THE NEW TOOLS OF RECONSTRUCTION:
Skin from a deceased donor's face // Fat // Milled bone chips // Resorbable tacks // Fibrin glue // Biodegradable scaffolding // And most critical, not expecting too much too soon.

Saving Faces

BY ANITA SLOMSKI

People who have suffered disfiguring injuries never grow accustomed to the stares, the double takes, the not-so-discreet shudders. Longing to disappear into the crowd, they may submit to dozens of unimaginably painful surgeries. To reclaim a burned face, for example, substitute patches of skin must be transplanted from elsewhere on the patient's body. Both sites—where the skin is taken and where it's sewn back into place—must heal, and infection is always a danger. If the skin is from another person, rejection is a risk. For most reconstructive surgeries, the degree of difficulty is high, and the probability of dramatic improvement can be low. And yet, so pronounced is the psychological trauma of disfigurement that there is never a shortage of volunteers for procedures that offer the possibility, however slim, of replacing what has seemed forever lost.

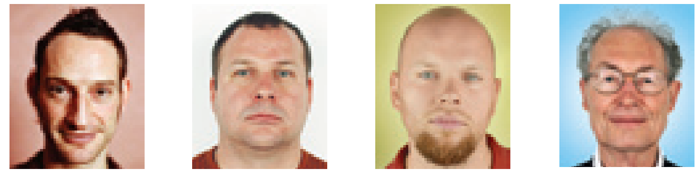
Maria Siemionow, director of plastic-surgery research and head of microsurgery training at the Cleveland Clinic, has been flooded with requests since the announcement in late 2004 that she is ready to transplant a face. But her search for the right combination of donor and recipient could take months, even years. Siemionow hopes to avoid the controversy surrounding the first partial face transplant, performed in France in November on a woman who had been mauled by her dog.

Similarly, transplant surgeon Joseph Vacanti and plastic surgeon Michael Yaremchuk at the Massachusetts General Hospital (MGH) in Boston must gently discourage all those hoping for too much too soon. Vacanti and Yaremchuk are working toward the day when it will be possible to fashion a wide range of human spare parts from cells implanted on a biodegradable scaffolding that dissolves as new tissue takes hold.

And after Hans-Peter Howaldt, a craniomaxillofacial surgeon at Germany's University of Giessen, began using stem cells harvested from a patient's own fat to repair skull defects, his office began receiving pictures of children whose parents hoped they might be candidates for the new procedure. Yet, for the most part, all of this pioneering work is years from routine clinical applications. For now, patients searching for alternatives to today's standard reconstructive approaches must content themselves with hints of what may someday come to pass.

By the time Howaldt saw "Maria," a seven-year-old who had nearly died from a fall out of a second-story window, two years of chronic infections and failed surgeries had left her skull so full of holes that she was wearing a helmet to protect her brain. Had Maria been older, Howaldt could have used a titanium implant or bone graft to repair the damage, but that wouldn't work with a skull that would continue to grow for years. What's more, because of Maria's youth, transplanting bone from elsewhere in her body wasn't an option. "You cannot harvest enough bone from a child that age," says Howaldt.

But for months, Howaldt had been ready to try an approach using stem cells, the primitive cells that maintain and repair the tissues and organs in which they reside. Though never before attempted on a patient, the procedure had shown promise in animals.



What's in a face? Appearance is more than skin-deep, with bone and cartilage shaping cheek, brow, nose and ear. A transplanted face may resemble neither donor nor recipient.

The stem cells in children and adults are more limited than undifferentiated embryonic stem cells. Not yet established as a nerve or blood or any of the body's numerous other cell types, embryonic stem cells can become almost any kind of cell, and researchers hope someday to coax them into a multitude of miraculous cures. Still, even adult stem cells are proving to be versatile and curative. (For example, those from bone marrow can be used to regenerate blood cells following high-dose chemotherapy.) And now scientists have identified stem cells in the liver, brain, blood and skin that, with prompting, can become a host of other cell types. The problem is that the cells in all those locales are few in number and difficult to extract.

Going where surgeons elsewhere have not yet been allowed to tread, Hans-Peter Howaldt in Germany fashioned stem cells and bone chips to patch a girl's riddled skull.

