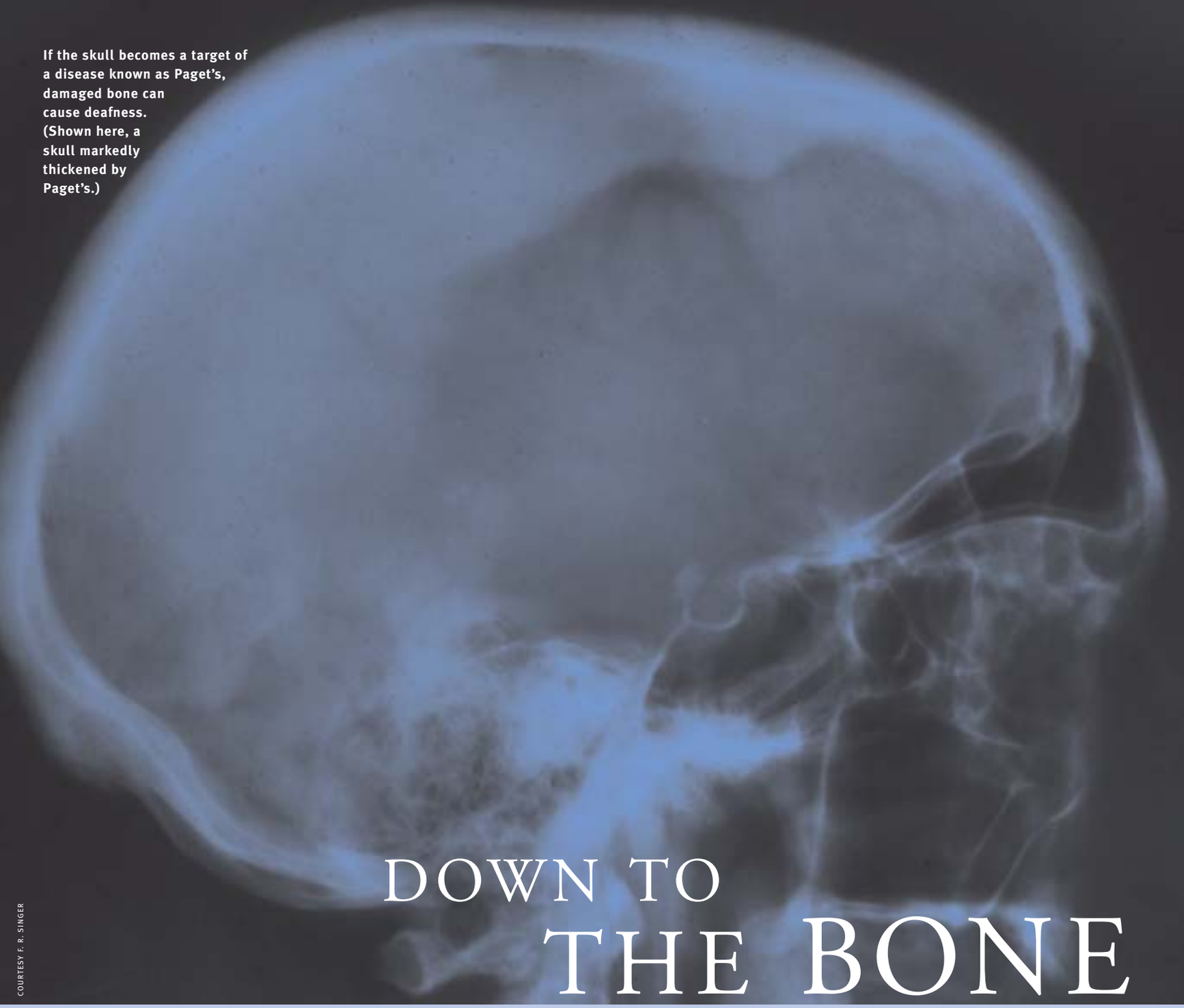


If the skull becomes a target of a disease known as Paget's, damaged bone can cause deafness. (Shown here, a skull markedly thickened by Paget's.)

COURTESY F. R. SINGER

DOWN TO THE BONE

DOES THE MEASLES VIRUS CAUSE A DEBILITATING BONE DISEASE?

