Along with their strength and teeth, the elderly typically lose their responsiveness to vaccines. Researchers are uncovering what goes wrong as we age, knowledge that might allow them to tailor vaccines for older folks or pep up the aging immune system. One failing is the disappearance of the thymus, the gland in which T cells mature. The blood also fills with inert T cells lacking a key surface molecule. These cells might accumulate because of infection with microbes that can lurk in the body for decades. Although researchers can’t yet rejuvenate the immune system, they are exploring options from reformulating vaccines to removing troublesome T cells from the blood.

Ah, fall, when we look forward to the World Series, Technicolor foliage, and the kids finally going back to school. The season brings another ritual—lining up at doctors’ offices and clinics for a flu shot. The U.S. Centers for Disease Control and Prevention (CDC) recommends annual vaccinations for everyone over age 50 because the influenza virus picks on the old. According to CDC figures, 90% of Americans who died from the germ in the 1990s were age 65 or above.

But for seniors, a sore arm doesn’t guarantee a flu-free winter. Even when the vaccines contain the right combination of viral strains—they didn’t last year—between 30% and 75% of older people won’t gain immunity to the disease. In contrast, only 10% of young adults fail to respond. Other vaccines also let down the elderly. For example, the preparation against the bacterium *Streptococcus pneumoniae*, which can abuse the lungs, leaves roughly 20% to 50% of older people vulnerable.

Failing immunity creates a Catch-22 for seniors. Because the immune system weakens over time, they need the protection vaccines confer more than ever. But they can’t muster this resistance because of their weakened immune systems.

This problem is growing in urgency for several reasons. For one, the elderly population will soar as the baby boomers enter their 60s, starting in 2006. In addition, as more people stay healthy past retirement age, they are traveling to parts of the world where they need vaccines against diseases such as yellow fever and typhoid—but nobody knows how much protection these shots provide to seniors. Moreover, researchers hope that therapeutic vaccines now under development will rouse defensive cells to take on cancer and other conditions. But a sluggish immune system could deny seniors the benefits of these advances. And the threat of bioterrorism elevates vaccine responses to a national security priority. To design a vaccine to combat a new bioweapon, scientists will have to contend with the graying immune system.

However, investigating the vaccine problem requires an about-face from researchers, says immunologist Cornelia Weyand of Emory University in Atlanta, Georgia. “For 50 years, we have focused on suppressing immunity” to allow organ transplants and pacify autoimmune diseases. “Now we have to look at the problem from the opposite angle.” But a string of recent discoveries might eventually help liberate old folks from their cruel bind. Researchers are beginning to understand the changes that muffle old-
er people’s response to vaccines. Some scientists are testing ways to beef up vaccines, such as by adding immune-stimulating compounds. Other researchers are toying with ideas for reviving the aged immune system, such as filtering faulty cells from the blood and regrowing the thymus in a culture dish.

The Persistence of Immune Memory

A vaccine works by duping the body’s defenses. It delivers a load of antigens, pathogen molecules that spur immune cells to react as if the blood swarmed with viruses or bacteria. The body pumps out B cells that gush microbe-neutralizing antibodies, cytotoxic T cells that assassinate infected cells, and helper T cells that orchestrate the body’s counterattack (see “Immunity Challenge”).

Some cells of each type linger as memory cells, the key to vaccination’s success. Memory cells can remain on duty for the rest of a person’s life. They prowl the blood and stake out the lymph nodes and spleen, which help screen the body for invading pathogens. If a real microbe carrying that vaccine antigen infiltrates the body, the immune system has ready-made defenses on alert.

Vaccines might seem like old hat—after all, Edward Jenner started immunizing people against smallpox more than 200 years ago. However, researchers have only recently started probing how vaccines work—or fail—in the elderly, says immunologist Rita Effros of the University of California, Los Angeles. Most vaccines are “developed in young, healthy animals and tested on young, healthy people,” she says. Even those immunology studies that focus on older subjects usually leave out the sickest people, says geriatrician Steven Castle of the Veterans Affairs Greater Los Angeles Health Care System. Immunologists typically choose their subjects using a set of guidelines called the SENIEUR protocol, which disqualifies all but the healthiest seniors. The protocol’s goal was laudable—to separate the effects of aging and disease—but the rules ended up excluding from immunity studies the people who most need protection, says Effros (see “Test Patterns”).