Not so for another source, which physicians first identified in 2001. The mother lode of adult stem cells, it turns out, is fat. Adipose tissue has the body's most accessible supply, and stem cells from a patient's own fat may offer considerable benefits. In hundreds of experiments on animals, researchers have discovered that adipose-derived stem cells can differentiate into various cell types. Whereas U.S. physicians are only now being allowed to start testing stem-cell therapies on human subjects, Europe's freer regulatory environment has permitted Howaldt to make remarkable strides. "As long as we can document that we won't harm a patient with an untried procedure," he says, "we are allowed to go ahead under special circumstances."

In the case of Maria, Howaldt shaved a small amount of bone from the girl's pelvis and, during the same procedure, took fat from her left buttock. Surgeons then removed scar tissue from around her skull and took an imprint of the skull surface, which was used to mold two macroporous sheets from a malleable polymer that the body will absorb over time.

Next, Howaldt and his colleagues milled the bone into chips, which they applied to the skull defects. Then they attached the protective sheets with resorbable tacks and soaked the milled grafts with stem cells injected through holes in the sheets. A fibrin glue, made from the girl's plasma, kept the cells in place. Howaldt hoped that adding stem cells to the small amount of bone from his young patient would stimulate bone regeneration. Three months later the girl's skull had healed.

Yet despite that and other early successes (physicians in Spain have used the cells to treat difficult-to-heal enterocutaneous fistulas, abnormal connections between an intestine and skin, and surgeons in Japan are using them to stimulate fatty tissue growth in and around the breast instead of implanting prostheses), how stem cells from fat promote healing is still mysterious. Marc Hedrick, president of Cytori Therapeutics, a biotechnology company conducting research on fat's reservoir of stem and regenerative cells, has one theory. "It may be," he says, "that when the body is revved up to heal—for instance, after a heart attack—it releases growth factors, proteins and other stimuli that could signal the stem cells to home in on the damaged area to repair or salvage it."

That theory is supported by animal studies in which Cytori researchers have found that stem cells from fat reduce damage to the heart after a heart attack by strengthening its ventricular function and laying down new vessels to produce greater blood flow. Similarly, in his work, Howaldt is convinced that bone fragments transplanted from the pelvis stimulate the stem cells to differentiate into bone tissue.

Whatever the underlying processes and however promising the work appears, Hedrick says it would be wrong to exaggerate the potential of the new therapy. "Stem cells aren't magical. Rather, think of them as a new class of pharmaceutical. Some diseases will be straightforward to treat with stem cells, others will be very hard, and some will be impossible." Still, he says, stem cells have the potential to change plastic surgery, giving surgeons a new approach for augmenting soft tissue after breast cancer surgery, healing wounds and treating bone defects.

PHOTOGRAPH OF DR. HOWALDT: BERND AUERS

Though in many ways a more radical procedure than the European experiments with stem cells, the face transplant that Siemionow hopes to perform breaks no new surgical ground. Plastic surgeons have long been able to transplant large skin flaps and their blood supplies from someone's own arm, leg or back. Even joining blood vessels a millimeter in diameter has become standard practice.

But it's difficult to harvest enough similar pieces of autologous skin to cover an entire face. And until recently, the problem with using skin from a deceased human donor has been rejection. Because skin is the first line of defense against infection, it triggers the strongest immune response and is the most difficult to transplant. It wasn't until 1998, when the first human hand was transplanted—by the same French surgeon who in November performed the partial face transplant—that doctors found the right combination of immunosuppressant drugs to enable recipients to even tolerate donated skin.

Siemionow and other surgeons point to the success of 24 hand transplants as evidence that a donated face should also take. Yet even now, a lifetime of immunotherapy to prevent the constant threat of rejection brings considerable risks, with side effects that may include life-threatening infections, malignancies, diabetes, and kidney and liver failure. The immunosuppressant drugs now in use, says Siemionow, could be expected to shave 10 to 15 years off a transplant recipient's normal life span.

Still, she says, immunosuppressant drugs may prove less toxic to otherwise healthy burn victims than they are to organ recipients whose bodies are already weakened by disease. And she predicts that, before long, a short course of immunosuppression may be enough to establish tolerance of the transplant. In her experiments, rats have accepted new faces, limbs and skin flaps after just a seven-day regimen of immunotherapy.

Even with immunosuppression, there is a 50% chance the face will fail, either during surgery or soon after. Such odds, says Siemionow, are "reasonable for a procedure that has never been done." But the consequences of failure must be carefully considered, says Ira Papel, president of the American Academy of Facial Plastic and Reconstructive Surgery, who advises that such procedures be approached with extreme caution.

