

NOT PREREQUISITES FOR OSTEOARTHRITIS:
Decades of dancing // multiple marathons // instead, a
complex collection of factors // from **lesions to leptin**.

Why Joints Fail

■ BY TIM GOWER // PHOTOGRAPHS BY PETER HAPAK

Most dogs love to run, and many develop joint problems late in life. The same thing often happens to their human companions, with or without pavement pounding. But arthritis researchers in Finland decided to speed up the process. In a yearlong study, they placed 10 female beagles on treadmills and made them run. By the time the study was coming to an end, the dogs were trotting at a brisk pace for 25 miles a day.

Tissue samples from the dogs' knees indicated that some regions of their joints had lost as much as 35% of their glycosaminoglycan, or GAG, an essential carbohydrate that strengthens and stiffens cartilage. This led the investigators to conclude that long-distance running had the potential to damage cartilage and eventually cause osteoarthritis, the most common form of joint disease. When their paper appeared in *Arthritis & Rheumatism*, in 1993, it cast a shadow over the presumably healthy habit of jogging. But the beagle trials also reinforced conventional medical wisdom, which at the time held that osteoarthritis, or OA, was a disease of failing cartilage brought on by wear and tear.

Since then, though, research has shown OA to be much more complicated. Not only has running been largely exonerated as a cause but studies also show that exercise normally strengthens cartilage. And while cartilage loss may indeed lead to OA, new evidence suggests that metabolic imbalances also play a vital role. Moreover, it has become clear that other parts of the joint, including bone and synovial tissue, also are crucial in the genesis of OA, says Steven B. Abramson, director of rheumatology at New York University's Langone Medical Center.





But while OA affects some 27 million Americans (who receive 1 million artificial knees and hips each year), it's often not considered a research priority. So earlier this year, the Arthritis Foundation began a campaign to raise awareness about the disease. Could a renewed focus and fresh ideas about OA lead to better treatments and preventive therapies? If so, the timing couldn't be better. With an aging population and rising rates of obesity—a chief risk factor for OA—the number of Americans with this disease is projected to nearly double by 2020.

A joint is simply the juncture of two bones. Some joints, such as those in the skull, are fixed in place. Only synovial joints (the name comes from synovium, a membrane that lines the noncartilage portion of a joint cavity and produces lubricating fluid), which allow bones to move about freely, are afflicted by OA. Cartilage protects the ends of bones in a synovial joint, and the bones are held together by sturdy bands, called ligaments, while cordlike tendons attach bones to muscles. The entire complex is encased in a fibrous joint capsule.

OA primarily strikes large synovial joints, such as the knee, hip, neck and lower back; pain, stiffness and swelling are the hallmark symptoms. For some patients, the pain becomes excruciating and debilitating.

Although osteoarthritis predates humanity (dinosaur fossils show signs of joint disease), clinicians didn't recognize OA as a pathological condition until the eighteenth century. The term itself came later, seemingly from the title of a book, *The Early Symptoms and the Early Treatment of Osteoarthritis*, published in 1889 by a British doctor, John Kent Spender. Spender set out to distinguish OA from other joint diseases, such as gout, with colorful descriptions of arthritic joints: "Cartilage is torn to shreds, bone is ground down to its primitive elements..."

Indeed, "if you open an osteoarthritic joint, the most obvious thing you see is cartilage damage," says Kenneth D. Brandt, a rheumatologist at the University of Kansas Medical Center. And the criteria for diagnosing OA are based on X-ray findings that measure narrowing joint spaces between bones

(though cartilage isn't visible on X-rays, the dwindling spaces indicate it's no longer there to cushion the joint).

Research involving machinists, farmers and other workers has suggested that years of repetitive movement may predispose a person to OA—an idea reinforced by the beagle study and other animal testing. But David J. Hunter, a professor of medicine at Australia's University of Sydney, who studies OA, and others suspect that the animal tests imposed mechanical stresses far exceeding normal human activity—which, it turns out, can safely include quite a lot of running. Consider John DiComandrea, 82, of Revere, Mass. The retired shop teacher runs three miles a day, and he once logged as many as 60 miles a week. DiComandrea has competed in more than 1,000 races, including some two dozen Boston Marathons, yet his leg joints feel fine. "My hips, knees, ankles—they're all good," he says.

Several studies have found that a lifetime of running—a perfect test for the "wear and tear" theory of osteoarthritis—doesn't increase risk for the condition. In the most recent, published in 2008, researchers at Stanford University School of Medicine began tracking the health of 45 long-distance runners (average age: 58) in 1984. Nearly 20 years later, X-rays showed their joints were unaffected. "We can find no evidence whatsoever that there's an increase in knee destruction in people who run for thousands and thousands of miles," says study co-author James Fries, professor emeritus of immunology and rheumatology.

Another problem with the narrow view of OA as a disease of worn-out cartilage is that loss of cartilage doesn't always produce pain. Moreover, some wear may benefit cartilage. "If you're young and your joint hasn't had any trauma, then activity and stress on the cartilage—within certain ranges—is actually good," says Thomas Andriacchi, a professor of mechanical engineering and orthopedic surgery at Stanford University's BioMotion Research Laboratory.

