Biotechnology's advance presents dark possibilities. Terrorists can develop biological weapons. Worse, the life sciences could give malefactors the ability to manipulate fundamental life processes—and even affect human behavior.

The Knowledge

By Mark Williams

In 1973, Soviet bioweaponeer Serguei Popov was a student in Novosibirsk, Siberia.

COURTESY OF SERGUEI POPOV

Last year, a likable and accomplished scientist named Serguei Popov, who for nearly two decades developed genetically engineered biological weapons for the Soviet Union, crossed the Potomac River to speak at a conference on bioterrorism in Washington, DC.

Popov, now a professor at the National Center for Biodefense and Infectious Diseases at George Mason University, is tallish, with peaked eyebrows and Slavic cheekbones, and, at 55, has hair somewhere between sandy and faded ginger. He has an open, lucid gaze, and he is courteously soft-spoken. His career has been unusual by any standards. As a student in his native city of Novosibirsk, Siberia's capital, preparing his thesis on DNA synthesis, he read the latest English-language publications on the new molecular biology. After submitting his doctorate in 1976, he joined Biopreparat, the Soviet pharmaceutical agency that secretly developed biological weapons. There, he rose to become a department head in a comprehensive program to genetically engineer biological weapons. When the program was founded in the 1970s, its goal was to enhance classical agents of biological warfare for heightened pathogenicity and resistance to antibiotics; by the 1980s, it was creating new species of designer pathogens that would induce entirely novel symptoms in their victims.

In 1979, Popov spent six months in Cambridge, England, studying the technologies of automated DNA sequencing and synthesis that were emerging in the West. That English visit, Popov recently told me, needed some arranging: "I possessed state secrets, so I could not travel abroad without a special decision of the Central Committee of the Communist Party. A special legend, essentially, that I was an ordinary scientist, was developed for me." The cover "legend" Popov's superiors provided proved useful in 1992, after the U.S.S.R. fell. When the Russian state stopped paying salaries, among those affected were the 30,000 scientists of Biopreparat. Broke, with a family to feed, Popov contacted his British friends, who arranged funding from the Royal Society, so he could do research in the United Kingdom. The KGB (whose control was in any case limited by then) let him leave Russia. Popov never returned. In England, he studied HIV for six months. In 1993, he moved to the University of Texas Southwestern Medical Center, whence he sent money so that his wife and children could join him. He remained in Texas until 2000, attracting little interest.

"When I came to Texas, I decided to forget everything," Popov told me. "For seven years I did that. Now it's different. It's not because I like talking about it. But I see every day in publications that nobody knows what was done in the Soviet Union and how important that work was."

Yet if Popov's appearance last year at the Washington conference is any indication, it will be difficult to convince policymakers and scientists of the relevance of the Soviet bioweaponeers' achievements. It wasn't only that Popov's audience in the high-ceilinged chamber of a Senate office building found the Soviets' ingenious applications of biological science morally repugnant and technically abstruse. Rather, what Popov said lay

EDITOR'S NOTE: *Conscious of the controversial nature of this article,* Technology Review *asked Allison Macfarlane, a senior research associate in the Technology Group of MIT's Security Studies Program, to rebut its argument: see "Assessing the Threat," page 34. We were also careful to elide any recipes for developing a biological weapon. Such details as do appear have been published before, mainly in scientific journals.*

so far outside current arguments about biodefense that he sounded as if he had come from another planet.

The conference's other speakers focused on the boom in U.S. biodefense spending since the attacks of September 11, 2001, and the anthrax scare that same year. The bacteriologist Richard Ebright, a professor of chemistry and chemical biology at Rutgers University, fretted that the enormous increase in grants to study three of the category A bacterial agents (that is, anthrax, plague, and tularemia) drained money from basic research to fight existing epidemics. Ebright (who'd persuaded 758 other scientists to sign a letter of protest to Elias Zerhouni, the director of the National Institutes of Health) also charged that by promiscuously disseminating bioweaponeering knowledge and pathogen specimens to newly minted biodefense labs around the United States, "the NIH was funding a research and development arm of al-Qaeda." Another speaker, Milton Leitenberg, introduced as one of the grand old men of weapons control, was more splenetic. The current obsession with bioterrorism, the rumpled, grandfatherly Leitenberg insisted, was nonsense; the record showed that almost all bioweaponeering had been done by state governments and militaries.

Such arguments are not without merit. So why do Serguei Popov's accounts of what the Russians assayed in the esoteric realm of genetically engineered bioweapons, using pregenomic biotech, matter *now*?

