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vaccine basics

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VACCINES ARE AMONG the most effective (and cost-effective) public health measures we have. They've wiped smallpox off the planet and come close to doing the same thing for polio. Every year they save many millions of lives from childhood illnesses like measles, mumps and whooping cough, and from a long list of other diseases—with the crucial caveat that lots of work still needs to be done so these life-saving products reach more people.

Yet familiar as vaccines are, many people don't understand how they work or how they are made. More specifically, even fewer people understand the unique challenges in developing a vaccine against HIV. So we begin this section about AIDS vaccine science with some background on ***immunity*** and vaccine development.

The immune system is the body's set of defenses for recognizing and eliminating germs that cause disease (called ***pathogens***). When functioning properly, the immune system can tell the difference between these invaders and the body's own cells and ***proteins***. In many cases, it can marshal an ***immune response*** that destroys the pathogen. When you get sick, some of the symptoms you experience—such as fevers and rashes—are actually signs of your immune system on the attack. For many diseases, once you get better you are then protected against that pathogen in the future.

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In fact, the field of immunology grew out of the observation that people who had recovered from certain infectious diseases were protected from ever getting the same disease again. In ancient Greece, it was known that only those who had recovered from the plague could nurse the sick because they would not contract it a second time.

With AIDS there is no proven instance of the immune system protecting an individual from infection or from ultimately succumbing to AIDS. But there are intriguing examples which suggest that at least partial natural protection occasionally occurs—for example, among a small percentage of commercial sex workers who are continuously exposed to HIV but remain uninfected, and in those few infected people who remain symptom-free for unusually long periods of time (called ***long-term non-progressors***). Scientists are trying to understand the reasons for this protection by studying the immune systems of these people, and then to develop AIDS vaccines that stimulate the same type of immunity.

Although making vaccines is now a high-tech undertaking, the concept of immunity was recognized as far back as 1000 years ago: The Arabo/Islamic medical literature contains accounts of healthy people being inoculated against smallpox by exposure to a small amount of fluid from the skin sores of smallpox sufferers (that is, to a low dose of pathogen). The technique spread to India and Persia, and was apparently also practiced in parts of Africa by the early sixteenth century. Although it was a highly risky procedure that caused some infections and deaths, it nevertheless improved the chance of survival during an epidemic, given the 30% death rate from smallpox.

It wasn't until the end of the eighteenth century that the English country doctor Edward Jenner developed the first true vaccine. Intrigued by the observation that milkmaids who contracted a mild disease called cowpox never became sick with smallpox, Jenner reasoned that cowpox fluid might be protective—and safe, since it was much weaker than smallpox (especially in humans). To test his idea, he inoculated an eight-year-old boy with the fluid and later intentionally infected him with smallpox. Although the experiment was certainly not safe or ethical by today's standards, his idea proved to be right: The boy remained healthy.

Jenner's technique spread quickly through Europe, but it was almost a hundred years later before French microbiologist Louis Pasteur applied it to other diseases. When Pasteur returned from vacation and injected some chickens with fluid containing the pathogen that causes cholera in chickens, and that had been fatal in earlier experiments, he was surprised to see that the chickens recovered. Aging had weakened the cholera bacteria—and Pasteur quickly discovered that this weakened ***(attenuated) strain*** protected animals against the fully pathogenic one. This finding led him to develop an attenuated vaccine against rabies, and over the next fifteen years attenuated or killed pathogens were also used to make human vaccines against cholera, typhoid and plague.

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Although Pasteur proved that vaccination worked, he didn't understand the mechanisms involved. He developed his vaccines empirically, that is, by trial and error. Even today, there is debate among AIDS vaccine developers about the right balance between basic studies to work out the mechanisms of protection against HIV, versus a more empirical approach.

Since Pasteur's time, vaccines have been developed for many diseases that were once major afflictions of humankind. Alongside the eradication of smallpox, vaccines have brought about dramatic declines diseases such as polio, diphtheria, tetanus, measles, mumps, whooping cough and German measles (rubella), along with certain types of pneumonia and meningitis. There are even vaccines that prevent selected cancers: ***Immunizing*** infants against hepatitis B prevents them from getting liver cancer caused by chronic infection acquired at birth, while a promising experimental vaccine against the ***human papilloma virus** (HPV)* may protect against cervical and rectal cancer.

Vaccines in use today follow only a few basic designs. Most common are attenuated vaccines (like the smallpox or oral polio vaccines), which contain a live pathogen that has been weakened to reduce or eliminate its potential to cause disease. Also common are vaccines made from pathogens that have been killed or rendered unable to multiply.

Until about 25 years ago, these were essentially the only two strategies for making vaccines. That's when new methods for ***genetic engineering*** ushered in another possibility: Making vaccines from just part of the pathogen rather than the whole thing, eliminating the tiny but real risk that the vaccine could cause the very disease it should prevent (for example, if an attenuated strain reverts to a more infectious one). In 1984—just as HIV was discovered as the cause of AIDS—a hepatitis B vaccine made with this technology was licensed, and hailed as the wave of the future. From that point on, traditional approaches were quickly put on the back burner, with vaccine developers reluctant to pursue them (in the case of HIV) because of their potential risk.

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Clearly vaccination is a powerful and cost-effective weapon against disease, as the conquest of smallpox dramatically demonstrated. But despite this progress, more than 2 million infants worldwide die each year from diseases that are preventable by existing vaccines. Although more than 350 million people are chronically infected with hepatitis B virus, globally the vaccine reaches only about 40% of those who should have it, according to the World Health Organization.

But it is critical to remember that vaccines have not yet tamed some diseases of great importance, including malaria, adult tuberculosis and several sexually transmitted diseases. Malaria and tuberculosis each cause roughly 2 million deaths per year, yet there are still no vaccines against either one.

And despite unprecedented efforts, no effective vaccine has yet been developed against HIV, which killed 3 million people in 2003—more than any other infectious disease—while some 40 million people now live with HIV/AIDS.

SINCE THE FIRST DISCOVERIES of the science called immunology, we have learned a great deal about how the immune system responds to the outside world. One important idea is that there are two kinds of disease-specific immunity:

- *Humoral immunity,*
  in which the immune system makes proteins called ***antibodies*** that recognize a specific pathogen like HIV in the blood and block (or ***neutralize***) its activity before it can infect the body's cells.
- *Cellular immunity,*
  which steps in once the pathogen has infected some of the body's cells. Its role is to recognize and destroy infected cells in a number of ways, so that virus cannot multiply and then spread to other cells.

(See chapter 5 for an illustrated primer on how these immune responses fight infection.)

Many scientists believe that both kinds of immunity will be needed for an AIDS vaccine which prevents infection. But while most AIDS vaccines in the pipeline stimulate at least some cellular immunity, so far they have not induced antibodies that are effective in neutralizing real-world (rather than laboratory-grown) HIV virus.

A related issue for vaccine development is the route of infection. Injection drug users become infected when HIV enters their bloodstream directly, while sexual transmission takes place when HIV crosses ***mucosal tissues*** that line the genital tract and other body cavities. The mucosa have their own immune system, which we know much less about. But a growing number of researchers believe that immunity at the mucosal surfaces may also be crucial for protection against HIV.

Other chapters in this section describe *how* AIDS vaccines are developed and *what types* of vaccines are being made.