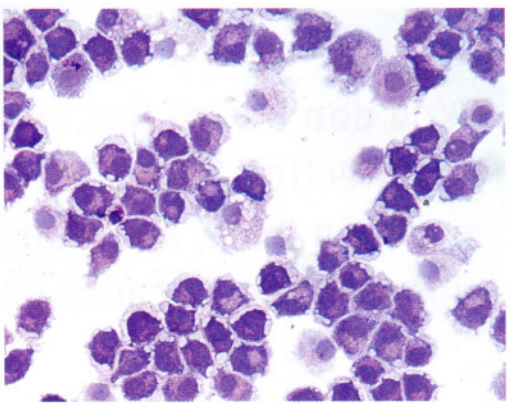
How Our Bodies Remember

The immune system's foot soldiers have long memories.

BY MARK CANTRELL



White blood cells are the body's foot soldiers.

WHEN YOUR BODY IS INVADED BY A VIRUS OR BACTERIA, IT BECOMES a war zone – complete with advance scouts, insurgents, troop surges and fierce battles. Even after the incursion has been crushed, your body's immune system remembers the intruders and can quickly mount a counterattack if they return – even if it's years later.

To understand how that's possible, it's helpful to know how the immune system is constructed. Its two main parts, the innate and adaptive systems, both fight infections. The innate immune system is the body's first line of defense, reacting quickly to pathogens but with a non-specific response. The adaptive system is able to create defenses tailor-made to fight the insurgent bacteria or virus and to remember them if a re-invasion should ever occur.

"Let's say you get bitten by a mosquito that's carrying the West Nile or yellow fever virus," explains Mark Slifka, Ph.D., associate scientist at the Vaccine & Gene Therapy Institute at the Oregon Health & Science University. "You'll get a local infection near the skin, and the viruses can eventually spread throughout your body. Fortunately, there are sentinels called dendritic cells that will grab some of the virus protein, run down to a local lymph node, and report that something bad is going on. That's part of the innate, very early part of our immune response."

Dendritic cells are so-named because they resemble neurons, which have surface projections called dendrites. The tentacle-like projections on dendritic cells are used to grapple invading organisms, or antigens, and drag them to a lymph node.

PREPARING FOR BATTLE

The lymph nodes and spleen are the boot camps of your body's immune system. "That's where the recruitment and training of your army happens," says Dr. Slifka. "The lymph nodes and spleen are great training facilities because they contain all the right cells to do the training. They can present the virus proteins in just the right way to stimulate T cells into action."

T cells are white blood cells, or leukocytes, that comprise the body's major defense system. When a dendritic cell arrives at a lymph node carrying its pieces of a virus or bacteria, it presents the material to a naive T cell, so-named because it has not yet been exposed to an antigen. "The T cells then 'hug' the dendritic cell that is carrying the virus proteins on its surface, and they memorize all the information about that pathogen," Dr. Slifka explains. Now the troop buildup begins: The T cells start to divide rapidly, and each new cell carries the blueprint of the virus or bacteria it is to attack.

"This proliferation of T cells is called clonal expansion," notes Cheong-Hee Chang, Ph.D., a professor in the department of microbiology and immunology at the University of Michigan Medical School. "Now we have a

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large number of T cells that all recognize the same pathogen. That's important because you want to have cells to fight a specific infection. When you have a bacterial infection, you don't want to generate cells that respond to viruses."

REPELLING THE INVASION

Once a T cell is carrying the blueprint for a pathogen, it's no longer naive. "We call them effector T cells at that point," says Dr. Chang. Now the new cells fan out through the body, swimming through the bloodstream to find a pattern that matches the one they carry. The effector T cells naturally migrate to areas of inflammation like soldiers heading for a combat zone.

"The cells can divide very rapidly; up to once every six to eight hours," says Dr. Slifka. "You can do the math – it's exponential growth. So they're able to quickly expand into tremendous numbers, then shoot into the body to search out and destroy the invaders."

It's worth noting that, by themselves, viruses can do nothing to harm the body. To do their damage, they must infect one of the body's own cells, in effect co-opting a cell's own replicating machinery and turning it into a factory that produces more viruses. That's why the quick reaction of the innate immune system is so important, followed by the more targeted attack from the adaptive system.

POSTWAR CLEANUP

Once the effector T cells have killed the invading hordes, there must be a troop drawdown. "You don't want this big army hanging around after you've cleared the infection," says Dr. Slifka. "It takes a lot of energy and space to maintain them, and if they accidentally shoot off their inflammatory signals, it could cause trouble."

Fortunately, the body has a built-in shutdown mechanism that causes the vast majority of T cell soldiers to die off – but not all of them. "The cell population doesn't go all the way back down to where it began," Dr. Slifka notes. "Before being infected with, say, measles, you might have a hundred cells that could recognize that pathogen. After clearing a measles infection you have millions of those cells, and afterward it'll drop down to hundreds of thousands. So you still have increased numbers."

