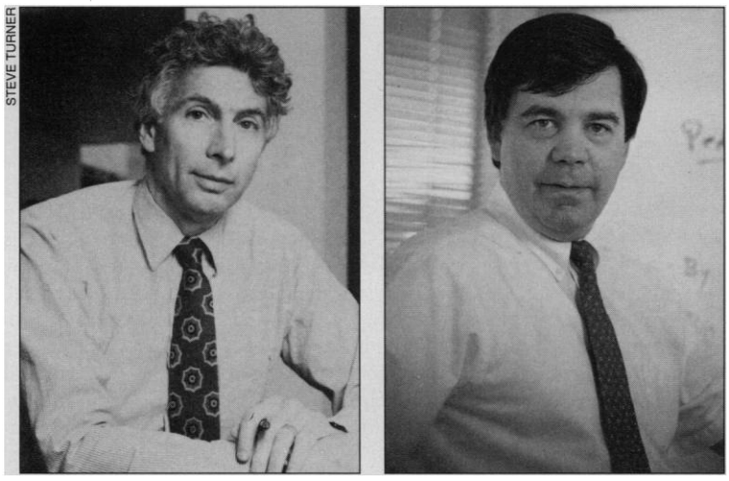
Is Liability Slowing AIDS Vaccines?

Some pharmaceutical and biotech companies, concerned about potential damage suits, are taking a tentative approach to the development of an AIDS vaccine

Since HIV was first isolated in 1983, researchers have been dreaming of a vaccine to prevent the devastating effects of AIDS. But from the earliest days, coiled in those dreams have been a swirl of nightmarish questions—questions having to do, not with molecules, but with legalities. Could any vaccine developer withstand damage suits filed by people who might be harmed by a vaccine? That's one of the nastiest of the quandaries, and from it flow others: Would liability fears keep veteran vaccine manufacturers out of the AIDS business altogether? Would the same fears lead companies that did become involved to abandon promising research? And could financial risks delay development of an effective vaccine?



STEVE TURNER

Where there's smoke. Attorney Robert Stein *(left)* thinks liability could be a concern in AIDS vaccine trials. NIH's Dan Hoth already sees "smoke"—indications that liability may be impeding vaccine research.

The good news is that, in the face of these worries, AIDS vaccine research is proceeding in companies, universities, and government labs around the world. But here's the bad news. A careful examination of AIDS vaccine research by *Science* shows that liability concerns have had negative effects, which include:

- Pushing a major pharmaceutical company with a successful AIDS vaccine project all but out of the AIDS vaccine business.
- Postponing human trials of an old-fashioned vaccine approach that has had the most success in monkey experiments.
- Halting yet another tried-and-true approach dead in its tracks before research could even begin on it.
- Compelling a leading California biotechnology company to scuttle its promising AIDS vaccine program, only to revive it when the state's legal climate changed, in part because of liability concerns.
- Scaring yet another company away from testing a vaccine in pregnant, infected women until a state law was changed.

These episodes show that fears among researchers and AIDS patients that liability concerns will slow the development of an AIDS vaccine aren't idle. And those episodes pale before the legal complexities that will arise when real-life, real-time tests of AIDS vaccines begin—perhaps in only 18 months. That's when the World Health Organization and the U.S. government plan to begin enrolling thousands of people at high risk of becoming infected with HIV. Some will become infected in spite of being vaccinated (even the best vaccines are not 100 percent effective) and they could blame their illnesses on the vaccine. So it's clear that more vaccination doesn't just mean more protected people; it also means more potential plaintiffs. Says D.C. attorney Robert Stein, who specializes in AIDS issues: "Given a litigious society, when there are things that go wrong, people are going to try to find a place to put the blame."

One of the things that make such fingerpointing more probable is that preventive vaccines, unlike drugs for treatment, are given to healthy people. Says one AIDS researcher at a major drug company, who insisted on anonymity: "If you can show in 50 people that you can prolong their lives with a drug and in 50 others do nothing, or even harm them—no problem." But he adds that "if a vaccine protects 99 people and one person develops complications and they trace that back to the vaccine, that one case will send the company down the drain."

Dan Hoth, head of the division of AIDS at the National Institute of Allergy and Infectious Diseases (NIAID), says he believes that these concerns are slowing progress in vaccine research. "At [NIAID's] AIDS Program Advisory Committee meetings everybody brings it up and wrings their hands. It's very hard to be specific, but there's certainly smoke and I have the perception that there is a problem."

