serve as a disincentive and help explain why so few companies are in the business.

Orenstein disagrees. Besides guaranteeing a large marketplace and a fair price, he says, the government creates huge markets for products it endorses, such as the new pneumococcal vaccine required of all school-age children. As for the influence of price caps, Orenstein notes that the 1993 program set limits only for existing vaccines—but that shortages have also occurred with newer ones that had no price controls.

One cost-free tactic that won widespread support at last month's meeting was greater communication among everyone involved. Shortages could be averted if manufacturers gave their competitors better advance warning before dropping a product, says Aventis's Pisano, or if the government were allowed to share confidential supply information with the private sector.

Confronted with the obvious failure of market mechanisms, some have long favored a radical overhaul of the system. The current crisis, coupled with the increased concerns about bioterrorism following 11 September, have revived a 1993 proposal by the Institute of Medicine (IOM) for a National Vaccine Authority that has at its center a government-owned vaccine manufacturing plant. The authority would oversee production and distribution of all vaccines, monitor supply and demand, and fill in gaps with government-made products. "We are not talking about competing with the private sector," stresses IOM president Kenneth Shine at the meeting. Senators Edward Kennedy (D–MA) and William Frist (R–TN) and other lawmakers have shown serious interest in the idea, which is widely opposed by industry representatives.

Instead, companies would prefer tax incentives, especially to refurbish manufacturing plants for older and cheaper "commodity" vaccines. The federal government, for example, pays 15 cents a dose for diphtheria-tetanus vaccine, whereas the new pneumococcal vaccine sells for $58.75.

Companies need to be able to make money on vaccines, says Klein. He and others say the most pressing problem is convincing the public to pay a fair price for vaccines that can save millions of lives. "You have to be as willing to pay for DTaP as you are for Viagra," he says. Unfortunately, it may take a resurgence in vaccine-preventable diseases to drive home the importance of these critical medicines.

–JON COHEN

With reporting by Katie Greene.

PUBLIC HEALTH
SMALLPOX

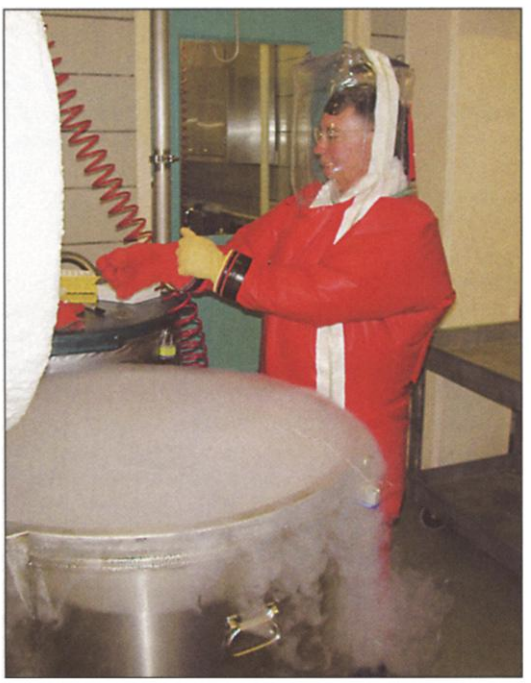
Dead Virus Walking

Smallpox, humankind's greatest scourge, was banished from the wild decades ago. New fears that bioterrorists may try to resurrect the virus have thrown two controversial research programs into high gear

KOLTSOVO, RUSSIA—Stalin's gulags have long since vanished from Siberia, but one remote outpost lays claim to the mantle of horror. The world's worst killers, among them Ebola, hantavirus, and Marburg, are kept here in a maximum-security facility, the State Research Center of Virology and Biotechnology. An urgent overhaul has turned this prison, better known as VECTOR, into a fortress. A new fence topped with razor wire encircles the lab complex, forming a no man's land between it and the old concrete wall. Entrance is via a checkpoint run by the military, but even that won't get you into VECTOR's inner sanctum. Only a handful of the staff can enter Building 6, wherein resides—Hannibal Lector–like—the most notorious inmate of all: smallpox.

During a millennia-long reign of terror, smallpox killed hundreds of millions of people before a concerted worldwide eradication campaign finally routed it in the late 1970s. The enormity of the public health threat is such that if smallpox were to escape from its cell here on the outskirts of Siberia's largest city, Novosibirsk, VECTOR would put in motion a government-approved plan to quarantine the 1.5 million inhabitants.

