A 'Manhattan Project' for AIDS?

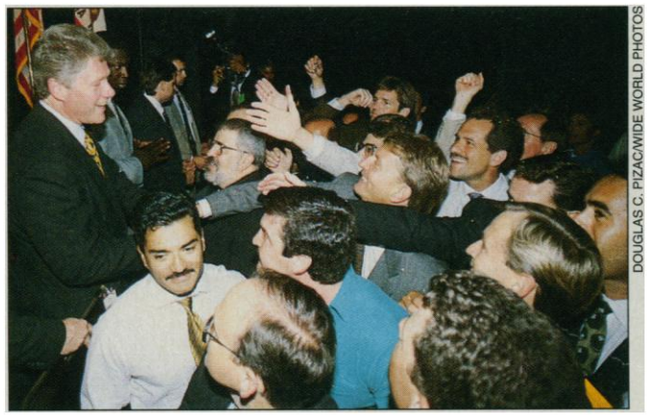
The idea of a centrally directed, all-out effort to find a cure or vaccine is supported by activists and some scientists, but other researchers are deeply wary

Late on Saturday evening, 4 April 1992, two dozen AIDS activists filled Bill Clinton's suite at a hotel near New York's Times Square. The situation was difficult for the presidential candidate. He'd been battered in the New Hampshire primary, and he badly needed a win in New York to prevent his campaign from turning terminal. But a few days before, he had been ambushed by an AIDS activist, who accused Clinton of "dying of ambition" while people were dying of AIDS—a dramatic, made-for-TV message that Clinton needed to counter, quickly. The hotel room conclave was a step in that direction.

One question tossed at Clinton during the meeting was: If elected president, what would your priorities for HIV research be? "He said he'd support a 'Manhattan Project' for AIDS," recalls David Barr, an activist with the Gay Men's Health Crisis, who was present. The phrase was resonant: a government-directed, all-out research effort, reminiscent of the effort that led to America's A-bomb, but this time aimed at curing rather than killing—by finding an AIDS cure or preventive vaccine. When Clinton repeated the idea at a largely gay fundraiser in Los Angeles on 18 May, headlines proclaimed that he was promising a Manhattan Project to cure AIDS. There was only one hitch—Clinton had failed to provide any details to flesh out what he meant by an AIDS Manhattan Project.

As long as Clinton was running for president, the concept could remain vague. Now that he's in the White House, the topic has moved to the front burner, and catch phrases are no longer enough. And there's no dearth of ideas. Scores of interviews by *Science* reveal that at least half a dozen proposals for streamlining the national AIDS research effort—some calling for bypassing the National Institutes of Health (NIH) and its peer-review system altogether—have been floated in political and scientific circles recently. The ideas, which come both from AIDS activists and from researchers, have yet to be widely circulated, yet already some influential scientists are lining up in support of the Manhattan Project concept.

Both scientists and activists are frustrated by the failure of science to come up with a vaccine or an effective therapy in the decade since HIV was first isolated. But that's not the only reason the proposals are flying now. Another is that a major shakeup in how government directs AIDS research is already afoot. Last month, the Senate, to the dismay of NIH institute directors and some academic scientists, introduced legislation aimed at restructuring NIH's $1.1 billion AIDS research effort. In addition, Clinton also promised in the campaign to name an AIDS "czar" to "oversee and coordinate all federal efforts related to this issue, a person with my ear...with the power to cut through red tape and the mandate to get results as quickly as possible."



DOUGLAS C. PIZAC/WIDE WORLD PHOTOS

Crowd pleaser. At this Los Angeles fundraiser last 18 May, presidential candidate Bill Clinton proposed a "Manhattan Project for AIDS"—but offered few details to flesh out the plan.

A critical time

With those shakeups in the offing, "now is a very critical time to change things, before AIDS becomes too institutionalized," says Art Ammann, head of the Pediatric AIDS Foundation. "It's time to look at what's been done and get people together to ask what are the unanswered questions that remain and what sort of priority should they be put in."

But is a "Manhattan Project" really what the doctor ordered for AIDS? *Science*'s informal survey found wide disagreement on the correct prescription for streamlining AIDS research. Proponents of a Manhattan-style approach argue that if the government stepped in and aggressively directed the scientific effort, redundancy would be eliminated, gaps in research would be filled, cooperation would be fostered, and answers would surface far more quickly. Opponents counter that not enough is known about HIV at the level of basic science to stage a goal-oriented project like the one that led to the making of an atomic bomb, and that any attempt to do so could stifle the scientific creativity needed to provide a cure or a vaccine.

