

# MALEVOLENT TRANSFORMATIONS

The runaway destruction of rheumatoid arthritis

BY SALLY POBOJEWSKI

**I**t started one morning several months ago when you woke up with some stiff joints in the fingers of your left hand. Hardly noticeable, really, and easily explained as the effects of overwork or aging. But the soreness and swelling never went away, and now the same joints in your right hand are stiff and swollen. You feel tired and achy all the time, especially first thing in the morning.

So you make an appointment with your doctor who orders some blood tests. Three days later, you get a phone call. It could be rheumatoid arthritis, says the doctor, who wants you to come in for more tests. It's a chronic, progressive disease that can be treated with powerful medications, but not cured. If your disease proves difficult to treat, you may need injections of drugs that cost between \$15,000 and \$40,000 per year. You'll probably have to take them for the rest of your life.



## BETTER THERAPIES, BASIC UNKNOWNNS

Rheumatoid arthritis is an unpredictable and mysterious disease. It strikes nearly twice as many women as men, and is usually diagnosed between the ages of 30 and 65. The disease can affect nearly every joint in the body or just a few. Symptoms can be mild or severe. Some patients have long periods of remission; others progressively get worse.

Because RA is difficult to diagnose and affects people in different ways, no one knows for sure how many people have it. Some studies have estimated that nearly 1 percent of the world's adult population is living with rheumatoid arthritis, although it is more common in some areas than others.

The good news is that people with RA are much better off today than they used to be. New therapies developed over the last decade can reduce symptoms and slow progressive joint damage for about 90 percent of people with the disease.

But in spite of years of research, scientists still have no definitive answers for fundamental questions like: What causes rheumatoid arthritis? Why does the immune system target certain joints and not others? What triggers the onset of symptoms? Why are some people affected more severely than others?

Healthy joints are surrounded by a fluid-filled sac lined with a thin membrane called the synovium. The membrane contains specialized cells that nourish and lubricate joints to

or injury. But instead of targeting an invading microbe or dying tissue, the immune system is attacking the patient's own body.

Rheumatoid arthritis is not the same as osteoarthritis, which causes the pain and degenerative changes in hips and knees that often come with aging or trauma. In osteoarthritis, the cartilage fails mechanically and there's an overgrowth of bone. "There can be some inflammation in the cartilage and the synovium, but it's much milder than in RA," explains David A. Fox, M.D., a professor of internal medicine who treats patients with RA and studies immune cells involved in one of the most visible effects of the disease — chronic inflammation. "In rheumatoid arthritis, the bone and cartilage are destroyed and inflammation can affect the entire body."

One of the earliest diagnostic tests for RA was for a substance called rheumatoid factor, an antibody found in the blood of about 75 percent of people with the disease. The problem with rheumatoid factor is that many patients who don't have RA — those with chronic infections, autoimmune diseases or even some healthy elderly people — also have the antibody. Diagnosing RA became easier five years ago when a new, more specific test for a different antibody called anti-CCP (cyclic citrullinated peptide) became available.

The disease actually begins long before any physical changes develop in the joints. "Rheumatoid factor and anti-

LIKE MOST CHRONIC DISEASES, RHEUMATOID ARTHRITIS IS THE RESULT OF COMPLEX INTERACTIONS BETWEEN MULTIPLE GENES AND ENVIRONMENTAL FACTORS. IT'S A PROGRESSIVE DISEASE THAT CAN BE TREATED WITH POWERFUL MEDICATIONS, BUT NOT CURED.

keep them moving smoothly. But in rheumatoid arthritis, something triggers a malevolent transformation in the synovium. It turns into a hornet's nest of angry immune cells primed to attack and destroy healthy joint tissue.

