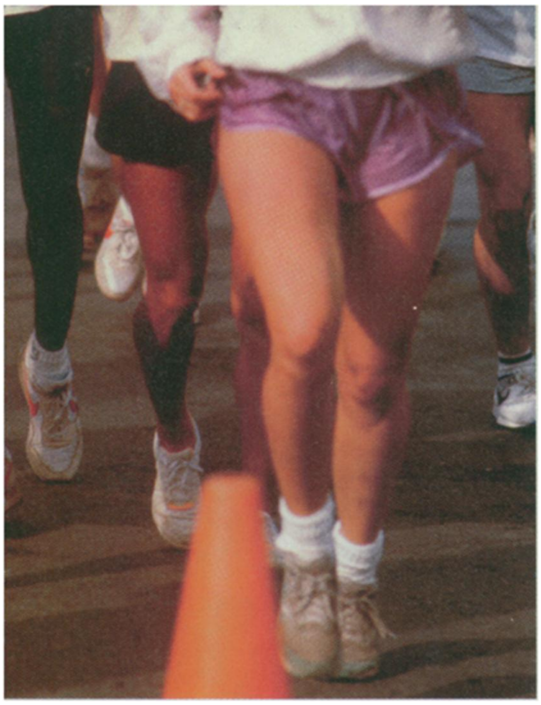


Mending Joints

Cell transplants put the kick back in injured knees

By TINA ADLER

Suffer enough knee injuries and pretty soon you don't need a weatherman to tell which way the wind blows. Such injuries often heal poorly, particularly those that put potholes in the smooth, elastic cartilage tissue that normally ensures smooth joint function. Physicians haven't been much help, because they have had few means of treating wounded joint cartilage.

Not that they haven't tried: Researchers have experimented for years with transplanting cartilage cells. They grow the cells in the laboratory and inject them into the injured joint. But they have had difficulty getting the new cells to form the tough hyaline cartilage found in joints and ensuring that the new growth adheres to bone and existing cartilage (SN: 4/25/92, p.270).

Recent efforts have proved more successful and may even cut back on the number of old-timey weather forecasters whose joints sound an alarm every time bad weather threatens. Cell transplantation "is definitely an interesting way to go, and it has a lot of applications in young patients," asserts Thomas P. Sculco, an orthopedic surgeon at the Hospital for Special Surgery in New York City, who performs about 200 total knee replacements each year.

Cell transplantation isn't designed to cure the sore, creaky knees that result from everyday living and mark many adults' entry into middle age. Instead, it is intended to help repair holes or breaks in cartilage — and in some cases the bone below it — that result from injuries and would normally lead to osteoarthritis. Researchers have tried transplantation techniques on people, racehorses, and other animals.

In a recent trial in Sweden, physician Mats Brittberg and his colleagues at the Sahlgrenska University Hospital in Göteborg grew cells called chondrocytes from cartilage they had removed from the knees of 23 patients age 14 to 48. As a result of injury, each of these patients had a cavity in the knee cartilage. The researchers sewed a layer of connective tissue over each cavity and injected the new cells under it.

Brittberg's group followed the study participants for 16 months to 5 1/2 years. All of the patients experienced less pain and swelling in their knees. In addition, their knees stopped locking up, indicating that no more cartilage fragments had torn loose and become stuck in their joints.

"The treatment resulted in the formation of new cartilage that was similar to normal cartilage," the researchers report in the Oct. 6 New England Journal of Medicine.

Not everyone healed equally well. Those with damaged cartilage on the femur fared better than those with patella, or kneecap, cartilage damage. Two years after the procedure, 14 of the 16 femur patients felt either mild or no pain from strenuous activity. Only two of the seven patella patients did as well. Kneecap injuries may result from misaligned knees, which may be more susceptible to injury and less apt to benefit from the surgery, suggests coauthor Anders Lindahl.

If the treatment hadn't been successful, all of the study participants' knee-joint injuries would probably have caused osteoarthritis, which includes progressive cartilage deterioration, says Lindahl. The actual holes in the cartilage were small, the authors note.

