

ATTACKING ANTHRAX

Promising new antibiotics, antidotes, and vaccines emerge

Anthrax stands apart in the rogue's gallery of bioterror diseases: the bacterial spores that cause it are relatively easy to acquire, mass-produce, and disseminate. They are extraordinarily lethal when inhaled, and antibiotic-resistant strains are easy to make. Moreover, as the five mail-attack deaths grimly demonstrated in 2001, modern medicine is powerless against late-stage anthrax, in which bacterial toxins cause deadly blood poisoning and organ damage.

"Biological weapons are the biggest national security threat facing the nation," says Tara O'Toole, director of the Center for Civilian Biodefense Strategies at Johns Hopkins University. Anthrax, she adds, is "a much more serious threat than smallpox. I think it's much easier to imagine terrorists getting hold of the bug, the technology, and disseminating anthrax than doing all this with smallpox."

But against these realities, significant progress is afoot. A host of rapidly emerging approaches promises to save lives in future anthrax attacks, whether on the battlefield or on the home front. New treatments that kill the bacterium—*Bacillus anthracis*—and deactivate the deadly toxins it produces should become available within the next year or two. And better vaccines are on the way to replace the 18-month-long vaccination regimen that is already standard for hundreds of thousands of military personnel.

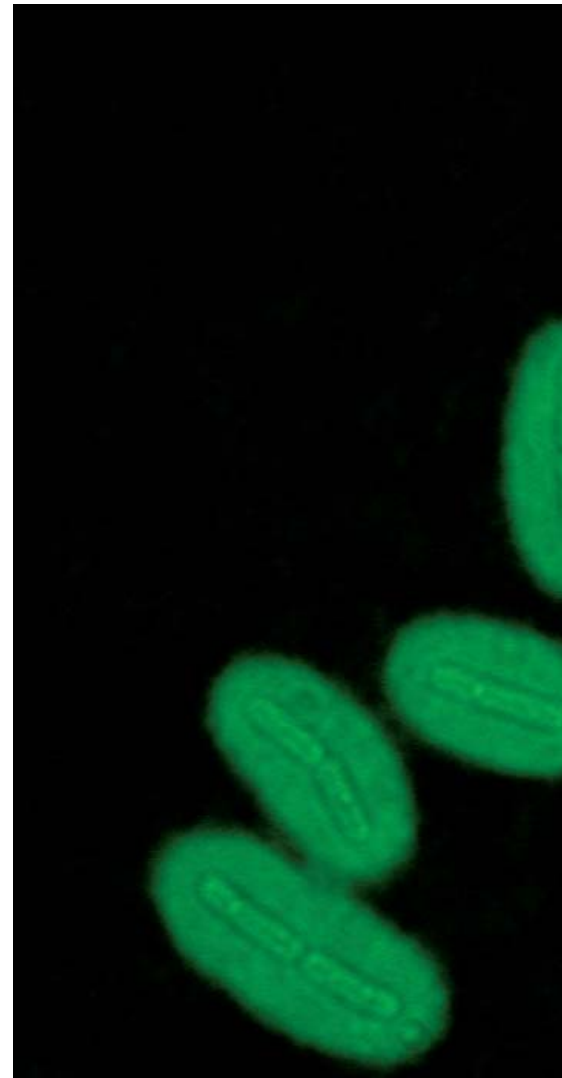
The first mission: combating antibiotic resistance. Anacor Pharmaceuticals in Palo Alto, CA, is developing a new class of antibiotics that block an enzyme certain bacteria—including *Bacillus anthracis*—need to replicate their DNA. Although the difference between this approach and the way some existing antibiotics work is subtle, it is significant enough to "increase the difficulty [for terrorists] by an order of magnitude," says Anacor CEO David Perry. That's because each new line of antibiotic attack makes it

less likely that the bugs will have evolved the means to escape or that rogue states or terrorists will have engineered the right type of resistance, he says. Anacor, which last year won a \$21.6 million grant from the U.S. Department of Defense to develop new compounds, has already started animal tests and expects to have drugs in human trials within three years.