Interviews by *Science* with dozens of people in vaccine research make it easier to provide specifics. One place where there is both smoke and flame is Bristol-Myers Squibb. Through Oncogen, a Seattle subsidiary, Bristol has become one of the leading AIDS vaccine developers in the world. Oncogen's vaccine, HIVAC-1e, contains live vaccinia virus (the smallpox vaccine) that has been genetically engineered to express the AIDS virus envelope protein, gp160. At last June's international AIDS conference in Florence, Vanderbilt University's Barney Graham presented data from human tests of HIVAC-1e followed by a boost with recombinant gp160 injected alone. The combination registered such a whopping immune response that a plenary session moderator hailed it as "the most promising" approach yet tested in humans. Oncogen also reported in Florence that by using a combination of the two vaccines, it had successfully protected four monkeys from a live virus challenge—the most dramatic success to date of all genetically engineered AIDS vaccines.

Knotty problem?

In spite of that promise, Oncogen is no longer producing HIVAC-1e. Bristol spokesperson Susan Yarin refused to say whether the company's decision was linked to liability fears. All Yarin would say is, "We met our obligation to provide HIVAC-1e for trials, which are now over." But a knowledgeable Oncogen vaccine researcher who insisted on anonymity argues strongly that fear of lawsuits from injured vaccine trial subjects played a major role in Bristol's decision. The scientist stresses that Bristol sees liability knotted together with other commercial negatives like a questionable market and patent snafus. "Bristol is short-sighted in terms of research," the researcher complains, noting that Oncogen's AIDS vaccine program still exists but is badly hobbled. "We're not even supposed to mention the dreaded 'V-word.'"

Vaccine liability fears have also impeded progress even at companies that are gung-ho on vaccines. California's Immune Response Corp. (IRC) was launched 5 years ago to specialize in vaccines. Cofounded by polio vac-

cine developer Jonas Salk, IRC is banking on an HIV vaccine made by the old-fashioned whole, killed-virus approach that Salk used with polio. Every other HIV vaccine developer has avoided this formulation because of the possibility that not all of the virus's genetic material would be killed and that it could infect someone who received the vaccine. As a result of those fears, almost all other researchers are relying on genetically engineered vaccines that contain no HIV genetic material.

Shortly after the company started, IRC began testing its vaccine in people already infected with HIV, hoping the vaccine might be able to delay or prevent the onset of AIDS. Those tests continue to this day, with no major liability issues to speak of. But *The Wall Street Journal* first reported on 6 March that liability concerns have delayed IRC's planned trials in uninfected people with the killed vaccine, which were slated to begin in 1991. This delay is especially troubling because the killed-HIV approach clearly has outperformed every other one tested in monkeys to date.

Science has learned that IRC itself has decided to assume the risk of conducting the initial trial, because it believes the preparation is safe and because it has lined up informed, motivated volunteers—including Jonas Salk. "We, as a company, are quite willing to go forward," says a member of IRC's board who did not want to be quoted by name.

Lots of Possible Solutions, Little Progress

Enough cases have turned up in which fears of AIDS vaccine liability have affected research to make it clear that a solution needs to be found. But what solution? There are plenty of candidates, but it isn't easy to decide among them. Showing just how tough the choices are, the search for a solution has been under way since 1988—with little progress to show for it.

In that year, a project at the Keystone Center in Colorado gathered lawyers, scientists, political staffers, and consumer and industry representatives. The Keystone group detailed solutions for clinical trials and marketed products, many based in principle on the National Childhood Vaccine Injury Compensation Act. Passed by Congress in 1986, the act came in the wake of liability disasters arising from vaccines for polio, diphtheria-tetanus-pertussis, and swine flu. The act established the National Vaccine Injury Compensation Program, a body that rewards victims without punishing responsible manufacturers.

That solution doesn't cover AIDS, because the no-fault program was designed to include only childhood vaccines. Furthermore, the childhood vaccine program is far from perfect: The fund it set up has been plagued by money shortages. In view of such problems, others aren't banking on that kind of solution to the AIDS vaccine liability quandary. They're proposing a welter of other plans.

