

Filling the Gap

■ BY ANITA SLOMSKI // ILLUSTRATIONS BY DANIEL CHANG

In the realm of scientific discovery, distraction osteogenesis qualifies more as happenstance than intentional innovation. Who knows whether anyone would ever have tried to pull a fractured bone apart to get it to heal if a patient hadn't accidentally reversed the tightening rod that was supposed to push together the ends of his fractured femur. And if the doctor who noticed the result—new bone filling in the gap between the separated segments—hadn't been Gavriil Abramovich Ilizarov, surgeons might not have practiced this revolutionary tissue-engineering technique until decades later, if ever. "I might have told the patient, 'Don't do that again,' but the genius of Ilizarov was that he wondered, 'How can I get this to happen again?'" says J. Tracy Watson, chief of orthopedic traumatology at the St. Louis University School of Medicine.

Most of the world didn't hear of Ilizarov's technique, which he named distraction osteogenesis in 1951, for more than 30 years. A general practitioner, and a Jew, Ilizarov had been ordered off to the industrial city of Kurgan in Siberia to tend to the wounds of soldiers returning from the Second World War.

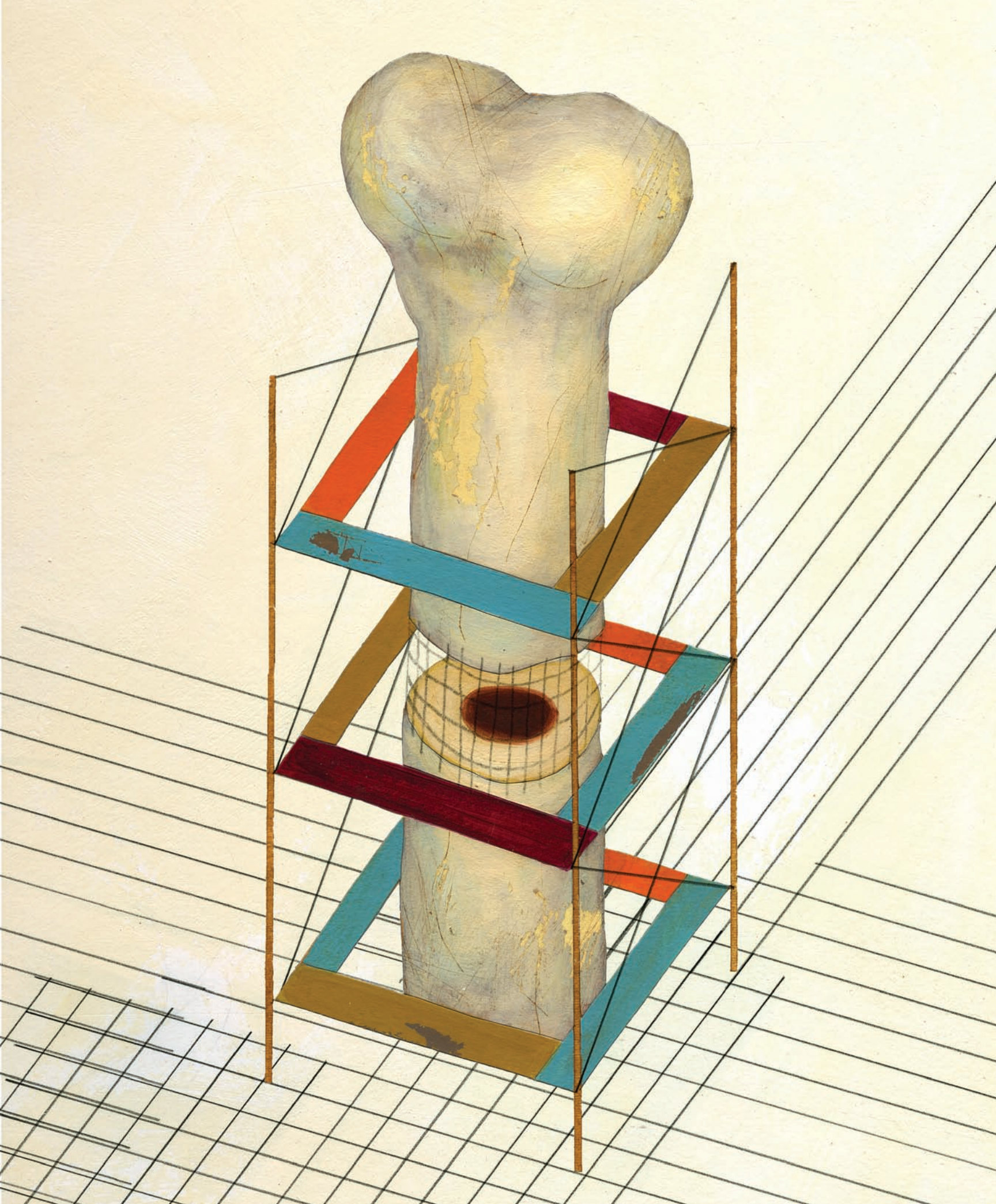
With so many patients suffering from bone infections and missing bone from bullet wounds, Ilizarov became an orthopedist by necessity. And with resources severely constrained, his distraction apparatuses were primitive. The external frame that encircled the outside of fractured bones was made from head gaskets cut from old tanks; the pins that he drilled through the fractured bone and affixed to the external frame