BY ROBIN MEJIA

Kenneth Halstead seemed too young to be suffering from bone aches. At 36, he was a successful design engineer at the Raleigh, N.C., Westinghouse plant in 1960. You may have the results of his efforts right outside your door. The plant produced most of the utility meters made in the country. His work wasn't physical labor, but it did involve a lot of walking around the 550,000-square-foot building to oversee the manufacturing of parts he'd designed. Even those walks were becoming difficult.

"When I'd get up, I'd have to walk a few steps to straighten all the way up," he says. He kept working, but it became harder to spend any length of time standing. His legs ached when he tried to straighten them. The pain kept him up at night. He started sleeping in his recliner.

Halstead's next-door neighbor, Thomas B. Dameron Jr., happened to be an orthopaedic surgeon. Dameron had Halstead come in to be x-rayed. When the slides came back, the two men looked at an image of hips covered with dark spots. Dameron said he didn't know what the spots were, so he scheduled a bone biopsy. Halstead started to worry that he might have cancer.

Two weeks later, he found out he was cancer free. He did, however, have an untreatable bone condition called Paget's disease, which he could expect to slowly worsen for the rest of his life.

Strangely, given how little-known it is, Paget's is the second most common bone disease in this country. Only osteoporosis affects more people. Most Paget's patients don't suffer the same level of pain Kenneth Halstead does. In fact, only 10 percent of the estimated 2 million Americans with Paget's complain to their doctors of symptoms. Many don't even know they have it. But for those 200,000 or so patients who experience symptoms, it can be an incredibly debilitating condition.

At a basic level, Paget's is a disease of the osteoclast. In most people, these cells keep bones healthy. As bone wears down or cracks, osteoclasts cover the damaged area and resorb it. This prepares the area for healing by osteoblasts. "People get [minor] cracks in their bones all the time," says David Roodman, University of Pittsburgh professor of medicine as well as the director of the Multiple Myeloma Center at the University of Pittsburgh Cancer Institute and a staff physician with the VA Pittsburgh Healthcare System. Without osteoclasts, the body couldn't make clean repairs. New bone would just get slapped down on top of old, creating layers and deformities.

In the case of Paget's, groups of osteoclasts go into overdrive. They become large and start devouring bone. They also limit the body's ability to lay down good replacement tissue, so most new bone is fragile and deformed. Depending on where someone gets Paget's, she might become bowlegged or lose inches from her height. Some bones are more likely to be damaged—for example, many people suffer Paget's in the hip and leg—but the disease can hit anywhere in the skeleton, affecting only one bone or many. Some patients get arthritis and fractures. Others lose their hearing.

Even though Paget's is a common disease, historically, it has been underdiagnosed. And when Halstead first noticed his problems, even a diagnosis offered little hope. In 1960, there were no treatments for Paget's; doctors could only monitor it. Halstead's case had struck unusually early in life, and it was aggressive. For the next decade, his doctors watched it worsen. Halstead ended up with Paget's in both hips, his legs, his spine, and his skull. At one point, doctors considered surgery on his spine to relieve nerve pressure, but in the end it looked like the risks outweighed the potential benefit. By 1972, when Halstead was first able to enroll in a clinical trial (for salmon calcitonin), if he tried to stand for 15 minutes, his legs went numb.

Today, doctors have many drugs at their disposal to treat the disease. However, what causes Paget's and what makes the osteoclasts go bad has until recently been a mystery. It's a mystery Pittsburgh's Roodman appears poised to unravel.



