DESIGNER BUGS

Four years ago a team of Australian scientists, attempting to create a genetically engineered virus to combat common pests, stumbled across a mechanism that could potentially increase the killing power of a host of human diseases. Their findings, published last year amid great controversy, bring to the fore a question of increasing urgency: Might technologies intended to improve the world provide terrorists and rogue nations with the means to build the ultimate bio-weapon?

BY JON COHEN

Illustrations by Marc Yankus

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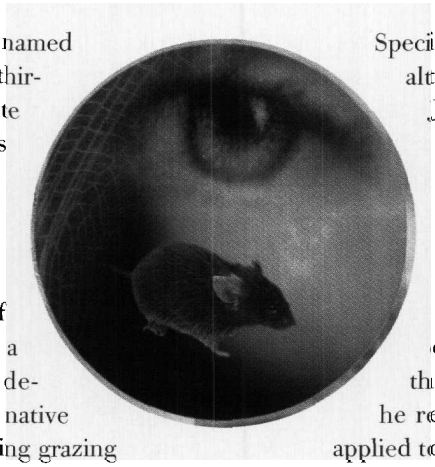
In 1859 a wealthy Australian grazier named Thomas Austin imported for sport thirteen wild English rabbits to his estate near Geelong, in Victoria. The rabbits did what rabbits do, and within three years 14,253 of them had been shot on Austin's land. By 1869 more than two million had been killed on a neighbor's property. Soon hundreds of millions of rabbits formed what became known as a "gray blanket" across the continent, destroying native plants, competing with native animals for food and shelter, and savaging grazing lands. In 1950 the government agreed to wage bio-warfare against them, and scientists released myxomatosis, a rabbit-specific pox virus from South America, into the wild. The virus quickly killed 99 percent of the country's rabbits. During the next three years, however, the kill rate among the initial survivors and their descendants dropped to 95 percent; it continued to decline until, eventually, it leveled off at about 50 percent. "It was a classic example of the co-evolution of virus and host," Frank Fenner told me recently. Fenner, a virologist at the John Curtin School of Medical Research, in Canberra, headed the studies analyzing why myxomatosis became less effective. In essence, he said, "you've got this arms race" in which the virus becomes weaker and the rabbit more resistant.



In 1988 a young virologist named Ron Jackson began working at what would later be called the Pest Animal Control division of the Cooperative Research Centre, in Canberra. His goal was to devise a solution that would sidestep those evolutionary forces and work indefinitely. Specifically, he hoped to produce a genetically altered virus that would sterilize rabbits. Jackson initially planned to use myxomatosis, but he couldn't easily get the rabbit genes he needed to engineer the virus. So he switched to mice and a virus called mousepox, intending to perform a "proof-of-concept" experiment that would allow him subsequently to proceed with rabbits. When the project showed early signs of success, he realized that the strategy might also be applied to mice, which bedevil Australia almost as much as rabbits do.

Every four years or so Australian mouse populations explode, causing what is referred to as a plague of mice. Each mouse plague costs the grain industry roughly $75 million in lost production. "So we view it very much that we're working on industry's behalf," Tony Peacock, the head of the Pest Animal Control division (essentially, Australia's Minister of Pests), told me recently. Mouse plagues also affect the general population, causing annoyances large and small; for example, mice are expert at chewing through electrical wires in people's homes.

And then there are rats, which cause widespread damage in Australia and destroy up to 20 percent of the world's rice crop—$4.5 billion worth—each year, and which carry some sixty viruses that can infect human beings. Research into contraceptives for rabbits and mice might ultimately have the added benefit of pointing to an effective strategy for controlling rats. Back in 1988 there seemed no reason not to pursue it.

"What Have We Created Here?"

Ten years later, on January 27, 1998, Ron Jackson's day began, like many of his days, with a drive along the winding roads of the Australian National University campus in Canberra. Eventually Jackson pulled up in front of the brick buildings of the John Curtin School, located across town from his own lab at the Cooperative Research Centre. The school is one of the few places in the world where researchers can work with mousepox. Although it is closely related to variola, the virus that causes smallpox in human beings, mousepox cannot harm people. It can, however, wipe out entire colonies of mice. An accidental release of mousepox among laboratory mice could ruin months' or even years' worth of experiments, so the school takes many precautions to ensure that the mousepox used there stays there.

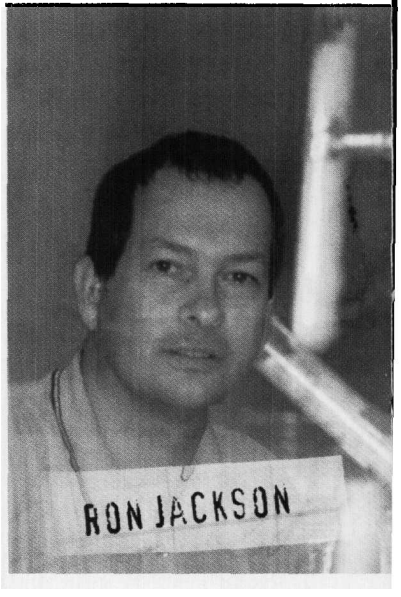
Jackson came first to the outer door of the animal lab. Next to it a sign warns, in block red letters, NO ADMITTANCE. HIGHLY INFECTIOUS AREA. After swiping his key card, he walked down the hall and entered the "clean room," a small vestibule lined with bright-green surgical gowns. He donned a gown and snapped on a pair of powder-blue polypropylene shoe covers. He then opened the door to the "dirty room," a facility with negative pressure to prevent air from escaping. Inside the dirty room, amid the odors of mouse food and urine, he padded over to two metal cages, each of which held five mice of the strain known in lab shorthand as Black 6.

Jackson and his fellow researchers, who included Ian Ramshaw, an immunologist at the Curtin School, were working with a genetically engineered mousepox that should have caused no serious harm to Black 6, which can survive even the most lethal known strain of the virus. Ideally, female mice infected with Jackson and Ramshaw's virus would become sterile and would also infect other females, sterilizing them as well. The virus would work like a vaccine, preventing pregnancy much as a vaccine prevents illness.