Another antibiotic approach pits a virus against anthrax. Rockefeller University microbiologist Vincent Fischetti identified an enzyme from a virus that infects only anthrax-causing and closely related bacteria. In test-tube experiments, the enzyme kills about a hundred million bacteria in two minutes or less. "It drills a hole in the cell wall, and the organisms explode," Fischetti says. He adds that the treatment should boost the power of existing antibiotics against anthrax, as well as kill resistant strains of the bacteria. His group is currently performing animal experiments to test the enzyme further.

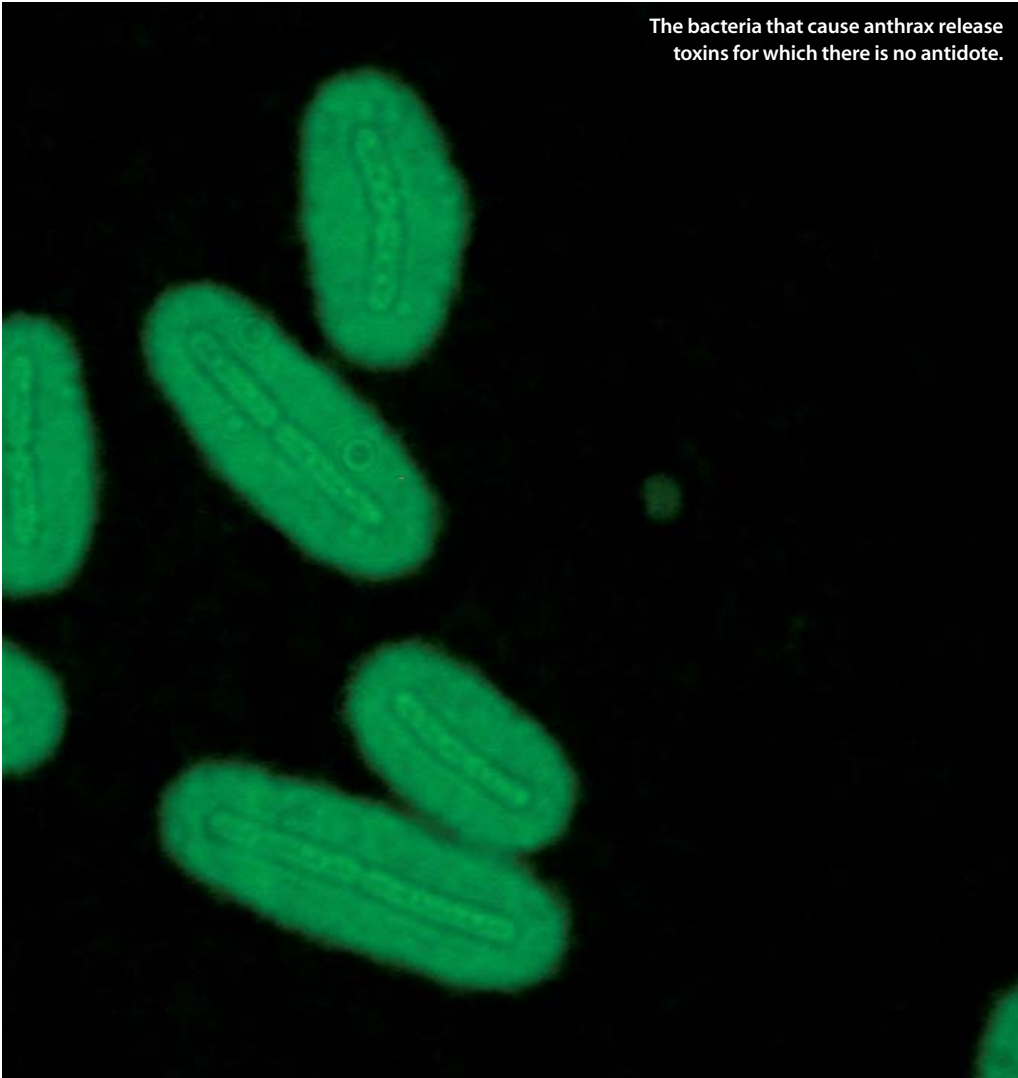
Such superantibiotics could play a critical role should an anthrax attack use an antibiotic-resistant strain. But what's needed most urgently is a treatment to counteract the potent toxins produced by *Bacillus anthracis*. These toxins attack the cells of those infected; in fact, researchers believe they are what killed the five anthrax victims in 2001, despite the patients' treatment with powerful antibiotics. Experimental anthrax infections in monkeys show that "there comes a point of no return," says Michael Mourez, who, as a postdoc in biochemist R. John Collier's lab at Harvard Medical School, studied anthrax toxin. "You can treat the animal and get rid of the bacteria, and yet the disease will progress towards death."

