# Bio Terror Bible

## EXPOSING THE COMING BIO-TERROR PANDEMIC

**BIOTERRORBIBLE.COM:** In the aftermath of man-made bio-terror generated pandemic, the government and media will be feeding the public any number of different scapegoats allegedly responsible for the pandemic that will likely kill millions.

While some scapegoats (see below) are indeed plausible, it is much more likely that the live pathogens or agents responsible for the pandemic will likely be dispersed via A) chemtrails by government airplanes or drones, B) by the U.S. Postal Service via Tide detergent samples, C) by the government and medical establishment via tainted vaccines, or by D) the portable petri dish commonly known as the Trojan condom.

**Bio-Terror Scapegoats:** Africa, Agriculture (Food & Animals), Airports & Air Travel, Al Qaeda, Bio Labs, Bio-Terrorism Is Easy, Bio-Terrorists (Bio-Hackers), Black Market, Bugs & Insects, Censorship / Lack Thereof, Domestic Terrorists, Exotic Animals (Zoonosis), Government Ineptitude, Mail-Order DNA, Mexico, Missile Shield Failure, Mutation, Natural Disaster, No Clinical Trials (Vaccines), and The Monkeys.

**Title:** Mail-Order Molecules Brew A Terrorism Debate
**Date:** July 17, 2002
**Source:** UCLA

**Abstract:** The orders arrive by fax and e-mail 24 hours a day from pharmaceutical companies, government agencies and academic scientists. And every day at Integrated DNA Technologies, an army of machines responds by producing hundreds of batches of microscopic merchandise: custom-designed snippets of genetic material.

Until recently the Coralville, Iowa, company prospered in quiet anonymity, spewing out for scientists round the world various made-to-order pieces of DNA, the molecular code upon which so much biotechnology research depends today.

But last week's announcement that scientists in New York had used the company's mail-order molecules to make polioviruses from scratch has prompted questions about whether the DNA synthesis industry deserves closer scrutiny, and whether strategies for preventing the proliferation of biological weapons need to be rethought.

For decades the United States and other nations have sought to limit the risk of biological warfare and bioterrorism by placing controls on the cultivation and shipment of dangerous microbes. The new work threatens to undermine that approach by proving for the first time that potentially deadly viruses can be built from the ground up.

If infectious agents can be made from off-the-shelf smidgens of DNA that are individually benign, then government regulators, law enforcement agencies and even DNA synthesis companies may have no way of knowing when someone is building a biological bullet.

"The customer gets to design the sequence they want manufactured and there is a limited ability for us to know what people are going to do with it," said Roman Terrill, vice president of legal and regulatory affairs at Integrated DNA Technologies.

Indeed, Terrill said, with perhaps $10,000 and a few months time, motivated scientists could manufacture the genetic components of a deadly virus. "You could buy your own used DNA synthesizer," he said, "and make whatever you want in the comfort and privacy of your own garage."

Integrated DNA is one of about a half-dozen major U.S. manufacturers of small DNA strands, which are known in the trade as oligonucleotides or "oligos." The bigger companies, including Qiagen Operon of Alameda, Calif., Invitrogen of Carlsbad, Calif., and Sigma-Genosys of Woodlands, Tex., make thousands of customized oligos each day.

Each oligo typically consists of about 25 or 30 units of DNA, representing a tiny fraction of an organism's entire genome (a full viral genetic code can be tens of thousands of units long or more). Scientists generally use the oligos as molecular tools to help them find genes in various organisms or to trigger biological chain reactions that allow them to mass produce DNA strands in test tubes.

Because they are so small, most individual oligos lack any "fingerprint" that might identify them as part of something dangerous. But it was just such oligos that Eckard Wimmer and two colleagues at the State University of New York in Stony Brook painstakingly stitched together into a full length, 7,741-unit poliovirus genome, which spontaneously began making infectious polioviruses.

The feat arguably fell short of creating life from scratch because most scientists maintain that viruses are not truly alive. But the implications were clear.

"If you can go from a viral DNA sequence on paper to an infectious agent using things you can order out of catalogues, obviously that has big implications for bioterrorism," said Mildred Cho of the Center for Biomedical Ethics at Stanford. Two years ago Cho chaired an expert panel on the implications of creating novel life forms.

In fact, it was the Department of Defense that funded the three-year research effort as part of a program to devise protections against "unconventional pathogens." In a statement, the department said Friday it did not believe that the techniques could be used to build viruses with greater bioterror potential, such as smallpox. But others disagreed.

"With a little more advancement in technology you could probably make something more complex than polio," said Jim Cornette, a retired Air Force colonel with a doctorate in biochemistry who served in the Defense Intelligence Agency and was involved in biodefense planning during Operation Desert Storm. "Smallpox is probably just two or three years down the road, maybe less," said Cornette, who now lives in Florida. "Then what about the things that are 'none of the above?' Something dangerous but totally new?"

Several scientists said in interviews they would be reluctant to see new layers of oversight slapped on oligo makers, which have become to the biotechnology industry what silicon chip makers are to the computer industry. But many suggested the time was ripe for a public discussion about how best to prevent nefarious use of the science.

Today most biodefense efforts focus on disease-causing organisms themselves, rather than the genetic instructions for making them. Federal regulations restrict shipments of dangerous microbes and toxins listed by the government as "select agents," but those rules do not apply to shipments of their DNA components, at least within the United States.

DNA exports are more strictly regulated, with the Commerce Department requiring licenses for overseas shipments of DNA deemed a threat to national security. But those rules are open to interpretation and are easily flouted, scientists inside and outside the government said.

When Terrill of Integrated DNA wanted to learn more about the export rules last year, he went to the Commerce Department's Bureau of Exchange Administration (renamed in April the Bureau of Industry and Security), which oversees and enforces export rules for "dual-use" technologies, including microbial DNA strands. He learned that the bureau restricts exports of genetic sequences "associated with pathogenicity," which means the ability to cause disease.

"The problem is the bureau has not released those sequences, so ... we would have to decide for ourselves whether a sequence is associated with pathogenicity," Terrill said. "But how pathogenic? And what does 'associated' mean? The phrase is difficult to get a grasp on. It's not really a scientific term. It's a lawyer's term."

Moreover, Terrill learned, the 370-person agency has only one microbiologist on staff to deal with the hundreds of biological export applications the agency receives annually.

That employee was away and not available to be interviewed this week. But another Commerce Department official, speaking on condition of anonymity, confirmed that it is "the responsibility of the exporter" to determine if a genetic sequence falls under the bureau's rules.

The official said the bureau engages in "outreach activities" to educate academic and commercial scientists about the export restrictions. But the official also acknowledged that many scientists -- especially university-based researchers -- have a tradition of sharing DNA freely through the mail, making enforcement difficult.

In any case, scientists said, rules that focus on "pathogenic" DNA sequences are meaningless in an era when manufacturers can make pieces of DNA that are individually benign yet can pose a serious threat if properly assembled.

"I don't know how you could overcome that problem," the Commerce Department official said. "You could get one part [of the sequence] from one company and another part from another company and completely circumvent the law."

Some experts have begun to consider whether manufacturers themselves should be brought under some kind of oversight. "We propose that ... those companies that produce the oligos should be asked to routinely check the sequences against those of known pathogens," said Wimmer, the scientist who led the polio project.

Several computer programs, most notably one known as BLAST, can quickly scan the genetic sequence of a large piece of DNA and report whether it is similar to other known sequences, such as ones encoding parts of a virus or toxin. But company officials said they were not enthusiastic about taking on the cost or legal responsibility of fingering potential perpetrators.

In any case, said Garry Merry, corporate vice president of genomic services at Qiagen Operon, a scientist could evade BLAST's eyes simply by ordering DNA components small enough to be completely generic, then assembling them later. "You could do it," Merry said, "and we couldn't tell."

As an alternative, some are calling for extra layers of institutional review for researchers who, like Wimmer, propose combining genetic components to make viruses or other dangerous entities.

"I would argue there needs to be more oversight in terms of getting approval," said Arthur Caplan, a University of Pennsylvania ethicist who sat on Mildred Cho's expert panel. "Are we going to be seeing this kind of thing done in a science fair soon? I'm in favor of tighter controls."

Craig Venter, president of the Center for the Advancement of Genomics in Rockville who last week called the polio work "irresponsible science," said the nation might need a special advisory committee to publicly review all such studies in advance, just as a National Institutes of Health panel reviews proposed gene therapy experiments as a way of watching for trouble and reassuring the public. Without such openness, Venter said, "this kind of work can set science back in the public eye."

But while institutional or government review may bring more oversight to legitimate research, others said, it's unlikely to deter those who wish to keep their work secret. And with the biotech revolution now 30 years old -- and trade in aftermarket equipment burgeoning -- deterrence may be difficult.

"You can buy an old synthesizer and some raw ingredients and no one would have any idea what you're doing or what you're making," said Terrill of Integrated DNA. With an old machine, he said, "it might take you a week longer. They're big and clunky. But a week isn't that long" (UCLA, 2002).

**Title:** Recipes For Death
**Date:** September 17, 2002
**Source:** New York Times

**Abstract:** On my desk is a set of self-help books that I've been buying at gun shows and on the Internet. If you want to kill a few thousand people, these are the books to consult.

