Leadership and money by themselves, of course, will not remove the largest obstacle that stands in the way of many of the most urgently needed vaccines: scientific unknowns. The vaccines at the top of today's scientific wish lists are often there because they're difficult to make. "The relatively easy ones we've solved," says polio vaccine developer Jonas Salk, who now is working on AIDS vaccines. With TB, HIV, RSV, and malaria, no researcher has yet demonstrated which immune responses provide protection. RSV and HIV vaccines lack good animal models. The protozoan that causes malaria has a complex life cycle, presenting the immune system with myriad challenges. HIV mutates rapidly to duck the immune system—and, potentially, any vaccine.

Salk believes one of the main scientific obstacles is that many scientists researching and developing vaccines "don't have a clue" what's required to make an effective vaccine. "It is chaos....There's going to be a need for more awareness not of the pathogen, but of the host," says Salk, who believes few vaccine makers focus on understanding the immune responses needed for protection.

A few points of light

Although the challenges of finding money, leadership, and scientific answers are daunting, there may be a few bright lights on the horizon. An International Vaccine Society, the first of its kind, was recently formed; Salk thinks the society "might provide some intellectual and scientific leadership." WHO's recent restructuring of its vaccine program aims to incorporate CVI; a meeting slated for 31 August in Geneva will specifically address the integration of CVI into WHO's existing vaccine programs. The Japanese recently launched a campaign to raise $100 million to support CVI, and, with help from the United Nations Development Fund, a new International Vaccine Institute, based in South Korea, is being set up to help countries in the region coordinate R&D for priority diseases.

The NVPO's Roy Widdus, director of the '80s IOM study, adds that the vaccine industry has been going through a rebirth in the last few years, as companies made money from sales of hepatitis B and *H. influenzae* vaccines. Start-up biotechnology companies also have become serious players in vaccine R&D. "There's a lot more interest from industry than there was in the mid-'80s," he says.

Those developments might help grease the vaccine machine and make the next decade a productive one for vaccinology. IOM, at NIAID's behest, also will convene a new committee soon to establish priorities for vaccine development once again. Perhaps this time around, more of the successes that appear "reasonably foreseeable" within the next decade will actually be seen.

–Jon Cohen

AIDS VACCINES

Are Researchers Racing Toward Success, Or Crawling?

In 1990, AIDS researchers and stock analysts hailed Repligen Corp., a Massachusetts biotechnology firm, as a leader—many said *the* leader—in the race to develop a vaccine against HIV. Not only was Repligen collaborating with top AIDS researchers and publishing impressive scientific papers, the start-up had won financial backing from pharmaceutical giant Merck & Co. A 1990 investors' guide from Shearson Lehman Hutton predicted that if human tests of the vaccine went well, Repligen and Merck might ask the U.S. Food and Drug Administration to license it as early as the end of 1994.

Fast forward to 19 July 1994. On that day, Repligen announced that, because of a "lack of available funding," it was axing its HIV vaccine research and development program. One way of interpreting this startling turnaround is to assume it's a normal development in a long-distance race; after all, the early leaders in the New York City marathon seldom stay the course. A more skeptical view, however, holds that there never was a "race" to make an AIDS vaccine.

That view may seem as surprising as Repligen's fade-out, but a growing number of AIDS researchers have come to this depressing conclusion. Jaap Goudsmit, a leading AIDS researcher at the University of Amsterdam, says of the alleged race, "I haven't seen it." Wayne Koff, former head of the AIDS vaccine program at the National Institute of Allergy and Infectious Diseases (NIAID), who is now developing an AIDS vaccine at New York's United Biomedical Inc., says the idea of a "race" is largely "a game" played at scientific meetings. "There's a lot of noise and a lot of posturing"—and little else, says Koff.

The reason pharmaceutical companies aren't pouring dollars and energy into AIDS vaccines the way they would into a hot new mood-elevating drug is simple: The AIDS vaccine market in developed countries is likely to be much smaller than early estimates indicated. As a result, only a handful of companies are committed to the search, mostly biotech start-ups. And most of these companies are taking the same narrow approach, which limits the chances of success, say Koff and Goudsmit.

Not everyone accepts this downbeat view. But even congenital optimists must have found it difficult to smile about the AIDS vaccine "race" in June, when two NIAID advisory panels decided that even the two most promising experimental vaccines are not ready for large-scale testing (*Science*, 24 June, p. 1839). NIAID director Anthony Fauci says the discussions by those panels "laid naked what a paltry effort" is being made to develop AIDS vaccines. "When all of the clothes get ripped away, what do we have?" asked Fauci.

Not a super market

Economics clearly isn't the only factor that is discouraging companies from entering the search for an AIDS vaccine. Another is the fact that the science is very tough. Animal models used to test AIDS vaccines have severe limitations; the genetic diversity of HIV may require an effective vaccine to be based on many viral strains; and no researcher has successfully demonstrated which immune responses correlate with protection from HIV.

