After months of ideological tugs-of-war over whether to vaccinate the public to protect against a bioterrorist attack, the Administration settled on a compromise that most scientists can live with

Rough-and-Tumble Behind Bush's Smallpox Policy

On the afternoon of Monday, 9 December, top public health officials met at Vice President Richard Cheney's residence for a crucial meeting to help hammer out the details of the Bush Administration's policy for smallpox vaccination. For some 7 months, a debate had raged within the Administration over how widely to distribute the vaccine. Now the scientists came armed with data they thought would, at long last, bring closure.

Without question, the decision to vaccinate against an eradicated virus required careful deliberations. The central issue: how to balance the known risks of the vaccine, which can injure and kill, against the unknown risk that rogue states or terrorists would use the smallpox virus as a weapon. Almost uniformly, the public health experts were opposed to immunizing the general public to protect against an uncertain attack. But there was strong support among some in the White House—and especially in the vice president's office—for widespread vaccination "pre-attack," in part because they questioned whether the Department of Health and Human Services (HHS) could halt an outbreak should a bioterrorist attack occur against a largely unvaccinated population.

Around the dining room table, HHS officials—including the heads of the Centers for Disease Control and Prevention (CDC) and the Office of Public Health Preparedness (OPHP)—unveiled a detailed plan to Cheney, his staff, and Homeland Security chief Tom Ridge on how an outbreak could be contained. If the unthinkable should happen, within 12 days highly coordinated public health teams would distribute millions of doses of vaccine, and disease detectives would fan out to find and isolate patients and vaccinate their contacts, derailing the virus before it could spread far beyond the initial victims.

By the end of the meeting, according to one participant, the scientists had convinced Administration officials that HHS's containment plan would work, leading them, at last, to a consensus that had eluded them to date. "Had we not reassured [Vice President] Cheney on that day that we really did know what we were talking about, I think the vaccine would have been offered more widely to the general public," says one scientist who attended the meeting.

Decision day. President George W. Bush—with HHS Secretary Tommy Thompson in the background—finally announced his vaccination policy on Friday, 13 December.

CREDIT: RON EDMONDS/AP

Four days later, on 13 December, President George W. Bush, with HHS officials at his side, announced the policy: immediate, mandatory vaccination of 500,000 military personnel and a voluntary campaign, to be completed by summer 2003, among a similar number of health care workers or "first responders"—those at highest risk of coming in contact with the virus. After that, the government would offer the vaccine to up to 10 million additional health care workers, police, firefighters, and other personnel deemed essential. Bush explicitly did not "recommend" that anyone beyond these groups receive the vaccine—indeed, he discouraged it by saying neither his family nor his staff would get it. If people "insisted" on being vaccinated, he said, the government would "work to accommodate" them.

Reaction in the public health community has largely been relief that mass vaccination was staved off. Ronald Atlas, for example, who heads the American Society for Microbiology and co-runs the Center for the Deterrence of Biowarfare and Bioterrorism at Kentucky's University of Louisville, calls the president's decision "prudent." Others, such as Tara O'Toole of the Center for Civilian Biodefense Strategies at Johns Hopkins University in Baltimore, Maryland, remain concerned that millions might still receive a live-virus vaccine that could pose a potential threat not only to themselves but also to others who come in contact with them. Extending vaccination to police and firefighters is unnecessarily risky, says O'Toole, because they're unlikely to encounter the virus.

To understand how the Bush Administration crafted its smallpox vaccination policy, *Science* spoke with several players in the tortuous negotiations. Experts entered with strongly held scientific concerns, but they quickly found that the issues went far beyond science. Public health officials found themselves wrestling with the traditional openness of scientific exchange versus the necessary secretiveness of intelligence data and a famously tight-lipped White House that, as one scientist close to the process said, "has a great concern for managing news." As making the difficult decision dragged on, one insider dubbed it "a soap opera."

Given the national security issues at stake and their close working relationships with the president and the vice president, many would speak candidly only if they remained unidentified. Most give the Administration credit for its willingness to dive into complex scientific issues, and several advisers came away impressed with

Treating Vaccine Reactions: Two Lifelines, But No Guarantees

The pictures are almost too gruesome to look at. Dozens of them, displayed in neat rows on an educational Web page* by the U.S. Centers for Disease Control and Prevention (CDC), remind viewers of the horrific side effects of the smallpox vaccine in a small minority of cases. Unfortunately, doctors will have only limited means to help such patients when the United States resumes vaccination. Although two treatments are recommended for vaccine complications, little hard evidence supports the efficacy of either one.