Mice, like human beings, coat their eggs in a jelly composed of several proteins. The jelly helps sperm to implant and protects the fertilized egg as it makes its way through the fallopian tube. Female mice normally do not mount an immune response to their own eggs; but Jackson and Ramshaw reasoned that if female mice became flooded with high doses of an egg-jelly protein, the mice's immune systems would "break tolerance" for the protein: the protein would, in effect, look like foreign material, triggering an antibody attack against the eggs. Because the protein is neither infectious nor transmissible, it would have to be carried by another agent—a sort of Trojan horse. Genetically engineered mousepox would serve as the Trojan horse.

Earlier that month Jackson and Ramshaw had published a paper suggesting that their virus could work: in one strain of mice it had sterilized 70 percent of the females they had tried it on. There was a big catch, however: it failed to work in two other mouse strains. To reduce mouse populations significantly, a sterilizing vaccine would, of course, have to work in many strains. The researchers decided to tackle the problem head on, refocusing their efforts on the most recalcitrant of the other two strains—Black 6.

Jackson and Ramshaw theorized that the immune system in Black 6 was so effective against mousepox that it was destroying the Trojan horse before it could breach cellular walls and deliver the protein. They decided, therefore, to tweak the immune system in two ways, simultaneously boosting its attack on the protein and blunting its attack on the mousepox. The researchers were encouraged to pursue such seemingly contradictory aims by the fact that the immune system has a seesaw-like mechanism. On one end of the seesaw are Y-shaped antibodies, which latch onto proteins and render them inert. On the other end are so-called killer cells, which target and destroy cells infected by foreign invaders. Tilting the seesaw toward a greater antibody response should, theoretically, push it away from producing killer cells, allowing more mousepox to survive long enough to deliver the protein.



In an effort to tilt the seesaw in this way, Jackson and Ramshaw inserted a gene for interleukin-4 into their mousepox. IL-4 is a chemical, secreted by the immune system, that boosts the production of antibodies in both mice and human beings. On January 21 the team injected ten Black 6 mice with the new version of mousepox. Six days later, when Jackson checked on the mice, he found that the IL-4 had had a vastly different effect from what he'd expected. One mouse was dead, its tissues badly swollen—a classic symptom of mousepox. Several others were hunched up and quiet. Two days later three more mice died; by the end of the month all ten were dead.

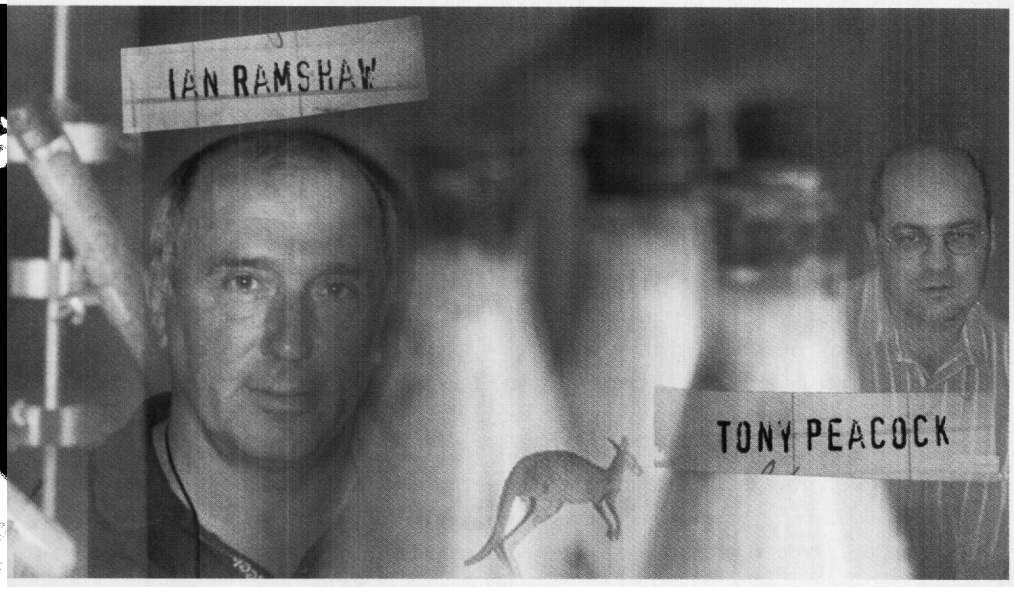
Jackson and his colleagues immediately realized the implications with respect to smallpox and its potential as a biological weapon. "We'd come up with, at least with mousepox, a highly effective mechanism for increasing lethality of a virus for genetically resistant animals," he explains. In short, they had stumbled on what might prove a relatively simple way to bolster the killing power of smallpox, already one of the most feared viruses of all time.

Soon the researchers would have data that were even more alarming. The mice, they realized, had died because the IL-4 had undermined their production of killer cells too well, leaving the animals vulnerable to a disease they

were normally able to resist. What would happen, they wondered, if they vaccinated Black 6 mice against mousepox before injecting them with the IL-4 version of the sterilizing virus?

By November, Jackson had the results: even in vaccinated mice the mousepox with IL-4 was lethal 60 percent of the time. He immediately went upstairs to Ramshaw's office to convey the news. "Oh, boy," Ramshaw said. "What have we created here?"

Again, the implications regarding smallpox were inescapable. The vaccine against smallpox was so effective that the World Health Organization eradicated variola from the human population more than two decades ago, and routine vaccinations were halted. All stockpiles of the virus were destroyed, save for two: one in a laboratory in Atlanta, Georgia, the other in a lab in Koltsovo, Russia. Mass vaccination would be our most effective defense should terrorists (or "rogue nations") obtain smallpox and use it as a weapon. But a version of variola containing IL-4 might render that defense useless.