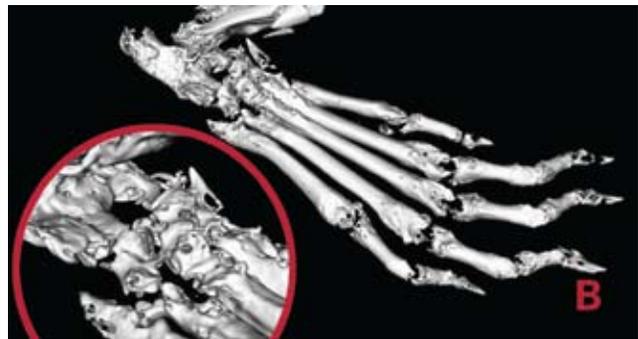
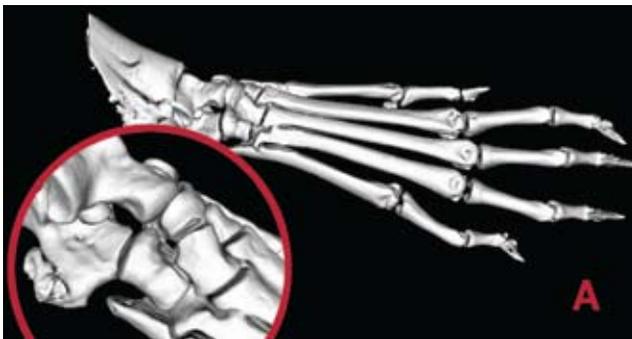
Fed by an overgrowth of new blood vessels, the inflamed synovium starts growing like a tumor, pumping out destructive enzymes and invading the surrounding cartilage and bone. The joint becomes swollen, red and feels warm — classic signs of the body's inflammatory response to infection

CCP antibodies have been found in stored serum samples from people who donated blood years before they had any signs of rheumatoid arthritis," Fox says.

Like most chronic diseases, rheumatoid arthritis is the result of complex interactions between multiple genes and environmental factors. Because RA is a disease that involves the immune system, scientists once thought viral or bacterial infections might stimulate the immune system into overdrive and trigger the onset of joint inflammation. Despite many



David Fox



MicroCT images from Fox's lab show the detail of healthy bone (A) and bone loss (B) in an arthritic mouse hind paw.

studies of many infectious organisms, however, scientists have been unable to confirm a connection.

There's nothing you can do about your genes, but Fox says there is something you can do to reduce your chances of getting rheumatoid arthritis: Don't smoke.

"Studies in several countries have confirmed that the risk of getting RA is two to three times higher if you smoke, compared to people who don't smoke with all other factors being equal," Fox says.