Like smallpox itself, complications from the vaccine—a live, replicating virus called vaccinia—were fading from memory until the terrorism threat brought them back. Most of the researchers who have witnessed these rare cases have retired or died, and most papers describing their work are more than 35 years old. Back then, expertise with the vaccine's side effects was concentrated at the University of Colorado Medical Center in Denver. There, a renowned pediatrician named Henry Kempe led a national reference center where patients—most of them children—were brought to be treated.

Kempe died in 1984, but his younger co-worker Vincent Fulginiti, now retired and living in Arizona, vividly remembers some of the children—especially those with progressive vaccinia, an uncontrollable and usually fatal infection, triggered by a malfunctioning immune system, that spread from the vaccination site. "The virus literally ate up their entire bodies," Fulginiti recalls.

In the 1950s, Kempe pioneered what is still the first line of defense for vaccine-induced disease: vaccinia immune globulin (VIG), a product made from the blood plasma of recently vaccinated people, which is high in antibodies against vaccinia. The United States has about 600 to 700 doses left from the 1960s, enough to treat the side effects expected when 4 million to 6 million people are vaccinated. But that cache is rapidly being supplemented with new VIG, produced by Cangene, a company in Winnipeg, Canada, and Dynport, a military contractor in Frederick, Maryland.

That's less reassuring than it sounds, because VIG is no wonder drug. Kempe became convinced early on of VIG's efficacy in treating some side effects, says Michael Lane, a former director of CDC's smallpox eradication unit, so he never carried out a controlled clinical trial. "He was a great clinician and a wonderful humanitarian but not a man of science," says Lane. In fairness to Kempe, Lane adds, there might not have been enough patients available for a rigorous trial. Instead, Kempe compared the fate of VIG-treated patients with historic data.

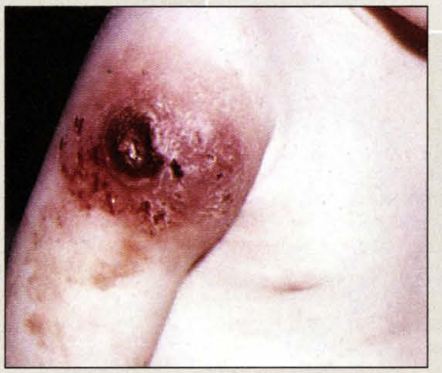
Those and other studies suggested that VIG worked well and reduced the death rate from eczema vaccinatum, an occasionally fatal complication in eczema patients, by as much as 70%. It also seemed beneficial in severe cases of generalized vaccinia, a pock-like rash that covers the body. But it rarely helped in progressive vaccinia, says Fulginiti, and it was useless against encephalitis. Anecdotal as they may be, such early experiences form the basis for today's treatment guidelines (see table).

Today's proposed dosing regimen is based on similarly soft data. In the 1960s, Fulginiti recalls, "we more or less went by the seat of our pants," starting out with 0.6 milliliters of VIG per kilogram of body weight and—absent improvement—ratcheting up to as much as 10 milliliters per kilogram.

In the past, VIG also has been used to prevent, rather than treat, side effects. In the Netherlands, for instance, adults routinely received a shot of VIG when they were vaccinated, after a 1962 trial suggested that this could cut the encephalitis rate by as much as 77%. (To mass-produce VIG, recalls former director Hans Cohen of the Dutch National Institute for Public Health, vaccinated military recruits were asked to donate plasma in return for "an afternoon off and a pancake.") But the Dutch had an unusually high encephalitis rate to begin with—perhaps because they used a more virulent vaccine strain—and little is known about VIG's ability to prevent other side effects. The United States has no plans to try a similar strategy today.

VACCINIA'S SIDE EFFECTS IN FIRST-TIME VACCINEES

	Frequency (per million)	VIG recommended?
Life-threatening		
Postvaccinial encephalitis	2.9–12.3	No
Eczema vaccinatum	10.4–38.5	Yes
Progressive vaccinia	0.9–1.5	Yes
Serious, non–life-threatening		
Inadvertent inoculation	25.4–529.2	Severe cases only; not in cornea infection
Generalized vaccinia	23.4–41.5	Severe cases only
Erythema multiforme	164.6	No



Bad reaction. Severe vaccinia side effects are rare but can be devastating, as in this 22-month-old boy.

