TO MAKE BONES ABOUT IT

Researchers now have used a bone-growing procedure to repair certain skull and facial deformities. The precise factors responsible for inducing such bone growth remain a mystery.

BY LINDA GARMON

During a routine examination, a dentist discovered that his 16-year-old, hockey-playing patient had more than the usual reasons to fear the flying pucks and swinging sticks encountered on the ice. A large bone cyst (a hole) had at one time formed and then failed to heal in the young man's lower jaw, leaving the roots of four of his teeth precariously dangling in an air-filled space. But the patient was not forced to hang up his skates to guard his teeth; instead, doctors implanted a special demineralized bone preparation that induced new bone growth, which virtually filled the cyst space.

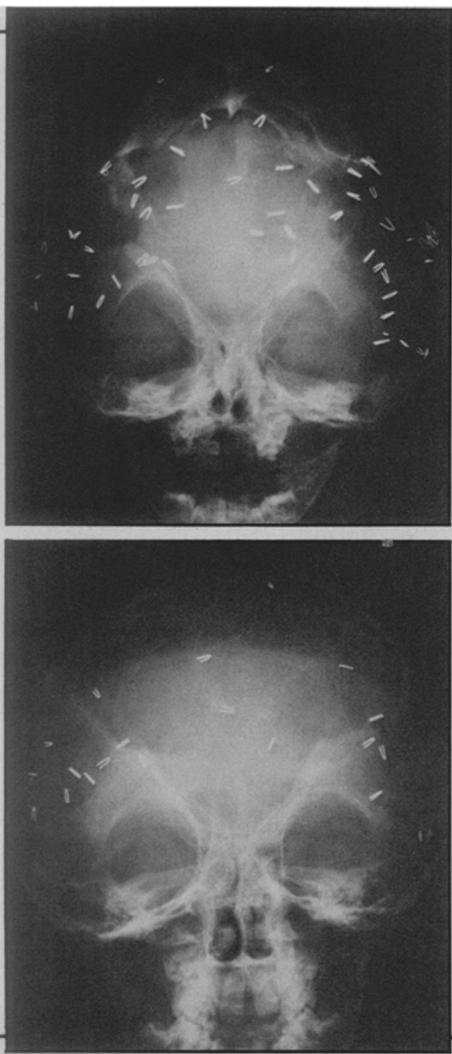
The hockey player is one of 44 patients with skull or facial deformities who have received the demineralized bone treatment under the direction of Julie Glowacki, Leonard B. Kaban, John B. Mulliken, Joseph E. Murray and Judah Folkman of Harvard Medical School in Boston, Mass. The treatment — described in the May 2 LANCET — has certain advantages over the conventional procedures for reconstructing skeletal deformities of the face and skull, the HMS researchers report.

Conventional procedures involve transplanting whole sections of bone from cadavers or from the patient's own body — grafts from the ribs, iliac crest (a part of the pelvis) or anterior tibia (shinbone), for example. Healing then occurs via osteoconduction — cells from intact bone migrate to the edges of the transplanted bone. But bone repair using osteoconduction has its drawbacks, Glowacki and colleagues say, because the grafts can be absorbed by the region under repair, thereby necessitating repeated operations. In addition, the amount that can be harvested from the patient's own body is limited, and such harvesting can leave infections, scars and chronic pain. Now, by using demineralized bone implants rather than grafts for craniofacial repairs, many of these problems have been avoided, says the HMS team.

The demineralized bone procedure the HMS researchers are using for craniofacial repairs is a modification of a bone-growing technique first reported in 1968 by Marshall R. Urist and colleagues at the University of California at Los Angeles. Bone — usually taken from cadavers — is converted into blocks, chips or powder and washed in hydrochloric acid to remove all minerals. (If the minerals are allowed to remain in the bone preparation, then the implant is absorbed by mononuclear cells, which are thought to come from the bloodstream.) The bone preparation then is dried and sterilized.

