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Quest for AIDS Vaccine Rises From Ashes of Dashed Hopes

By DENISE GRADY

Seventeen years have passed since federal officials and a prominent scientist, in a moment of wishful thinking that they will never live down, stood up at a news conference and announced that an AIDS vaccine would be ready for testing in two years, and on the market in three.

There is still no AIDS vaccine. None is even close. Globally, 36 million people are now infected; 21.8 million have died, including 3 million last year. Each year, 5.5 million people are newly infected, 15,000 a day.

An AIDS vaccine never was a given. Not every disease gives way to a vaccine. There is still no vaccine for malaria, and no truly effective one for tuberculosis, even though each disease has been known and studied far longer than AIDS.

AIDS is nothing like polio, measles, smallpox or any other viral infection in humans for which a vaccine has been created. People do not routinely become immune to H.I.V., the AIDS virus, after being infected. The virus destroys the immune system itself, killing the very cells that should repel it and that a vaccine should call to action.

Since 1987, 30 experimental H.I.V. vaccines have been tested in people, and an effective one has yet to be found. In the 1990's, the field fell into a funk, with every setback another stinging reminder of the folly of optimistic predictions.

And so it may seem remarkable that experts now dare to say they may finally be on a path to a vaccine that will offer at least some protection. They are hedging their bets, cautioning that a finished product is probably still 10 years away. But scientific advances have led to renewed enthusiasm.

Spending on vaccine research by the National Institutes of Health is projected to be \$282 million this year, 12.6 percent of the budget for AIDS and twice the amount spent in 1997. And several large drug companies, which previously saw little promise in the field, are now interested.

"These are very good days," said Dr. Norman Letvin, a professor at Harvard Medical School. "I'm the most dour, cynical, pessimistic guy. I've been at this for decades, too long to be anything but shellshocked. And I am very optimistic."

Dr. Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases, said: "I think we will have a vaccine. I'm not so sure it's going to be a vaccine in the classic mode we make for other preventable diseases where the major objective, the successful endpoint, is to prevent completely the infection in a particular population."

Many researchers agree that at least for now, the goal of preventing infection may be out of reach. They have shifted their sights and strategies. Recent studies suggest that it may be possible to develop a vaccine that instead of preventing infection, will control it, prevent the progression of disease and reduce a person's risk of transmitting H.I.V., by holding down the levels of virus in the bloodstream and secretions.

More than one type of vaccine, or a combination of vaccines and antiviral drugs, may be needed. And the first vaccines may not work for a high percentage of the population. But researchers say that in places like Botswana and South Africa, where infection rates are high, even a partly effective vaccine can make a big difference.

Dr. Letvin said, "What this takes is a rethinking of what a vaccine should be."

A vaccine is desperately needed. Margaret McCluskey, coordinator of a vaccine study being conducted in Washington by Johns Hopkins University and VaxGen, a vaccine manufacturer, said: "Most public health professionals agree that unless we find a definitive vaccine, which is questionable, we may not see an end to the pandemic in our lifetime. Not just an end to it. We may not even be able to control it."

Although AIDS can be prevented, global prevention efforts have been weak, with education negligible and condoms scarce in some countries, unavailable or frowned upon for religious or cultural reasons.

Antiviral drugs have worked wonders for individual patients, but they will never contain the epidemic. The drugs can reduce the spread of disease by lowering the amount of virus in blood and secretions, but usually, by the time people start taking the medicine, it is too late: they have already passed H.I.V. to others.

From the start, it was obvious that AIDS differed sharply from other viral diseases for which scientists had been able to make vaccines, like smallpox, polio and measles.

With those illnesses, vaccine researchers knew that people who got sick and recovered also became immune and did not catch the same disease again. It was reasonable to think that a vaccine might be able to harness the body's ability to defend itself.

But AIDS is different. People who get sick do not routinely recover and become immune.

And H.I.V. is like a shape shifter from the pages of science fiction, mutating so fast that the immune system cannot keep track of it. Worse still, unlike other viral infections, it selects the cells of the immune system as its primary targets.

An AIDS vaccine, then, must teach the immune system to fight H.I.V. in a way it does not normally do. The task is not impossible, scientists say, but it will not be easy.

One difficulty will be in deciding how to tell whether a vaccine works. There is no test that measures immunity to H.I.V.: scientists do not even know what the signs of immunity might be. They may be hard to distinguish from signs of infection. And if a vaccine is given to infected people who are also taking antiviral drugs, it will be even harder to figure out what is going on.

Researchers say they know surprisingly little about how vaccines work. Vaccines now in use for diseases like polio, mumps and measles are thought to act mostly by stimulating one of the two arms of the immune system: the one called humoral or antibody-mediated immunity. Antibodies are proteins that stick to viruses and other invaders and prevent them from entering cells. Keeping viruses out of cells is an important means of defense, because all viruses, H.I.V. included, need to penetrate their hosts' cells to replicate.

There are backup forces, too. The second arm of the immune system, cell-mediated immunity, includes several types of white blood cells that destroy cells that have been infected by viruses. Cell-mediated immunity eliminates viruses that manage to get past the antibodies.