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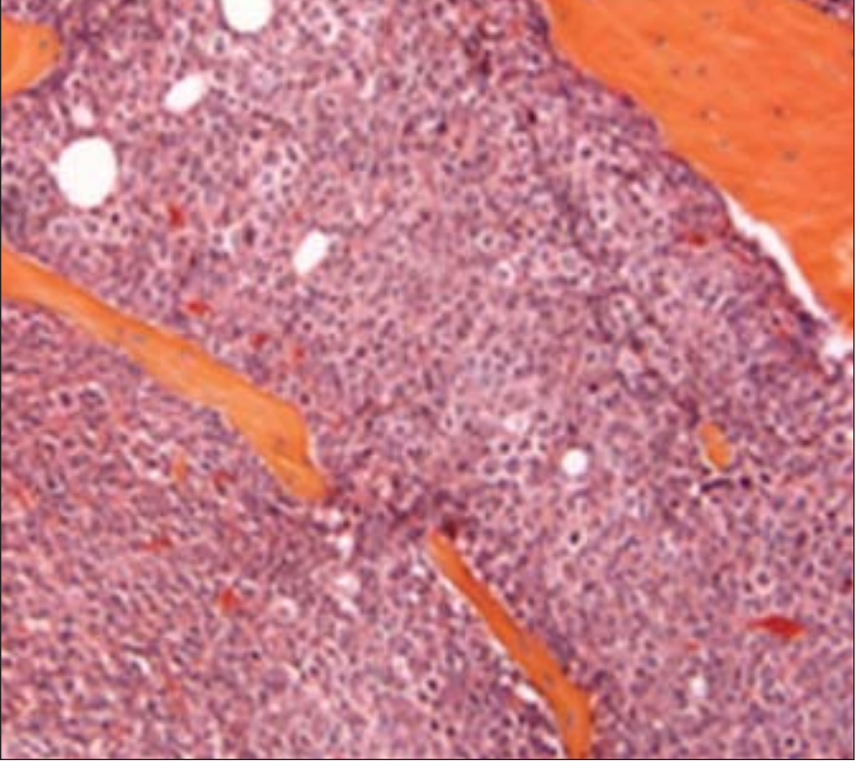
David Roodman

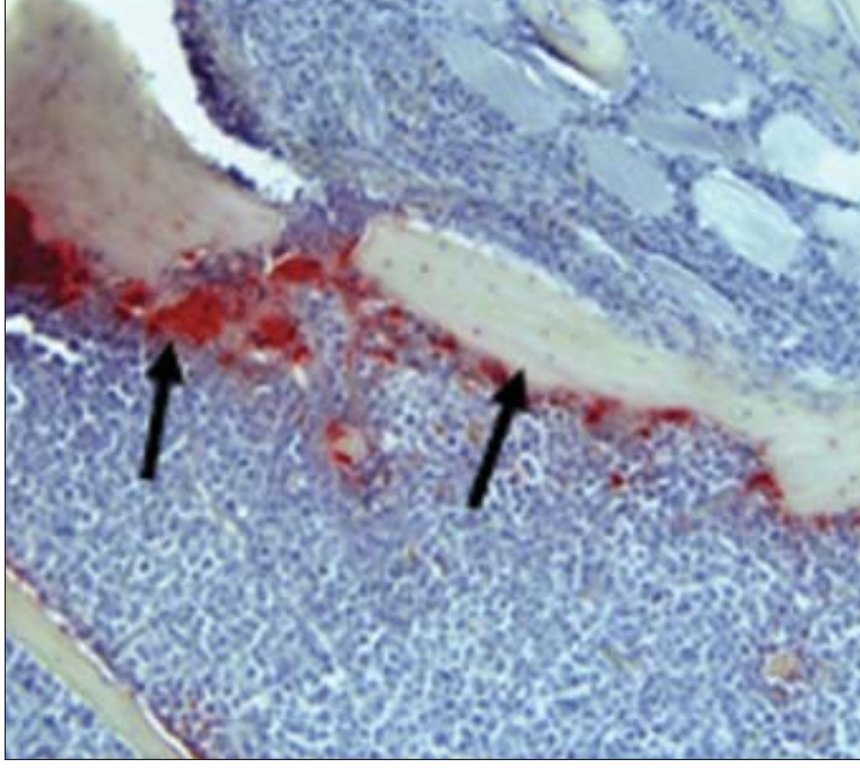
Roodman never set out to become a bone doctor. That just happened. He says that ever since he took his first genetics class, he has been intrigued by cell differentiation. In medical school at the University of Kentucky, he discovered hematology, and he's a hematologist today. (Kentucky is also where he got his PhD in biochemistry and discovered his "greatest collaborator," Mona Burton, now Mona Burton Roodman, who at the time was working in a biochemistry lab.) He says hematology appealed to his interest in how the body's precursor cells differentiate into their final state. Precursor cells in bone marrow differentiate into various types of grown blood cells. Studying blood also offered a unique advantage over the study of most internal organs, notes Roodman: "It was easy to get samples to work on."