Every one of the remaining T cells, known as memory T cells, remembers exactly what a measles virus looks like and is ready to surge back into battle should a reinfection occur. Having such a rapid deployment force in reserve means a much faster immune response the second time around. "There are two reasons for that," says Dr. Slifka. "One is that we already have part of the army waiting. The second is that you don't have to start from scratch. The cells already know what they're looking for; they just need a signal that it's time to go out on a search and destroy mission.

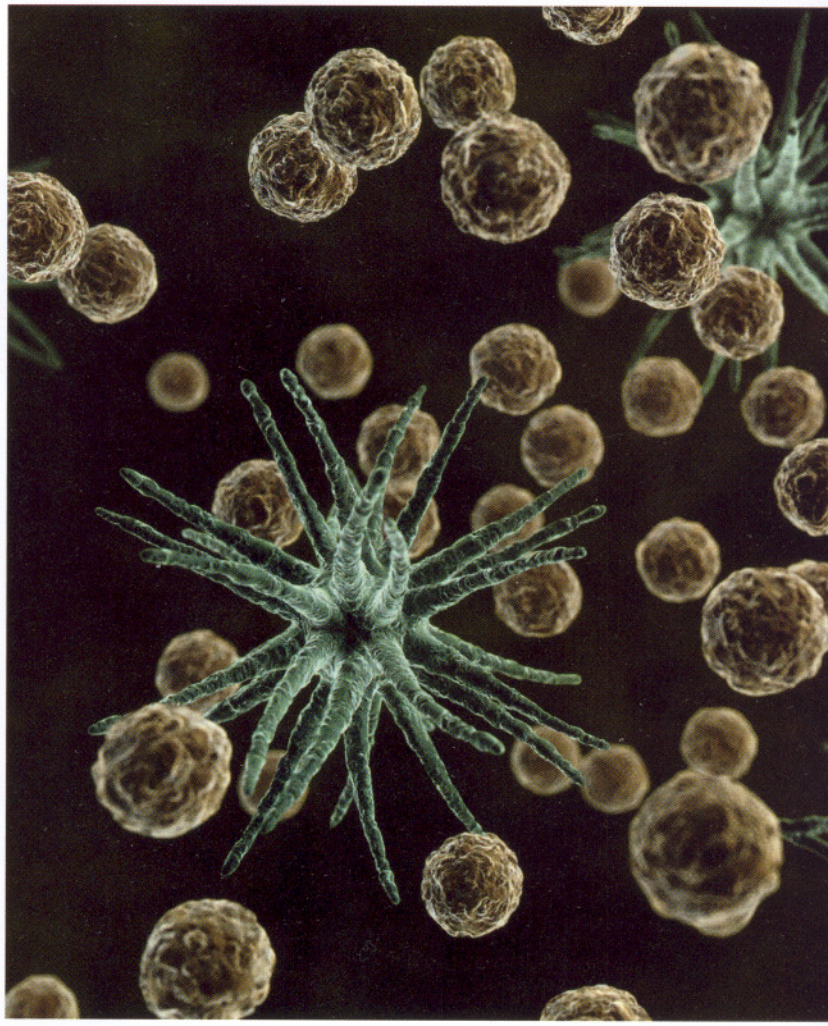
"When T cells are in the naive stage, it's like boot camp. When they're first exposed to a bug, they have to be trained, and that takes time. They have to go through a lot of signaling back and forth, which is the immune system's way of being sure the right pathogen is being attacked. But with memory T cells, they can start dividing and expanding right away, giving you a much quicker immune response."

Dr. Chang notes that there's yet another reason for the rapid reaction: "Not only do the memory T cells react quickly, but at the same time you may activate another set of naive cells with the same pathogen. So now you have two different types of T cells reacting: one set of memory cells and another set of naive cells."

THE BODY'S PLAN B

In addition to T cells, the body's immune system also includes B cells, which produce antibodies. When an antigen binds to a B cell's surface receptors, helper T cells stimulate the B cell to begin reproducing rapidly. Most of those cells begin producing antibodies, while a few become memory cells that continue to circulate in the bloodstream after the threat has been neutralized. In a paper published in the *New England Journal of Medicine,* Dr. Slifka and colleagues postulate that the immunity conferred by memory B cells could last much longer than currently believed – possibly for life.

"We know from our research that those antibody-secreting cells can live as long as a mouse – up to two years. That may also be the case with humans," says Dr. Slifka. "We have heart cells, brain neurons and islet cells in our pancreas that live as long as we do, so it's possible."



» Dendritic cells act as immune system sentinels. When a pathogen enters the body, they grab part of the invader's protein and report the antigen back to the lymph nodes.

POINT OF CONTACT:

» For more information about your immune system, visit the National Library of Medicine Web site, www.nlm.nih.gov, and search for "immune response."