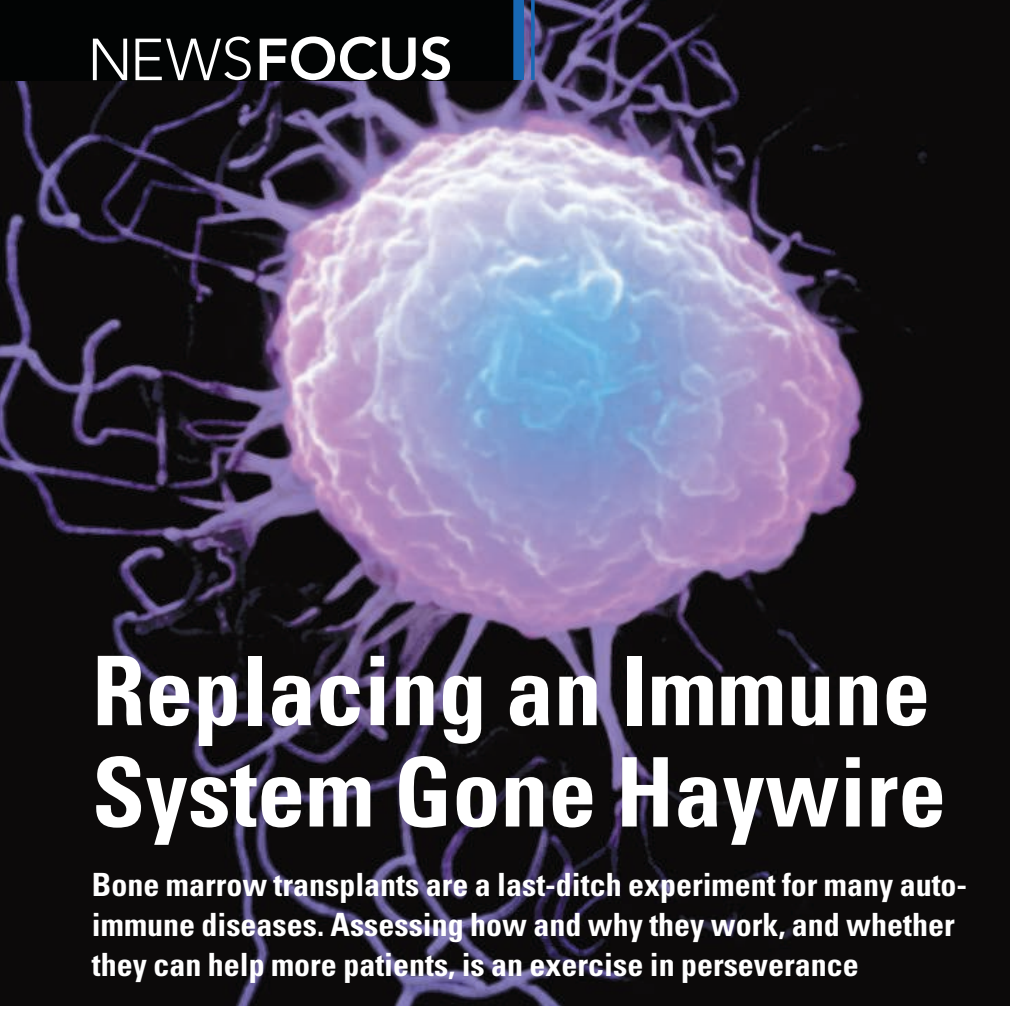

Replacing an Immune System Gone Haywire

Bone marrow transplants are a last-ditch experiment for many autoimmune diseases. Assessing how and why they work, and whether they can help more patients, is an exercise in perseverance

In the fall of 1996, more than 200 immunologists and oncologists gathered in Basel, Switzerland, to discuss a drastic, life-threatening strategy to beat back autoimmune disease: Destroy a patient's immune system with a blitz of chemotherapy and radiation before providing them a bone marrow transplant. Then watch and wait and hope the immune system is reborn, pristine and free of disease.

