THREE YEARS after scientists identified the virus that causes AIDS, somebody has finally crossed the starting line in the race to prevent the incurable wasting disease. In recent weeks scientists at the National Institutes of Health in Bethesda, Maryland, began trials on human subjects to determine the safety of an experimental vaccine. (Under standard Food and Drug Administration procedures, human tests of its effectiveness cannot start until 1990 at the earliest.) The genetically engineered drug, manufactured by MicroGeneSys of West Haven, Connecticut, a small, four-year-old biotechnology company, is the first potential AIDS vaccine to win FDA approval for preliminary testing.

It won't be the last. At least two dozen companies, from tiny university research spinoffs to pharmaceutical giants like Merck and Bristol-Myers, are vying in the AIDS vaccine race. But it will be years, perhaps decades, before a winner is declared. "We're just witnessing the start of a great scientific marathon," says Anthony S. Fauci, director of the NIH unit sponsoring the current trials.

To cross the finish line, scientists will have to defeat a fiendishly ingenious adversary quite unlike any mankind has encountered before: the AIDS-causing human immunodeficiency virus (HIV), a microscopic killer that shatters the immune system.

Of all the challenges facing medical researchers, none is more fraught with hope and risk than the effort to develop an AIDS vaccine. For sheer boldness, the quest rivals the war on cancer that President Nixon declared in the early 1970s, and ultimately it may take that sort of national commitment to bring the AIDS epidemic under control. Right now the prospects look grim. Developing an effective AIDS vaccine will require major scientific breakthroughs in virology and immunology, and the practical barriers are just as daunting. Because it is impossible
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The odds are long, since of all the companies in the field only one may hit the jackpot. In any case, the opportunity to make big money remains far in the future: Any investment in research that lasts years or decades necessarily takes a long time to pay for itself. But few contenders seem deterred. If anything, research is accelerating. Large pharmaceutical companies view AIDS research as an obligation. A Merck spokesman says simply, "The spread of AIDS is a major health problem that has to be addressed."

For many biotech companies, AIDS vaccine research is also an opportunity to work on the cutting edge of science, where intellectual competitiveness, the drive to tackle seemingly insurmountable difficulties, and the hope of glory often vie with mundane business considerations. Says David W. Martin, chief of research at Genentech in South San Francisco: "The risk is what drives us. The scientists here really want to be overwhelmed with a challenging problem." Adds Bernard Fields, chairman of Harvard's microbiology department, who works closely with Cambridge BioScience in Worcester, Massachusetts: "There is a lot of excitement about trying to solve this problem. It's a perfect merging of the talents of these companies with a very positive goal."

In fact, AIDS vaccine research is a godsend for many young biotech companies. Since the advent of gene splicing in the late 1970s, scientist-entrepreneurs have been looking for projects that put their specialized know-how to work. Most of these start-ups have focused on health care, which offers vast markets for useful new drugs. But few biotech companies can conduct specialized research without outside financial help.

As the epidemic worsens, money is flowing into biotech houses in ever-increasing amounts. Some comes from NIH, which has earmarked $135 million for AIDS research. Established pharmaceutical companies are big investors. Merck, for example, is bankrolling research at Repligen Corp. in Cambridge, Massachusetts; more than a third of Repligen's 60 scientists are working on an AIDS vaccine. The Institut Merieux of Lyons, a French company that sells vaccines in 150 countries, is financing the AIDS research team at Cambridge BioScience. Ciba-Geigy, the Swiss pharmaceutical giant, has formed a joint venture with Chiron Corp. of Emeryville, California, that will perform AIDS vaccine research.

These deals represent major coups for the biotech companies involved. Repligen got $7.5 million from Merck in the first year of its agreement, along with guarantees of further financial support and of royalties from any AIDS vaccine marketed by Merck. Cambridge BioScience likewise won commitments for research funding over several years and for product royalties from the Institut Merieux, although neither company has disclosed the size of the deal. Ciba-Geigy

THE KILLER WITH A SUGAR COATING

A nightmare of nature, the spherical AIDS virus (left) thrives in the very cells that normally help destroy invaders. The virus's outer shell consists of sugars, glycoproteins, shown here as knobby protruberances, that lock onto the surface receptors of a helper T cell, a type of white blood cell that is part of the body's defenses. The virus core contains a genetic blueprint for its replication (the red strands); it also holds an enzyme, reverse transcriptase (green dots), which helps the virus insert its genes into the nucleus of an infected cell. Scientists hope an AIDS vaccine will produce antibodies to block the virus from fusing with the helper T cell (below).
is funding six vaccine projects at Chiron, including herpes and malaria as well as AIDS.