VECTOR is one of only two places on Earth where it is permitted to keep live smallpox virus, also known as variola. The other repository—the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta—guards its stock just as zealously. To access the virus storage, two CDC researchers have to enter the facility simultaneously with different keys. Armed security guards and cameras keep a close watch.



CREDIT: ROBERT O. BAKER/USAMRIID

Pandora's box? Peter Jahrling takes smallpox samples out of deep freeze.

Over the past few years, both labs have taken the virus out of the freezer for limited studies. And now, spurred on by the events of 11 September and the fear of new bioterrorist attacks, both labs are about to ramp up their research programs. Their goal: to develop modern-day diagnostics, safer vaccines, and new drugs against the disease.

The researchers are in a hurry, because the variola virus may not be long for this world. In January, the executive board of the World Health Organization (WHO) recommended giving the virus—which had been slated for destruction several times before—another stay of execution to allow researchers more time to study it (*Science*, 25 January, p. 598). "It's clear we cannot destroy the virus at this stage," declares virologist Antonio Alcami of the University of Cambridge, U.K., a mousepox expert and adviser to WHO's variola panel. But the decision to hold onto smallpox must be approved by the World Health Assembly (WHA) in May. Although nobody expects it, WHA could vote to proceed with the virus's scheduled destruction by the end of 2002. More likely, it may set a new deadline, say, 3 years from now.

That's why, starting later this month, CDC will devote one of its two maximum-containment laboratories exclusively to smallpox research, "for as long as it takes," says James LeDuc, who leads the studies. "That's a huge commit-

Is Live Smallpox Lurking in the Arctic?

KOLTSOVO, RUSSIA—The scene: the village of Pokhodsk, high above the Arctic Circle, on a muggy July day in 1991. A team of Russian bioweapons experts in blue respiratory suits enters a wooden vault full of 19th century smallpox victims mummified in the permafrost. More reminiscent of the *Blair Witch Project* than a scientific project, a homemade documentary—rarely shown outside a small circle of experts—follows the scientists from the VECTOR laboratory near Novosibirsk and their Yakutian colleagues as they wade through icy cold water into the chamber. In the dim light, several corpses come into view. Some are intact and beginning to thaw.

Worried that spring flooding might wash the remains into inhabited areas—and possibly resurrect the smallpox virus—authorities in Yakutsk had summoned the team to this nightmarish place near the Kolyma River. The camera zooms in as the researchers huddle around a mummified child half-submerged in thawing mud. They gently peel away a few layers of deerskin clothing to reveal blackened skin pocked with blemishes characteristic of smallpox pustules. As they cut into a wizened leg, liquid oozes from the spongy flesh. Some minutes later they finish their work and douse the tomb with disinfectant to try to prevent anyone else from carrying smallpox out with them—accidentally or otherwise.

Horror show. Team from VECTOR and Yakutsk inspects a corpse dug up from Siberian permafrost for signs of smallpox.

Back in the lab, VECTOR researchers said they failed to isolate live virus from the tomb samples. The pathogen may have been destroyed by severe temperature fluctuations, as the Pokhodsk victims had lain near enough to the surface to have thawed and refrozen numerous times. But that does not mean that smallpox cannot survive in frozen flesh. "I'm not sure if you would be able to recover infectious particles," says Antonio Alcami, a poxvirus expert at the University of Cambridge, U.K. "But it's not impossible."

Citing persistent rumors that rogue nations may have secret stashes of smallpox, Russia and the United States have argued for retaining the smallpox stocks—sanctioned by the World Health Organization (WHO)—to test improved vaccines and new drugs in the event that terrorists were to unleash the virus. "Undisclosed stocks are the biggest threat," says VECTOR virologist Elena Ryabchikova. But experts also worry that a sophisticated terrorist team might follow VECTOR's lead and go smallpox hunting on the permafrost. A terrorist "would only need to find a little bit of live virus to be successful," notes Alcami. That's the urgent rationale for trying to discover whether the frozen ground might serve as a viral reservoir.

There are also purely scientific reasons for unearthing smallpox victims, argues Lev Sandakhchiev, VECTOR's director-general. During the 19th century, he says, Yakutia (now called the Sakha Republic) appears to have been ravaged by smallpox strains of extraordinary lethality. Comparing the genetic sequence of such a strain with the more recent strains in the WHO repositories might yield insights into which genes are most important for lethality and how smallpox strains have evolved, he says. "I don't know how much information you can get after 100 years; it depends on how much you could sequence," says Alcami. "But I do like evolutionary studies."