Part of what makes H.I.V. so formidable is that it kills a vital part of the cellular immune system, CD4 lymphocytes or helper T-cells. Helper T-cells orchestrate the workings of both arms of the immune system; losing the cells cripples the system.

When a person is infected by H.I.V., both arms of the immune system react, deploying many types of antibodies and immune cells. But in the vast majority of people, the antibodies do not block infection, possibly because the virus mutates so rapidly that the immune system cannot design new antibodies fast enough to keep up.

But cellular immunity is effective, often for years. In most people, virus levels rise and then fall, beaten down mostly by a white blood cell called a killer T-cell.

In the end, though, the virus wins. Helper T-cells gradually die off, the immune system falters, and opportunistic infections, the hallmark of AIDS, set in.

The idea behind vaccines is to give the immune system a head start, so that when a virus tries to invade, the vaccine has already trained the immune system to recognize it, and the system can react fast enough to outpace the attack.

The first efforts to make an AIDS vaccine followed the traditional path, and set out to stimulate the immune system to make antibodies that would prevent infection. Even though infected people do not produce effective antibodies, scientists hoped they could develop a vaccine that would do what the body alone could not.

Most of the first AIDS vaccines tested in people were unlike the classic, successful vaccines for measles and polio, which use whole viruses, either killed or weakened, to turn on the immune response. Scientists feared that a weakened H.I.V. might mutate and regain its ability to cause AIDS, and that even a killed virus preparation could be dangerous if a mistake in processing left any live virus.

Instead, the earliest efforts at AIDS vaccines used harmless fragments of the virus in hope of activating the immune system. The fragments included stretches of viral DNA or proteins found in the outer coat or envelope of the virus.

The results were disappointing. Although the vaccines did stimulate antibody production, the antibodies were not the "broadly reactive" kind that seem to be essential for protection. Tested in the laboratory, the antibodies could neutralize only the strain of virus that the vaccine was made from, and not virus samples taken from patients. Their odds of success against rapidly mutating viruses in the real world seemed small.

Nonetheless, a vaccine made of an envelope protein called gp 120, developed by VaxGen, is being tested for effectiveness in thousands of people in the United States and Thailand, with results expected in 2002. It is the first vaccine in the United States to reach large-scale efficacy trials, known as Phase 3 studies.

Although many scientists doubt that the vaccine will protect against infection by itself, some say it may be useful when combined with other types of vaccines.

Many scientists are more enthusiastic about recent advances involving vaccines that focus on stimulating cellular immunity, rather than just antibodies.

Several research teams, one led by Dr. Letvin, another by Dr. Harriet Robinson at Emory University and others by Dr. Emilio Emini and Dr. John Shiver at Merck, a major vaccine manufacturer, have had extremely encouraging results in monkeys that were given experimental vaccines and were then exposed to a virus that normally gives monkeys an unusually severe and rapidly progressive AIDS-like illness.

The vaccinated animals became infected, but their killer T-cells managed to keep the virus in check, and they never got sick. Meanwhile, unvaccinated animals exposed to the same virus became severely ill.

The groups tested different vaccines, but they were variations on the same theme: stirring up the immune system with various stretches of DNA from the AIDS virus, none capable of causing infection. In some experiments, DNA alone was used, but the strongest responses occurred when animals were first given shots of a DNA vaccine and later a booster shot in which the DNA was spliced into a harmless virus that would further stimulate the immune system.

"These most recent studies have been more promising than any previous ones," Dr. Fauci said. "It's exciting data that is now capturing the imagination of people in the field." But, he added, "We don't know if it will be extrapolated in humans."

There is reason to be cautious. Monkeys are not people, and the virus they were given was not the same one that causes AIDS in people. Some researchers say that the virus used in the studies is much easier to control than H.I.V., and that the vaccine may not work so well in the real world. In addition, the animals could still get sick. People infected with H.I.V. can take 10 years or more to come down with AIDS.

"This would not be the first time a model didn't reflect the reality of what goes on in humans," Dr. Fauci said. "To be honest, I wouldn't be surprised if it didn't."

The only way to find out is to do tests in humans. Merck's approach is already being tried in people, and Dr. Robinson's will be put into human trials within a year. The studies will be Phase 1 trials, pilot studies in small groups of people, mainly designed to check for safety and to test the body's reaction to different doses. The vaccines will be tested in healthy people as well as in some who are infected by H.I.V. to see if the infection's course can be changed.

Seven other vaccines, including some designed to stimulate cellular immunity and some designed to stimulate both arms of the immune system, are also being tested in the United States, Canada, Thailand, Kenya, Uganda, Holland and Britain. If any work, it is still unlikely that a product will be marketed before 2010.

Twenty other potential vaccines are still being developed.

Dr. Donald Burke, director of the center for immunization research at Johns Hopkins, warned that if an effective vaccine was created, developing countries, which have the most urgent need, might not be able to afford it.

"There's every likelihood that we will see a replay of the AIDS drugs access issues," he said. "Who will produce it, at what price, how to distribute it, what populations will have top priority? I hope we can maybe do it a little better with the AIDS vaccine."

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