Why would AIDS activists and some top AIDS scientists think fundamental changes need to be made in the system that powers AIDS research? The main concern seems to be that, in the face of a spreading global epidemic, the ordinary administrative processes of scientific funding and peer review may be too cumbersome to produce rapid results. Most of those interviewed for this article cited bureaucratic obstacles and argued strongly for swifter means of getting dollars to innovative researchers. The concept of a "Manhattan Project means a lot of things to a lot of people," says the National Cancer Institute's (NCI) Robert Gallo, the most prominent government scientist advocating the idea. "To me it means one thing: a little more urgency."

Gallo says that in addition to freeing researchers of administrative time drains and speeding the sharing of reagents—two problems he says slow his lab—a Manhattan Project would raise "enthusiasm and optimism at a time when there is pessimism and sadness in the field." And even if it doesn't lead to a cure, he says, "it will upset the apple cart enough that we'll all rethink, retry, recompete, and maybe do better."

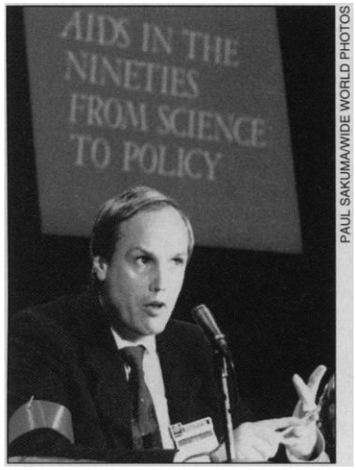
David Ho, head of New York's Aaron Diamond AIDS Research Center, says the critical problem is how long it takes NIH to fund extramural research. The NIH funding process "is a fair system—and that's very important," says Ho. But, he says, because AIDS is an emergency, "we need to have a mechanism—and this cannot be abused, obviously—where some group of individuals can say, 'Hey, that's a great idea, let's just move.'"

Nobel laureate David Baltimore of Rockefeller University, a longtime proponent of a Manhattan-style project, agrees: "NIH just doesn't have the bureaucratic style or the regulatory authority to handle goal-directed research."

Veteran vaccine developer Maurice Hilleman of Merck argues that bureaucracy isn't the only hurdle. He thinks a large stumbling block is built into the scientific culture—

which isn't a comfortable home for directed research. "In the United States, investigator-initiated research is holy, you see," says Hilleman. "You can't say anything against it. But when you try and apply it, it is all these little pieces. It's all R and no D."

If criticisms of the status quo are widely shared among researchers, most are hesitant to offer a detailed vision of possible fixes—though Baltimore knows his starting point: "Have a few strong people take a snapshot of where we are, decide where we want to go, and then design a program." AIDS activists meanwhile are stealing a march on the scientists and drafting detailed plans, at least three of which, widely circulated in political circles, fit the Manhattan Project mold:



PAUL SAKUMA/WIDE WORLD PHOTOS

Panelist. Martin Delaney proposes a panel to evaluate AIDS research.

■ Activist and playwright Larry Kramer, who spelled out his proposal in *The New York Times* and in letters to the Clinton Administration, suggests establishing a "joint chiefs of staff for AIDS" consisting of leaders in industry, government, and academia to speed research, drug development, clinical trials, and drug approvals.

The scientist who heads the AIDS "joint chiefs" would have emergency powers to hire and fire staff, authorize spending without peer review, and answer only to the president. Rather than corralling researchers in a Los Alamos-like setting, Kramer would have people stay in their labs and be detailed to the project. In his most controversial notion, Kramer believes all federal AIDS research money should be devoted to this Manhattan Project—cutting NIH out altogether as a funder. "I don't think there's a hope in hell that any cure will ever come out of NIH," he says.

■ Martin Delaney of San Francisco's Project Inform also has been peppering the Clinton Administration with Manhattan Project ideas, one of which is a blue-ribbon panel that would swiftly evaluate programs and options. Delaney shares Kramer's skepticism about NIH, asserting that training NIH to deal with directed research would be like "teaching an elephant to tap dance." Unlike Kramer, however, Delaney doesn't think NIH should be cut out altogether; he wants to see a Manhattan-type project work in parallel with NIH, receiving an annual budget of, say, $50 million to $100 million.

A "respected" chief scientist working with a scientific advisory board would make research decisions, and most of the scientific team would work at a single headquarters (pet ideas include vacant buildings at NCI's Frederick Cancer Research Center and San Francisco's Presidio Army Base), though the project would fund researchers off-site, too. Commercial collaborators would receive special tax and patent benefits. To reduce red tape, the team would have a "one-stop" scientific and human subjects review and a single Food and Drug Administration team assigned to monitor and assist the work.