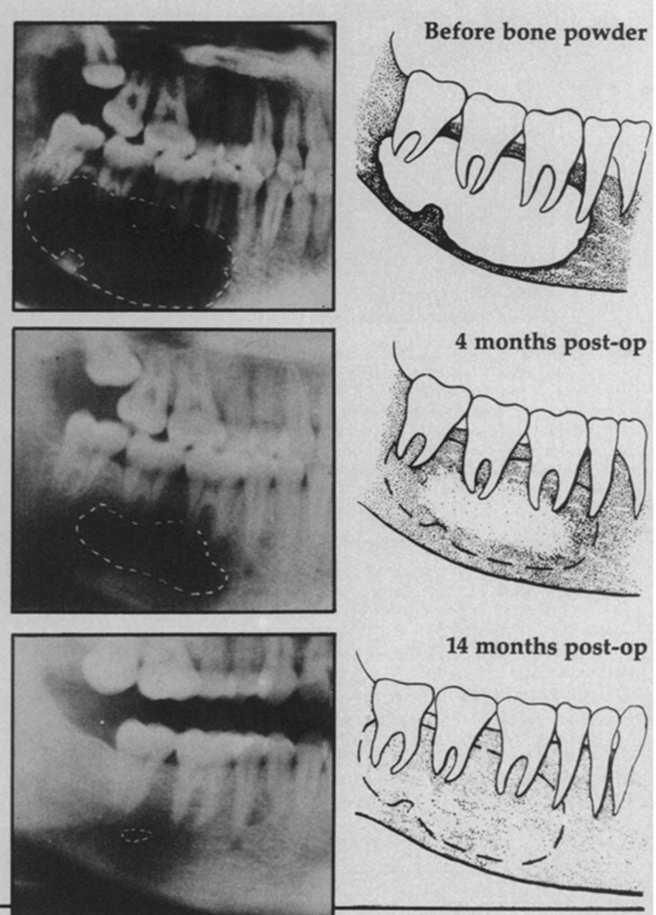
When this demineralized bone is implanted, it causes growth of new bone not through osteoconduction, but rather through osteoinduction, or induced osteogenesis. Through osteoinduction, the implant causes fibroblasts, which usually form scar tissue, to start producing cartilage. "When they touch the bone material, fibroblasts change behavior and start to produce cartilage," Glowacki explains.

Among those treated with demineralized bone was a 6-year-old boy with a cloverleaf skull (upper X-ray). A neurosurgeon removed nearly all of the skull, leaving intact the dura — the thin, leather-like lining over the brain. Doctors waited three weeks for the child's brain to reshape itself and then placed demineralized bone powder on the patient's dura. The lower X-ray shows the new skull 14 months after administration of bone powder. (The silver clips are remnants of earlier surgical attempts to correct the skull deformity.)



Children's Hospital Medical Center

A large cyst had failed to heal in the lower jaw of a 16-year-old boy. New bone began growing four months after administration of the demineralized, pulverized bone.



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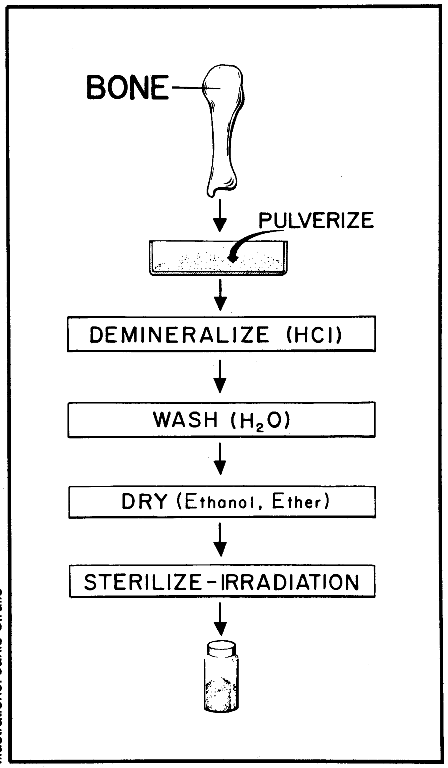
"Fibroblasts don't usually do this—chondroblasts do."

The fibroblasts-turned-chondroblasts begin producing cartilage about 10 to 14 days after implantation. Months later, new blood vessels penetrate the cartilage, triggering its conversion to bone.

The HMS researchers have taken advantage of this osteoinductive process to induce bone growth where bone has not previously existed. And therein lies the novelty of their work. While UCLA researchers have been applying a similar technique for years, their work has focused on adding bone to bone, such as in rebuilding limb bones. By contrast, Glowacki and colleagues have used the technique to construct new bone in soft tissue (to replace a congenitally absent nose, for example) to fill gaps (such as the roof-of-the-mouth hole in patients with a cleft palate) and to augment forehead or cheek contours.