And if we want to reduce the risk of terrorist attacks using bio- or chemical weapons, we have a target closer to home than Iraq: these books and the presses that publish them. If these presses were in Baghdad, the Pentagon would be itching to blow them up.

Right now I'm leafing through "Assorted Nasties," which has detailed instructions on how to make sarin, VX gas and even mustard gas.

Then there's "Silent Death," with 30 pages about manufacturing nerve gases like sarin, tabun and soman. The book also contains a helpful description of the best ways to disseminate gases so as "to lay waste to a metropolitan area."

"For those who have whole armies to conquer singlehandedly," the introduction suggests, "I'm sure the section on the production and use of nerve gases will interest you."

Then there's a three-volume set of books, "Scientific Principles of Improvised Warfare," which offers details on where to find anthrax spores and how to cultivate them and turn them into an aerosol.

"If you can make Jell-O," the book promises, "you can wipe out cities. Enjoy!"

Fortunately, it's not that easy. But still, do we as a nation really want to permit books that facilitate terrorism and mass murder? As Justice Arthur Goldberg declared in a 1963 Supreme Court case, the Constitution "is not a suicide pact."

A main barrier to the use of chemical or biological weapons has been knowledge. It's hard to weaponize sarin or anthrax, and so the I.R.A., the Basque separatist group E.T.A., the Tamil Tigers and even Al Qaeda (not to mention people like the Unabomber) have relied on conventional weapons and explosives.

But the information needed to produce lethal cocktails is beginning to spread, partly because these books are getting better. For example, the Japanese group Aum Shinrikyo tried to kill people with anthrax but never got hold of the proper spores. If it were trying today, it could consult one of these books and learn where to obtain deadly spores.

"I do think that there is forbidden knowledge, and for me the 'cookbooks' fall into that class of information," said Dr. Ronald M. Atlas, the president of the American Society for Microbiology. "I do not want to see them out there for potential use by terrorists."

In fairness, much of the information in the gun-show books is "garbage," notes Milton Leitenberg, an expert on weapons of mass destruction at the University of Maryland. Another bio-warfare specialist, Raymond Zilinskas of the Monterey Institute of International Studies, also notes that bio- and chemical weapons are very hard to get right – although he adds that the "cookbook" recipes are getting better.

All three experts reluctantly favor curbs on information about bio-, chemical and nuclear weapons.

Whether such curbs are constitutional is uncharted legal territory. But in 1979 a U.S. District Court temporarily blocked The Progressive from publishing an article about the hydrogen bomb because of the risks to national security.

In the 1990's the Senate several times passed measures that would have banned weapons cookbooks. But because of concerns about constitutionality, the final version that became law in 1999 was neutered. It allows prosecution only if the publisher intends for the information to be used to break federal laws. That is usually an impossible test to meet.

We rightly complain about weapons proliferation by China and Russia. But we also need to confront the consequences of our own information proliferation. Our small presses could end up helping terrorists much more than Saddam ever has.

I'm a journalist, steeped in First Amendment absolutism, and book-burning grates on my soul. But then again, so does war. As we prepare to go to battle to reduce our vulnerability to weapons of mass destruction, it seems appropriate for us in addition to consider other distasteful steps that can also make us safer.

We have a window now, while terrorists still have difficulty obtaining reliable recipes for bio- and chemical weapons. If we continue to allow these cookbooks to improve, buttressed by helpful articles in professional journals, then over the next 10 years we may empower terrorists to kill us on an unimaginable scale (New York Times, 2002).

**Title:** In Attics And Closets, 'Biohackers' Discover Their Inner Frankenstein
**Date:** May 12, 2009
**Source:** Wall Street Journal

**Abstract:** In Massachusetts, a young woman makes genetically modified E. coli in a closet she converted into a home lab. A part-time DJ in Berkeley, Calif., works in his attic to cultivate viruses extracted from sewage. In Seattle, a grad-school dropout wants to breed algae in a personal biology lab.

These hobbyists represent a growing strain of geekdom known as biohacking, in which do-it-yourselfers tinker with the building blocks of life in the comfort of their own homes. Some of them buy DNA online, then fiddle with it in hopes of curing diseases or finding new biofuels.

But are biohackers a threat to national security?

That was the question lurking behind a phone call that Katherine Aull got earlier this year. Ms. Aull, 23 years old, is designing a customized E. coli in the closet of her Cambridge, Mass., apartment, hoping to help with cancer research.

She's got a DNA "thermocycler" bought on eBay for $59, and an incubator made by combining a styrofoam box with a heating device meant for an iguana cage. A few months ago, she talked about her hobby on DIY Bio, a Web site frequented by biohackers, and her work was noted in New Scientist magazine.

That's when the phone rang. A man saying he was doing research for the U.S. government called with a few polite, pointed questions: How did she build that lab? Did she know other people creating new life forms at home?

The caller said the agency he represented is "used to thinking about rogue states and threats from that," recalls Ms. Aull, a recent Massachusetts Institute of Technology graduate.

The man on the other end of the line was Nils Gilman, a researcher with Monitor 360, a San Francisco company that provides "geo-strategic" research. Mr. Gilman declined to identify his client, saying only that it's a branch of the U.S. government involved in biosecurity. "I think they want to know, is this something we need to worry about?" he said -- particularly, could the biohackers' gadgets and methods, in the wrong hands, create dangerous pathogens?

Mr. Gilman's claim that he is working for the U.S. government couldn't be verified. A Department of Homeland Security official said "it does not appear that we contract with Monitor 360." A spokesman for the Federal Bureau of Investigation declined to comment, and a Department of Defense official said he couldn't find any record of the department hiring Monitor 360 or its parent company, Monitor Group. But he said another arm of Monitor Group has done work for the department in recent years.

Previously, some researchers and law-enforcement officials have raised red flags. In a paper published in Nature Biotechnology in 2007, a group of scientists and FBI officials called for better oversight of so-called synthetic DNA, an ingredient widely used by professional biologists and hobbyists, saying it could theoretically lead to the creation of harmful viruses like Ebola or smallpox, since their genomes are available online. "Current government oversight of the DNA-synthesis industry falls short of addressing this unfortunate reality," the paper said.

Ms. Aull, who lives with a cat and three roommates who are "a little bit weirded out" by her experiments, says the worries are overblown. DIY biologists are trying to "build a slingshot," she says, "and there are people out there talking about, oh, no, what happens if they move on to nuclear weapons?"

Other biohackers argue that Mother Nature is more likely than any home hobbyist to create dangerous new pathogens. They cite the current A/H1N1 "swine flu" virus, which is a made-in-the-wild brew of human, bird and pig influenzas. Mackenzie Cowell, a founder of DIY Bio, says members aim to do good and are committed to working safely.

The movement has made big strides recently thanks to the commercial availability of synthetic DNA. This genetic material, normally found inside the nucleus of cells, can now easily be purchased online. That provides any amateur with the ingredients for constructing an organism.

Dan Heidel, a 32-year-old aerospace employee and former molecular biology student in Seattle, has rented a 300-square-foot space in an old warehouse to make genetically modified algae that he thinks might be useful in producing cheap biofuels. The space is stuffed with $20,000 worth of secondhand lab equipment he bought on eBay, including, he says, centrifuges, a liquid-nitrogen storage unit and "a bunch of stuff for water purification."

"It's frankly a run-down, piece-of-crap warehouse, half falling apart," says Mr. Heidel. But "the landlord basically stays out of everyone's hair as long as they don't burn the building down, which is really pretty ideal."

The easy availability of synthetic DNA is at the heart of some scientists' concerns. The National Science Advisory Board for Biosecurity, a government body, has recommended that companies selling DNA be required to screen all orders for signs that the buyers might have nefarious intent. Some biologists argue that anyone wishing to custom-make new organisms, even if it's just glow-in-the-dark bacteria (a popular trick among biohackers), should have to get a license first.

Currently, regulation of labs like these is murky. It's unclear what agency, if any, is responsible.

So far, most garage biologists playing around with synthetic DNA are simply adding a gene or two to an existing organism, a fairly standard scientific practice involving some test-tube mixing, and not something biosecurity experts are very worried about. But technology promises to allow the creation of entire organisms from scratch -- something academics are aiming to do in university labs -- and that has some experts worried.

A senior official in the FBI's Weapons of Mass Destruction Directorate says the bureau is working with academia and industry to raise awareness about biosecurity, "particularly in light of the expansion of affordable molecular biology equipment" and genetic databases.

George Church, a professor of genetics at Harvard Medical School, says anyone using synthetic DNA should have to have a license, including garage biologists. But he says he's not too concerned by the current home hobbyists. "The younger generation need something they feel they can do, in the same sense that my generation was inspired by NASA and home chemistry kits," he said.

Phil Holtzman, a college student and part-time DJ at dance parties in Berkeley, Calif., is growing viruses in his attic that he thinks could be useful in medicine someday. Using pipettes and other equipment borrowed from his community college, he extracts viruses called bacteriophage from sewage and grows them in petri dishes. Mr. Holtzman's goal: Breed them to survive the high temperatures of the human body, where he thinks they might be useful in killing bad bacteria.