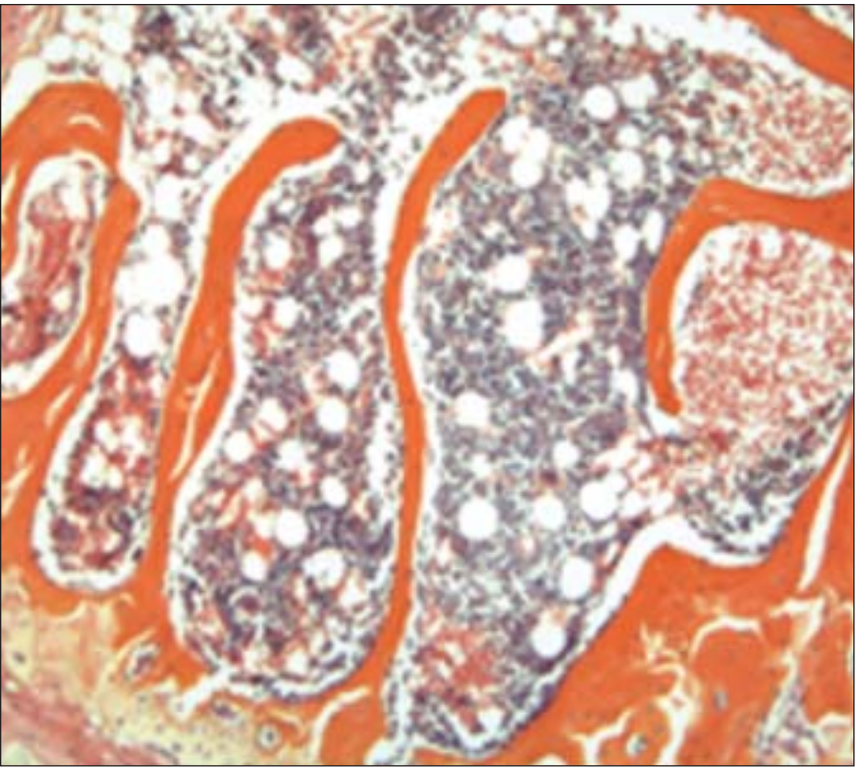
In 1980, he took a position in the University of Texas Health Science Center at San Antonio. There, he found himself in an office across the hall from the center's chief endocrinologist, Greg Mundy. Mundy was an internationally known bone specialist.

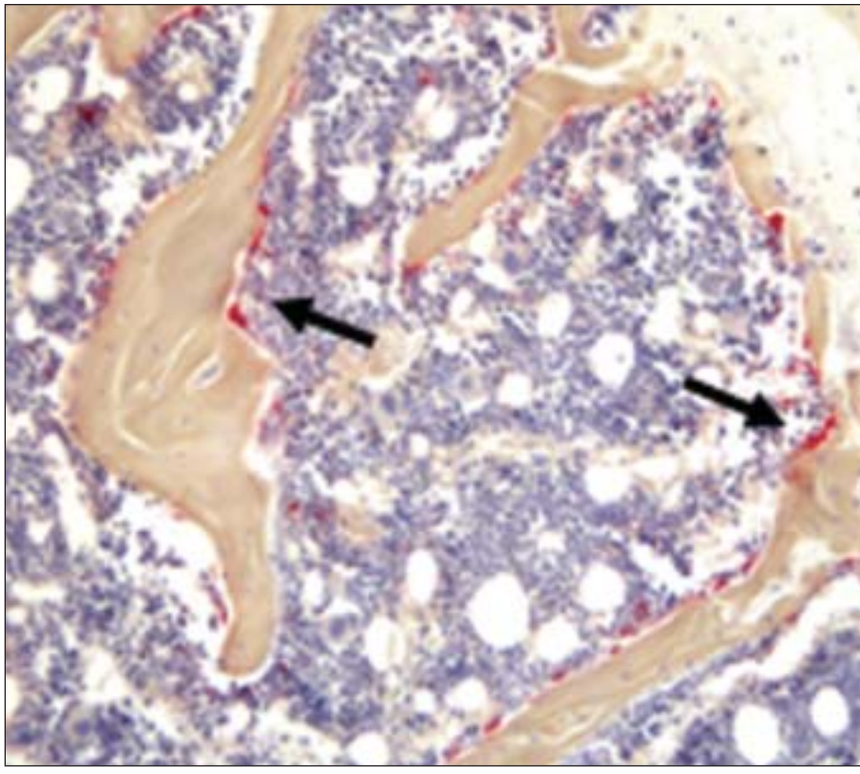
"I didn't know one end of a bone from another," says Roodman, whose influential bone studies are now supported by the National Institutes of Health, the Multiple