were fashioned from bicycle spokes. By tightening the spokes, Ilizarov would slowly force the bone segments apart.

Experimenting on dogs, Ilizarov found that new bone would spontaneously form if broken bone was distracted at the rate of one millimeter per day—coincidentally, the same rate at which stretched nerves will regenerate. Distracting just 0.25 millimeters at a time, four times a day, worked even better and caused less pain. But the Cold War and a repressive medical bureaucracy kept Ilizarov's discovery buried until 1967, when he cured the badly broken and infected tibia and fibula of Valery Brumel, a Soviet high jumper and Olympic gold medalist. Then, more than a dozen years later, Ilizarov used distraction to mend the infected tibia of the Italian mountaineer Carlo Mauri. That finally attracted the attention of European surgeons, and during a trauma fellowship in Switzerland, in 1986, Watson saw distraction osteogenesis being performed.

"I sneaked over to Germany and saw surgeons sticking piano wires into skin to pull apart bone," he recalls. "I couldn't believe what I was seeing. At first look, you had to say it was insane."

For years, that was the consensus among Western doctors—that distraction osteogenesis was the antithesis of rational medical practice. In 1987, when Watson, then at the Cleveland Clinic, used the technique to save the leg of a patient whose badly fractured tibia had refused to heal, a senior doctor termed the procedure "the tool of the devil." But Watson and other orthopedists, including James Aronson, director of the Laboratory for Limb Regeneration Research and chief of pediatric orthopedics at Arkansas Children's Hospital in Little



