27] Also known as the Select Agent List. This list is defined in 42 CFR 72.

[28] "Conducting Research During the War on Terrorism." op. cit.

[29] Designation Under Executive Order 12958. Federal Register. Vol. 66. No. 239. p. 64347 December 12, 2001 and Designation Under Executive Order 12958. Federal Register. Vol. 67. No. 90. p.31109. May 9, 2002.

[30] For more information on this topic see CRS Report RL31354 *Possible Impacts of Major Counter Terrorism Security Actions on Research, Development, and Higher Education*.