They matter because the Russians' achievements tell us what is possible. At least some of what the Soviet bioweaponeers did with difficulty and expense can now be done easily and cheaply. And *all* of what they accomplished can be duplicated with time and money. We live in a world where gene-sequencing equipment bought secondhand on eBay and unregulated biological material delivered in a FedEx package provide the means to create biological weapons.

Build or Buy?

There is growing scientific consensus that biotechnology—especially, the technology to synthesize ever larger DNA sequences—has advanced to the point that terrorists and rogue states could engineer dangerous novel pathogens.

In February, a report by the Institute of Medicine and National Research Council of the National Academies entitled "Globalization, Biosecurity, and the Future of the Life Sciences" argued, "In the future, genetic engineering and other technologies may lead to the development of pathogenic organisms with unique, unpredictable characteristics." Pondering the possibility of these recombinant pathogens, the authors note, "It is not at all unreasonable to anticipate that [these] biological threats will be increasingly sought after…and used for warfare, terrorism, and criminal purposes, and by increasingly less sophisticated and resourced individuals, groups, or nations." The report concludes, "Sooner or later, it is reasonable to expect the appearance of 'bio-hackers.'"

Malefactors would have more trouble stealing or buying the classical agents of biological warfare than synthesizing new ones. In 2002, after all, a group of researchers built a functioning polio virus, using a genetic sequence off the Internet and mail-order oligonucleotides (machine-synthesized DNA molecules no longer than about 140 bases each) from commercial synthesis companies. At the time, the group leader, Eckard Wimmer of the State University of New York at Stony Brook, warned that the technology to synthesize the much larger genome of variola major—that is, the deadly smallpox virus—would come within 15 years. In fact, it arrived sooner: December 2004, with the announcement of a high-throughput DNA synthesizer that could reproduce smallpox's 186,000-odd bases in 13 runs.

The possibility of terrorists' gaining access to such high-end technology is worrisome. But few have publicly stated that engineering certain types of recombinant microörganisms using older equipment—nowadays cheaply available from eBay and online marketplaces for scientific equipment like LabX—is *already* feasible. The biomedical community's reaction to all this has been a general flinching. (The signatories to the National Academies report are an exception.) Caution, denial, and a lack of knowledge about bioweaponeering seem to be in equal parts responsible. Jens Kuhn, a virologist at Harvard Medical School, told me, "The Russians did a lot in their bioweapons program. But most of that isn't published, so we don't know *what* they know."

On a winter's afternoon last year, in the hope of discovering just what the Russians had done, I set out along Highway 15 in Virginia to visit Serguei Popov at the Manassas campus of George Mason University. Popov came to the National Center for Biodefense after buying a book called *Biohazard* in 2000. This was the autobiography of Ken Alibek, Biopreparat's former deputy chief, its leading scientist, and Popov's ultimate superior. One of its passages described how, in 1989, Alibek and other Soviet bosses had attended a presentation by an unnamed "young scientist" from Biopreparat's bacterial-research complex at Obolensk, south of Moscow. Following this presentation, Alibek wrote, "the room was absolutely silent. We all recognized the implications of what the scientist had achieved. A new class of weapons had been found. For the first time, we would be capable of producing weapons based on chemical substances produced naturally by the human body. They could damage the nervous system, alter moods, trigger psychological changes, and even kill."

When Popov read that, I asked him, had he recognized the "young scientist?" "Yes," he replied. "That was me."

After reading *Biohazard*, Popov contacted Alibek and told him that he, too, had reached America. Popov moved to Virginia to work for Alibek's company, Advanced Biosystems,

and was debriefed by U.S. intelligence. In 2004 he took up his current position at the National Center for Biodefense, where Alibek is a distinguished professor.

Regarding the progress of biotechnology, Popov told me, "It seems to most people like something that happens in a few places, a few biological labs. Yet now it is becoming widespread knowledge." Furthermore, he stressed, it is knowledge that is Janus-faced in its potential applications. "When I prepare my lectures on genetic engineering, whatever I open, I see the possibilities to make harm or to use the same things for good—to make a biological weapon or to create a treatment against disease."

The "new class of weapons" that Alibek describes Popov's creating in *Biohazard* is a case in point. Into a relatively innocuous bacterium responsible for a low-mortality pneumonia, *Legionella pneumophila*, Popov and his researchers spliced mammalian DNA that expressed fragments of myelin protein, the electrically insulating fatty layer that sheathes our neurons. In test animals, the pneumonia infection came and went, but the myelin fragments borne by the recombinant Legionella goaded the animals' immune systems to read their own natural myelin as pathogenic and to attack it. Brain damage, paralysis, and nearly 100 percent mortality resulted: Popov had created a biological weapon that in effect triggered rapid multiple sclerosis. (Popov's claims can be corroborated: in recent years, scientists researching treatments for MS have employed similar methods on test animals with similar results.)