ROCKEFELLER FOUNDATION

A rocky start. The Rockefeller Foundation invited these vaccine experts to Bellagio, Italy, where they criticized the way the search for an AIDS vaccine is being conducted.

Yet even with these high scientific hurdles, you might think the market for AIDS vaccines would have companies salivating. And early estimates did get their juices flowing. In Shearson Lehman's 1990 report, analysts estimated the market in the United States and Europe would include more than 67 million people, including homosexuals, intravenous drug users, health-care workers, prisoners, and college-age heterosexuals. If, on average, 15% to 20% of these people took a vaccine priced at $150, it could be a $1.6-billion-plus market.

Yet those estimates are rapidly deflating. In July the Rockefeller Foundation released a report, "Accelerating the Development of Preventive HIV Vaccines for the World,"

that portrays a much smaller AIDS vaccine market in the United States and Europe. The report recaps a 4-day meeting on AIDS vaccine development in Bellagio, Italy, held last March and attended by 24 influential AIDS researchers, public health officials, and representatives of philanthropic organizations. These invited experts said they thought heterosexuals in the industrial countries might not account for much of a market, because only "a very small proportion" consider themselves to be at risk of HIV infection. And they estimated that sexually active homosexuals (Shearson Lehman hadn't distinguished between sexually active and sexually inactive homosexuals) and intravenous drug users combined would total only 5 million, a far cry from the 37 million Shearson calculated for the same populations.

These financial and scientific uncertainties, coupled with fears of government regulation and lawsuits from people claiming to have been injured by vaccines, have let the steam out of the commercial search for an AIDS vaccine. "The investment community over the last 3 years has become increasingly disillusioned about AIDS vaccines," says Bellagio attendee Dennis Panicali, who heads Therion, a Massachusetts biotech company developing HIV vaccines. Adds AIDS vaccine researcher Dani Bolognesi of Duke University: "The perception out there is this stuff is so difficult and the likelihood of anything working is so slim that it's not worth it."

Those pessimistic views are reflected in the small amount industry is investing. The Bellagio report estimates industry invests less than $25 million a year worldwide in AIDS vaccine R&D. The U.S. government is by far the biggest contributor, spending $111 million, the lion's share of a global total of less than $160 million.

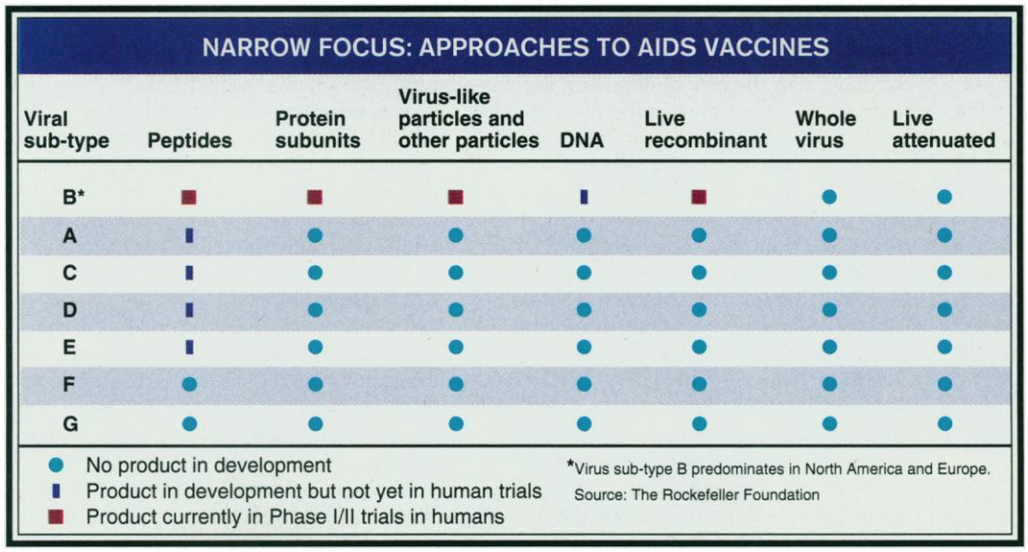
And much of the $25 million being spent by industry isn't coming from the pharmaceutical giants: Most of the dozen or so companies in the business are cash-strapped start-up biotech firms like Repligen. "The development has fallen on the shoulders of small biotechnology companies because no one else wants to do it," laments Therion's Panicali. Interestingly, several of these outfits, like Connecticut's MicroGeneSys Inc., have shifted their focus to HIV vaccines that aim to treat, rather than prevent, HIV infection.