Clearly, a safe and effective AIDS vaccine would be a blockbuster product. With estimates of the number of Americans now harboring the virus ranging from 800,000 to more than two million, the spread of HIV—which can be transmitted sexually or by contact with infected blood—is already a major social catastrophe. People in the highest risk groups for AIDS, which in the U.S. are largely male homosexuals and intravenous drug users, are obvious candidates for an AIDS vaccine. So are promiscuous heterosexuals.

Though only 1,644 cases of AIDS resulting from heterosexual activity have been recorded by the Public Health Service—a mere 4% of the U.S. total—that represents a 69% increase in just 12 months. Some specialists argue that this development calls for a wide-reaching response. Says Dr. Paul Volberding, head of the AIDS clinic at San Francisco General Hospital: "It's hard to say somebody isn't a member of a risk group. The gradual leakage of the virus to the broad population cannot be wished away. There is only one way to deal with an epidemic like AIDS, and that is to immunize everyone against it."

Short of that, besides the two principal risk groups, anyone who could be accidentally infected by HIV-contaminated blood could benefit from an AIDS vaccine. That includes millions of health care workers and law enforcement officers as well as virtually anyone likely to require a blood transfusion. The Centers for Disease Control in Atlanta estimates that some 1,100 Americans have been infected by the AIDS virus from transfusions. Most cases occurred before 1985; after that, rigorous screening programs reduced the incidence of the virus in blood supplies to less than one unit in 50,000. But since more than 8.5 million transfusions take place in the U.S. each year, as many as 170 new AIDS cases annually could result from that cause alone.

THE DIFFICULTIES that lie in the way of stopping the AIDS virus are humbling. With most diseases, the immune system ultimately beats back an infectious invader and produces substances called antibodies that guard against future attacks. The underlying principle of most vaccines is to use a nonviable or killed strain of the disease-causing microbe to stimulate the immune system's defenses before they are needed. Polio and measles vaccines—both of which took decades to develop—work precisely this way. "Vaccines don't protect you from getting infected," says John Lifter, Cambridge BioScience's vaccine chief. "They simply accelerate your immune response. They put your troops on the beach when the invader arrives."

But conventional vaccine strategies fail miserably against the AIDS virus, which is a master of biological subterfuge. HIV belongs to a little-understood class of microbes called slow viruses that manage to enter the body without tripping an immune response for weeks, even months. As a result, vaccine- created antibodies might never detect HIV in time to stop it from spreading.

Once they are established, HIV infections last for life. Increasingly, researchers believe that everyone who is infected with the virus will eventually develop AIDS and die. (For a look at research into treatments for those who already have the virus, see box.) The AIDS virus is one of a group known as retroviruses, which insert their own genetic code into the cells they invade. With particular malice, HIV picks on cells that normally recognize (see illustration). HIV mutates rapidly. Hundreds of different strains have already been identified; as with the flu virus, a vaccine designed to stimulate antibodies against one strain may be worthless against the others. Many scientists consider such rapid mutations a clever viral survival tactic, tossed out like chaff that foils radar, to preoccupy the immune system while HIV goes about its deadly business. Says George Washington University biochemist Allan Goldstein: "HIV is like a combination lock whose code constantly changes. Each infected individual could have a different combination, and within each individual the numbers can continually shift." Neither the MicroGeneSys vaccine nor any other prototype under consideration for human trials is likely to be effective against the full array of AIDS viruses.

FINALLY, there is no natural, nonviral form of HIV that scientists can mimic with a vaccine. The discovery of such weakened strains was crucial to the development of the polio and measles vaccines. (Only 5% of the people infected by the polio virus ever developed the full-blown disease.) Virologists also worry that a killed AIDS virus could still contain enough genetic information to cause the disease they are trying to prevent.

To overcome these obstacles, scientists are deploying a variety of experimental vaccine strategies based largely on gene-splicing techniques. As a safer alternative to killed AIDS viruses, most vaccine teams are following the lead of MicroGeneSys in trying to construct a genetically engineered agent. By cultivating nonlethal fragments of the virus in test tubes, researchers hope to trick the body's immune system into responding as it would to an HIV infection. But which fragments will elicit the greatest number of protective antibodies? Most teams, including those at Repligen, Chiron, MicroGeneSys, and Genentech, are experimenting with proteins found on the outer shell of the AIDS virus, since it is the part of the invading microbe that the immune system eventually recognizes (see illustration).

Yet experimental vaccines based on this approach have failed to protect chimpanzees, the only other animals susceptible to the AIDS virus. Researchers believe that the trial vaccines did not work because they knocked out only a single strain of HIV. Repligen aims to overcome this problem by preparing a cocktail of five or six synthetic virus fragments in the hope of neutralizing a broad range of strains. Another solution, proposed
by researchers at Viral Technologies, a small AIDS vaccine company in Washington, D.C., is to develop a vaccine that simulates HIV's inner core, which varies little from one form of the virus to another.