Bone marrow transplants, now called hematopoietic stem cell transplants, had been part of oncology's arsenal for many years to rid patients of blood cancers—and many patients have died from the intensity of the transplant or its aftermath. But that September more than 13 years ago, there was optimism, from animal studies and a handful of anecdotes in humans, that gentler transplants were possible and that they might reset a malfunctioning immune system as no other treatment could. The Basel group set out to test their hunch, launching a number of small clinical trials.

In medicine, mainstream treatments often start as the therapy of last resort: toxic, risky, desperate strategies to save the sickest patients. Time refines them; science clarifies who will benefit and who won't. To date, roughly 1500 adults and children worldwide have received stem cell transplants for a host of autoimmune diseases, including multiple sclerosis (MS), scleroderma, lupus, diabetes, and juvenile arthritis. Nearly all have been carefully tracked and monitored, with many giving blood and other tissue so that scientists can parse the evolution of their new immune system over months and years.

The results have been mixed, but there are startling success stories: About one-third of participants—many debilitated by their disease, in wheelchairs, or facing imminent death—go into remission and no longer need medication long-term, something that can't be achieved with existing treatments. Another third benefit, but only for a year or two, before relapsing. And a third don't respond at all, with about 1% to 5% dying from the treatment.

Scientists can't yet explain why some do so well following transplant and others don't, partly because they don't understand how, exactly, the transplants are rewiring a faulty immune system. And they worry that even as the field matures and the number of trials expands, assessing how well transplants really work is growing ever more difficult. Roadblocks include paltry funding—the trials lack commercial support because they're not testing new drugs—and difficulty finding patients, because rheumatologists and neurologists are skeptical of transplants, and new, promising, and generally safer biologic therapies are competing for patients' attention.

There's also growing evidence that stem cell transplants work best in healthier people whose disease hasn't damaged major organs. But for the most part, those aren't the patients receiving transplants: The toxicity of the treatment, uncertainty over how best to coax it to work, and tight restrictions from regulatory agencies over whom to transplant mean that many studies are restricted to the sickest of the sick—and that the therapy risks performing below its full potential.

Back in charge. There are hints that regulatory T cells tame the immune system after a transplant.

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Pressing the reset button

Physicians came to transplantation from different starting points. For Keith Sullivan, an oncologist and transplant physician at Duke University in Durham, North Carolina, success in a disease outside his area drew him to autoimmune conditions. In the 1990s, he and his colleagues found that young adults with sickle cell disease, which causes excruciating pain and strokes, responded remarkably well to stem cell transplants. "We said, 'Okay, … you can put a new blood-forming system in a patient with sickle cell disease and essentially cure' " that person, something not possible with existing treatments. So why not try "putting a new immune system in a patient with autoimmune disease?"

In stem cell transplants for cancer, patients are generally bombarded with near-lethal doses of chemotherapy and often radiation, which wipe out blood-forming cells in the marrow—along with any lingering malignant cells—to make room for healthy cells infused from a donor. Over time the donor cells proliferate, spawning a new blood system of T cells, B cells, and other immune components.

Most cancer patients undergoing transplants will die from their disease without one. Autoimmune diseases are less often fatal. Because of that, physicians focused on safer autologous transplants, which use cells from the patient, rather than allogeneic ones, in which cells are drawn from a donor, such as a sibling. In the late 1990s, when transplants for autoimmune diseases began in earnest, 3% to 5% of patients died from autologous transplants; 15% to 35% died from allogeneic ones.

Transplant physicians worried, however, whether they would be trading safety for effectiveness. If their patients' cells were pre-

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disposed to attack their own tissue, wouldn't the disease come back after reinfusing them? "That's what we kind of thought going into this," says Sullivan.