Of the big-league companies like Merck that claim to be seriously involved, none, except France's Pasteur-Mérieux Serums and Vaccines, has an AIDS vaccine program that's visible to expert researchers. "It's hard to prove a negative, but the sense is [the large companies] are not doing much of anything," says Bellagio attendee Donald Burke, an Army colonel who heads the U.S. military's AIDS research program. Peter Piot, also at Bellagio, echoes Burke's concerns. "It's very disappointing," says Piot, an official at the World Health Organization's (WHO's) Global Programme on AIDS.

R. Gordon Douglas, president of Merck's vaccine division, rejects the perception that his company isn't working hard enough on an AIDS vaccine. "Our AIDS program, in total, is the largest research program Merck has ever committed to," says Douglas. "And that program has supported both vaccine research and anti-virals." Merck CEO Roy Vagelos recently testified to Congress that Merck has spent more than $359 million on its AIDS program to date, although he won't reveal how much has gone toward vaccines (as opposed to drugs for treating HIV disease).

Pasteur-Mérieux is a large company that is investing aggressively in AIDS vaccines, with four different approaches now being developed. "It may look a little strange," says Philippe Kourilsky, who heads research there, "but the spirit of Pasteur-Mérieux has not always been driven by profits." Public health, Kourilsky says, has always been a top priority of the Mérieux family and the Pasteur Institute, the company's parents. Pasteur-Mérieux was, however, recently taken over by the enormous Rhône-Poulenc, which may have different ideas. So far, though, Kourilsky says, Rhône-Poulenc has exerted "no pressure whatsoever" to rein in the program.

Two well-financed biotechs have also made a serious, high-profile investment in AIDS vaccine research: Genentech and Chiron (with its corporate partner Ciba-Geigy). But their interest could soon cool, say insiders, because it was their vaccines that were being considered for large-scale U.S. testing when NIAID pulled the plug in June. Genentech's Donald Francis says NIAID's decision infuriated management: "Almost with a spur-of-the-moment decision, [NIAID] pulled out of a partnership." Genentech, several sources say, is shopping for a business partner to share the cost of its AIDS vaccine program. Chiron's Dino Dina says the NIAID decision sent shock waves through his company. Management understands "commit, spend, and fail," Dina explains, but does not accept "commit, spend, commit, spend, and never get anywhere."



The gap

Even if only a few companies were searching for AIDS vaccines, they might have a reasonable chance of success if they were all taking unique approaches. But they aren't. As the Bellagio report pointed out, the AIDS vaccine enterprise has been "catering to the needs of the developed world," whose populace accounts for fewer than 10% of the world's new HIV infections. This, in turn, has led industry to focus on "a small number of the potential vaccine approaches" and created "important gaps" in ongoing research. Many observers argue that at least one of those gaps exists because some promising strategies were initially dismissed as old-fashioned and unsafe.

Most HIV vaccines developed to date—such as those made by Genentech, Chiron, MicroGeneSys, and Austria's Immuno—are genetically engineered versions of HIV's surface protein. These vaccines have the virtue of containing no HIV genetic material; they are perceived as safer than traditional viral vaccines, made by weakening or killing the virus.

While developed countries have little tolerance for any risk from an AIDS vaccine, that's not necessarily the case in countries with higher rates of infection, maintains the Bellagio report, and meeting participants "expressed concern" that riskier classical vaccine strategies aren't being "championed."

The University of Amsterdam's Goudsmit argues that this "'50s technology" is "the first thing that should have been done." (Therion is, to a limited degree, pursuing a live, attenuated HIV vaccine, and Immuno recently has begun developing a whole, killed one.)

Not only are most experimental vaccines taking the same genetically engineered approach, they are focusing on a single strain of the virus: the B subtype, which predominates in Europe and the United States, but not in the developing world. This focus may result in vaccines with little relevance to many of the poor countries where HIV is spreading rapidly. Although one immune response might protect against different genetic subtypes of HIV, Bellagio participants felt that vaccines would be more likely to work if they were based on the viruses found in the population where they are being tested. But until now, companies have been reluctant to make different vaccines for different populations. Their strategy is to prove they could protect against the B subtype and then, if necessary, make vaccines from other subtypes. Epidemiologist John McNeil of the Walter Reed Army Institute of Research says that when he and his colleagues gave several companies HIV strains from Thailand hoping someone would make a vaccine, "for the first 18 months to 2 years, we basically didn't have anyone who was willing to do anything."

The real race

As story after story like McNeil's piles up, those in the field are discovering that the race for an AIDS vaccine is really a crawl. The Rockefeller Foundation's Seth Berkley, an internist and epidemiologist who organized the Bellagio meeting, says that not long ago, he thought the AIDS vaccine search was on track. "I had assumed—and I feel like a fool to say this—that the vaccine effort was taken care of and that everything was going great. But as I began to look at it closely, I saw that the vaccine effort was in trouble. And the situation was getting worse, not better, in terms of incentives for industry and the attention paid to the developing world."