"Any kind of microvascular transplant is all or nothing," says Papel. "If you have a complication—perhaps the blood supply to the transplanted tissue is interrupted or the vessels aren't capable of maintaining circulation—you could lose the entire face, a devastating complication." If the transplanted face sloughs off, the patient will likely have to repeat the multiple skin grafts she may already have endured. "That could set a patient back years in terms of physical pain and emotional suffering," Papel says.

Even a successful transplant may leave the recipient with significant psychological issues. Though he or she won't assume the donor's facial features—a common notion Siemionow ascribes to *Face/Off*, a 1997 movie in which two men trade faces—it's not clear exactly what the recipient will look like.

At least initially, candidates for a face transplant (technically, a facial composite tissue allograft) will be burn victims whose soft tissues, facial muscles and bones are intact. The donor will provide only the envelope of skin, with attached fatty tissue, nerves and blood vessels, to resurface the recipient's face, leaving the eyes, mouth and ears largely unchanged. Yet while

Staring down critics, Cleveland Clinic's Maria Siemionow awaits only the right match of deceased face donor and disfigured recipient.

PHOTOGRAPH BY BEN BAKER

he or she will lose the aftereffects of previous reconstructive procedures—typically, a patchwork of unmatched skin grafts and feature-contorting scar tissue—the recipient is unlikely to regain a fully expressive face because nerve hook-ups aren't perfect and the facial muscles may have been damaged by scarring.

What will it be like to awaken from surgery with a new face, however much or little it resembles the recipient's old one? That's something most burn victims have already experienced, says Siemionow. "People who have been burned no longer look like themselves. They lose their identity not only after a terrible accident but also after each reconstructive procedure, and 30 to 50 surgeries are typical after a severe injury."

// Life After a New Face

One look at the patient consent form enumerating every possible risk of a face transplant and it's obvious that only the deeply courageous would dare sign. Yet something even more heroic is asked of candidates: proof that they're coping with their disfigurement.

"Someone with very low self-esteem and a poor support network will have more difficulty reintegrating into society" after a face transplant, says psychiatrist Joseph Locala, who provides psychiatric care for Cleveland Clinic patients. "I'll want to make certain that face-transplant candidates have developed a personal identity based upon attributes other than appearance." And though critics question whether it makes sense to subject a healthy person to such an extreme experiment, Locala notes that facial disfigurement brings with it a fivefold greater risk of psychiatric problems.

Still, a successful face transplant is likely to pose numerous psychological issues. Recipients may need therapy to learn how to interact without automatically assuming that each encounter will be emotionally painful. Transplant surgery, postoperative pain and the effects of medications could set off a recurrence of post-traumatic stress disorder, which afflicts as many as 30% of disfigured burn patients. And episodes of anxiety and depression, common in a third of transplant patients, are possible, says Locala.

Yet, after years of managing transplant patients, Locala is confident that any psychiatric problems can be treated. "Patients who have received solid-organ transplants initially complain about the burden of their medication regimen and the fear of complications or immediate graft rejection, but within six months to a year, their lives typically begin to regain a sense of normalcy," he says.

Siemionow is not the only surgeon who wants to push forward with the face transplant. Doctors in Spain and at the University of Louisville also hope to gain approval. Meanwhile, in November, Jean-Michel Dubernard, the French surgeon who performed the first hand replacement, transplanted the nose, lips and chin from a brain-dead woman to the face of a severely disfigured 38-year-old woman. Some physicians have criticized the French surgical team for not first attempting conventional reconstructive procedures, but Dubernard has said that more conservative surgery would not have worked for an injury that left his patient unable to speak or chew.

Ethics committees in France and England have refused to allow full transplants, arguing that the risks outweigh potential benefits. But the French group permits the less radical partial procedure. When the Cleveland Clinic gave Siemionow the go-ahead in 2004 after a 10-month review, it went against a position statement from the American Academy of Facial Plastic and Reconstructive Surgery that calls for the first face transplants to be conducted on people with severe facial trauma, tumors or burns—whereas Siemionow is seeking candidates (primarily burn victims) whose bone structure is intact and who are free of disease or other complications. So far, though, she has found neither an ideal candidate nor potential donors. Yet Siemionow remains optimistic that success will come—and that once adult transplants are routine, surgeons will be able to replace the faces of severely burned children.