This transplantation technique has its limits. It can't mend multiple defects or widespread cartilage destruction, and it has been used only on knees. About half of all knee injuries include damaged cartilage, Lindahl notes.

In addition, the Swedish patients' defects were quite rare, Sculco says. They had a hole in their cartilage, whereas athletes usually have a tear.

The team's findings are preliminary, other researchers agree. The patients were fairly young and their lesions may have healed without the surgery, says Victor M. Goldberg of Case Western Reserve University School of Medicine in Cleveland. Also, the scientists had followed the participants for only a short period before reporting their findings. How the repairs hold up remains to be seen.

Nonetheless, "it's exciting that here's a clinical study that demonstrates there's some efficacy in using this kind of an approach to repairing cartilage, which up until now has been very difficult," Goldberg adds.

Shigeyuki Wakitani of Osaka University Hospital Medical School in Japan, Goldberg, and their colleagues studied the benefits of using osteochondral progenitor cells to heal injuries that penetrated the cartilage and the bone below it in rabbits, they report in the April Journal of Bone and Joint Surgery. Unlike chondrocytes, which only grow into cartilage, the progenitor cells can also form muscles, ligaments, or bones, depending on where they are injected, says Goldberg. They are more likely than chondrocytes to develop into normal hyaline cartilage, the researchers believe.

They took the cells from connective tissue covering bones or from bone marrow, grew them in a laboratory culture, and added a collagen gel to help them adhere to bones. They then filled holes that they had drilled in the cartilage and bone of the animals' knees with the cell mixture.

"This approach . . . may have useful applications in the repair of large, full-thickness defects of joint surfaces," the researchers assert. They performed the procedures at Case Western Reserve University School of Medicine.

Both the bone marrow and connective tissue cells helped form new hyalinelike cartilage and heal the damaged tissue and bone, they report. However, 24 weeks after the transplant, the new tissue was more elastic than normal cartilage and in some cases appeared to have thinned or split. Also, the new and old cartilage didn't become strongly attached in some places.

"I don't think we're anywhere near recommending [this procedure] for a significant loss of cartilage — from arthritis, for example," Goldberg says. "Our aim is to get to that."

Horses, including racehorses, are also benefiting from a cell transplant procedure, according to veterinarian Alan J. Nixon at Cornell University in Ithaca, N.Y. Nixon and his colleagues are using transplanted chondrocytes to mend joint fractures and torn cartilage. Since the beginning of the year, they've treated about a dozen horses. The surgery "will definitely be used in people," though not for many years, Nixon contends.

They describe their findings from earlier experiments, in which they used this technique on eight horses, in the October JOURNAL OF ORTHOPAEDIC RESEARCH.

The procedure helps only animals with recent, serious bone fractures and cartilage damage in their joints. It's not for horses that have had arthritis for more than about 6 months, Nixon says.

He and his colleagues take cartilage cells from dead horses, freeze the cells, and then grow them on an as-needed basis. They hope to develop a way to use the injured horse's own cells, thus avoiding any immune response to the foreign cells. As far as Nixon knows, however, no such reaction has occurred yet.

The horses get two mixtures at the same time. One includes chondrocytes and a protein called fibrinogen, which helps glue the cells in place and prevents them from taking on the shape of scar tissue cells. The other contains growth factors and thrombin, which activates the fibrinogen. The investigators use a thin surgical tool called an arthroscope to inject the substances. In 6 to 8 months, the animals appear to function normally, and the racehorses can return to the track, he says.

Nixon believes that this approach has numerous advantages over the Swedish method. For one, it requires less invasive surgery. Also, because his group uses growth factors, fibrinogen, and more cartilage cells, "I suspect we'll have a better outcome," he asserts. □

Battling bad knees

The den in 72-year-old Suzanne Dettmer's house looks like a coach's office. It's the shelves. They are loaded with trophies. She and her husband won them running races, a sport she took up about 20 years ago. But in recent years, doctors who examined one of her knees grimaced. Among other problems, most of the knee's cartilage was gone.