VECTOR wants to mount another expedition to look for frozen smallpox, but a price tag of roughly $200,000 means it must look for international partners. So far, Sandakhchiev has failed to entice the lab's main foreign benefactor, the U.S. government. One U.S. official puts a decidedly Cold War spin on VECTOR's arctic aspirations. Noting that in 1991 VECTOR was still receiving most of its funding from the Ministry of Defense, the official charges that the expedition may have had more than just scientific goals.

Sandakhchiev rejects that suggestion, insisting that the expedition was a quest for knowledge, not for an edge in bioweaponry. He also says that the Sakha government—not the military—footed the expedition's bills.

The bottom line is that "it's still quite possible that live smallpox exists in the permafrost," says VECTOR's Evgeny Belanov, who led the Pokhodsk expedition. That excites different feelings in different people. "I'll bet other countries might invest" in a reprise of the 1991 expedition, says the U.S. official, who nonetheless would prefer to see smallpox—live or dead—rest in peace in its icy tomb.

–R.S.

ment," notes Jonathan Tucker, a smallpox expert with the Monterey Institute of International Studies in Washington, D.C. At VECTOR, too, scientists are preparing for an intensive 3-year variola program that may receive a large chunk of its funding from the Russian government, augmenting the grants it receives for such work from the U.S. government.

The revved-up research effort is catching a fair share of flak. China and a handful of other countries frown on the U.S.-Russian monopoly on variola; they are expected to reiterate their desire to set a firm destruction date at WHA's May meeting. And vocal critics within the United States—many of them veterans of the battle to eradicate the disease—are lobbying the government to abandon the research. Pandora's box, they say, should remain closed (see p. 2005). Even CDC does not exude much enthusiasm about the project—if only because of the amount of maximum-security lab space it uses. "We were told to do it," says LeDuc, "and we're doing it to the best of our ability."

But many of the scientists involved see the new program as a breathtaking opportunity—a last-gasp chance to modernize the world's armory against this scourge. "Smallpox was eradicated before the modern era of molecular biology," says VECTOR's Nina Tikunova. "We have a chance to make great strides in the science of this disease."

On death row

The eradication of smallpox was one of the triumphs of 20th century public health. Once it was complete, every country that held stocks of variola either transferred them to central repositories in Russia and the United States or annihilated them. In the 1980s, a consensus emerged that even those last two stocks should be destroyed, so that the world could forever be free of smallpox. That plan has been intensely debated ever since.

Until the past few years, smallpox rarely made it out of the freezer at either

CREDIT: E. BELANOV/VECTOR

location. Exceptions occurred in the early 1990s, when researchers at CDC and the National Institutes of Health (NIH) sequenced the entire 186,000–base pair genome of a variola strain called Bangladesh-1975. Russian scientists did the same for another strain, India-1967, and then joined forces on a third strain from Brazil. They viewed their efforts as a prelude to the virus's destruction—an effort to at least save its genetic blueprint before the remaining vials were sterilized.

But that complacency was shattered in the early 1990s by a defector's revelations that the Soviet Union had developed a massive, illicit program to turn the smallpox virus into a weapon—raising questions about whether other countries, such as Iraq, Iran, or North Korea, have kept secret stashes of the virus as well. "Many countries studied smallpox before 1980, and at –20°C, it's easy to hold onto for decades," says VECTOR's Alexander Ilyichev.

