They Keep Asking,

Some OU scientists, such as hematologist Rodger McEver, at right, are also physicians and continue to see patients. Others, like his frequent collaborator, OU biochemist Richard Cummings, left, devote their careers exclusively to research and teaching. Both men hold George Lynn Cross Research Professorships.

"What if?"

Dealing with the fundamentals of science may not be glamorous, but basic researchers experience a thrill with each tiny step forward.

BY JUDITH WALL • *OU Public Affairs*

PHOTOS BY LANNY DAVID

The men and women who pursue basic science research are the dreamers and hypothesizers. They are the ones who ask *What if?*—then spend years searching for the answer.

These individuals belong to an exclusive fraternity that requires its members to be passionately dedicated and possess endless patience. Basic science is as much a calling as it is a profession.

But when it comes to understanding what basic scientists really do, those of us who inhabit the non-scientific world have a hard time understanding just what goes on in those cluttered laboratories.

We make the mistake of asking what disease they are trying to cure.

They explain that before a disease can be understood, there must be a complete understanding of fundamental biological processes of the human body. That's what they do—the fundamental stuff.

Long before any drug is approved for use, long before there is even an idea for such a drug, basic scientists are wondering why something in our bodies works the way it does.

Such is the case with two researchers at the University of Oklahoma Health Sciences Center who have spent a decade investigating the mechanisms that allow white blood cells to carry out their missions.

The Secret Drama

Biochemist Richard Cummings and hematologist Rodger McEver are intrigued by the secret drama of life and death that takes place in our bodies whenever white blood cells launch themselves from the blood stream to war against invading bacteria or to repair damaged tissue.

Cummings and McEver are known in scientific circles for their discovery of the mechanism that allows the free-flowing white blood cells—or leukocytes—to stop themselves prior to their exodus from the blood stream. More recently, they have discovered a way to block that process, which could have far-reaching implications for a number of diseases.

Scientists have long known that when inflammation occurs in the body, the cells that line the blood vessel walls become sticky, a property that slows down the white blood cells. "You can actually see this under a microscope," Cummings says. "Some of the leukocytes start bumping against the walls. The stickiness makes them slow down, then roll to a stop."

McEver compares the action of these molecules to grasping hands and offers the analogy of a receiving line at a social event. The progress of guests down the line is slowed by all those handshakes, just as the progress of leukocytes in the blood stream is slowed and eventually stopped by grasping molecules.

This interaction is brought about by molecules on the cell walls interacting with molecules on the white blood cells.

It was these molecules that initiated Cummings and McEver's unusual decade-long collaboration. (Normally, interdisciplinary scientific collaboration tends to be short term, with researchers coming together long enough to address a particular concern.)

continued

In describing the mechanisms that allow white blood cells—leukocytes—to carry out their missions in the blood stream, OU's Richard Cummings and Rodger McEver often use the graphic illustration above from Joseph Alper's article in the March 23, 2001, issue of *Science* magazine.

The Collaboration

As a hematologist, McEver focuses his research on blood cells. While studying how blood cells interact with blood vessel walls, he discovered an intriguing new protein molecule (P-selectin). Through DNA sequencing, he was able to determine that this protein was related to a family of carbohydrate-binding proteins. This finding led him to a hypothesis:

Maybe these protein molecules were binding with carbohydrate-containing receptors on white blood cells. Maybe this explained the peculiar braking system.

McEver realized he needed an expert on carbohydrates to assist with this investigation. He contacted Cummings—then at the University of Georgia—whose basic interests concerned carbohydrate structures that attach themselves to protein and other molecules in our bodies.

"We molecularly dissected these protein molecules, trying to determine how the interaction works and understand its molecular mechanism," McEver explains, holding up a graphic rendering of leukocytes traveling past the cells lining the vessel walls. Both sets of cells are bristling with tiny projections. "It turns out the interaction occurs on the tips of these molecules," he says, pointing to structures at the ends of the projections.