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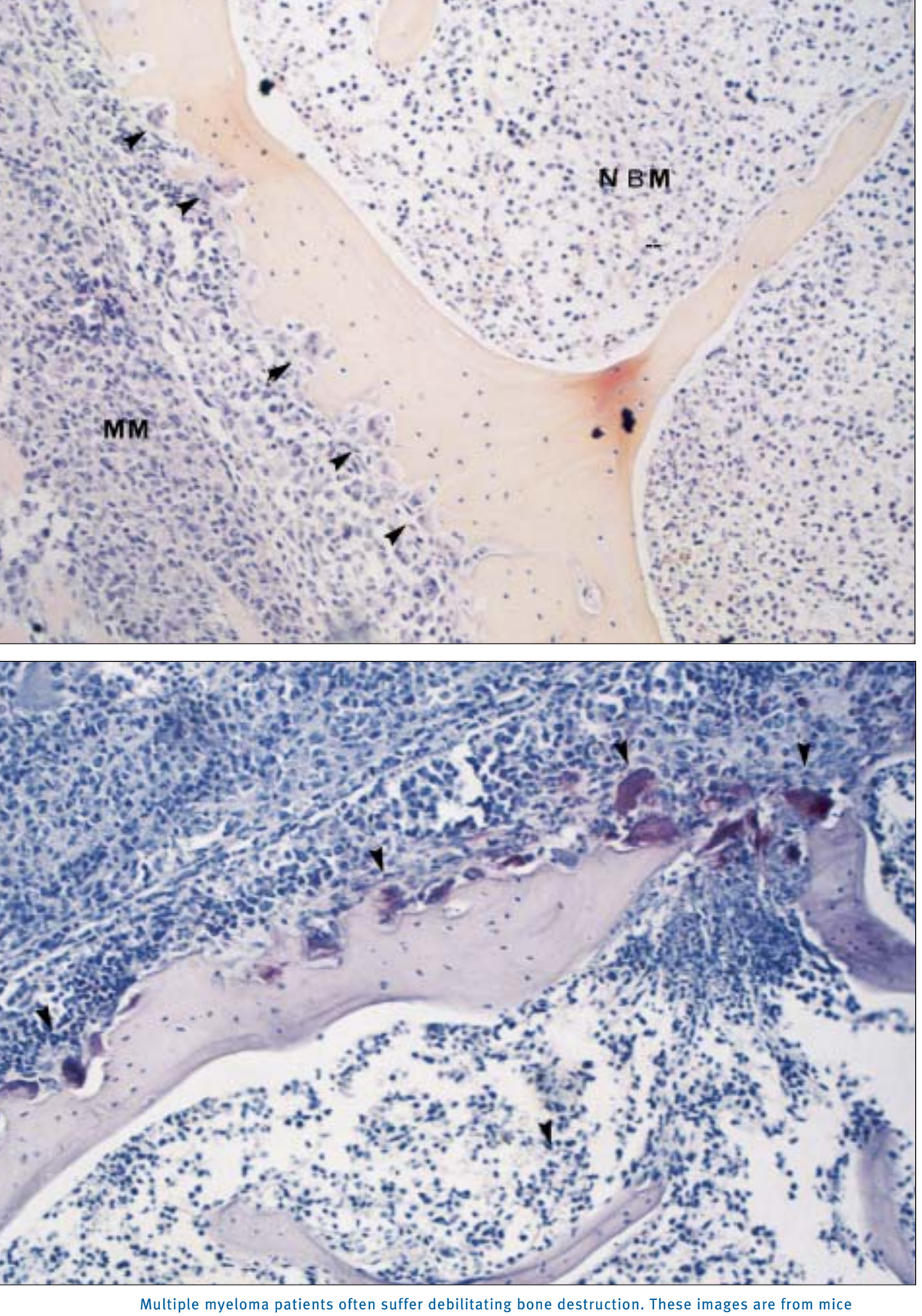


Myeloma Research Foundation, and the Department of Veterans Affairs. When he met Mundy, Roodman may not have known much about bone, but he did know a lot about cell differentiation, and he was having success developing difficult cell cultures.