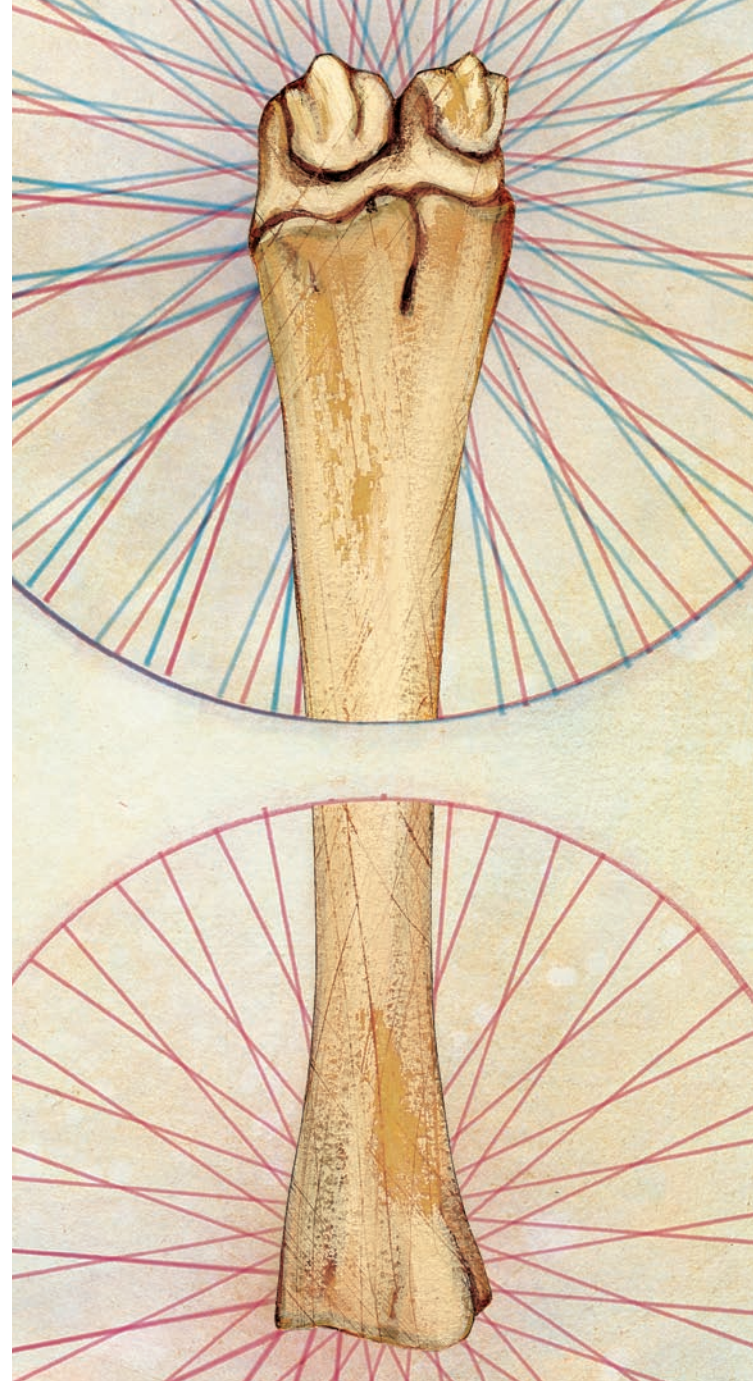
Rock, pursued the technique. Ilizarov (accompanied by KGB agents) eventually traveled to the United States, and two dozen American doctors, including Watson and Aronson, visited his institute in the USSR, where they operated on Soviet patients. Slowly the approach gained acceptance, and today distraction osteogenesis is used to treat some of the most challenging orthopedic conditions: fractures that won't mend, limb deformities and bone defects from trauma, infection or cancer.

Theoretically, any bone can be distracted, and in Russia, surgeons actually distract the skull after a stroke with something “that looks like a medieval torture device,” Watson says. “Distraction causes microcapillaries to form and creates a new blood supply to the area. So by freeing up small sections of bone over the area of the brain that has sustained the stroke, you increase the blood flow. But of course, we'd be probably thrown out of the hospital if we tried that treatment here.”

For defects elsewhere in the head, however, maxillofacial and plastic surgeons have enthusiastically embraced distraction. “It has revolutionized and simplified craniofacial surgery,” says Joseph McCarthy, professor of plastic surgery and director of the Institute of Reconstructive Plastic Surgery at New York University Langone Medical Center. McCarthy performed the first craniofacial distraction procedure in 1989 and now does at least 50 a year to correct such defects as cleft palate, malformed jaws that interfere with breathing and Crouzon syndrome, in which premature fusion of skull bones prevents the skull and facial bones from developing normally. “For children with Crouzon syndrome, for example, we can use distraction to move the upper jaw, the cheekbones, the nose and the eye sockets in one block,” McCarthy says.