Collier's group has developed several molecules that effectively protect animals against the toxins. Rats typically die within 90 minutes of being injected with anthrax toxin. If the rodents are given one of these antidotes, however, they survive. Even before the 2001 attacks, Collier



had formed PharmAthene, a Potomac, MD-based company, to develop one such antidote into a drug. The treatment the company is testing is a mutant version of one of the proteins that make up the toxin; it binds to the other components to prevent the formation of active toxin. This protein could act as both a vaccine and a drug. If testing goes well, Collier anticipates that the treatment may be available in limited quantities next year.

That's an optimistic timetable: drug development typically takes 10 years. But Collier may well meet his goal because last year the U.S. Food and Drug Administration moved to speed approval of treatments that improve the nation's readiness to respond to bioterrorism.



The bacteria that cause anthrax release toxins for which there is no antidote.

Modern medicine is powerless against the late stages of anthrax. But urgent research efforts are yielding new ways to kill the bacterium and neutralize its deadly toxins.

Rather than undergoing the usual extensive preclinical animal testing and three-phase human trials to establish drug safety and efficacy, treatments such as Anacor's, Fischetti's, and PharmAthene's will have only to demonstrate effectiveness in two different animal models and safety in one human trial.

Improved vaccines are also critical. Current anthrax vaccines are safe and effective, but for full protection, recipients require six doses over 18 months, a delay that could be costly for military troops

who will be the main beneficiaries of any new vaccines. But fast-acting vaccines could also allow civilians to live or work in contaminated areas after an attack. The anthrax spore is difficult to destroy: even now, the Washington, DC, postal facility that handled two contaminated letters in 2001 remains shut down.

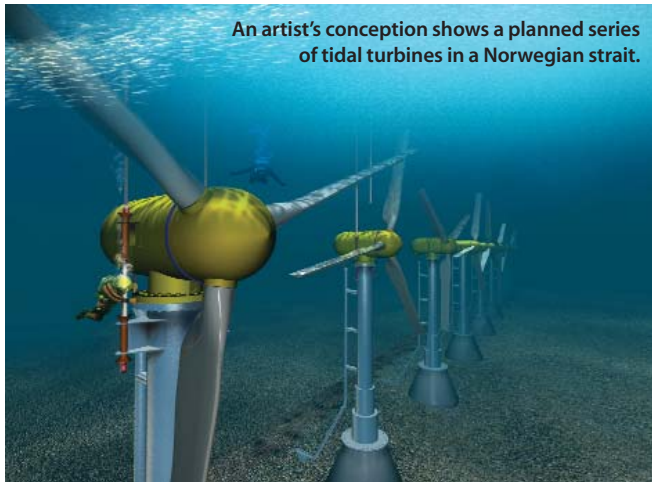
In an effort to reduce both the number of doses and the time needed to protect people from anthrax, researchers at Frederick, MD-based DynPort Vaccine and Avant Immunotherapeutics in Need-

ham, MA, have developed a vaccine they hope will induce protective antibodies more quickly. The current vaccine is basically a "soup" of bacterial cell parts; the new vaccine comprises only protective antigen, the same toxin subunit on which Collier's treatment is based. This specificity should help avoid side effects while speeding the body's immune response. Clinical trials started in October 2002.

Avant plans to go even further. It recently received a government subcontract to create a single-dose oral vaccine that will shield against both anthrax and plague, a flea-borne bacterial disease that could also be a bioweapon. Contracted through DynPort from the Defense Department's Joint Vaccine Acquisition Program, the project's costs may exceed \$8 million over two years. "This isn't just a research idea," says Una S. Ryan, Avant's president and CEO. "It's pretty well down the development line."

