Coral Chemistry Leads to Human Bone Repair

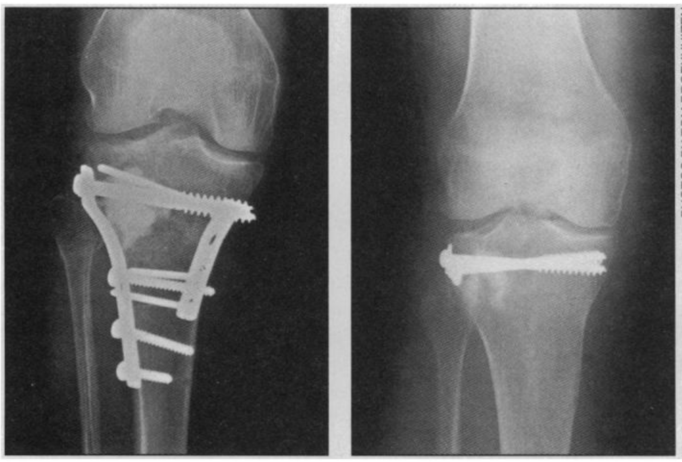
Not everyone who breaks a bone gets away from the hospital with only a plaster cast for loved ones to scribble on. Some are outfitted with enough screws, pins, and metal plates bolted to their bones to deplete a hardware store shelf. To buttress a common type of hip fracture, for instance, surgeons attach a metal plate and pin it to the femur with large screws—major surgery that results in hospital stays averaging 11 days and more surgery later to remove the hardware. Not only are such procedures painful and risky (there's a chance of infection, and the screws can further damage the bone), they're expensive: Hip fractures alone cost the United States an estimated $10 billion each year.

That expense, pain, and danger may be coming down soon, if a new type of artificial bone bears out its initial promise. On page 1796 of this issue, a group of materials scientists and surgeons led by Brent Constantz of the Norian Corp. in Cupertino, California, report on a new material that is prepared as a paste and injected directly into a fracture site. The paste hardens in minutes, providing support for pieces of broken bone, and cures to a strength equal to that of natural bone within 12 hours. Equally important, bone cells grow into the implant, gradually replacing it with fresh, living bone and making the fracture whole again.

In clinical trials in Sweden and the Netherlands, surgeons have used the paste to treat dozens of patients with fractures of the hip, knee, shoulder, and wrist; compared with conventional procedures, the operations went faster, the bones needed fewer plates and screws, and the patients resumed normal activities sooner. "It looks promising," says Tom Broekhuizen, chief of the trauma surgery department at the Academic Medical Center in Amsterdam. More trials are needed, he says, but "if it is what we think it is, it could be revolutionary."

The promise Broekhuizen and others see arises from the new material's usefulness in treating a particularly difficult class of fractures—damage to the ends of long bones, such as those of the arms and legs. These pieces of the skeleton consist of two types of bone: solid, cortical bone surrounding a core of cancellous—or porous—bone, which predominates at the bone tips. A fracture at a tip can crush the cancellous bone, leaving a dent or hole. In a tibial plateau fracture, for example, the shinbone breaks just below the knee, pushing the cancellous bone downward. Surgeons shove this core bone back up and then fix it in its new position with the necessary hardware. But the procedure leaves a gap in the cancellous bone inside the cortical bone sheath which, if not filled, could allow the fracture to reopen.

The way many surgeons now fill the void is to cut pieces of bone from the pelvis and stuff them into the hole, but this involves more surgery and, Broekhuizen says, is often more painful than the fracture repair. Alternatively, the surgeon can fall back on a material such as hydroxyapatite, a crystalline substance with a chemical structure similar to that of bone, but it's difficult to handle and few surgeons use it. And neither bone chips nor hydroxyapatite can support much weight, and so until new bone fills in, the patient can put little load on the joint.



PHOTOS BY TOM BROEKHUIZEN

Less hardware. The fractured shinbone at left has been treated with metal plates and screws, plus a new biomaterial. The material is strong enough to support another shin fracture *(right)* with less heavy metal.

The new material—called Norian SRS, for "skeletal repair system"—offers a third option. The paste is injected into the void in the bone. The mixture hardens within 10 minutes, forming a custom implant that conforms to the contours of the gap and supports the cancellous bone much more firmly than bone chips or hydroxyapatite. This solid support allows the doctor to make do with much less hardware, and sometimes none at all.

After surgery, SRS brings other benefits. Depending on the type of fracture, it may allow the patient to begin physical therapy sooner. In one type of hip fracture, for example, the design of the metal buttresswork makes walking quite painful. Eliminating the need for this type of hardware should help get patients out of bed within 2 or 3 days, Constantz says. Merely cutting 3 to 4 days off the average hospital stay for a hip fracture, he adds, could save billions a year in health care costs.

Over the long term, SRS has another advantage: It is so similar in structure to bone that the body treats it as such, gradually resorbing it and replacing it with new bone growth. Natural bone is preferable to implants because the body constantly reworks bone to adapt to stresses. A needlessly rigid implant will take too much load off surrounding bone and weaken the whole area; the body only lays down new bone in response to a stressful load. Such feats have been impossible with the bone repair materials available until now, notes chemist Richard Lagow of the University of Texas, Austin.

Constantz got the idea for SRS in 1985, while a graduate student at the University of California, Santa Cruz. He was studying coral, which form their skeletons differently than do humans. Bone formation in vertebrates is directed by proteins, which guide the bone's mineralization, slowly producing a porous, slightly disordered crystalline structure. Coral, on the other hand, produces its skeleton with no protein guidance. Because no one has yet been able to mimic protein-directed bone growth to produce whole segments of bone quickly (*Science*, 21 January 1994, p. 324), Constantz decided the natural alternative was to mimic coral, building bone via physiochemically controlled reactions.

Constantz formed a company to pursue this vision, the Norian Corp., named after the geologic epoch in which reef-building corals first appeared. He quickly found that if he combined a dry calcium source with a crystalline form of phosphoric acid and mixed that with a sodium-phosphate solution, he got a paste that would crystallize into a material very much like bone. That turned out to be the easy part. Constantz and colleagues spent the next several years varying that basic recipe to optimize such properties as ease of injection and hardness after crystallization. It took 1200 different formulations before they settled on the present brew.

But that long effort is paying off. SRS is beginning clinical trials at 12 different hospitals in the United States. If the material is as successful here as it has been so far in Europe, and if it can secure approval from the Food and Drug Administration, there may soon be more syringes than screwdrivers in orthopedic surgery rooms.

–Robert Pool