One is tort reform—an overhaul of the way damage suits are filed and adjudicated. A bipartisan product liability bill currently in the U.S. Senate, backed by Vice President Quayle and his Council on Competitiveness, would make it nearly impossible to sue a drug company for punitive damages if a product had FDA approval and the manufacturer had behaved responsibly. Such a "government standard" would free manufacturers from "strict liability." D.C. attorney Victor Schwartz, who has written four books on product liability and serves as general counsel for the reform-seeking Product Liability Alliance, argues that this bill would address the main fears of pharmaceutical companies. "The problem with the current system," says Schwartz, "is it doesn't separate the dolphin from the tuna—the careful drug manufacturer from the careless one."

The Senate bill would limit punitive damages, which are designed to punish manufacturers. But some argue that's not enough. Another need, they say, is a cap on compensatory damages, which cover actual losses and pain and suffering. Several states have already capped compensatory damages for medical malpractice, and the same could in theory be done for AIDS vaccine liability.

The World Health Organization (WHO), which plans to begin efficacy trials in four countries by 1994, is currently analyzing the liability issue and expects to weigh in with potential solutions by next September. But David Heymann, head of WHO's Global Programme on AIDS research office, maintains that liability risks ultimately do not fall on the doorstep of WHO, which will have an umbrella role in these trials, overseeing ethics and scientific standards. "If development of a product will commercially benefit a pharmaceutical manufacturer, we feel it's the responsibility of the manufacturer to assume liability risks in the trial," says Heymann.

Another proposed solution is universal health care. Although the connection between AIDS vaccine liability and nationalized medicine may not be immediately clear, Wendy Mariner, a law professor at Boston University School of Medicine and Public Health who took part in the Keystone project, believes that if the U.S. had a national health care system and long-term disability coverage, people injured by vaccines would be less likely to sue manufacturers. Mariner doesn't think the solution is to give AIDS vaccines a special legal status. "My concern," says Mariner, " is if you solve the liability issue, do you wind up with more and better vaccines? Not necessarily."

Another solution that has been proposed is for an international organization to manufacture and distribute the AIDS vaccine and in this way assume all liability. That possibility has its drawbacks—like all the others—and the AIDS vaccine liability question remains difficult to answer. But if no solution is perfect, perhaps a number of different ones will have to be tried, because there is mounting evidence that liability fears are delaying research and impeding solution of the real problem: stopping HIV.

–J.C.

AIDS Vaccine Liability–What Is the Solution?

"Government Standard"	Legislation holding that if a vaccine met FDA safety standards, an injured party could not recover damages
Cap Compensatory Damages	Several states have capped compensatory damages for medical malpractice.
Limit Punitive Damages	A bill currently on the U.S. Senate floor would eliminate most punitive damages for FDA-approved products.
Compensation Systems	A trust fund could reimburse victims for medical expenses, lost earnings, and pain and suffering.
International Manufacturer	Harvard's Jonathan Mann has suggested a patent-exchange scheme in which the developer of an AIDS vaccine would give the patent to an international organization in exchange for patent benefits on other products.
National Healthcare	Boston University's Wendy Mariner believes national healthcare would make people injured by vaccines much less likely to sue manufacturers.

But the board member says IRC contracted with another company to actually make the vaccine—and that company is unwilling to take the risk. IRC believes the trial, although delayed, will go forward, because it has found what the board member would only describe as "an alternative solution."

Jonas Salk isn't the only AIDS vaccine researcher to run into liability roadblocks when trying to apply tried-and-true methods to AIDS vaccines. Virologist and pediatrician Stanley Plotkin—who has worked on vaccines for polio, rubella, chickenpox, rotavirus, rabies, and cytomegalovirus—wanted to design a live but weakened version of HIV to test as a vaccine. Many researchers think this method, like Salk's whole, killed approach, is too risky, and Plotkin, then at the University of Pennsylvania and head of the infectious diseases division at Philadelphia's Children's Hospital, was repeatedly denied funding. "One of the reasons for not funding the project was safety issues," says Plotkin, who recently joined Pasteur-Merieux-Connaught in France, which has a multipronged AIDS vaccine program. "Therefore," Plotkin thinks, "the likelihood is that liability was a factor." He believes "the reviewers—in addition to their scientific criticisms—must have had liability in mind."