Research on the elderly’s diminishing immunity is perking up, says Effros, and drug companies are taking an interest in declining vaccine effectiveness. But seniors can’t yet walk into the doctor’s office and ask for a batch of vaccines tailored for their immune system. This fall, octogenarians and their 4-year-old grandchildren will still get the same flu shot.

Of all the vaccines used in the elderly, immunologists know the most about why the influenza injection fails, notes geriatrician Janet McElhaney of the University of Connecticut Health Center in Farmington. “If you look at all other infections, nothing so selectively hits the aging immune system,” she says. The virus is particularly dangerous for the elderly because it changes its coat rapidly, so vaccines or infections don’t provide long-term immunity. The memory cells aim at a surface molecule that the virus has long ago reshaped.

Help, I Can’t Find My Thymus

You’d notice if your liver or stomach disappeared. But the thymus, which is almost as large as the heart at birth, vanishes as we grow old without so much as a farewell. After puberty, the spongy gland nestled behind the breastbone begins to wither and fill with fat. By age 60, it’s virtually gone.

Its loss undermines the immune system’s response to vaccines, because the thymus serves as a finishing school for T cells. Born in the bone marrow, the cells mature in the thymus, graduating as what are called naïve T cells. These immunological innocents have never encountered their target antigen and are crucial for the immune system’s response to a new pathogen or vaccine. Naïve T cells fight off the initial exposure to a pathogen, and some morph into memory cells that fend off repeat infections. Without the thymus, “you are dependent on the [naïve] T cell pool generated while you are young,” says immunologist Beatrix Grubeck-Loebenstein of the Institute for Biomedical Aging Research in Innsbruck, Austria.

These T cells become scarce in old age. The weaker the initial response involving naïve T cells, the weaker subsequent responses from memory cells—and the less protection a vaccine provides. “The T cell system is the only system in the body that becomes cut off from its stem cells,” says Grubeck-Loebenstein.

Signs of Decline

Just as some 70-year-olds can still run the Boston Marathon, some seniors can manage a hearty response to vaccines—even with no thymus. Exactly how is a mystery. In any case, aging seems to spare some older people’s immune systems. Researchers see an increase in variability with age, not a uniform decline across individuals, says Weyand. Right now, doctors lack a test to predict whether an elderly person’s immune system will respond to a shot, she says. But researchers have pinpointed molecular markers on T cells that hint at vaccine failure or success.

Three years ago, for instance, Weyand and colleagues gauged immunity in retirement home residents vaccinated against flu. To ensure protection against the range of viruses that might appear in a particular year, the mixture usually includes antigens from three strains. Weyand says “we were very surprised” at how few patients mustered antibodies to all the strains—a mere 17%. Delving further, the researchers discovered that patients whose immune system ignored the vaccine carried large numbers of one type of cytotoxic T cell. The cells had lost a receptor, called CD28, normally found on their surfaces. This protein helps activate the cell to battle pathogens and allows it to move from the blood into the organs, so cells without CD28 are poor fighters.

A 2002 study by Grubeck-Loebenstein and colleagues also detected an abundance of CD28-lacking cells in patients who didn’t respond to flu shots. The next year, her team showed that elderly people who made copious amounts of antibodies after vaccination carried a different form of cytotoxic T cell, which bore a particular type of the CD62L receptor. Although such cells don’t appear in people under 40, they show up in more than one-third of patients over 60. The researchers suspect that cells toting this version of CD62L amp up immunity, and if so, tests for the protein might help doctors recognize patients who will benefit from vaccination.

“The T cell system is the only system in the body that becomes cut off from its stem cells.”
—Beatrix Grubeck-Loebenstein

sageke.sciencemag.org/cgi/content/full/2004/27/ns4
Cytotoxic T cells can also run low on a key piece of their arsenal, according to work by McElhaney and colleagues. The researchers discovered that T cells from patients who don’t respond to flu shots produce less of an enzyme called granzyme B, which helps punch holes in infected cells.

More controversial is whether aging alters the “temperament” of the immune system, triggering a shift from one pathogen-fighting mode to another. How the immune system responds to antigens depends on the types of cytokines, or chemical messages, cells pass back and forth. When helper T cells release so-called Th1 cytokines, immune workhorses such as cytotoxic T cells go into attack mode. The signals also provoke inflammation. Th2 cytokines, by contrast, cause B cells to release antibodies and spur reactions such as allergies.