He focused on one of the most vicious autoimmune diseases, a severe form of scleroderma called systemic sclerosis, for which there are few treatments and high rates of mortality. Like other transplant physicians working on autoimmune conditions, Sullivan also dialed down the toxicity of the treatment pretransplant because he didn't need to destroy cancer cells, too. First, he collected blood from his patients and singled out CD34 progenitor cells—primitive blood cells that differentiate into more mature blood and immune players. These are the cells his patients would receive in the transplant.

Meanwhile, other physicians were experimenting as well. Paolo Muraro, a neuroimmunologist now at Imperial College London, was working at the U.S. National Institutes of Health in Bethesda, Maryland, from 2001 to 2005, studying blood cells from patients with MS who had received stem cell transplants to treat their MS. "The first question we asked: Is there the so-called immune resetting" after transplant? "Does it actually take place?"

Studying these cells, gathered over time, Muraro discerned a large number of T cells that had recently filtered out of the thymus—an indicator that they were newly formed. "It was not 100% renewal," he says; some cells that were present pretransplant remained. But enough young T cells were flourishing that Muraro concluded that a new immune system had seeded. He published the work in 2005 in *The Journal of Experimental Medicine*.

The lab findings matched what physicians were seeing in some patients. Sullivan's fear of a disease resurgence after a transplant did come true for certain individuals, but others stayed in remission for years. He attributes that to the particular set of circumstances that launched an autoimmune attack initially, some combination of environmental triggers, such as a viral infection, and unlucky genetics. Because the new immune system regenerates later in time, the environmental factors that originally triggered autoimmune attacks may be absent. "That may trump the fact that you have genetic predisposition," Sullivan says.

More recently, a number of studies have dug deeper, probing how the transplants are altering immunity. Last year, a German group described findings from five people with lupus who had been in remission for as long as 8 years since their transplants. All five had lost pathogenic antibodies linked to lupus, and the number of B cells in their blood had normalized. Other researchers are finding hints that in various diseases, regulatory T cells, which keep the immune system from acting out, flourish post-transplant.

These are just pieces of a larger puzzle, and it has many gaping holes. "There's a huge black box here: Why is this working?" asks Ann Woolfrey, a pediatric hematologist-oncologist at the Fred Hutchinson Cancer Research Center in Seattle, Washington. It's not clear which cells must be destroyed prior to transplant. Nor is it known which ones keep disease at bay afterward.

A SAMPLING OF TRANSPLANT TRIALS

Disease	Number Enrolled	Enrollment Goal	Principal Investigator	Status
Multiple sclerosis	Not available	155	Richard Burt, U.S.	Ongoing
Multiple sclerosis	28	25	Richard Nash, U.S.	Ongoing
Multiple sclerosis	21	200*	Gian Luigi Mancardi, Italy	Closed due to lack of participants
Scleroderma	156	150	Jaap Van Laar, U.K.	Transplants complete, follow-up continues
Scleroderma	Over 170**	100	Keith Sullivan, U.S.	Ongoing
Type 1 diabetes	23	12	Júlio Voltarelli, Brazil	Transplants complete, follow-up continues
Crohn's disease	20 [approx.]	48	Christopher Hawkey, U.K.	Ongoing

*Enrollment goal later scaled back to 30 and trial redesigned
**More patients are enrolled than can participate, because insurance often declines to pay for transplants. 60 have been randomized so far.

Slow ahead

In some, however, the transplants work wonders. In 2006, researchers reported that 50% with lupus remained in remission, along with about 30% who had either MS or scleroderma. A team of Europeans last year looked back over 12 years and 900 transplants and found that 59 patients had died from transplant-related complications, and about 40% had experienced no disease progression.

But as hopeful as most of these numbers are, nearly everyone agrees that stem cell transplants will remain forever experimental unless they compare favorably to other treatments, particularly in their ability to induce lasting remission. Although most physicians agree that patients should try safer therapies first before resorting to a risky stem cell transplant, even the best biologic therapies hitting the market won't work for everyone—and when they do help, they must often be taken for life. Randomized trials to match transplants against standard therapy mean juggling stringent regulatory requirements, a constant need for funding, and sluggish patient recruitment. "It takes time and endurance" to pull this off, says Alan Tyndall, a rheumatologist at the University of Basel, and, with Basel transplant physician Alois Gratwohl, a pioneer in the field. "It's exhausting."