To address those problems, the Bellagio report calls for a global HIV vaccine initiative. Though the report doesn't detail what the initiative would look like, it floats several ideas, including a task force, a consortium, or a nonprofit institute. Berkley says his next steps are to develop a scientific plan laying out specific gaps and a business plan with estimated costs. "More has to be done," says José Esparza, who heads AIDS vaccine development at WHO. "If we maintain the present level of effort, we're not going to have a vaccine in a reasonable amount of time." And that could be a disaster, because the one thing AIDS vaccine developers are truly racing against is time.

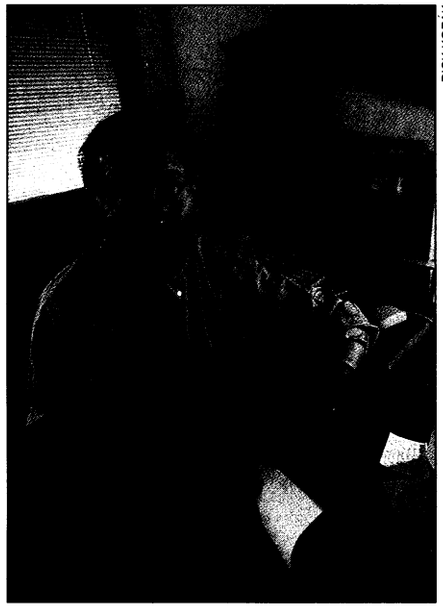
–Jon Cohen

VACCINE POLICY

U.S. National Program Is Going Nowhere Fast

Vaccination seems like simplicity itself: a jab in the arm that offers a lifetime of protection. Yet the political mechanisms underlying the creation of these remarkable elixirs are nothing if not complex. Developing a new vaccine requires cooperation among a multitude of groups whose interests often conflict, including researchers in academia and industry, regulatory agencies such as the U.S. Food and Drug Administration (FDA), drug manufacturers and distributors, public health officials, medics, educators, and epidemiologists.

Traditionally, coordination of these diverse interests has been a hit-or-miss affair, dependent as much on market forces as on the clear and present needs of the public's health. But market forces are poor cultivators of vaccines, because these preparations are rarely big moneymakers. As a result, only about 20 vaccines have ever reached the clinic. In an attempt to get vaccine development to hit its public health targets more often, Congress created the National Vaccine Program (NVP) in 1986 and charged it with choreographing the vaccine-related activities of federal agencies and industry, as well as defining what vaccines are needed and how to provide them. NVP is currently a 35-person unit, with half of its staff in the Office of the Assistant Secretary for Health (OASH) in the Department of Health and Human Services (HHS) and half in other agencies.



RICK KOZAK

Shot out from under him? Anthony Robbins thinks Congress wants to put his vaccine office out of business.

But NVP, like an unvaccinated youngster, has led a sickly existence. And now it may be in its death throes—a victim, say insiders, of underfunding, poor leadership, and turf wars involving the very federal agencies NVP was supposed to coordinate. Congress is on the verge of gutting the program by transferring almost all of its staff to the Centers for Disease Control and Prevention (CDC). And many vaccine experts, while insisting there's a dire need for a body to coordinate vaccine development in the United States, think NVP isn't up to the job.

"NVP was a very good idea, but I don't think it seized the opportunity it had," says R. Gordon Douglas, president of the vaccine division at the pharmaceutical giant Merck & Co. and a member of NVP's advisory committee. Douglas blames NVP leadership for failing to "raise NVP's accomplishments to a level at which it gets recognition." Indeed, one of the few tangible proofs of NVP's 8-year existence is a handful of reports—one of which, the U.S. National Vaccine Plan, was issued after a pachydermal gestation period of more than 7 years. Even Anthony Robbins, the full-time consultant who effectively heads the National Vaccine Program Office (NVPO) and is its director-designate, admits NVP has not reached its full potential. Part of the problem, he says, is that NVP got off to a slow start because the "the [Reagan] Administration did not eagerly embrace the program."

Congress was also less than enthusiastic. Authorization for the program slipped into law as a 1986 amendment to the Public Health Service Act. The lack of political interest in the program is reflected in the status of its directors. The NVPO has had a full-time director for only 3 of its 8 years; Robbins has been waiting more than a year for OASH to appoint him to full status.

In addition, it wasn't until fiscal year 1989 that Congress actually appropriated funds—a measly $0.5 million, increased to $5.9 million the following year. With this small budget, the agency set about its mission: coordinating vaccine activities at FDA, CDC, the National Institutes of Health (NIH), the Department of Defense (DOD), the U.S. Agency for International Development (USAID), and industry; providing discretionary funds for urgent vaccine projects that did not fall under the jurisdiction of any one