When I asked about the prospects for creating bioweapons through synthetic biology, Popov mentioned the polio virus synthesized in 2002. "Very prominent people like [Anthony] Fauci at the NIH said, 'Now we know it can be done.'" Popov paused. "You know, that's…naïve. In 1981, I described how to carry out a project to synthesize small but biologically active viruses. Nobody at Biopreparat had even a little doubt it could be done. We had no DNA synthesizers then. I had 50 people doing DNA synthesis manually, step by step. One step was about three hours, where today, with the synthesizer, it could be a few minutes—it could be less than a minute. Nevertheless, already the idea was that we would produce one virus a month."

Effectively, Popov said, Biopreparat had few restrictions on manpower. "If you wanted a hundred people involved, it was a hundred. If a thousand, a thousand." It is a startling picture: an industrial program that consumed tons of chemicals and marshalled large numbers of biologists to construct, over months, a few hundred bases of a gene that coded for a single protein.

Though some dismiss Biopreparat's pioneering efforts because the Russians relied on technology that is now antiquated, this is what makes them a good guide to what could be done today with cheap, widely available biotechnology. Splicing into pathogens synthesized mammalian genes coding for the short chains of amino acids called peptides (that is, genes just a few hundred bases long) was handily within reach of Biopreparat's DNA synthesis capabilities. Efforts on this scale are easily reproducible with today's tools.

What the Russians Did

The Soviet bioweapons program was vast and labyrinthine; not even Ken Alibek, its top scientific manager, knew everything. In assessing the extent of its accomplishment—and thus the danger posed by small groups armed with modern technology—we are to some degree dependent on Serguei Popov's version of things. Since his claims are so controversial, a question must be answered: Many (perhaps most) people would prefer to believe that Popov is lying. Is he?

The Russians' achievements tell us what is possible. At least some of what the Soviet bioweaponeers did with difficulty and expense can now be done easily and cheaply. And *all* of what they accomplished can be duplicated with time and money.

Popov's affiliation with Alibek is a strike against him at the U.S. Army Medical Research Institute of Infectious Diseases (Usamriid) at Fort Detrick, MD, where Biopreparat's former top scientist has his critics. Alibek, one knowledgeable person told me, effectively "entered the storytelling business when he came to America." Alibek's critics charge that because he received consulting fees while briefing U.S. scientists and officials, he exaggerated Soviet bioweaponeering achievements. In particular, some critics reject Alibek's claims that the U.S.S.R. had combined Ebola and other viruses—in order to create what Alibek calls "chimeras." The necessary technology, they insist, didn't yet exist. When I interviewed Alibek in 2003, however, he was adamant that Biopreparat *had* weaponized Ebola.

Alibek and Popov obviously have an interest in talking up Russia's bioweapons. But neither I, nor others with whom I've compared notes, have ever caught Popov in a false statement. One must listen to him carefully, however. Regarding Ebola chimeras, he told me when I first interviewed him in 2003, "You can speculate about a plague-Ebola combination. I know that those who ran the Soviet bioweapons program

studied that possibility. I can talk with certainty about a synthesis of plague and Venezuelan equine encephalitis, because I knew the guy who did that." Popov then described a Soviet strategy for hiding deadly viral genes inside some milder bacterium's genome, so that medical treatment of a victim's initial symptoms from one microbe would trigger a second microbe's growth. "The first symptom could be plague, and a victim's fever would get treated with something as simple as tetracycline. That tetracycline would itself be the factor inducing expression of a second set of genes, which could be a whole virus or a combination of viral genes."

In short, Popov indicated that a plague-Ebola combination was theoretically possible and that Soviet scientists had studied that possibility. Next, he made another turn of the screw: Biopreparat had researched recombinants that would effectively turn their victims into walking Ebola bombs. I had asked Popov for a picture of some worst-case scenarios, so I cannot complain that he was misleading me—but the Russians almost certainly never created the plague-Ebola combination.

One further testimonial to Popov: the man himself is all of a piece. Recalling his youth in Siberia, he told me, "I believed in the future, the whole idea of socialism, equity, and social justice. I was deeply afraid of the United States, the aggressive American military, capitalism—all that was deeply scary." He added, "It's difficult to communicate how people in the Soviet Union thought then about themselves and how much excitement we young people had about science." Biological-weapons development was a profession into which Popov was recruited in his 20s and which informed his life and thinking for years. To ask him questions about biological weapons is to elicit a cascade of analysis of the specific cell-signaling pathways and receptors that could be targeted to induce particular effects, and how that targeting might be achieved via the genetic manipulation of pathogens. Popov is not explicable unless he is what he claims to be.