He collects partly treated sewage water from a network of underground tunnels in the Berkeley area, jumping a chain-link fence to get to the source. But Mr. Holtzman says his roommates are "really uncomfortable" with him working with sewage water, so he's trying to find another source of bacteriophage (Wall Street Journal, 2009).

**Title:** The Worry Of Biohacking: Closet Frankensteins Or Kafkaesque Government?
**Date:** May 12, 2009
**Source:** Discovery

**Abstract:** There's a piece in the *Wall Street Journal* today about biohacking: people experimenting with genetically engineered microbes and viruses at home. It tries to inject anxiety into your brain right from the start, with a headline, "In Attics and Closets, 'Biohackers' Discover Their Inner Frankenstein–Using Mail-Order DNA and Iguana Heaters, Hobbyists Brew New Life Forms; Is It Risky?"

I was surprised, however, to discover that the reporter does not mention the one time that somebody actually got arrested and charged with biohacking. At last year's World Science Festival, I moderated a panel with the artist Steven Kurtz, who had just finished navigating a Kafkaesque experience with the FBI for having a PCR machine and some harmless soil bacteria in his house. While we certainly need protection against bioterrorism and risky experiments, we definitely do not need the sort of ignorance of basic biology that was on display in the Kurtz affair.

Eyebeam, the New York gallery that hosted the panel, later posted the talk in several parts on YouTube. Kurtz has a sad and surreal story to tell (Discovery, 2009).

**Title:** Could Terrorists Exploit Synthetic Biology?
**Date:** Spring 2011
**Source:** New Atlantis

**Abstract:** The emergence over the past decade of synthetic genomics, a set of methods for the synthesis of entire microbial genomes from simple chemical building blocks, has elicited concerns about the potential misuse of this technology for harmful purposes. In 2002, scientists at Stony Brook University recreated the polio virus from scratch based on its published genetic sequence. This demonstration prompted fears that terrorist organizations might exploit the same technique to synthesize more deadly viral agents, such the smallpox virus, as biological weapons. Since then, legitimate scientists have recreated other pathogenic viruses in the laboratory, including a SARS-like virus and the formerly extinct strain of influenza virus responsible for the 1918-19 “Spanish Flu” pandemic, which is estimated to have infected a third of the world population and killed three to five percent. (The scientific rationale for resurrecting the 1918 influenza virus was to gain insight into the genetic factors that made it so virulent, thereby guiding the development of antiviral drugs that would be effective against future pandemic strains of the disease.)

In assessing the risk that would-be bioterrorists could misuse synthetic genomics to recreate dangerous viruses, a central question is whether they could master the necessary technical skills. Skeptics point out that whole-genome synthesis demands multiple sets of expertise, including considerable “tacit knowledge” that cannot be transmitted in writing but must be gained through years of hands-on experience in the laboratory. Other scholars disagree, arguing that genome synthesis is subject to a process of “de-skilling,” a gradual decline in the amount of tacit knowledge required to master the technology that will eventually make it accessible to non-experts, including those with malicious intent. This debate is of more than academic interest because it is central to determining the security risks associated with the rapid progress of biological science and technology. The Role of Tacit Knowledge

Sociologists of science distinguish between two types of technical knowledge: explicit and tacit. Explicit knowledge is information that can be codified, written down in the form of a recipe or laboratory protocol, and transferred from one individual to another by impersonal means, such as publication in a scientific journal. Tacit knowledge, by contrast, involves skills, know-how, and sensory cues that are vital to the successful use of a technology but that cannot be reduced to writing and must be acquired through hands-on practice and experience.Scientific procedures and techniques requiring tacit knowledge do not diffuse as rapidly as those that are readily codified.

Tacit knowledge can itself be divided into two types. Personal tacit knowledge is held by individuals and can be conveyed from one person to another through a master-apprentice relationship (learning by example) or acquired by a lengthy process of trial-and-error problem solving (learning by doing). The amount of time required to gain personal tacit knowledge depends on the complexity of a task and the level of skill involved in its execution.Moreover, such knowledge tends to decay if it is not practiced on a regular basis and transmitted to the next generation. Communal tacit knowledge is more complex because it is not held by a single individual but resides in an interdisciplinary team of specialists, each of whom has skills and experience that cohere into a larger scientific project or experimental protocol. This social dimension makes communal tacit knowledge particularly difficult to transfer from one laboratory to another, because doing so requires transplanting and replicating a complex set of technical practices in a new context.

Field research by sociologists of science has shown that advanced biotechnologies such as whole-genome synthesis demand high levels of both personal and communal tacit knowledge. For example, Kathleen Vogel of Cornell University found that the Stony Brook researchers who synthesized the polio virus did not rely exclusively on written protocols but made extensive use of intuitive skills acquired through years of experience. Tacit knowledge was particularly important in one step of the process: preparing the cell-free extracts needed to translate the synthetic genome into infectious virus particles. If

the cell-free extract was not prepared correctly by relying on subtle tricks and sensory cues, it proved impossible to reproduce the published experiment.

Based on her empirical research, Vogel concludes that biotechnology is a “socio-technical assemblage” — an activity whose technical and social dimensions are inextricably linked.Such factors help to explain the problems that scientists often encounter when trying to replicate a research protocol developed in another laboratory, or when translating a scientific discovery from the research bench to commercial application. Despite the ongoing “revolution” in the life sciences, these traditional bottlenecks persist. Other case studies of technological innovation have confirmed the importance of the socio-technical dimension, which includes tacit knowledge, teamwork, laboratory infrastructure, and organizational factors.

In the field of whole-genome synthesis, for example, the importance of socio-technical factors continues to grow as scientists take on larger and more complex genomes. Researchers at the J. Craig Venter Institute announced in May 2010 that they had synthesized an artificial bacterial genome consisting of more than one million DNA units, a task that required a unique configuration of expertise and resources. In an interview, Dr. Venter noted that at each stage in the process, a team of highly skilled and experienced molecular biologists had to develop new methodologies, which could be made to work only through a lengthy process of trial and error. For instance, because the long molecules of synthetic bacterial DNA were fragile, they had to be stored in supercoiled form inside of gel blocks and handled carefully to keep them from breaking up. “As with all things in science,” Venter explained, “it’s the little tiny breakthroughs on a daily basis that make for the big breakthrough.”

Recent developments in scientific publishing also reflect the fact that the growing complexity of research tools and processes has increased the importance of tacit knowledge. One online scientific publication, the Journal of Visualized Experiments, has since 2006 used video recordings of experimental techniques to portray subtle details that cannot be captured in written form. Other online repositories of research-protocol videos include Dnatube.com and SciVee.tv. Based on such evidence, Vogel, along with Sonia Ben Ouagrham-Gormley of George Mason University, have concluded that the technical and socio-organizational hurdles involved in whole-genome synthesis pose a major obstacle to the ability of terrorist organizations to exploit this technology for harmful purposes. The De-skilling Dynamic

Some scholars, however, have come to the opposite conclusion of those who emphasize the hurdles associated with tacit knowledge. Members of this second school point to a contradictory trend in biotechnological development that they claim will ultimately prove stronger. They note that the evolution of many emerging technologies involves a process of de-skilling that, over time, reduces the amount of tacit knowledge required for their use. Chris Chyba of Princeton, for example, contends that as whole-genome synthesis is automated, commercialized, and “black-boxed,” it will become more accessible to individuals with only basic scientific skills, including terrorists and other malicious actors.

De-skilling has already occurred in several genetic-engineering techniques that have been around for more than twenty years, including gene cloning (copying foreign genes in bacteria), transfection (introducing foreign genetic material into a cell), ligation (stitching fragments of DNA together), and the polymerase chain reaction, or PCR (which makes it possible to copy any particular DNA sequence several million-fold). Although one must have access to natural genetic material to use these techniques, the associated skill sets have diffused widely across the international scientific community. In fact, a few standard genetic-engineering techniques have been de-skilled to the point that they are now accessible to undergraduates and even advanced high school students, and could therefore be appropriated fairly easily by terrorist groups.

Gerald Epstein, of the Center for Science, Technology, and Security Policy, writes that whole-genome synthesis “appears to be following a trajectory familiar to other useful techniques: Originally accessible only to a handful of top research groups working at state-of-the-art facilities, synthesis techniques are becoming more widely available as they are refined, simplified, and improved by skilled technicians and craftsmen. Indeed, they are increasingly becoming ‘commoditized,’ as kits, processes, reagents, and services become available for individuals with basic lab training.” In 2007 Epstein and three co-authors

predicted that “ten years from now, it may be easier to synthesize almost any pathogenic virus than to obtain it through other means,” although they did not imply that individuals with only basic scientific training will be among the first to acquire this capability.

To date, the de-skilling of synthetic genomics has affected only a few elements of what is actually a complex, multi-step process. Practitioners of de novo viral synthesis note that the most challenging steps do not involve the synthesis of DNA fragments, which can be ordered from commercial suppliers, but the assembly of these fragments into a functional genome and the expression of the viral proteins. According to a report by the U.S. National Science Advisory Board for Biosecurity, a federal advisory committee, “The technology for synthesizing DNA is readily accessible, straightforward and a fundamental tool used in current biological research. In contrast, the science of constructing and expressing viruses in the laboratory is more complex and somewhat of an art. It is the laboratory procedures downstream from the actual synthesis of DNA that are the limiting steps in recovering viruses from genetic material.”