Another place where flames are appearing through the smoke is Genentech. The company has had an on-again, off-again AIDS vaccine effort and many believe that those ups and downs were due solely to lab successes and failures. But liability was a key issue there, too. The pioneering south San Francisco biotech company was one of the first out of the gate in the race to make an anti-HIV vaccine—but the company wanted some legal protection before running the course. In 1986, Genentech attorneys helped move a bill through the California legislature to protect HIV vaccine developers from litigation unless they failed to inform people of the risks or if the injury was caused by their negligence or misconduct. Paul DeStefano, then Genentech's general counsel, recalls being asked at an official hearing whether Genentech would drop out of the business unless such protection was mandated by law. "Yes, that's what I'm telling you," DeStefano says he replied.

Though the bill passed, DeStefano contends it was significantly watered down by the consumer-oriented California Trial Lawyers Association. "For that reason—though I'm not saying it's the sole reason—Genentech dropped its AIDS vaccine program," says DeStefano, who says other major factors included the dissappointing performance of a prototype vaccine, which had just failed to protect chimpanzees in a challenge experiment.

Only 2 years later, the same factors—legal climate plus research results—turned Genentech around. In 1988, the California Supreme Court handed down a decision saying that manufacturers of drugs (and presumably vaccines) can be held responsible for the damages caused by a properly made preparation only "if it was not accompanied by a warning of dangers that the manufacturer knew or should have known about." The so-called Brown ruling was so favorable to manufacturers that the California legislature rescinded its AIDS vaccine indemnification law. DeStefano says the Brown decision, coupled with success in the lab, led Genentech back into the business. A current Genentech insider adds that insurance companies also have become less skittish about AIDS in general, making it easier for the company to buy insurance for trials, offering "a risk spreading mechanism."

Whereas favorable resolution of liability issues affected Genentech's participation in the vaccine business in California, similar issues led another major biotech company, Connecticut's MicroGeneSys, out of research in one state—and into it in another. Researchers at Tennessee's Vanderbilt University had hoped to begin tests in pregnant, HIV-infected women of a recombinant gp160 vaccine made by MicroGeneSys, the aim of the trial being to treat the women and simultaneously stimulate antibodies that might prevent transmission of HIV to their fetuses. Those plans were thrown off by liability concerns last summer, when MicroGeneSys decided not to hold the trials at Vanderbilt. The reason? Tennessee's laws don't offer the vaccine maker much protection against liability.

By contrast, a new Connecticut law had just entered the books, offering substantial legal protection to companies testing AIDS vaccines in pregnant women. And it wasn't an accident that the law appeared in the company's home state: Attorney J. Michael Epstein and lobbyist Charles Duffy, both working for MicroGeneSys, were prime movers behind the legislation. The company decided to hold the trials at Yale instead, but at a cost—delay of a trial.

Different strokes. Paul DeStefano *(left)* argued that Genentech needed liability protection in California to stay in the AIDS vaccine business. Wendy Mariner thinks AIDS vaccine makers shouldn't get special legal protection.

The White House weighs in

While it is impossible to measure the delay exactly (the Vanderbilt trial was still in its planning stages, animal safety tests are still under way, and the Yale trial has not begun), word of the delay made it all the way to the White House. "I'm told of an experimental vaccine that might reduce the incidence of HIV-positive babies born to mothers with AIDS," said Vice President Dan Quayle in a tort reform speech he gave to the American Bar Association last October. "This is a wonderful development; but for fear of lawsuits, companies have been reluctant to proceed with testing."

Pediatrician Peter Wright, who was slated to head the now-defunct Vanderbilt trial and who will still be the principal investigator of the one at Yale, explains that liability was a key issue because "pregnancy has a finite rate of abnormal outcomes and any thing could be blamed on vaccines." The usual risks were heightened by the fact that many of the HIV-infected mothers being considered for the trial became infected through intravenous drug use, increasing the probability of a birth defect. Wright says MicroGeneSys, which recently linked with Wyeth-Ayerst, simply didn't want to assume those risks. That statement couldn't be confirmed officially, because MicroGeneSys and Wyeth-Ayerst did not return repeated phone calls to discuss the trial.

These examples don't prove that Dan Hoth's smoke metaphor conceals a raging wildfire out there in the biotech world. Yet they do show that there are some flames—and that getting out of the path of the flames has caused companies to take a defensive, conservative approach that may well not be the quickest route to an AIDS vaccine. And that's a pity, because even without the additional legal obstacles, it's becoming clear that developing a safe, effective AIDS vaccine is going to be a formidable challenge.

–Jon Cohen

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