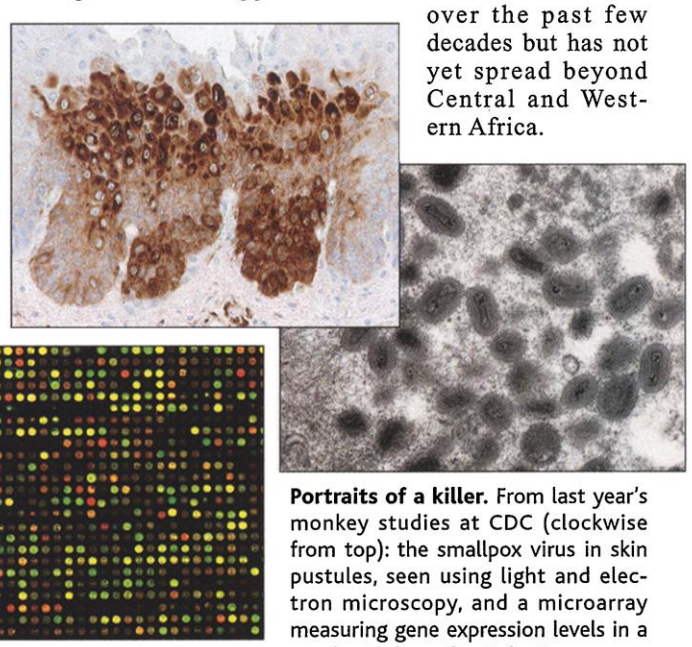
Such fears prompted the U.S. government to start a new research program in 1999. Overseen by WHO and guided by a 1999 Institute of Medicine report, the program essentially aims to bring smallpox research into the 21st century. While the virus was dormant in its freezers, advances in molecular biology revolutionized virology and immunology, and researchers developed powerful antiviral drugs and vaccines with fewer side effects. "We had a lot of catching up to do," LeDuc says.

CDC has a collection of 461 different virus isolates, saved from epidemics across the globe. Working with 45 of them, the CDC team has since developed several new diagnostics tests, including one based on the polymerase chain reaction, which can detect the virus directly by looking for its DNA. The researchers also started charting genetic diversity across the isolates to better understand the threat different strains may pose and sequenced the genomes of eight new isolates.

But to understand how the virus wreaks havoc in the body, researchers needed an animal model that mirrored the human disease. Creating one, however, proved dauntingly difficult. In mid-2001, a team from the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) in Fort Detrick, Maryland, finally succeeded. Working at the CDC lab in Atlanta, USAMRIID virologist Peter Jahrling managed to infect 14 cynomolgus monkeys, using one of two virulent strains and exposing the animals to extremely high doses, either by injection or by both injection and aerosol. All of the monkeys got sick and 12 of them died, most within 4 to 6 days.

Critics of the smallpox program are unimpressed with the model. They argue that its similarity to human smallpox—and hence its usefulness—is limited because the infection route was artificial and the animals died fast. Jahrling agrees that it needs to be "refined" to cause a more protracted disease, which he intends to do this year. Still, "the great success of Jahrling was to get reproducibility" of the disease, says Lev Sandakhchiev, VECTOR's director-general.

The USAMRIID team took large numbers of samples during and after the study, for instance measuring the levels of antibodies and other key molecules involved in the immune response, as well as virus levels in various organs. A group led by Stanford University's David Relman studied the expression levels of about 15,000 genes in the sick monkeys using DNA microarrays. Although he's still processing the data, "some striking stereotypic patterns are emerging," says Relman.



Portraits of a killer. From last year's monkey studies at CDC (clockwise from top): the smallpox virus in skin pustules, seen using light and electron microscopy, and a microarray measuring gene expression levels in a monkey 2 days after infection.

Inner sanctum. VECTOR's Building 6 is reserved exclusively for research on the smallpox virus.

CREDITS: (ABOVE, CLOCKWISE FROM TOP) MARK MARTINEZ/USAMRIID; THOMAS GEISBERT/USAMRIID; KATHLEEN RUBINS AND ADELINE WHITNEY

A void to be filled?

Turning their bioweapons expertise to peaceful research, VECTOR scientists have been busy as well. In 1991, VECTOR researchers led an expedition to a Siberian town to see whether 19th century smallpox victims interred in the permafrost might still harbor live virus (see p. 2002). And over the past few years, VECTOR's smallpox researchers have teamed up with their U.S. counterparts on several key projects. One concern they've probed together is whether the eradication of smallpox from the wild has created a void that other poxviruses might fill. The biggest perceived threat is monkeypox virus, which has triggered several outbreaks in humans over the past few decades but has not yet spread beyond Central and Western Africa.

A big question is whether monkeypox virus might mutate into a form that spreads more easily through the human population. To assess that potential, USAMRIID, CDC, NIH, and VECTOR jointly compared the genetic sequences of a monkeypox strain isolated in a 1996 outbreak in Zaire with the sequences of two smallpox strains. In *FEBS Letters* last November, they reported that although the central regions of the strains' genomes are "nearly identical," there were "considerable differences" at the ends of the genome where genes for virulence and its affinity for different hosts are located. These differences mean that monkeypox virus cannot evolve into a duplicate of smallpox virus, says Bernard Moss, an NIH poxvirus expert who collaborated on the study. "Of course, this does not rule out the possibility that monkeypox could better adapt in its own way to humans," he says.