One of the biggest challenges has been finding patients. A European trial for MS closed in December after recruiting just 21 people out of the once-hoped-for 200. In pediatrics, Woolfrey and her colleague Carol Wallace, at Seattle Children's Hospital, have sought patients for more than 5 years for a trial in pediatric autoimmune disease and transplanted only four, all with juvenile arthritis. Another study of pediatric autoimmune disease, led by Mitchell Cairo, a pediatric hematologist-oncologist at Columbia University, shut down several years ago. "We couldn't get rheumatologists to [refer] patients," says Cairo, who performed just two transplants for the study before giving up.

The problem, physicians agree, is that transplant experts, accustomed to treating cancer patients in dire straits, eye risk through a fundamentally different prism than do the neurologists, rheumatologists, and other spe-

CREDITS (TOP TO BOTTOM): (SOURCE) COMPILED FROM RESEARCH GROUPS LISTED; KIM WARREN

Weighing the alternatives. The option of new biologic therapies, which this little girl is receiving for her juvenile arthritis, make trial recruitment difficult.

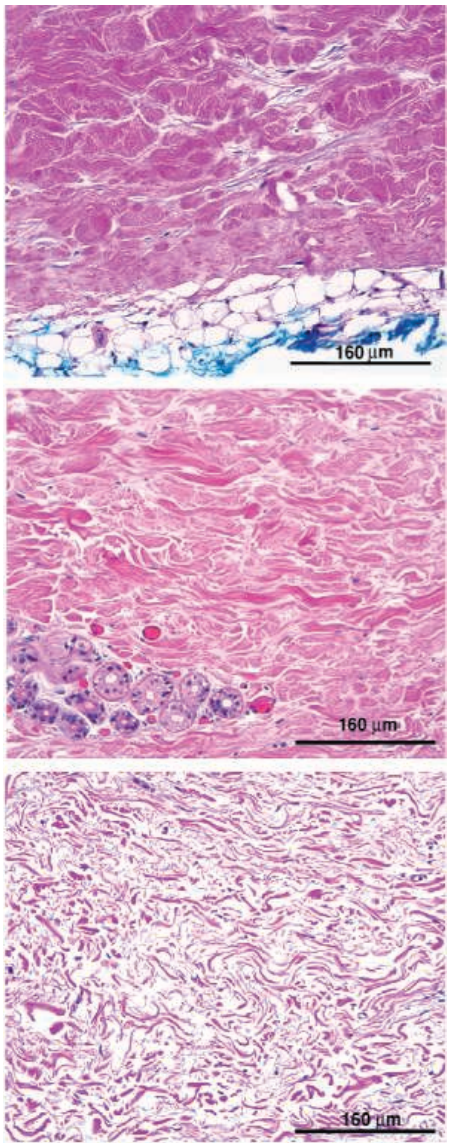
cialists who see autoimmune patients day in and day out. "From a transplant perspective, 5% mortality [from the treatment] is great," says Camillo Ricordi, scientific director at the Diabetes Research Institute at the University of Miami in Florida. "In a diabetes treatment, 1% mortality will be unacceptable."

Death rates from the transplants have dropped in the past 10 years, although they vary depending on the approach. Some physicians are experimenting with riskier allogeneic transplants in small trials, collecting cells from donors that they believe make a cure more likely. Others are moving in the opposite direction, jettisoning radiation and lightening the chemotherapy load as much as possible.

Physicians are also walking a tightrope in identifying which patients to transplant. "Transplantation is what you call a one-shot treatment," which makes picking the right patients critical, says Riccardo Saccardi, who performs bone marrow transplants at the Careggi Hospital in Florence, Italy, and who also chairs the working party on autoimmune diseases of the European Group for Blood and Marrow Transplantation. Early trials in those with advanced MS generally failed to help; trials in scleroderma on people with severe lung disease had high mortality.