Because of innovations in distraction devices for both facial bones and the long bones of legs and arms, distraction osteogenesis promises to gain wider acceptance. Once announced by huge, unsightly metal cages and bars, *in vivo* tissue engineering now occurs silently and invisibly, supported by ingenious internal mechanical scaffolds. It's the second groundbreaking phase of Ilizarov's remarkable procedure.

After a surgeon slices through bone that is to be distracted, there's a one- to two-day wait before the bone can be pulled apart. During this latency period, fibroblasts, which play a crucial role in wound healing, and



new blood vessels invade the fracture site. The fibroblasts start laying down a matrix of collagen fibers, and once this sticky bridge, called callus, has formed, the bone can be distracted. As it is pulled apart, bone-producing cells known as osteoblasts migrate from both sides of the fracture and begin depositing osteoid, a bone matrix that hasn't yet calcified. “Think of stalactites coming out of both ends of the bone,” says plastic surgeon Michael Longaker, director of the Children's Surgical Research Lab at the Stanford School of Medicine. Once distraction ceases, osteoblasts complete the bony bridge with mineral deposits that turn the soft bone into normal bone.

Compared with other craniofacial reconstructive techniques, distraction osteogenesis has several advantages. It doesn't require surgery at a second site, as bone grafts do, and it can be performed on children as young as a recent two-year-old patient of Maria Troulis, director of the Skeletal Biology Research Center at the Massachusetts General Hospital and associate professor of oral and maxillofacial surgery at the Harvard School of Dental Medicine. Since birth, the girl had been forced to breathe through a hole in her neck because her lower jaw was too small to pull her tongue forward and keep the airway clear. To remedy that, the jawbone would have to be stretched six centimeters on either side. "She was so small, there was no way we could have taken 12 centimeters of bone from elsewhere in her body," Troulis says. "In addition, the soft tissue would not accommodate such a large skeletal movement to pull the jaw back to its original size." But using distraction, Troulis successfully lengthened the girl's jaw.

Still, the large, external hardware needed for expanding facial bones is hardly ideal. Most distractors consist of an external metal bar with multiple joints to move the bone in different directions, and connected to the bone with metal pins inserted through the skin. A screw mechanism that the patient or a

have a jaw shape similar to that of humans. Though he was off on the timetable—it's been 13 years—the device exists, and Troulis and Kaban are inching toward a model for human use.

The first challenge was to devise a way for the fixator to move the jawbone in three directions in incremental steps. With an external fixator, surgeons can make adjustments to move the jaw, but with an implanted device, there's no chance for mid-course changes of direction without operating. "Getting the bone movement right is a problem, because teeth have to interdigitate accurately," Kaban says.

Ed Seldin, an oral and maxillofacial surgeon on Kaban's research team, used Euclidean geometry to show that any three-dimensional surgical movement follows a curved path with specific parameters. In 1996, working in his home machine shop, he built a curvilinear distractor that uses a rack-and-

The pins attached to the fixator track through the skin as the bone moves, causing permanent scars.

family member turns every day during the distraction phase moves the bone apart. For every millimeter the bone is distracted—at one millimeter per day—the external fixator stays in place twice as long. So if the distraction phase is 35 days, fixation is another 70. Add in the necessary latency period, and the patient must wear the device for about 16 weeks. The pins attached to the fixator track through the skin as the bone moves, causing permanent scars. Moreover, because the patient controls the distractor, there's a chance of human error.

To improve on that, Leonard B. Kaban, chief of the department of oral and maxillofacial surgery at the MGH and chairman of oral and maxillofacial surgery at the Harvard School of Dental Medicine, resolved in 1995 to create a hidden, implantable, motorized device capable of three-dimensional movements that could be remotely activated. The bone could be distracted continuously in tiny increments, which may lead to faster bone growth, according to preliminary evidence.