If VIG doesn't work, CDC recommends an experimental antiviral drug called cidofovir. Cidofovir is already approved to treat cytomegalovirus infections of the retina in AIDS patients, so many hospitals have the drug on hand and doctors have some experience with it. In lab studies, cidofovir halts vaccinia's replication in the test tube and can save mice from otherwise lethal vaccinia infections.

But whether the mouse data are applicable to humans remains to be seen, because vaccinia gives mice a very severe pneumonia instead of the side effects seen in humans, says John Huggins of the U.S. Army Medical Research Institute of Infectious Diseases in Fort Detrick, Maryland. Good animal models for side effects such as progressive vaccinia and eczema vaccinatum don't exist and would be hard to develop, says Huggins. Cidofovir can also have severe side effects.

The bottom line, says Lane, is that sick vaccinees have two potential lifelines, but neither one offers any guarantees. That makes it all the more important to ensure that those with known risk factors, such as eczema or compromised immune systems, don't get the vaccine. Even with those precautions, as vaccination rates rise, so does the likelihood that Kempe's work will have a 21st century follow-up—and nobody's looking forward to it. **–M.E.**

SOURCE: CDC

* www.bt.cdc.gov/training/smallpoxvaccine

Cheney's grasp of the current data. "There was a complete lack of trying to bully public health officials," insists Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases (NIAID). And in the end, the White House arrived at a compromise that most of the scientists felt was, in Fauci's words, "reasonable."

Supply and demand

Fears of a smallpox attack erupted after 11 September and the subsequent anthrax attacks, but a public vaccination campaign was then not even on the agenda. The government had only about 15 million doses of an old vaccine called Dryvax on hand, so discussions focused on how to increase the supply—fast—to be prepared should an outbreak occur.

The tenor of the discussions changed last winter. Studies showed that some 85 million doses of another old vaccine donated to the government by Aventis Pasteur, the Franco-German pharmaceutical giant, remained potent. And government-sponsored scientists reported that even when diluted five or 10 times, Dryvax remained effective. From then on, there was enough vaccine to cover the entire country before a single case of smallpox even occurred, says HHS's Philip Russell, a special adviser on vaccines at OPHP.

The first indication of an ideological rift between the White House and HHS surfaced soon thereafter. In late winter, General Bruce Lawlor of the Office of Homeland Security, at policy-coordinating committee meetings that included top brass from different agencies, began to raise questions about how quickly HHS could vaccinate the public, sources say. Lawlor suggested that it made sense to immunize the public widely before an attack occurred. That would make an attack easier to contain, resulting in less panic and far less economic damage; vaccination might even preempt an attack altogether because a largely immune population would make an unattractive terrorist target. Donald A. Henderson, then head of OPHP (and now a key adviser to that office), was said to be "quite of-

Looking for Vaccines That Pack a Wallop Without the Side Effects

Like many pox researchers, Bert Jacobs of Arizona State University in Tempe believes it is "premature" to distribute the smallpox vaccine widely. The threat of an outbreak is uncertain, he points out, and dangerous side effects from the existing vaccine, which contains vaccinia virus, are all too real. Why not wait, he wonders, given that "we have the potential for alternatives, at least in advanced research, in the next couple of years."

Since the 11 September terrorist attacks, the quest for a safer smallpox vaccine has taken on a new urgency, drawing in a number of leading labs. (These efforts are in addition to the vaccinia already in production at Acambis, a U.S.–U.K. biotech company in both Cambridge, Massachusetts, and Cambridge, U.K. Scheduled to reach the market by 2004, the Acambis vaccine is not expected to be much safer than the existing one is.) Some researchers have dusted off experimental vaccines from the 1970s; others have turned to cutting-edge genetic approaches. "There are really exciting new ways to possibly immunize against smallpox," says Alfred Prince, head of virology at New York City's New York Blood Center, who collaborates with Jacobs. Among the new approaches:

Modified vaccinia Ankara. MVA is a weakened strain of vaccinia developed 40 years ago by Anton Mayr and colleagues at Munich University in Germany. The German researchers reported that by 1978, 120,000 people had received it without any serious side effects. Unlike garden-variety vaccinia, MVA cannot replicate in human cells, but this key safety feature means it may not generate a protective immune response. And MVA never received a real-world test in an actual smallpox outbreak. Researchers have a myriad of tests planned on monkeys and humans over the next several months. In one study, researchers will vaccinate monkeys and then "challenge" them with monkeypox, a simian virus akin to smallpox. A human study will compare vaccinia and MVA head to head, challenging with vaccinia and carefully assessing immune responses.