Cambridge BioScience, Genentech, and Chiron are trying to boost the response of the immune system to their vaccines with specialized compounds called adjuvants. Although these substances have no therapeutic value, they function as irritants that alert the body to the presence of a vaccine. Says Harvard AIDS researcher William Haseltine: "We have to present something that looks like the virus to our bodies and at the same time provokes a much more powerful immune response."

Researchers at Chiron hope their adjuvants will elicit other powerful defense mechanisms in the immune system. Dino Dina, the company's chief virologist, explains, "When you get the flu, a whole host of nonspecific immune responses—which are what make you feel sick—kill the virus. Then you develop antibodies. We think HIV might establish itself by evading those mechanisms." As a result, he wants to mount a Star Wars attack on the AIDS virus that incorporates a number of adjuvant-stimulated defenses—including the release of immune system boosters, called lymphokines, which command the body to produce specialized killer T cells that can attack and destroy HIV-infected tissue. Says Dina: "When you don't know what to hit specifically, you have to try to hit everything. We want to attack it at every known level to kill the first invading cell as soon as possible, either with antibodies or by some other means."

EVEN AT BEST, Chiron thinks its vaccine might stop HIV only half the time. But, says Dina, "when you are talking about AIDS, you really have done something if you reduce the chance of infection by a factor of two. We would pursue FDA approval if we could stop a majority of all strains. At that point it becomes a game of chipping away at the viruses you haven't covered yet."

Still-newer strategies are reaching the drawing boards as the first experimental vaccines move into clinical testing. One of the most novel proposals, devised by Harvard's Fields and immunologist Mark Greene of the University of Pennsylvania, attempts to fashion a facsimile of the outer shell of a virus with a process that resembles casting a plaster of Paris mask. With this approach, scientists first induce animals to make antibodies to the AIDS virus. These antibodies are then injected into other animals, causing them to produce a second antibody, which Fields calls an anti-idiotype. The hope is that this second antibody, which resembles the shell of the original virus, will work as a vaccine.

Other scientists are beginning to explore the possibility of producing prophylactic chemicals that will poison and kill the AIDS virus, much as quinine, a chemical extracted from plants, can prevent malaria by attacking and killing the parasite that causes the disease. The trick with this approach, says Haseltine, one of its strongest advocates, "is to find compounds that are easily administered, have no side effects, and are cost effective. And that is still a fairly tall order."

Nearly everyone working on an AIDS vaccine agrees that all the programs are hampered by gaps in scientists' understanding of
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virology and immunology. Says Dina of Chiron: "We haven't the slightest idea how the virus causes AIDS. We know that in an infected person only one cell in 10,000 harbors the virus, so it's difficult to explain how so little virulence can cause such a disastrous defeat. That creates a problem in terms of how to attack." Answering these questions could lead to a breakthrough not only for AIDS research but also for a host of other diseases. Says Genentech's Martin: "We're going to learn so damn much about virology and immunology by understanding AIDS that in some ways it may be a blessing in disguise. Spinoffs from this work will help research on cancer, infectious diseases, and even autoimmune diseases, such as arthritis."

At many companies the initial surge of excitement at the start of the AIDS vaccine race is giving way to the recognition that the marathon could go on for decades. Nevertheless, most scientists believe that someday AIDS will be stopped. "There are some grounds for hope," says Robert C. Gallo, the scientist at the National Cancer Institute who played a major role in identifying HIV. "We've never seen a patient infected by more than one strain of the virus. But we know some of these people were exposed several times. Somehow they are protected from infection against other strains." Ronald Ellis, head of Merck's cellular and molecular biology research labs, is also hopeful. A veteran of at least four successful vaccine projects, most recently hepatitis B, he believes that there is a good chance scientists will learn how to stop AIDS as well. "What the public doesn't begin to appreciate is how complex these projects are," he says. "We built up 15 years of knowledge about hepatitis B before we developed a vaccine. It took decades to reach a comparable level of understanding of some other viruses. The AIDS virus has only been known about for three years. This is still a brand-new area."

Taking the long view is especially difficult with AIDS, which kills everyone who gets it. The history of vaccine development offers some consolation, because it has been marked by lucky accidents. Nearly 200 years ago the English physician Edward Jenner invented the world's first vaccine after noticing that milkmaids exposed to the cowpox virus, which is harmless to people, did not contract smallpox. With so many scientists focused on AIDS, at any moment one of them could stumble across an idea that makes everything fall into place.