Mundy had been asking around, looking for someone who could help him culture cat bone marrow, and he heard about Roodman. Roodman knew that sheep marrow had been cultured, and figured, *Sure, we can do cats.* The two teamed up. They succeeded with culturing bone marrow from cats, and then went on to make human- and mouse-marrow cultures, along with cultures from baboons. Before Roodman and Mundy got started, people had cultured bone marrow, but those cultures didn't form a key ingredient—osteoclasts.

Using Roodman's techniques, you could take bone marrow from sick patients and grow it in the lab. This meant researchers could study diseased osteoclasts up close and

Roodman has been able to minimize multiple myeloma bone disease in mice. The lower images have fewer myeloma cells and less bone destruction. Roodman used a treatment in these cases that targets a protein called MIP-1 alpha. The bone sections shown on top were not treated and show bone degeneration and myeloma cells. Arrows point to osteoclasts.



Multiple myeloma patients often suffer debilitating bone destruction. These images are from mice injected with human multiple myeloma. TOP: Osteoclasts near the multiple myeloma cells pit bone (see area marked "MM") while the osteoclasts near normal bone marrow don't (see area marked "NBM"). BOTTOM: Arrows point to stained osteoclasts that resorb bone.

over time. They could also manipulate the cells and experiment on them in ways that were impossible in living patients.

"Up until that time, they had been very hard cells to study," Mundy says. "Most people around the world use the technique he developed or techniques derived from it."

Roodman is more modest about his achievement. He considers his meeting Mundy a serendipitous event that shaped his career.

After he cultured osteoclasts in the early '80s, Roodman turned his attention to diseases that involved the cells. He used the new culture techniques to study the bone disease wrought by an aggressive adult hematologic cancer called multiple myeloma. Like leukemia, multiple myeloma is a cancer of the blood. Specifically, it's a cancer of the plasma cells. If plasma cells become cancerous, they congregate in bone marrow, crowding out normal marrow cells that would produce red and white blood cells as well as blood-clotting platelets. Sometimes the myeloma cells form tumors.

Before chemotherapy, the life expectancy for someone with multiple myeloma was dismal, an average of seven months after diagnosis. Today, with treatment, the average has increased to around three years, and patients strong enough to get stem-cell transplants live, on average, five to seven years.

Much of the pain patients experience results not from the tumors, but from the cancer cells' interaction with osteoclasts. The cancer cells stimulate nearby osteoclasts, causing them to alter the bone. As the disease progresses, the bones ache terribly, eventually becoming deformed and unbelievably fragile. "Myeloma patients can fracture a humerus by closing a car door," says Roodman.

He has delved into the question of what causes this bone destruction. And now he is pinpointing the factors that drive the osteoclast frenzy; his results may also shed

ALSINA, M., BOYCE, B., DEVLIN, R.D., ANDERSON, J.L., CRAIG, F., MUNDY, G.R., ROODMAN, G.D., DEVELOPMENT OF AN IN VIVO MODEL OF HUMAN MULTIPLE MYELOMA BONE DISEASE. *BLOOD* 1996;87:1495-1501. COPYRIGHT AMERICAN SOCIETY OF HEMATOLOGY; USED WITH PERMISSION.

light on the cancer itself.

In cases of myeloma, the osteoclasts themselves are normal—unlike in Paget's disease, where there are simply way too many of the cells working way too hard. Drugs exist that can inhibit osteoclast activity. Unfortunately, they inhibit all the osteoclasts in the body. Since myeloma cells only affect nearby osteoclasts, this approach is less than ideal. After all, osteoclasts are essential to the maintenance of healthy bones.

So how do myeloma cells trigger the nearby bone disease? Roodman has identified a protein that may be myeloma's messenger to the osteoclasts, macrophage inflammatory protein–1 alpha, or MIP-1 alpha for short. If he's right, his research raises the possibility of targeted treatments that would only affect the diseased regions.

Bill Bensinger, a professor at the Fred Hutchinson Cancer Research Center in Seattle, says Roodman worked for years without great recognition in the field, but that's now changing as researchers realize that his work is providing keys to understanding how bone disease operates. (Roodman's CV includes pages of impressive awards and positions, including service on national advisory groups, the board of the Paget's Foundation, and the editorial board of *The Journal of Clinical Investigation*.)