Popov's research in Russia is powerfully suggestive of the strangeness of recombinant biological weapons. Because genetics and molecular biology were banned as "bourgeois science" in the U.S.S.R. until the early 1960s, Popov was among the first generation of Soviet university graduates to grow up with the new biology. When he first joined Vector, or the State Research Center of Virology and Biotechnology, Biopreparat's premier viral research facility near Novosibirsk, he didn't immediately understand that he had entered the bioweaponeering business. "Nobody talked about biological weapons," he told me. "Simply, it was supposed to be peaceful research, which would transition from pure science to a new microbiological industry." Matters proceeded, however. "Your boss says, 'We'd like you to join a very interesting project.' If you say no, that's the end of your career. Since I was ambitious then, I went further and further. Initially, I had a dozen people working under me. But the next year I got the whole department of fifty people."

Access codes were stamped on Serguei Popov's Biopreparat ID.

In 1979, Popov received orders to start research in which small, synthesized genes coding for production of beta-endorphins—the opioid neurotransmitters produced in response to pain, exercise, and other stress—were to be spliced into viruses. Ostensibly, this work aimed to enhance the pathogens' virulence. Popov shrugged, recalling this. "How could we increase virulence with endorphins? Still, if some general tells you, you do it." Popov noted that the particular general who ordered the project, Igor Ashmarin, was also a molecular biologist and, later, an academician on Moscow State University's biology faculty. "Ashmarin's project sounded unrealistic but not impossible. The peptides he suggested were short, and we knew how to synthesize the DNA."

COURTESY OF SERGUEI POPOV

Peptides, such as beta-endorphins, are the constituent parts of proteins and are no longer than 50 amino acids. Nature exploits their compactness in contexts where cell signaling takes place often and rapidly—for instance, in the central nervous system, where peptides serve as neurotransmitters. With 10 to 20 times fewer amino acids than an average protein, peptides are produced by correspondingly smaller DNA sequences, which made them good candidates for synthesis using Biopreparat's limited means. Popov set a research team to splicing synthetic endorphin-expressing genes into various viruses, then infecting test animals.

Yet the animals were unaffected. "We had huge pressure to produce these more lethal weapons," Popov said. "I was in charge of new projects. Often, it was my responsibility to develop the project, and if I couldn't, that would be my problem. I couldn't say, 'No, I won't do it.' Because, then, what about your children? What about your family?" To appease their military bosses, Popov and his researchers shifted to peptides other than beta-endorphins and discovered that, indeed, microbes bearing genes that expressed myelin protein could provoke animals' immune systems to attack their own nervous systems. While the Vector team used this technique to increase the virulence of vaccinia, with the ultimate goal of applying it to smallpox, Popov was sent to Obolensk to develop the same approach with bacteria. Still, he told me, "We now know that if we'd continued the original approach with beta-endorphins, we would have seen their effect."

This vision of subtle bioweapons that modified behavior by targeting the nervous system—inducing effects like temporary schizophrenia, memory loss, heightened aggression, immobilizing depression, or fear—was irresistibly attractive to Biopreparat's senior military scientists. After Popov's defection, the research continued. In 1993 and 1994, two papers, copublished in Russian science journals by Ashmarin and some of Popov's former colleagues, described experiments in which vaccines of recombinant tularemia successfully produced beta-endorphins in test animals and thereby increased their thresholds of pain sensitivity. These apparently small claims amount to a proof of concept: bioweapons can be created that target the central nervous system, changing perception and behavior.

I asked Popov whether bioweaponeers could design pathogens that induced the type of effects usually associated with psychopharmaceuticals.

"Essentially, a pathogen is only a vehicle," Popov replied. "Those vehicles are available—a huge number of pathogens you could use for different jobs. If the drug is a peptide like endorphin, that's simple. If you're talking about triggering the release of serotonin and dopamine—absolutely possible. To cause amnesia, schizophrenia—yes, it's theoretically possible with pathogens. If you talk about pacification of a subject population—yes, it's possible. The beta-endorphin was proposed as potentially a pacification agent. For more complex chemicals, you'd need the whole biological pathways that produce them. Constructing those would be enormously difficult. But any drug stimulates specific receptors, and that is doable in different ways. So instead of producing the drug, you induce the consequences. Pathogens could do that, in principle."

Psychotropic recombinant pathogens may sound science fictional, but sober biologists support Popov's analysis. Harvard University professor of molecular biology Matthew Meselson is, with Frank Stahl, responsible for the historic Meselson-Stahl experiment of 1957, which proved that DNA replicated semiconservatively, as Watson and Crick had proposed. Meselson has devoted much effort to preventing biological and chemical weapons. In 2001, warning that biotechnology's advance was transforming the possibilities of bioweaponeering, he wrote in the *New York Review of Books*, "As our ability to modify life processes continues its rapid advance, we will not only be able to devise additional ways to destroy life but will also become able to manipulate it—including the fundamental biological processes of cognition, development, reproduction, and inheritance."