To start making this vaccine, Avant's scientists have removed disease-causing genes from cholera and salmonella bacteria. They plan to insert genes that code for proteins made by anthrax- and plague-causing bacteria. The resulting proteins should prompt the body to produce disease-fighting antibodies. "You'll get protection against cholera, anthrax, and plague with one swig-and-go," says Ryan. Avant's plans call for beginning human tests of this vaccine within two years, she adds.

Indeed, more effective vaccines and treatments for anthrax won't be the only payoffs from the current surge of bioterror defense research. Anacor's new antibiotics, for example, should work not only against anthrax and other bioweapons, but also against such common diseases as pneumonia and bacterial meningitis and staph infections. "All this money is not only going to be useful for biowarfare organisms," Fischetti says. "It's going to be a real shot in the arm for how we deal with infectious diseases." But even without such medical windfalls, these new treatments for anthrax will help build much-needed defenses against this major bioterror threat. —Erika Jonietz



An artist's conception shows a planned series of tidal turbines in a Norwegian strait.

TAPPING THE TIDES

First “underwater windmill” hitting the grid

ENERGY | A handful of tidal-power plants dot the world, and most of them are sprawling facilities that impound incoming water in estuaries, block shipping, and disrupt marine life. But 50 meters under the sea, at the bottom of a remote Norwegian strait, the world's first unobtrusive, grid-connected “watermill” will soon produce power for the world's northernmost town.

It looks like a wind turbine, except it's anchored to the seabed. Tidal currents moving at 2.5 meters per second spin three 10-meter fiberglass blades, generating power that is sent to the grid via a cable. When the tide turns, the blades twist 180

degrees, reversing the direction of the watermill's rotation. Electricity from the 200-ton apparatus is expected to hit the grid this spring, providing enough power for between 40 and 50 houses. “This is the first mill-type system hooked up to the grid,” says Anthony Jones, a San Francisco-based ocean-energy consultant. “I'm betting that they'll be quite successful.”

That's partly because Hammerfest Strom, the company behind the project, tapped ocean-engineering expertise from partners that include Zurich, Switzerland-based ABB and Statoil in Stavanger, Norway. Project leader Bjorn Bekken says a modular design allows replacement of broken parts, while redundant hydraulics and control systems should minimize service calls. Eventually, repairs will be performed by remotely operated vehicles similar to those used on offshore oil platforms.

The prototype is the first and smallest of 20 mills slated for the Kvalsund Strait—near the town of Hammerfest, 1,360 kilometers north of Oslo. They will supply enough power for 800 to 1,000 houses within a few years. Although it is twice as costly as wind power right now, “the watermill has just started its development, and I think it will be competitive with the windmill within 10 years,” says Ole G. Dahlhaug, an engineer at the Norwegian University of Science and Technology in Trondheim, Norway.

Hammerfest Strom isn't the only company aiming to build watermills. Hampshire, England-based Marine Current Turbine plans to install a prototype watermill just beneath the waves off the coast of Lynmouth, England, by early summer. Together, these efforts could turn the tide for this renewable power source. —*Steve Mollman*

NEW VEIN FOR SKIN GRAFTS

BIOTECH | Replacement skin could save the lives of severely burned patients and spare them from painful skin-graft-harvesting operations. But today's “artificial skin” products are used only as temporary dressings for wounds, not permanent grafts for burns, in part because they're made without something vital to the survival of skin grafts—blood vessels. A handful of researchers are working to change that.

One method combines several types of cells with genetic engineering. Yale University dermatologist Jeffrey Schechner starts with dermis—the skin's bottom layer—from organ donors. He strips cells from this tissue and adds keratinocytes—the cells that make up the top layer of skin—from the foreskins of circumcised baby boys. Next he adds endothelial cells that come from the lining of veins in umbilical cords and have been genetically engineered to produce a growth-promoting protein.

These cells multiply and line the channels left by the dermis's original blood vessels.

All this may sound a bit ghastly, but it seems to work as Schechner described last spring at the annual meeting of the Society for Investigative Dermatology. Schechner grafted the new skin onto the back of a mouse, and two weeks later he found red blood cells in the channels of the graft—an indication that the mouse's blood vessels had linked with the synthetic ones. Schechner is now fine-tuning his system.