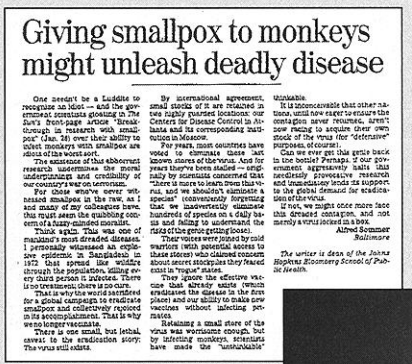
Vaccine revamp

In the new round of research planned for 2002, U.S. and Russian scientists hope to test new vaccines—provided they can make their animal model more realistic. The currently available smallpox vaccine

'Destructionists' Fight to Keep A Dream Alive

Seeing smallpox with your own eyes changes you forever, says Alfred Sommer: The agonizing death of the virus's victims instills a permanent hatred. That's why Sommer, dean of the Johns Hopkins School of Public Health in Baltimore, Maryland, admits that he went "berserk" last month after reading in a news article that a U.S. team had developed an animal model of smallpox by injecting monkeys with huge doses of the virus. Within minutes, Sommer had written an op-ed piece in which he labeled the research "abhorrent" and the scientists "idiots of the worst sort." Then he hit the 'Send' button.

His piece in the *Baltimore Sun* on 4 February was the latest flare-up in a long-running battle between destructionists—those who believe the last known stocks of the variola virus should be destroyed—and retentionists, who want to keep them around for study. Although the two sides have been at loggerheads for over a decade, Sommer's broadside was unusually harsh. "It was such a hysterical tirade," huffs one of the more visible retentionists, virologist Peter Jahrling of the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) in Fort Detrick, Maryland.



Giving smallpox to monkeys might unleash deadly disease

One needn't be a Luddite to recognize an idiot — and the government scientists gloating in *The Sun*'s front-page article "Breakthrough in research with smallpox" (Jan. 28) over their ability to infect monkeys with smallpox are idiots of the worst sort.

The existence of this abhorrent research undermines the moral underpinnings and credibility of our country's war on terrorism.

For those who've never witnessed smallpox in the raw, as I and many of my colleagues have, this must seem the quibbling concern of a fuzzy-minded moralist.

Think again. This was one of mankind's most dreaded diseases. I personally witnessed an explosive epidemic in Bangladesh in 1972 that spread like wildfire through the population, killing every third person it infected. There is no treatment; there is no cure.

That is why the world marshaled for a global campaign to eradicate smallpox and collectively rejoiced in its accomplishment. That is why we no longer vaccinate.

There is one small, but lethal, caveat to the eradication story: The virus still exists.

By international agreement, small stocks of it are retained in two highly guarded locations: our Centers for Disease Control in Atlanta and its corresponding institution in Moscow.

For years, most countries have voted to eliminate these last known stores of the virus. And for years they've been stalled — originally by scientists concerned that "there is more to learn from this virus, and we shouldn't eliminate a species" (conveniently forgetting that we inadvertently eliminate hundreds of species on a daily basis and failing to understand the risks of the genie getting loose).

Their voices were joined by cold warriors (with potential access to these stores) who claimed concern about secret stockpiles they feared exist in "rogue" states.

They ignore the effective vaccine that already exists (which eradicates the disease in the first place) and our ability to make new vaccines without infecting primates.

Retaining a small store of the virus was worrisome enough, but by infecting monkeys, scientists have made the "unthinkable" unthinkable.

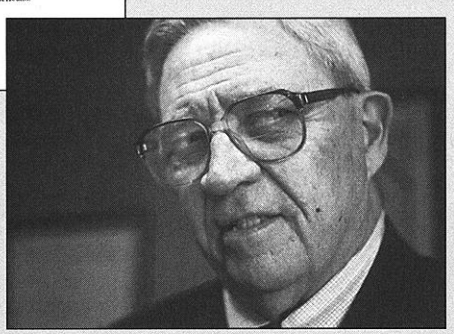
It is inconceivable that other nations, until now eager to ensure the contagion never reunites, aren't now racing to acquire their own stock of the virus (for "defensive" purposes, of course).

Can we ever get this genie back in the bottle? Perhaps, if our government aggressively halts this needlessly provocative research and translates lends its support to the global demand for eradication of the virus.