In choosing patients for trials, many physicians are torn between instinct and reality. Their gut tells them that the therapy is most likely to help those early in disease, who don't yet have damage to their brain, their kidneys, or their lungs. But the risks of transplant, and uncertainty around whose disease will progress without it, makes transplanting such patients ethically questionable.

Some have forged ahead regardless. In January 2004, clinical immunologist Júlio Voltarelli of the University of São Paulo in Brazil and Richard Burt, who oversees immunotherapy for autoimmune disease at Northwestern University in Chicago, Illinois, began transplanting teenagers and young adults with type 1 diabetes, after spending more than 2 years seeking, and achieving, approval from an ethics board in Brazil. Their rationale: Diabetes destroys insulin-producing cells in the pancreas soon after diagnosis, and the window to act is a narrow one. Voltarelli has done 24 transplants and published findings from most of them in 2007 and 2009 in *The Journal of the American Medical Association*. "We can induce remission in almost all patients," he says, although about half later relapsed and resumed insulin therapy



Calm after the storm. A scleroderma patient suffered hardening of the skin (*top*), with collagen deposits in dense pink. One year after transplant (*middle*), skin was improving, and 5 years later, it was back to normal (*bottom*).

The diabetes study startled the field. "There was a lot of concern, taking these otherwise healthy individuals and giving them high-dose chemotherapy," says Richard Nash, a transplant physician at the Fred Hutchinson. In diabetes, many young patients don't develop major complications from the disease, such as kidney failure, for decades. Although none of the Brazilians died from the transplant, several suffered serious side effects, such as severe pneumonia and low sperm count that could affect fertility.

Still, the work has intrigued those who treat diabetes. "They show that you can stop the clock of autoimmunity," says Ricordi, who is interested in examining the treatment himself.

Burt argues that the chemotherapy given was relatively mild compared with that used in other studies—and that "there is no need" for more toxic regimens that some transplant experts are promoting. Others dispute that, saying that killing more cells up front in the patient may help a new immune system take root. Two ongoing trials in scleroderma should go a long way toward answering this question. In Europe, researchers have randomized 156 patients with the disease, with half receiving chemotherapy and then a transplant; in the United States, a similar trial takes a much more aggressive approach, by adding high-dose radiation. Both are at least 2 years away from reporting results.

That the scleroderma trials will even run their course is considered an enormous accomplishment. In the United States, insurance companies often decline to pay for the transplants, deeming them too experimental, thereby limiting trial enrollment; commercial funding is not an option because new drugs are not being tested. In Europe, government restrictions often control how many transplants can be performed at a given site. At University Medical Center Utrecht in the Netherlands, for example, national insurance companies will pay for about 35 stem cell transplants a year, says Nico Wulffraat, a pediatric rheumatologist at the hospital. Most of those go to cancer patients.

Clinical trials for new biologics also compete for the same participants, and that makes recruitment even harder, says Tyndall. Burt is running an MS trial and is recruiting in São Paulo and Prague, as well as Chicago and Calgary. Regulations around cell-therapy trials in the United States are so stringent as to virtually halt clinical research, many transplanters complain. "We're blocking this with incredible rules and requirements before you even do a pilot trial," says Ricordi. He is working with centers in China and Argentina on other types of cell transplants for diabetes to get around the roadblocks.

Tyndall hopes that the scleroderma trials will change the landscape. "If we can show with a disease like scleroderma, where there's nothing else to offer, that it actually does put people into long-term remission," then transplants might shift toward mainstream medicine. The therapy's hazards are "pretty clear," he says. The question is, "Which patients would justify that risk?"

–JENNIFER COUZIN-FRANKEL

CREDIT: R. A. NASH *ET AL.*, *BLOOD* 110 (15 AUGUST 2007)