Kaban figured his team could produce a prototype within six months, and he wanted Troulis to test it in mini pigs, which

pinion drive mechanism. Two years later, Troulis tested a more advanced version of the device in the jaws of mini pigs.

That still left the challenge of controlling the implanted distractor. Working with Kaban's group, the Harvard Surgical Planning Laboratory created a computerized treatment planning system, called Osteoplan, that writes a prescription—based on a three-dimensional model of a patient's skull made from a CT scan—that specifies the exact radius of curvature and length of the device needed to correct specific jaw defects. The surgeon can use the program to determine where to cut existing bone and place the distractor.

The laboratory also modeled more than 400,000 theoretical bone corrections in the jaw and found that a set of four distraction devices, each with a unique radius of curvature, would accommodate the full range of surgical movement. "That meant a manufacturer could make a kit for the operating room with just four curved distractors," Kaban says. The surgeon can choose which device will work for a particular patient.

The custom-made device Kaban and Troulis have begun to

use in patients has all the elements of Kaban's original vision, minus an implanted motor. A thin cable projecting out of the patient's skin—the only visible sign of the fixator—ends in a hexangle nut that the patient turns daily, rotating a gear inside the implanted device and distracting the bone. Within three to four years, Kaban and Troulis expect to add a micromotor and battery to the device. Troulis has already tested the motorized distractor on pigs, but the wallet-size battery is too large to implant. "If we can't make the battery small enough to implant in, say, the chest, then we'll have a patient plug two tiny wires into an external battery at night," Troulis says. "But the goal is to implant the battery so continuous distraction is possible."

Distractor osteogenesis tends to work better for facial bones than those in the arms or legs. Bones heal and grow more quickly in the face, there are fewer infections, and the amount of new bone that's needed is smaller. But the long bones of the arms and legs are straighter than facial bones, and new devices are addressing many of the problems inherent in distracting long bones.

"With the Ilizarov frames, you had to create a complicated system of connecting hardware to correct bone deformities, which are usually multidimensional," says Mikhail Samchukov, who was deputy director of Ilizarov's research institute in Kurgan and is now co-director of the Center for Excellence in Limb Lengthening and Reconstruction at Texas Scottish Rite Hospital for Children in Dallas. "And you had to continually reconfigure the frame."

With one new device, the Fitbone, everything is automatic. The only electrically driven, totally buried fixator, it consists of a "nail," or rod, containing a micromotor that a surgeon inserts into the cavity of the bone that is to be distracted and attaches it with small screws. There's also an antenna, connected to the nail, that's implanted beneath the skin. Three times a day, for 90 seconds, the patient places a handheld transmitter against the skin that sends a high-frequency signal, via the antenna, to a motor in the implanted distractor. The telescoping nail gradually lengthens, distracting the bone.

"The Fitbone uses the kind of induction energy that drives an electric toothbrush," says orthopedic surgeon Peter Thaller, who does about 50 Fitbone procedures each year at the Limb Lengthening Center in Munich, Germany. Thaller works with Rainer Baumgart, an inventor of the Fitbone.

"Patients can use their legs better with the Fitbone than with an external fixator, and they complain of much less pain than when they have a frame around the leg," says Samchukov. "And you eliminate the possibility of irritation and infection around the wires and pins of an external fixator."

But the Fitbone, which can lengthen a long bone as much as 8.5 centimeters (3¹/₃ inches), is only rarely applied to children because the nail, inserted in the lower leg or arm bone, would perforate the growth plate and might disturb the developing tissue near the ends of long bones. "At age 15 to 17 the growth plate is closed, and that's when we can more easily use the Fitbone," Thaller says.

John Birch, Samchukov's colleague at Texas Scottish Rite, is the only orthopedic surgeon in the United States who has implanted the Fitbone. He has received special permission from the U.S. Food and Drug Administration to use the implanted

Making Bone Grow Faster //

Speeding up distraction's consolidation phase would make the procedure easier to bear. Several approaches seem promising.