Along similar lines, virologist Jens Kuhn has called for a more nuanced assessment of the technical challenges involved in de novo viral synthesis. He notes, for example, that constructing the polio virus from scratch was fairly straightforward because its genome is small and consists of a single positive strand of RNA that, when placed in a cell-free extract, spontaneously directs the production of viral proteins, which then self-assemble to yield infectious viral particles. By contrast, the genomes of negative-strand RNA viruses, such as Ebola or the 1918 strain of influenza, are not infectious by themselves but require the presence of viral helper proteins, which must be synthesized and present in the host cells in the right numbers. Because such reverse-genetic systems are relatively difficult to create, only a limited number of scientists have the requisite skills and tacit knowledge.

It is also important to note that developing and producing an effective biological weapon involves far more than simply acquiring a virulent pathogen, whether by isolating it from nature or synthesizing it from scratch. Tacit knowledge also plays an important role in the “weaponization” of an infectious agent, which includes the following steps: (1) growing the agent in the needed quantity, (2) formulating the agent with chemical additives to enhance its stability and shelf life, (3) processing the agent into a concentrated slurry or a dry powder, and (4) devising a delivery system that can disseminate the agent as a fine-particle aerosol that infects through the lungs. According to Kuhn, “The methods to stabilize, coat, store, and disperse a biological agent are highly complicated, known only to a few people, and rarely published.” Thus, even if terrorists were to synthesize a viral agent successfully, “they will in all likelihood get stuck during the weaponization process.” Synthetic Biology’s De-skilling Agenda

The debate over de-skilling has focused not only on whole-genome synthesis but also on the related but broader field known as “synthetic biology.” Despite the overlap between these two disciplines, there are important differences. Whereas synthetic genomics is an “enabling” technology that makes possible many other technological applications, synthetic biology is an umbrella term that covers several distinct research programs. Two prominent and outspoken scientists, Thomas Knight of M.I.T. and Drew Endy of Stanford, advocate a particular synthetic-biology paradigm that aims to facilitate biological engineering through the development of a “tool kit” called the Registry of Standard Biological Parts. These parts, also known as “BioBricks,” are pieces of DNA with known protein-coding or regulatory functions that behave in a predictable manner and have a standard interface. In principle, such parts can be joined together to create functional genetic “circuits,” much as transistors, capacitors, and resistors are assembled into electronic devices. A major goal of parts-based synthetic biology is to design and build genetic modules that will endow microbes with useful functions not found in nature, such as the ability to produce biofuels or pharmaceuticals.

At least in theory, the use of standard genetic parts and modular design techniques should significantly reduce the need for tacit knowledge in the construction of synthetic organisms. As Gautam Mukunda, Kenneth A. Oye, and Scott C. Mohr of M.I.T. and Boston University have argued, “De-skilling and modularity ... have the potential to ... decrease the skill gradient separating elite practitioners from non-experts.” Nevertheless, not everyone in the synthetic biology community has bought into the standardized-parts approach, and some believe that it is destined to fail — or, at the very least, not to live up to its ambitious claim of providing a simple and predictable way to design and build artificial genomes.

One problem is that many biological parts have not been adequately characterized, so their activity varies depending on cell type or laboratory conditions, and some parts do not function optimally, or at all, because they are incompatible with the biochemical machinery of the host cell.

In other cases, the characteristics of individual biological parts may be well understood, but the parts do not behave as expected when combined as an intended functional module. Indeed, even fairly simple genetic circuits tend to be "noisy," operating stochastically rather than predictably. Furthermore, as the size of synthetic biological constructs increases, nonlinear interactions among the genetic and epigenetic elements may become increasingly difficult to predict or control, resulting in unexpected behaviors and other emergent properties. It is therefore conceivable that large genetic constructs could pose safety hazards that are impossible to predict in advance. (This possibility was discussed in these pages by Raymond Zalinskas and the author; see "The Promise and Perils of Synthetic Biology," Spring 2006.) In sum, although certain aspects of parts-based synthetic biology may well become more accessible to non-experts, the field's explicit de-skilling agenda is far from becoming an operational reality. Democratizing Synthetic Biology

Another element in the agenda of parts-based synthetic biology, as conceived by Knight and Endy, is to make the Registry of Standard Biological Parts freely available to interested researchers without patents or other restrictions. Over 130 academic labs now participate in the Registry community. An important vehicle for this "open-access biology" movement is the International Genetically Engineered Machine competition (iGEM), held annually at M.I.T. by the BioBricks Foundation. The goals of iGEM are "to enable the systematic engineering of biology, to promote the open and transparent development of tools for engineering biology, and to help construct a society that can productively apply biological technology." Starting in 2003 with a small group of student teams from American universities, iGEM has since become a global event: in 2010, 118 teams from 26 countries participated. Nevertheless, many of the teams have had trouble creating or using biological parts that work reliably and predictably in different contexts.

In May 2008, a group of amateur biologists in Cambridge, Massachusetts, launched another open-access initiative called DIYbio ("do-it-yourself biology") with the goal of making biotechnology more accessible to non-experts, including the potential use of synthetic-biology techniques to carry out personal projects. DIYbio has since expanded to other U.S. cities as well as internationally, with local chapters in Bangalore, London, Madrid, and Singapore. Although the group's technical infrastructure and capabilities are still rudimentary, they may become more sophisticated as gene-synthesis technology matures.

Some observers contend that the de-skilling and open-access agendas being promoted by iGEM and DIYbio will unleash a wave of innovation as a growing number of people from different walks of life acquire the ability to engineer biology for useful purposes. According to a team of social scientists affiliated with the Synthetic Biology Engineering Research Center (SynBERC) at the University of California, Berkeley, "The good news is that open access biology, to the extent that it works, may help actualize the long-promised biotechnical future: growth of green industry, production of cheaper drugs, development of new biofuels and the like." Extrapolating from these trends a few decades into the future, the physicist Freeman Dyson published a controversial article in 2007 envisioning a world in which synthetic biology has been de-skilled to the point that it is fully accessible to amateur scientists, hobbyists, and even children:

There will be do-it-yourself kits for gardeners who will use genetic engineering to breed new varieties of roses and orchids. Also kits for lovers of pigeons and parrots and lizards and snakes to breed new varieties of pets. Breeders of dogs and cats will have their kits too.... Few of the new creations will be masterpieces, but a great many will bring joy to their creators and variety to our fauna and flora. The final step in the domestication of biotechnology will be biotech games, designed like computer games for children down to kindergarten age but played with real eggs and seeds rather than with images on a screen. Playing such games, kids will acquire an intimate feeling for the organisms that they are growing. The winner could be the kid whose seed grows the prickliest cactus, or the kid whose egg hatches the cutest dinosaur.

Whether such rosy predictions come true will depend on, among other things, the degree to which

synthetic biology is de-skilled in the future. Looking at the historical record, scientific claims about de-skilling have been made repeatedly in the past but have often failed to materialize. For example, Helen Anne Curry, a graduate student in the history of science at Yale, has studied the development of plant-breeding techniques from 1925 to 1955. She found that during this period, agricultural interests promised that the use of radium, x-rays, and chemicals to generate genetic mutations would facilitate the creation of new and useful plant varieties, and that these methods would soon become available to amateur gardeners. But in fact, although the breeding techniques did result in novel varieties of roses and orchids, the predictions about de-skilling never came to pass. How Great Are the Risks?

In addition to the potential benefits of de-skilling and open access, a number of commentators have warned that the democratization of synthetic biology could give rise to new safety and security risks. One concern is that substantially expanding the pool of individuals with access to synthetic-biology techniques would inevitably increase the likelihood of accidents, creating unprecedented hazards for the environment and public health. Even Dyson's generally upbeat article acknowledges that the recreational use of synthetic biology "will be messy and possibly dangerous" and that "rules and regulations will be needed to make sure that our kids do not endanger themselves and others."

Beyond the possible safety risks, Mukunda, Oye, and Mohr warn that the de-skilling of synthetic biology would make this powerful technology accessible to individuals and groups who would use it deliberately to cause harm. "Synthetic biology," they write, "includes, as a principal part of its agenda, a sustained, well-funded assault on the necessity of tacit knowledge in bioengineering and thus on one of the most important current barriers to the production of biological weapons." Drawing on the precedent of "black-hatted" computer hackers, who create software viruses, worms, and other malware for criminal purposes, for espionage, or simply to demonstrate their technical prowess, some have predicted the emergence of "bio-hackers" who engage in reckless or malicious experiments with synthetic organisms in basement laboratories. Such nightmare scenarios are probably exaggerated, however, because the effective use of synthetic biology techniques relies on socio-technical resources that are not generally available to hobbyists. According to Andrew Ellington, a biochemistry professor at the University of Texas, "There is no 'Radio Shack' for DNA parts, and even if there were, the infrastructure required to manipulate those parts is non-trivial for all but the richest amateur scientist."