One issue: how to ensure that a graft doesn't trigger an immune reaction. “Endothelial cells are extremely immunogenic—they're one of the main targets of rejection in organ transplantation,” says François Auger, director of the Laboratory of Experimental Tissue Engineering at Canada's Laval University. Researchers at Laval and at Shriners Burns Hospital in Cincinnati plan to use patients' own cells,



This engineered skin includes blood vessels.

multiplied in the lab, to grow skin. The Shriners team seeds the cells on a fabric-like collagen scaffold. The Laval group coaxes the cells to secrete the proteins necessary to build their own scaffolding.

It will be at least a year before any of these new skins is ready for human testing. But given that burns each year hospitalize 45,000 people in the United States and kill hundreds of thousands worldwide, successful approaches could mean less pain and save more lives. —*Rebecca Zacks*

COURTESY OF JEFFREY SCHECHNER (SKIN); COURTESY OF TORGEIR AUNE (TIDES)



A MORE ANONYMOUS INTERNET

ENCRYPTION | Identity theft and credit card fraud are surging international problems, fueled partly by the need to reveal credit card and Social Security numbers in the course of common Internet transactions. Although most businesses immediately encrypt such numbers, researchers at IBM's Zurich Research Laboratory and elsewhere are devising ways to avoid having to submit the numbers in the first place.

IBM calls its solution Idemix. The software could, for example, allow you to prove to online merchants that you have a valid credit card with certain spending limits, without actually entering the card number. The software starts by enabling you to get an anonymous digital credential from the bank that issued your credit card. This credential contains a pseudonym you choose, the credit card number and its expiration date, and encoded data from the bank that helps verify the credential later.

Then, let's say you want to buy a Kenny G. disc online. The Idemix software in your PC sends information encrypted in the credential to the online music store, informing it that you have a valid credit card. At the store's payment center, another part of the Idemix software reads that information. It uses cryptographic algorithms to confirm bank authorizations and spending limits and to collect payment—all without knowing your actual card number. "This set of techniques is really out in front," says Ronald Rivest, a computer scientist at MIT and a coinventor of a widely used encryption algorithm. Idemix changes the encrypted version of your credential each time you use it, making it harder for Web sites to track your habits.

Just as banks could issue anonymous credentials, so too could government agencies that issue driver's licenses, Social Security numbers, and other forms of identification. Consider car rentals: an anonymous credential could allow you to prove you are a licensed driver without your having to hand over your actual license. IBM already has prototypes running and could have a version ready for market in one to two years, says Jan Camenisch, lead cryptographer of the Idemix project in Zurich.

Of course, IBM isn't the only company trying to provide secure e-commerce. Credentica of Montreal, Quebec, is also working to commercialize digital credentials for broader applications. And many academic and corporate research groups are pursuing strategies for more anonymity on the Internet. There's good reason for all this research: last year, according to the Federal Trade Commission, 162,000 identities were stolen in the United States alone, and Internet fraud cost consumers more than \$122 million. And someone out there knows you love Kenny G. —Tracy Staedter

SPACE REPAIRMAN

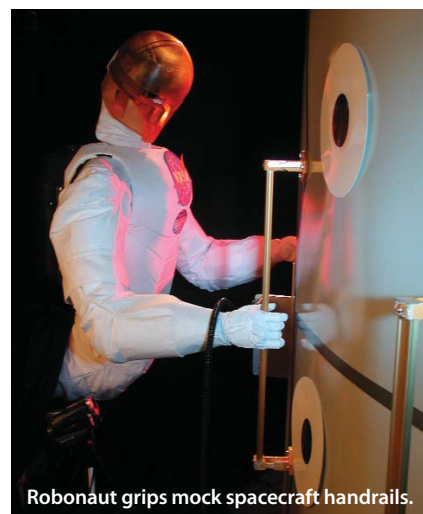
ROBOTICS | Although the events that doomed the space shuttle Columbia may never be fully understood, investigators have focused on damage to thermal tiles inaccessible to the astronauts. In the future, says Robert Ambrose at NASA's Johnson Space Center in Houston, crews on the International Space Station or a shuttle might include a robotic repairman.