Distraction osteogenesis proceeds at its own pace, optimally about one millimeter per day. But for every day a bone is distracted, more than one day is required for consolidation, during which newly formed bone hardens. "Consolidation is the time killer," says Michael Longaker, director of the Children's Surgical Research Lab at the Stanford School of Medicine. "There's no reason we can't accelerate that phase."

Longaker's lab is pursuing four strategies to speed hardening. The first calls for isolating mesenchymal stem cells from bone marrow or fat. These stem cells can become other kinds of cells, including those needed for bone formation. "During the surgery to cut the bone,

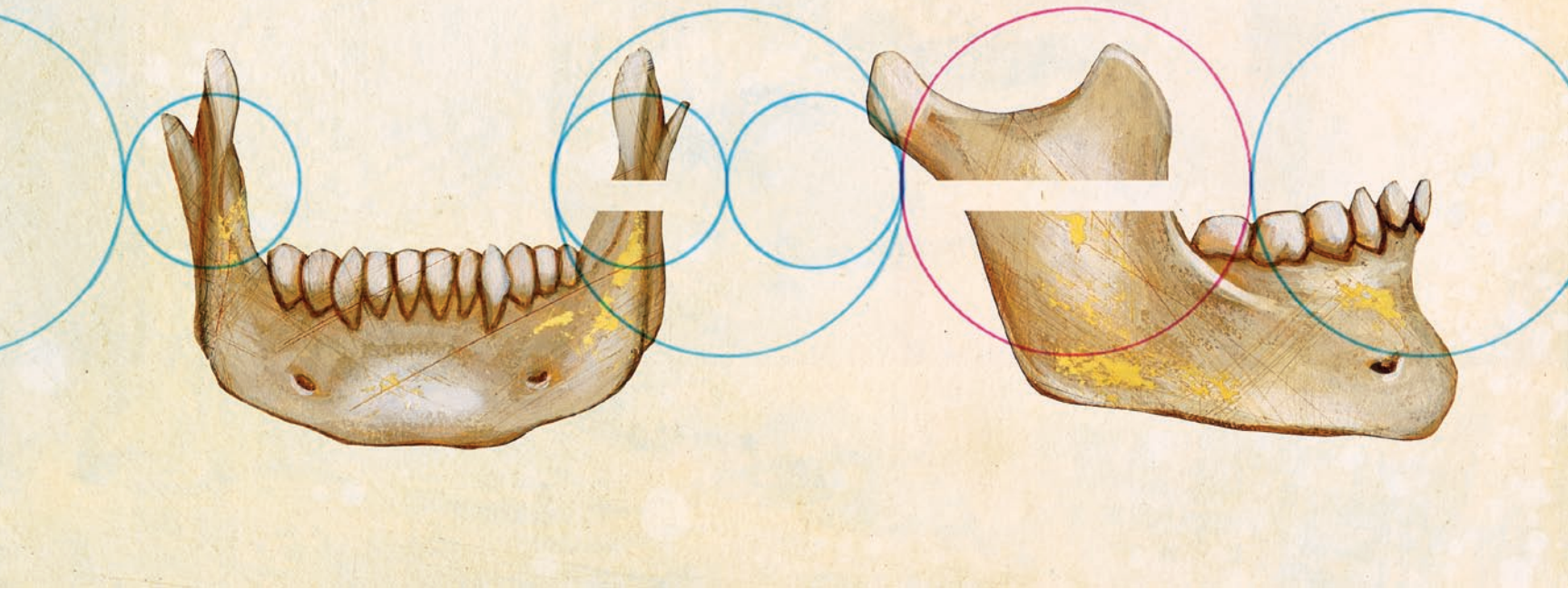
you could insert a scaffold that mimics the structure of bone so stem cells immediately start forming bone," Longaker says.