Jackson and Ramshaw knew that the bio-weapon they had created to combat common pests—a weapon whose mechanism might be used to intensify a host of human diseases, not just smallpox—fundamentally altered the world's terror equation, much as suicide hijackers did again three years later. What they did not know was how to handle their findings, or even whether to publish them at all—a quandary that molecular biologists will increasingly face. Their uncertainty would be borne out: when they did publish their results, in February of last year, they found themselves at the center of a media storm that distorted many of the details and implications of their work. People would soon begin imagining the worst: terrorists unleashing a virulent disease and public-health officials mounting enormous vaccination campaigns, only to see those vaccinated rapidly succumb; health-care workers dying by the hundreds; panic sweeping the populace, with some people blocking access to their communities and others taking to the backwoods with food and weapons in an effort to escape. Moreover, the media's handling of the story would muddy a vital discussion about how to gauge the threats posed by natural and engineered bio-weapons and how to determine what steps scientists, policymakers, and the public should take.

The Perils of Playing Ostrich

The mousepox–IL-4 results surfaced at a time when the public had an unusually hearty appetite for such information. The late 1990s had brought startling revelations about bio-weapons programs in the former Soviet Union and Iraq, along with rising concerns about emerging viruses such as Ebola and West Nile. Some scientists had begun to discuss the potential of genetic engineering to create bugs that could cause mayhem. Steven Block, a biophysicist at Stanford University, quickly established himself as a leading oracle of doom, albeit one with a carefully reasoned argument based on cutting-edge science.

To Block, the mousepox–IL-4 data represented a vindication of sorts. "I was enormously relieved that someone did this," Block told me when I visited him in his lab last winter. "We needed at least one example like this to galvanize our thinking and our actions. I believe on balance they've done us a service."

Block came to bio-weapons through JASON, an elite, semi-secretive group of nearly fifty primarily academic scientists who provide independent advice about national-security issues to the U.S. government. (The group is named after the figure in Greek mythology who set out with the Argonauts to fetch the golden fleece.) In 1997 Block led a JASON study of the threats posed by recent advances in molecular biology. The results, published in a collection of essays called *The New Terror* (1999), in a chapter titled "Living Nightmares," constitute a chilling overview of the ways in which new technologies might allow the creation of "designer bugs" that would be everything a terrorist could hope for: safer than conventional bugs to handle, easier to distribute, more contagious, deadlier, and better at dodging existing drugs and vaccines.

Cradling a cappuccino (brewed on his lab's $5,000 Italian espresso maker) as we spoke, Block mixed rapid-fire discussion of "stealth viruses," "binary weapons," and "gene

shuffling" with references to a fictional "Q" bomb (from *The Mouse That Roared*) and H. G. Wells's warnings in *The Outline of History* (human beings more and more often find themselves in "a race between education and catastrophe"). A clock with a photo of Albert Einstein on its face hung on the wall, and a row of trophies that Block won in banjo-playing competitions adorned one shelf. "There have been a lot of criticisms of the JASON report that said, 'Block, this is all good and well, but that stuff is so far out there, it's so futuristic, it's so weird, we shouldn't devote any of our time to this sort of fictional nonsense—let's worry about the real world here,'" Block told me. The mousepox experiment, he emphasized, shows that the threat of designer bio-weapons must now be considered part of the real world.

In "Living Nightmares," a document studded with exclamation marks, Block highlighted the "lamentable ease" with which modern bio-science can manipulate genes to create weapons of mass destruction—or, more likely, mass disruption, as the anthrax attacks last fall suggest. Unlike nuclear weapons, which require scarce and expensive materials, most genetically engineered bio-weapons can be made from raw materials that are found in abundance (smallpox is an exception). And there is no shortage of biologists with the ability to manipulate bugs; such manipulation usually requires relatively inexpensive machinery and relies on well-documented techniques. Indeed, in military circles bio-weapons are sometimes referred to as "the poor man's nukes."

However, Block also stresses the paradox that underpins every discussion of bio-weapons: the same technologies that could destroy civilization could also build a healthier world. "Merely because a technology has a dual use is not a reason to stop it," he told me. "Information is information. It doesn't have a white hat or a black hat. It's neither good nor bad. It just is."

"Living Nightmares" compiled a long list of horrors that twenty-first-century "black biology" could conceivably create. For example, as scientists sequence the complete genomes of ever more pathogens, it will become easier to manufacture viruses that combine, say, a common strain of flu with the nastiest genes from a rare strain—or to create mixtures of two entirely different bugs. Bio-terrorists could equip a relatively harmless vector (for example, adenovirus, a common respiratory virus) to deliver a payload of deadly genes—ones that could, for example, prevent blood from clotting. They could concoct a genetically engineered stealth virus—one that, like many naturally occurring viruses, including herpes simplex, would infect a person but remain harmless unless triggered by a specific stimulus. (Herpes simplex is triggered by sunlight or stress.) Scientists might engineer pathogens that would direct the body's immune-system cells to commit mass suicide, or would cause pancreatic cells suddenly to secrete enormous amounts of insulin. To circumvent the dangers of handling such deadly bugs, they could make binary weapons: for instance, they could remove the portion of DNA that makes a particular strain of *E. coli* dangerous, and could safely manufacture large amounts of the neutered *E. coli* and also of the DNA fragment. A terrorist could recombine the two at the moment of attack.

"Living Nightmares" acknowledged that this "exercise in imagination" has led to some "rather fanciful" ideas. Still, in view of accounts from scientists who participated in the former Soviet Union's clandestine bio-weapons program, it has to be seen as more than just a dark parlor game. In his book *Biohazard* (1999), Ken Alibek, a former top official in the Soviet program, described how a decade earlier he attended a conference near Moscow during which molecular biologists reported success in creating a bubonic-plague bacterium that included a gene for the nerve-damaging myelin toxin; an anthrax strain impervious to five antibiotics; and a drug-resistant form of glanders, a horse bacterium that can infect and kill human beings. "You read Alibek's book and wonder how much of it is fish story and how much of it is real," Block says. "But of course even if only ten percent of it is real, there's a great deal to be concerned about."