Dettmer, my aunt, thinks an injury she suffered as a young woman never healed properly. If she had received a cartilage cell transplant at that time, she might have avoided developing osteoarthritis, according to her physician, Thomas P. Sculco, an orthopedic surgeon at the Hospital for Special Surgery in New York City. It's too late for the technique now, however.

Eventually, like many other people with her condition, Dettmer had to have a surgeon outfit her with an artificial knee, one of the few available treatments for cartilage problems in that joint. Physicians have no way of actually repairing the damaged tissue, which heals poorly on its own, they acknowledge. And generally only people over age 60 get a knee prosthesis, since the device wears out in about 15 years and must be replaced.

Robert Dettmer

For now, Dettmer is happy with her new knee, which she got in January 1993. It's holding up well, despite a rather tough trial run: In October, she competed in her first triathlon since getting the device. And she completed the event — a half-mile swim, a 14-mile bike ride, and a 3.1-mile run — in 2 hours and 24 minutes.

In terms of age, she outranked her competitors by 12 or 13 years. Still, she didn't come in last, she cheerfully points out. — *T. Adler*

Computers

Ivars Peterson reports from Fairfax, Va., at Visualization '94

Illuminating the fourth dimension

A photograph in a magazine or an image on a computer screen is inherently two-dimensional. Nonetheless, such representations often contain visual cues that help create an illusion of three dimensions. For example, by taking into account the size, relative placement, and shading of familiar objects in a scene, one can get a remarkably complete three-dimensional picture of a two-dimensional view.

Analogous visual cues may also enable viewers to "see" four-dimensional objects in three-dimensional settings, says computer scientist Andrew J. Hanson of Indiana University at Bloomington. Hanson and graduate student Robert A. Cross have developed a scheme for viewing a knotted sphere — the four-dimensional analog of a knotted string. In this case, the fourth dimension is simply an additional spatial coordinate.

Suppose one were creating a two-dimensional picture of a knot in a string. As a mathematical object, the knotted string would be invisible because it has no thickness. In drawing a mathematical knot, one is forced to thicken the line to make it visible. Moreover, because the knot itself is a three-dimensional object, one must use shading or breaks in the drawn line to show which parts cross over or under each other.

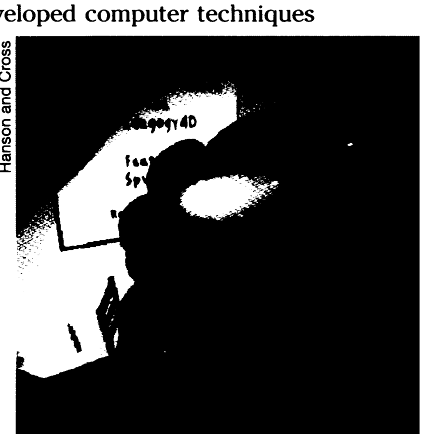
Visualization experts face similar problems in creating an image of a knotted sphere. The four-dimensional object's infinitely thin, three-dimensional shell must be thickened and crossings suggested by suitable markings. It's also possible to go a step further by making the shell shiny. Illuminated by a single light source and seen from different angles, various points on the shell reflect light in particular directions.

"The direction of the light tells us an amazing amount — much more than a [knot] crossing diagram," Hanson says. "It gives us additional information about where the object is facing in the fourth dimension."

After developing techniques that allow the generation of such three-dimensional images in fractions of a second, Hanson and his coworkers displayed their knotted sphere in the Cave Automatic Virtual Environment (CAVE) at the National Center for Supercomputing Applications, located at the University of Illinois at Urbana-Champaign. Here, the viewer can don stereo glasses to interact with three-dimensional graphical images projected into the CAVE room.

But the knotted sphere visualization didn't work very well in the CAVE. "It's hard to see the thing unless you have some additional human context — like shadows and familiar objects," Hanson says. Cross has now developed computer techniques for rapidly creating graphic representations of rich, three-dimensional environments to serve as nonthreatening settings for exploring the strange, unfamiliar realm of four-dimensional objects.

Hanson and Cross



Computer visualization of a four-dimensional knotted sphere floating in a three-dimensional setting. The glint on the object's surface appears inconsistent with the shadows and provides a hint of its four-dimensional character.