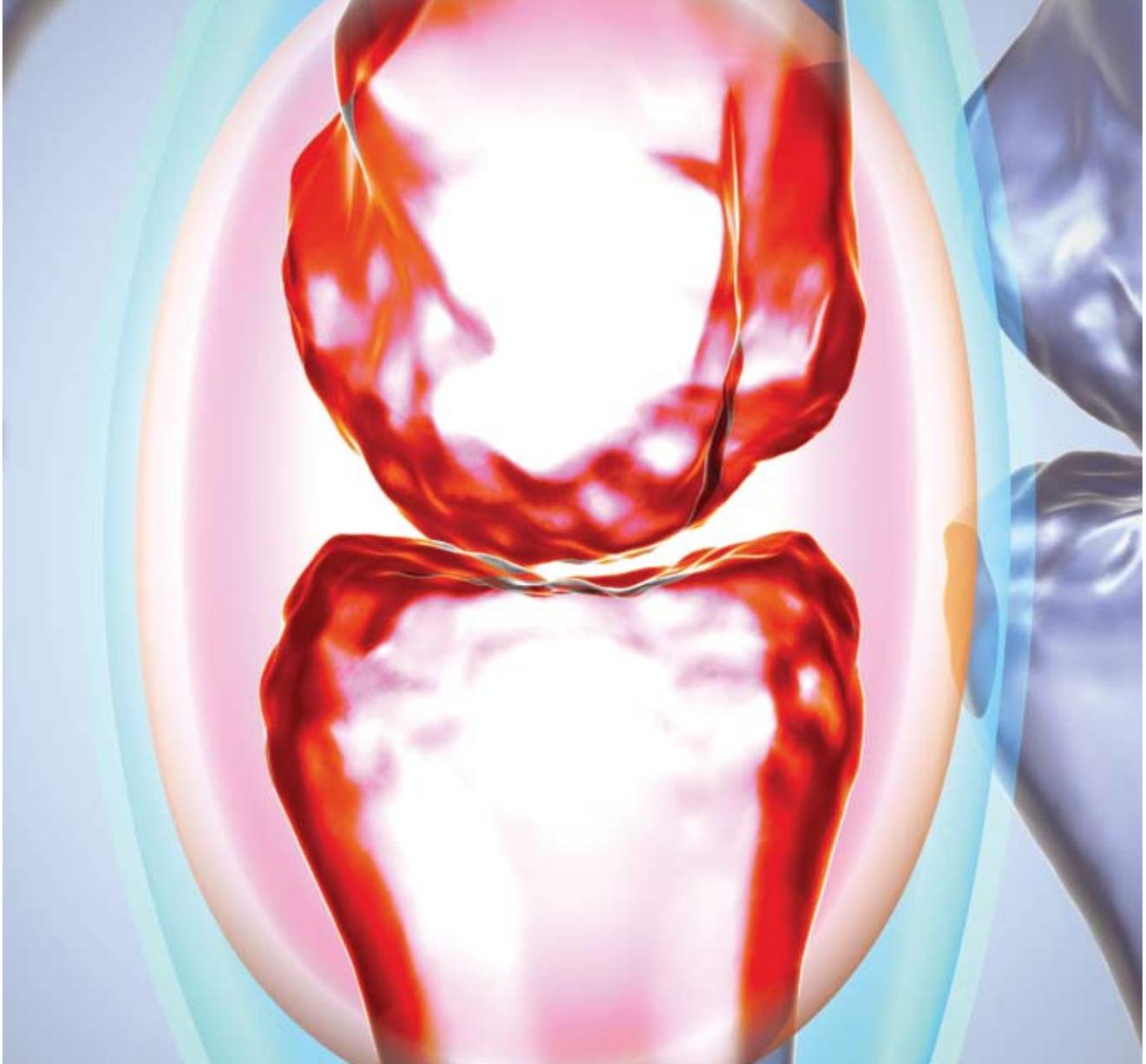
### BRIDGING THE MORTALITY GAP

Years ago, people with rheumatoid arthritis usually became totally disabled after five to 10 years, and had a shortened life expectancy. Anti-inflammatory drugs, steroids and a chemotherapy drug called methotrexate reduced pain and swelling. But for about half of those with RA, these drugs did not stop the progressive destruction of affected joints.

A big step forward occurred in 1998 when a new type of therapy for RA was approved by the U.S. Food and Drug Administration. Called biologics, these drugs are designed to mimic the effects of natural substances produced by the human immune system. The first biologics were etanercept (Enbrel), infliximab (Remicade), and adalimumab (Humira). They prevent runaway inflammation in joints by blocking a protein called tumor necrosis factor-alpha that triggers the inflammatory process. Since then, several new biologic agents targeted at other immune system proteins have been approved for treatment of rheumatoid arthritis.

"These new drugs dramatically changed the outcome of the disease," says Mariana Kaplan, M.D. (Residency 1998), an assistant professor of internal medicine.

Unlike traditional therapies, biologics do more than just treat symptoms of the disease. In most patients, they can actually prevent joint damage — or at least slow it down. Physicians still start most patients on traditional treatments,



In the joints of people with RA, the synovium (pink) recruits immune cells that attack and destroy healthy cartilage and bone — creating pain, swelling and inflammation.

but if active disease persists, they will try to nip joint damage in the bud by prescribing biologics as part of a comprehensive treatment strategy.

Biologic therapies are expensive. But biologics gave RA patients hope that they could live a normal lifespan with minimal pain and disability. Unfortunately, this hope didn't last long. Researchers found that people with rheumatoid arthritis were still dying prematurely. They were just dying of something else.

"Today, the No. 1 cause of death in RA patients is atherosclerosis [clogged arteries] from cardiovascular disease," Kaplan says. "Even though we're now much better at treating RA, the mortality gap between patients and the general population is widening. We think the development of premature cardiovascular disease is related to the ongoing inflammation that occurs with rheumatoid arthritis, but the exact mechanisms have not been established."