■ Perhaps the most intricate proposal yet drafted comes from ACT UP/New York, which last month began circulating its Manhattan Project plan to the Clinton Administration and Congress. Named the "Barbara McClintock Project to Cure AIDS," after the Nobel Prize–winning corn geneticist, this project, too, would be separate from NIH. Primary research staff would work at a central location for "instant cross-fertilization of ideas." Scientists representing "divergent approaches" and diverse populations would govern the project, which will have "extraordinary powers," including the capacity to use any government-funded facilities or staff to test promising cures, to obtain data from any public or private research outfit, and to exercise the right of eminent domain to test potential cures if companies fail to do so promptly on their own.

The three plans floated by the activists all call for much more central direction of research—much like the centralized selection of problems and team leaders that characterized the original Manhattan Project. So far, these plans are too new to have caused much of a reaction in the scientific community, but some researchers familiar with the push to streamline AIDS research are wary. Take virologists Lawrence Corey of the University of Washington and William Haseltine of the Dana-Farber Cancer Institute, who do not believe that additional direction from the center is the missing ingredient in AIDS research. Both assert that what's needed is to attract more basic researchers to the field, which in turn would augment what's known about HIV and about AIDS. Only when the knowledge base has grown, they contend, will a cure and a vaccine become practical. Accordingly, each has proposed a national AIDS effort focused on more basic research—not on centralized dictates.

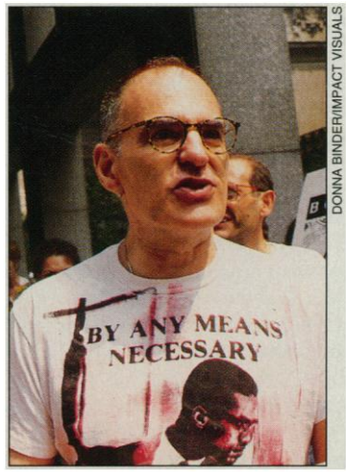
Discovery channel

Corey argues that "what is needed at present to break open this field is more discovery. Discovery requires more technology and more trained people." Specifically, Corey has proposed that the government devote $180 million to building six national centers for AIDS research and add grant programs to attract graduate students and accomplished scientists from other fields.

Haseltine is also convinced that additional, heavy-handed direction of basic research will have a low yield. Haseltine's solution, which he has offered up in various public forums, centers on doubling the AIDS research budget by 1995. Furthermore, Hasel-

THAT MANHATTAN STYLE

Concept (Originator)	Description
"Joint Chiefs of AIDS" (Larry Kramer)	A program outside NIH, but not at a central facility, that has emergency powers and consolidates all government-funded AIDS research under a "joint chiefs of staff."
"Distributed Institute" (Martin Delaney)	A program outside NIH with a $50 million to $100 million annual budget that contracts out work but has a central facility for a scientific leader and an advisory team of scientists.
"McClintock Project" (ACT UP/New York)	A centrally located program separate from NIH governed by scientists representing "divergent approaches" who will have "extraordinary powers."
"Research Centers" (Lawrence Corey)	Construct six new centers of excellence for HIV research affiliated with academic institutions to attract researchers to the AIDS field, which, in turn, will lead to new discoveries.
"Budget Boost" (William Haseltine)	By 1995, double the AIDS research budget and quadruple the funds spent on biomedical research to support good ideas that are untested and attract researchers from other fields to work on AIDS.



DONNA BINDER/IMPACT VISUALS

Playing for keeps. Playwright and AIDS activist Larry Kramer.

tine says he doesn't believe that "the answer to AIDS will necessarily emerge from AIDS research." Because "our ignorance of biology is so great," he says, the key findings might surface in studies of cell biology, immunology, or genetics that initially seem unrelated to AIDS. Hence, he says, the entire basic research budget for biomedical research should be quadrupled.

Though there is wide consensus inside and outside NIH that government-funded AIDS research could be better coordinated, many researchers—and even some leading activists—believe staging a Manhattan-style project would be overkill. For some, especially those deeply invested in NIH, what's needed is fine-tuning of the existing funding mechanisms. For others, the blueprint for improvement already has been drawn up, in the form of a bill now making its way through Congress.

Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases—which receives 43% of NIH's AIDS research budget—says, "The science base isn't there for a Manhattan Project for AIDS." Still, Fauci says, he would welcome additional coordination among the branches of the government—a need he believes the incoming AIDS czar will address. "A lot of things people want us to do, we're already doing," says Fauci, citing a strategic plan recently drawn up for AIDS vaccines and one in the works on AIDS pathogenesis. That kind of strategic thinking "has not been well advertised," says Fauci, "so people think it's not occurring."

Howard Temin, who shared the Nobel Prize with Baltimore for discovering reverse transcriptase, still has a bad taste in his mouth from President Richard Nixon's War on Cancer, a directed-research program that failed to deliver on its promise of a cure (see box on this page). Says Temin: "An enormous reorganization of NIH probably will turn out to be enormously destructive to AIDS and other research." Yet he allows that, when the research base has increased, a Manhattan Project might be useful to develop an AIDS vaccine quickly.