Indeed, when assessing the risk of misuse, it is important to distinguish among potential actors that differ greatly in financial assets and technical capabilities — from states with advanced bio-warfare programs, to terrorist organizations of varying size and sophistication, to individuals motivated by ideology or personal grievance. The study of past state-level bio-warfare programs, such as those of the Soviet Union and Iraq, has also shown that the acquisition of biological weapons requires an interdisciplinary team of scientists and engineers who have expertise and tacit knowledge in fields such as microbiology, aerobiology, formulation, and delivery.States are generally more capable of organizing and sustaining such teams than are non-state actors.

Conceivably, the obstacles posed by the need for personal and communal tacit knowledge might diminish if a terrorist group managed to recruit a group of scientists with the required types of expertise, and either bribed or coerced them into developing biological weapons. But Vogel and Ben Ouagrham-Gormley counter this argument by noting that even in the unlikely event that terrorists could recruit such a scientific A-team, its members would still face the challenge of adapting the technology to a local context.Dysfunctional group dynamics, such as a refusal by some team members to work together, would also create obstacles to interdisciplinary collaboration in areas requiring communal tacit knowledge.

Taking such factors into account, Michael Levi of the Council on Foreign Relations has questioned the ability of terrorists to construct an improvised nuclear device from stolen fissile materials. He notes that the process of building a functional weapon would involve a complex series of technical steps, all of which the terrorists would have to perform correctly in order to succeed. The same is true of assessing bioterrorism risk: one must examine not only the likelihood of various enabling conditions, but also the probability that all of the steps in the weapon development process will be carried out successfully.

Finally, problem-solving is crucial to the mastery of any complex technology. Biotechnologists must be

creative and persistent to overcome the technical difficulties that inevitably arise during the development of a new process. Thus, a key variable affecting the risk that terrorists could exploit synthetic biology for harmful purposes would be their ability to perform multiple iterations of a technique until they get it right, a requirement that presupposes a stable working environment and ample time for experimentation. Such amenities would probably be lacking, however, for individuals working in a covert hideaway or conducting illicit activities (such as the synthesis and weaponization of a deadly virus) in an otherwise legitimate laboratory. Resolving the Debate

Whether commercial kits and automation will merely make it easier for experienced scientists to perform certain difficult or tedious operations more quickly and easily, or whether de-skilling will truly make advanced biotechnologies available to non-experts — particularly those with malicious intent — is still an open question and will probably remain so for some time. To resolve the debate over the extent to which terrorists could misuse synthetic biology to cause harm, it is important to determine whether de-skilling affects those aspects of the technology that currently require personal or communal tacit knowledge.

Preliminary evidence suggests that de-skilling does not proceed in a uniform manner but affects some biotechnologies more than others. A number of techniques have proven resistant to de-skilling for the reasons mentioned, including the complexity of biological organisms and the critical role of tacit knowledge and other socio-technical factors. Moreover, although scientists commonly use genetic-engineering “kits” containing all of the materials and reagents required for a particular laboratory procedure, these kits do not necessarily remove the need for tacit knowledge when applied in the context of a particular experiment.
Instead of making assertions based on anecdotal evidence about whether or not synthetic biology will become de-skilled and accessible to non-experts, it would be more useful to conduct empirical research on the nature of tacit knowledge and the process of de-skilling. Shedding new light on the debate will require addressing several questions about the role of tacit knowledge and other socio-technical factors in biotechnological development: First, what are the specific conditions, skills, and socio-organizational contexts that are required for advanced biotechnologies to work reliably? Second, why do certain tools, techniques, and practices of biotechnology become de-skilled, while others do not? Third, what are the conditions, both technical and social, that facilitate or hamper the process of de-skilling?

Possible methodological approaches for answering these questions include the analysis of past efforts to transfer complex technologies from one laboratory setting to another, in-depth interviews with practicing scientists about the role of tacit knowledge and other socio-technical factors in their research, and the close ethnographic observation of laboratory work. Such studies should permit a more nuanced assessment of the safety and security risks associated with synthetic biology and other emerging biotechnologies, and will help policymakers determine which areas warrant oversight or regulation to prevent deliberate misuse (New Atlantis, 2011).

**Title:** Synthetic Biology Raises Bioterror Fears
**Date:** October 24, 2011
**Source:** Bio Prep Watch

**Abstract:** The potential for synthetic biology to become a tool for bioterrorists has caused a rift within a coalition of research laboratories heavily funded by the National Science Foundation.

A dispute over security procedures at the Synthetic Biology Engineering Research Center, led by the University of California 0 Berkeley, has highlighted the potentially dangerous consequences of the research, according to the New York Times.

The controversy centers on the resignation of a biosafety expert Paul Rabinow, who left SynBERC because he believed the coalition was not doing enough to prevent a future biological disaster.

Rabinow was initially hired to evaluate the ethical and security ramifications of the center's research and to report his findings to the top administrators, including the National Science Foundation, which granted SynBERC $23.3 million.

"It had begun to worry me how profoundly irresponsible these guys are," Dr. Rabinow said, the New York Times reports. "There are possibilities of all kinds of nefarious things happening. There is no reason that someone couldn't modify a virus; you could release it on an airplane or subway, and it could have profound terror effects."

Jay Keasling, SynBERC's director, disagrees with Rabinow's assessment and said that Rabinow had failed to do his job.

"Paul failed in two realms: actively communicating what he wanted to do and actively carrying them out," Dr. Keasling, who is also an executive of the United States Department of Energy's Joint BioEnergy Institute, said, the New York Times reports. "It became clear over time that he wasn't going to do the job."

Rabinow is particularly concerned that hackers or rogue scientists could use seemingly benign DNA sequences to manufacture a deadly virus. SynBERC scientists possess the technology to identify which DNA sequences can be used to modify genes to create novel functions, but the sequences are stored in public databases.

"DNA synthesis companies have no way of currently telling, once the sequences are put together, what the result will be," Dr. Rabinow said, according to the New York Times. "Somebody could manufacture pathogens that are dangerous to the environment."

Keasling said that synthetic biologists diligently police themselves and added that the notion of a terrorist using a company to acquire and customize genetic sequences is "far-fetched" (Bio Prep Watch, 2011).

**Title:** The Bioterrorist Next Door
**Date:** December 15, 2011
**Source:** Foreign Policy

**Abstract:** In September, an amiable Dutchman stepped up to the podium at a scientific meeting convened on the island of Malta and announced that he had created a form of influenza that could well be the deadliest contagious disease humanity has ever faced. The bombshell announcement, by virologist Ron Fouchier of Erasmus Medical Center, sparked weeks of vigorous debate among the world's experts on bioterrorism, influenza, virology, and national security over whether the research should have been performed or announced and whether it should ever be published.

Meanwhile, a joint Japanese-American research team led by the University of Wisconsin's Yoshihiro Kawaoka says that it, too, has manufactured a superflu. Additionally, a team at the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta has acknowledged doing similar research, without successfully making the über flu. The U.S. National Science Advisory Board for Biosecurity is now deliberating whether to censor publication of the Fouchier and Kawaoka papers, though it lacks any actual power to do so: It could so advise scientific journals, but editors would still decide. The advisory board is expected to release its decision on Dec. 15.

The interest in this brave new world of biology is not limited to the scientific community. U.S. Secretary of State Hillary Clinton made a surprise visit to Geneva on Dec. 7, addressing the Biological Weapons Convention review conference. The highest-ranking U.S. official to speak to the biological weapons group in decades, Clinton warned, "The emerging gene-synthesis industry is making genetic material widely available. This obviously has many benefits for research, but it could also potentially be used to assemble the components of a deadly organism."

"A crude but effective terrorist weapon can be made by using a small sample of any number of widely available pathogens, inexpensive equipment, and college-level chemistry and biology," Clinton also stated. "Less than a year ago, al Qaeda in the Arabian Peninsula made a call to arms for, and I quote, 'brothers with degrees in microbiology or chemistry to develop a weapon of mass destruction.'"

Noting that "It is not possible, in our opinion, to create a verification regime" for biological weapons compliance under the convention, Clinton called for voluntary transparency on biological experimentation among the 165 countries that have signed the agreement.

Officials throughout the U.S. government are declining to comment on the influenza experiments or elaborate on Clinton's comments and appearance in Geneva. The influenza scientists were politely but firmly instructed recently by U.S. officials to keep their mouths shut and provide no data or details regarding their experiments to anybody. Sources inside the Dutch, German, and French governments say that discreet agreement was reached among Western leaders to greet the influenza pronouncements with a wall of silence, pending the advisory board's decision and detailed analysis of the experiments by classified intelligence and scientific bodies.

Should we worry? If these scientists have indeed used the techniques that they have verbally described (but not yet published) to produce a highly contagious and virulent form of the so-called "bird flu," the feat can at least theoretically be performed by lesser-skilled individuals with nefarious intentions. Perhaps more significantly, the evolutionary leaps might be made naturally, via flu-infected birds, pigs, even humans. In other words, the research has implications for both terrorism and a catastrophic pandemic. Moreover, several experimental antecedents involving smallpox-like viruses and polio lend credence to the idea that concocting or radically altering viruses to create more lethal or transmissible germs is becoming an easier feat and an accidental byproduct of legitimate research.