The Th1 response is usually stronger in young mice. But in old animals, Th2 often predominates, and many immunologists assert that the same transformation occurs in people. The shift could undermine vaccination in the elderly by shackling cytotoxic T cells, says McElhaney. These cells are vital for immunity against flu because they root out viruses hiding within body cells, she says. If the idea is right, tweaking cytokines might rejuvenate the immune system—an approach that’s already in practice for a less deadly but still excruciating condition. Every year, millions of people undergo a therapy—allergy shots—that nudges the immune system’s dial from Th2 to Th1.

But Grubeck-Loebenstein’s work suggests that the “Th1 good, Th2 bad” notion is backward. Her results show that people who release hefty amounts of antibodies in response to the influenza vaccine produce relatively large numbers of cells that emit Th2 cytokines, whereas sick older folks are overstocked with Th1 cytokines, which means that the immune system is aging gracefully. Researchers need further experiments to determine how the balance of Th1 and Th2 cytokines changes with age and to nail down the effects on vaccine responsiveness.

**War Without End**

Just as an old soldier can show off his scars, the elderly immune system bears the telltale signs of past battles. The CD28-lacking T cells that build up in some aged patients are vestiges of a long-term struggle against viruses and might end up throttling the immune system, according to one hypothesis. T cells in the culture dish lose CD28 after duplicating repeatedly and entering a semidormant state called replicative senescence, in which they can no longer divide (see “More Than a Sum of Our Cells”†). The observation that cultured T cells and those from older patients lack CD28 and carry tattered telomeres suggests that the

† sageke.sciencemag.org/cgi/content/full/2001/1/oa4
latter have also reached their division limit, says Effros.

But these old soldiers don’t just fade away. They stick around and cause trouble. Some evidence suggests that they suppress the immune system—patients with an abundance of these cells are less likely to reject transplanted organs—and might even weaken the skeleton (see “Many Roads to Ruin”). Researchers aren’t sure how CD28-lacking cells undermine the immune system, says Effros, but the body seems to have a “set point” for the number of T cells, and the duds might crowd out more useful ones. The senescent cells might also release cytokines that impede other defensive cells.

What drives certain T cells in the body to divide again and again, Effros and Grubeck-Loebenstein argue, are chronic infections with certain viruses, especially cytomegalovirus (CMV). The immune system can’t eighty-six CMV from the body, and it must continually pump out T cells targeted against the bug. After decades of fighting, the body’s ranks of T cells contain large numbers of just a few types of cells. Grubeck-Loebenstein’s most recent work shows that the CD28-lacking cells that she found in previous studies are specialized to battle CMV, supporting the hypothesis. The bad news, she says, is that nearly everybody catches the virus sometime during life.

Harnessing Darwin to Beat Bugs

T cells hog the attention, but faults in B cells can also interfere with vaccines, says immunologist Garnett Kelsoe of Duke University in Durham, North Carolina. A vaccine or infection activates only B cells whose antibodies match the foreign antigen. The immune system fine-tunes these antibodies through an evolutionary assembly line that occurs in the germinal centers, tiny clumps in the spleen and lymph nodes. There, hundreds of B, T, and other immune cells mingle in what Kelsoe calls “tiny Darwinian archipelagoes.” B cell genes that encode antibodies mutate rapidly, generating many slightly different versions of the proteins. Cells that make antibodies that best match the antigen survive; the others die. Within just a few weeks, multiple rounds of “hypermutation” and natural selection hone antibodies. The immune system filters the troublemaking T cells that lack CD28 from the blood, using a procedure akin to dialysis for kidney patients, Effros says. None of these ideas is ready for the clinic, and the more than 35 million Americans over age 65 will have to take their chances with the flu vaccine this fall. But within a few years, researchers might be able to ensure that seniors get more from a shot than an aching arm.

Mitch Leslie writes and hides from shots in Albuquerque, New Mexico.

References

10. S. Schwaiger et al., IL-4-producing CD8+ T cells with a CD62L+ (bright) phenotype accumulate in a subgroup of older adults and are associated with the maintenance of intact humoral immunity in old age. J. Immunol. 170, 615–619 (2003).