The longest follow-up period among those patients has been two and a half years, Glowacki says, and the results are encouraging. Still, she says, "I'm going to be happier with four or five years of follow-ups." The researchers still do not know, for example, how strong the new bone is and to what extent the absorption common to bone graft procedures has been avoided.

In addition to keeping a close watch on their 44 patients in an attempt to answer



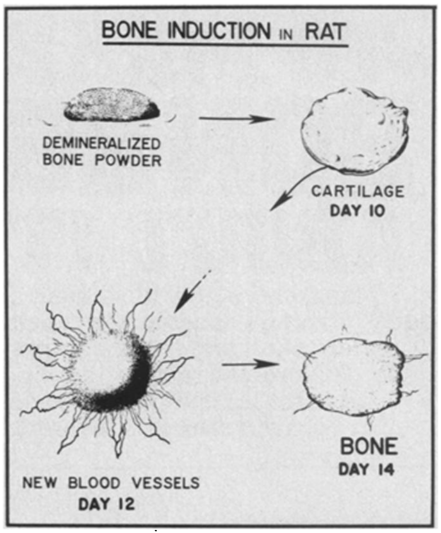
Illustrations: Janis Cirulis

The drawing depicts the preparation of demineralized bone. Researchers have used both patient's own and cadaver bone.

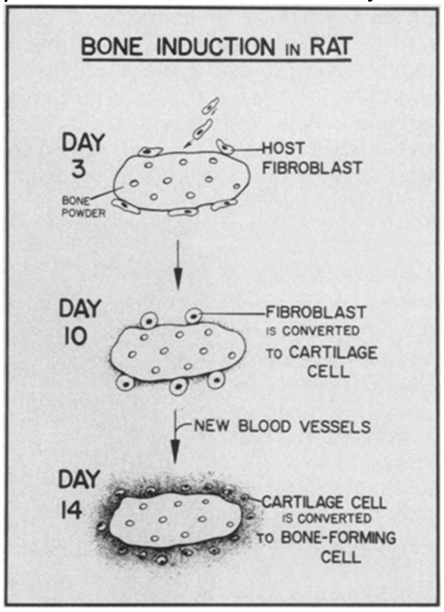
such questions, Glowacki and colleagues also are trying to unravel the mysterious subcellular mechanism responsible for the transformation of fibroblasts. "We think that it may be an electrochemical charge [an ionic charge, not an electric current] that is transmitted through the cell membranes and somehow causes a change in the genetic expression of the fibroblasts, causing them to become no longer scar-tissue-producing, but skeletal-producing cells," Glowacki says. UCLA researcher Gerald Finerman, on the other hand, says, "While it is popular right now to think that the thing that induces bone formation is an electrochemical signal...a process that utilizes a protein also seems possible." Finerman and Urist now direct most of their research energy toward trying to isolate and purify just such a protein—the "bone morphogenetic protein," or one responsible for inducing bone growth.

Identifying the factors responsible for inducing bone growth is top-priority work among the bone-growing researchers. "Once these are determined, we can synthesize materials with those specific factors," Glowacki explains. In addition, once the details are understood, researchers will be able to manipulate the mechanism. "For example, it would be very nice to have a material that would stop at the cartilage [producing] stage to construct ears and tips of noses and to treat degenerative bone diseases where there is a loss of cartilage," Glowacki says. "This, of course, is a long-term goal."

Meanwhile, Glowacki and colleagues



Glowacki and colleagues studied bone induction in rats before their clinical trials with demineralized bone. The induction process is slower in the human body.



At the cellular level, bone induction involves the transformation of fibroblasts, which normally produce scar tissue, into cartilage-producing cells.

are working toward more widespread use of the demineralized bone treatment at its current stage of development. The Monsanto Co. of St. Louis, Mo. — which provided part of the funds for the HMS research — recently licensed California's Collagen Corp. to manufacture and sell the demineralized bone. "The technology is being transferred to them right now," Glowacki says, "and they've already started making it." Collagen also will be responsible for collecting research results from various university hospitals that will be repeating the HMS bone-growing experiments and sending those data to the U.S. Food and Drug Administration for wider-marketing approval. "According to our timetable, the data will be collected for about a year," Glowacki says, "and then, it will be in FDA's hands." □

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