To AIDS activist Mark Harrington, a member of the New York-based Treatment Action Group (TAG), the push for a Manhattan Project reflects the "great hunger for a scientific superfather" and the thinking that "if you gave a lot of money, all would be fixed." This, charges Harrington, ignores the fact that the making of the bomb relied on an existing mathematical model. "You could make predictions," he says. "In biology, you can't do that." Yet Harrington does not believe nothing needs to be done on the AIDS front. Indeed, TAG has been a prime mover behind the legislation now moving through Congress (*Science*, 12 February, p. 889).

Discreet funding

The proposed law, strongly backed by the Clinton Administration, would funnel AIDS research money through NIH's Office of AIDS Research (OAR)—as opposed to distributing it to each institute. This, the bill's backers think, would strengthen OAR's ability to plan and coordinate the search for answers to the most puzzling questions. It would also establish a discretionary fund that the OAR director could use to fund research quickly. While the OAR overhaul would not explicitly create a Manhattan Project, the discretionary fund might end up being used as the financial basis for such a project or several "mini" efforts at directed research.

David Mixner, a gay activist who served as a senior adviser to Clinton during the campaign and transition, says whoever is selected as Clinton's AIDS czar will have much say over what type of Manhattan Project is fashioned. The czar, says Mixner, will be a White House-level appointee and will have "a great deal of influence" on Clinton. "Once the czar's appointed," says Mixner, "you'll see that person will quickly be given authority to reorganize, streamline, and gather the best and the brightest to launch a major campaign to find a cure." How that is done poses some very big questions—questions Bill Clinton didn't answer on that night in New York but will have to start answering very soon.

–Jon Cohen

History's Winners and Losers

The original Manhattan Project was a thundering success: In the 35 months leading up to July 1945, an explosive device based on atomic fission moved from theory to reality. Experts on the Manhattan Project say several elements were key to its success, among them strong leadership, minimal bureaucracy, unlimited funds, and a sense of urgency. Can the same experience be applied to AIDS, leading to a cure or a vaccine?

Perhaps. A variety of proposals for Manhattan-style AIDS projects are now being floated (see main story). But one experience closer to the biomedical arena shows that large-scale directed research isn't a magical route to success. In 1971, after lobbying by patient advocates, Congress introduced the National Cancer Act and unanimously passed a resolution that called for a cancer cure by 1976. President Richard Nixon embraced the idea of a "War on Cancer," declaring in his 1971 State of the Union address that "the same kind of concentrated effort that split the atom...should be turned toward conquering this dread disease." Later that year, the National Cancer Act became law.

Cancer, however, was not cured in 1976. In fact, one of the most high-profiled, well-funded parts of the War on Cancer, the National Cancer Institute's Special Cancer Virus Program, eventually imploded. The program, says the University of Wisconsin's Howard Temin, "became individual fiefdoms without outside review. It got too much of a stench and was summarily stopped."

Rockefeller University's David Baltimore concedes that the War on Cancer wasn't an overall success. In fact, he says, when an Institute of Medicine (IOM) panel he sat on in 1986 discussed a Manhattan Project for AIDS, memories of that war helped scotch the idea post haste. But, cautions Baltimore, AIDS is not cancer. "With cancer, we didn't have any solid ideas of what was going on," he says. "We know more about HIV than [the Manhattan Project physicists] knew about atomic energy. Sure, there are mysteries, but the core causation is known: It's a virus."

If history offers failures in directed biomedical research, it also offers examples of successes, among them the National Foundation for Infantile Paralysis, commonly known as the March of Dimes. Started in 1935, the March of Dimes was run by Basil O'Connor, Franklin Roosevelt's former law partner. "Basil O'Connor had a lot of power," says Frederick Robbins of Case Western Reserve University, whose work the foundation funded. O'Connor's clout was key to the success of the project, which began even before basic pathogenesis questions about poliovirus were understood.

Robbins, who won the Nobel Prize for growing poliovirus in tissue culture, says the foundation's genius was that it emphasized basic research on all viruses. Robbins' breakthrough, which made a polio vaccine possible, began as an attempt to isolate what he suspected was a different virus altogether—one causing infantile diarrhea.

Jonas Salk, who, with the foundation's support, developed the first effective polio vaccine in 1955, also praises its approach. "I always felt like I was working with more of a patron than a faceless bureaucrat," says Salk. "My relationship was, 'Do what you're doing and we'll pay the bills.'" And the emphasis on applications rather than basic research was "in the same spirit as the Manhattan Project" says Salk.

Decades later, after the success of the March of Dimes and the missteps of the War on Cancer, the key question is: Which model should present-day policy makers learn from?

–J.C.