The advisory board is debating whether the work, as well as details on how the flu viruses were deliberately mutated, should be published. That is the wrong question. As a practical matter, experimental results are now shared with lightning speed between laboratories, and I know that several leading scientists outside Fouchier's and Kawaoka's labs already recognize exactly how these experiments were executed. The genie is out of the bottle: Eager graduate students in virology departments from Boston to Bangkok have convened journal-review debates reckoning exactly how these viral Frankenstein efforts were carried out.

The list of attempts by governments to stifle scientific information is lengthy and marked by failure. I was at a 1982 optical engineering meeting in San Diego that was disrupted by a censorship order handed down by the Ronald Reagan administration's security chief, Adm. Bobby Ray Inman, compelling seizure of about 100 papers. The administration claimed the findings in those mathematics papers would, in Soviet hands, pose an existential threat to the United States --an assertion that proved laughable when the studies soon saw the light of day. In 2006, George W. Bush's administrationtried to block climate change–related presentations by NASA scientist James Hansen; every single one of Hansen's data points swiftly appeared on the Internet.

Rather than trying to censor research because its inevitable release might be harmful, we ought to be having a frank, open discussion about its implications. The correct questions that scientists, national security and political leaders, and the public ought to be asking are: How difficult was it to perform these experiments? Could they be replicated in the hands of criminals or would-be terrorists? What have these experiments shown us about the likelihood that the H5N1 "bird flu" virus will naturally evolve into this terrifying form? Are we safer, or less secure, today due to the post-2001 anthrax-inspired proliferation of high-security biological laboratories?

**What Genie Has Popped from Which Bottle?**

In 1997, the form of influenza now dubbed H5N1, or avian flu, emerged in Hong Kong, killing six people and forcing the destruction of every chicken in the protectorate. The virus had been circulating in aquatic migratory birds and domestic poultry flocks within mainland China for at least two years, but it was not recognized as a unique entity until the Hong Kong outbreak. The spread of H5N1 was temporarily halted by Hong Kong health official Margaret Chan, who ordered the mass culling of the area's poultry. Chan now serves as director general of the World Health Organization (WHO).

The virus reappeared in Thailand in 2003, killing flocks of chickens and ducks that November and infecting humans in January 2004 in Thailand and Vietnam. The H5N1 virus mutated in 2005 as it spread among various species of birds migrating through northern China, giving avian flu the capacity to infect a far greater range of bird species, as well as mammals -- including human beings. That year, human and animal outbreaks of H5N1 appeared across a vast expanse of the globe, from the southernmost Indonesian islands, up to central Siberia, and as far west as Germany.

By mid-2011, H5N1 had become a seasonal occurrence in a swath of the world spanning 63 countries of Asia, the Pacific Islands, Eastern and Western Europe, the Middle East, and North and West Africa. Since its 2004 reappearance, H5N1 has sickened at least 565 people, killing 331, for an overall mortality rate of 59 percent. The Ebola virus can be more lethal -- as high as 90 percent -- but is not terribly contagious. Rabies, in the absence of vaccination, is 100 percent lethal, but it can only be transmitted through the bite of an animal. It is estimated that in pre-vaccine days, the smallpox virus killed about a third of the people it infected.

Only influenza holds the potential of both severe contagion and, in the case of H5N1, astounding mortality rates, ranging from about 35 percent in Egypt (where the virus circulates widely) to more than 80 percent in parts of Indonesia (where 178 confirmed cases have resulted in 146 deaths). The virulence of H5N1 is far higher than that seen with any other influenza, including the notorious 1918 flu that killed an estimated 62 million people in less than two years. (Some reckonings of 1918 death tolls in poor countries that lacked epidemic reporting systems, such as China, India, and all of Africa, put the final mortality at 100 million, when the world population was just 1.8 billion and commercial air travel did not exist.) Six years ago, the spread of H5N1 sparked concern in the Executive Office of the Secretary-General of the United Nations, the White House, and many of its counterpart centers of government worldwide. Tremendous efforts ensued to kill infected domestic poultry, rapidly identify outbreaks, and pool scientific resources to track and scrutinize various H5N1 strains as they emerged. Some 400 million domestic birds were killed between 2004 and 2010, at an estimated global cost of $20 billion. It all seemed to work: By the end of 2008 the annual number of poultry outbreaks of H5N1 had shrunk from 4,000 down to 300.

In fearful anticipation, health and virus experts also watched for signs that the virus was spreading from one person to another. Although there were clusters of victims, infected families, and isolated person-to-person possible infections, the dreaded emergence of a form of humanly contagious H5N1 never occurred. By 2010, many leading virologists concluded that H5N1 was a terrifying germ -- *for birds*. The confident consensus, however, was that the mutations that avian flu would have to undergo to be able to spread easily from one human lung to another's were so complex as to approach evolutionary impossibility.

By mid-2011 the global response to avian flu had grown lethargic and complacent. Predictably, in the absence of vigilant bird-culling and vaccination efforts, trouble emerged as outbreaks mounted across Asia. Between January 2010 and the spring of 2011 more than 800 outbreaks were dutifully logged by government officials worldwide. In late July, a 4-year-old girl died of H5N1 in Cambodia, making her the seventh avian flu mortality in a country that had been free of the microbe for a long time.

On Aug. 29, the Food and Agriculture Organization sounded a mutation alarm, noting a new strain of the virus, dubbed H5N1-2.3.2.1, had surfaced in wild and domestic bird populations in Vietnam. Vietnam was one of six countries (including Bangladesh, Egypt, Indonesia, China, and India) in which avian flu had become *endemic*, meaning it permanently circulated among local and migratory birds. A week later, a Boston biotech company called Replikins announced the discovery of a mutant combinationof the avian H5N1 flu and the so-called "swine flu" that spread swiftly among people during the 2009 global pandemic. Replikins's claim implied that the highly virulent bird flu could gain the capacity to spread rapidly between people by absorbing infection genes from the contagious-but-wimpy H1N1 swine influenza.

Although these announcements sparked a minor panic in Asia, further scrutiny of both the 2.3.2.1 and Replikins's claim left the WHO convinced that no new human threat loomed. In early September, a collective sigh of public-health relief was expelled.

Three days later, the conference of the European Scientists Fighting Influenza (ESWI, the Romance-language acronym) convened in Malta, opening with scientific evidence of current pandemic potentials. The stage was set by renowned University of Hong Kong flu scientist Malik Peiris, who described with exquisite precision which genetic factors made the "swine flu," H1N1, highly contagious between pigs, ferrets, humans, and other mammals. Peiris offered evidence that the 2009 H1N1 pandemic started among American pigs but had been circulating in swine populations throughout North America and China for decades before making the mutational steps that sparked global spread.

Fouchier, the Dutch scientist, who has tracked H5N1 avian flu outbreaks in Indonesia for years, then suggested that vaccines used for years on chicken farms are now failing. Perhaps under selective evolutionary pressure, forms of vaccine-resistant H5N1 have appeared, Fouchier told the Malta meeting, adding, "We discovered that only one to three substitutions are sufficient to cause large changes in antigenic drift." In other words, naturally occurring, infinitesimal changes in the flu's genetic material are sufficient to render vaccines useless.

Fouchier went on to describe what he dubbed his "stupid" experiment of infecting ferrets in his lab sequentially with H5N1. One set of the animals would be infected, and then Fouchier would withdraw nasal fluid from the ferrets and use it to inoculation-infect a second set of animals. After 10 repeats, the superkiller H5N1 emerged, spreading through the air rapidly, killing 75 percent of the exposed animals. (Because Fouchier's work has not been published, accounts of the experiment vary, based on reporting from those who were present to hear his Malta speech. In some accounts the superlethal bird flu resulted from only five serial passages in ferrets -- a number far more likely to occur randomly in nature.)

"This virus is airborne and as efficiently transmitted as the seasonal virus," Fouchier told the Malta crowd, adding that he had identified which specific five mutations were necessary. Only five minute switches in RNA nucleotides -- the most basic elements of genetics -- were needed.

"This is very bad news, indeed," a sober Fouchier concluded.

The five dire mutations (technically, single nucleotide changes occurring inside two genes) have been separately found in influenza viruses circulating in the world. The actual mutations are not, therefore, unique. Fouchier's only innovation was in making all five occur inside the same virus at once. The more famous flu researcher from Erasmus, Albert Osterhaus, told reporters that what is done in the lab can happen in nature, adding, "Expect the unexpected.… *The mutations are out there, but they have not gotten together yet*."

Under questioning in Malta, Fouchier said his ferret form of H5N1 would certainly spread among humans and is "one of the most dangerous viruses you can make."

Shortly after Fouchier's announcement, Kawaoka, the University of Wisconsin scientist, let it be known that he, too, has made an airborne-transmissible H5N1 that readily spreads among mammals. Kawaoka's

efforts were jointly executed by teams he heads at the University of Wisconsin and the University of Tokyo. No further details regarding this effort are publicly available, though Kawaoka has submitted a paper detailing his techniques and discoveries for review by the U.S. National Science Advisory Board for Biosecurity, as has Fouchier. Both scientists wish to publish their work in major scientific journals.