The increased risk of cardiovascular disease starts early —

long before joint inflammation develops. People who have just been diagnosed with rheumatoid arthritis already may show signs of vascular damage, according to Kaplan. Even more alarming, people with RA are less likely to have the classic warning signs of a heart attack or heart failure, like chest pain, so they may not realize they have cardiovascular disease.

An additional reason for concern, according to Kaplan, is that some physicians may not realize their RA patients are at high risk for cardiovascular disease. She emphasizes that all physicians who treat rheumatoid arthritis patients must watch for cardiovascular risk factors like smoking, high blood pressure, high cholesterol and obesity, and treat them aggressively and early. Even though smoking is associated with RA, it doesn't account for all of the increased risk of heart disease in patients with rheumatoid arthritis.

"I think physicians are not as aware as they should be about this," Kaplan says. "Mild cases of RA are often treated initially

by primary care physicians, who may not refer the patient to a rheumatologist until later on. By then, the cardiovascular damage may already have occurred.”

## THE EPITOPE CONNECTION

While U-M physician-scientists focus on the most effective ways to treat patients with rheumatoid arthritis, they also are trying to figure out what causes the disease in the first place.

Most immunologists believe RA is an autoimmune disease like lupus or type 1 diabetes. In autoimmune diseases, the immune system mistakenly reacts to something in the body as if it were an antigen — a foreign substance flagged by

an HLA gene called HLA-DR. In the language of science, it’s called the shared epitope, and it is the most significant genetic risk factor for rheumatoid arthritis.

How could such a tiny difference — just five little amino acids — cause the immune system to shift into overdrive and turn normal, nurturing synovial cells into crazed, out-of-control killers?

To find the answer, Alisa Koch, M.D., the Frederick G.L. Huetwell and William D. Robinson Professor of Rheumatology, is bringing together a team of U-M scientists who study different aspects of the RA puzzle. Koch focuses on angiogenesis, the development of new capillaries from existing blood vessels. Working with Holoshitz, she hopes to learn whether signals

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dendritic cells (the sentinel cells of the immune system) to trigger an immune response. As it tries to destroy the “foreign” antigen, the immune system can do major damage to healthy cells and tissue. It’s a logical hypothesis, but Joseph Holoshitz, M.D., an associate professor of internal medicine, has a different idea.

If RA was an autoimmune disease, he says there’s a good chance someone would have discovered the antigen by now. “Researchers have had 30-40 years to find the antigen, and I don’t think anybody has found it yet,” he says.

Holoshitz believes the underlying cause of the disease is in our DNA, specifically within human leukocyte antigen (HLA) genes.

HLA genes hold the genetic code for your personal immunological identity — the blueprint for a unique set of cell surface markers that tells your immune system: “Back off. I belong here.”

To an extent much greater than other genes, HLA genes contain small variations in the building blocks of DNA that provide codes for the amino acids used to make proteins. Several forms of these variations have been identified within the same sequence of five amino acids in the protein for

from the shared epitope can control angiogenesis.

“In rheumatoid arthritis, we think the large inflamed synovial tissue mass that invades cartilage and bone is the result of an overgrowth of blood vessels,” Koch says. If she could stop the growth of excess blood vessels in synovial tissue, Koch thinks she might be able to shut off the incoming supply of immune cells and signaling molecules that drive inflammation and bone erosion in joints.

Koch’s work with angiogenesis is connected to David Fox’s research with a recently identified type of immune system T cell known as Th17. These cells make a cytokine, or signaling protein, that stimulates the growth of blood vessels and intensifies inflammation. Researchers in Fox’s lab have found intriguing evidence suggesting that Th17 cells play a major role in the development of rheumatoid arthritis and other diseases.

By pooling their expertise and looking for connections among their different areas of research, U-M scientists hope to find answers to questions that have baffled researchers since rheumatoid arthritis was first identified early in the 1800s. Millions of people who must cope every day with the pain, disability and expense of the disease are hoping they will succeed. [M]