Research conducted more openly, with benign aims, has also underscored the need for concern. For example, in 1998, at the Imperial College in London, investigators manufactured a hepatitis C virus that contained genes from the dengue-fever virus. They hoped that the dengue would provide critical factors that would allow them to grow hepatitis C in laboratory cultures; the inability to grow unadulterated hepatitis C has hampered vaccine and drug development for many years. Intense public criticism of the hybrid arose after government inspectors made an unannounced visit to the lab and found several health and safety violations. (Last July the college agreed to pay fines and costs of $65,000 but stressed that "no member of the public was at risk at any time.") A news article that appeared in *Science* in August linked the experiment to the Australian work on mousepox, quoting a bio-weapons expert who said, "No matter how cautious you are, you get situations where you create something of a far higher risk than predicted."

Block says that some of his colleagues play ostrich with respect to such issues, for fear that addressing them will provide fodder for the growing opposition to biotechnology and will lead to new restrictions on their work. Other biologists contend that open discussion risks supplying terrorists with blueprints for mayhem.

To Block, these arguments are naive or worse. Not only do they exaggerate the dangers of openly discussing the issues but they downplay a danger we might be able to address: the realpolitik that could make bio-terrorism attractive to terrorists or certain nations. "In the past it was argued that no one would want to release a contagious disease that killed a third of all the individuals on the planet," Block says. "You'd be shooting yourself in the foot. But a country like Afghanistan loses a third of its population, and after mourning the loss of so many individuals, the country

goes on pretty much as it did. An agrarian nation remains an agrarian nation. A developed country has farther to fall. Society as we know it would come to a grinding halt if we suffered such a significant loss of population. Therefore the release of an incredibly lethal contagious disease would perversely level the playing field. And in this new world order some of the undeveloped countries might have a better crack at the big time than they do under the current status." We need to confront such scenarios squarely, Block argues, rather than bury our heads in the sand.

THE MEDIA STORM

On a bookshelf in Frank Fenner's office at the John Curtin School stands a file box labeled "Smallpox post 1980"—the year that the World Health Organization declared its eradication campaign a success. Fenner recently added another word to the label: "bio-terrorism."

On a shelf below sits a heavy red book titled *Smallpox and Its Eradication* (1988), which at nearly 1,500 pages is perhaps the longest book ever written about a single disease. Fenner wrote the book with D. A. Henderson, who headed the World Health Organization campaign and is now the top bio-weapons expert in the U.S. government; it has become the field's bible. As the book sets forth in painstaking detail, smallpox killed 25 to 30 percent of those it infected, and blinded and disfigured many of those who survived. Some 300 million people died from smallpox in the twentieth century alone—roughly three times the number who died in armed conflicts.

Fenner's other writings include a book about Australia's attempt to use myxomatosis to control rabbits and one about the family of pox viruses. So it made perfect sense that his Curtin colleague Ian Ramshaw—who had no intention of playing ostrich about the mousepox results but did not want to inadvertently help terrorists—would turn to Fenner for advice.

Fenner's position was clear: he thought the researchers should share their findings. "There was no point in holding up publication, because other people would do the same sort of thing," he told me. And although the results surprised him, he did not see much reason for alarm. "I thought it probably wouldn't work in a way that would make smallpox a more deadly bio-terrorist weapon than it already is," he explained. "If you have something that kills twenty-five percent of the unvaccinated population and spreads reasonably well, then what more can you ask from a bio-weapon?"

Fenner believes that anyone attempting to use a smallpox–IL-4 virus as a weapon would face three main obstacles. First, what worked with mousepox might not work with variola—and terrorists would have no way of testing their construct short of conducting experiments on human beings. Second, a virus that can defeat vaccination poses serious risks for the scientists who engineer it and for anyone who tries to release it. Third, even if terrorists could engineer and release an IL-4–containing variola that mimicked the mousepox–IL-4 results, the virus would probably kill people so quickly that they would be unable to spread the infection to others, thus negating one of the qualities—contagiousness—that makes smallpox an attractive bio-weapon to begin with. (Bio-terrorists, wanting to be able to control their attacks, have traditionally favored diseases that are not easily spread from person to person, such as Q fever, plague, tularemia, botulism, and anthrax. The relatively recent interest in smallpox and other contagious diseases reflects the increasing recklessness of would-be bio-terrorists.)

Over the next few months Ramshaw polled other colleagues. No one advocated withholding the mousepox data. His thinking was also influenced by the fact that he had published the results of a somewhat similar experiment two years before without raising any hackles. In the earlier experiment Ramshaw's lab had shown that when IL-4 was added to vaccinia (the virus used as the smallpox vaccine) and injected into mice, it slowed the immune system's production of killer cells. This finding was not nearly as worrisome as the mousepox findings: the earlier research simply investigated an immunologic response, not whether it would lead to disease and death, and the scientists did not explore—as they did in the later experiment—whether their virus could defeat vaccine-induced immunity. Still, the idea that smallpox might become more virulent if it contained IL-4 had already appeared in the scientific literature.

Across town, at the Cooperative Research Centre's Pest Animal Control facility, Ron Jackson was similarly seeking advice from colleagues.