It also turns out that the tips of these molecules could have important implications for a number of disease processes. They have led Cummings and McEver down a long road of discovery. Initially, their collaboration was carried on long distance, then Cummings joined the OU faculty in 1992.

The Discoveries

White blood cells, in their quest for alien bacteria, make a beeline for inflamed tissue, the two OU scientists explain. But inflammation is not always associated with infection. Diseases such as arthritis, asthma and lupus also are characterized by inflammation. An attack by white blood cells on this sort of inflammation destroys otherwise healthy tissue.

McEver has determined that, in addition to inflammation, oxygen deprivation in tissue also can mobilize white blood cells. But when a blood clot cuts off the oxygen supply to tissue, as in a myocardial infarction or stroke, invading white blood cells once again attack healthy tissue.

Wayward white blood cells also can sabotage an organ transplant. The donated organ is without circulating blood to supply oxygen while it is being transported to a donor. Once the organ is attached, the donor's white blood cells begin to attack its oxygen-deprived tissue.

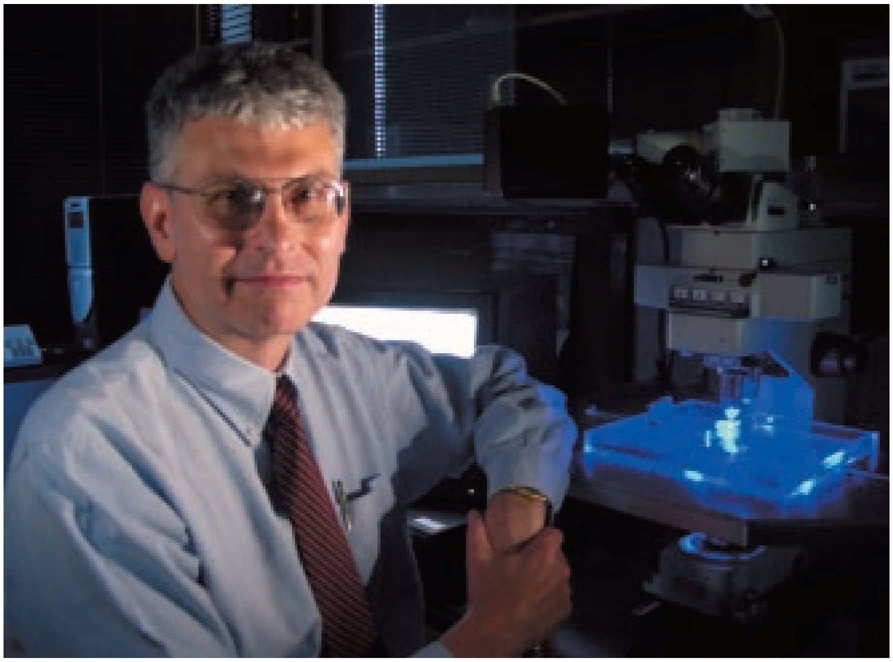
How to prevent unneeded white blood cells from causing harm has been a perplexing problem for medical science. Cummings and McEver believe the answer lies in those little tips with their protein-binding carbohydrates.