I asked Meselson if he still stood by this. "Yes," he said. After telling him of Popov's accounts of Russian efforts to engineer neuromodulating pathogens, I said I was dubious that biological weapons could achieve such specific effects. "Why?" Meselson bluntly asked. He didn't believe such agents had been created *yet*—but they were possible.

No one knows when such hypothetical weapons will be real. But since Popov left Russia, the range and power of biotechnological tools for manipulating genetic control circuits have grown. A burgeoning revolution in "targeting specificity" (targeting is the process of engineering molecules to recognize and bind to particular types of cells) is creating new opportunities in pharmaceuticals; simultaneously, it is advancing the prospects for chemical and biological weapons. Current research is investigating agents that target the distinct biochemical pathways in the central nervous system and that could render people sedate, calm, or otherwise incapacitated. All that targeting specificity could, in principle, also be applied to biological weapons.

The disturbing scope of the resulting possibilities was alluded to by George Poste, former chief scientist at SmithKline Beecham and the sometime chairman of a task force on bioterrorism at the U.S. Defense Department, in a speech he gave to the National Academies and the Center for Strategic and International Studies in Washington, DC, in January 2003. According to the transcript of the speech, Poste recalled that at a recent biotech conference he had attended a presentation on agents that augment memory: "A series of aged rats were paraded with augmented memory functions…. And some very elegant structural chemistry was placed onto the board…. Then with the most casual wave of the hand the

presenter said, 'Of course, modification of the methyl group at C7 completely eliminates memory. Next slide, please.'"

Basement Biotech

The age of bioweaponeering is just dawning: almost all of the field's potential development lies ahead.

The recent report by the National Academies described many unpleasant scenarios: in addition to psychotropic pathogens, the academicians imagine the misuse of "RNA interference" to perturb gene expression, of nanotechnology to deliver toxins, and of viruses to deliver antibodies that could target ethnic groups.

This last is by no means ridiculous. Microbiologist Mark Wheelis at the University of California, Davis, who works with the Washington-based Center for Arms Control and Non-Proliferation, notes in an article for *Arms Control Today*, "Engineering an ethnic-specific weapon targeting humans is...difficult, as human genetic variability is very high both within and between ethnic groups...but there is no reason to believe that it will not eventually be possible."

But commentators have focused on speculative perils for decades. While the threats they describe are plausible, dire forecasts have become a ritual—a way to avoid more immediate problems. Already, in 2006, much could be done.

Popov's myelin autoimmunity weapon could be replicated by bioterrorists. It would be no easy feat: while the technological requirements are relatively slight, the scientific knowledge required is considerable. At the very least, terrorists would have to employ a real scientist as well as lab technicians trained to manage DNA synthesizers and tend pathogens. They would also have to find some way to disperse their pathogens. The Soviet Union "weaponized" biological agents by transforming them into fine aerosols that could be sprayed over large areas. This presents engineering problems of an industrial kind, possibly beyond the ability of any substate actor. But bioterrorists might be willing to infect themselves and walk through crowded airports and train stations: their coughs and sniffles would be the bombs of *their* terror campaign.

Difficult as it may still be, garage-lab bioengineering is getting easier every year. In the vanguard of those who are calling attention to biotechnology's potential for abuse is George Church, Harvard Medical School Professor of Genetics. It was Church who announced in December 2004 that his research team had developed a new high-throughput synthesizer capable of constructing in one pass a DNA molecule 14,500 bases long.

Church says his DNA synthesizer could make vaccine and pharmaceutical production vastly more efficient. But it could also enable the manufacture of the genomes of all the viruses on the U.S. government's "select agents" list of bioweapons. Church fears that starting with only the constituent chemical reagents and the DNA sequence of one of the select agents, someone with sufficient knowledge might construct a lethal virus. The smallpox virus variola, for instance, is approximately 186,000 bases long—just 13 smaller DNA molecules to be synthesized with Church's technology and bound together into one viral genome. To generate infectious particles, the synthetic variola would then need to be "booted" into operation in a host cell. None of this is trivial; nevertheless, with the requisite knowledge, it could be done.

I suggested to Church that someone with the requisite knowledge might not need his cutting-edge technology to do harm. A secondhand machine could be purchased from a website like eBay or LabX.com for around $5,000. Alternatively, the components—mostly off-the-shelf electronics and plumbing—could be assembled with a little more effort for a similar cost. Construction of a DNA synthesizer in this fashion would be undetectable by intelligence agencies.