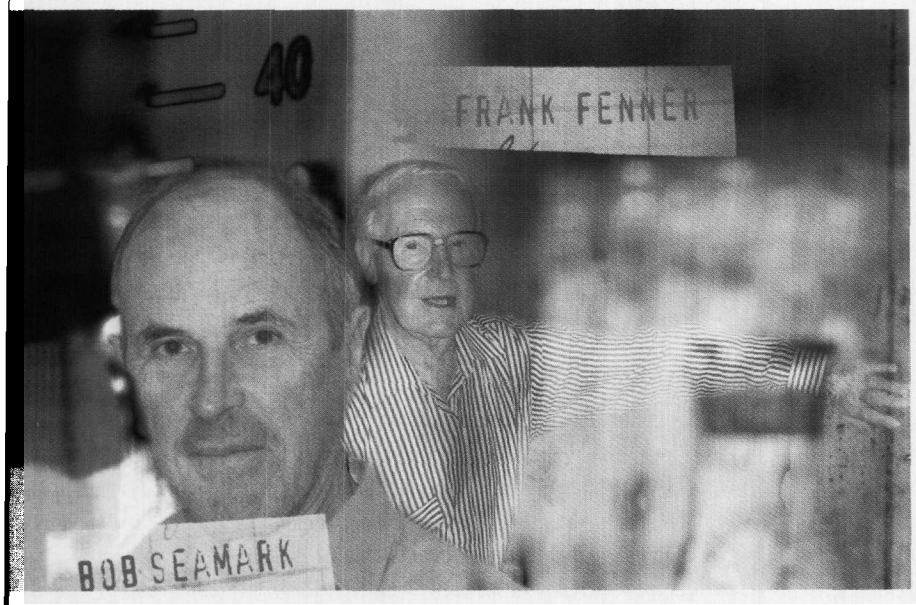
The grounds at Pest Animal Control are something of an anomaly in Canberra. Australia's capital city, and one of its few large population centers inland, Canberra is a terrifically tidy place, dominated by shiny new buildings and large street signs that point the way to virtually every destination. Even Canberra's residents commonly refer to it as "sterile." Pest Animal Control, set on the property of an 1862 English-style stone house, is anything but. Located off a rural road at the city's northern edge, the division at first glance resembles a zoo. Red kangaroos hop around in wire-fenced pens, as do their wallaby cousins. Bleating sheep stroll in another enclosure. Foxes occupy a fenced-off area of their own. In addition to the ubiquitous eucalyptus trees, a host of exotic conifers are scattered about the grounds, each with an identifying wooden plaque. Large white cockatiels perch in the canopies.

Inside the laboratories are many kinds of mice and rabbits. Posters in the hallways and offices declare war on the animals (FIGHTING FERALS FOR THE FUTURE OF OUR NATIVE FLORA AND FAUNA, one proclaims). Jackson's lab is in a quiet space in the basement, where there are few distractions. He is a scientist's scientist, choosing his words cautiously ("I wouldn't disagree with that"), questioning every assumption, reining in speculation at every turn. The fact that others had already published findings pertaining

to smallpox and IL-4 did not altogether relieve his fears about sharing the mousepox data. But, like Ramshaw, he also struggled with the possible negative consequences of suppressing the data. "If I'd kept this secret and someone had done IL-4 with humans, and people had died, I couldn't have lived with myself," he told me.

In addition, Jackson faced other, more parochial issues. Unlike his academic collaborators, he reports to a boss who of necessity has the institution's practical goals, not the abstract furthering of knowledge, at the front of his mind. At the time, the head of Pest Animal Control was Bob Seamark. Seamark, in turn, had to answer to a broad constituency of universities, federal agencies, and industry funders.

Earlier in his career Seamark, a reproductive biologist, had become embroiled in a debate about genetically modified organisms after creating transgenic pigs that grew more quickly than normal pigs do. When Jackson told Seamark that the vaccinated mice had died, Seamark knew he had a problem on his hands. He also knew that if mishandled, the situation could taint the institution.



As a scientist, Seamark found the mousepox results deeply disturbing. "We now have the capacity to approach the creation of new pathogens in a Lego-type way—mixing and matching," he told me. "If the purpose is for biological weapons, for evil purposes, we can be as evil as you bloody well like. Be warned." In particular, the speed with which this genetic engineering could be accomplished concerned him. "It's like the transgenic pig that we developed with enhanced growth characteristics," he explained. "The breeders said to us, you've achieved in one year what would take us thirty years to do. We can develop a bug in a fortnight, max. In times of war those are things that become critical. How fast can you be? When can you get the thing out there? How much lab time do you need to do your development and get out before any surveyor comes around?" He took little comfort in the argument that an engineered smallpox would not be transmitted as readily as the natural form of the virus. "In a biological-warfare system we don't need transmission between people," he said. "We can deliver to every individual, in a variety of ways."

Still, Seamark thought it made no sense to try to quash publication of the mousepox data; in fact, he told me, he yearned for a vigorous public discussion of the issues. His position required him to consult with the Commonwealth Scientific and Industrial Research Organization, the main government funder of science, which in turn consulted with the country's Department of Defence. Again, no one expressed any reservations about publishing the data.

Jackson and Ramshaw finished their experiment, analyzing the various immune responses discernible in the blood of surviving mice and in the organs of dead ones. By the time they solicited advice, applied for a patent to protect their invention of an infectious contraceptive vaccine, and drafted a manuscript, more than a year had passed. When they did submit the manuscript, to the *Journal of Virology* in July of 2000, it said nothing about the link between their work and potential bioweapons. "What we wanted was a presentation of just cool scientific fact," Seamark says. Neither the editors of the journal nor either of the independent scientists who reviewed the paper raised the larger implications.

In December of 2000, a few weeks before the paper was set to appear online, Ramshaw was interviewed by Rachel Nowak, a reporter for *New Scientist* magazine, about AIDS-vaccine work—the main focus of his lab. Nowak asked him if he had anything else interesting under way. In an unguarded moment he told her about the upcoming *Journal of Virology* paper, and even spelled out the dilemma it posed. Nowak shifted gears and pursued the mousepox story full bore.

After the interview Ramshaw realized that his comments might concern his colleagues, so he called Seamark, who says that he expected some uproar but was not upset. "Things like that excite me," he told me. "It's a test of your ability to manage." Seamark then spoke with Nowak, as did Jackson.

On January 10, a few days before the publication of Nowak's mousepox story, *New Scientist* faxed its piece to Seamark, as agreed: the researchers had asked for time to prepare for questions from journalists. Upon seeing the slant of the piece ("Killer Virus: An engineered mouse virus leaves us one step away from the ultimate weapon") and of an accompanying editorial ("The genie is out: Biotech has just sprung a nasty surprise. Next time, it could be catastrophic"), the Cooperative Research Centre prepared a press release, with its own spin, for issue the following day: "Discovery Prompts Call for Biowarfare Review." In it Seamark was quoted as saying that the "best protection against any misuse of

this technique was to issue a worldwide warning." The release also highlighted the need to strengthen the Biological Weapons Convention, a thirty-year-old agreement among nearly 150 nations not to develop, produce, or stockpile biological-warfare agents except for peaceful purposes. (The treaty has been blatantly violated by several signatories—for instance, the Soviet Union *started* its bio-weapons program the year after signing it—and attempts at crafting verification measures have largely failed. The United States, fearing that drug companies would be forced to reveal trade secrets, has been among those resisting such measures.)