Scientists are deeply divided regarding publication. "If I were a journal editor and I received an article that said how to make a bioweapon, I'd never publish it, but that would be based on self-regulation, not any government restriction," anthrax expert and retired Harvard University professor Matt Meselson told an interviewer. "I've never heard of a case where the government has restricted publication. I don't think it would work." But fellow anthrax researcher Paul Keim, who chairs the advisory board, told reporters, "I can't think of another pathogenic organism that is as scary as this one. I don't think anthrax is scary at all compared to this."

Perhaps the most intriguing comments came from Australian scientist Ian Ramshaw, who suggested that the Fouchier or Kawaoka papers could serve as bioterrorism blueprints: "As a researcher you do the good thing, but in the wrong hands it could be used for evil. In this case I'm not so worried about bioterrorism. It's the disgruntled researcher who is dangerous -- the rogue scientist," Ramshaw warned, according to the *Canberra Times*. Ten years ago Ramshaw accidentally made a superkiller form of mousepox, the rodent version of smallpox, in his Australian National University laboratory. He injected lab mice with the pox virus to test out a completely unrelated contraceptive vaccine, but the experiment transformed the virus into a deadly monster with a 100 percent fatality rate. In 2001 Ramshaw's work spurred high-level concern about the use of genetically modified smallpox by a rogue nation or terrorist group, launching the vigorous, multibillion-dollar post-9/11 American smallpox vaccine effort, as detailed in my new book, *I Heard the Sirens Scream*.

Within two years of Ramshaw's accidental mousepox creation, separate labs deliberately created viruses. In 2002, researchers at the State University of New York in Stony Brook built a polio virus from its genetic blueprint. This constituted a proof of principle, demonstrating that in a sufficiently skilled laboratory, all that is required to make a deadly virus is its nucleotide sequence -- details of which are now routinely published for everything from anthrax to the Ebola virus. At the time, Eckard Wimmer, the lead scientist on the project, warned: "The world had better be prepared. This shows you can re-create a virus from written information."

The following year another scientific team deliberately mimicked Ramshaw's mousepox accident, not only with the rodent form of pox but also with pox viruses that infect rabbits and cows. And in 2005 the CDC famously joined fragments of RNA from thawed tissue of victims of the 1918 flu, re-creating the original superkiller.

**The Genie Is Out of the Bioterrorism and Pandemic Bottles: How Scared Should We Be?**

This April, a team of CDC scientists published word that it had tried to **manipulate H5N1 genes** to render the avian virus a human-to-human spreader, but could not make it work. The team used a different method from the one apparently deployed by Fouchier and Kawaoka's team: The CDC group directly altered the genes of viruses, rather than sequentially infecting ferret after ferret. The CDC concluded, "An improvement in transmission efficiency was not observed with any of the mutants compared to the parental viruses, indicating that alternative molecular changes are required for H5N1 viruses to fully adapt to humans and to acquire pandemic capability."

That seemed comforting.

But in 2007 a different CDC team did to the SARS virus what Fouchier apparently has done to H5N1, with lethal results. Just as Fouchier produced highly infectious bird flu in ferrets by sequentially infecting one group of animals after another, the CDC group passed the SARS virus through one group of mice after another. Mice are normally harmlessly infected by SARS, which cannot cause disease in the rodents. But

after 15 such passages, the team got a 100 percent fatal form of the virus. Moreover, it was an airborne killer, sniffed out the air. (SARS, or severe acute respiratory syndrome, killed more than 900 people worldwide in 2002 and 2003, mostly in China.)

The University of Minnesota's Michael Osterholm, an expert on both bioterrorism and pandemics, thinks that understanding how animals might pass a virus like SARS or H5N1 among themselves, in a fashion in nature that mimics the laboratory experiments, may hold a vital key to predicting future epidemics. "We don't want to give bad guys a road map on how to make bad bugs really bad," he recently told *Science* reporter Martin Enserink. Health experts, however, do applaud the controversial research because it shows which mutations are necessary and at least one way they might arise.

There is no way to put a number on the probability of such natural mutational events. Are the odds 50-50 that a deadly, contagious form of H5N1 will wreak havoc across the world in the next 10 years? Anybody who claims to answer such a question, or pooh-pooh the asking of it, is a fool or a charlatan. It is an unknown.

**What About the Proliferation of High-Security Biology Labs: Good or Dangerous?**

Before the anthrax mailings terrorized America in 2001, there were only a handful of top security Biosafety Level 4 (BSL-4) labs in the world and a few dozen of the next-level BSL-3 facilities. The CDC and U.S. Army had the two largest pre-2001 BSL-4 labs, which nested like matryoshka dolls, with one layer of security inside another and another. The innermost labs required identity clearance, scientists wore protective space suits, and all air and water were specially cleansed and filtered to prevent accidental escape of Ebola, smallpox, and dozens of other superlethal organisms. The world's most dangerous known microbes were carefully kept under lock and key in a clearly identified handful of BSL-4 labs.

Even the less-secure BSL-3 labs required that scientists undergo security checks, wear spacesuits, and breathe through special respirators. Their numbers were finite and known, and researchers working on influenza, anthrax, or other deadly-but-treatable microbes represented a fairly small pool of scientists.

Since the 9/11 terrorist attacks, however, the number of such laboratories has proliferated spectacularly, not only inside the United States, but all over the world. In 2001 the United States had five "centers of excellence," as they were called, devoted to bioterrorism. By the end of 2002, more than 100 such centers were named, amid a record-breaking expansion in the numbers of laboratories and scientists studying anthrax, smallpox, Ebola, botulism, and every other germ somebody thought could be weaponized. After 9/11, the European Union saw the number of BSL-4 labs grow from six to 15. In the United States: from seven to 13. Canada built a BSL-4 complex in Winnipeg. Just as possession of rockets in the 1950s or nuclear power plants in the 1960s seemed the marks of a serious state power, so having BSL-3 and BSL-4 labs suddenly became a mark of national significance in the world -- an achievement to which countries should aspire. This year India opened its first BSL-4 facility, and it is rumored that Pakistan is now building one.

The proliferation of high-security labs means a great deal more than the mere construction of physical buildings. Where 10 years ago a finite pool of predominantly senior scientists toiled in such facilities, today thousands of graduate students, postdoctoral fellows, technicians, and senior researchers work in facilities stocked with humankind's worst microbial foes. Accidents have occurred with alarming regularity since the lab proliferation commenced, as I have detailed in my book. The facilities also constitute locations wherein individuals could theoretically execute experiments to produce supergerms without risking harm to themselves or others, regardless of whether the intent were noble, as appears to be the case for Fouchier and Kawaoka, or whether the intent were evil, as was the case with those responsible for the anthrax mailings.

Since 2005, several flu experiments conducted under BSL-3 conditions have raised eyebrows, as critics have charged the work should have been done inside the far more difficult but secure BSL-4 conditions. The original 1918 virus was "revived" from a long-frozen human body and grown inside a BSL-3 lab. Experiments were done on the 1918 virus in an effort to discover what genes made it so lethal. And the research that the CDC team, Fouchier, and Kawaoka performed on the H5N1 virus was all done in BSL-3 labs.

In September, when news of the Fouchier work started to appear in science magazines, Thomas Inglesby of the Center for Biosecurity at the University of Pittsburgh told *New Scientist*, "Small mistakes in biosafety could have terrible global consequences." His Pittsburgh colleague D.A. Henderson concurred: "The potential for escape of that virus is staggering."

According to the FBI, the culprit behind the 2001 anthrax mailings was Bruce Ivins, who worked in the U.S. Army's BSL-3 and BSL-4 labs in Maryland. Whether or not the FBI caught the right man -- a point of controversy among scientists -- it remains extraordinary that the response to what the agency calls "Amerithrax" is the creation of more such facilities in which more "Ivins" might toil.

The questions that arise from these H5N1 experiments have nothing to do with publication of the Fouchier and Kawaoka papers. We should be asking what we can do to ensure that such terrible man-made viruses never accidentally escape their laboratory confines or are deliberately released. And we should heed the question posed in the recently released Hollywood thriller Contagion when a Homeland Security character queries a CDC scientist:

"Is there any way someone could weaponize the bird flu? Is that what we're looking at?"

"Someone doesn't have to weaponize the bird flu," the CDC scientist responds, "The birds are doing that" (Foreign Policy, 2011).

**Title:** Should Medical Journals Print Info That Could Help Bioterrorists?
**Date:** December 27, 2011
**Source:** TIME

**Abstract:** Bird flu is deadly, but it generally does not spread easily from human to human. Now, scientists in Wisconsin and the Netherlands have created a strain of bird flu that can spread through the air — a virus that could kill millions if terrorists managed to create a batch and weaponize it. This raises a thorny question: Should medical journals be allowed to print the details of how the virus is made?

A government advisory board has urged two scientific journals to omit some of the specifics about the virus — the first time it has issued such a request. Supporters insist that the board's request is a much-needed precaution that could save millions of lives. But critics say that the government is engaging in censorship and interfering with academic freedom.