NASA's "Robonaut" is getting close to realizing that vision. With its human-size palm, four fingers, and an opposable thumb, Robonaut is "phenomenally dexterous," says Alan Peters, a researcher at Vanderbilt University's Center for Intelligent Systems. "It has the best hands of any robot on the planet." This allows Robonaut to use wrenches and other hand tools.

Currently, sensors on a human operator's body translate the operator's movements into the robot's actions. The human sees what Robonaut "sees," thanks to cameras mounted in the robot's head. But mechanical engineer Marcia O'Malley at Rice University is developing a sleeve containing tactile vibrators that will enable the operator also to feel what the robot "feels." The payoff: more accurate control.

This tactile dimension might also let Robonaut learn what jobs should feel like, Ambrose says. This could help the robot become fully autonomous, a goal of research collaborators at the University of Southern California. Robonaut could be headed for space in three years.

—Gregory T. Huang



Robonaut grips mock spacecraft handrails.



A Thales center in Aberdeen, Scotland, beams out corrected satellite-derived location signals.

FIXING THE LOCATION FIX

Ten-centimeter GPS resolution is quite close to being here

SOFTWARE | Hikers and drivers who use satellite-derived location information may not need to know their latitude and longitude down to the decimeter. But phone company workers digging near fiber-optic cables, drillers working on offshore oil-and-gas rigs, and farmers tracking crops row by row do need that kind of accuracy. Right now, though, they depend on expensive, localized ground-based reference-and-correction systems to get high precision from the 24 satellites of the Global Positioning System (GPS), run by the U.S. Department of Defense.

That's about to change. Thales, the French aerospace giant, says it has developed the first GPS-correction service that's accurate to within 10 centimeters virtually everywhere on the planet—compared to the one-meter precision guaranteed by similar existing services. "This makes something that was once very difficult much easier, because you won't need expensive equipment," says Andrew Barrows, president and founder of

Thales double-checks the coordinates reported by the satellites. Then it corrects for atmospheric disturbances that might alter signals' travel time and for known errors within the clocks aboard each satellite. Finally, the company maintains 85 ground-based reference stations worldwide. The correct coordinates of these fixed stations are known, and they are continually compared against the coordinates reported by GPS. By this summer, Thales expects to beam ultracorrected GPS signals from outposts in Singapore and Aberdeen, Scotland, to paying customers.

The system will help farmers spread seed and fertilizer only where needed and even track individual plants for research. The technology should be a special boon for offshore oil-and-gas drilling industries, which need precise information to map their work locations and can't install fixed-reference stations at sea. And it could help utilities map existing rights of way and workers dig without disturbing buried cables.—*David Talbot*

MACHINING MELODIES

ARTIFICIAL INTELLIGENCE | The marriage of computers and music has spawned digital instruments that sound "real," an interface—the musical-instrument digital interface—that's now an industry mainstay, and composition software that helps generate ideas, assemble phrases, and analyze existing works.

But now machines are actually learning to compose music of their own. Eduardo Miranda at England's University of Plymouth has developed software that generates music from scratch. Other composition software tools rely on high-level mathematical rules, but Miranda's approach is "bottom-up," he says. His software, which grew out of his research at the Sony Com-

puter Science Lab in Paris, France, adapts ideas from the field of artificial intelligence to create a sort of virtual orchestra. Ten "players" get together and generate simple sequences of musical notes. Each player is programmed to listen, evaluate, imitate,



and generate variations. After running for a few days, the artificial society produces haunting melodic streams.

These melodies are still ploddingly crude. "This is a beginning to getting a computer to create something new," Miranda says. The next step, he adds, is to evolve rhythms and dynamics.

It's too soon to say whether creative machines will supplant their flesh-and-blood counterparts, but "the technology is here," says Rodney Waschka II, a North Carolina State University researcher. Initially, such technology will help human composers by speeding the process and providing new ideas. In the long run, boy bands beware.—*Gregory T. Huang*

JAMES YANG (ILLUSTRATION); COURTESY OF THALES (FIXING THE LOCATION)