Though a transplanted face could eventually bring relief to burn victims and others with major facial disfigurement, it's unlikely to be a perfect solution. Much better, suggests Vacanti, chief of pediatric surgery and director of pediatric transplantation at the MGH, would be to coax Mother Nature into giving such patients new skins. "Imagine you start with the patient's own cells, infuse them on a structure that duplicates the face, use computer-chip technology to fabricate blood vessels down to submicron levels, hook up those blood vessels and reanimate the tissue with nerves," says Vacanti. "You'd have a better face transplant than with donated skin, and you wouldn't need immunosuppression."

Vacanti and his brother Charles pioneered the field of tissue engineering along with two of their brothers during the mid-1980s and are still among its leading lights. Using a combination of biodegradable polymer scaffolding and chemical compounds to urge cells to grow outside the body, the Vacantis are responsible for such medical feats as rebuilding a 12-year-old's deformed sternum and chest wall with the boy's own cartilage cells; using bone-marrow cells and

Joseph Vacanti of the Massachusetts General Hospital holds a microengineered device primed to produce liver tissue complete with blood vessels. In time, he thinks, a new face could be lab-grown too.

PHOTOGRAPH BY BEN BAKER

sea coral to fashion a thumb for a man who severed his in an accident; and getting paraplegic rats to walk after implanting lab-grown spinal-cord tissue.

While the transplant of a bioengineered liver grown on a lab bench may be years away, other researchers have made strides in creating less complex autologous body parts such as ears, which don't need a blood supply and can survive by diffusion from surrounding tissues. Yaremchuk has made vast improvements to an ear grown from cartilage cells in 1995 by Charles Vacanti, now chairman of the anesthesiology department at Brigham and Women's Hospital. Using a quarter-inch piece of cartilage from behind the ear or inside the nose, Yaremchuk has been able to grow a human-size, flexible ear by seeding chondrocytes—cartilage cells—on a degradable ear-shaped polymer matrix and laminating them between layers of swine perichondrium, the connective tissue that surrounds ear cartilage.

"The standard approach for creating a replacement ear is to make a big incision in someone's chest, harvest cartilage from two ribs, carve it up, join it with wires and sutures in the shape of the ear and cover it with tissue from the ear area," says Yaremchuk. "But that's very tedious, there is deformity where you harvested the cartilage, and only a few people are really good at it. Now we can make an ear from 1,000 cells instead of eight inches of rib cartilage." Yaremchuk is also working on injectable cartilage that can resurface arthritic joints, potentially saving millions of people from knee and hip replacements.

With most medical breakthroughs come concerns about moving too quickly or provoking unintended consequences, and these advances in reconstructive surgery are no exception. In the case of Howaldt's stem-cell work, for example, Gregory Evans, chief of the Aesthetic and Plastic Institute at the University of California at Irvine, thinks more must be known about the underlying science before large-scale human trials begin. "There is a big jump from converting adipose-derived stem cells into other types of cells and having them actually function as nerve, muscle, cartilage or bone. It may be that adult stem cells have already differentiated too far while they are in fat to truly change into a new cell," says Evans.

Yet Evans, who is studying whether adipose stem cells can transform into nerve cells, remains guardedly optimistic. "Even though our criteria for using these advances may change drastically during the next few years, adult stem cells and tissue engineering have great potential for all of medicine," he says.

Facial transplantation, too, could have far-reaching implications. Beyond transforming the lives of disfigured patients, it might pay unexpected dividends. For example, if Siemionow's work leads her or others to conquer the perils of immunosuppression, it could dramatically improve the prospects for transplanting not only faces but also organs, hands, skin, nerves, muscles and bones. ■

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1. **"Allotransplantation of the Face: How Close Are We?" by Maria Siemionow and Galip Agaoglu, *Clinics in Plastic Surgery*, 32 (2005).** Excellent overview of the medical advances that have made the face transplant possible and the challenges that remain.
2. **"On the Ethics of Facial Transplantation Research," by Osborne P. Wiggins et al., *American Journal of Bioethics*, 4 (3) (2004).** Detailed assessment by the University of Louisville transplant team of the risks of a transplant, followed by valuable commentary from supporters and critics.
3. **"Tissue Engineering: The Design and Fabrication of Living Replacement Devices for Surgical Reconstruction and Transplantation," by Joseph P. Vacanti and Robert Langer, *The Lancet*, 354(suppl1) (1999).** Comprehensive description of the history and techniques of tissue engineering.