Bensinger is encouraged by the prospects for improved treatment of myeloma bone disease coming out of Roodman's lab:

"He's honing in on several new pathways that I think have been unrecognized. Once you understand the signals, you can disrupt that pathway."

A couple of years ago, when Roodman was deciding if he should come to Pitt, he was being courted by four other major research centers. And when he came to Pitt in 2001, his entire lab agreed to join him. Now that he's here, Roodman is studying the effects of MIP-1 alpha in mice that have modified immune systems and have been inbred to be genetically identical. These mice let researchers test one factor, in this case MIP-1 alpha, without worrying about teasing out other influences, like genetic variability. So far, the results are positive. When Roodman injected the mice with human multiple myeloma cells, they developed such severe bone disease the myelomas impinged on the spine and they became paraplegic. When he injected the mice with human myeloma cells but blocked MIP-1 alpha activity, the mice didn't get bone disease, and they also ended up with fewer tumors. He hopes the research will lead to clinical trials in the next few years.

Like myeloma bone disease, Paget's is a condition whose root cause has eluded scientists, even as treatments have improved. It's clear that the osteoclasts in Paget's patients are diseased; they are abnormally large and have as many as 100 nuclei. (Normal osteoclasts have perhaps two to four nuclei.) These osteoclasts also respond to extremely low levels of hormones, which throw off the mechanisms the body would normally use to regulate these cells. What's been less clear is how the osteoclasts get that way. This is a question that's driven the other main branch of Roodman's work.

Fred Singer, a nationally recognized leader in the treatment of Paget's, studies the disease at the John Wayne Cancer Institute in San Diego, even though Paget's isn't a cancer. Singer is painfully aware of how little information doctors used to have about Paget's; he has done clinical research and treated Paget's patients for 30 years. About a decade ago, Singer got a call from then-stranger Roodman, who was at San Antonio at the time. Roodman said he'd been working on aspirated bone marrow cultures and was wondering if Singer wanted to collaborate on Paget's research. Singer said yes, and the two have been working together since.

"It's been one of the most fruitful relationships I've ever had, short of my wife," said Singer. "I think it's no understatement to say that he's been the single most important person in the field in understanding this disease."

It seems most likely that, like many cancers, Paget's results from a confluence of factors. The disease clearly runs in families. Kenneth Halstead has two brothers with it, and his mother was diagnosed with Paget's at the age of 101. Ten to twenty percent of patients have a relative with the disease. Today, most doctors accept that Paget's is probably caused by a combination of genetics and environmental influences.

Roodman has been trying to decipher what the environmental factors are. He thinks that a viral infection is key in causing Paget's in genetically susceptible people. The culprit? Roodman suspects the virus may be the same one that causes measles. The circumstantial evidence is enough to push his research forward, but Roodman tempers his excitement with disclaimers, stressing that he hasn't proved the link.

Yet Roodman is not the only one excited about the possibility.

"The fat lady hasn't sung yet… [but] I think he's right," says Mundy.

Others, including Singer, think so too, but they agree that it's still an open debate.

What Roodman has discovered is evidence of viral transcription in the osteoclasts of Paget's sufferers. Essentially, the transcription evidence is like a calling card, showing that the virus has been there and been active. Of course, not everyone who gets measles gets Paget's, but it could be that measles is a trigger in susceptible people. Because the measles vaccine is now widely used, Paget's could become much less common in the future.

One doctor told him Paget's must have been described on the last page of the textbook, the page he didn't read. He was also told that doctors used to diagnose the disease only after patients' heads grew so big their hats no longer fit.

But many must live with it today. Every year, Paget's patient Halstead is invited to talk to a new crop of medical students and others at Duke University to help them understand the disease that has so shaped his life. He says when he started years ago, one doctor told him Paget's must have been described on the last page of the textbook, the page he didn't read. He was also told that doctors used to diagnose the disease only after patients' heads grew so big their hats no longer fit. (Halstead outgrew his hats.) Though a cure wouldn't undo the damage to his body, Halstead would like to see it available to others. He himself has benefited from treatment advances through the years. The new drugs have provided relief from the constant pain; and, he notes, with treatments now available, people diagnosed today could avoid the level of bone degeneration he has suffered.

Fortunately, his children show no signs of Paget's so far. But they get tested regularly. With four cases in the family, it's a possibility that's always out there lurking. ■