It is a classic clash of liberty versus security. The question is such a difficult one because whichever course the government takes carries risks and costs. Which option — blocking publication or allowing it — is the lesser of two evils?

It is not hard to see why the government is seeking to keep details of the virus out of print. The H5N1 bird-flu virus rarely infects humans. But when it does cross the species barrier, the mortality rate can be as high as 60%. If terrorists were able to use the new research to make a contagious strain of the virus, the result could be a real-world version of the movie *Contagion*. That is: worldwide panic and mass deaths.

The government is trying to avoid this by urging scientific journals to describe the virus only in general terms and keep out the sort of details that could be used to replicate it. The National Science Advisory Board for Biosecurity, which was created after the deadly anthrax attacks of 2001, asked the journals *Science* and *Nature* to be selective when they published articles on the highly contagious strain of H5N1.

So what's the problem? Critics say the government is engaging in censorship by telling the media what it should and should not write about. It sets a terrible precedent, they argue, for the government to set itself up as a national-security censor. The next time, they say, the government will try to prevent the publication of information that is far less dangerous than contagious bird flu.

Press-freedom watchdogs have a point: the government often trots out national security to try to intimidate the press into not doing its job. A few years back, the New York *Times* was about to expose the NSA spying program, in which the government was intercepting emails and phone calls without getting court orders. President George W. Bush called the paper's top brass down to the White House and warned them that exposing the program would compromise national security. The *Times* went ahead and published — and we are all still here.

The skeptics raise another important concern: the long tradition of scientific openness. Research science works by having experiments reported publicly, so other scientists can test the findings — and build on them with their own research. This tradition breaks down when the government puts a shroud of secrecy on some research.

The editor of *Science* has suggested that his journal might agree to withhold the information the advisory board is worried about — provided that the government creates a system that would allow legitimate scientists to access the full results.

That sounds like the right answer. We should be wary of government attempts to stop the media from publishing information. But in extreme cases, it may be necessary — and weaponizable highly contagious bird flu could be just such a case.

What factors should we be looking for in considering whether the government should try to stop publication? First, the threat of harm should be real and it should be truly extraordinary. That is a test the contagious strain of H5N1 seems to meet. Second, it should be clear that the government has no ulterior motives — that it is acting to protect the nation, not to advance a political agenda.

That can be a tough thing to evaluate — governments that use national-security arguments for political goals are quick to deny that they are doing so. The best check on this sort of politicization is making sure that anyone who feels pressure from the government not to publish or speak is able to challenge the policy in court. Judges are in the best position to balance risks of serious harm against the infringement on speech — and to determine whether the government is crossing any First Amendment lines.

Those who oppose the Scientific Advisory Board's decision are right that we must be wary whenever the government tries to suppress speech. As Supreme Court Justice Potter Stewart said, censorship is "the hallmark of an authoritarian regime." But the board's defenders are right that ultimately the government has a duty to protect the public from the most serious threats. They can cite Supreme Court Justice Robert Jackson, who noted that the Constitution is not a suicide pact (TIME, 2011).

**Title:** The Polio Genome
**Date:** 2012
**Source:** NMAH

**Abstract:**

It's now possible to go from data printed on a piece of paper or stored in a compute and, without the organism itself, re-construct a life form.

John LaMontagne, National Institute of Allergey and Infectious Diseases, 2002

A genome is the genetic material of an organism. In 1981, two different research groups, Vincent Racaniello and David Baltimore at Massachusetts Institute of Technology and Eckard Wimmer's team at State University of New York, Stony Brook, published the poliovirus genome. They used an enzyme to switch the single strands of viral ribonucleic acid—RNA—to double strands of deoxyribonucleic acid—DNA—and then determined the sequence of adenine, thymine, guanine, and cytosine encoding the five molecules that are the substance of the virus's existence.

Poliovirus lacks the ability to correct its mutations, so its genome evolves at one to two nucleotide substitutions per week. It is always changing.

In 2002, investigators at the State University of New York in Stony Brook used the published genetic sequence to synthesize a DNA version of poliovirus. Then they used an enzyme to convert the DNA to RNA and grew the virus in a cell-free extract. Animal tests showed that the synthesized poliovirus caused paralysis.

"I did not use any machine for sequencing the poliovirus genome. It was all done by hand—my hands! I used what was known as the 'Maxam-Gilbert' method, in which four different chemical reactions are carried out on the DNA. The products are then fractionated on thin polyacrylamide gels, which were poured manually, run, and then carefully removed from the plates, dried, and exposed to X-ray film. The sequencing 'ladders' were then read by myself on a light box and entered manually into a computer. But we didn't have individual computers back then, so I used a terminal hooked up to an MIT central computer."
—*Vincent Racaniello, 1981* (NMAH, 2012).

**Title:** 'Biohackers' Get Their Own Space To Create
**Date:** January 12, 2012
**Source:** Wall Street Journal

**Abstract:** Silicon Valley has sprouted numerous "hacker spaces" in recent years, where software geeks get together to program and build new Web creations. Now there's a hangout for "biohackers," too.

BioCurious, a 2,500-square-foot community lab in a low-slung office building in Sunnyvale, opened in November as a place where scientists, entrepreneurs and others can meet to conduct biology experiments and innovate on everything from bacteria to thermal cyclers. The facility also offers classes on topics ranging from DNA sequencing to microfluidics.

So far, the lab has attracted about 30 members who shell out $100 a month for use of the facility, says Raymond McCauley, one of half a dozen co-founders of BioCurious and the chief science officer of genomics start-up Genomera. At some point, he adds, the nonprofit may also launch a for-profit incubator program to cultivate and fund biotechnology start-ups.

"We're applying Silicon Valley principles to biotech and allowing people to just roll on in their projects," says Mr. McCauley, 45 years old.

George Church, a genetics professor at Harvard Medical School who has visited BioCurious, says the lab is part of a growing do-it-yourself biology movement. Many do-it-yourselfers see the biotech field as being at the same point that the personal-computer industry was more than 30 years ago, when Steve Jobs and Steve Wozniak debuted what became the Macintosh computer and founded Apple Inc.

"I compare BioCurious and other such labs to the 1970s electronics hackers in their garages," says Mr. Church.

BioCurious arrives amid a wave of new hacker spaces for computer programmers, such as Hacker Dojo in Mountain View, and a flood of tech start-up incubators such as Y Combinator. But while tech hacker spaces typically only require a physical space with Internet access, a biohacking space is complicated to launch because labs usually need expensive biochemistry equipment and procedures for dealing with biohazardous materials.

Mr. McCauley says the lab navigated city, county, state, federal and water-district rules on zoning and safety issues. The lab launched with about $35,000 in funding from volunteers and has relied on donated equipment, including a thermal cycler that copies DNA sequences.

BioCurious has since gotten some commercial sponsorships from biotech start-ups and equipment makers, Mr. McCauley says. With 30 paying members, "we're right about at break-even," he adds.

One regular user of BioCurious is Ron Shigeta. Mr. Shigeta, a 47-year-old Emeryville-based bioscientist, has been going to the lab once a week to work on learning more about the genes associated with the E. coli bacterium and is now collaborating with other scientists he has met at the facility on the project. "We're sharing the work," he says.

Patrik D'haeseleer, a computational scientist at Lawrence Livermore National Laboratory, says he has been going to BioCurious recently to work on a community project to hack an inkjet printer and make it a "bioprinter" that can print out cells, among other things.

"In my day job, I'm on the computational side but I don't get to get my hands dirty," says the 45-year-old. "So BioCurious is my opportunity to learn what my colleagues say is 'real' biology" (Wall Street Journal, 2012).

**Title:** E. Coli Vials Found In Arkansas Apartment Used To Treat Aliment
**Date:** February 13, 2012
**Source:** Fox News

**Abstract:** Two dozen vials of E. coli were left in the refrigerator of two Arkansas college students when they vacated their apartment are now being tested by state health officials, though the bacteria isn't thought to pose a health threat.

The bizarre discovery Friday set off a storm of panic, as state and federal agencies sent HazMat teams to the apartment complex in Jonesboro, Ark. Two of the vials were unsealed, and the samples are to be tested Monday at a state Health Department lab as a precaution, county officials said.

One of the tenants was located by authorities and said that his roommate, who returned a week ago to his native home of South Africa had the vials to treat an ailment, officials said.

“We spoke to his roommate, who told us that he used it to treat an illness and that it was a common treatment in his country,” David Moore, director of the Craighead County Office of Emergency Management told FoxNews.com. “We looked into it and we were satisfied with the fact that it was used for medical reasons."

Certain strains of E. coli are used to treat a number of gastrointestinal ailments, including irritable bowel disorder.

A maintenance worker who was cleaning out the apartment found the vials, marked “E-Coli,” inside a foam container after opening the refrigerator, officials said. He notified the building manager, who called the Arkansas Department of Health and the Centers for Disease Control and Prevention. Local authorities, along with the National Guard, immediately shut down the area and spent a majority of the day securing the medical-grade vials for removal.

The apartment complex was not evacuated at the time, and tenants were told there was no danger posed from the discovery. Representatives from the Willow Creek Apartment Complex, where the bacterium was found, did not immediately return calls for comment (Fox News, 2012).