Weak in review. Can an old attenuated vaccinia called MVA safely protect against smallpox?

If the vaccine looks promising, the U.S. National Institute of Allergy and Infectious Diseases may contract for 30 million doses. Even if MVA does not produce an impressive immune response by itself, the earlier German studies suggest it might work as a prevaccine to blunt vaccinia's side effects. Bavarian Nordic, a German-Danish company headquartered in Copenhagen, has begun manufacturing the vaccine; it recently announced that it sold 1 million doses to the German army for that purpose.

LC16m8. This is another weakened vaccinia strain but, unlike MVA, it replicates in human cells. Developed at the Chiba Research Institute in Japan, LC16m8 caused few side effects when tested in 50,000 children in the 1970s. But some leading poxvirus researchers have serious reservations about LC16m8 because it doesn't go through the stage in the viral life cycle called extracellular enveloped virus, which produces the main protective antibody response in vaccinia.

"We're pushing a rapid research agenda into LC16 very hard," says Donald A. Henderson, a key biodefense adviser to the U.S. Department of Health and Human Services. With his help, VaxGen of Brisbane, California, recently struck a deal with Japan's Kaketsuken to start clinical trials of the vaccine.

Vaccinia-tetracycline combo. Paula Traktman, a poxvirus researcher at the Medical College of Wisconsin in Milwaukee, and her co-workers have genetically engineered vaccinia, stitching in a repressor that shuts down specific viral genes unless the antibiotic tetracycline is present. In theory, a person could take tetracycline and the vaccine simultaneously. If an adverse reaction occurred, stopping the drug immediately would shut down the vaccine virus. Traktman, in collaboration with Prince, is considering testing the idea in humans.

Engineered vaccinia mutants. Like Traktman, Jacobs genetically engineers various versions of vaccinia to study it. By mutating specific genes that control vaccinia's virulence, Jacobs and co-workers have created mutants that replicate well but, when injected into the brains of mice, seem much less likely to cause neurological damage. Clinical trials are a long way off, but a similar vaccine in humans might avoid the brain swelling caused by vaccinia, one of its most devastating side effects.

–JON COHEN

CREDIT: BAVARIAN NORDIC

fended" by Lawlor's arguments.

When *The New England Journal of Medicine* published the dilution studies on 25 April, the issue went public. In an accompanying editorial, William Bicknell, a former commissioner of the Massachusetts Department of Public Health, made the case for reducing the threat by allowing the public to receive the vaccine; in another article, Fauci called for "an open and public dialogue on the advantages and disadvantages of universal voluntary vaccination."

By then, a vociferous debate was already raging behind the scenes. Henderson, Russell, Fauci, and others urged the White House to move slowly in vaccinating the public, stressing that, short of convincing evidence that a smallpox attack was imminent, the benefits simply did not outweigh the risks.

The existing smallpox vaccine—a living, replicating virus called vaccinia—causes side effects ranging from minor to life threatening (see sidebar, p. 2313). Even with rigorous screening to rule out high-risk people, for each 1 million people vaccinated, between 49 and 935 are expected to suffer severe adverse reactions, and one or two will die. In addition to individual reactions, the vaccine virus can spread inadvertently to unimmunized persons, such as household members or colleagues, simply by rubbing the vaccination site. Because these people did not choose to be immunized and may be at higher risk of side effects, "it's not just about individual rights," as some libertarians argue, says O'Toole. "It's a societal issue."

Some also worried that the severe side effects could undermine public confidence in both the government's biodefense effort and vaccination in general. "Once the first two kids with progressive vaccinia are on TV, the public could decide that the government has no idea what it's talking about," says O'Toole.