> "I was in charge of new projects. Often, it was my responsibility to develop the project, and if I couldn't, that would be my problem. I couldn't say, 'No, I won't do it.' Because, then, what about your children? What about your family?"

The older-generation machine would construct only oligonucleotides, which would then have to be stitched together to function as a complete gene, so only small genes could be synthesized. But small genes can be used to kill people.

"People have trouble maintaining the necessary ultrapure approach even with commercial devices—but you definitely could do some things," Church acknowledged.

What things? Again, Serguei Popov's experience at Biopreparat is instructive. In 1981, Popov was ordered by Lev Sandakhchiev, Vector's chief, to synthesize fragments of smallpox. "I was against this project," Popov told me. "I thought it was an extremely blunt, stupid approach." It amounted to a pointlessly difficult stunt, he explained, to impress the Soviet military; when his researchers acquired real smallpox samples in 1983, the program was suspended. A closely related program that Popov had started, however, continued after he departed Vector for Biopreparat's Oblensk facility in the mid-1980s. This project used the poxvirus vaccinia, the relatively harmless relative of variola used as a vac-

cine against smallpox. Not only was vaccinia—whose genome is very similar to variola's—a convenient experimental stand-in for smallpox, but its giant size (by viral standards) also made it a congenial candidate to carry extra genes. In short, it was a useful model for bioweapons. For at least a decade, therefore, a team of Biopreparat scientists systematically inserted into vaccinia a variety of genes that coded for certain toxins and for peptides that act as signaling mechanisms in the immune system. Though Popov had directed that the recombinant-vaccinia program should proceed through the genes coding for immune system–modulating peptides, he left before the researchers finished with the interleukin genes. But it would be surprising if the Vector researchers did not reach the gene for interleukin-4 (IL-4), an immune-system peptide that coaxes white blood cells to increase their production of antibodies and then releases them.

There is some evidence that the Russians discovered the effects of inserting the IL-4 gene into a poxvirus. Those effects are deadly. In 2001, Ian Ramshaw and a team of virologists from the Australian National University in Canberra spliced *IL-4* into ectromelia, a mousepox virus, and learned that the resulting recombinant mousepox triggered massive overproduction of the IL-4 peptide. Even the immune systems of mice vaccinated against mousepox could not control the growth of the virus: a 60 percent mortality rate resulted. Other experiments have confirmed the lethality of the recombinant pathogen. The American poxvirus expert Mark Buller, of Saint Louis University in Missouri, engineered various versions of the recombinant, one of which maintained the mousepox virus's full virulence while generating excessive interleukin-4. *All* the mice infected with this recombinant died. The BBC reported that when asked about the Australian experiment, Sandakhchiev, Vector's director, remarked, "Of course, this is not a surprise."

Because vaccinia is universally available, it is fortunate that a vaccinia-*IL-4* hybrid would not be an effective biological weapon: vaccinia has limited transmissibility between humans. Still, there are other poxviruses that *are* transmissible. Smallpox, the most infamous, is nearly impossible for aspiring bioterrorists to acquire. But another, varicella-zoster, or common chickenpox, is easily acquired and even more infectious than smallpox.

What would happen if bioterrorists spliced *IL-4* into chickenpox and released the hybrid into the general population? Perhaps nothing. Very often, the Soviet bioweaponeers successfully spliced new genes into pathogens, only to find that infected test animals showed no symptoms. One reason was that the genetically engineered microbes were often "environmentally unstable"—that is, they did not retain the added genes. Engineering recombinant pathogens can be ineffective for other reasons, too: the foreign gene might be expressed in the "wrong" organ. But according to several virologists with knowledge of biological weapons, the result of splicing *IL-4* into chickenpox might be to suppress the immune response to the disease. According to these virologists, the effect would be similar to what happens to cancer patients when they catch chickenpox. They often die—even when treated with antiviral therapies. For healthy children or adults, chickenpox is usually a superficial disease that mainly affects the skin; but depending on the immunosuppressive state of an infected cancer patient, chickenpox lesions can be slow to heal, and the viscera—that is, the lungs, the liver, and the central nervous system—become progressively diseased.