If not, we might once more face this dreaded contagion, and not merely a virus locked in a box.

Alfred Sommer
Baltimore

The writer is dean of the Johns Hopkins Bloomberg School of Public Health.



Virulent debate. Alfred Sommer's op-ed (*above*), and D. A. Henderson, former leading opponent of variola research.

Many in the destructionist camp, including Sommer, helped flush smallpox from its last hideouts in the 1970s. Their intention was to rid the planet of the virus once and for all. After smallpox vanished from the wild more than 2 decades ago, the last known lab preps of live virus were consolidated in the United States and the Soviet Union and slated for destruction. Recently, the World Health Organization (WHO) recommended postponing the virus's annihilation to enable an ambitious new research program to proceed (see main text). The latest developments, fueled by bioterrorism fears after last fall's attacks, have left destructionists deeply disillusioned.

Jahrling and others argue that keeping the variola virus is essential to get new candidate drugs and vaccines tested and approved. Both are vital, he says: Without antiviral drugs, doctors would be powerless to treat patients with advanced smallpox, should an outbreak occur; and the current vaccine puts people with weakened immune systems and eczema at risk of serious side effects. "I don't think we can just write off these groups," says USAMRIID's John Huggins.

Sommer, however, says that developing any new antiviral is a costly enterprise that's unlikely to succeed anytime soon. And he says vaccine safety concerns could be addressed in different ways—for instance, by finding drugs that quell side effects. Destroying the virus, he argues, would send a strong signal to any country with illicit stocks that holding smallpox in reserve as a possible weapon is morally repugnant. "The world would be a much safer place if we all decided we want to get rid of it, instead of playing with it," he says.

For now, however, the retentionist philosophy is carrying the day. The 11 September terrorist attacks have "muted the criticism of the research pretty substantially," says Jonathan Tucker of the Monterey Institute of International Studies in Washington, D.C. What's more, the destructionists recently saw one of their most formidable spokespeople decommissioned. Since joining the Bush Administration last fall to coordinate bioterrorism policy, D. A. Henderson, who led WHO's eradication effort and had argued aggressively for destruction, has hewed to the government's retentionist line—although few experts believe his private views have changed.

Henderson's comrades in arms are forging on without him. Sommer—who admits his op-ed was a "gut reaction" that he wishes he had given another read—has circulated a more circumspect petition among the 31 deans of U.S. schools of public health, calling on the government to proceed on the path to destruction. About half are likely to sign it, he says. Although the manifesto is unlikely to alter U.S. policy, Sommer acknowledges, sustaining the debate may help keep the virus on death row.

Jahrling, meanwhile, says he's bracing for more criticism, especially after he and others publish their latest results in the next couple of months. He insists he's not looking to pick a fight. "The less people are worried about what I'm doing, the better I like it," he says. "Just let me do my job."

–M.E.

is a very crude preparation of the vaccinia virus that can cause serious side effects, even death, especially in those with eczema or weakened immune systems. A huge new batch of vaccine, currently manufactured by a U.S.-British company called Acambis, is essentially the same vaccine, although produced using a different method, and it is expected to have the same problems. But several more weakened vaccinia strains might serve as a future alternative—if they can be shown to be protective.

The animal model could also be used to test new antiviral drugs against smallpox—or to treat serious side effects from the vaccine. One candidate developed is cidofovir, a drug already approved to treat cytomegalovirus infections in HIV-infected people. The drug works well in animal models with other poxviruses, but it has not been tried in smallpox. VECTOR, too, plans to test dozens of antiviral compounds against smallpox strains, first in cell culture and then possibly in monkeys. They will also continue characterizing the Russian smallpox collection and comparing it with the CDC strains. Examining differences between these strains, says VECTOR's top smallpox researcher, Sergei Shchelkunov, will aid in a Russian initiative to develop DNA microchips for rapid identification of the virus in the event of an outbreak.

Both centers must report periodically to WHO's variola committee. In a few years' time at the latest, that panel will decide whether the smallpox research effort has better equipped the world to deal with an outbreak. "My prediction is that there will be new arguments for retaining the stocks," says WHO adviser Alcami, such as pleas for additional time to develop promising antivirals. "They will never finish," he says. To some scientists who think that smallpox has long outlived its time on death row, that's a chilling thought.

–MARTIN ENSERINK AND RICHARD STONE

CREDITS: (TOP TO BOTTOM) *THE BALTIMORE SUN*; PETER VERMIJ