Behind closed doors

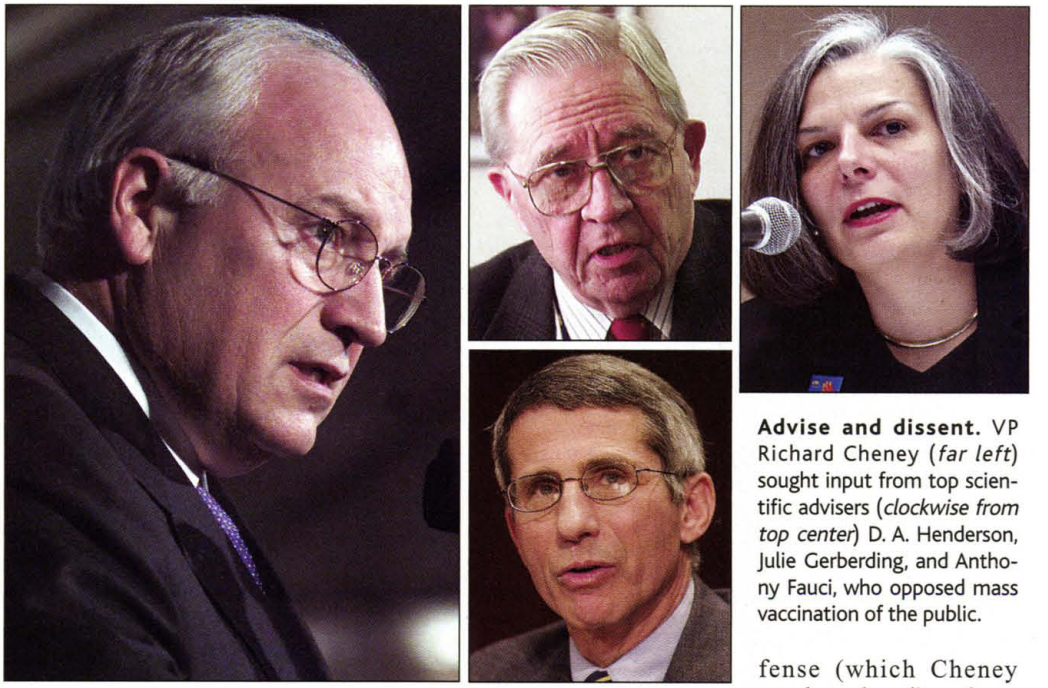
In June, CDC's Advisory Committee on Immunization Practices (ACIP) held a special meeting about the issue. After 2 days of intense debate, the panel recommended a cautious approach: vaccination of "smallpox response teams" that would investigate suspect cases, as well as a limited group of workers in a small number of hospitals specially designated to treat smallpox patients. That would result in, at most, 20,000 vaccinations, ACIP chair John Modlin told reporters after the meeting. The committee recommended against vaccinating the general population.

Within the Administration, this "minimalist" view initially seemed to prevail. On 18 July, Cheney and his staff invited the main players, including OPHP's new director, Jerome Hauer, Henderson, and their vaccination coordinator Russell, to a "surprise" visit at the CDC in Atlanta "to thank the frontline troops" for protecting the nation from bioterrorism. Aboard Air Force II, vaccination policy dominated the discussions. "I think we all walked away and said, 'very good meeting,' " recalls Henderson, who headed the World Health Organization's program that by 1977 had eradicated smallpox. "We finally got all the facts out. There was general unanimity that we have to move deliberately." To Henderson, that meant vaccinating the frontline responders at highest risk and leaving the public out of the equation. "From the beginning, I've had the feeling we were best off if we took one step at a time," Henderson says.

But over the summer, the mass-vaccination forces gained momentum. In hearings, op-ed pieces, and back-channel phone calls, Republican Senators Bill Frist, Arlen Specter, and Judd Gregg made the case that anyone who wanted the vaccine should have it. Cheney shared this opinion. According to several sources close to the process, Cheney's chief of staff, Lewis Libby, argued forcefully for widespread immunization. "There's little doubt [that] Libby is the driver," said one scientific adviser. Cheney staffer Carole Kuntz was also "very animated" about the issue.

Neither Libby nor Kuntz would speak to *Science*. Several sources ascribe their motives to the libertarian argument, described in an April report by the Cato Institute think tank, that the government has no business telling informed citizens that they cannot have a vaccine bought with tax dollars.