The second explores the potential of boosting the effect of bone morphogenic proteins (BMPs), which the body manufactures naturally to heal fractures. These proteins are already commercially available, and Longaker imagines "either adding BMP-type substances, or decreasing the effects of BMP antagonists (which inhibit the action of BMPs), or both."

Third, because distraction is faster and has fewer complications in the face than in the long bones (because the face is highly vascular), Longaker is researching whether having more blood vessels at the distraction

site would speed bone formation. Vascular endothelial growth factor creates blood vessels when it is released by tumors or by stem cells after a bone injury. "If you created a matrix that released VEGF and added cells that formed bone, that would hasten healing," says Longaker.

The fourth possibility would use mechanical loading to stimulate bone formation. Bone demineralizes quickly when no force is applied. Longaker is experimenting with devices to see whether movements as imperceptible as one-millionth of a millimeter might make bone harden more quickly. "If we could reduce the consolidation period by half," he says, "that would be great."



distractor when external devices would increase the risk of complications. But a more widely available implantable fixator, the Intramedullary Skeletal Kinetic Distractor, or ISKD, received FDA approval in 2001. This device uses a telescoping two-part metal nail inserted in the hollow center of a femur or tibia. When the patient moves his or her knee or ankle, either through normal daily activity or during special exercises, the lower part of the rod rotates and increases in length, which distracts the bone. A handheld external sensor tracks the lengthening progress.

Besides being unsuitable for children, the implanted nails of the Fitbone and the ISKD don't work well in bent or infected bones. "It's difficult to get a nail down twisted, badly aligned bone," Watson says. So he uses a Taylor Spatial Frame, an external fixator that corrects multiple deformities simultaneously using a computer-generated prescription for correcting the limb.

"Instead of all the pins and wires we used to have, newer designs let us use two rings with very few pins or wires," Watson says. "It simplifies the process of straightening a bone."

Yet despite recent advances in distraction, it's currently practiced by only about 150 orthopedic surgeons in the United States. "Most orthopedic surgery is a quick fix—a total knee or hip replacement," explains James Aronson of Arkansas Children's Hospital. "Here you have to see the patient every week during the distraction, and of the surgeons who initially showed interest, most don't do it because it's so demanding in terms of time and understanding."

Still, the technique has allowed practitioners to correct more severe deformities than had been possible. And distraction osteogenesis has spurred research that is finding ways to promote bone healing and growth in diseases that compromise bone health, such as diabetes, alcohol abuse and aging. Researchers are now experimenting with ways to generate bone more quickly so distraction osteogenesis won't be such a long, uncomfortable procedure. What started as an accident has become a viable option for otherwise hopeless cases. And continuing advances, suggests Troulis, could have another effect. "People may opt to correct lesser deformities with this revolutionary technique," she says. ■

→ DOSSIER

1. "Basic Science and Biological Principles of Distraction Osteogenesis," by James Aronson, in *Limb Lengthening and Reconstruction Surgery*, eds. S. Robert Rozbruch and Svetlana Ilizarov (New York: Informa Healthcare, 2006). In this textbook chapter, Aronson describes a variety of his discoveries, including the fact that speeding up the rate of distraction beyond two millimeters per day led to poor bone formation.
2. "Mandibular Advancement by Distraction Osteogenesis for Tracheostomy-Dependent Children With Severe Micrognathia," by Derek M. Steinbacher, Leonard B. Kaban and Maria J. Troulis, *Journal of Oral and Maxillofacial Surgery*, August 2005. Study demonstrates that distracting the jawbone with a semi-buried device can eliminate the need for an artificial airway.
3. "Craniofacial Bone Tissue Engineering," by Derrick C. Wan, Randall P. Nacamuli and Michael T. Longaker, *Dental Clinics of North America*, April 2006. Reviews research into enhancing distraction osteogenesis as well as advances in cell-based tissue engineering for cases in which bone cannot be reconstructed with distraction.