The Cooperative Research Centre release fanned media attention. When Jackson turned on the television on the morning of January 12, he heard a reporter saying that he and his colleagues had re-created smallpox. During the next two weeks the story reverberated across Australia and the world. Jackson found himself fretting about his reputation, the time he was spending talking to reporters, even his family's safety.

Ramshaw had a more philosophical reaction. "I'm a great believer in the rice-grain hypothesis," he says. "You have a pile of rice, and if you add one more grain, you can have a massive avalanche. Minor things make a big difference. There are minor things that created this whole issue, such as the publication in *New Scientist*, a reporter coming along to talk." But he, too, was unprepared for the onslaught of attention. And he experienced some disapprobation: one colleague came up to him and asked, point-blank, "Why did you do this experiment?"

Most of the media reports twisted some aspects of the story and neglected others. Some writers implied that the researchers sat on their data for more than two years as they wrestled with the question of whether to publish. (That probably delayed them no more than six months.) Smallpox with IL-4 is surely not the ultimate bio-weapon; as Fenner argues, it may not even be a very good one. An emphasis on the accidental nature of the discovery—especially coming at a time when debates raged over genetically modified plants, mad-cow disease, and foot-and-mouth—created the mistaken impression that once again arrogant scientists had bumbled, this time creating a Frankenvirus. But most disappointing of all to the Australian researchers is that many stories failed to examine the very question that Ramshaw's colleague had confronted him with: Why *did* they do this? The impulse informing their work was largely ignored.

DNA ORGIES

The southern shore of San Francisco Bay is home to a host of biotechnology companies. One of them, a company called Maxygen, came into existence because of a technology that, perhaps more than any other, illustrates the hairline borders between bio-medicine, bio-weapons, and bio-defense. The technique, called gene shuffling, was invented by one of the company's founders, Willem "Pim" Stemmer. It enables scientists to "maximize genetic diversity"—the phrase from which the company's name was drawn.

Maxygen's 1999 annual report describes gene shuffling—which the company also refers to by the trademarked term MolecularBreeding—in a lavish display. Pages 4 and 5 of the glossy report display evenly spaced passport-size photos of thirty-two purebred dogs. Labels on some of the photos identify the dog pictured as a herder, a rescuer, a helper, a worker, a hunter, a fighter, or a racer. "Over thousands of years, humans have used classical breeding to produce dogs that can serve almost any task and survive in almost any environment," a caption reads. "Maxygen's MolecularBreeding™ technologies mimic classical breeding at the molecular level, creating new generations of high quality products."

Maxygen has built its business around the search for new drugs, vaccines, disease-resistant plants, and industrial biochemicals. In addition to helping other companies speed the creation of better drugs to treat allergies, multiple sclerosis, and psychiatric diseases, it is working to develop its own therapies for auto-immune diseases and cancer. The International AIDS Vaccine Initiative has hired Maxygen to help develop an HIV vaccine. And the company has several contracts with the U.S. Defense Advanced Research Projects Agency (DARPA), the branch of the Defense Department that, among other things, supports high-risk research designed to combat bio-weapons.

The company's Web site displays a "Statement of Ethical Principles." The principles are explicit. Maxygen does not do human cloning. It does not "conduct any research intended for use in developing, testing or producing biological weapons." But the first paper Stemmer published about gene shuffling, when he was working for a business that preceded Maxygen, caused other scientists to posit links between the technology and bio-weapons.

The article, published in a 1994 issue of *Nature*, described the breeding of bacteria. Stemmer had adapted a technology known as the polymerase chain reaction, or PCR. Commonly referred to as a molecular photocopier, PCR works by heating DNA until the strands of the double helix uncoil. Chemicals are then added and the temperature is lowered, allowing each strand to replicate itself and form a new double helix. Repeated many times over, the process can turn minute amounts of DNA into large quantities in a matter of hours.

Working with *E. coli*, Stemmer discovered that PCR could be used to create DNA orgies, in which mixtures of uncoupled strands randomly pair with one another rather than with their twins. Stemmer—who for a time called the technique "sexual PCR"—could then select the new DNA for specific characteristics, much as dog breeders select for hunters or racers. He demonstrated that by using sexual PCR he could quickly "direct evolution" to select for an *E. coli* that was 32,000 times as resistant to a given antibiotic as the *E. coli* with which he had started.

Stemmer's was another proof-of-concept experiment: the

antibiotic resistance served as a marker, a way to measure success, but was meant to have no practical application. But the experiment generated alarm. Even before Stemmer published his results, the company he was working for at the time, the Affymax Research Institute, in Palo Alto, directed him to stop using antibiotic-resistance markers in his experiments.

When the *Nature* paper appeared, Affymax asked Stemmer not to share his mutant *E. coli* with colleagues. Stemmer says that this caused him some professional pain, since scientists commonly share material with one another. "But we were afraid that someone might, a few years later, find the same mutations in the wild and blame us for having released it. We wanted to make sure that this was not possible," he told me. Stemmer shared the *E. coli* with only one collaborator and stored the rest in a laboratory freezer at −112°.

Maxygen spun off from Affymax in 1996, moving a few miles away to a standard-issue 1970s office park in which one shoebox-shaped building is virtually indistinguishable from another. Shortly after the move Stemmer received a letter out of the blue from several prominent microbiologists, asking him to destroy his *E. coli*. The officers of the company decided that he should comply with the request. A few days later Stemmer removed the tiny test tubes containing mutant *E. coli* from the freezer. He took them down the hall to an autoclave, an ovenlike device used to sterilize equipment. He then put them in a red biohazard bag and went back to more-meaningful work.

Recalling the incident, Stemmer shakes his head. "It was stupid, it was silly," he says. "Whether it sits in the freezer or gets autoclaved, it really doesn't make much difference. I don't think sending it out would have made much difference either, but we destroyed it for perception purposes."