Another source cited the "Dark Winter" scenario, an exercise staged a year before, in which a simulated epidemic spiraled out of control after a smallpox release at shopping malls. Both Libby and Kuntz also have strong ties to the Department of Defense (which Cheney used to head), where pressure was mounting to "take that card from Saddam's deck" before an attack on Iraq. But the vice president also had on his staff voices of moderation, including Noreen Haynes, a physician at Johns Hopkins University. She and her husband Seth Carus, a bioterrorism expert at the National Defense University, were said to play an important role.



Advise and dissent. VP Richard Cheney (*far left*) sought input from top scientific advisers (*clockwise from top center*) D. A. Henderson, Julie Gerberding, and Anthony Fauci, who opposed mass vaccination of the public.

The debate ratcheted up in July, when the Monterey Institute of International Studies published a report suggesting that a smallpox outbreak in the former Soviet Union in 1971 had been caused by secret bioweapons tests on Vozrozhdeniye Island in the Aral Sea. The study offered the first, chilling evidence that smallpox could be successfully "aerosolized" and transported by the wind over many kilometers. Some saw this as another argument for widespread vaccination, especially because Russian authorities were unwilling to help study the incident or the virus strain.

Even so, insiders, including NIAID's Fauci, who had ties to Cheney and Bush as close as those of any scientist involved in the process, were caught off guard in

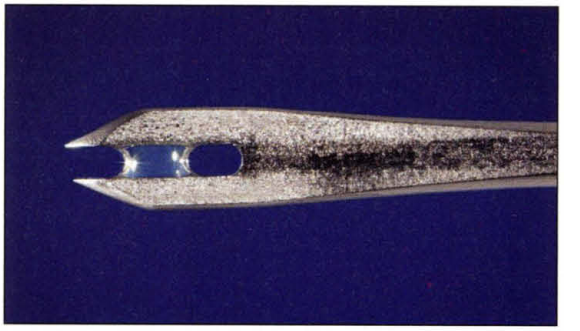
September, when the Associated Press reported that the Bush Administration planned to offer the vaccine to every American. Although the Administration denied that any decisions had been made, a 4 October press briefing in Washington, D.C., reinforced that perception. HHS officials outlined to reporters what indeed seemed to be a surprisingly broad vaccination policy. "Right now, our thinking is in favor of making vaccine available to the general public," said CDC director Julie Gerberding, although she and others again stressed that no policy had been decided. Indeed, behind the scenes, Gerberding was arguing forcefully for limiting vaccination. "[Gerberding] felt very adamant about this," says one source.

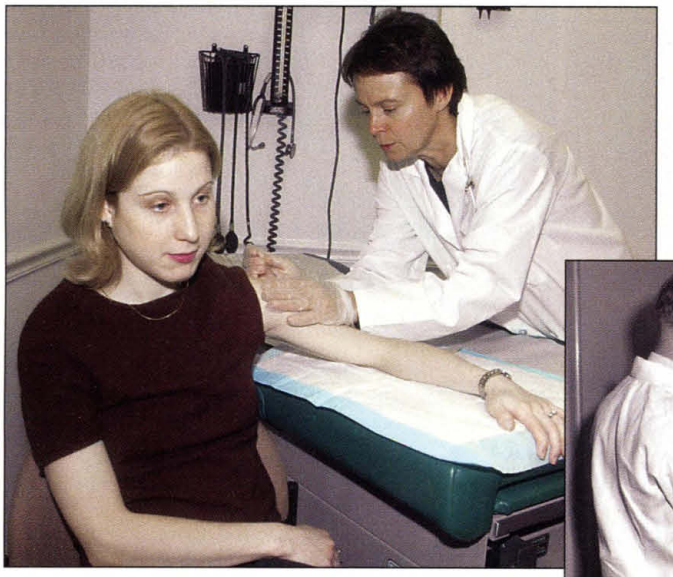
Later that month, ACIP met again to advise CDC on a number of specific questions, such as what types of workers to vaccinate at each hospital and how to bandage each person's vaccination site to prevent inadvertent spread. As part of those deliberations, ACIP significantly upped the number of frontline responders to be vaccinated. In a press conference, ACIP's Modlin said half a million might be the right number. (The lone dissenter was Paul Offit of the University of Pennsylvania School of Medicine in Philadelphia, who wanted to stick with the original recommendations.)