In 2004, Andriacchi's group used motion-capture technology and quantitative magnetic resonance imaging (which

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provides detailed information about the shape and volume of tissue) to study how humans walk. The stress of exercise made the study subjects' cartilage thicker and healthier by encouraging the tissue to maintain a balance between synthesizing new chondrocytes (cartilage cells) and breaking down old ones. In contrast, getting too little exercise can shrink cartilage, which lacks a blood supply and must absorb nutrients and expel wastes through passive diffusion. Stress on the joint enhances that process.

Eventually, though, for reasons not yet known, cartilage loses the ability to generate chondrocytes and repair itself. For most people, the tipping point occurs around age 50, Andriacchi says. After that, changes to the load on a joint may cause the cartilage to start to degrade. Trauma to ligaments, even if repaired, can change the mechanics of walking and shift loads on knee cartilage. Weakened muscles also can alter gait and threaten cartilage. But weight has by far the greatest impact. "If we were able to deal with obesity effectively, about 50% of osteoarthritis would just go away," says Hunter, who notes that obese people with OA who lose just 5% of body weight experience at least a 25% reduction in symptoms. "That's equal to the best anti-inflammatories."

Still, new research suggests that how and why extra pounds hurt joints isn't a simple matter of putting more stress on them. If that were the whole story, why would overweight people also have an unusually high risk for OA in non-weight-bearing joints, such as those in the hand? And what about runners, who aren't overweight but whose knee joints bear up to five times their body weight during a run? Why don't they have a high risk of OA, too?

About five years ago, Farshid Guilak, director of the orthopedic bioengineering laboratory at Duke University Medical Center, and his colleagues began studying whether obesity's influence on OA was solely mechanical. They were aware of work by metabolic researchers who had shown that adipose tissue—body fat—produces immune system substances called cytokines, which travel throughout the body and generate low-grade inflammation.

Other research indicated that leptin, an appetite-curbing hormone produced by adipose cells, governs the actions of the cytokines. In a study that Guilak's group reported last fall in *Arthritis & Rheumatism*, researchers fed one group of mice a diet high in saturated fat, which caused them to gain weight and to develop OA in their knees. Next, the scientists raised genetically altered mice that had no leptin. Without the hormone, which serves as an "off switch" for appetite, the rodents became massively obese. But their knee cartilage remained pristine.



The Power of Platelets //

Could self-donated plasma help soothe arthritic joints?

When standard treatments for osteoarthritis fail, a growing number of physicians are turning to a relatively untested alternative: platelet-rich plasma, or PRP, therapy, in which patients are injected with an altered version of their own blood.

In theory, PRP therapy uses the healing power of blood platelets: a rich source of substances known as growth factors, which promote tissue repair and may help rebuild cartilage, reduce inflammation and lubricate joints, says physician Steven Sampson, director of the Orthohealing Center in Los Angeles. Despite limited and conflicting evidence that it works, golfer Tiger Woods has said he used PRP to speed recovery from injuries, and football player Hines Ward of the Pittsburgh Steelers is said to have used it.

In a typical PRP treatment, 30 to 60 milliliters of blood is drawn and spun in a special centrifuge to concentrate the platelet level in plasma—the fluid that carries blood components, including red and white blood cells and platelets—to four to six times the normal level. That plasma is then injected into and around the joint.

PRP treatments cost \$1,000 or more, and the therapy has yet to be proved effective in randomized trials. But many physicians, including Joanne Borg-Stein, medical director of Spaulding Rehabilitation Hospital's Wellesley, Mass., location, have tried PRP on the basis of observational evidence showing the treatment helps heal joint tissue. Borg-Stein has treated roughly 100 OA patients, typically as a last resort before knee replacement, and says her patients have had significantly less pain and improved function.

Others see mixed results. Elizaveta Kon of the Rizzoli Orthopaedic Institute in Bologna recently completed a study showing PRP to be more effective than another OA treatment, hyaluronic acid. But Kon, who has found that PRP primarily benefits patients younger than 50 with mild arthritis, says, "It's not holy water."

"Leptin may be one factor breaking down cartilage," says Guilak, whose team is now studying obese OA patients to see how their participation in a weight-loss program affects their pain, joint loading and cytokine levels. If research confirms that leptin is a significant cause of cartilage damage, drug developers might be able to design medications that block the hormone's inflammatory effects without inhibiting its crucial role in weight control, says Guilak.

But saving cartilage, by whatever means, won't necessarily eliminate osteoarthritis. "OA is a disease that involves all of the tissues of the joint," says Brandt, "and it can start in any one of them." For example, crucial alterations in bone often occur early in the evolution of OA, says David T. Felson, a rheumatologist at Boston University School of Medicine. Felson and his colleagues have shown that any loss of cartilage increases the risk of bone marrow lesions, or BMLs. "Under a microscope, you see bone that looks like it has been pounded," says Felson.