Stemmer does not dismiss the possibility that terrorists could use novel biotechnologies to create new pathogens. But he questions whether they would bother with gene shuffling, which he says is not a good technology for making a deadlier bug ("*I* wouldn't know how to do it," he told me). And he points out that many natural pathogens are sufficiently dangerous for a terrorist's purposes. Stemmer emphasizes another illogicality in the objections to his antibiotic-resistance *E. coli* work: his experiment yielded a bug that could, he predicted, evolve naturally under the right conditions. Indeed, four years after Stemmer's *E. coli* paper appeared, another lab reported that it had found a remarkably similar antibiotic-resistant mutation in a patient with pneumonia who was taking an antibiotic closely related to the one he had worked with.

As this story demonstrates, the lines that separate natural and laboratory-made organisms are often blurry, and the distinction between natural and unnatural that looms so large in many people's concern about designer bugs may sometimes be a fiction. Most vaccines, after all, are designer bugs. They are deadly pathogens rendered harmless by scientific manipulation—and they have done more to improve public health than any single measure other than sanitation. This fact should inform our calculations of the threat posed by technologies or experiments that create designer bugs. But it rarely does.

The mousepox story likewise demonstrates that the man-made exotica of biology tend to stir up more fears than natural bugs that may be just as ominous. In 1997, four years before Jackson and Ramshaw published their data in the *Journal of Virology*, a group of researchers from New Zealand and Australia reported in the same journal an astounding finding regarding another relative of smallpox, a virus called Orf. Primarily found in sheep and goats, Orf appears to have picked up a sheep gene that codes for a protein that resembles interleukin-10, a close relative of IL-4 that tilts the immune system's seesaw in similar ways. In other words, nature had already performed an experiment similar to the mousepox–IL-4 study. But outside the small circle of pox virologists, the published de-

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BARDO

... dark wide realm where we walk
with everyone.
—Thom Gunn

Dangerously frail is what his hand was like
when he showed up at our house,
three or four days after his death
and stood at the foot of our bed.

Though we had expected him to appear
in some form, it was odd, the clarity
and precise decrepitude of his condition,
and how his hand, frail as it was,

lifted me from behind my head, up from the pillow,
so that no longer could I claim it was a dream,
nor deny that what your father wanted,
even with you sleeping next to me,

was to kiss me on the lips.
There was no refusing his anointing me
with what I was meant to bear of him
from where he was, present in the world,

a document loose from the archives
of form—not spectral, not corporeal—
in transit, though not between lives or bodies:
those lips on mine, then mine on yours.

—MICHAEL COLLIER

Michael Collier is the director of the Breadloaf Writers' Conference and a co-director of the creative-writing program at the University of Maryland. His fourth book of poems is The Ledge *(2000).*

scription of the Orf-IL-10 findings generated little attention.

Recent discoveries about influenza similarly highlight our tendency to fear the unnatural and the unknown over the natural and the familiar. The influenza virus—the cause of the common flu—rarely receives public attention as a potential bio-weapon. The political scientist John Steinbruner, a vice-chair of the arms-control committee of the U.S. National Academy of Sciences and a leading nonscientific voice about bio-weapons, has long wondered why influenza has been left out of discussions about bio-terrorism. "It's far and away the most dangerous thing out there," he says. Sergei Popov, a former Soviet bio-weapons scientist who defected to the United States, says that a genetically modified influenza was on the list of potential agents in the Soviet program. Influenza spreads at a faster rate than any other known virus, and immunity is largely strain-specific, which is why scientists must develop a new vaccine each year. Of particular danger are new strains—for example, the highly virulent 1997 Hong Kong flu—and strains that have not circulated for many years; the 1918 Spanish flu caused one of the worst epidemics in recorded history.

Four days before the September terrorist attacks the journal *Science* published two papers that offered new details about those strains. One explored the origins of the genetic changes that may have produced the Spanish flu. The other offered a detailed analysis of those that created the 1997 Hong Kong flu. The papers were accompanied by two editorial commentaries, neither of which mentioned the potential for bio-terrorists to exploit this information.

Because the National Institutes of Health had funded the work of the lead researcher in the study about the Hong Kong strain, a virologist at the University of Wisconsin at Madison named Yoshihiro Kawaoka, it issued a press release about Kawaoka's article. The headline read, "A SMALL GENETIC CHANGE MAKES FLU VIRUS DEADLY." Not a single news agency picked up on the bio-weapons implications of the release.

The lack of attention to influenza as a weapon has also surprised Adrian and Mark Gibbs (father and son), researchers at the Australian National University and the authors of the paper about the Spanish strain. I met with them recently in Mark's lab, which he shares with a dragonfly researcher; hundreds of dead specimens, each floating in its own jar, line the shelves. Mark told me that he finds it "very strange" that people have shown so little interest in influenza as a weapon. "When you think about it, it killed twenty to forty million people in two years," he said, referring to the 1918 strain. "And the world population was considerably smaller. So in proportionate terms it was a horrendous thing."

The Gibbses have deep reservations about a push within the community of influenza researchers to sequence and publish all the genes of the 1918 strain. "That is really dangerous stuff," Adrian says. "It is totally feasible to reconstruct that virus. And we know that if we got the sequence right, it would go." By which he means that the virus, if obtained by terrorists or accidentally released from a legitimate lab, would quickly infect people and spread, possibly killing millions.

The Gibbses and Kawaoka had no qualms about publishing their work, they told me, explaining that many technical and practical hurdles stand between this information and the ability to make weapons. Strictly speaking, they are right. But the same could be said about the mousepox experiment. The point is not that we have nothing to fear from terrorists' exploiting the mousepox–IL-4 experiment. Rather, it is that we should beware of letting exaggerations of potential man-made threats blind us to threats that may already exist, hidden in plain sight.

Directing Our Tangled Destinies

Until last November, D. A. Henderson, Frank Fenner's collaborator, directed the Center for Civilian Biodefense Studies at Johns Hopkins University, in Baltimore. After the anthrax attacks he accepted an appointment as director of the newly created Office of Public Health Preparedness, at the Department of Health and Human Services. Henderson well recognizes the threat posed by designer bugs. But he is a practical and blunt man who has studied these issues longer and harder than most, and he speaks with the certainty and inclemency of a soldier who has seen battle. "One can come up with all sorts of what-ifs," he says. "You can play the Armageddon game very easily. At this point we need to get ourselves prepared to deal with two biological agents: smallpox and anthrax. If we do that, we're going to be ready to deal with a lot of things."