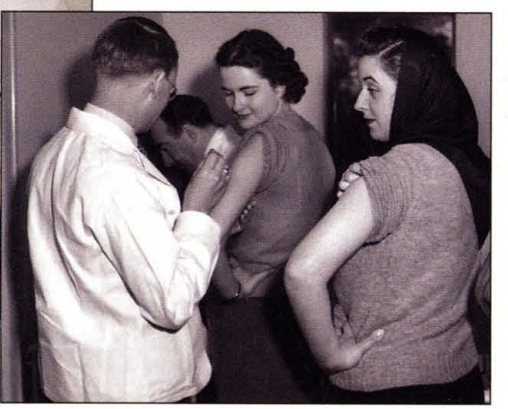
Some observers contend that the Administration pressured ACIP into toeing the party line. Others say the panel changed its mind to avoid a huge rift with the government policy that seemed to be shaping up. The new recommendations were "fairly careful waffling," says Michael Lane, a former director of CDC's smallpox eradication unit, who followed the discussions closely. "They wanted to accommodate the government, create a little wiggle room."

Not so, Modlin told *Science*. The numbers changed because since its June meeting, HHS had convinced the committee that the strategy of treating patients in a small number of "designated hospitals" would never work. Hospitals were reluctant to assume this responsibility, for fear that even one suspected case could lead all other patients to avoid them; they also thought that smallpox patients would simply show up at the nearest emergency room. So instead of just a couple of hospitals, HHS had argued, every acute-care hospital in the country had to prepare. "We accepted that," says Modlin.

Media attention was now riveted on the debate. News stories began appearing nearly every week, all indicating that the policy would extend far beyond the 500,000 that Modlin had mentioned. But despite predictions that a policy statement was imminent, Bush remained mum. Some top officials became frustrated by the delays. "This is complicated, but it's not that complicated," said one official. The University of Louisville's Atlas decided that the Administration was floating one trial balloon after another to see how they fared. "They're trying to do what they do during political campaigns," complained Atlas.







Déjà vu. Students at the University of Washington, Seattle, get vaccinated against smallpox in 1946 (*right*); Sharon Frey of the University of St. Louis vaccinates a grad student participating in a dilution study in November 2001 (*above*). Vaccinators still use the same bifurcated needle (*top of page*) as they did in the past.

CREDITS: (TOP TO BOTTOM) CDC; JAMES A. FINLEY/AP; *SEATTLE POST-INTELLIGENCER*/CORBIS

20/20?

To almost everyone's surprise, Bush finally revealed a few details about the policy in an interview with Barbara Walters on ABC's *20/20* program, snippets of which the network aired on Wednesday, 11 December. The president made clear that the general public could get the vaccine. First Lady Laura Bush added that she would be comfortable having her children vaccinated, a remark that seemingly signaled government support for general vaccination.

But in the official announcement 2 days later, Bush's tone was much different: This time, the message had been very carefully crafted. The government does not recommend widespread vaccination, he said, but for those who "insist" on receiving it, the government would develop ways to give them access. As Administration officials made clear later, this will be anything but easy. To get the vaccine right away, members of the public will have to enter clinical trials of the preparation, assuming they are eligible, and agree to potentially cumbersome follow-up studies. If more than 10,000 people—the number that can be accommodated in the trials—request the vaccine, HHS plans to organize special access to the Aventis Pasteur vaccine, which is not yet licensed, as an Investigational New Drug.

Still, shortly after the White House announcement ceremony, many at HHS rubbed the sweat off their brows. Fauci, who flanked the president during the announcement, said he was glad the Administration had chosen the option it did, but he still felt unsettled. "I'm not happy that we're dealing with a disease that so much effort was put into eradicating and that was such a public health triumph," said Fauci. "But the fact is, we do have to deal with it." And, he concluded, "if we do face the horrors of an attack, then we'll be very glad we went through this." As another high-ranking HHS official said, "Given the world situation, the uncertainty of the threat, the number of voices and noises out there, and the combination of public health and political considerations, this isn't a bad place to be."

–JON COHEN AND MARTIN ENSERINK