BMLs and other bone changes, Felson thinks, could help explain why some people with little or no cartilage loss nonetheless experience aching joints. In a 2001 study, Felson's research group found that 36% of OA patients who reported pain had large BMLs, while the BMLs occurred in just 2% of people with cartilage loss who were pain-free.

Other joint tissue, including intact ligaments and tendons, may also trigger OA pain. In a 2006 study, high-resolution MRIs of 20 patients with painful finger joints diagnosed as osteoarthritis revealed inflammation, thickening and other abnormalities in the ligaments, in many cases before there had been any cartilage loss. Other researchers have observed similar lesions in intact ligaments in the knees of patients with OA. And in a 2007 study, Hunter and several colleagues linked increasing synovitis—inflammation of the synovial membrane that occurs as cartilage and other joint tissue break down and debris from spent cells is taken up by the synovium—to worsening of knee pain.

Destructive inflammation may also originate with the cartilage itself. "A breakthrough finding has been that cartilage doesn't just fray and wear out like an old rug," says New York University's Abramson. "It's active tissue that makes destructive enzymes and inflammatory molecules."

So far, today's increasingly nuanced understanding of osteoarthritis hasn't resulted in breakthrough therapies. People with OA may get some relief from anti-inflammatories, but nothing stops the progression of the disease. Some compounds that had seemed promising, including the dietary supplements glucosamine and chondroitin, haven't proved consistently more effective than placebos in clinical trials. If the pain becomes sufficiently debilitating, the only real hope is joint replacement. And artificial joints have a limited life span.

Still, there are several new therapeutic approaches that may help. One is a class of medications known as disease-modifying osteoarthritis drugs, or DMOADs, and several human clinical trials are testing compounds designed to block the damaging effects of the inflammatory cytokines. Yet the search for DMOADs has proved to be an exceptional challenge, largely because osteoarthritis usually progresses slowly, with few patients reporting worsening symptoms during the space of a clinical trial, which typically lasts months, not years.

One solution would be to identify potential study subjects at risk for severe, rapidly progressing OA. Last November, Abramson and several colleagues reported in *Annals of Rheumatic Diseases* that variations in genes that regulate a cytokine



called interleukin 1 appear to promote severe OA. Interleukin Genetics, a Waltham, Mass., biotechnology company, is now working on a “biomarker” test for OA, which could be used in drug development and for early identification of people likely to develop the disease.

Another innovation—an enhanced MRI technique called delayed gadolinium-enhanced MRI of cartilage, or dGEMRIC, developed by engineers at Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center—is aiding early detection by measuring GAG, which provides about 80% of cartilage’s mechanical strength. “This lets us look at the microstructural damage that occurs before tissue is actually lost,” says Young-jo Kim, an orthopedic surgeon at Children’s Hospital Boston. “We’ve shown that, at least in surgical therapies, understanding what’s happening early is helpful,” Kim says.

Meanwhile, engineers have been studying ways to rebuild cartilage, including by using stem cells, which can develop into many different types of specialized cells, to create cartilage. Obtaining stem cells for this purpose usually involves drilling into the pelvis to extract marrow. But Duke’s Guilak uses a much more readily available source of potential cartilage cells: fat cells. A discovery by a colleague involved in obesity research—he left a flask of immature fat cells in an incubator for several weeks, and the cells hardened into mineral—led Guilak and his colleagues to conclude that preadipocytes are actually a type of adult stem cell that can become cartilage cells. His group designed a scaffold made of polycaprolactone fibers (used to make dissolving sutures) to act

as a foundation for the stem cells, which are suspended in a gel containing growth factors that coax the undifferentiated cells to become cartilage. Guilak is currently testing this fat-derived cartilage in animals.

Considering that, within a decade, more than 50 million Americans could suffer from osteoarthritis, research on early detection and effective treatments seems increasingly urgent. But with improved diagnostic tools and preventive therapies—coupled with weight loss and other lifestyle changes—this degenerative disease could become one that rarely reaches end stage. In an ideal world, the need for joint replacements will plummet, and OA will become a condition that, in most cases, people simply outrun. ■

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1. “Developments in the Scientific Understanding of Osteoarthritis,” by Steven B. Abramson and Mukundan Attur, *Arthritis Research & Therapy*, May 2009. An excellent review of current osteoarthritis research, covering genetics, epidemiology, biomechanics and molecular biology.
2. “The Futility of Current Approaches to Chondroprotection,” by David T. Felson and Young-jo Kim, *Arthritis & Rheumatism*, May 2007. Most drugs in development to treat osteoarthritis are designed to protect cartilage—an approach, the authors argue, that is likely to fail because it doesn’t address other major causes of pathology.
3. “Extreme Obesity Due to Impaired Leptin Signaling in Mice Does Not Cause Knee Osteoarthritis,” by Timothy M. Griffin, Janet L. Huebner, Virginia B. Kraus and Farshid Guilak, *Arthritis & Rheumatism*, October 2009. The authors offer powerful evidence that body fat raises the risk for osteoarthritis not only by crushing cartilage but also by producing systemic inflammation that destroys joint tissue.