The White House has budgeted nearly $6 billion over the next year to prepare for the threat of bio-terrorism. Henderson expects that we will soon have large stockpiles of vaccines and drugs. The budget also provides for intensive efforts to rebuild the country's decaying public-health system, increase surge capacity at hospitals, and improve the training of emergency-room staff. Funding for basic research will be sharply increased, which should have long-term payoffs such as better vaccines against potential bio-weapons and effective drugs against some diseases that, like smallpox, are currently untreatable. New systems are being installed to help hospitals improve their reporting of unusual diseases. And bio-sensors that can detect minute amounts of pathogens are under development.

Such measures will not, of course, guarantee that new biological weapons won't proliferate or that attacks won't occur. Some analysts therefore advocate a better Biological Weapons Convention—one with teeth. The nuclear truce of the past fifty years proves that negotiations (coupled with threats) can be effective.

In the long term, Henderson and others argue, even strengthening international agreements won't be as effective as simply helping the developing nations of the world. In this vein it is not hard to imagine that the very technolo-

gies that might lead to bio-terrorism might be used to reduce the threat of it. For instance, although the Canberra researchers abandoned the idea of making a sterilizing vaccine with mousepox plus IL-4, they may try to use it, or some version of it, to kill mice. "It probably could be developed to be one of the best rodenticides on the market," Bob Seamark says. "And using similar ingredients, you might develop one for rats." In that case the mousepox experiment might lead not to a nastier smallpox but to a means of increasing the food supply, and the prosperity, of millions of the world's poor—thus reducing one of the factors that may motivate terrorists. Sitting in his living room, enjoying a glass of whiskey at the end of a fine summer's day, Frank Fenner smiled broadly at the notion. "It's a lovely idea," he said, tinkling the ice in his glass. "It really is."

The National Museum of Australia, in Canberra, houses an exhibit called "Tangled Destinies," about the introduction of rabbits and other species and the attempts to control them. In one glass case rests an old syringe. Behind it a placard explains that in 1951, the year after the myxomatosis release, several people in Murray Valley, one of the affected regions, developed a swelling of the brain. This generated intense public fear that the two events were connected. Three Australian scientists, including Frank Fenner, injected themselves with myxomatosis to prove that they were not. (The culprit turned out to be encephalitis.)

The mistrust of science—the fear that people with an impenetrable language of their own are tinkering with things that are better left alone—has always run deep. In the best cases scientists have responded to this fear head on, encouraging discourse, publicly exploring the limits and the unknowns, and even, as Fenner did, occasionally putting their lives on the line to make a point. There is a growing sense among many biologists that they need to address more directly the issues raised by designer bugs. "From the earliest days of fission and fusion weapons there were physicists who were galvanized to political action," Steven Block says. "In the biological community you haven't seen this kind of response. Part of the reason is that there's been no single transcendent event like the Hiroshima bomb blast." September 11 and the subsequent anthrax attacks, he believes, might prove to be that trigger.

In 1975, amid escalating fears about the newly discovered ability of scientists to transfer DNA from one organism to another, biologists convened a now famous international gathering known as the Asilomar Conference, in Pacific Grove, California, and drew up guidelines for genetic engineering. Molecular biologists need to hold a similar meeting to discuss designer bugs. In the meantime, the National Academy of Sciences has begun selecting members for a committee to study the subject. Margaret Hamburg, an expert on bioweapons at the Nuclear Threat Initiative, a Washington-based nonprofit organization that is helping to fund the study, expects that the committee will debate whether it makes sense to restrict scientists' access to sensitive information like the genetic sequence of the 1918 influenza virus. She also hopes that it will discuss improving security in labs, where dangerous material is often kept in unlocked refrigerators, and where background checks on workers are rare.

Such discussions will undoubtedly lead to some useful recommendations. But they are not enough. In the end, scientists, policymakers, and the public should take a lesson from journalism: freedom of speech comes at a steep price, but it's well worth it.

Scientists and journalists have much in common. Both investigate subjects and report their findings, with little control over where those ideas will lead or what effect they will have on others. Both cherish independence of thought. Both grimace at the muck that some of their colleagues put into print; but when the muck becomes dangerous (HIV doesn't cause AIDS; one race is inferior to another), counterbalances come into play, chiefly in the form of public criticism.

On occasion scientists and journalists withhold what they know. Scientists routinely do this if they have yet to file a patent application for a discovery. Journalists often omit troop locations and other sensitive details from their stories, for reasons of national security. But in such instances the decision to withhold is made by individuals or the institutions they work for. And so it should continue.

But if scientists do not stand up for themselves, the government will step in: indeed, it has begun to do so. In February, *The New York Times* revealed that the Bush Administration had quietly removed from public access thousands of long-available federal reports about germ warfare, and had begun drafting a new "information security" policy. White House science advisers have had exploratory discussions with the American Society for Microbiology, which publishes ten journals, including the *Journal of Virology*, about the possibility of withholding potentially dangerous articles, or at least excising details that would allow other labs to replicate the work described.

Mandating that review panels assess which scientific studies should be censored would reek of the way things worked in the former Soviet Union—and it would surely backfire. Such policies are ham-fisted and, in the end, counterproductive. Knowing the mousepox data, scientists can now work on fashioning vaccines and drugs to combat an enhanced version of smallpox, should it ever surface as a weapon. The experiment also crucially raised our awareness of the threats posed by designer bugs and garden-variety pathogens alike. On balance, then, the publication of the mousepox data and the intense discussions surrounding it have in all likelihood made the world a safer place.

Jon Cohen has written extensively about vaccines for Science *magazine. His story "The Hunt for the Origin of AIDS" appeared in the October 2000 issue of* The Atlantic. *He is the author of* Shots in the Dark: The Wayward Search for an AIDS Vaccine *(2001).*