Bioterrorists could create a varicella-*IL-4* recombinant virus more easily than they could acquire or manufacture the pathogens that top the select-agents list. *IL-4* is one of the standard genes used in medical research; a plasmid of human *IL-4* could be ordered from one of the DNA synthesis jobbing companies and delivered via FedEx for $350. If our hypothetical bioterrorists were worried about detection, they might avoid the DNA synthesis companies altogether. Conveniently, without its junk DNA, *IL-4* is only about 462 base pairs long. It's possible to download *IL-4*'s genetic sequence from the Internet, use a basic synthesizer to construct it in five segments, and then assemble those segments "manually," as Popov's scientists did. The other principal tools needed would be a centrifuge—like the $5,000 DNA synthesizer, cheaply available via Internet sites—and a transfection kit, a small bottle filled with reagent that costs less than $200 and which would be necessary to introduce the *IL-4* gene into chickenpox. Finally, the terrorists would also require an incubator and the media in which to grow the resulting cells. The total costs, including the DNA synthesizer: probably less than $10,000.

Be Afraid. But of What?

In the public debate about how to defend ourselves against biological weapons, the advance of biotechnology has been little discussed. Instead, most biologists and security analysts have debated the merits and shortcomings of Project BioShield, the Bush administration's $5.6 billion plan to protect the U.S. population from biological, chemical, radiological, or nuclear attack. After last year's bioterrorism conference in DC, I called on Richard Ebright, whose Rutgers laboratory researches transcription initiation (the first step in gene expression), to hear why he so opposes the biodefense boom (in its current form) and why he doesn't worry about terrorists' synthesizing biological weapons.

"There are now more than 300 U.S. institutions with access to live bioweapons agents and 16,500 individuals approved to handle them," Ebright told me. While all of those people have undergone some form of background

check—to verify, for instance, that they aren't named on a terrorist watch list and aren't illegal aliens—it's also true, Ebright noted, that "Mohammed Atta would have passed those tests without difficulty."

Furthermore, Ebright told me, at the time of our interview, 97 percent of the researchers receiving funds from the National Institute of Allergy and Infectious Diseases to study bioweapon agents had never been funded for such work before. Few of them, therefore, had any prior experience handling these pathogens; multiple incidents of accidental release had occurred during the previous two years.

Slipshod handling of bioweapons-level pathogens is scary enough, I conceded. But isn't the proliferation of bioweaponeering expertise, I asked, more worrisome? After all, what reliable means do we have of determining whether somebody set out to be a molecular biologist with the aim of developing bioweapons?

"That's the most significant concern," Ebright agreed. "If al-Qaeda wished to carry out a bioweapons attack in the U.S., their simplest means of acquiring access to the materials and the knowledge would be to send individuals to train within programs involved in biodefense research." Ebright paused. "And today, every university and corporate press office is trumpeting its success in securing research funding as part of this biodefense expansion, describing exactly what's available and where."

As for the threat of next-generation bioweapons agents, Ebright was dismissive: "To make an antibiotic-resistant bacterial strain is frighteningly straightforward, within reach of anyone with access to the material and knowledge of how to grow it." However, he continued, further engineering—to increase virulence, to provide escape from vaccines, to increase environmental stability—requires considerable skill and a far greater investment of effort and time. "It's clearly possible to engineer next-generation enhanced pathogens, as the former Soviet Union did. That there's been no bioweapons attack in the United States except for the 2001 anthrax attacks—which bore the earmarks of a U.S. biodefense community insider—means *ipso facto* that no substate adversary of the U.S. has access to the basic means of carrying it out. If al-Qaeda had biological weapons, they would release them."

Milton Leitenberg, the arms control specialist, goes a step further: he says because substate groups have not used biological weapons in the past, they are unlikely to do so in the near future. Such arguments are common in security circles. Yet for many contemplating the onrush of the life sciences and biotechnology, they have limited persuasiveness.

I suggested to Ebright that synthetic biology offered low-hanging fruit for a knowledgeable bioterrorist. He granted that there were scenarios with sinister potential. He allowed that biotechnology could make BioShield, which focuses on conventional select agents such as smallpox, anthrax, and Ebola, less relevant. Still, he maintained, "a conventional bioweapons agent can potentially be massively disruptive in economic costs, fear, panic, and casualties. The need to go to the next level is outside the incentive structure of any substate organization."

Even those who are intimately involved with biodefense often support this view. For an insider's perspective, I contacted Jens Kuhn, the Harvard Medical School virologist. The German-born Kuhn has worked not only at Usamriid, and at the Centers for Disease Control in Atlanta, but also—uniquely for a Westerner—at Vector.

Kuhn, like Ebright, is no fan of how the biodefense boom is unfolding. "When I was at Usamriid, it exemplified how a biodefense facility should be," he told me. "That's why I'm worried—because the system worked, and the experts were concentrated at the right places, Fort Detrick and the CDC. Now this expertise gets diluted, which isn't smart."