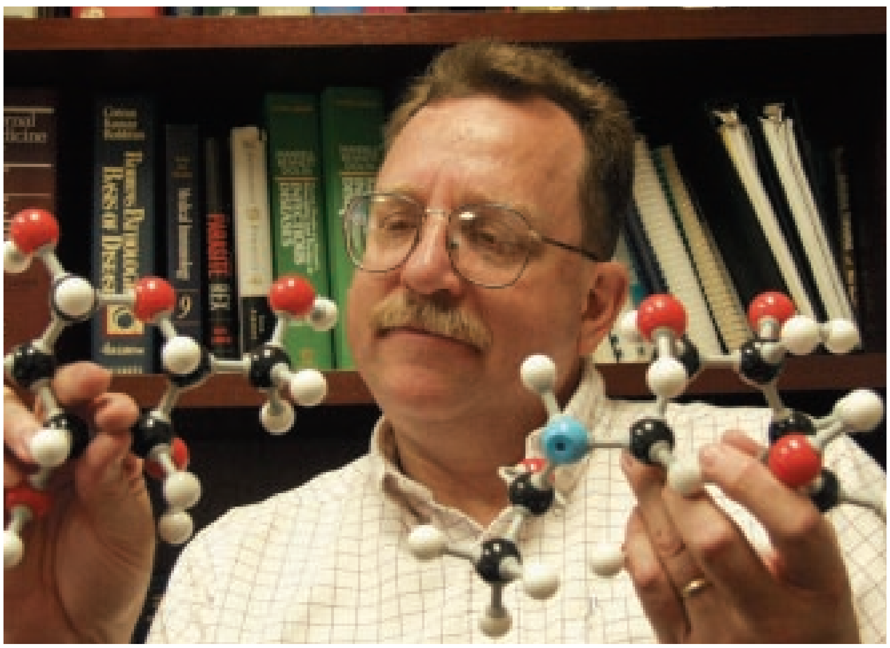
They have synthesized tips that have the ability to mimic the real thing.

When launched into the blood stream, the imitation tips occupy all the available tips on the cells that line the blood vessels, preventing interaction with receptor tips on the white blood cells and thereby disabling the braking system. As a result, the white blood cells sail right on by and never exit the blood stream.

The two researchers also have discovered a process that appears to speed up the death of unneeded white blood cells before they are able to damage healthy tissue.

And conversely, another line of investigation potentially could increase the life span of white blood cells. Since chemo-





TOP: While studying the interaction of blood cells with blood cell walls, hematologist Rodger McEver discovered a new protein molecule that he hypothesized was binding with carbohydrate-containing receptors on white blood cells. He needed an expert on carbohydrates to continue the investigation.

BOTTOM: The carbohydrate expert McEver sought to confirm his theory was biochemist Richard Cummings, whose research interests dovetailed perfectly. Originally at the University of Georgia, Cummings later joined the OU faculty to continue their decade-long collaboration.

> "We constantly challenge and criticize each other."

therapy suppresses their growth, this knowledge might lead to drugs that help cancer patients get maximum use out of available white blood cells.

The Joy

"Potentially, our discoveries will be clinically useful," McEver says.

Cummings agrees with a nod. "Yes, we believe they have great promise. But even if we looked in a crystal ball and saw that these little tips we have synthesized will never be useful as a drug, we would not stop this line of investigation."

"Whatever we learn, combined with what other researchers learn, eventually will be useful," McEver says. "Cumulative knowledge ultimately is beneficial."

The two are founding members—with Cummings serving as director—of an OU-based center dedicated to the study of the role complex carbohydrates play in health and disease. The Oklahoma Center for Medical Glycobiology is only the third such center to be established in the United States. A recent major equipment award from the Presbyterian Health Foundation is allowing the new center to quickly become competitive. Cummings is optimistic that an additional grant from the National Institutes of Health may soon be forthcoming.

While they shy away from the word "pioneering," they were pleased when their latest grant review from the National Institutes of Health described them as being "at the forefront" of the developing field of glycobiology. Either separately or in collaboration, they have been consistently funded by the NIH for the past 20 years.

"For years, people have been studying carbohydrates without having direct proof they actually have a function," Cummings points out, adding that their discovery of the role protein-binding carbohydrates plays in leukocyte mobilization has been "great news" in the field.

"I have to say that this is one of the clearest demonstrations of how proteins binding to carbohydrates regulate important biological processes," he adds with a proud grin.

The researchers each have their own lab and work on projects independently, but with the gratifying success of their lengthy association, they definitely plan to continue collaborating. They meet several times a week and e-mail continually. "It keeps us intellectually challenged," Cummings says. "We constantly challenge and criticize each other."

McEver explains that discoveries don't happen overnight. He describes what they do as "gradual," adding they get excited over each tiny step forward. "We experience the joy of seeing something new."