Kuhn believes, nevertheless, that some kind of national biodefense program is needed. He just doesn't think we are preparing for the right things. "Everybody makes this connection with bioterrorism, anthrax attacks, and al-Qaeda. That's completely wrong." Kuhn recalled his time at Vector and that facility's grand scale. "When you look at what the Russians did, those kinds of huge state programs with billions of dollars flowing into very sophisticated research carried on over decades—they're the problem. If nation-states start a Manhattan Project to build the perfect biological weapon, we're in deep shit."

But doesn't modern biotechnology, I asked, allow small groups to do unprecedented things in garage laboratories?

Kuhn conceded, "There are a few things out there" with the potential to kill people. But weighing the probabilities, he saw the threat in these terms: "Definitely more biowarfare than bioterrorism. Definitely more the sophisticated bioweapons coming in the future than the stuff now. There's danger coming towards us and we're focusing on concerns like BioShield. I don't think that's the stuff that will save us."

Is Help on the Way?

The 21st century will see a biological revolution analogous to the industrial revolution of the 19th. But both its benefits and its threats will be more profound and more disruptive.

The near-term threat is that genes could be hacked outside of large laboratories. This means that terrorists could create recombinant biological weapons. But the leading edge of bioweapon research has always been the work of government labs. The longer-term threat is what it always has been: national militaries. Biotechnology will furnish *them* with weapons of unprecedented power and specificity. George Poste, in his 2003 speech to the National Academies, warned his audience that in coming decades the life

sciences would loom ever larger in national-security matters and international affairs. Poste noted, "If you actually look at the history of the assimilation of technological advance into the calculus of military affairs, you cannot find a historical precedent in which dramatic new technologies that redress military inferiority are not deployed."

Harvard's Matthew Meselson has said the same and added that a world in which the new biotechnology was deployed militarily "would be a world in which the very nature of conflict had radically changed. Therein could lie unprecedented opportunities for violence, coercion, repression, or subjugation." Meselson adds, "Governments might have the objective of controlling very large numbers of people. If you have a situation of permanent conflict, people begin contemplating things that the ordinary rules of conflict don't allow. They begin to view the enemy as subhuman. Eventually, this leads to viewing people in your own culture as tools."

COURTESY OF SERGUEI POPOV

In 1987, Biopreparat conducted a "pathogens class" at its research complex in Obolensk. Serguei Popov is in the back row, far right.

What measures could mitigate both the near and the more distant threats of bioweaponry? BioShield, as it is now constituted, will not protect us from genetically engineered pathogens. A number of radical solutions (like somehow boosting the human immune system through generic immunomodifiers) have been proposed, but even if pursued, they might take years or decades to develop.

More immediately, no one has a good idea about what should be done. Some scientists hope to arrest the spread of bioweapons knowledge. Rutgers's Richard Ebright wants to reverse what he believes to be counterproductive in the funding of biodefense. More dramatically, Harvard's George Church is calling for all DNA synthesizers to be registered internationally. "This wouldn't be like regulating guns, where you just give people a license and let them do whatever they want," he says. "Along with the license would come responsibilities for reporting." Furthermore, Church believes that just as all DNA synthesizers should be registered, so should any molecular biologists researching the select agents or the human immune system response to pathogens. "Nobody's forced to do research in those areas. If someone does, then they should be willing to have a very transparent, spotlighted research career," Church says.

But enactment of Church's proposals would represent an unprecedented regulation of science. Worse, not all nations would comply. For instance, Russian biologists, some of whom are known to have worked at Biopreparat, have reportedly trained molecular-biology students at the Pasteur Institute in Tehran.

More fundamentally, arresting the progress of biological-weapons research is probably impractical. Biological knowledge is all one, and therapies cannot be easily distinguished from weapons. For example, a general trend in biomedicine is to use viral vectors in gene therapy.

Robert Carlson, senior scientist in the Genomation Lab and the Microscale Life Sciences Center in the Department of Electrical Engineering at the University of Washington, believes there are two options. On the one hand, we can clamp down on biodefense research, stunting our ability to respond to biological threats. Alternatively, we can continue to push the boundaries of what is known about how pathogens can be manipulated—spreading expertise in building biological systems, for better and for worse, through experiments like Buller's assembly of a mousepox-*IL4* recombinant—so we are not at a mortal disadvantage. One day, we must hope, technology will suggest an answer.

Serguei Popov has lived with these questions longer than most. When I asked him what could be done, he told me, "I don't know what kind of behavior or scientific or political measures would guarantee that the new biology won't hurt us." But the vital first step, Popov said, was for scientists to overcome their reluctance to discuss biological weapons. "Public awareness is very important. I can't say it's a solution to this problem. Frankly, I don't see any solution right now. Yet first we have to be aware." TR

Mark Williams is a contributing writer to Technology Review.